A KNOWLEDGE MANAGEMENT FRAMEWORK TO DEVELOP, MODEL, ALIGN AND OPERATIONALIZE CLINICAL PATHWAYS TO PROVIDE DECISION SUPPORT FOR COMORBID DISEASES

by

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DEDICATION

To my father, Late S. Durrey Hassan Kazmi - I hope I have made you proud

and

To Raza, Ebad and Hani - ones who bore the brunt and were steadfast in their love, support and encouragement

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ABSTRACT

In this thesis we present an ontology based decision-support framework for handling co-morbidities by the alignment of ontologically modeled clinical practice guidelines (CPGs). The objective of this thesis is to formalize, model, align and operationalize the evidence-based clinical algorithms of co-morbid chronic heart failure (CHF) and atrial fibrillation (AF) in order to provide evidence-based clinical recommendations, care coordination and decision support to general practitioners[1](GPs) for effective management of CHF and AF. In this regard, the thesis addresses the following healthcare knowledge modeling issues: (a) modeling of healthcare knowledge, especially in terms of clinical guidelines and clinical pathways, to develop an ontology-based healthcare knowledge model for handling co-morbid diseases; (b) computerization of clinical pathways to offer point-of-care decision support; (c) alignment of ontologically-modeled disease-specific clinical pathways to handle co-morbid diseases; and (d) the provision of computerized decision support to general practitioners, based on modeled clinical guidelines and pathways, to assist them in handling chronic and co-morbid diseases. An elaborate OWL CP ontology for co-morbid CHF and AF—the CP ontology was developed that can be executed to support the diagnosis and management of co-morbid CHF and AF in a general practice setting. We have developed a decision support framework termed COMET (Co-morbidity Ontological Modeling & ExecuTion) that can handle three patient care scenarios, (i) patient has CHF; (ii) patient has AF; and (iii) patient develops a co-morbidity of both AF and CHF. COMET is accessible by web and is designed for GPs. COMET has been evaluated, both by simulated cases and by health professionals (GP and specialist), for its ability to handle single disease and comorbid care scenarios based on patient data and related constraints. The output at every phase is compared with the expected output as per single disease or comorbid management. Our results show that the resultant sequence of plans and their outcomes are comparable to the CP knowledge. Also, our ontology was able to handle any updates in the CP knowledge as advised by the domain experts

[1] In this thesis term general practitioners (GP) is interchangeable with family physician

LIST OF ABREVIATIONS USED

ACC= American College of Cardiology

ACEI= Angiotensin-Converting Enzyme Inhibitors

AF= Atrial Fibrillation

AHA= American Heart Association

ARB= Angotensin Receptor Blocker

BB= Beta Blocker

BC-DSS= Breast Cancer Decision Support System

BNP= Brain Natriuretic Peptide

BP= Blood Pressure

CAD= Coronary Artery Disease

CHF= Chronic Heart Failure

CIHR= Canadian Institute of Health Research

COMET= Co-Morbidity Ontological Modeling and ExecuTion

CP = Clinical Pathway

CPG = Clinical Practice Guideline

CDSS = Clinical Decision Support System

DL= Descriptive Logic

DSS= Decision Support System

DTD= Data Type Definition

EBCA= Evidence Based Clinical Algorithm

ECG= Electrocardiography

ED= Emergency Department

EMR= Electronic Medical Record

GEM= Guideline Element Model

GLIF= Guideline Interchange Format

GP= General Practitioner

HL7= Health Level 7

HTML= Hyper Text Markup Language

IHD= Ischemic Heart Disease

INR= International Normalized Ratio

JVP= Jugular Venous Pulse

K= Potassium

LVSD= Left Ventricular Systolic Dysfunction

Na= Sodium

NYHA= New York Heart Association

OWL= Ontology Web Language

PC= Prostate Cancer

PND= Paroxysmal Nocturnal Dyspnea

RDF= Resource Descriptive Framework

RDF-S = RDF Schema

SEMPATH= Semantic Adaptive and Personalized Clinical Pathways

URI= Uniform Resource Identifiers

XML= Extended Mark-up Language

XML-S = XML-Schema

GLOSSARY OF TERMS

Annotation – notes added by way of comment or explanation

Annotation property - Annotation properties can be used to add information (metadata—data about data) to classes, individuals and object/datatype properties

Asserted hierarchy – in protégé OWL manually constructed hierarchy is called asserted hierarchy

Binary relation – a relation between two things

Cardinality restriction - In OWL we can describe the class of individuals that have at least, at most or exactly a specified number of relationships with other individuals or datatype values. The restrictions that describe these classes are called cardinality restrictions. For a given property P, a Minimum Cardinality Restriction specifies the minimum number of P relationships that an individual must participate in. A Maximum Cardinality Restriction specifies the maximum number of P relationships that an individual can participate in. A Cardinality Restriction specifies the exact number of P relationships that an individual must participate in.

Class – In OWL classes are interpreted as sets that contain individuals. They are described using formal descriptions that state precisely the requirements for membership of the class

Classification of taxonomy – automated computing of superclass-sub-class relationships by reasoner

Classifiers - Reasoners are also known as classifiers. DL Classifiers such as Pellet, FaCT++ or RACER are used for reasoning of an ontology, i.e. to check class consistency and taxonomy for the defined concepts. These automatically reason over the properties of the classes to classify the ontology and check inconsistencies. They check for any unexpected or implied relationships. The task of computing inferred hierarchy is also called 'classifying the ontology'

Concept – word concept is sometimes used in place of class. Classes are concrete representation of concepts

Concept Constructors in OWL - OWL constructs such as Equality, InEquality, Property Restrictions, Property Characteristics, Cardinality Restrictions, Class Intersection, Datatypes, Boolean Combination of class expressions used to concepts in OWL

Context – a general condition, i.e. circumstance in which an event, action and so on takes place

Conceptualization – abstraction of some real world phenomenon

Concrete concepts – corresponds to specific objects in the domain, i.e. individuals (as appose to more abstract concepts, i.e. classes)

Declarative semantics – declarative specification of entities and relationships with each other in order to provide representation to the meaning of the data

Datatype property – link an individual to an XML Schema Datatype Value

Decidable Logics – logics are decidable if computations/algorithms based on the logics will terminate in a finite time

Defined class - a class that has at least one set of necessary and sufficient conditions. This class has a definition, and any individual satisfies this definition will belong to this class. This can be stated as; if an individual is a member of 'NamedClass' then it must satisfy the conditions. If some individual satisfies the conditions then the individual must be a member of that class.

Descriptive Logics (DL) – are a family of formal knowledge representation languages. A DL models contain concepts, roles and individuals. Main idea of DL is to describe the world in terms of properties or constraint that specific individuals have to satisfy, thereby making them instances of specific concepts. DL are a decidable fragment of First Order Logic and therefore are amendable to automated reasoning

Disjoint with – is an OWL vocabulary axiom, which specifies that an individual who is a member of one class cannot be a member of other class. In other words it cannot be an instance of more than one of the classes

Domain of discourse – domain we are interested in

Domain of a property – the class an individual belong to. It is the class of the subject individual in a subject-predicate-object triple

Existential restrictions - for a set of individuals, an existential restriction specifies the existence of a (i.e. at least one) relationship along a given property to an individual that is a member of a specific class. (Also called some restrictions)

Explicit – clear cut declarative meaning

First Order Logic – like natural languages assumes that world contain, objects, relations and functions

Formal – machine processable

Formal definition of ontology terms – when definitions of terms (vocabulary) are specified using a formal language such as OWL or predicate logic. The advantage of using formal definition is that these definitions allow a machine to perform much deeper reasoning

Formalization – formal codification of knowledge using formats, such as OWL language, so that the knowledge can be interpreted by computers

Formal semantics – describes meaning of the knowledge precisely. Precisely means that the semantics does not refer to subjective intuition, nor it is open to different

interpretation by different people or machines. Formal semantics allows the machines to reason about the knowledge. Thus, formal semantics is a pre-requisite for reasoning support

Functional property - an individual can only have relationships with at most one other individual along a functional property

Individual – represent objects in the domain that we are interested in

Inferred hierarchy – The hierarchy that is automatically computed by a reasoner is called inferred hierarchy. One of the main services offered by a reasoner is to test whether or not one class is a subclass of another class. By performing such tests on all of the classes in an ontology it is possible for a reasoner to compute the inferred ontology class hierarchy. Such testing is also called subsumption testing and the description of the classes is used to determine if a superclass-subclass relationship exist between them

Instance – Individuals are also called instances. Individuals can therefore be referred to as instances of classes.

Instantiation – adding individuals (instances) to classes

Level of evidence - Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses, Level of Evidence B: Data derived from a single randomized clinical trial or non-randomized studies, Level of Evidence C: Consensus of opinion of experts and or small studies

Object property – link an individual to an individual

owl:Thing – is the class that represents the sets containing all individuals. Because of this all cases are subclasses of owl:Thing. The empty ontology contain one class, i.e. owl:Thing

Planning – is a process of selecting and sequencing activities in such a way that the activities achieve one or more goals and satisfy a set of domain constraints

Primitive class – a class that only has necessary conditions. Necessary conditions can be read as; if something is a member of this class then it is necessary to fulfill these conditions. (use existential, i.e. someValueFrom restriction)

Property – Properties are binary relations on individuals, i.e. properties link two individuals together

Property characteristics - OWL allows the meaning of properties to be enriched through the use of property characteristics, such as, functional, inverse function, symmetrical and transitive properties

Property restrictions – are used to restrict individuals that belong to a class. These are of three main types: Quantifier, Cardinality and hasValue restrictions

Protégé metamodel – Protégé's model is based on a simple yet flexible metamodel. It basically can represent ontologies consisting of classes, properties (slots), property characteristics (facets and constraints), and instances

Quantifier – there are two types of quantifiers: Existential quantifier that can be read as at least one or some and, Universal quantifier that can be read as only

Quantifier property restriction – composed of a quantifier, a property and a filler

rdfs:Label - is an instance of rdf:Property that may be used to provide a human-readable version of a resource's name

rdf Literal – is a class of literal values such as strings and integers. There are two types of RDF literals: Plain and Datatype literals. Plain Literal is a sub-class of RDF literal that can take 1 or 2 parameters, i.e. String (the actual information contained in the literal) and Language (i.e. the language of this literal. This uses the XML:Lang attribute). Datatype literal uses datatype (by default it is XML:String) of the literal in addition to the information and language

Range of a property – the class of the object individual (or a datatype if the property is a datatype property) in a subject-predicate-object triple

Reasoners - Reasoners are also known as classifiers. DL Classifiers such as Pellet, FaCT++ or RACER are used for reasoning of an ontology, i.e. to check class consistency and taxonomy for the defined concepts. These automatically reason over the properties of the classes to classify the ontology and check inconsistencies. They check for any unexpected or implied relationships. The task of computing inferred hierarchy is also called 'classifying the ontology'

Reasoning – automatic checking of class consistency and taxonomy for the defined concepts by reasoners.

Specification – definition

Subsumed by - subclasses are specialized by their super-classes

Subsumption relationships – superclass-subclass relationships

Subsumption hierarchy - superclass-subclass hierarchy

Taxonomy – when classes are arranged in sub-class-super-class hierarchy

Time annotation – any temporal information associated with tasks or treatments

Universal property restrictions – are used to restrict the relationships for a given property to individuals that are members of a specific class. They constrain the relationships along a given property to individuals that are members of a specific class (also called all restrictions)

Vocabulary (ontology) – terms for classes and their relationships

XML Schema Datatype value – XML schema datatype specification defines numerous datatypes for validating the element content and the attribute value (string, Boolean, integer, float, decimal, date, time, duration, gYear, gYearMonth). These datatypes can be used to validate only the scalar content of elements.

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CHAPTER 1 INTRODUCTION

This thesis aims to provide a solution for the provision of knowledge-based clinical decision support to handle co-morbid diseases at the point-of-care. In this regard, the main focus of this research is to investigate and develop methods to formalize, model, align and operationalize Evidence Based Clinical Algorithms (EBCAs) to provide evidence based clinical recommendations, care coordination and decision support for co-morbid diseases.

Comorbidity is the existence of other medical conditions simultaneously with the primary condition in the same patient (National Center of Health Statistics, 2007). Chronic diseases are frequently associated with comorbidities. Utilization of hospital resources, physician's services, and length of hospital stay are directly related to the number of comorbidities a patient has (National Center of Health Statistics, 2007). With regards to this research, we define comorbidity as a condition(s) that is causally related to or is a complication of the index disease. Chronic heart failure (CHF) is one such index condition, which is associated with comorbidities such as AF. Comorbid atrial fibrillation (AF) can be cause or the consequence of the index disease - CHF. Thus, we consider CHF-AF as comorbidities. CHF is a complex, progressive and relapsing syndrome characterized by the impairment of the pumping ability of the heart (Lip, Gibbs & Beevers, 2000). Atrial fibrillation (AF), the most prevalent sustained cardiac dysrhythmia, is a common comorbidity of CHF. AF is more prevalent in patients with advance heart failure. It is estimated that overall about 15% to 30% of patients with CHF will develop concurrent AF. (Ehrlich, Nattel & Hohnloser, 2002). The concurrent presence of these two illnesses complicates patient management. The choice of treatment in such a situation depends on individual factors and needs to be personalized (Lip, Beevers, Singh & Watson, 1995). Effective management of CHF and its comorbidities, such as AF, by the general practitioner has great potential for reducing admission rates and associated burden of illness. Unfortunately, CHF is quite difficult to diagnose clinically given that many clinical features are not organ-specific. Furthermore, a significant care gap, that represents discrepancy between the evidence-based care

processes and standard care, exists in the management of the cardiovascular diseases in Canada (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004).

Knowledge translation tools such as Evidence Based Clinical Algorithms (EBCAs), which include clinical practice guidelines (CPGs) and clinical pathways (CPs), have enormous potential to reduce this care gap due to lack of up-to-date knowledge, more so in general practice settings (Brush, Radford & Krumholz, 2005). CPGs are based on a critical appraisal of scientific evidence about a specific medical condition/disease/procedure, designed to offer explicit recommendations to assist clinical decision making and to provide supporting evidence (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999). CPs are used to implement these recommendations in actual clinical practice (Kitchiner & Bundred, 1996). CPs stipulate the clinical processes and their workflow to implement the CPG in a specific clinical setting. In this way, a CPG entails *medical knowledge* whereas a CP entail *operational knowledge* about how to execute the CPG—i.e. the institution-specific protocols specifying the actual sequencing, decisions and scheduling of clinical tasks, as per the CPG, for the entire clinical course (Pearson, Goulart-Fisher & Lee, 1995).

Despite the availability of a large number of paper-based CPGs and CPs for a range of medical conditions, the utility of these knowledge translation tools at the point-of-care is still rather low (Ma, Monti & Stafford, 2006; Bloom, de Pouvourville, Chhatre, Jayadevappa & Weinberg, 2004; Crim, 2000; Cabana et al, 2000 Brand, Newcomer, Freiburger & Tian, 1995). This is largely due to the fact that paper-based CPGs and CPs are difficult to incorporate, in a timely manner, in active clinical practices (Alexandrou, Xenikoudakis & Mentzas, 2009). For optimal utility of CPGs and CPs it is imperative that the knowledge needs of the health practitioner are addressed at the point-of-care when he/she needs additional knowledge to either make or substantiate a clinical decision (Abidi, Abidi, Hussain & Butlor, 2008). This demands that the relevant task-specific heuristics are to be distilled from the CPGs based on the patient information and then presented in a usable format at the point of care (Brush, Radford & Krumholz, 2005). Furthermore, the knowledge being derived from a CPG and presented to the health practitioner should concur with the overall health profile of the patient. For instance if the

patient has co-morbidities then the knowledge being presented to assist clinical decision making should account for the patient's co-morbidities; this does not imply the provision of distinct clinical knowledge about the two diseases but the provision of knowledge that relates the two co-occurring diseases such that their physiology and treatment impact each other. The presentation of patient-specific knowledge from a CPG is a much-researched area, but the presentation of CPG-mediated knowledge that accounts for patient co-morbidities is an emerging and rather challenging research topic.

The complexity concerning decision-support for handling co-morbidities can be understood by the fact that CPGs are disease-specific and CPs are process-specific (Pearson, Goulart-Fisher & Lee, 1995) — i.e. the task-specific heuristics from CPGs are systematized within CPs. Therefore, the challenge is to *align* multiple CPs of the comorbid diseases whilst maintaining the integrity of medical knowledge and task pragmatics, and ensuring patient safety. Furthermore, CPs contains task-specific heuristics concerning a particular clinical scenario within a specific clinical setting, and hence they are not patient-specific (Abidi, 2009; Alexandrou, Xenikoudakis & Mentzas. 2009). But, to handle co-morbidities it is necessary to align the care processes of the different co-morbid CPs with respect to the patient profile. Given the above mentioned challenges in handling co-morbidities, we argue that one possible solution to CPG-mediated decision-support for co-morbidities is to (a) computerize CPs (for potential co-morbid diseases) in terms of semantically defined medical knowledge objects and clinical processes; (b) align the individual computerized co-morbid CPs along common or co-related clinical processes to realize an extended CP that can handle the patient's co-morbid conditions; and (c) execute the comorbid CPs at the point-of –care, with respect to the patient's information, to derive patient-specific care plans.

This thesis aims to provide a solution for the provision of knowledge-based clinical decision support to handle co-morbid diseases at the point-of-care. In this regard, the main focus of this research is to investigate and develop methods to formalize, model, align and operationalize Evidence Based Clinical Algorithms (EBCAs) to provide evidence based clinical recommendations, care coordination and decision support for co-morbid diseases. For the purposes of this research, we will be considering the rather

prevalent co-morbid diseases of chronic heart failure (CHF) and atrial fibrillation (AF), and we will focus on the knowledge needs of family physicians by developing a CPG-based clinical decision support system to assist general practitioners (GPs) to effectively manage patients with CHF and AF.

The research conducted in this thesis is in the realm of healthcare knowledge management, with particular emphasis on healthcare knowledge modeling and execution of the modeled knowledge to render clinical decision support for handling comorbid diseases. The overall research contributes along four main aspects:

The first aspect concerns knowledge acquisition. The knowledge acquisition phase entails knowledge identification and synthesis to develop CPs for handling the diagnosis and management of (i) CHF, (ii) AF and (iii) co-morbid CHF-AF by GP. This involved a review of a large number of existing CPGs for CHF and AF, and then the selection, interpretation and augmentation of the CPG statements and logic to derive clinically useful task-specific heuristics. The systematic organization of the task-specific heuristics, with respect to clinical workflow and pragmatics, resulted in our CPs for CHF and AF. The research contributes in terms of two new CPs for CHF and AF that target the knowledge needs and clinical pragmatics of GPs, especially those working in Nova Scotia. Although, the newly developed CPs are based on existing CPGs, they also incorporate the medical knowledge of cardiologists working in Nova Scotia, who have contributed to both the CP development and its evaluation from a medical standpoint. More so, the development of CPs for GPs is a major contribution as the source CPGs are typically designed for tertiary care setting, whereas GPs are the first point of care for the community yet there exists a lack of knowledge at the GP level on how to handle CHF and AF. The expert advice for the development of these CPs were, however primarily sought from the cardiologists instead of the GPs. This is because we were primarily concerned about the correctness of the medical knowledge used and we believe that this can be adequately determined by the cardiologists. Also, cardiologists were able to determine, what interventions are clinically possible at general practice setting. Hence, the clinical knowledge is primarily based on the input of cardiologists and the GPs are the potential ‘users’ of this knowledge.

The second aspect concerns knowledge modeling and involved the ontology-based modeling of the CHF and AF CPs, in order to semantically describe the diagnostic and treatment concepts in terms of explicitly defined clinical processes, tasks, decision-points, patient data, recommendations and information items. The knowledge modeling exercise resulted in an elaborate ontology that describes the CHF and AF diagnostic and treatment concepts and their interrelationships in a formal language. The thesis contributes in terms of (a) explicating the rather elaborate process of ontology engineering for computerizing paper-based CPs and (b) presenting an elaborate CP ontology that formalizes the CHF and AF CPs knowledge and the underlying decision logic. The feature of the CP ontology is that the encoded knowledge can be executed through computerized clinical decision support systems to offer patient-specific CPG-based recommendations.

The third aspect extends the knowledge modeling exercise to deal with the rather complex task of handling comorbidies through the systematic *alignment* of the individual CP of the comorbid diseases. In this regard, an ontology alignment approach was developed to align ontologically-modeled CPs to handle comorbidites. Our ontology alignment approach formalizes the functional relationships between the care processes within different CPs leading to them being combined to handle comorbidities whilst maintaining clinical pragmatics. The thesis contributes through (a) an ontology alignment approach for aligning multiple CPs, and (b) offers an ontologically-modeled co-morbid CHF-AF CP (using the modeled CHF and AF CPs).

The fourth aspect concerns the development of an online (web-based) clinical decision support system to assist GPs to handle CHF, AF and comorbid CHF-AF. The thesis pursues the execution of the ontologically-modeled CPs (developed in aspects 2-3) in order to guide GPs with diagnostic and therapeutic recommendations based on the patient information. The thesis contributes by generating patient-specific care-plans by a GP for either a single disease or co-morbid diseases.

This thesis presents the COMET (Co-morbidity Ontological Modeling & ExecuTion) system that is capable of handling three patient care scenarios for GPs: (i) patient has CHF; (ii) patient has AF; and (iii) patient develops a co-morbidity of AF and CHF.

COMET is not designed to generate a list of differential diagnoses but rather to assist the GPs to handle patients with moderately-high suspicion of CHF or AF based on best evidence.

1.1. RESEARCH PROBLEM

The research pursued in this thesis is in the realm of healthcare knowledge management, and concerns the modeling of healthcare knowledge to support clinical decision-making for handling comorbidities.

From a knowledge modeling perspective, the research problem being investigated in this thesis is how to formally model the structural, functional and conceptual knowledge encapsulated within individual disease-specific CP so that one can systematically align and execute multiple CPs to handle comorbid diseases, whilst maintaining the integrity of medical knowledge, task pragmatics, coordination of care and patient safely.

This health informatics thesis, therefore, is concerned with developing a competent and functional technical solution to address the above mentioned research problem from a healthcare knowledge management point of view. It may be noted that the success criterion for this research, therefore, is the ability to model CPG knowledge in terms of pragmatic CPs to handle comorbidities.

The medical CPs developed and applied in this research are used as exemplar CPs to demonstrate the efficacy of the knowledge modeling solution, and to provide a real clinical perspective to this research so that the knowledge modeling research has a clear clinical focus and purpose. Significant research has been conducted to develop these exemplar CPs and to ensure that they are based on best evidence, clinical practices and in line with the knowledge of domain experts. Nevertheless, it is not the intention of this research to validate these CPs through a clinical study—at this stage validation by domain experts has been completed and will suffice for addressing the research problem being pursued in this thesis.

The COMET system developed in this thesis is to serve as a proof-of-concept for handling comorbidities through a knowledge modeling approach. The success criteria for COMET are therefore its ability to correctly utilize the encoded knowledge to provide the right recommendations and information to GPs when they are taking care of CHF, AF and CHF-AF comorbidities. Given that COMET is a prototype system, its degree of usability in an actual GP clinical setting is not deemed as an evaluation criterion for this research. We realize that to incorporate COMET in a clinical setting it is necessary to develop more intuitive user-interfaces with input from GPs and to establish patient data input mappings with electronic medical systems—these technical extensions are quite possible but were not considered in this thesis as they are simply implementation issues that are beyond the research problem being addressed.

1.2. RESEARCH OBJECTIVES

This research pursues four main objectives as follows:

i. Development of Clinical Pathways (CPs) for handling CHF, AF and co-morbid CHF-AF. This involved the acquisition of clinically useful task-specific heuristics from the CPGs, through the processes of selection, interpretation and augmentation of the guideline statements and logic. The heuristics are then temporally organized to realize CHF and AF CPs;

ii. Modeling the CHF and AF CPGs in terms of a semantically-rich ontology that describes the CHF and AF diagnostic and treatment concepts and their interrelationships in a formal language.

iii. Aligning the ontologically-modeled CPs in a systematic manner to handle co-morbidities. The CHF and AF CPs are to be aligned to handle CHF-AF comorbidity, whilst ensuring the integrity of medical knowledge, task pragmatics, coordination of care and patient safely

iv. Execution of the formalized CP knowledge, modeled as the CP ontology, to provide patient-specific decision support to GPs based on patient data.

1.3. RESEARCH CHALLENGES

In order to achieve the above objectives, the following challenges were addressed:

i. Identification of valid, useful and readily accessible sources of CPG based knowledge on CHF, AF and most importantly comorbid CHF-AF to develop clinically pragmatic CPs that are applicable for GPs, especially in Nova Scotia
ii. Disambiguation and synthesis of the CP knowledge so that it can be systematically modeled and then computerized for execution purposes
iii. Handling of comorbidities through the modeling of the complex clinical processes related to comorbid disease management in a formal, structured, unambiguous and semantically rich format. This was important because to handle comorbidities it is important to establish the functional and temporal relations between the overlapping processes across the comorbidites.
iv. Development of a mechanism to execute the encoded knowledge to generate patient specific plans, advice and recommendations

From a knowledge modeling perspective, in order to handle comorbidities in a decision support and care planning framework, we had to address some specific ontology-related challenges, as follows:

i. Avoidance of replication of the clinical tasks such as diagnostic tests, therapies, examinations
ii. Identification of common comorbid care activities across comorbidities
iii. Ascertaining the temporal relationships between the activities in context of comorbidities
iv. Explicit statement of the preconditions for specific care plans in context of comorbidities
v. Affirmation of potential risks and harmful events while aligning the comorbid processes
vi. Care coordination[2] given that the comorbidities may involve various specialties.

[2] Since this research aims to provide a decision support solution to the GPs, care coordination within the scope of this thesis means that the CPs delineate specific events in the course of patient management that require referrals, along with appropriate referrals. These referrals might be to a cardiologist, emergency, nephrologists or radiology/labs.

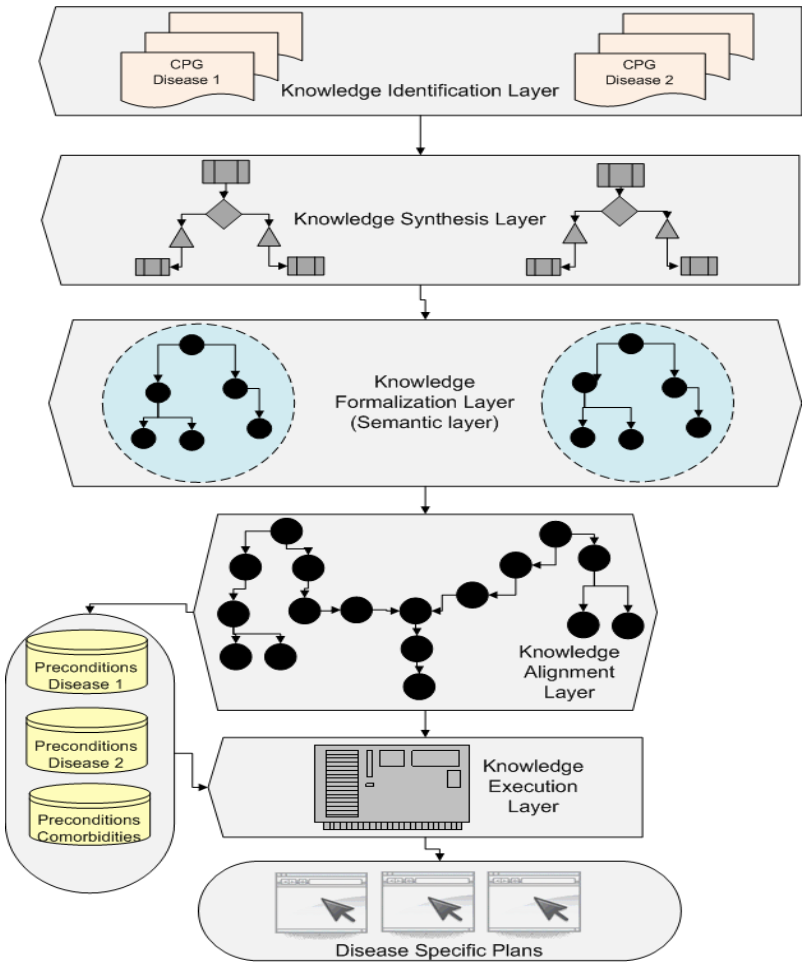

Figure 1: Framework for ontology based modeling and alignment of comorbid CP

1.4. RESEARCH SOLUTION APPROACH

To address the research objectives, we have taken a knowledge management approach to model the CPGs and to execute the resultant CPs. Our research approach spans a sequence of research phases, where in each phase we address a particular task, that cumulatively yield a framework for ontology-based modeling and alignment of comorbid CPs. Figure 1 illustrates our multi-layered research approach that comprises the following phases:

i. Knowledge Identification: Identification of valid knowledge sources to formulate the CPs

ii. Knowledge Synthesis: Synthesis of knowledge from different sources to realize the CP (CHF & AF) packages that are medically correct and clinically pragmatic.

iii. Knowledge Formalization: Modeling the knowledge within the CPs—i.e. processes, tasks, decisions, recommendations, patient data and various constraints and algorithms—to develop a semantically-rich CP ontology that can instantiate the AF and CHF CPs. A Web Ontology Language (OWL) based CP ontology is developed in this phase.

iv. Knowledge Alignment: Formalizing the functional relationships between care processes across different CP so that the multiple CPs can be semantically aligned—i.e. via ontology alignment—to handle comorbidities. The knowledge alignment phase ensures that when the different CPs are aligned the ensuing care process is medically valid in that the care quality and patient safety is ensured.

v. Knowledge Execution: Executing the CP ontology (with the instantiated CPs) to realize a clinical decision support system that can provide CPG-based recommendations to handle both a single disease and co-morbid diseases, depending on presence or absence of co-morbidity

1.4.1. KNOWLEDGE IDENTIFICATION

The purpose of this phase was to identify valid sources of relevant patient management knowledge concerning CHF and AF. The knowledge sources considered not only entailed evidence-based recommendations but also specific tasks and procedures and their scheduling information. A number of knowledge sources were identified during this phase, including CPGs, institution specific drug management protocols, journal publications, and most importantly domain experts (cardiologists at Queen Elizabeth II (QEII) hospital).

1.4.2. KNOWLEDGE SYNTHESIS

This phase involved the acquisition of the clinically useful task-specific heuristics from the identified knowledge sources through the processes of selection, interpretation and augmentation of the guideline statements and logic. If necessary, the heuristics were

further decomposed into atomic tasks and temporally organized to develop two CHF and AF CP packages containing clear and relevant evidence based diagnostic and therapeutic plans for patient care management, especially by GPs.

1.4.3. KNOWLEDGE FORMALIZATION

In this phase, the synthesized knowledge was modeled and formalized in terms of a dedicated CP ontology; developed using the Web Ontology Language (OWL). It may be noted that an ontology is the standard knowledge representation for the Semantic Web framework. The choice of OWL was guided by the fact that it offers declarative semantics that allows us to associate natural language descriptions with formal statements, thereby allowing human and machine readability of knowledge and subsequent execution of the knowledge. In this phase, the comorbid clinical processes in the CP ontology were hierarchically decomposed into component tasks, based on the available evidence for specific single disease and comorbid scheduling constraints. This ensured the conceptualization of the domain into an unambiguous model, thereby determining any implicit constraints on the relationships between the domain concepts, particularly to assist the alignment of concepts in handling comorbidities.

1.4.4. KNOWLEDGE ALIGNMENT

This phase involved ontology alignment—i.e.alignment of discrete and ontologically defined care plans in response to single disease or comorbid preconditions. The alignment of comorbid CPs is achieved at knowledge modeling level by developing unified ontological model that encompass the combined knowledge of aligned CPs. Since, knowledge alignment was pursued at the ontology level, therefore all ontological constraints about knowledge consistency were observed in the ontologically-modeled CHF-AF CP that entails a network of specific classes and the relationship between them. This is a complex activity as the alignment of comorbid plans needed to take into account the medical correctness and clinical pragmatics of the resultant CHF-AF CP.

1.4.5. KNOWLEDGE EXECUTION

This phase concerns the execution of the CP ontology in order to provide decision support to GPs, in terms of patient-specific care-plans, when concurrent AF or CHF is identified. An ontology-based execution engine was developed that manifests as a web-

based clinical decision support system that can be accessed by GPs—GPs are guided through the care process and, in response to patient data, CPG-mediated recommendations are provided to them. The entire session with the patient can be saved and the care process can resume from the last stage in the next visit of the patient. Technically speaking, a client-server programming model was used to develop the execution engine that uses the ontology as the knowledge-base. The .owl files are manipulated using the Protégé-OWL programming library on the server. The main ontological structures used for the execution purpose are Resources (classes), Properties and Property-Values. The client visualizes and enables the navigation of the ontology by presenting the properties of the current resource to the user who then selects the desired property-values and sends them back to the server for processing the next task. The CP is deemed to be complete when the next task is 'Pathway Ends' in the ontology. The execution engine, which was introduced earlier as COMET, offers a user friendly interface allowing GPs to navigate through the CPs for both single disease and/or comorbidity.

1.4.6. KNOWLEDGE EVALUATION

This phase involved the evaluation of the CP ontology for logical consistency, completeness, and conciseness. Through a series of explorations, the CP ontology was determined to be semantically and logically consistent, with adequate representational capacity to capture both the comorbid domain and procedural concepts and relationships. Also, by computing the inferred hierarchy we were able to determine that there were no redundant arcs in the model, so that the ontology is concise. Evaluation from a clinical pragmatics perspective was performed by both researcher and domain experts, using single disease and comorbid case scenarios. For each case scenario, the output at every phase was compared with expected output as per single disease or comorbid management. Our results showed that the sequence of plans and their outcomes are comparable to the intended output, i.e. in accordance to CP knowledge. The domain expert evaluation resulted in some advice for improvement in medical knowledge in the application. Our ontology was robust enough to withstand these alterations. In general, the knowledge encapsulated within the CP ontology was determined to be both consistent

and useful for offering clinical decision support to GPs to handle CHF, AF and CHF-AF patients.

1.5. THESIS ORGANIZATION

The overall organization of the thesis is as follows;

Chapter 2 provides an overview of the relationship between CHF and AF as comorbid conditions. This chapter includes the descriptions of CHF and AF, in terms of their epidemiology, clinical presentations, diagnosis, and management approach. This chapter also includes a discussion of the complex interaction between these two well-documented comorbidities and the unique challenges faced by the clinicians during the diagnosis and management processes while dealing with these two comorbidities. Furthermore, a discussion on available research on the management of heart failure and its comorbidities in general practice, specifically its problems, challenges, care gaps and possible solutions is also included.

Chapter 3 includes a discussion about the existence of care gaps in health care delivery and the concept of knowledge translation and its intended role in closing this gap. A description of knowledge translation tools such as CPGs and CPs, along with their differences, purposes, usefulness, potential benefits and limitations is also included. This chapter also deals with the issues related to computerization of the EBCAs and advantages and challenges associated with the computerization. It presents an overview of some of the representation formalisms[3] available such as Arden Syntax, EON, GLIF, PROforma and ASBRU.

Chapter 4 covers a general description of ontology, specifically types of healthcare ontologies and the advantages of adopting the ontological approach towards knowledge modeling in the healthcare domain. This chapter also presents an overview of the Semantic Web technologies with a main emphasis on RDF and OWL, related previous work and our own previous experiences in this regard.

[3] In health informatics literature formalisms refers to formats or languages used to formally describe health care knowledge, e.g. CPG, so that it can be interpreted by computers. An ontology is a formalism.

Chapters 5 & 6 present methods and materials utilized in this research. Chapter 5 presents the knowledge acquisition phase of this research. This chapter deals with the identification of relevant sources of the patient care knowledge, and the steps taken for its organization and synthesis, so that the resultant CPs are unambiguous enough to be formalized as ontology. Chapter 6 presents the introduction and an overview of the knowledge formalization phase of this research. Section 6.2 presents the knowledge conceptualization and section 6.3 contains information regarding the CP knowledge representation, which includes the class hierarchy and relations between the classes along with the restrictions on these relations. Section 6.4 details the comorbid knowledge alignment strategy. Section 6.5 explains the knowledge execution phase of this research.

Chapter 7 incorporates the strategy for evaluation of this research methodology and the relevant results.

Chapter 8 is the concluding chapter of this thesis. It provides concluding remarks along with a discussion of the lessons learned from this research endeavor, contribution, strengths and weaknesses of this approach. This chapter also highlights the possible future directions this research might take.

CHAPTER 2 COMORBIDITIES OF CHRONIC HEART FAILURE AND ATRIAL FIBRILATION

2.1. INTRODUCTION

Comorbidities are conditions that exist at the same time as the primary condition in the same patient. (National Center of Health Statistics, 2007). Chronic diseases are frequently associated with comorbidities. Published studies have reported the health (Rijken, van Kerkhof, & Dekker, 2005; Black, 1999) and economic burden of chronic diseases with comorbidities (Eaddy, Shah, Orsolya, & Stanford, 2009; Schmid, Schneider, Golay and Keller, 2004; Simpson, Corabian, Jacobs, & Johnson, 2000). Health challenges and the resource utilization associated with chronic diseases increases as the number of comorbid conditions increases (Rapoport, Jacobs, Bell & Klarenbach, 2004). According to a 2004 study (Rapoport, Jacobs, Bell & Klarenbach, 2004) about 10% of the population aged 60 years or younger has at least three chronic diseases and 10% or more of patients aged more than 60 years have at least seven chronic diseases. Utilization of hospital resources, physician's services, and length of hospital stay is related to the number of comorbidities a patient has (Rapoport, Jacob, Bell & Klarenbach, 2004). This study indicates that an additional comorbidity is associated with more than 12 visits to the physician per year. Also, an additional comorbidity raises the probability of hospitalization in the previous year by 44% in patients of less than 60 years of age and by 27% among people over 60 years of age (Rapoport, Jacobs, Bell & Klarenbach, 2004).

Chronic heart failure (CHF) is one such chronic condition that is frequently associated with comorbidities such as diabetes, chronic lung disease, atrial fibrillation (AF) and stroke (Masoudi and Krumholz, 2003). Comorbidities of CHF and AF are frequently referred to as "two new epidemics of cardiovascular disease" (Wang et al. 2003, p. 2920). These comorbidities are much more common among the elderly, with increasing incidence as the age progresses and, are associated with significant morbidity, mortality and economic burden (Wang et al. 2003). The heath and the economic burden of these two conditions is expected to increase as the population ages (Wang et al. 2003). Moreover, the coexistence of these conditions is attributed not only to their shared risk factors but also to the fact that one condition may directly predispose to the other (Wang et al. 2003). Not only do CHF and AF coexist, they also complicate management of each

other (Roy, 2004) so that the choice of the treatment depends on individual factors and therefore, needs to be individualized.

A more recent multicenter randomized trial (Roy et al. 2009) compared the rhythm control with rate control in 1376 patients with CHF and AF. Thirty one percent of these patient were in NYHA class III and IV (the rest were in NYHA class I and II). This study concluded that there were no significant differences between the two therapies when it comes to the number of deaths from cardiovascular causes, death from any cause, stroke, worsening heart failure, and the composite of death from cardiovascular causes, stroke, or worsening heart failure. Moreover, the researchers did not find any significant differences that favor either therapy in any pre-defined group of patients. This research concluded that in patients with CHF-AF rhythm control therapy does not reduce the rate of death from cardiovascular causes as compared to rate control.

This chapter provides descriptions of CHF and AF, in terms of their epidemiology, clinical presentations, diagnosis, and management approach. This chapter also includes a discussion of the complex interaction between these two well-documented comorbidities and unique challenges faced by clinicians during diagnosis and management processes while dealing with these two comorbidities. We further present the available research on management of heart failure and its comorbidities in general practice, including its problems, challenges and possible solutions.

2.2. CHRONIC HEART FAILURE

CHF is a chronic, complex, relapsing and progressive syndrome resulting from any structural or functional cardiac disorder which impairs the pumping ability of the heart necessary to support normal circulation. An estimated 200,000 to 300,000 Canadians are affected by heart failure (Weil & Tu. 2001). CHF is the most common cause of hospitalization of people over 65 years of age and is responsible for 9% of all deaths (Canadian Heart Failure Network, n.d.). In spite of recent advancement in the management of CHF, research suggests that the mortality rate for patients with CHF following two years of remedy is between 40% and 50% (Canadian Heart Failure Network, n.d.). Furthermore, being a relapsing and progressive disease, CHF is associated with episodes of acute symptomatic exacerbations which require repeated

hospital readmissions resulting in increased resource utilization and rising health care costs (Tsuyuki, Shibata, Nilsson & Harves-Malo, 2003). This scenario becomes even more burdensome when CHF is associated with AF, thus resulting in significant morbidity, mortality and economic burden (Wang, et al. 2003). It is therefore imperative to take proactive approaches to improve the quality of CHF care and control mortality, morbidity and resource utilization associated with CHF and its comorbidities. One such approach is to promote more optimal out patient management of CHF and its comorbidities at the general practice level as a means of seeking to prevent or delay hospitalization.

2.2.1. CLINICAL FEATURES AND DIAGNOSIS OF CHF

CHF is frequently associated with coronary artery disease (CAD) risk factors such as smoking, diabetes, family history of coronary artery disease, hypertension and high serum glucose (Lip, Gibbs & Beevers, 2000). Patients with CHF commonly present with non-specific symptoms and signs such as fatigue, dyspnea, swelling of ankles, exercise intolerance, hypotension and tachycardia that might be difficult to interpret (Watson, Gibbs & Lip, 2000; Khunti, Baker & Grimshaw, 2000). More specific symptoms and signs include orthopnea, paroxysmal nocturnal dyspnea (PND), nocturnal angina, raised jugular venous pulse, abnormal heart sounds, displaced cardiac apex and lung crackles (Watson, Gibbs & Lip, 2000; Khunti, Baker & Grimshaw, 2000).

Despite the fact that heart failure often presents with non-specific signs and symptoms, detailed clinical assessment is essential before ordering any investigations. It is appropriate to perform tests such as routine blood work, chest X-ray and 12 lead ECG before referring for echocardiography. A chest radiograph may show findings consistent with pulmonary congestion and cardiomegaly, but the absence of an enlarged heart does not rule out heart failure. An ECG is frequently abnormal in cases of CHF, but can be normal in about 10% of cases. Measurement of baseline serum electrolytes levels and renal function tests are necessary before starting any treatment regimen. (Davies, Gibbs & Lip, 2000). Brain natriuretic peptide (BNP), which can be used in ambulatory settings, is a particularly useful for patients who present with acute unexplained dyspnea. Low Brain natriuretic peptide (BNP) level in dyspneic patients, whose symptoms are attributed

to heart failure, provides an increased assurance that these symptoms are caused by some condition other than heart failure. However, a negative BNP in patients suspected of having heart failure does not by itself rule out heart failure (Felker, Petersen & Mark, 2006). The next step requires a careful evaluation of clinical features, and other diagnostic tests along with BNP (Felker, Petersen & Mark, 2006). Once other possible causes of dyspnea and other symptoms are ruled out, then left ventricular systolic function can be assessed by echocardiography. This provides a definitive and more objective assessment of any structural or functional cardiac abnormality consistent with CHF (Davies, Gibbs & Lip, 2000).

2.2.2. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

The New York Heart Association (NYHA) functional classification is a simple scheme to determine the severity of heart failure and monitor the therapeutic response. NYHA classification uses a patient' symptoms and exercise capacity to place him in one of four classes. The New York Heart Association (NYHA) functional classification is described as follows (Watson, Gibbs & Lip, 2000);

- ***Class I: Asymptomatic*** - No symptoms and limitation in ordinary physical activity despite presence of heart disease.
- ***Class II: Mild*** – Mild symptoms such as mild shortness of breath and mild angina and slight limitation during ordinary physical activity
- ***Class III: Moderate*** – Marked limitation in activity due to symptoms, even during less-than-ordinary activity, for example, when walking short distances. Patient is comfortable at rest.
- ***Class IV: Severe*** – Severe limitations on physical activity. Patient experiences symptoms even while at rest. These are mainly bed bound patients.

2.2.3. MANAGEMENT OF HEART FAILURE

Management of CHF depends on whether it is compensated, i.e. with stable symptoms, or decompensated, i.e. when overt features of fluid retention are present resulting in the inability to perform daily activities without symptoms of dyspnea or fatigue. Atrial

fibrillation is commonly present along with decompensated heart failure, but can also be present with compensated heart failure and therefore needs to be treated as well. The management of heart failure includes several themes such as (Millane**,** Jackson**,** Gibbs & Lip**,** 2000);

- Patient education and counseling - which involves symptoms and their severity, drug compliance and administration, social activity and employment and necessity of vaccination.
- General measures - such as dietary restrictions on salt and fluid intake, restriction on smoking and alcohol, and education regarding appropriateness and level of exercise and physical activity.
- Pharmacological treatment options – such as angiotensin converting enzyme inhibitors, beta blockers, diuretics, and digoxin

According to Canadian Cardiovascular Society Consensus conference recommendations on the diagnosis and management of heart failure (2006) and the ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adults, all patients with symptoms of heart failure and reduced left ventricular ejection fraction <40% should be prescribed an angiotensin-converting enzyme inhibitors (ACEI) in combination with a beta blocker unless there is an absolute contraindication to these therapies. According to the Canadian guideline, angiotensin-converting enzyme inhibitors (ACEIs) are also recommended for patients who are asymptomatic yet have a left ventricular ejection fraction <35%. These guidelines recommend substitution of angotensin receptor blocker (ARB) for ACEI in patients who are intolerant to ACEI. Careful evaluation of electrolytes, renal function and blood pressure is essential before initiating pharmacological therapy. Specific contraindications and cautions to therapy need to be identified and dealt with before any treatment can be commenced.

Treatment with ACEI/ARB and beta blockers should be initiated at low doses, followed by gradual uptitration depending on the patient's tolerance and response to the treatment. Renal function, blood pressure and serum potassium needs to be evaluated 1 to 2 weeks after the initial drug dose and after every uptitration. Patients should be informed about

mild and severe adverse effects and the common risks associated with therapy, and educated regarding the importance of stopping treatment and calling the doctor or of proceeding to an emergency department (ED) depending on the severity of adverse reaction.

Canadian and ACC/AHA guidelines also recommend the addition of a loop diuretic, such as furosemide, to the therapy for most patients with congestive symptoms. However, it is also recommended that once acute congestion is cleared, diuresis should be maintained at the lowest minimal dose which is compatible with stable signs so as to prevent recurrence of volume overload. Any electrolyte imbalance needs to be corrected aggressively, and serum potassium specifically maintained at 4mmol/L, so that diuresis can be continued until fluid retention is eliminated. For some patients with recurrent fluid overload, it is often possible to teach them to adjust their diuretic dose based on their symptoms and body weight.

2.3. ATRIAL FIBRILLATION

Atrial fibrillation is the most prevalent sustained cardiac dysrhythmia which according to the Canadian Cardiovascular Society Consensus Conference on Atrial Fibrillation (2004) affects approximately 200,000 to 500,000 Canadians. Although relatively uncommon before the age of 50 years, it is increasingly common after 65 years of age, when the prevalence of AF can be as high as 2% to 4% of the population (Kerr et al. 2005). Due to its associated complications, such as thromboembolism and stroke, AF can result in considerably increased morbidity and mortality. Symptoms associated with AF such as palpitations and decreased cardiac output can also cause significant impairment of quality of life. Ischemic heart disease (IHD) is suggested to be the most common underlying cause of AF. Other common etiologies of AF include hypertension, rheumatic heart disease, sick sinus syndrome, pre-excitation syndromes such as Wolff-Parkinson-White syndrome, heart muscle disease, pericardial disease, atrial septal defects, thyroid disease and alcoholism. In some cases AF is labeled as lone or idiopathic, when it cannot be attributed to any known predisposing factor or cardiac lesion.

AF is also frequently associated with heart failure. AF and CHF have a two-way relationship. While on the one hand AF may precipitate overt heart failure, especially in patients with already reduced left ventricular function, on the other hand the presence of CHF may encourage the development of AF because of atrial dilatation and increased load as well as conduction disturbances associated with heart failure. The presence of AF in patients with CHF often results in increased mortality and significant rise in thromboembolic risk (Lip, Beevers, Singh & Watson 1995).

2.3.1. CLINICAL FEATURES OF ATRIAL FIBRILLATION

AF is characterized by the absence of atrial systole and a rapid and irregular ventricular response. A consequence of this hemodynamic disturbance is loss of cardiac output which can be up to about 10% in otherwise normal individuals and much higher in patients who are older or have preexisting impairment of left ventricular function or both (Lip, Beevers, Singh & Watson, 1995). Although patients with AF may present with non-specific symptoms such as dyspnea, angina, palpitation, dizziness, more common presentations include reduced exercise tolerance and clinical features of heart failure (Lip, Beevers, Singh & Watson, 1995).

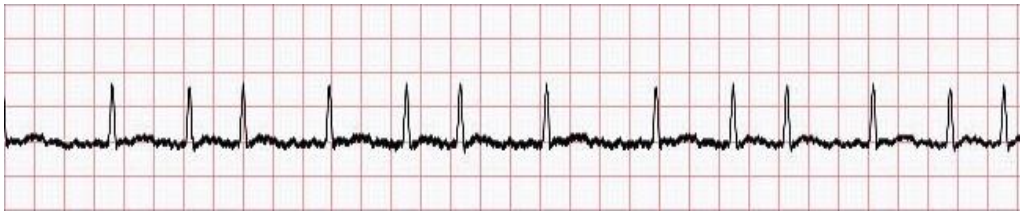

Figure 2: f-waves on ECG seen in patients with AF

A pulse which is irregular in rate, rhythm and volume and abnormalities of the first heart sound are the most important signs of atrial fibrillation. In some cases, patients may present to emergency departments with signs and symptoms consistent with hemodynamic instability such as syncope/presyncope, severe lethargy and fatigue, dyspnea, gross pulmonary edema, angina and poor cerebral perfusion (Lip, Beevers, Singh & Watson, 1995).

In addition to a history and presence of an irregular pulse, AF can be easily diagnosed by the presence of electrocardiographic evidence of rapid, irregular fibrillation waves called f-waves (Fig. 2) and the resulting irregular ventricular response (Tse & Lip, 2007).

2.3.2. TEMPORAL PATTERN OF ARRHYTHMIA IN ATRIAL FIBRILLATION

AF is regarded as recurrent when a patient develops two or more episodes of AF. Recurrent AF can be paroxysmal when the episodes stop spontaneously within 7 days, or persistent if cardioversion either electrical or pharmacological is needed to terminate the arrhythmia. If however, cardioversion is unsuccessful and the patient remains in AF or in cases where cardioversion is deemed unsuitable, the AF is regarded as permanent (Lip & Tse, 2007).

2.3.3. MANAGEMENT OF ATRIAL FIBRILLATION

The management of AF, irrespective of its temporal arrhythmic patterns, depends on patients' symptoms and signs, hemodynamic stability and the presence of concurrent diseases. Initial therapeutic goals in patients with AF are hemodynamic stabilization, control of ventricular rate and prevention of thromboembolism. Patients who are hemodynamically unstable require immediate electrical cardioversion. (King, Dickerson, & Sack, 2002). Since AF increases the risk of thromboembolism by 4 to 5 fold, it is imperative to identify individual thromboembolic risk factors and provide appropriate antithrombotic treatment such as warfarin or heparin or an anti-platelet such as aspirin (Lip & Tse, 2007).

Management of arrhythmia in AF includes two main approaches; rate control and rhythm control. According to the recommendations of the Canadian Cardiovascular Society Consensus Conference (2004) on AF, there is no evidence that one treatment approach is superior to the other. The AF guideline recommendation has also been corroborated by a more recent multicenter randomized trial (Roy et al. 2009) that compared the rhythm control with rate control in 1376 patients with CHF and AF. This study concluded that there were no significant differences between the two therapies when it comes to number of deaths from cardiovascular causes, death from any cause, stroke, worsening heart failure, and the composite of death from cardiovascular causes, stroke, or worsening heart

failure. Moreover, the researchers did not find any significant differences that favor either therapy in any pre-defined group of patients (Roy et al. 2009). This research concluded that in patients with CHF-AF rhythm control therapy does not reduce the rate of death from cardiovascular causes as compare to rate control.

The 2004 Canadian AF guideline recommends that the choice of rate control or rhythm control should be tailored based on the patient's clinical picture and presence of comorbidites such as CHF. The 2009 update (Howlett et al 2009) recommends rate control therapy for the treatment of AF in patients with stable heart failure. In fact, Roy et al (2009) also suggest that rate control "should be considered a primary approach for patients with atrial fibrillation and congestive heart failure" (Roy et al. 2009, p 2675), since it eliminates the need for repeated cardioversion.

The goal of rate control is to achieve a rate of less than 100 beats per minute without any specific attempt to restore and maintain sinus rhythm and this is conventionally regarded as the first step in AF therapy. Rate control therapy includes calcium channel blockers, beta blockers and digoxin. The calcium channel blockers and the beta blockers provide rapid ventricular rate control during rest as well as exercise. Digoxin is less effective in controlling rate, especially during exercise, and therefore is more affective as adjunctive therapy. However, due to its positive inotropic effects, it is very useful when AF is concurrent with CHF. (King, Dickerson & Sack, 2002). Calcium channel blockers, because of the risk of further deterioration of left ventricular function, should either be avoided or given with extreme caution to the patient with AF and CHF (Masoudi & Krumholz, 2003).

Once the ventricular rate has been controlled and the patient has been stabilized, he is considered as a possible candidate for rhythm control. Cardioversion can be pharmacological or electrical and the choice of cardioversion is also individualized. Pharmacological cardioversion requires careful assessment of the risks and benefits associated with anti-arrhythmic medications. Careful anticoagulation before and after rhythm control is essential because of increased risk of systemic embolism associated with AF and the high chance that the arrhythmia will recur in many patients depending on underlying cause (King, Dickerson & Sack, 2002).

2.4. COMORBIDITY OF CHF AND AF – MANAGEMENT CHALLENGES

CHF and AF are two increasingly prevalent heart disorders, which often coexist in the same patient and are responsible for significant morbidity and mortality, impairment of quality of life and increase in burden of illness (Wang et al. 2003). AF is more common in patients with advanced heart failure. About 40% to 50% of heart failure patients in New York Heart Association (NYHA) functional class IV have AF. Nevertheless, it is also present, though less commonly, in relatively stable heart failure patients; for example, it occurs in about 10% of patients in NYHA functional class II. It is estimated that overall about 15% to 30% of patients with CHF will develop concurrent AF. (Ehrlich, Nattel & Hohnloser, 2002).

AF can be regarded as either a cause or consequence of heart failure. The onset of AF is associated with a rapid ventricular response, which may then precipitate overt heart failure, especially in patients whose left ventricular function has already been compromised. CHF, because of increased atrial load, atrial dilatation, local conduction disturbances, and some level of atrial fibrosis, may increase the risk of AF up to six-fold (Ehrlich, Nattel & Hohnloser, 2002). Conversely, once developed, AF can further increase the risk of progressive ventricular dysfunction and thereby exacerbate heart failure symptoms, thus causing a vicious cycle (Nueberger et.al. 2007). According to the Framingham Heart Study, CHF preceded AF (41%), almost as often as AF preceded CHF (38%); and in almost one-fifth (21%) of the participants, CHF and AF were diagnosed on the same day (Wang et al. 2003). A 2002 Dutch study indicated that there is an increased risk of mortality in patients with mild to moderate heart failure in conjunction with AF and it seems that AF per se is an independent predictor of mortality in such patients (Nueberger et.al. 2007). This was also seen in the Framingham study (Wang et al. 2003), where development of new AF in patients with CHF was associated with increased mortality. Also previously existing CHF has been associated with an adverse impact on the prognosis of AF. (Wang et al. 2003). Furthermore, the presence of AF concurrent with heart failure exponentially increases the risk of thromoembolism (Watson, Gibbs & Lip, 2000).

Not only do CHF and AF frequently co-exist, they complicate management of each other. Treatment of AF in the setting of CHF is based on three basic principles: heart rate control, cardioversion and maintenance of sinus rhythm, and prevention of thromboembolism. The subject of rhythm control versus rate control as the preferential therapeutic strategy for long term therapy of AF in HF is controversial and debatable. The choice of treatment depends on individual factors and needs to be individualized. However the Canadian Cardiovascular Society consensus conference on atrial fibrillation (2004) recommends ventricular rate control through use of beta blocking agents in combination with digoxin for patients with CHF and AF. Also, the Canadian Cardiovascular Society Consensus Conference on heart failure (2004) suggests that using rate control therapy in patients with CHF and AF is associated with fewer hospitalizations and fewer drug related side effects.

2.4.1. MANAGEMENT OF CHRONIC HEART FAILURE AND ITS COMORBIDITIES IN GENERAL PRACTICE

According to the Canadian Heart Failure Network, about 50% of CHF cases overall are treated by general practitioners at family clinics in Canada. (Canadian Heart Failure Network, n.d.). Unfortunately, heart failure is quite difficult to diagnose clinically given that many clinical features are non-organ-specific (Watson, Gibbs & Lip, 2000). Often, there are few signs and symptoms in the early stages of CHF. Management of heart failure is also an extremely complex process. CHF management requires prescription of parallel therapies derived from varied medication groups such as ACEI, beta blockers and diuretics to control a myriad of symptoms. Furthermore, careful uptitration of these medications are required to reach desired effects. Frequent monitoring of these regimens through frequent blood and other tests are necessary to gauge the effectiveness of the treatments and to identify, prevent and treat the adverse effects associated with them.

Although, CHF management is quite common in general practice, research shows that heart failure diagnosis and management in this setting is not entirely without problems (Davis, Hobbs & Lip, 2000). A study conducted in Finland (Hobbs, Davis & Lip, 2000) suggests that only about 32% of patients who were suspected of having heart failure by their general physician (GP) actually had definite heart failure as concluded by a scoring

system based on clinical and radiographic findings. This result is similar to another related study conducted in England (Hobbs, Davis & Lip, 2000), in which only 29% of 122 patients who received diagnosis of CHF for the first time in a general practice setting had objective evidence of heart failure and a demonstrable abnormality of cardiac function. Similar findings were echoed in another English study (Hobbs, Davis & Lip, 2000) in which only about 22% of patients diagnosed as having heart failure by their GPs had definitive evidence of left ventricular systolic dysfunction on echocardiography. An even more interesting finding with respect to this research is that about 23% of these patients had concurrent AF, which was undiagnosed by the GPs. (Hobbs, Davis & Lip, 2000). These findings indicate a gap in diagnoses provided by GPs and the actual condition of patients as verified in the specialized clinics and hospitals.

GPs are also frequently concerned about starting and monitoring the treatment of heart failure in general practice. The first line of conventional treatment for CHF is initiation and uptitration of angiotensin-converting enzyme inhibitors (ACEI). It is now accepted that the general practice setting is a safe and viable alternative to hospitalization for initiation, uptitration, maintaining and monitoring treatment with ACEI in patients with mild to moderate heart failure, normal renal function and a systolic blood pressure of more than 100mmHg (Hobbs, Davis & Lip, 2000). The picture, however, becomes increasingly complex when the general practitioners (GPs) are required to treat coexisting conditions, especially when a particular medication needed to treat a specific comorbidity is either contraindicated in patients with heart failure or require great caution and monitoring. For example, Nondihydropyridine calcium channel blockers, a group of drugs commonly used as rate control agents for atrial fibrillation may further deteriorate left ventricular function in patients with concurrent left ventricular systolic dysfunction (LVSD) (Masoudi & Krumholz, 2003). Instead, with respect to rate control therapy, the Canadian Consensus Conference of Atrial Fibrillation (2004) clearly recommends beta blockers with digoxin for patient with CHF-AF, and calcium channel blockers or beta-blockers in active or young patients with only AF.

Thus, although diagnosis and management of CHF and its comorbidities in the general practice setting is a widespread in Canada and other parts of the developed world, there

remain significant care gaps and challenges in this environment. One approach to optimize such care is to facilitate the adoption of practices and implementation of treatments espoused in available evidence-based clinical practice guidelines and clinical pathways.

2.5. CONCLUSION

Research shows that, like in other clinical domains, care gaps exist in the management of cardiovascular diseases (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004). This care gap represents a discrepancy between the evidence-based cardiovascular care processes labeled as best practice and the standard cardiovascular care provided to patients (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004). Evidence-based clinical algorithms such as clinical practice guidelines and pathways have enormous potential to reduce such care gaps. They may be extremely valuable tools to help GPs navigate through the complex maze of diagnoses and managements of complex diseases such as CHF and AF. Evidence-Based Clinical Algorithms (EBCAs) guided practices are particularly useful when these two conditions are to be treated concurrently. The Canadian Cardiovascular Society has produced clinical practice guidelines for diagnosis and management of heart failure and atrial fibrillation. Extraordinary effort, time and dedication have been devoted to the development of these CPGs. Although they contain the current state of scientific knowledge, they are not written to be directly incorporated into routine practice. CPs, on the other hand, contain task-specific heuristics derived from CPGs, which can be made available relatively easily to the clinician during everyday practice. Most disease-oriented guidelines are focused on a single disease and their limitations when comorbidities are present, especially among elderly, is well described (Starfield, 2006; Boyd, Darer, Boult, Fried, Bult & Wu, 2005; Dawes, 2010).

Chapter 3 provides a detailed look at Evidence-Based Clinical Algorithms (EBCAs) in general, their structures, differences, usefulness and limitations when it comes to their role in clinical decision making. Additionally, this chapter discusses the advantages of computerization of EBCAs for decision support purposes and the various approaches to computerization of EBCAs.

CHAPTER 3 EVIDENCE BASED CLINICAL ALGORITHMS: ORIGIN, PURPOSE & COMPUTERIZATION

3.1. INTRODUCTION

An Evidence Based Clinical Algorithm (EBCA) is an expression that encompasses evidence based knowledge, which is codified within Clinical Practice Guidelines (CPGs) and Clinical Pathways (CPs). EBCAs are tools that organize best evidence as clinical rules, decision points and health care action plans pertaining to a specific health care domain (Gaddis, Greenwald & Huckson, 2007). EBCAs are developed to enable clinicians to apply evidence-based and up-to-date healthcare knowledge to improve patient care. EBCAs are regarded as evidence to practice pipelines (Lang, Wyer & Haynes, 2007) as they translate best evidence into practice. By codifying available best evidence into specific rules and action plans they exemplify the process of knowledge translation, thereby enabling clinicians to provide care which is credible, effective and efficient (Gaddis, Greenwald & Huckson, 2007).

EBCAs manifest in terms of CPGs and CPs, which are both designed to provide evidence-based health care for specific clinical scenarios and to reduce the variations in clinical practice. However, it may be noted that there are some significant differences between CPGs and CPs. While CPGs entail general recommendations about diagnostic and therapeutic procedures that are applicable to a specific disease, they do not consider the institution-specific implementation of the recommendations (Campbell, Hotchkiss, Bradshaw & Porteous, 1998; Cheah, 1998). CPs are usually derived from evidence based CPGs and are multidisciplinary, locally agreed upon guidelines for use within a particular health care institution, by the clinical stake holders at that institution (Campbell, Hotchkiss, Bradshaw & Porteous, 1998; Cheah, 1998). CPs are concerned with the institution-specific implementation of best evidence (most likely in terms of a CPGs) within a specific institution. Depending on institutional practices and resources, a CP can be developed based on evidence derived from more than one CPGs or by allied health professionals from a particular institution (Vlayen, Aertgeerts, Hannes, Sermeus & Ramaekers, 2005).

This chapter discusses the existence of care gaps in health care delivery and the notion of knowledge translation and its role in closing such gaps. We present a description of knowledge translation tools such as CPGs and CPs with a report on efforts to computerize them so that they can be used at the point-of-care as decision support tools.

3.2. HEALTH CARE GAP AND KNOWLEDGE TRANSLATION

Research shows that a wide gulf remains between the best clinical evidence available and the actual care received by patients (Gaddis, Greenwald & Huckson, 2007, Davis, Evan, Jadad, Perrier, Rath et.al, 2003). This care gap is also referred to as knowledge translation gap (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004). According to an estimate, while evidence-based and effective remedies are omitted in about 30% to 40% of the patients, it is observed that unproven, useless or even harmful treatments might be provided in about 20% to 25% of cardiovascular patients (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004). Similar disparities between the practice and the available best evidence have also been recorded in the use of other common cardiovascular medical treatments such as aspirin, statins (Ma, Monti & Stafford, 2006) and beta blockers (Follath, 2006). These practices are not only potentially harmful to patients, but also increasingly burden the health care systems (Gaddis, Greenwald & Huckson, 2007, Davis, Evan, Jadad, Perrier, Rath et.al, 2003). Given the above situation, a number of approaches have been proposed to address the under-application of best evidence in clinical practice. These approaches range from continuing medical education to continuing professional development to knowledge translation (Davis, Evan, Jadad, Perrier, Rath et.al, 2003).

According to the Canadian Institute of Health Research (CIHR), knowledge translation is "a dynamic and iterative process that include synthesis, dissemination, exchange, and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system" (Canadian Institute of Health Research. 2008). According to CIHR, *Synthesis* in the context of Knowledge Translation refers to "the contextualization and integration of research findings of individual research studies within the larger body of knowledge on the topic". *Dissemination* means "identifying the appropriate audience, and tailoring the

message and medium to the audience". Dissemination of synthesized knowledge among other approaches also includes implementation of plans and tools. Evidence-Based Clinical Algorithms (EBCAs) such as Clinical Practice Guidelines (CPGs) and Clinical Pathways (CPs) are tools that exemplify the knowledge synthesis component of knowledge translation. The purpose of these tools is to represent knowledge in an unambiguous, concise and user friendly format, thereby facilitating the uptake and utilization of evidence-based knowledge in clinical practice.

This thesis is mainly concerned with the processes of *Knowledge synthesis* and *knowledge dissemination,* which are exemplified by three main phases:

i. Knowledge engineering which involves the development of CPs using several evidence based guidelines and institution specific protocols
ii. Knowledge modeling which involves the reprsentation of CPs in a formal representation, such as an ontology
iii. Knowledge operationalization which involves the alignment of multiple disease-specific CPs to handle co-morbidities, and the execution of the modeled CPs to disseminate evidence based knowledge for on-line care planning and decision support

3.3. EVIDENCE-BASED CLINICAL ALGORITHMS AS KNOWLEDGE TRANSLATION INTERVENTIONS

In Canada, Evidence-Based Clinical Algorithms (EBCAs) are developed by national and provincial professional societies, Health Canada, centers of excellence, hospitals and other groups for a number of clinical areas, such as: diagnosis and treatment of medical conditions, disorders and diseases, various clinical procedures, and administration of clinical trials. During the EBCA development process, the specific topic for which an EBCA is to be developed has to be explicitly identified and refined so that the evidence can be evaluated for that particular clinical area and precise and relevant issues can be addressed (Shekelle, Woolf, Eccles & Grimshaw, 1999). Development of a Clinical Practice Guideline (CPG) for a specific topic involves a number of labor intensive tasks such as review of the current literature, critical appraisal, consultation with

multidisciplinary stake holders, classification of recommendations and grading of the evidence (Campbell, Hotchkiss, Bradshaw & Porteous, 1998).

Despite the fact that development of a CPG is an intellectually intensive process, when it comes to compliance research shows that the CPGs are underutilized (Ma, Monti & Stafford 2006; Bloom, de Pouvourville, Chhatre, Jayadevappa & Weinberg, 2004; Crim, 2000; A; Cabana et al, 2000; Brand, Newcomer & Freiburger & Tian, 1995). A Clinical Pathway (CP), unlike a CPG, conforms to locally agreed upon standards and practices, and for this reason has a higher level of compliance than a CPG (Panella, Marchisio & Di Stanislao 2003; Weiland, 1997). Although one of the main purposes of the CPs is the standardization of care, they allow practitioners to divert from the CPs based on the patent's situation—this is known as CP variance and this flexibility is one reason for the high compliance of CPs (Campbell, Hotchkiss, Bradshaw & Porteous, 1998).

3.3.1. PURPOSES AND POTENTIAL BENEFITS OF EBCAs

One of the main purposes of EBCAs is to enhance informed decision making and to control inappropriate variations in health care delivery with the objective of improving the quality of care (Wollersheim, Burgers & Grol, 2005). By managing unnecessary variations and discouraging potentially harmful treatments and procedures, Evidence-Based Clinical Algorithms (EBCAs) not only improve healthcare quality but also help to conserve valuable resources, which help to improve the efficiency of healthcare (Wollersheim, Burgers & Grol, 2005; Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999). EBCAs are at times regarded as the gold standard against which clinical practice can be compared during a clinical audit. An EBCA can potentially be used as an education aid in order to revise and enhance both undergraduate and professional development curricula (Open Clinical, 2006). Simplified versions of EBCAs can also be used as tools for informing and empowering patients to enable them to make more informed healthcare choices (Wollersheim, Burgers & Grol, 2005).

3.3.2. EBCAS VS. PRACTICE STANDARDS

Despite the fact that standardization of healthcare is promoted as one of the main reasons for the adoption of EBCAs in clinical practice, both CPGs and CPs are *not* deemed as a practice standard. Practice standards detail absolute limits on acceptable clinical practice,

and are defined by a regulatory body, for example the standards of nursing practice developed by the College of Registered Nurses of Nova Scotia (College of Registered Nurses. 2003) On the other hand EBCAs are utilized on a voluntary basis by practitioners to assist them in applying the best evidence available to practice and for informed clinical decision making (Canadian Chiropractic Clinical Practice Guidelines. 2002).

3.3.3. CLINICAL PRACTICE GUIDELINES

According to the definition provided by the American Institute of Medicine, CPGs can be defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999, p. 527). The motivation behind the entire CPG movement is to translate best evidence derived from research into concise and convenient recommendations on various aspects of clinical practice. Thus, they are based on a critical appraisal of scientific evidence and offer explicit recommendations for clinical decision making along with grading of quality of the supporting evidence using standardized and widely used formats (Wollersheim, Burgers & Grol, 2005).

3.3.3.1. POTENTIAL LIMITATIONS OF CPG IN PRACTICE

Despite numerous potential benefits of Clinical Practice Guidelines (CPGs), the healthcare community has often expressed concerns regarding the adoption of the CPGs in their practice. Probably, the most common phrase cited in the literature is dependence on "cook book medicine" (Wollersheim, Burgers & Grol, 2005). Critics argue that CPGs cannot replace the clinical judgment and expertise that are needed to solve complex clinical problems (Wollersheim, Burgers & Grol, 2005; Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999). Thus, it is claimed that since a CPG is an effort to standardize care delivery, it ultimately becomes an impediment to individualized care given that it cannot address specific patient features, available local resources and specific care settings (McCollom, & Allison, 2004). CPG development is a major undertaking as it requires a great deal of time, resources and knowledge to appraise every single bit of evidence before it can be translated into a recommendation. CPG development teams are required to weigh benefits of an intervention against the harm associated with it before recommending it. The resulting recommendations, therefore, are based on this value

judgment for a patient with unique clinical features (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999). Some clinicians might also have legal concerns; for example, use of CPGs as a citable evidence for malpractice litigation and its economic implications (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999). It is also argued that even if the guidelines are of high quality they still are inconvenient and time consuming to use (Woolf, Grol, Hutchinson, Eccles & Grimshaw, 1999).

3.3.4. CLINICAL PATHWAYS

A Clinical Pathway (CP) has been defined as *"*an interdisciplinary plan of care that delineates assessment, interventions, treatments and outcomes for a specific health related condition" (Beyea, 1996, p. 4). The CPs are structured health care management plans, which depict clinical goals for the patients and formalize ideal sequence of steps to achieve those goals as efficiently as possible (Pearson, Goulart-Fisher, & Lee, 1995). CPs are also known as integrated care pathways, multidisciplinary pathways of care, care maps, collaborative care pathways and critical pathways. Like CPGs, CPs requires revisions as new evidence and methodologies for care processes emerges (Cheah, 2000).

3.3.4.1. STRUCTURE OF CLINICAL PATHWAY

A Clinical Pathway (CP) provides a roadmap and timeline of the patient's course of treatment and also lists the demands, activities and the capacity at the health care facility (Pearson, Goulart-Fisher & Lee. 1995; Bryan, Holmes, Postlethwaite, Carty, 2002). A CP can be represented in a simple algorithm, a flow chart of activities or as a time-task matrix in which multidisciplinary tasks are positioned on one axis and cross-aligned with time to be performed on the other axis (Zander, 2002).

In general, a CP contains two types of tools; content tools and action tools. The content tools include evidence-based clinical indicators derived from the relevant practice guidelines, inclusion and exclusion criteria for the target population, and expected clinical outcomes. The action tools encompass clinical assessment, including record sheets for vital signs and other aspects of physical exam, diagnostic clinical orders such as laboratory tests, radiology procedures and so on, variance audit forms and patient or family education material. In summary CPs (Fig. 3) consist of four main components (Hill, 1998)

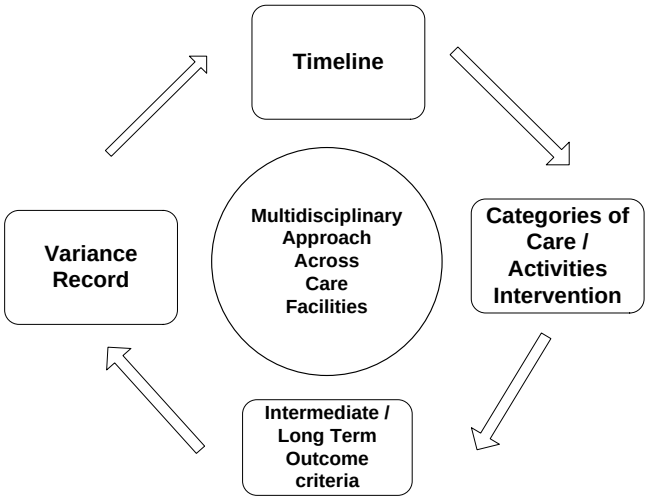

Figure 3: Components of Clinical Pathway

- *A timeline;* A Clinical Pathway (CP) may be represented either as an algorithm (flow-chart) or a time-task matrix. In any case, transition points between the tasks are explicitly specified along with staff activities to achieve those transitions for optimal efficiency (Cheah, 2000; Pearson, Goulart-Fisher & Lee, 1995).
- *Categories of care activities and their interventions*. These include clinical assessments, diagnostic testing, prognosis and care plans (Zander, 2002)
- *Intermediate and long-term outcome criteria.* These are either pre-defined or identified and evaluated by multidisciplinary teams where predefined outcomes are not applicable due to specific clinical features (Zander, 2002)
- *Variance record.* This allows the documentation and analysis of any deviation in the care processes from the predetermined course, i.e., difference between the activities expected within a specific time slot and the actual event that occurred (Zander, 2002). Once identified, these variations can be grouped, analyzed and used to modify and hence improve the quality of CP.

In addition, some CPs may also contain *evidence based key indicators* to measure the progress of the patient along the pathway (Zander, 2002). These are milestones to indicate where a patient should be at precise stages during the care process. A CP can be monitored to ensure that a patient is receiving quality care and can be used to alert the care provider when an activity has not reached a desired outcome.

3.3.5. RELATIONSHIP BETWEEN CPG AND CP

Table 1 summarizes the relationship between CPG and CP.

Table 1: Comparing CPG and CP

	CLINICAL PRACTICE GUIDELINE	CLINICAL PATHWAY
Purpose	Offers explicit recommendations of clinical decision making	Implement CPG recommendation in actual practice
Scope	Usually covers specific clinical circumstances	Charts the care to be given for the entire clinical course
Developers	Governmental and non-governmental agencies	A group of local doctors and nurses
Use	Not institution-specific	Institution-specific
Timelines	No timelines provided	Designed around specific timelines
Patient Progress	Do not trace a patient's outcomes	Expected intermediate patient outcomes to evaluate a patient's progress

While Clinical Practice Guidelines (CPGs) are based on a critical appraisal of scientific evidence and offer explicit recommendations for clinical decision making along with supporting evidence, CPs are used to implement these recommendations in actual clinical practice (Kitchiner & Bundred, 1996). CPGs are usually developed by governmental and non-governmental agencies, whereas Clinical Pathways (CPs) are institute specific, developed by a group of doctors, nurses and other health professionals with the purpose of applying CPGs at the local level, specifically at the patient-provider interface. While a CPG provides recommendations and indications for a diagnostic test or a therapy, a CP focuses on improving efficiency and quality of care once such decisions have been made (Pearson, Goulart-Fisher, & Lee, 1995). Although, the main purpose of both CPGs and CPs is to improve clinical decision making, control variance in practice and therefore enhance quality of care, a CP typically charts the care to be given for the entire clinical course rather than for one specific clinical task, such as diagnosis or treatment. As a result, as in the case of this research, a CP typically incorporates key elements from several guidelines (Vlayen, Aertgeerts, Sermeus & Ramaekers, 2005). Another distinguishing feature of CPs is that they are designed along precise timelines, so that sequencing and scheduling of the tasks are explicitly stated, sometimes even in hour-by-hour detail. CP often lists the expected intermediary patient outcomes that in turn serve as the indicators of performance of the pathway and chronicle the progress of the patient

(Pearson, Goulart-Fisher & Lee, 1995). Any deviation from the expected course means that variance has taken place. A CP frequently allows documentation of this variance (Zander, 2002).

In summary, a CP unlike a CPG conforms to locally agreed upon standards and practices, and for this reason they are more adopted by practitioners in comparison to the CPGs, which are not derived from local consensus (Panella, Marchisio & Di Stanislao, 2003; Weiland, 1997).

3.4. INTEGRATING EVIDENCE-BASED CLINICAL ALGORITHMS INTO ROUTINE CLINICAL PRACTICE

Medical practice involves numerous interactions between multiple partners to solve complex clinical problems. The clinical services being provided are becoming increasingly specialized with more and more clinicians being involved in the care of a single patient, especially patients with comorbidities, thereby further complicating the already complex interactions (Brush, Radford & Krumholz, 2005). To make health care systems more efficient, providers are under more pressure to reduce the length of hospital stay and to align diagnostics and therapeutic procedures in more efficient ways.

General practice care settings present peculiar challenges when it comes to care delivery. While in hospital settings clinical decisions are more likely made during rounds through consensus among the teams of clinicians headed by the most senior practitioner, in a general practice setting an individual General Practitioner (GP) is expected to make decisions solitarily, and is accounted solely for these decisions (Brush, Radford & Krumholz, 2005). Therefore, a GP at a family clinic is under tremendous pressure to confront the complexity of today's health care system and navigate through extremely complicated diagnostic procedures and treatment modalities (Brush, Radford & Krumholz, 2005). In addition, the GPs are expected to incorporate the best evidence into everyday practice.

We argue that, in order to determine the most appropriate means by which best evidence can be incorporated in the routine practice, we need to review the decision making behavior of clinicians and the role of heuristics or cognitive short cuts in clinical practice.

We can then determine how we can use these heuristics to determine the format that is most suitable for the integration of EBCAs into the clinical practice.

3.4.1. CLINICAL DECISION MAKING: USE OF HEURISTICS

Clinicians use cognitive short cuts called heuristics whenever they come across uncertainties during clinical decision making (Brush, Radford & Krumholz, 2005). These heuristics originate from the years of practice and self-education and constitute the intuition or tacit knowledge of clinicians (Brush, Radford & Krumholz, 2005). Clinical heuristics include *representativeness heuristics,* which are simple rules of thumb, and *availability heuristics,* which include cognitive processes that enable clinicians to derive conclusions from the readily available sources of information (Brush, Radford & Krumholz, 2005). While representativeness heuristics enable clinicians to condense large chunks of information into simple routine practices of do's and don'ts and rules of thumbs, the availability heuristics cause them to overvalue the events that are promptly recalled because, for example, they are readily available, more recent, more talked about, more emphasized, or more vivid, as opposed to being more common in reality (Elstein & Schwarz, 2002). Although clinicians use representativeness heuristics to recognize a clinical problem and the known solution to this problem, it is the use of availability heuristics that equip clinicians to identify a suitable solution to that problem (Brush, Radford & Krumholz, 2005). Availability heuristics enable clinicians to sort through different sources of information such as medical literature, continuing medical education, seminars and discussions, past experiences, and, practice guidelines and clinical pathways during the process of clinical decision-makings. Thus, clinical judgment more likely is influenced by the information that is more easily remembered as opposed to the best of evidence that is not readily recalled. Thus in order to be effective, best evidence in the CPGs and CPs needs to be made readily available to clinicians, especially at the point-of-care (Brush, Radford & Krumholz, 2005). Based on the above, we argue that for better uptake of Evidence-Based Clinical Algorithms (EBCAs) by clinicians, it is important that EBCAs are made available and operationalized in the clinical workflow at the point of care.

3.5. PROBLEMS WITH EXISTING FORMATS OF EBCAs

For scientific evidence to guide decision making it should be made available to the decision maker at the right time and place. However, most of the EBCA are not written in a format that can be easily incorporated in routine clinical workflow (Brush, Radford & Krumholz, 2005). For example, while working with the Canadian guideline on heart failure, we discovered that if a practitioner wanted to ask a simple question, "Which of my patients with heart failure should receive beta-blockade", she would have to interpret at least five class 1[4] and three class IIa [5] recommendations related to beta blockade to distill a desired task-specific heuristic, which read;

"*Beta blockade is recommended for CHF patients with (a) left ventricular ejection fraction <40%, however, those who are in New York Heart Association (NYHA) class IV should be stabilized before initiation of beta blocker, (b) for most heart failure patients with preserved systolic function, (c) for asymptomatic Atrial Fibrillation (AF) patients with left ventricular ejection fraction <40%, and (d) for symptomatic AF patients where beta blockers can be added to digoxin once patient has stabilized*".

We argue that one way to distill the practice-related knowledge in Evidence-Based Clinical Algorithm (EBCA) into clinically useful task-specific heuristics is to derive CPs from CPGs in the form of an algorithm or a workflow (Brush, Radford & Krumholz, 2005). However, there are two potential problems: (1) The Clinical Pathways (CPs) derived from Clinical Practice Guidelines) CPGs are in paper format and hence are static documents; and more so, any change in the evidence or local policies requires the CP to be modified thus making them resource intensive (Alexandrou, Xenikoudakis & Mentzas, 2009); and (2) The heuristics in CP are designed around a specific clinical scenario and not for a specific patient (Abidi, 2009, Alexandrou, Xenikoudakis & Mentzas, 2009). Both these problems render a CP rather difficult to deploy at the point of care (Abidi, Abidi, Hussain & Butlor, 2008).

[4] Evidence or general agreement that a given procedure or treatment is beneficial, useful and effective
[5] Weight of evidence is in favor of usefulness or efficacy (Source: Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and Management.

Most current paper-based EBCA describing patient care are single-disease oriented documents (Dawes, 2010), and hence lack the flexibility to treat patients with comorbodities (Starfield, 2006; Boyd, Darer, Boult, Fried, Bult & Wu, 2005; Dawes, 2010).

We argue that in order to deal with scenarios involving concurrent illnesses, the CPs of comorbid conditions need to be aligned along common processes, recommendations and decisions. The main goal of CP alignment is to,

i. Avoid the replication of clinical tasks such as diagnostic tests, therapies and examinations
ii. Identify tasks and activities which are common in comorbidities
iii. State the temporal relationships between activities to be performed in the context of comorbidities
iv. State the preconditions and post-conditions for specific tasks in the context of comorbidities
v. Identify potential risks and harmful events such as; drug interactions, prescription of a drug indicated for a particular condition and contraindicated for its comorbidity
vi. Standardize the role of healthcare professionals, the various health care specialties and the care process when dealing with comorbidities.

We argue that in order to align multiple CPs to handle comorbidities it is important to explicitly identify, state and organize all the task-specific heuristics that are common to the comorbidities.

3.5.2. OPERATIONALIZATION OF EBCAs

For optimal use, the best evidence should be tailored towards the task under consideration—this means that the task-specific heuristics in the pathways should be distilled in a format that can be aligned and operationalized seamlessly in routine clinical practice (Brush, Radford & Krumholz, 2005).

The operationalization of Evidence-Based Clinical Algorithms (EBCAs) involves: (i) computerization of EBCAs into a formalized model so that they can be automatically

aligned if needed and executed by computer based reasoners, (ii) systematic incorporation within a Clinical Decision Support System (CDSS), thereby making them executable at the point of care; and (iii) seamless integration of these computerized and executable EBCAs into clinical workflow through CDSS (Abidi, 2007). We believe that care planning and decision support systems guided by EBCAs are especially valuable in clinical settings where a non-specialist practitioner such as a family physician is required to manage challenging scenarios including the presence of comorbidites.

3.6. EBCAs AS HEALTH CARE WORK FLOW TOOLS

Coordination and management of health care activities is one of the fundamental premises behind the drive for adoption and operationalization of EBCAs (Kumar, Smith, Pisanelli, Gangemi, & Stefanelli, 2003.). While a CPG often promotes the adoption of evidence based care processes, such as indication of a diagnostic test or a therapy, a CP, often derived from CPGs focuses on the quality and efficiency of care through multidisciplinary coordination and the streamlining of these processes to manage the patient (Pearson, Goulart-Fisher & Lee, 1995). Nevertheless, it is not uncommon to see EBCAs being depicted as clinical algorithms that unfold over time by specifying the order of tasks in terms of a process flow model. This process model is also frequently referred to as health care workflow (Mulyar, van Der Aalst & Peleg, 2007). Although, paper-based EBCAs document the care process, it may be noted that due to their representation medium they lack the flexibility to adapt dynamically to changes in the clinical or operational context or even in the medical knowledge (Abidi, 2009, Alexandrou, Xenikoudakis & Mentzas, 2009). One solution to overcome the static nature of paper-based EBCAs is to computerize them, using an EBCA knowledge model that elicits the main concepts and establishes the inherent relationships among the concepts, so that they can be adapted with respect to the clinical context and the clinical workflow in a more efficient manner. The idea for the EBCA knowledge model is to identify first the various care tasks and then sequence them according to the causal and temporal aspects of the clinical workflow whilst dealing with the constraints regarding scheduling of resources essential for the efficient execution of these tasks in a primary care environment (Tu et al. 2004). As per this approach, the workflow is referred to as health care flow and the process logic is captured within the clinical algorithm itself.

One of the main challenges in dealing with comorbidities is adjusting the health care flow so as to simultaneously treat multiple diseases without affecting the overall care process. This may involve aligning the health care flow of the multiple (disease-specific) CPs to realize a unified health care flow that coordinates the care activities necessary for handling the comorbidities—this is different from simply concurrently executing the health care flow for individual diseases. The idea of the unified health care flow is to (a) minimize the redundancies of tasks that may happen when treating multiple co-existing diseases, for instance the ordering of the same blood tests by the CPs of two co-existing diseases; (b) order the care tasks, such as treatments, diagnostic tests and other interventions, in an optimal manner so that not only redundancies are avoided but also the clinical pragmatics is maintained; and (c) ensure patient safety in terms of discharging care that do not contravene the comorbid conditions. We posit that to develop health care flow for comorbidities it is necessary to align the health care flows—these are typically represented in terms of disease-specific CPs—at the medical knowledge level so that the aligned CPs are medically sound and clinically pragmatic. In this thesis, we investigate the alignment of two CPs, at the medical knowledge level through an ontology-based knowledge model, to handle comorbidities.

To pursue the alignment/synchronization of comobidity care flow, we need to represent the EBCA formally and unambiguously so that the alignment points are explicitly stated with their expected outcomes and associated information for the health practitioners. Below, we provide a detailed description of available EBCAs knowledge representation and management approaches.

3.7. COMPUTERIZATION OF EBCA

Evidence-Based Clinical Algorithms (EBCAs) have enormous potential to be used as the basis of clinical decision support systems to provide tailored recommendations at the point of care and outline appropriate subsequent steps during the health care process. Although, a vast volume of relatively structured medical knowledge in the form of EBCAs is widely available, it is difficult to readily convert them to an executable format (Miksch, 1999). Thus, successful harnessing of EBCAs for computerized decision support purposes involves several research challenges, such as: (a) abstracting practice-

oriented knowledge from EBCAs, (b) representing this knowledge in a manner that is formal, structured, unambiguous, and semantically rich, (c) integrating computerized EBCAs with patient data and clinical applications, (d) real time execution of computerized EBCAs to provide point of care decision support (Abidi, 2008). Computerized clinical workflow systems based on EBCAs have been developed for a number of conditions such as; stroke, diabetes, and radiation therapy, with related studies showing the positive effects of such systems on health care delivery (Kumar, Smith, Pisanelli, Gangemi, & Stefanelli, 2003).

Computerization of EBCAs has the advantage of them being executed with the patient data in order to provide focused decision support—that means patient-specific diagnostic and therapeutic recommendations—at the point of care. Research shows that the computerization of EBCAs makes them easier to retrieve and apply in a care setting and thus improves their compliance, leading to the delivery of evidence-based care (Mulyar, van Der Aalst & Peleg, 2007; Szpunar, Williams, Dagraso, Enberg & Chesney, 2006; Lobach & Hammond, 1997; Lobach, 1996). The advantage of computerizing CPGs and CPs is that it allows the simultaneous execution of multiple care processes, whilst maintaining a record of active care processes and their outcomes that may impact the follow-up care processes. Moreover, the computerization of EBCAs allows them to be connected with electronic medical record systems, thus ensuring a direct data feed to and from the medical record that ensures the availability and currency of the patient information in the decision-making process. From an operational standpoint, the computerization of EBCAs allows us to manage the clinical workflow—that means starting and terminating care processes on time, avoiding repetition of care tasks and providing alerts and reminders for potential adverse events, errors and omissions (Kumar, Smith, Pisanelli, Gangemi, & Stefanelli n.d.). The computerization of EBCA also assists in their maintenance, especially when new knowledge needs to be incorporated—this simply means adjusting the knowledge structures encapsulating the EBCA content. For instance, if the EBCA is computerized using an ontology then any updates to the EBCA can be easily incorporated by changing the instantiations within the ontology whilst maintaining the overall integrity of the knowledge within the ontology.

A key advantage of computerization of EBCAs is that they can be used to address the specific healthcare needs of individuals and the resources available at a particular facility—i.e. they lead to the concept of personalized healthcare (Abidi, 2008). For the purposes of this thesis, a computerized Evidence-Based Clinical Algorithm (EBCA) is of particular importance because we need to deal with comorbidities, where the patient care plan needs to be adjusted with respected to the comorbid conditions. In this case, the disease-specific EBCA for the comorbid diseases need to be systematically adjusted to account for the comorbidites—i...e the EBCA of the comorbid diseases needs to be aligned along common care processes, outcomes, decisions and care team roles. We believe that to handle comorbidities in a computerized decision support framework it is essential that the EBCAs are computerized, using a semantically rich and explicit knowledge representation scheme, such as an ontology. Such a knowledge model can be executed in response to patient information to provide patient-specific recommendations that are in line with the patient's comorbidities. We believe that the handling of comorbidities through computerized EBCAs also offers operational incentives as it will prevent the duplication of care tasks and help clinicians appreciate specific constraints associated with concomitant administration of treatments.

3.8. EBCAs KNOWLEDGE REPRESENTATION FORMALISMS

The main purpose of knowledge representation is to model domain-specific information in a format that can be efficiently processed by intelligent computer systems. In the medical domain, knowledge can be divided into two types: *declarative knowledge* and *procedural knowledge*.

- Declarative knowledge contains statements about the world called *propositions* that are either true or false. These propositions can be combined by Boolean operators such as 'and', 'or' and 'not' to form *sentences* (Kong, Xu & Yang, 2008).
- Procedural knowledge on the other hand provides explicit information about the action(s) to be taken or the conclusion(s) to be drawn from the declarative knowledge (Kong, Xu & Yang, 2008).

In EBCAs, procedural knowledge is evident as the algorithmic specification of guideline logic and declarative knowledge as the definition of abstract terms, their attributes and relationships.

A major concern for a healthcare flow technology is to model the workflow logic embedded in the clinical processes in an unambiguous manner and to provide suitable run-time support for these processes to be executed. The workflow logic needs to be represented in terms of execution rules that then need to be contextualized with respect to the clinical processes present in the EBCAs. Therefore, it is apparent that in order to represent the complexities of the medical knowledge we need a formalism that is rich enough to combine procedural representation with the logical clarity of declarative knowledge expressiveness (Sutton & Fox, 2003). A number of modeling languages have been developed in the health care domain, such as Asbru, PROforma, and Guideline Interchange Format (GLIF). These languages are regarded as knowledge rich formalisms because they permit the coupling of abstract labels called knowledge roles to domain knowledge in the EBCAs. These roles specify the role of the knowledge during the inference process, thus enhancing the expressiveness of the formalism and promoting its programming ability (Miksch, 1999). Other formalisms, such as Arden Syntax, take a more procedural approach to knowledge representation, which is an obstacle for knowledge reuse (Hripcsak, 1994).

A brief review of some of these representation formats, such as Arden Syntax, EON, GLIF, Asbru, and PROforma, is presented, followed by discussion of specific constructs called representative primitives (Wang, et al., 2002), which are common to most of these languages.

3.8.1. ARDEN SYNTAX

Arden Syntax (Hripcsak, 1994), a standard procedural language adopted by the American Society of Testing and Materials, is used to represent protocols or plans in medical algorithms as independent knowledge modules (single step IF and THEN rules) called Medical Logic Modules. Medical Logic Modules execute serially as a sequence of instructions as logic statements, queries, and calculations. The logic in each Medical Logic Module is adequate for a single medical decision. The main purpose of Arden

Syntax is to allow embedding of Medical Logic Modules in clinical information systems to generate coded messages such as *Alerts* (a clinical warning), *Interpretations* (for example of a blood test), *Screen* (evaluate if a patient fulfills certain criteria, for example for a clinical trial) and *Management* (administration purposes) for health care providers.

The target users for Arden Syntax are clinicians with no knowledge of programming languages. In fact, Medical Logic Modules can be written in any text editor and can be stored as simple ASCII files. The procedural orientation of Arden Syntax prevents it from dissociating factual medical knowledge from the knowledge of how the medical facts should be applied to a specific clinical scenario. Lack of this dissociation results in redundancy and prevents reusability of the knowledge. Each Medical Logic Module encodes a single decision and related actions, and a Medical Logic Module must invoke other Medical Logic Modules if needed. Although, Arden supports invoking of a Medical Logic Module by another Medical Logic Module, the syntax itself does not provide a methodology to model the structure to steer these invocations (de Clercq, Blom, Korsten, & Hasman, 2004). As a result, its expressivity is limited. The ability of Arden Syntax to represent complete guidelines, especially if they are complex and multistep such as those of chronic diseases (e.g. heart failure), is quite constrained (Hripcsak, 1994).

Arden Syntax does not have formal semantics but achieves interoperability through formal syntax. One significant drawback of Arden Syntax is “curly braces problem”. Arden Syntax specifies that all clinical data references to a clinical data base (to provide alerts and reminders) should be contained within curly ["{}"] braces in a Medical Logic Module. However, Arden’s syntactic description does not support any data modeling. Therefore, definition of data in a Medical Logic Module is left to local sites to implement. This means that a particular Medical Logic Module has to be adapted to suit each individual clinical system, which has to fill in the curly braces to fit its architecture, thereby decreasing its interoperability and reusability (Bilykh, Jahnke, McCallum & Price, 2006).

3.8.2. EON

EON (Miksch, 1999), developed at Stanford University, defines an architecture comprised of a set of cooperating components to automate various tasks associated with

protocol based care. As in the case of Medical Logic Modules, EON provides recommendations in accordance with patient specific clinical features and produces alerts on interventions by practitioners if they vary from the actions recommended by the protocol. EON's protocols are arranged hierarchically, which can be further decomposed into various levels of granularity. Each protocol has a declarative and a procedural component. The declarative component is modeled as an ontology, which includes specific classes of protocols for different clinical domains and their relationships. The procedural component, which is defined by a directed graph and a state model, specifies temporal sequencing, branching and looping of interventions suggested in the protocol.

Although EON is a powerful and knowledge rich representation of protocols, it might not be suitable for the implementation of complex, multistep, and nested guidelines such as those of chronic diseases. Flow-chart representation of a protocol's logic limits the potential of EON's approach since such lack of flexibility prevents incorporation of certain features in complex guidelines such as temporal uncertainty. Moreover, EON provides no temporal constraints between non-subsequent tasks (Miksch, 1999).

3.8.3. GUIDELINE INTERCHANGE FORMAT 3 (GLIF 3)

The GLIF 3 model (Boxwala, 2004), developed by InterMed Collaboratory (Stanford Medical Informatics, Harvard University, McGill University and Columbia University), is an object-oriented format. It consists of classes, their attributes, and the relationships among the classes. A CPG can be modeled at three levels of abstraction using GLIF;

- Level A - a conceptual flow chart of temporally sequenced nodes called Steps such as decision, action, branch and synchronization and patient state step,
- Level B – a computable specification when details such as decision criteria, relevant patient data definition, triggering events, and iteration information are formally specified using an expression language derived from Arden syntax,
- Level C – an implementable specification, which can be incorporated into a particular application. This includes a medical ontology, which allows the use of standard controlled vocabularies and the Reference Information Model to link the

patient data, medical knowledge and clinical actions, thereby allowing a sharing of guidelines among medical facilities.

The medical ontology consists of three layers: the first layer is Core GLIF, which defines the medical data model. The second layer is Health Level 7 (HL7)'s Reference Information Model, which defines class hierarchy that organizes medical concepts into classes and their attributes. The third layer is the Medical Knowledge Layer, which is still under development and will specify the methods for interfacing to medical knowledge sources such as Electronic Medical Records (EMRs), controlled vocabularies, medical knowledge bases and decision support systems. GLIF 3 provides a framework for developing guidelines, which are modeled as flow charts depicting the logical flow of actions. Such an approach limits the ability to implement complex guidelines containing features such as temporal uncertainty. Also, implementation of GLIF currently is very limited. Furthermore, when it comes to execution of guidelines in GLIF, there exists only a commercial execution engine called GLEE (Guideline Execution Engine).

3.8.4. PROforma

PROforma (Sutton & Fox, 2003) is developed by the Advanced Computational Laboratory of Cancer Research UK. PROforma is intended to support the complete development of a decision support system from the knowledge acquisition phase to the construction of an executionable system. A clinical protocol in PROforma is built in two phases: in the first phase, a graphical editor is used to build a high level graphical description of a protocol, and in the second phase the protocol is enacted by instantiating the graphical description with necessary knowledge.

PROforma defines a guideline as a set of PROforma components which can be tasks and data items. Tasks are arranged hierarchically into Plans. There are four classes of tasks,

- *Actions*: procedures that are to be executed in the external environment
- *Enquiries*: points in the Clinical Practice Guideline (CPG) where information is required either from a person or the external system
- *Decision*: when a choice has to be made

- *Plans:* collection of tasks representing the options which are to be considered when a decision is to be taken

These processes are represented as a graph of nodes and arcs, so that nodes represent tasks and arcs represents scheduling constraints. Each task is represented by a particular shape of node. Thus Actions are represented by squares, Decisions are represented as circles, and Enquiries are modeled as diamonds and the Plans as rounded rectangles. The CPG starts with a root plan which can be recursively decomposed into sub-plans. Each task can be interpreted with the help of values held by its properties. The value of the property can be a scalar value such as an integer, an expression or an object that has its own properties.

PROforma has a precise syntax and semantics. PROforma specifies an expression language, which is used to define pre-conditions that must be true before a task is activated. It is also used to specify the criteria that must be fulfilled for an argument to be true. (Sutton, Taylor & Earle, 2006). Arezzo (InferMed Ltd) and Tallis (Cancer research UK) are two commercially available implementations of PROforma.

When it comes to abstraction of temporal data, PROforma may not provide adequate facilities and continual support for diagnosis and treatment (whereby diagnosis and treatment are tightly integrated allowing each one to support the other) (Seyfang, Miksch & Marcos, 2002).

3.8.5. ASBRU

Asbru (Miksch, 1999) is a skeletal plan representation language developed by the Asgaard project led by Vienna University of Technology and Stanford University. Analogous to artificial intelligence planning techniques, Asbru regards a medical protocol as skeletal plans[6] with sub-plans. In addition to actions of a plan, Asbru also specifies intention of plans. It also includes rich language constructs which specify time annotations that represent temporal scope of a plan.

[6] Reusable plans. Skeletal plans are powerful ways to reuse existing domain-specific procedural knowledge

The main constituents of an Asbru plan include (Marcos, Balser, ten Teije, van Harmelen, & Duelli 2003);

- *Preferences,* which are used to constrain the selection of a plan to achieve a particular goal
- *Intentions,* which are high level goals of a plan that signify states or actions in a protocol that can be intermediate or final states to be achieved, maintained or avoided
- *Conditions,* which define various phases of execution of a plan and include preconditions, abort conditions, complete conditions; activate conditions that might be automated or manual.
- *Effects,* which describe the possible effects of a plan's execution, whether they are desirable or not.
- *Plan-body,* which contains sub-plans and actions in a plan to be executed.

In addition, Asbru also includes *wait strategy*, which uses constructs such as 'wait-for ALL' or 'wait-for-ONE' or 'wait-for some specific plan' to model a situation when all or certain sub-plans must be completed before a parent plan can be considered to be successfully completed. Also, *Time annotation* (minimum and maximum duration, reference point, start and end) can be assigned to various Asbru components such as intentions and sub-plans/actions.

Visualization and development tools such as AsbruView are available to model guidelines in the Asbru language. As mentioned earlier, Asbru is a time-oriented formalism where intentions, conditions, effects and world states are patterns with strong temporal orientation and are continuous. These temporal patterns are in fact basic syntactic constructs supported by Asbru. All conditions for the transition from one plan state to another are expressed in terms of these temporal patterns. As a result Asbru might be more suitable when it comes to modeling and execution of plans in high frequency domains such as intensive care unit. Plan execution in the intensive care unit presents additional challenges, since it requires tight integration of temporal data abstraction and plan execution to achieve the necessary intelligent reaction to unpredictable changes in

the environment such as minute to minute changes in patient state (Seyfang, Miksch, & Marcos, 2002). However, when modeling Evidence-Based Clinical Algorithms (EBCAs) of low frequency clinical conditions that are chronic with often vague and less tight temporal constraints, as in the case of diabetes or chronic heart failure, such detail acquisition of temporal patterns and time annotation might not be necessary and perhaps an overstatement. In low-frequency domains, when values are only to be obtained a few times per day or even per week, it might be troublesome and needless to cope with all possible orders of plan execution and exception conditions.

3.8.6. COMMON REPRESENTATIVE PRIMITIVES

The modeling languages explained above exhibit specific health care flow constructs or representative primitives[7]. These constructs are organized to form a specific health care workflow or process model (Wang et al., 2002). Below is a brief summary of representative primitives common to the formalisms[8] discussed above (see Table 2):

Table 2: Representation Primitives and Scheduling Constraints in Guideline Representation Formats; *(Adapted from Wang, Peleg, Tu, Boxwala, Greenes, Patel et al. 2002)*

	GLIF	EON	PROforma	Asbru	Arden
Action	Action step	Action Step	Action	Plan	Action Slot
Decision	Decision Step	Decision Step	Decision	Condition/ Preference	Logic Slot
Patient state	Patient state Step	Patient Scenario	-	Temporal Patterns	-
Scheduling Constraints	Next/After Branch Step Synchronization Step	Next/After Branch Step Synchronization Step	Next/After Branch Step Synchronization Step	Ordering Constructs/ Continuation Conditions	Module Invocation
Nesting of Guidelines	Sub-Guideline	Sub-Guideline	Plans	Plans	-

Actions represent clinical interventions or tasks related to diagnosis, management or patient education such as data collection, ordering of test, drug administration, wait action and so on. These are represented as *action slot* (Arden Syntax), *action step* (GLIF), or an *atomic plan* (Asbru).

[7] Language constructs in representation formats such as GLIF, Arden, Asbru and other languages to represent specific clinical tasks in a guideline, such as actions, decisions, entry and exit points in a guideline

[8] Guideline representation formats or languages such as GLIF, Arden, Asbru, PROforma and so on.

Decisions represent the decision making process where, based on pre-defined criteria, a specific option from a set of alternatives is selected. A decision can be modeled as *decision steps* (Guideline Intercahnge Format and EON), *logic slot* (Medical Logic Module), *conditions and preferences of a plan* (Asbru). ***Patient states*** represent specific clinical circumstances related to a patient's clinical status at a particular point in the workflow. Patient states act as specific entry and exit points at various levels in a guideline or a pathway, especially for complex guidelines, such as those of chronic diseases such as chronic heart failure or diabetes. Depending on patient's past and current clinical status, patients can enter or exit a guideline at various levels. Patient states are represented by *patient state step* (Guideline Interchange Format), or *patient scenario* (EON).

Process model (or health care flow model) defines scheduling constraints on these constructs or representation primitives, as well as nesting of guidelines in case of complex guidelines.

Scheduling constraints represent temporal relationships between actions to be taken and decisions to be made. Actions or decision steps in a guideline can be executed sequentially, i.e., one by one or concurrently, in parallel, or in any order. In a representation, sequential executions can be exhibited as a simple sequence whereby the scheduling order of two consecutive steps can be specified by simple relations such as *next* or *after* (Guideline Interchange Format and PROforma). To model sequence, concurrence or more complex sequences of unknown order, Asbru uses two constructs such as *ordering constraints,* which take on value *parallel, any order* or *total order* and *continuation conditions* which take on value *all completed* or *some completed.* The two constructs, if combined, will model five different types of scheduling constraints: *do all together, do some together, do all any order, do some any order,* and *do all sequentially.* EON and Guideline Interchange Format (GLIF) use *branch step* (a point followed by multiple paths in parallel or in any order) and *synchronization step* (concurrence of paths) to model complex sequences. These models then use a logical expression to specify continuation criteria following the synchronization step.

Nesting of guidelines provides a view to a guideline with multiple level of abstraction. This feature is essential for representation of multi-step chronic disease guidelines, such as those of diabetes or heart failure. The nesting that provides different level of granularities for these multi-step guidelines is supported by all reviewed formats except Arden Syntax. Examples of nesting are *sub-guidelines* in GLIF and EON, and specification of *plans* in Asbru and PROforma.

The above analysis concerning commonality of the representative constructs in the formalisms helps us to understand the critical prerequisites to model healthcare flow in EBCAs. From the above discussion, we can deduce that a guideline representation model must indicate; what clinical activity should be performed in a specific context of a guideline and the model should be able to specify criteria to select relevant option(s) from a set of available alternatives. In other words, for the operationalization of Evidence-based Clinical Algorithms (EBCAs) for decision support a guideline modeling tool should provide facilities for context specification, such as pre-conditions and post-conditions. Contextualization provides a specific scenario where domain knowledge about a particular problem is used. In reality, the inability to specify the context of an application effectively is one of the main reasons why decision support tools have not made a very favorable impact on health care providers (Kumar, Ciccarese, Smith & Piazza, 2004).

Although these formalisms have some strengths and weaknesses, the greatest limitation to their use in this research is the uniqueness of our problem to be solved, which is, alignment of comorbid Clinical Pathway (CP) based plans—these formalisms contain a number of constructs to represent guidelines but they lack specific constructs that are necessary to align the comorbid processes.

3.9. CONCLUSION

Although Clinical Practice Guidelines (CPGs) encompass evidence-based recommendations, the utilization of these recommendations at the point-of-care is not optimal. Clinical Pathways (CPs), on the other hand, can be used to implement CPGs in a specific health care facility as task-specific heuristics in accordance with the resources available at the care setting. Existing CPs are in a paper format and hence are static

documents that cannot be adapted to individual clinical features especially when dealing with comorbidities. In order to support the execution of diagnostics and treatment schemes based on Evidence-Based Clinical Algorithms (EBCAs), in accordance to a specific patient comorbid or single disease profile, it is argued that the CPs should be computerized—i.e. domain and procedural knowledge should be formalized using a computational representation formalism—so that they can be enacted at the point-of-care as decision-support tools.

A number of representation formalisms and methodologies have been developed to represent EBCAs with varying levels of granularity and efficiency. Most of these formalisms represent medical knowledge as an ontology of task network models in which recommendations are hierarchically decomposed into networks or component tasks that unfold in accordance to specific scheduling constraints (Tu et al. 2004). We observed that most of these formalisms have some common constructs or representation primitives to represent guideline steps such as actions, decisions and patient states as well as scheduling constraints on these steps. Together these steps with the scheduling constraints form a process model representing the clinical work flow of EBCAs. A number of these formalisms use domain ontologies to capture declarative knowledge within EBCA because ontologies provide a high level, expressive, conceptual agreed upon approach to knowledge modeling. The added advantage of using ontologies is that they provide the necessary expressiveness and reasoning capabilities to develop decision support systems that use the ontologically-modeled knowledge to provide recommendations. Although the existing formalisms offer ontological representations of varying granularity and efficiency, it may be noted that the execution of ontologies for decision support purposes is yet to reach its full realization. Since the focal point of this research is the formalization of comorbidity clinical pathways as Web Ontology Language (OWL) ontologies, the following chapter focuses on the concept of ontology in general and the Semantic Web ontology in particular.

CHAPTER 4 ONTOLOGY, SEMANTIC WEB AND SEMANTIC WEB APPROACHES TO EBCA MODELING & MERGING

4.1. INTRODUCTION

An ontology is regarded as an explicit specification of the conceptualization of a community's knowledge of a domain. Conceptualization[9] involves an explicit statement of entities, the relations they hold and the constraints on them within a specific domain (Stevens, Goble & Bechhofer, 2000). The rationale behind specification of conceptualization is to generate an agreed[10] upon format and semantic structure that will enable the exchange of information about a domain (Stevens, Goble & Bechhofer, 2000). It is important to distinguish ontologies from terminologies—terminologies are static structures that are used for knowledge referencing, whereas ontologies are designed for knowledge inferencing and reasoning (Jovic, Prcela & Gamberger, 2007).

For healthcare knowledge modeling purposes, a number of guideline modeling languages such as Guideline Interchange Format (GLIF) and EON use ontology based models to capture the medical knowledge encapsulated within Evidence-Based Clinical Algorithms (EBCAs) (Abidi, 2008). As much as ontologies are useful for the organization, disambiguation and formalization[11] of medical knowledge, they offer the ability to integrate and align heterogeneous sources of medical knowledge such as clinical practice guidelines and clinical pathways. Our research shows that ontologies have enormous potential to formalize the distilled task-specific heuristics in comorbidity EBCAs, such that the modeled knowledge can then be executed to provide decision support services to health professionals.

This chapter presents a general description of ontology, types of healthcare ontologies and the advantages of adopting an ontological approach towards knowledge modeling in healthcare. Furthermore, we will briefly chronicle Semantic Web technologies with a main emphasis on RDF and OWL, related previous work and our own previous experiences in this regard.

[9] Abstraction of some real world phenomenon
[10] Agreed upon domain terminology by domain experts , e.g. orthopnea is a symptom, smoking is a risk factor and renal artery stenosis is a contraindication
[11] Formal codification of knowledge so that the knowledge can be interpreted by computers

4.2. ONTOLOGY

Ontologies have been used in the area of artificial intelligence domain since the late 20th century as a means to express formally[12], a shared understanding of the concepts in a domain and the associations among these concepts. Ontologies are used to capture and represent knowledge in a format that can be understood by humans and executed by computer systems by reasoning over the knowledge. Ontologies also provide a formal vocabulary for the exchange of information (Noy, Sintek, Decker, Crubezy, Fergerson & Musen, 2001). A distinct characteristic of an ontology is that it is re-usable. This aspect distinguishes an ontology from a database schema. While a database schema is developed to be utilized by a specific application, an ontology can be recycled for many applications (Stevens, Goble, & Bechhofer, 2000). For example, an ontology to model a particular disease—such as CHF—can be used in different applications, such as decision support for CHF diagnosis and therapy recommendations, patient education about CHF risks and alerts, data collection for CHF treatment plans and so on.

The main components of an ontology are *concepts, relations, instances* and *axioms* (Stevens, Goble & Bechhofer, 2000).

1. **Concept** refers to a set of classes of entities or things within a domain. Concepts are of two types;
   - *Primitive concepts*, which have necessary[13] conditions in terms of their properties for membership of the class. For example, if something is an ACE_INHIBITOR it is necessarily a MEDICATION and it is necessary for it to have at least one uptitration (at least one relationship with UPTITITRATION_SCHEDULE class). However, there could be other things that have uptitration schedule but are not ACE_INHIBITOR. Thus ACE_INHIBITOR is a primitive concept.

[12] I.e., uses formal semantics that describes meaning of the knowledge precisely. Precisely means that the semantics does not refer to subjective intuition, not it is open to different interpretation by different people or machines. Formal semantics allows the machines to reason about the knowledge. Thus, formal semantics is a pre-requisite for reasoning support

[13] Necessary condition means that if something is a member of this class then it is necessary to fulfill these conditions. With necessary conditions alone we cannot say that if something fulfills these conditions then it must be a member of this class.

- *Defined concept,* whose description is both necessary and sufficient [14]of a thing to be a member of the class. We can convert sub-classes ACE_INHIBITOR class into a defined concept as follows. If something is an ACE_INHIBITOR then it is necessary that it is a MEDICATION and it is also necessary that it has at least one uptitration (that is a member of class UPTITRATION_SCHEDULE). Moreover, if an individual is a member of class MEDICATION and it has at least one *has_uptitration_schedule* relationship with a member of class UPTITRATION_SCHEDULE, then these conditions are sufficient to determine that that individual must be a member of ACE_INHIBITOR[15].

2. **Relations** refer to properties of the concepts (relationships between the concepts). There are two main types of relations;
   - *Taxonomic* relations, which organizes the concepts in sub-class and super-class hierarchies.
   - *Associative* relations, which relate the concepts across the hierarchical tree structure derived from taxonomical relations.
3. **Instances** are things represented by concepts.
4. **Axioms** are used to constraint values for classes or instances. The restrictions on the relationships (properties) are a kind of axiom. For example, a property axiom in Web Ontology Language (OWL) <owl:ObjectProperty rdf:ID="hasSymptom"/> defines the relation (property) with the restriction that its value should be an individual (instance) of class SYMPTOM .

4.2.1 TYPES OF HEALTHCARE ONTOLOGIES

There are three main types of ontologies in the field of healthcare.

[14] If an individual is a member of a named class then it must satisfy the conditions. If some individual satisfies the conditions then the individual must be a member of the named class.

[15] While defining these classes and relationships, multiple classes: ACE_INHIBITOR, BETA_BLOCKER, ARB and DIURETIC are expressed in the domain of the property *has_uptitration_schedule* .When multiple classes are expressed in the domain, Protégé-OWL interpret the domain to be the union of domain classes. Therefore in reality, if an individual is a member of class MEDICATION and it has at least one *has_uptitration_schedule* relationship with a member of class UPTITRATION_SCHEDULE, then these conditions are sufficient to determine that the individual must be a member of ACE_INHIBITOR **OR** BETA_BLOCKER **OR** ARB **OR** DIURETIC.

Generic ontologies—also called upper-level ontologies—that capture common high-level concepts such as time, space, matter and events that apply to all domains. Such ontologies, although not adequate enough to represent a particular domain, do however make explicit differences between concepts such as substances and processes (Bodenreider, Mitchell, & Mccray, 2003). An example of upper-level ontology in the field of biomedicine is GALEN (Open GALEN, n.d), which uses upper level concepts, such as, process, structure, substance and modifier (Rector, Rogers, & Pole, 1996) to represents biomedical concepts such as anatomy, drugs, diseases, gender, history, care settings, protocols and so on.

Domain-oriented ontologies are formal ontologies that focus on a specific area or domain, such as heart failure, anatomy, healthcare enterprise and so on. (Stevens, Goble & Bechhofer, 2000). Thus the heart failure domain ontology will contain concepts and resulting vocabulary from the domain of heart failure. A domain-specific ontology might include some terms with a higher level of generality that belong to a generic ontology (Chandrasekaran, Josephson & Benjamins, 1999).

Task-oriented ontologies define key task concepts and their input and output to facilitate a workflow (Stevens, Goble & Bechhofer, 2000). Task ontology contains descriptions and vocabulary related to a generic task, for example diagnosis. Development of a task ontology encompasses two main processes: *task decomposition,* which includes dividing a task into sub-tasks, setting goals for each sub-task, and describing control-flow (scheduling constraints) among these sub-tasks; and *knowledge roles* which are used to specify concepts and relations appearing in the task of interest (Ikeda, Seta, Kakusho & Mizoguchi, 1998). Ideally, once created a task ontology should be reused across several domains and a domain ontology across several tasks (Ikeda, Seta, Kakusho & Mizoguchi, 1998).

Thus, while an ontology of medical procedures is a domain ontology since it will contain vocabulary related to various medical procedures, an ontology representing tasks associated with a specific procedure such as surgery will be a task ontology. It may be noted that most bio-medical ontologies will be a mixture of generic, domain and task oriented ontologies (Stevens, Goble & Bechhofer, 2000).

4.2.2. ADVANTAGES OF USING ONTOLOGY FOR HEALTHCARE KNOWLEDGE REPRESENTATION

Research involving ontologies has contributed to a number of fields such as natural language processing (Hahn, Romacker, and Schulz, 1999) and accessing heterogeneous sources of information, including the Semantic Web (Pisanelli, Gangemi, Battaglia and Catenacci, 2004). Therefore, it does not come as a surprise to see ontology as a key knowledge representation enabler in a variety of biomedical and healthcare applications (Musen, 2002; Chandrasekaran, Josephson, & Benjamins, 1998). Although, the use of ontologies in the medical/healthcare domain is mainly for the purpose of organization and disambiguation of medical terminologies, they play a significant role in harnessing Evidence-Based Clinical Algorithm (EBCAs) for decision support and care planning (Abidi, 2008).

The key feature of ontologies, in particular for clinical decision support, is that they provide a clear and effective conceptualization of the healthcare domain, which is extremely important when one is required to make inferences over the domain knowledge. For example, when dealing with co-morbidities we need to align multiple Clinical Pathways (CPs) at the knowledge level. When an ontology describing the form and function of CPs clearly specifies the health care processes in terms of their actions, outcomes and constraints, it is feasible to identify common processes (both from medical and operational standpoints) and to align them to handle comorbidities.

Most clinicians believe that the description of logic and variability in healthcare knowledge requires the flexibility of natural language and it is generally desirable that the representation of medical concepts should not hinder the conventional approach to medical information exchange and recording (Ceustersa, Smith & Flanagana, 2003). Thus, recently, arguments have been made in favor of using natural language for the representation of medical knowledge for the purpose of information exchange, retrieval and decision support services (Ceustersa, Smith & Flanagana, 2003). It is worth noting that the conceptualization phase of ontology engineering involves identifying key concepts in a domain along with the relationships between them and their attributes. This is achieved by identifying natural language terms to refer to these concepts, relations and

attributes so that the domain knowledge is structured into an explicit conceptual model (Stevens, Goble, Bechhofer, 2001). A logic based ontology language such as OWL is endowed with declarative semantics[16] and therefore allows the association of natural language descriptions (attained during the conceptualization) with formal statements[17], thereby allowing human and machine readability. Web Ontology Language (OWL) is a standard, computer interpretable *Semantic Web* notation for representation of knowledge as an ontology. We believe that using OWL as the representation formalism has some advantages over existing formalisms as it is derived from descriptive logic, OWL supports formal semantics and consequently reasoning support. Thus, an OWL ontology in conjunction with domain-independent, high performance reasoners such as JENA and Racer Pro. provides a generally recognized decision support system development framework.

4.3. THE SEMANTIC WEB

Due to the enormous growth of the web, it is becoming progressively more complex to locate, categorize and integrate available knowledge. Web technologies, in their present state, are causing grave obstacles to further growth in terms of searching, extracting, maintaining and generating information, rendering computers as mere devices that place and deliver information, without having access to the actual semantics of the information. Although currently computers do have limited ability to access and process information, they are unable to extract and interpret it for the human users (Fensel, & Musen, 2001). The Semantic Web is an evolving extension of the WWW in which the information on one hand is human readable, i.e., expressed in natural language, and on other hand is interpretable by software agents, which by using standard vocabularies can populate the Semantic Web and provide intelligent services to their human users. By adding machine interpretable semantics to the information, the new Web will be able to search for information based on its meaning rather than its syntactic form, automatically integrate data from different sources, and perform various tasks such as location, organization and integration of information for the human users (Heflin, Sheth & Hendler, 1998). The

[16] Declarative specification of entities and their relationships with each other, in order to provide a representation of the meaning of data

[17] Machine process-able. Meaning that OWL not only specifies vocabulary, but also formally define it in such a way that it works for automatic reasoning

Semantic Web adds a new layer of machine interpretable data on top of human readable Web pages by using HTML (Hyper Text Markup Language), which mainly describes the structure of the document. The Semantic Web uses formal specifications to express precisely the knowledge content in underlying HTML pages or databases. It can also portray implicit information included in multimedia such as images and videos (Kalyanpur, Halaschek-Wiener, Kolovski, & Hendler, 2005). These specifications are used to formally[18] describe concepts, terms and the relationships between the concepts in a specific domain. Thus, we believe that Semantic Web technology provides an open, standards-based, computer-interpretable and executable framework on which the clinical guidelines and protocols can be published. These formalized medical knowledge artifacts can then be aligned and executed dynamically providing online decision support.

Where the conventional Web uses Markups to represent data and knowledge, the Semantic Web uses descriptive and extensible languages. These include:

- Extensible Mark-up Language (XML)
- Resource Descriptive Framework (RDF)
- Web Ontology Language (OWL)

These languages are regarded as metadata, which can be used to describe the data contained in the Web.

4.3.1. EXTENSIBLE MARK-UP LANGUAGE

eXtensible Markup Language (XML) is a mark-up language for structured documents and therefore an extensible technology. Structured documents contain information about content, such as words or pictures and some suggestion of what role that content plays. XML provides hierarchically arranged mark-up tags (elements) without providing any vocabulary. Vocabulary, in terms of names of allowable elements and their attributes, are specified by XML schemas and document type definition (DTD), which can be used to validate the document against the prescribed document type definition (DTD) or XML schema. XML schema does not provide semantics of the data within the tags. Since

[18] So that can be reasoned by computers, i.e. computer applications (such as classifiers) can check if the consistency and hierarchy of the classes, presence of any unexpected or implied relationships. Knowledge can be only inferred if the class specifications are formally defined and have been reasoned.

element names are not predefined, XML uses namespaces to avoid element identification related conflicts when two documents use the same element names (Klein, 2001). Although XML can code different kinds of data structures in an unambiguous syntax, it does not imply any specific use, interpretation or semantics of data (Klein, 2001).

Therefore, being syntactic and document-centric, XML cannot possibly achieve the level of interoperability required by highly dynamic and integrated applications such as clinical protocol based decision support systems with an added challenge of aligning of comorbidity Clinical Pathways (CPs). Since the descriptions of relationships among medical concepts are essential prerequisites to answering complex medical queries, especially while dealing with comorbidities, we need a descriptive platform for health care knowledge representation.

4.3.2. RESOURCE DESCRIPTIVE FRAMEWORK

Resource Descriptive Framework (RDF) is a descriptive Semantic Web technology to describe resources. Thus, according to RDF, everything is a resource that is related to other resources via properties. This relationship is represented by RDF statements or triples. A triple (Fig. 4) is a declaration in the form of <subject><predicate><object>, meaning that a subject has a property predicate whose target value is an object. This value of the object can be another resource specified by a Uniform Resource Identifier (URI) or a literal value, which may be a simple string or other data type such as is an eXtensible Markup Language (XML) markup. Thus, an RDF triple is a directed graph such that subject and objects are nodes and the predicate is the arc.

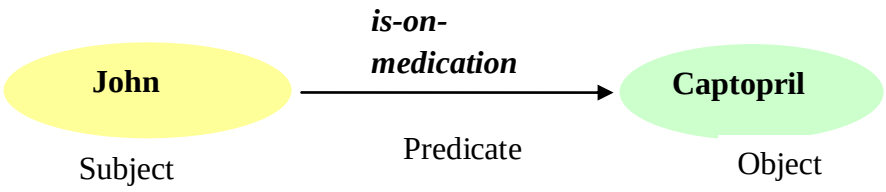

Figure 4: RDF Triple

This simple form of knowledge representation has proved to be highly expressive and allows for representation and execution of knowledge in every domain including complex domain such as healthcare. There are two main reasons for this. Firstly, every concept in

RDF has a unique identifier called Uniform Resource Identifier (URI). As opposed to eXtensible Markup Language (XML), where uniqueness of its identifiers is guaranteed within the document, the URI in Resource Descriptive Framework (RDF) ensures the universal uniqueness of resources. Since it is impossible in RDF for two concepts to be identified by a single URI, there is no ambiguity in the Semantic Web, an extremely essential requirement for healthcare knowledge representation. Secondly, RDF provides simple predicates to express knowledge and the description of this semantic relationship is explicit. This feature not only allows for human interpretation of knowledge but also makes machine processing of the knowledge base expressed in Resource Descriptive Framework (RDF) easier, thereby solving the problem of knowledge execution and operationalization (Nardon & Moura, 2004).

Although, an RDF model expressed as a graph is oblivious to both syntax and semantics, it can be serialized in the syntax of XML, and the semantics can be obtained via two of its extensions: RDF schema language (RDFS) and web ontology language (OWL). Both these languages are layered on top of RDF to offer support for inference and axiom, thus allowing knowledge representation (as appose to data representation) and execution.

While RDF Schema provides basic vocabulary for defining RDF classes (resources) and properties and their hierarchies (such as rdf:Class, rdf:subclassOf, rdf:Property, rdf:subPropertyOf, rdf:domain, rdf:range, Individual), OWL provides extended vocabulary for defining added restrictions on classes and properties to be modeled as ontologies, so that the expressiveness of the language is further enhanced (Klein, 2001).

4.3.3. WEB ONTOLOGY LANGUAGE

Web Ontology Language (OWL) has a larger vocabulary and richer syntax then Resource Descriptive Framework Schema (RDFS) and therefore allows superior interpretability. This extended vocabulary, which is built on RDFS includes constructs to represent constraints such as cardinality (e.g. minimum cardinality=1), equality (e.g. equivalent classes), relationships between classes (e.g. disjointWith), and characteristics of properties (e.g. FunctionalProperty).

There are three sub-languages of OWL (W3C OWL Recommendation. 2004),

OWL Full: It is an extension of Resource Descriptive Framework RDF. It permits an ontology to enhance the semantics of a pre-defined RDF/OWL vocabulary. A remarkable feature of OWL Full is that it allows a class in an ontology to be expressed as an individual[19] as well. It promotes maximum expressiveness and syntactic freedom of RDF with no computational guarantees. It is implausible that any reasoner will be able to provide complete reasoning for each and every element of OWL Full.

OWL DL: It is a part of OWL Full that is in the Descriptive[20] Logic framework. It supports maximum expressiveness while preserving computational completeness[21] and decidability[22]. Although OWL DL contains all OWL language constructs, they can be utilized under specific precincts. For example, a class cannot be an individual of another class.

OWL Lite: It is a subset of OWL DL. It supports classification hierarchy and simple constraints such as simple cardinality constraints (number of restrictions, i.e., how many values a predicate can hold) with values only 0 and 1. Tool support and reasoning is much simpler for OWL Lite.

OWL DL provides maximum expressiveness along with computational guarantees and allows decidable reasoning. Given the complex nature of our domain, we believe that OWL DL is the best choice for representation of knowledge in the form of domain ontology. OWL DL as opposed to OWL Full has specific rules, for instance a class in OWL DL cannot be an individual or a property and a property cannot be an individual or class at the same time.

4.4. SEMANTIC WEB APPROACHES TO EBCAs BASED HEALTH CARE PLANNING

Recently, Semantic Web technologies are receiving increasing awareness within the sphere of automated clinical decision support and care planning (Hussain, Abidi & Abidi,

[19] In OWL an instance of a class is referred to as an "Individual".
[20] A family of logic-based knowledge representation formalisms that form the formal foundation of OWL. DL specify - concepts, roles (binary relations between the concepts, individuals), constructors (union, intersection, value and number restriction) and axiom (subsumption).
[21] All conclusions are guaranteed to be computable.
[22] All computation will finish in finite time.

2007; Colantonio, et al. 2007; Abidi, & Chen, 2006; Casteleiro & Diz, 2008; Dasmahapatra et al. 2004; Abidi, Abidi, Hussain & Butler, 2008). Semantically rich formalisms such as OWL ontology have enormous potential for description[23] of concepts in the medical domain on one hand and the characteristics of functionalities of these concepts, i.e. health care flow on the other hand (Ye, Jiang, Diao, Yang & Du, 2009; Danyal, Abidi & Abidi, 2009). An OWL ontology can model a workflow by establishing the relationships between the domain concepts and care flow through inputs, outputs, preconditions and effects of each CP task (Danyal, Abidi, & Abidi, 2009)

Below we mention some research pertaining to the application of semantic web and ontologies in the healthcare domain.

In related previous research, we developed an ontology driven interactive breast cancer decision support system (BC-DSS) based on a Canadian guideline for the delivery of follow-up care related to breast cancer (Abidi, Abidi, Hussain & Shepherd, 2007). The goal of our research was knowledge operationalization, whereby tailored evidence-based trusted recommendations and customized patient education were provided at the point of care. We took the Semantic Web approach to model CPG knowledge as OWL ontologies. These ontologies include; (a) *CPG ontology* based on Guideline Element Model (GEM) that represents the structure of the CPG; (b) *Breast Cancer Domain Ontology* that represents the medical knowledge encapsulated within the CPG and general breast cancer related concepts; and (c) *Patient Ontology* that models the patient parameters. The ontologies are developed using the ontology editor Protégé and are in OWL format. The breast cancer CPG is executed through a logic based CPG execution engine using multiple ontologies. It provides functionality to define CPG-specific decision logic rules based on patient clinical data to provide CPG-based recommendations.

[23] Class definitions (axioms) in terms of six types of OWL concept constructors such as, class identifier (i.e., class name syntactically represented as URI reference), enumeration of individuals which form instances of a class, a class of individuals which satisfies a particular property (relation) restriction, a class that satisfies Boolean combination of class descriptions i.e. Intersection (of two or more classes), Union (of two or more classes) and Complement (of a class) which can be respectively seen as logical AND, OR and NOT operators.

In a European research project of HEARTFAID, researchers framed an expert system design for the management of heart failure within the elderly population (Prcela, Gamberger & Jovic, 2008). This research focused on providing innovative knowledge-based services for the early diagnosis and management of heart failure in elderly patients. In the first step of the project, a detailed, descriptive ontology in the domain of heart failure was developed in Web Ontology Language (OWL). The domain concepts derived from the Clinical Practice Guidelines (CPGs) of congestive and acute heart failure were presented as over 200 classes. The ontology also included concepts relevant to complications of Heart Failure (HF), other organs, and systemic clinical features related to heart failure pathology. This research does not deal with care planning, as in our case in which we have synthesized and formalized clinical pathway workflow based on CHF and AF CPGs. Also, it does not take into account comorbidities, as in our approach where the main purpose is to align comorbid CHF and AF to provide care planning and decision support to patient with or without comorbidities. Therefore our approach involves the formalization of specific constructs to capture knowledge related comorbid alignment. Moreover, the HEARTFAID platform is in contrast to our research whereby scope is limited to diagnosis and management of CHF and AF at the family practice. Also, in our case we have used specific OWL constructs, such as object properties, to capture the procedural rules. The HEARTFAID framework is not meant for dynamic alignment of the care processes to manage comorbidities.

SEMPATH -Semantic Adaptive and Personalized Clinical Pathways - is a more recent endeavor towards EBCAs based automated care planning (Alexandrou, Xenikougakis & Mentzas, 2009). The intent of this research is to support the execution of treatment schemes based on a clinical pathway, dynamically adapting the treatment processes, and to provide decision support services to handle any deviations from the course. In order to meet these requirements, the SEMPATH framework combines a workflow management engine with a rule base. Presently, a prototype of SEMPATH has been developed, which consists of three main components: (a) *Semantic Info-structure* with OWL ontology at its core, containing knowledge elements required for modeling CP, creation of rules and patient instantiations; (b) *Rule Execution Environment,* which maintains SWRL

(Semantic Web Rule Language) rules and when triggered selects and executes relevant rules from the repository; and (c) *Clinical Pathway Execution Environment,* containing a workflow execution engine. The interface between the workflow engine and the rest of the components is the Clinical Pathway Manager. Any exception during the pathway execution triggers the system so that the message produced is forwarded to the Rule Engine in order to run the complete rule set for the pathway causing appropriate adaptation.

K4CARE (www.k4care.net) is a joint effort of thirteen European institutional partners. The purpose of this initiative is to implement and test a technology-based incremental and adaptable model to assist the care of elderly at home. K4CARE include two models (Riano, Real, Campana, Ecolani & Annicchiarico, 2009). The Agent Profile Ontology that formalizes the management issues related to home care and the Case Profile Ontology that formalizes knowledge related to assessment, diagnosis and treatment of the elderly patients at home. The Case Profile Ontology (Riano, Real, Campana, Ecolani & Annicchiarico, 2009) has been developed in OWL using Protégé. The Case Profile Ontology represents activities that trace a path that begins with the assessment of a problem to the deployment of a care plan appropriate for that problem.

CAREPLAN is yet another Semantic Web approach towards evidence-based clinical algorithms based care planning proposed in the literature (Abidi & Chen, 2006). The intent of the CAREPLAN platform is to combine heterogeneous healthcare knowledge sources with the available patient information, reason over this knowledge and adapt pathways towards personalized healthcare plans. These knowledge sources include, patient information derived from online health reporting documents, best evidence present in clinical practice guidelines, care processes and resource constraints specified in clinical pathways and web-based heterogeneous medical knowledge sources. The main purpose of the CAREPLAN framework is to access, integrate, adapt and manipulate heterogeneous healthcare knowledge in response to available patient information. For this purpose, the CAREPLAN framework offers a mechanism for case-specific morphing (or

fusion) of knowledge sources by creating links between two or more knowledge objects that are contextually[24] compatible.

We note the large number of research initiatives to operationalize clinical practice guidelines and clinical pathways to achieve clinical decision making using Semantic Web technologies. However, it may be noted that the problem of automated alignment of clinical pathways to handle comorbidites has not yet been tackled due to the apparent complexity of dynamically aligning multiple clinical pathways whilst maintaining clinical pragmatics and medical correctness. In this regard, in this thesis we have taken the approach of aligning multiple clinical pathways (CPs) at the knowledge modeling level as opposed to the knowledge execution level (Abidi & Abidi, 2009). Our approach is to model the CPs using an OWL ontology, and then merge the common/overlapping processes within the ontology to realize an instance of a comorbid clinical pathway. Our approach towards developing comorbid CPs features a Semantic Info-structure containing an OWL ontology that is instantiated by clinical pathways. We argue that our research challenge, which is alignment of the clinical pathways of comorbidities, is greater than achieving the mere adaptability of the clinical pathways. To account for the complexity of the task at hand, we have built in constructs depicting the comorbid plans along with specific single disease and comorbid preconditions in the ontology. Any exception due to selection of comorbid preconditions will trigger the actual alignment of plans during execution of the clinical pathways.

4.5. ONTOLOGY BASED ALIGNMENT OF CLINICAL PATHWAYS OF COMORBIDITIES

Alignment of comorbid CPs care processes entails the alignment of the task-specific heuristics. An ontology uses common terms, semantics and agreed upon vocabulary, to make its concepts and their relationships more explicit. This explicit declaration of all assumptions regarding the domain knowledge and the knowledge roles is the key to CP alignment.

[24] The context of the objects is compatible. Context is any information that can be used to characterize the situation of an entity (e.g., identity of an entity, location of an entity and relevant temporal information) where an entity can be a person, place, physical or computational object. Ontology is a powerful tool to model context.

Although there is a scarcity of literature surrounding the issue of electronic alignment of Evidence-Based Clinical Algorithms (EBCAs) of comorbidities, we have gained some valuable insights into the issue of CP alignment from our previous work, whereby we successfully computerized and merged three institution specific Clinical Pathways (CPs) for diagnosis and management of Prostate Cancer (Abidi, Abidi, Hussain & Butler, 2008). The merging of institution specific (Halifax, Calgary and Winnipeg) CPs for a particular condition such as prostate cancer posed a different set of challenges as compared to the alignment of CPs of comorbid conditions such as CHF and AF. We nevertheless did gain valuable lessons from this experience, such as the avoidance of duplication of activities, treatments and diagnostics is an issue common to both synchronization problems. However, unlike alignment of comorbid CPs, the merging of institute specific pathways of a single disease management does not pose a risk of prescription of contradictory or harmful treatments. The main problem with regards to the merging of institution-specific CPs is identifying and sequencing both common and institution-specific diagnostic and therapeutic tasks and their scheduling constraints to achieve a flexible model. Alignment of CPs of comorbidities requires sequencing of the activities and clinical tasks based on whether a patient does or does not have specific preconditions related to comorbidities. Moreover, it is imperative that explicit measures are taken to avoid duplication of treatments or any harmful events or drug interactions due to alignment of treatment plans. Thus, specific rules should be formalized in the ontology to avoid such problems.

EBCAs can be merged/aligned at the knowledge representation/modeling level or at the knowledge execution level (Abidi & Abidi, 2009). Our approach is to pursue the alignment of EBCAs at the knowledge modeling level—this approach is supported by our medical background which supports the modeling of healthcare knowledge, as opposed to alignment at the knowledge execution level, which demands a sound computer science background.

4.5.1. ALIGNMENT OF EBCAs AT THE LEVEL OF KNOWLEDGE REPRESENTATION

Aligning Evidence-Based Clinical Algorithms (EBCAs) at the knowledge modeling level entails the development of a unified knowledge model that encapsulates all the EBCAs that are to be aligned. Such a model encompasses the combined knowledge of aligned EBCAs. Alignment is carried out by conceptual mapping between common concepts across different institution or across different diseases. The aligned or unified model represents each EBCA as a combination of both common and unique concepts, thus ensuring that each modeled EBCA maintains its unique identity (Abidi & Abidi, 2009).

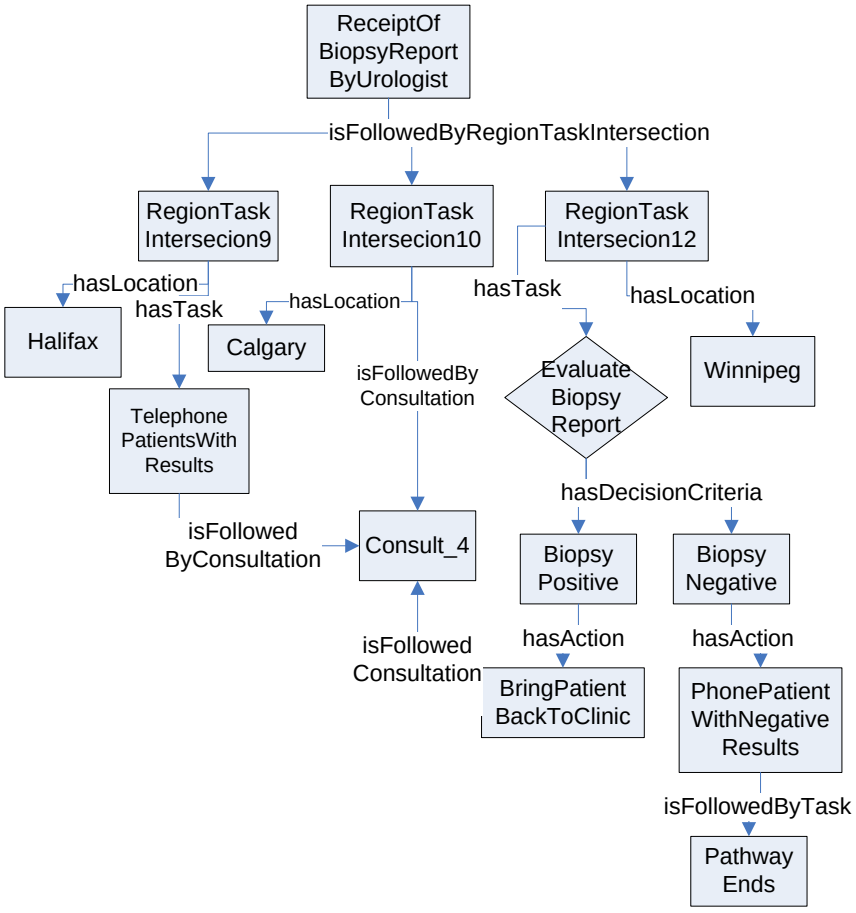

Figure 5: Branching and Merging of Institution-specific CPs

In our previous related research (Abidi, Abidi, Hussain, & Butler, 2008), alignment of prostate cancer CPs was pursued by modeling the task-level similarities among the three institution-specific CPs. For this purpose we developed a unified and coherent OWL

ontology to represent the prostate cancer domain and workflow concepts with their relationships. The unified models contain four Plans representing four consultations during the course of treatment and diagnosis of prostate cancer. Within each Plan, we identified the points where a location-specific Clinical Pathway (CP) is pursuing a unique set of tasks, treatment regimens, follow-ups, clinicians who provide care, interval duration for a specific event related to prostate cancer care, and frequency of related activities. We created classes representing these intersection points between the above concepts and a specific region i.e. Halifax, Calgary or Winnipeg. These classes are labeled as: RegionTaskIntersection (Fig. 5), RegionTreatmentIntersection, RegionFollowUpIntersection, RegionClinicianIntersection, RegionIntervalIntersection and RegionFrequencyIntersection. All these classes have two object properties. One is *hasRegion*, which is common to all intersection nodes and specifies the location of the patient. The other property related these nodes to another specific concept such as Task to be performed or Treatment to be provided, where it is intersecting with the location. For example, RegionTaskIntersection has object property *hasTask* so that a specific region will have a specific task at a specific location (Fig. 5); RegionTreatmentIntersection has property *hasTreatment*, which will capture specific treatment provided at a specific location, and so on.

This common model will branch off at one of the intersections in the ontology. All branches merge back at a common node, which is a Task or a Plan that is common to all locations, as shown in Fig.5, where all branches merge at Consult_4 (consultation no. 4). The common ontology is then resumed from this point till it branches out again. This approach ensures that multiple CPs from the same domain are modeled jointly while maintaining the unique behaviors of independent CPs.

Our approach to solve the problem of alignment of comorbid pathways from different domain (CHF and AF) is based on knowledge modeling activity, whereby we aim to maintain the unique behaviors of single disease CPs whilst allowing the synchronization of common care processes across different disease-specific pathways to support comorbid care planning.

4.5.2. ALIGNMENT OF EBCAs AT THE LEVEL OF KNOWLEDGE EXECUTION

In the knowledge execution approach towards alignment of Evidence-Based Clinical Algorithms (EBCAs) (Abidi & Abidi, 2009), the knowledge model is instantiated by multiple EBCAs. The model does not exhibit any kind of intersection nodes as in the previous case, rather the instantiation of tasks, resources or treatments across multiple EBCAs are aligned, where required, by writing specific rules. Since recommendations that are common across multiple Clinical Pathways (CPs) or Clinical Practice Guidelines (CPGs) might not necessarily administer at the same time, execution level merging requires proper synchronization of steps in multiple CPs or CPGs. In such a case, where a step common to the two CPs or CPGs is recommended in the model, both CPs and CPGs are aligned at the common steps during the execution and then each subsequently branches off to their respective paths. This alignment at the common step is carried out by applying rules at the common steps.

We believe that either of the two potential approaches can be applied to solve the problem of integrating the Clinical Pathways (CPs) of comorbidities. However, notwithstanding the scarcity of literature surrounding the issue of electronic merging of comorbidity EBCAs, and taking into account our previous successful attempt towards institution specific Clinical Pathway (CP) merging, we believe that alignment at the level of knowledge modeling is the optimal solution for this problem. Also as mentioned earlier, given our medical background, this approach is more intuitive to us.

4.6. CONCLUSION

We conclude that ontologies contribute significantly to the design and implementation of healthcare knowledge models that can be used for clinical decision support applications. Given the depth and the breadth of knowledge in the field of medicine, the complexity of relations between medical categories and the ambiguity typically associated with medical text, it is conceivable that ontologies can help to organize this knowledge for both timey knowledge access and execution for decision support. Web Ontology Language (OWL) is

a Semantic Web notation recommended by World Wide Web Consortium[25] (W3C) to represent ontology formally. OWL has more facilities for expressing semantic relations between the concepts than eXtensible Markup Language (XML), Resource Descriptive Framework (RDF), and RDF-Schema (RDF-S). There have been a number of research initiatives towards achieving operationalization of Evidence-based Clinical Algorithms (EBCAs) in clinical decision making using Semantic Web technologies with considerable success. However, the problem of automating the alignment of clinical pathways of comorbidites to achieve adaptability of the pathways based on the presence of comorbidities has not yet been adequately addressed. Using a knowledge rich Semantic Web notation such as Web Ontology Language (OWL) ontology to formalize the knowledge before it can be aligned is a novel approach to solve this complex problem. In the next chapter, we will present a detailed description of the steps of our approach towards ontology based modeling and alignment of comorbidity Clinical Pathways (CPs).

[25] The World Wide Web Consortium (W3C) is an international community where Member organizations, a full-time staff, and the public work together to develop Web standards

CHAPTER 5 KNOWLEDGE ACQUISITION

5.1. INTRODUCTION

This chapter presents the process of knowledge acquisition that involved identification, analysis, and disambiguation of the medical knowledge. The main purpose of this phase in our methodology is to synthesize the medical knowledge in the Clinical Practice Guidelines (CPGs) in a form that is suitable for computerization. We may like to point out that although we synthesized the Clinical Pathways (CPs) based on the evidence in the CPGs, we do not claim that the resultant CPs are directly applicable in the clinical setting at this point because they have not been validated through a clinical trial. For the purposes of this thesis, the CPs are manifestations of healthcare knowledge that have been used as exemplars to demonstrate how to model CPs to handle comorbidities. The resultant CPs have been developed based on the medical knowledge in the CPGs and have been reviewed by the domain specialist (cardiologist).

Although, knowledge acquisition (knowledge identification and synthesis) is the first step of our framework, it has been presented as a separate chapter. This is because our research is interdisciplinary and separating the medical and computational phases of the methodology will enhance the clarity and understandability of the thesis. This chapter also presents the knowledge alignment approach.

Based on the challenges identified in this research, a detailed review of available literature and our previous experiences with guideline knowledge modeling, we have developed a decision support framework to handle comorbidities (see fig 1). Our approach is to pursue Clinical Pathway (CP) alignment at the knowledge modeling/representation level, whereby we aim to align ontologically modeled CPG plans based on preconditions derived from single disease or comorbid processes. The methodology to develop our decision support framework, termed COMET, comprises the following phases;

i. Knowledge acquisition – that includes two phases
    a. Knowledge identification – identification of knowledge sources
    b. Knowledge synthesis - resulting in CHF and AF CP packages

ii. Knowledge formalization – achieving CP knowledge and decision logic as executable Web Ontology Language (OWL) CP ontology and its instantiation with AF and CHF CPs
iii. Knowledge alignment - formalizing functional relationships between care processes of multiple ontologically-modeled CPs so handle co-morbidities
iv. Knowledge execution – execution of the CP ontology and its incorporation in Clinical Decision Support System (CDSS) resulting in the execution of single disease and co-morbid care-plans depending on the presence or absence of co-morbidity
v. Knowledge evaluation – evaluating the correctness of the medical knowledge encapsulated in the CP ontology, and its utility for decision support.

This chapter presents the process of knowledge identification and synthesis, which resulted in the development of two CP packages for CHF and AF.

5.2. KNOWLEDGE IDENTIFICATION & SYNTHESIS: DEVELOPMENT OF CHF & AF PATHWAYS

Clinical Practice Guidelines (CPGs) and Clinical Pathways (CPs) that are based on solid evidence, provide unambiguous and concrete steps for modifications in practice, and do not entail knowledge or skill sets outside of the practitioner's existing range are more likely to lead to compliance and improved care (Panella, Marchisio & Di Stanislao, 2003; Weiland, 1997; Grol, Dalhuijsen, Thomas, Veld, Rutten & Mokkink, 1998; Smith & Hillner, 2001). However, most CPGs, while containing best evidence, are not written to be used during a patient-physician encounter due to their very format (Brush, Radford & Krumholz, 2005), such that recommendations and the quality of supporting evidence are given as lengthy systematic reviews (Brush, Radford & Krumholz, 2005). Clinicians, when confronted with uncertainties during clinical decision making tend to use task-specific and availability heuristics for problem solving (Brush, Radford & Krumholz, 2005). This decision making behavior of clinicians has implications for incorporating evidence based practices in routine work flow (Brush, Radford & Krumholz, 2005). This is especially important when solving complex problems that arise from dealing with comorbid complex diseases such as CHF and AF. Therefore, our research methodology

involved the distilling task-specific (representativeness) heuristics from CPGs, followed by identifying the specific decision and non-decision making tasks within these heuristics, along with the guideline logic, task dependencies, and scheduling constraints. The heuristics were then packaged as two separate CPs based on CHF and AF CPGs.

Our main criteria for the creation of these CPs include: (i) the CPs must exclusively focus on the patients who are relatively stable (New York Heart Association (NYHA) class I & II), and therefore constitute the population of interest with respect to general practice, (ii) the CPs must include heuristics derived from mainly Class I[26] or in some cases Class IIa [27]recommendations, since this evidence is regarded as most robust, (iii) the CPs must be comprehensive and unambiguous in the interpretation of the guideline logic so that eligibility of each decision criteria is made clear. This step is extremely important in the context of computerization and alignment of comorbid CPs.

5.2.1. KNOWLEDGE IDENTIFICATION

As mentioned earlier, the main purpose of a CP is to implement the recommendations in a CPG as task-specific heuristics, which can be integrated easily in clinical decision making. Since a CP typically charts the care to be given for an entire clinical course rather than for one specific clinical circumstance, we incorporated elements relevant to care planning in the domain of AF and CHF from several evidence based CPGs. Also, in order to delineate the scheduling of treatment tasks, given the resources available at a general practice in Nova Scotia, we incorporated relevant information from locally developed treatment protocols and the advice of domain experts.

5.2.1.1. KNOWLEDGE SOURCES FOR CHRONIC HEART FAILURE CPs

i. Canadian Cardiovascular Society Consensus Conference Recommendations, Heart Failure 2006: Diagnosis and Management

[26] Evidence or general agreement that a given procedure or treatment is beneficial, useful and effective (Source: Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and Management

[27] Weight of evidence is in favor of usefulness or efficacy (Source: Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and Management

ii. ACC/AHA Guidelines for Evaluation and Management of Chronic Heart Failure (2005)
iii. Capital[28] Health Interdisciplinary Clinical Manual Protocols for Up Titration of Angiotensin Converting Enzyme Inhibitors
iv. Capital Health Interdisciplinary Clinical Manual Protocols for Up Titration of ARB
v. Capital Health Interdisciplinary Clinical Manual Protocols for Up Titration of Beta Blockers
vi. Capital Health Interdisciplinary Clinical Manual Protocols for Up Titration of Diuretics (Furosemide)

The Capital Health interdisciplinary protocols are the product of a collaborative effort with the Atlantic Health Sciences Corporation in St. John, New Brunswick and Capital District Health Authority (CDHA) in Halifax. These directives are used by registered nurses to titrate most heart failure therapies at the Heart Function Clinic in Halifax. These protocols were provided by the domain expert and are in accordance with the practices at the local hospital and therefore are institute-specific. Not only do these manuals contain information about drug uptitration, they also contain information regarding serious and non-serious adverse effects, circumstances under which it is necessary to refer a patient to emergency and situations when uptitration should be halted and the patient referred to a cardiologist. These protocols guide uptitration of heart failure medications in accordance to pre-established procedure to optimize dose and thereby reduce morbidity and mortality. Additionally, these protocols also contain material for patient education, which is essential for the management of heart failure. Such information is extremely vital in a general practice where family physicians are frequently required to provide necessary health education to their patients.

Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009 (Howlett et al. 2009) have been published. However, we used the 2006

[28] These protocols are medical directives for registered nurses in the heart function clinic, in QEII hospital in Halifax. They are not publically available or published. They were given to us by Dr. Howlett.

guideline, since we completed our ontology and its instantiation[29] before the 2009 update was released. The topics in the 2009 update include, best practices for the diagnosis and management of right–sided heart failure, myocarditis and device therapy. The topics of right sided-heart failure, myocarditis and device therapy are beyond the scope of this research. This research only deals with diagnosis and treatment of CHF involving left ventricular systolic dysfunction and AF. The 2009 update also included a review of recent important or landmark clinical trials. The only review that is relevant from the perspective of this research is about the rhythm vs. rate control of atrial fibrillation in heart failure. The recommendation provided in this respect states that, "In patients with stable heart failure and atrial fibrillation (AF), rate control is an acceptable management strategy and routine rhythm control is not required (class I, level B)" (Howlett et al. 2009, p. 100). The target population for COMET are patients with New York Heart Association (NYHA) class I and II symptoms, who are regarded as having stable heart failure. The AF treatment for patient with comorbid CHF incorporated in our CPs and the ontology is also rate control therapy, as advised by Dr. Jafna Cox. Thus, the knowledge related to this recommendation in the 2009 update is already present in the pathways and the ontology. This means that despite the fact that the 2009 update has been released; there was no need for any update in the ontology. However, we would like to mention at this point that since we have used an ontology to define processes, tasks, decision nodes and decision options in the CPs, as well as to establish functional relationships between these components, one of the benefits of using such an approach is that such a representation is expressive and extensible[30]. Therefore, we can expand or add to its capabilities in order to incorporate new concepts or relationships in a domain, which might arise due to updating of the evidence. Moreover, since we already have a representation model for the domain, new updates in knowledge can be very easily incorporated just by updating the instantiation[31] in the ontological model.

[29] Adding individuals or the instances (i.e. CP knowledge)
[30] OWL is an extensible language because in OWL new terms can be formed by combining existing ones through concept constructors such as: IntersectionOf, UnionOf. Thus we can expand or add to its capabilities in order to incorporate new concepts or relationships in domain, which may arise due to update of evidence.
[31] Adding individuals or the instances.

5.2.1.2. KNOWLEDGE SOURCES FOR ATRIAL FIBRILLATION CPs

- Canadian Cardiovascular Society Consensus Conference on Atrial Fibrillation (2004)
- National Health Service Protocol for the Management of Atrial Fibrillation in Primary Care (Brighton and Hove City. 2007)

5.2.1.3. DOMAIN EXPERTS

In addition to these knowledge sources, we sought expert advice from domain experts regarding the suitability of specific Clinical Practice Guideline (CPG) recommendations for a general practice setting, information regarding relationships between the tasks, especially with respect to comorbid CHF and AF, institution specific ordering of these tasks and availability of resources. During the initial stages of this research we sought advice from Jonathan Howlett, MD, who at that time was associated with the Faculty of Medicine at Dalhousie University and was medical director of the Queen Elizabeth II Heart Function and Transplantation Program in Halifax. Currently, he is a clinical professor of Medicine at the University of Calgary. Later, we sought guidance from Jafna Cox MD, who currently is a professor of Medicine, in the Division of Cardiology at Dalhousie University. Since at this stage we were dealing with specialized medical knowledge and critical insights of domain experts, we did not directly involve a General Practioner (GP) during the knowledge synthesis phase. We believe that the involvement of GPs is more pertinent at a later stage of the project when this 'proof of concept' is to be turned into a clinical application that GPs can use at the point-of-care. Given that our knowledge base is an ontological model, modifications to suit the specific feedback provided by GPs can be readily incorporated in the future.

5.2.1.4. KNOWLEDGE SOURCES REGARDING ISSUE OF ALIGNMENT OF CPs FOR CHF AND AF

In addition to deriving information regarding relationships between the comorbid CHF and AF from the CPGs, we have also reviewed a number of journal publications (Efremedis, Pappas, Sideris & Filipatos, 2008; Lip & Tse, 2007; Padeletti, Pieragnoli, Jentzen & Schuchert, 2007; Neuberger, Mewis, van Veldhuisen, Schotten, van Gelder,

Allessie & Bohm, 2007; Joachim, Nattel & Hohnloser, 2002; King, Dickerson, & Sack, 2002) to better understand issues related to diagnosis and management of these conditions when they co-exist.

5.2.2. DISTILLATION OF TASK- SPECIFIC HEURISTICS FROM CPGs

Our first step was to identify essential task-specific heuristics in the Clinical Practice Guideline (CPGs) that need to be incorporated in the decision making process at a general practice setting. However, in order to identify a known solution which is useful in practice, we needed to frame a problem explicitly (Brush, Radford & Krumholz, 2005). For example, a known solution (task-specific heuristics) in the CHF CPG states that "Angiotensin Receptor Blocker (ARB) should be used in patients who cannot tolerate Angiotensin-Converting Enzyme Inhibitor (ACEI)" (Arnold et al. 2006, p. 29). Here the problem is what a General Practioner (GP) should do if a patient is intolerant to ACEI. The importance of the explicit statement of a problem and finding its known solution from the CPGs becomes even more evident when we are to align the comorbid CPs. For examples, what should be an appropriate treatment that a GP can provide to a patient with CHF with New York Heart Association (NYHA) class I or II and concomitant asymptomatic AF? In such a case we extracted a task-specific heuristic from both comorbid CPGs stating that, "Administer beta blocking agents, digoxin or a combination to control ventricular rate" (Arnold et al. 2006, p. 32; Canadian Cardiovascular Society consensus conference Atrial Fibrillation, 2004, p. 61). Synthesis or distillation of heuristics for management of comorbidities requires that all assumptions regarding the salient points of patient care with respect to comorbidities are explicitly stated and discussed.

Alignment of the two CPs not only involves recommendation of appropriate actions when the patient has concomitant illnesses, but it is also necessary to inform the GP about any harmful event that might take place when prescribing concurrent treatments for the comorbidities. For example; an appropriate heuristic extracted from the AF CPG states that "Administer nondihydropyridine calcium channel blocking agent (diltiazem, verapamil) or beta blocking agents as initial rate slowing therapy" Canadian

Cardiovascular Society consensus conference Atrial Fibrillation, 2004, p. 61. Although this is recommended treatment for AF patients, we anticipate a problem while aligning the treatment processes from the two CPs. This is because calcium channel blockers have a negative inotropic effect and therefore can be detrimental to patients with Left Ventricular Systolic Dysfunction (LVSD). A GP needs to be explicitly informed about potential harmful effects of a treatment when dealing with comorbidities. Therefore, in order to avoid such scenarios, we need to incorporate specific heuristics which can prevent potential harmful events. Since the CPGs have generally cautioned against the use of calcium channel blockers in cases of LVSD, we have extracted a relevant heuristic from the CPGs that states that calcium channel blockers should be avoided since they can exacerbate Left Ventricular Systolic Dysfunction (LVSD)[32].

In collaboration with the domain experts, it was agreed that patients whose profiles suggested that they would be more complicated to manage than the average patient in a general practice setting should be referred to a specialist. For example, for the problem statement: what should a GP do when (Angiotensin-Converting Enzyme Inhibitors (ACEIs) are contraindicated in a particular patient? Although a known solution to this problem has been provided in the CHF CPG, which states that, "consider Angiotensin Receptor Blockers (ARBs) as adjunctive therapy to ACEI" (Arnold et al. 2006, p. 29), it was nonetheless concluded that, given the complexity of this scenario, that is, the presence of contraindications to Angiotensin-Converting Enzyme Inhibitor (ACEI) such as severe aortic stenosis, outflow tract obstruction, or renal artery stenosis, the appropriate response of a GP would be to refer this patient to cardiology. Moreover, it was also agreed that patients with heart failure who do not have clear evidence-based treatment, such as those with diastolic heart failure, should be referred to a specialist. Similarly, actions and treatments corresponding to the concurrent illnesses were also scrutinized to see if these practices are viable in a general practice. For example; although the Canadian AF CPG recommends 'amiodarone' as the first choice chronic anti-arrhythmic drug for conversion of AF (Canadian Cardiovascular Society consensus

[32] The domain experts have also validated that Ca channel blockers should not be prescribed for patient with AF and comorbid CHF (Left Ventricular Systolic Dysfunction). In fact the domain experts have advised that the GPs should be cautioned against using Ca channel blockers in such patients.

conference Atrial Fibrillation, 2004, p.39) in patients with Left Ventricular Systolic Dysfunction (LVSD) with or without CHF, heuristics recommending amiodarone were eliminated from the resultant CPs. This is because it was agreed that the CPs only apply to patients with New York Heart Association (NYHA) class I and II symptoms. Rate control therapy such as beta blockade or digoxin is a better option for these patients. This is also in accordance with the 2009 update on heart failure guidelines (Howlett et al 2009).

The extraction of these task-specific heuristics was done manually. Most CPGs are written as systematic reviews and are very lengthy documents. For instance, the Canadian CPG on CHF is 23 pages long and that on AF is 213 pages long, while its executive summary is 41 pages long. As a result, the essential do's and don'ts of practice are embedded in extensive and complicated documents (Brush, Radford & Krumholz, 2005). Most of the do's and don'ts of practice were extracted by scanning the entire documents for class I and class IIa recommendations, which were then translated into task-specific heuristics. In accordance with Canadian Cardiovascular Society Consensus Conference Recommendations on Heart Failure 2006: Diagnosis and Management (Arnold et al. 2006), Class I recommendations refer to "evidence or general agreement that a given procedure or treatment is beneficial, useful and effective", and Class IIa recommendation means "weight of evidence is in favor of usefulness or efficacy". As a result we regard class I and class IIa recommendations as being the most reliable evidence[33]. Often, a single heuristic has been distilled from several class I and IIa recommendations. For example, suppose a GP wants to know which of her heart failure patients should be prescribed an Angiotensin-Converting Enzyme Inhibitor (ACEI)? In order to answer this query we had to comb through five class I level A, one class I level B and one class IIa recommendations in the Canadian CPG on heart failure and the resultant heuristic read as follows (Arnold et al. 2006, p. 28, 29):

'ACEI should be used in all patients as soon as safely possible after acute myocardial infarction, in all asymptomatic patients with left ventricular ejection fraction <35%, in

[33] Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses, Level of Evidence B: Data derived from a single randomized clinical trial or non-randomized studies, Level of Evidence C: Consensus of opinion of experts and or small studies. (Source: Arnold et al. 2006)

all patients with symptoms of heart failure with left ventricular ejection fraction <40%, and if patient is intolerant to ACEI then it should be substituted with ARB'.

Combing through the entire document and extracting essential heuristics is indeed a resource-intensive and intellectually stimulating exercise.

5.2.3. ORDERING & SEQUENCING OF TASKS & IDENTIFICATION & INTERPRETATION OF GUIDELINE LOGIC

Once the task-specific heuristics are distilled from the Clinical Practice Guidelines (CPGs), the next step is to chart the steps that must be carried out in an orderly fashion to formulate a care plan. To operationalize the heuristics extracted from the CPGs that concern more general actions, it was determined that they require more specific information about schedules regarding diagnostics testing, correction of electrolytes, dosage and dose increment, identifying specific contraindications and monitoring of adverse events and subsequent steps to be taken and so on. Such elaborate information is sporadically provided in the CPGs. Therefore, in order to get more practice-oriented information necessary to operationalize these heuristics, we referred to the Capital Health protocols for uptitration as in conjunction with some research papers mentioned in section 6.2.1.1.

5.2.3.1. ORDERING OF TASKS

Since the Clinical Pathways (CPs) are regarded as institution-specific documents, the main developmental challenge was to determine the ordering of the tasks with respect to practices in Halifax and in line with the resources available to a General Practioner (GP). The basic requirement was to achieve a well-defined patient assessment process, which provides explicit instructions for therapy interventions at the level of a GP. For example, with respect to diagnosis of heart failure, the Canadian CPG provides 5 main recommendations, summarized as follows:

- Clinical history, physical exam, and lab testing on all patients with suspected heart failure
- Tranthoracic echocardiography for all patients with suspected heart failure to assess ventricular size and function

- Coronary angiography for suspected or known cases of coronary artery disease
- A validated measure of functional capacity, such as New York Heart Association (NYHA) classification to document functional capacity
- B-type Natriuretic Peptide (BNP) measurements, where available, when clinical uncertainty exists

These heuristics needed to be ordered so that diagnosis of heart failure can be carried out effectively, logically and efficiently by a General Practioner (GP). In this case, we gave special emphasis to the initial clinical presentation and evaluation of initial test results to exclude heart failure as the diagnosis before echocardiography was ordered. Ordering of these activities also meant categorizing the patients according to the NYHA functional classification at the appropriate point in time during the diagnostic process. This is important from the perspective of a general practice setting, because we want to identify patients with relatively stable and milder disease (class I & II) who can be safely managed by a GP, while more severe cases (NYHA class II & IV) with increasing medication requirements and stringent dose adjustments are referred to specialist care right away.

In order to incorporate initial clinical presentation and tests to derive a more objective clinical picture, we used a scoring scheme called the Boston Criteria (Yturralde, & Gaasch 2005; Bari et al. 2004; Shamsham & Mitchell, 2000) which uses a point score system for diagnosis of CHF using various symptoms, abnormal physical and radiological findings. The Boston[34] criteria have been shown to have the highest combined sensitivity, which is 50 percent and specificity, which is 78 percent (Shamsham & Mitchell, 2000).

[34] Boston score is not used for final diagnosis. Only if all initial tests such as X-ray, BNP, ECG are normal in addition to Boston score being less than 4, can the CHF be ruled out. If any of the initial tests are abnormal, even if Boston score is less than 4, the application will still recommend Echocardiography for final diagnosis. Boston score was added at the advice of Dr. Howlett

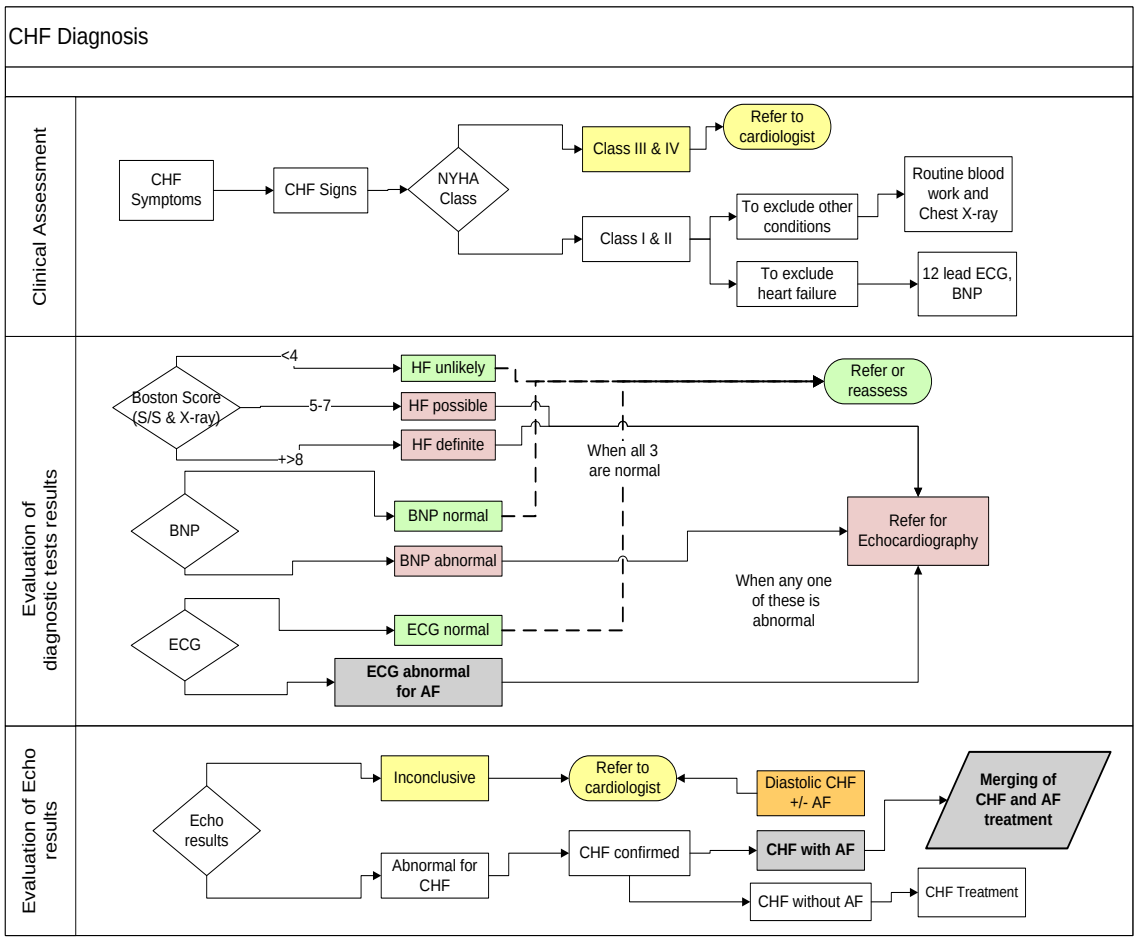

Figure 6: Algorithm for diagnosis of heart failure

Based on the combined (clinical features and chest X-ray) scores, CHF is regarded as definite with 8-12 points, possible with 5-7 points, and unlikely with 4 points or less. In order to get a clearer picture of the patient's condition, other tests such as B-type Natriuretic Peptide (BNP) and the electrocardiography (ECG) are also recommended. Although no specific ECG feature is indicative of heart failure, it does help to identify a comorbid condition such as AF. Identifying this point is essential when aligning the CPs of heart failure and AF. The scheduling of the tasks is such that if the Boston score is 4 points or less, and the ECG and BNP are normal then CHF can be ruled out and the patient should be reassessed or referred to specialist care. If, however, the Boston score is in between 5 -12 points or ECG or BNP is abnormal then it is essential to perform echocardiography to determine left ventricular ejection fraction for diagnosis of systolic ventricular failure and to distinguish systolic from diastolic CHF. A patient with diastolic

heart failure should be referred to specialist care sooner than later. The algorithm for diagnosis of heart failure derived from the scheduling of the heuristics is shown in Fig 6.

5.2.3.2. IDENTIFICATION AND INTERPERTATION OF GUIDELINE LOGIC

We know that CPs are inherently developed as algorithms but these algorithms need to be explicated through two main steps: (i) determine the temporal relationships and logic of the CP, and (ii) incorporate the appropriate task-specific heuristics distilled from the CPGs. The logic determines the decision nodes and branching of the activities that incorporate sequential management decisions. The CPGs, though providing recommendations, are inadequate when it comes to explicitly annotating many of the algorithm's branching points. Although such formatting may be acceptable for guidelines since they offer evidence-based general guidance to practitioners, automating them to access and enhance clinical performance is difficult if eligibility for each decision is unclear. For example, the Canadian CHF CPG contains some specific recommendations for patients with "severe persistent symptom or for patients with "persistent heart failure symptoms who are assessed to be at increased risk of heart failure hospitalization" (Arnold et al. 2006) in terms of:

"Angiotensin Receptor Blocker (*ARB) should be added to an Angiotensin-Converting Enzyme inhibitor(ACEI) for patients with persistent heart failure symptoms who are assessed to be at increased risk of heart failure hospitalization"* (Arnold et al. 2006, p. 30).

The decision logic here is "persistent heart failure symptoms that are assessed to be at increased risk of heart failure hospitalization". Operationalization of this decision logic or of "severe persistent symptoms" entails explicit information about it. Therefore, we used the New York Heart Association (NYHA) functional classification to arbitrarily define "persistent heart failure symptoms that are assessed to be at increased risk of heart failure hospitalization" or "severe persistent symptoms" as NYHA class III & IV, which represent the IF part of logical statement. Thus, all such patients are referred to the specialist care, despite the treatment recommendations provided in the CPG.

5.2.3.3. DISAMBIGUATION OF STATES AND MODIFIERS

CPGs entail vague statements that need to be clarified for them to be properly modeled for use in a decision support system. In this regard, we clarified the definition of states, for example; 'drug intolerance' (to ACEI in CHF CPG) or 'risk of bleeding' (with anti-coagulation therapy in AF CPG), or with respect to modifiers, for example, 'frequently' or 'recurring episodes (of pulmonary edema)'. Such vague descriptions can potentially open up a dispute regarding the eligibility of a patient for a certain treatment plan. We argue that for the purposes of alignment and automation of CPGs, it is important that the decision points are redefined in terms of explicit values of readily available information. Definition of most of the states was therefore clarified in collaboration with domain experts and the medical literature. For example, intolerance to Angiotensin-Converting Enzyme Inhibitor (ACEI) meant new or worsening dry cough; and risk of bleeding referred to current major trauma or surgery, alcoholism, a bleeding diathesis, active peptic ulcer and so on. The precise description of modifiers was extremely difficult and in most cases the fuzziness was incorporated in the CPs.

5.2.3.4. OPERATIONALIZATION OF HEURISTICS CONTAINING GENERAL DISEASE MANAGEMENT INFORMATION

The Clinical Practice Guidelines (CPGs) contained several general heuristics regarding the drug treatment of CHF or AF. For example: the CHF CPG says that "*specific contraindications to individual drugs should be identified in each patient*" (Arnold et al. 2006, p. 27). Operationalization of this heuristic resulted in an elaborate algorithm which includes identification of various contraindications and cautions to heart failure therapies, such as electrolyte imbalance, low blood pressure and other specific conditions such as history of angioedema. The necessary information for operationalization of this heuristic was mainly obtained from the Capital Health protocols for uptitration provided to us by the domain expert. The resultant algorithm is depicted in Fig 7, which shows the identification of abnormalities of serum electrolytes and their correction.

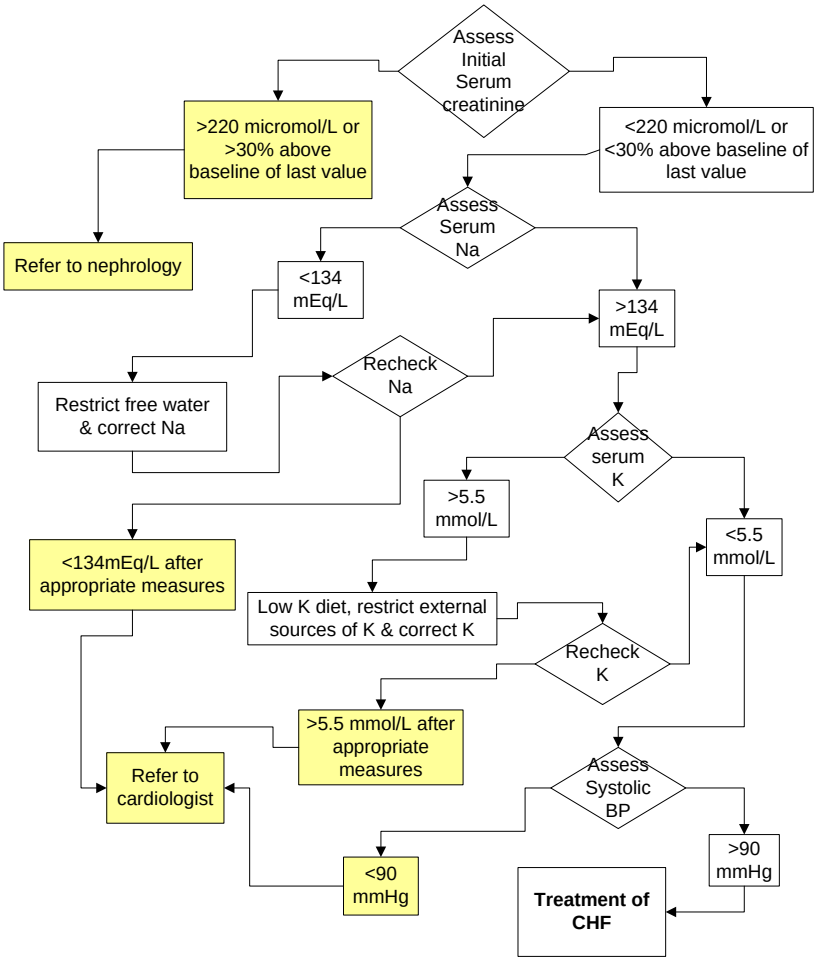

Figure 7: Algorithm for pre-treatments assessment and correction of electrolytes

Other specific contraindications to Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB) and Beta Blocker (BB) were distilled from these protocols and incorporated in separate algorithms developed for the uptitration of these medications. These uptitration algorithms (Fig. 8) were developed to operationalize additional heuristic extracted from the CPG, which state that; "*All patients with heart failure and left ventricular ejection fraction <40% should be treated with ACEI in combination with Beta Blocker (BB) unless a specific contraindication exists*" (Arnold et al. 2006, p. 27, 28) and "*The target dose should be either the dose used in large scale clinical trials or a lesser or maximum dose that is tolerated by patient*" (Arnold et al. 2006, p. 28).

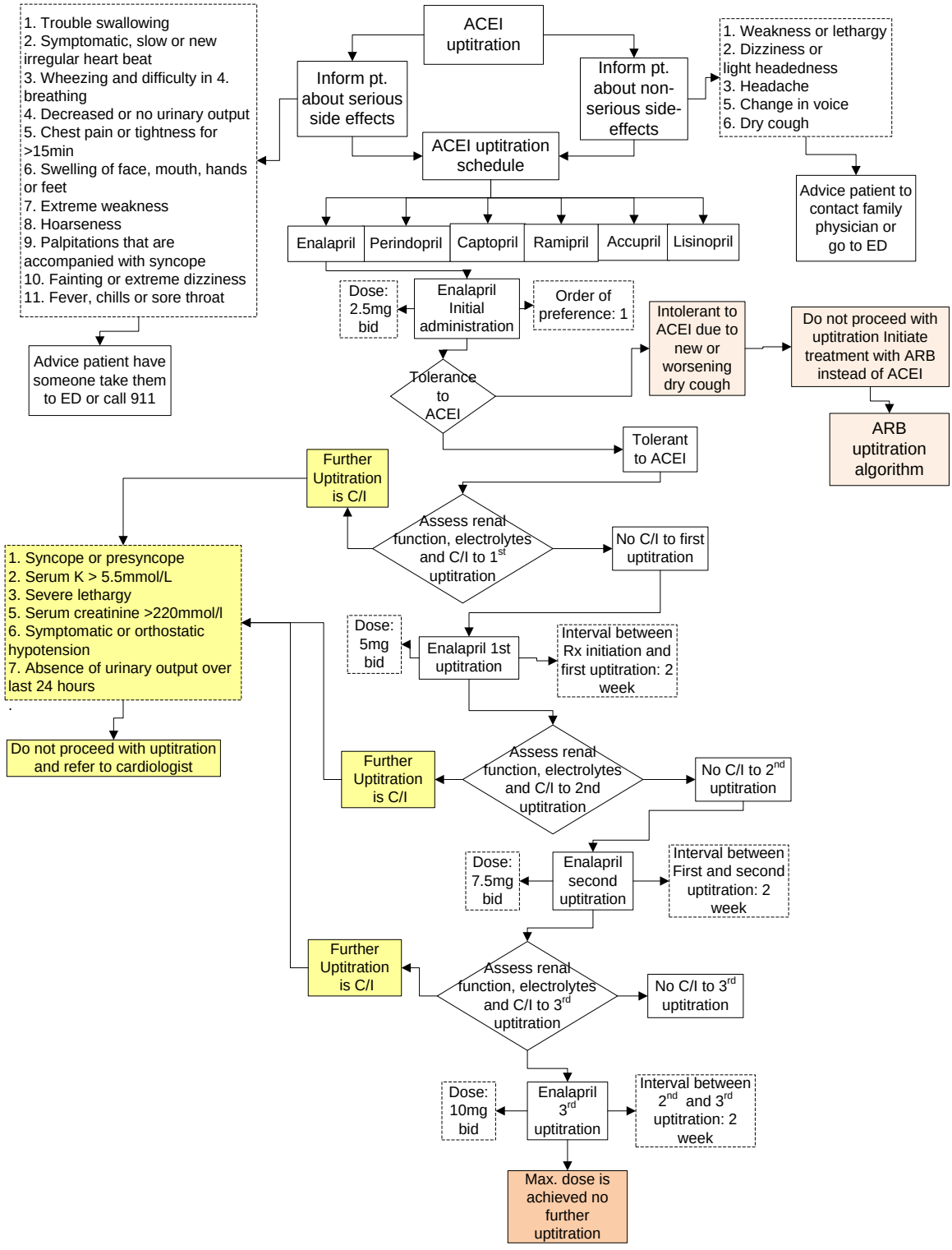

Figure 8: ACEI uptitration algorithm

The uptitration protocols provide information regarding the gradual increments of dose of these medications especially the intervals between these doses, the parameters that should be evaluated during these intervals, and the eligibility criteria for deciding whether a practitioner should continue with uptitration or maintain a dose or refer the patient to cardiology. Similar broad task-specific heuristics were also extracted from the AF CPG, which were then operationalized using information gained from various sources such as research papers and other CPGs as mentioned above.

The CPs are comprised of multiple algorithms depicting the care plans corresponding to various patient care activities and interventions, such as the initial clinical assessment, diagnostic investigations, pre-treatment evaluation and correction of electrolytes, treatment plans and patient education.

The purpose, target users, format and the content of the resultant CPs are described below.

5.2.4. PURPOSE OF CPs

We believe that unambiguous algorithmic representation of the Clinical Practice Guideline (CPG) knowledge has a central position in the entire cycle of knowledge acquisition, representation, alignment and dissemination. Therefore, the main purpose of development of the Clinical Pathways (CPs) was to distill CHF and AF task-specific heuristics form the respective CPGs, in terms of their decision logic, available decision options and actions to be taken, and temporal ordering of these primitives in accordance with facilities available at a general practice setting, which can be computerized and aligned. The target users of these pathways and the comorbid CP based application are the general practitioners.

5.2.5. PATIENT SELECTION

The CPs have been developed for adults (18 years or older) with CHF and AF. Since the main purpose of the CP-based application is to provide evidence -based decision support in a general practice setting, specific inclusion and exclusion criteria for the patient were defined based on expert advice. For example, any patient suspected of having CHF and identified with NYHA functional class I and II symptoms during initial assessment was

included in the pathway, while those with New York Heart Association (NYHA) functional classes III and IV were excluded and referred to cardiology. Similarly, a patent suspected of AF, with clinical features of hemodynamic instability, was also excluded from the CP and referred to an emergency department.

When a specific contraindication to a specific treatment exists, for example, a history of renal artery stenosis in the case of Angiotensin Converting Enzyme Inhibitor (ACEI), or the presence of severe reactive airway disease in the case of beta blockers, the patient is to be taken off the CP and is to be referred to cardiology. Also, these pathways at the moment do not contain information regarding management of other common comorbid conditions such as ischemic heart disease or hypertension.

5.2.6. CLINICAL PATHWAY FORMAT

The task-specific heuristics distilled from the CPGs were used to create a series of temporally sequenced graphs (flow-charts) for diagnosis, initiation of treatment and uptitration of drugs. The flow-chart format was chosen because it utilizes temporal logic within a guideline to express precisely step-wise and iterative execution of a guideline. Given the complexity of CHF and AF, each CP constitutes several flow-charts, reflecting care-plans corresponding to various stages during diagnosis and management in a general practice environment. Thus, each flow-chart in the CPs corresponds to a particular patient state; for example, Initial Assessment, Diagnostic Testing or Treatment. The CPs also exhibit nesting of flow-charts. In case of CHF, the drug uptitration flow-charts have been nested within a CHF drug treatment flow-chart (Fig. 9).

All diagnostic and treatment activities are clearly demarcated. Each flow chart unambiguously depicts decision logic in the care-flow, along with decision options and resultant action when a particular option is chosen. Points where the execution of activities has to be aborted because of, for example, specific contraindication to a treatment or adverse event, or when it is only appropriate that the patient should be referred to cardiology, are explicitly identified. Being a depiction of process flow, these algorithms, by their very nature, demonstrate the scheduling constraints such as sequencing, concurrence, branching and synchronization of various activities in the care-flow. We believe that the flow-chart format is an extremely useful tool for

comprehension of logic within extremely complex and lengthy domain and therefore is more amenable to computer-based applications.

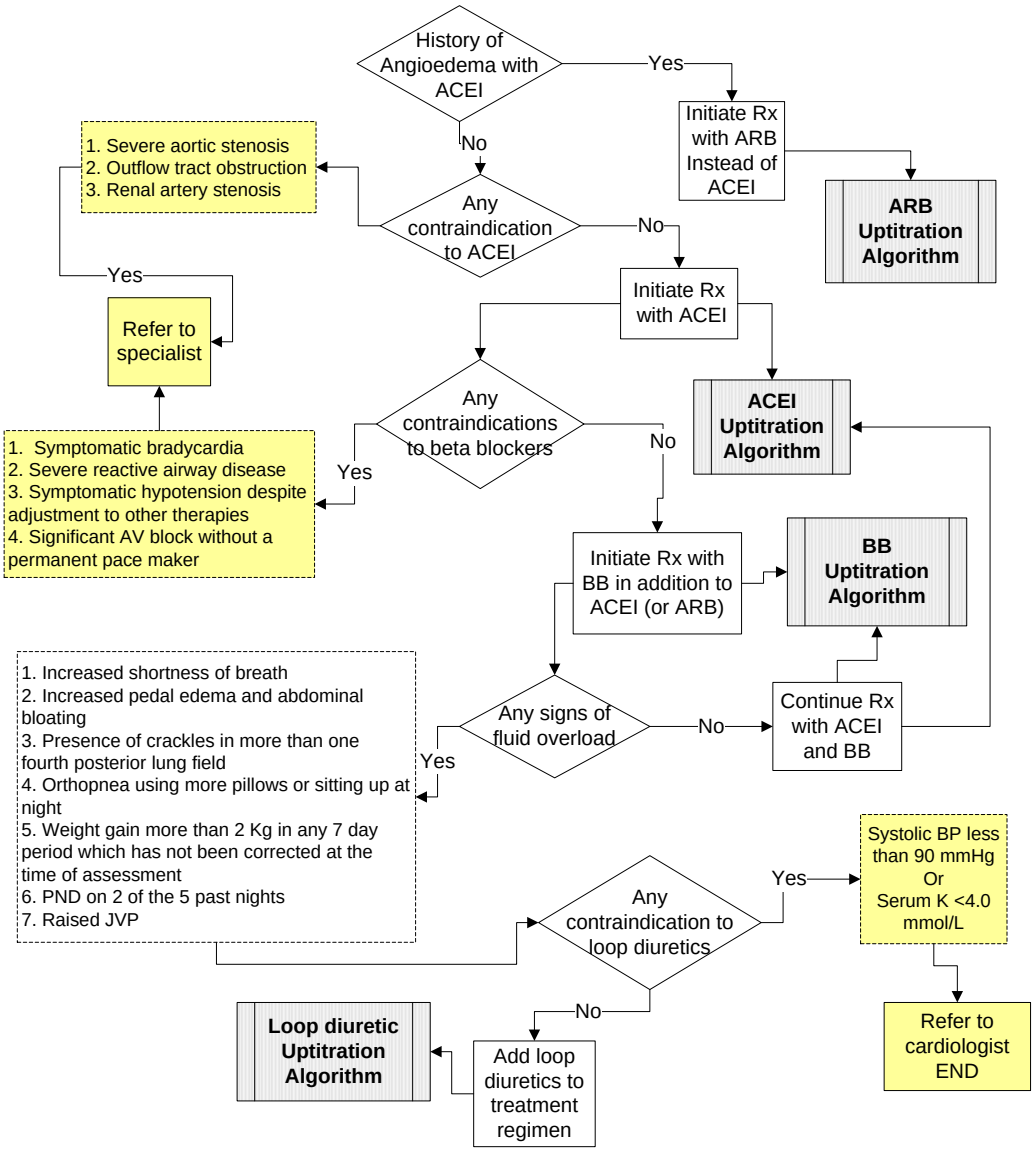

Figure 9: CHF drug treatment algorithm with nesting of ACEI, ARB, BB & diuretic uptitration algorithms (grey boxes)

5.2.7. CONTENT OF CLINICAL PATHWAYS

We developed clinical pathway packages, one for each comorbidity, as a progressive schema of patient care activities leading from initial clinical assessment, diagnostic investigation and evaluation of tests results, pre-treatment evaluation and correction of electrolytes (for CHF CP), and finally to treatment (including thromboembolic risk

assessment and anti-coagulation therapy for AF CP) and patient education. Within each of these care processes, there are individual care activities, such as, clinical assessment incorporate events such as clinical history, physical exam and New York Heart Association (NYHA) classification (Figures 6 & 10).

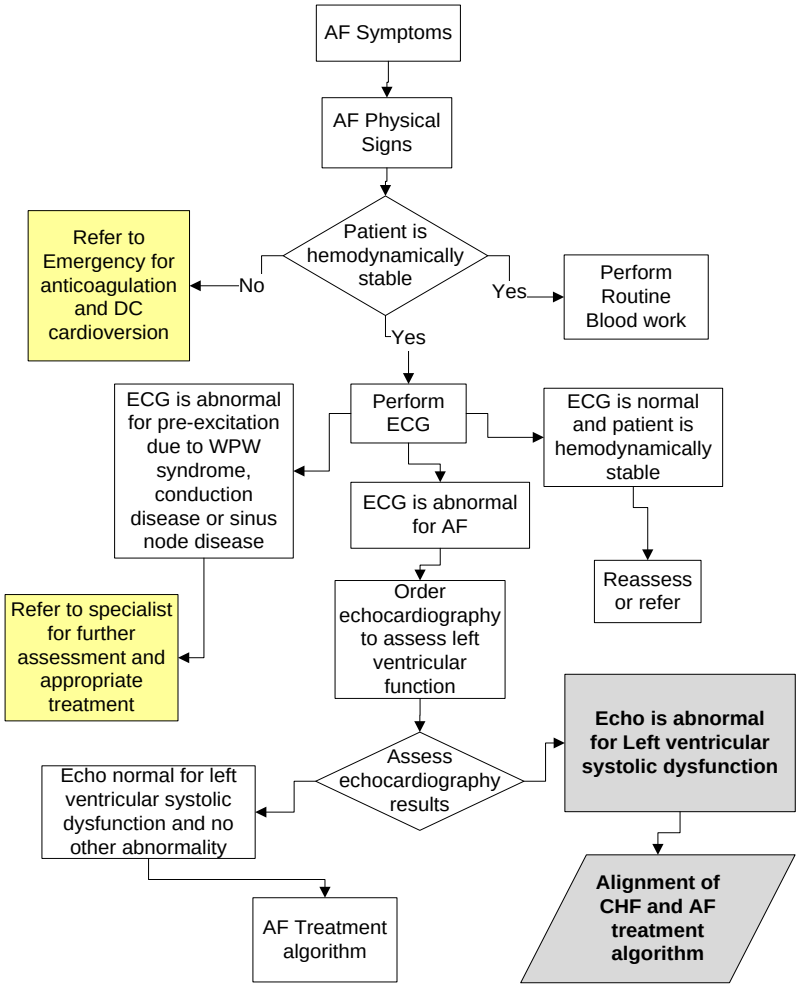

Figure 10: Algorithm for diagnosis of AF with and without comorbid LVSD

The algorithms for clinical assessment and tests evaluation for CHF and AF (Fig. 6 & 10) were developed with the understanding that the General Practioner (GP) would have a moderate suspicion of underlying disease. The intention of these algorithms is not to yield a directory of differential diagnosis, but rather to enable the GPs to check their intuition against a pattern of signs and symptoms and the tests results, which are used to include or exclude the diagnosis or CHF and AF. The assessment algorithms also identify the points in the diagnostic process where the comorbid condition is also confirmed along

with the main suspected disease. These points are denoted with grey boxes in Figures 6 and 10.

The algorithm for pre-treatment evaluation and correction of electrolytes (Fig. 7) illustrates steps such as evaluating serum creatinine, sodium and potassium concentrations and systolic blood pressure, before treatment with Angiotensin-Converting Enzyme Inhibitor (ACEI) and Beta Blocker (BB) can safely be commenced in patients with CHF. This algorithm guides a GP in a stepwise fashion to evaluate these important parameters. The algorithm begins with an evaluation of renal function serum creatinine.

If the creatinine level is found within normal limits, then a GP can proceed to the next step, which is the evaluation of serum electrolytes; otherwise, the patient is referred to a specialist for further renal function evaluation. This algorithm also depicts some specific measures a GP can take to correct any electrolyte imbalance that she may encounter, such as free water restriction when serum sodium is less than 134mEq/L, and low potassium diet and restriction of external sources of potassium when serum potassium is more than 5.5mEq/L. If after re-evaluation, the electrolytes are still not within the normal range then the patient is referred to cardiology; otherwise, the next step is the evaluation of blood pressure. This is important since any patient with a systolic BP of less than 90mmHg should be referred to cardiology while the rest should be evaluated for any history of angioedema, a contraindication for ACEI, in which case ARB should be substituted instead of ACEI. Information in the Capital Health protocols and guidance of domain experts was used to develop this algorithm. This algorithm is shown in Fig. 7. The treatment algorithms corresponding to therapies for CHF and AF are based on best evidence. The treatment schedules include elaborate schemas depicting temporal and spatial relationships such as uptitration schedules (as in CHF) and situations when a drug is contraindicated or when a particular medication or its uptitration should be halted altogether and the patient referred to a cardiologist. The drug uptitartion schemas along with dosage information for medications used in the treatment of CHF are derived from the Capital Health protocols, and are developed as separate algorithms (Fig. 8). They are nested within the CHF treatment algorithm (Fig. 9).

The AF treatment algorithm includes rate control therapies such as the administration of beta blockers or calcium channel blockers. Since initiation of rhythm control therapy is more complex and high risk, the only treatment deemed suitable for patients with co-morbid CHF and AF in the general practice is digoxin in addition to beta blockers. While treatment with beta-blockers has been covered in the CHF treatment algorithms, the algorithm for administration of digoxin for patients with AF and CHF has been developed separately (Fig. 11). The dosage and administration schema for digoxin has been distilled from the Canadian and American CPGs. Once computerized, the alignment of digoxin and CHF treatment algorithms will take place during the execution of the computerized CPs.

Another significant aspect of the treatment of AF is thromoembolic risk stratification and prescription of either aspirin or anti-coagulation based on the patient's individual risk. The risk of thromboembolism is particularly significant in patients who have concurrent CHF and AF. Consequently, based on the Canadian and National Health Service guidelines, an algorithm is developed depicting thromboembolic risk stratification based on patient's age, and presence of other risk factors, such as hypertension, diabetes, vascular disease and prior episode(s) of cerebrovascular accident (Fig. 12). Depending on a patient's profile, the risk of thromboembolism may be low, moderate or high. In accordance with the guidelines, treatment with aspirin is sufficient for the patients with low or moderate risk, while the patients with high risk require anti-coagulation with warfarin.

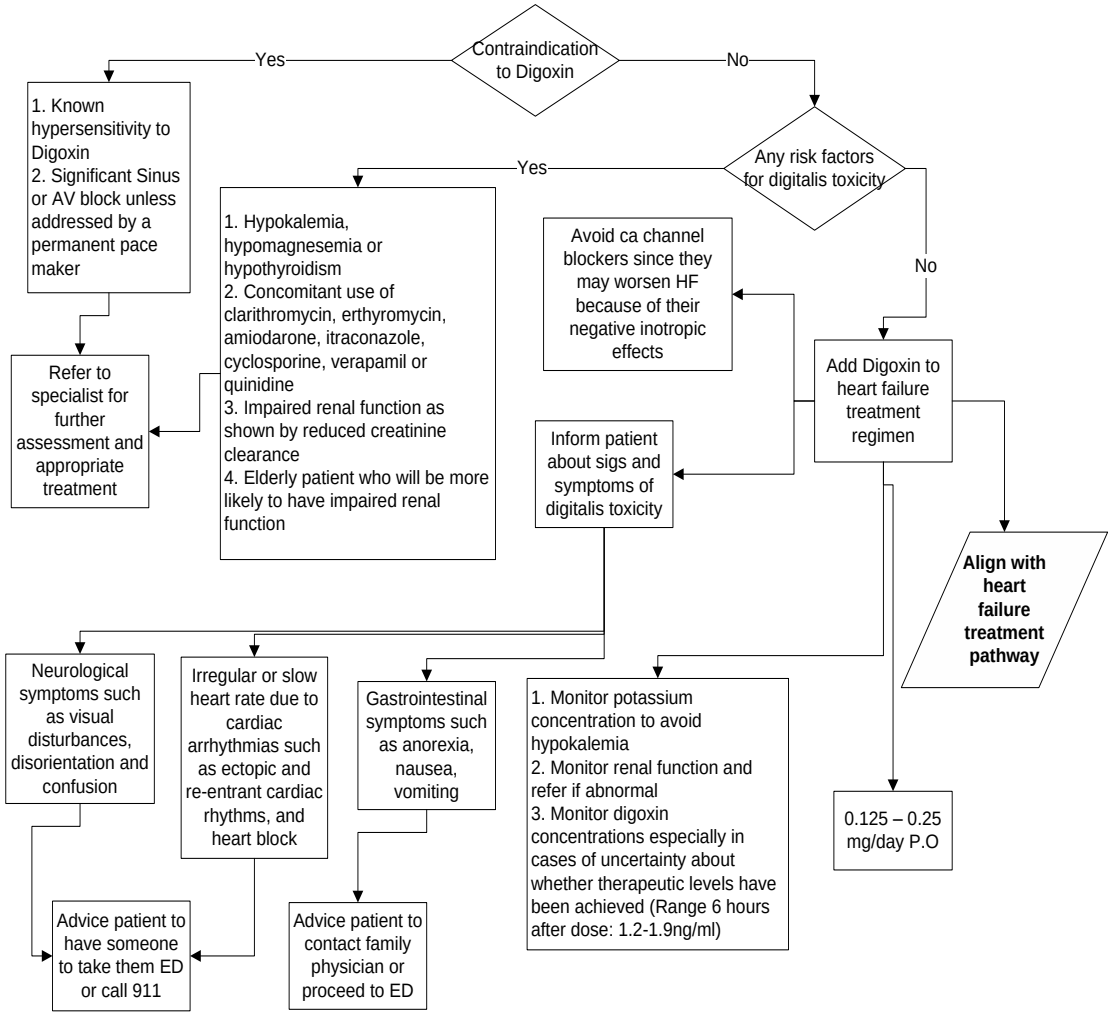

Figure 11: Algorithm for the digoxin treatment. Also grey box depicting the alignment point with CHF treatment pathway

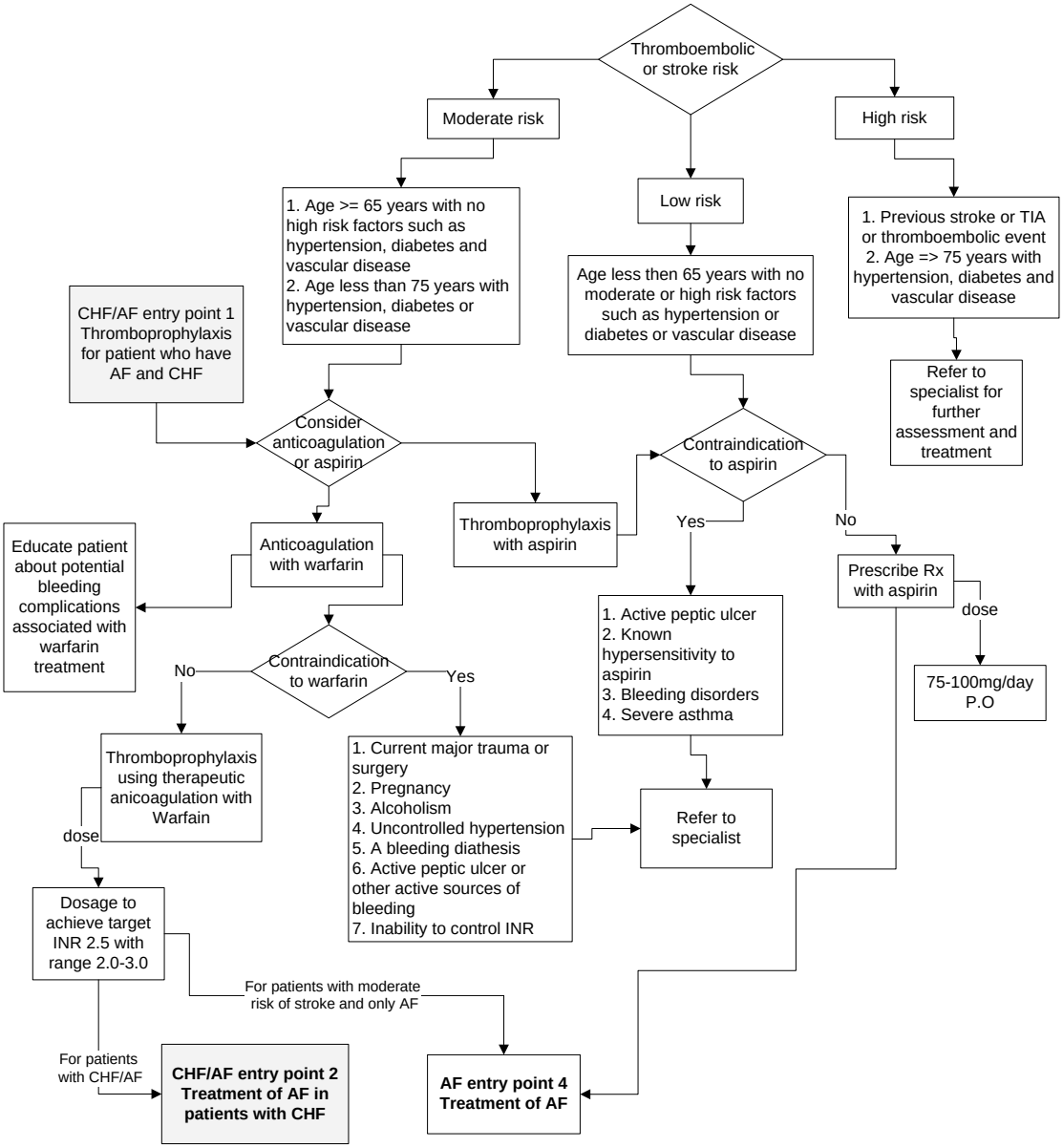

Figure 12: Pathway to determine and manage thromboembolic risk in patients with AF and comorbid AF and CHF

The algorithm also includes contraindication to treatment and measures to be taken to ensure safe drug administration. For example, in the case of warfarin administration, the algorithm contain a heuristic stating that; ‘dose should be adjusted to achieve International Normalized Ratio (INR) of 2.5 with a range between 2.0-3.0’. However, due to lack of essential and valid information regarding the frequency of INR monitoring, a schedule for INR monitoring has not been included in the current algorithm.

As mentioned earlier, since patients with comorbid CHF and AF have high thromboemolic risk, a portion of this algorithm, which depicts the steps related to warfarin therapy, will be aligned with the CHF pathway for patient with these two comorbidities during the execution of computerized pathways (Fig. 12).

5.3. APPROACH TOWARDS COMORBID KNOWLEDGE ALIGNMENT

Alignment of comorbid CPs has been achieved at the knowledge modeling level. Our approach towards comorbid knowledge alignment is to develop a unified ontological model that encompasses the combined knowledge of aligned CPs. We have aligned the candidate CPs (AF and CHF CPs) in a planned manner by establishing conceptual mapping between the common concepts across the comorbidities within the ontological model. The unified ontological model represents each CP as a combination of both common and unique concepts thus ensuring that each modeled CP maintains its unique identity. Knowledge alignment in the context of this research is defined as alignment of discrete and ontologically defined care plans in response to single disease or comorbid preconditions.

From a knowledge management perspective, there are two main approaches to aligning multiple CPs to handle comorbidities: (a) Aligning CPs at the knowledge modeling level; and (b) Aligning CPs at the knowledge execution level (Abidi & Abidi, 2009). In both these CP alignment scenarios, the paper-based CPs are required to be modeled using representation schema, such as ontologies.

Aligning CPs at the knowledge modeling level involves the development of a unified knowledge model that encapsulates the medical and process knowledge to handle specific comorbid diseases. In a planned and manual manner, the knowledge modeler aligns the ontologically-modeled individual CPs by establishing a conceptual mapping between common concepts across the CPs of the comorbid diseases, resulting in a comorbid CP ontological model.

Aligning CPs at the knowledge execution level involves the dynamic alignment of multiple ontologically-modeled CPs at execution time to create an adaptable CP that

modulates with respect to the patient conditions. Typically, ontology alignment[35] and reconciliation techniques (Euzenat & Shvaiko 2007) are used to establish linguistic, terminological and conceptual correspondences between the candidate CP's ontological models. This is a challenging alignment process because a unified comorbid knowledge model is not developed a priori; rather CP alignment is intended to take place as and when needed during execution. It may be noted that at present there do not exist any systems that offers execution level CP alignment, largely because it is not possible to dynamically validate the dynamically aligned CP model before it is applied to the care process.

We have applied the knowledge modeling approach (Abidi & Abidi, 2009) to align the independent AF and CHF CPs to develop the comorbid CHF+AF CP knowledge model. As per the knowledge modeling approach for aligning different CPs, our main steps were:

Step 1: It may be noted that during the knowledge synthesis phase, for each disease-specific CP we identified discrete plans that capture the individual diagnostic and treatment processes involved in the management of that specific disease. We developed management plans within CPS for CHF, AF and also comobid CHF-AF.

Starting with the paper-based CPs for individual conditions (i.e. CHF and AF), we:

- Modeled and represented the CHF and AF CPs using a semantically-rich representation language—i.e. an ontology—in order to realize a high-level CP knowledge model that represents the CHF and AF CPs as independent CPs. The CP knowledge model provides a semantically rich template to represent a CP's medical and process related concepts in terms of classes and relationships between classes.

[35] String-based techniques that match name description of entities. So that more similar the string, more likely they are to denote the same concept; Language-based techniques that consider names as words in some natural language and use morphological properties of input words to match the entities; Constraint-based techniques that use algorithms, which deal with internal constraints such as cardinality of properties to match entities; Graph-based techniques that uses graph algorithms, which consider the input ontology as labeled graphs. The similarity comparison between a pair of nodes from two ontologies is based on analysis of their position; Taxonomy-based techniques that also uses graph algorithm. But it consider only the specialization relation

- Instantiated the ontological CP model using the discrete plans for CHF and AF CPs. This results in the computerization of the individual CPs, such that the instantiated disease-specific CPs can now be executed (with necessary applications) at the point-of-care execution. The CPs are instantiated within the CP ontology in a planned and deterministic manner and are instantiated in the ontology in accordance to this planned sequence. Each plan is represented by a class in the ontology called ENTRY_POINT that represents entry point into the application. Each ENTRY_POINT involves execution of a plan until a condition is met when the plan is aborted (a contraindication to a treatment or a test result that suggests a condition that cannot be treated at general practice) or is completed and then the next plan come into effect. The modeling details and the ontology based alignment of these plans are discussed in detail in chapter 6.

Step 2: It may noted that during the knowledge synthesis phase, we identified (a) the specific preconditions that might trigger comorbid plans, and (b) 'alignment' points between the two individual CPs to realize a comorbid (CHF+AF) CP. An example of a comorbid trigger point is as follows: In CHF patients, detection of an ECG abnormality that is suggestive of AF is a precondition for triggering of the comorbid CHF-AF plans.

As per our the knowledge modeling approach, based on the comorbid CHF+AF CP the ontologically-modeled CPs are systematically aligned by mapping common processes, actions, recommendations within the individual CHF and AF CPs, and by adding additional constraints and conditions. A typical usage of the aligned CHF-AF CP is to avoid the duplication of treatments. For instance, the Canadian guideline (Howlett et al. 2009) recommends rate control treatment for the management of AF in patients with stable heart failure. The domain expert advised us to include beta blocker as the rate control agent for this purpose. However, beta blocker is also a recommended treatment for the treatment of CHF irrespective of the comrobidity. Therefore, we have to take care that while aligning the comorbid care plans, duplication of beta blocker treatment plans must be avoided. Our approach prevents such redundancies. This is because whenever a

condition indicating comorbidity is detected it acts as a precondition for triggering of comorbid CHF-AF plans (CHF-AF ENTRY_POINT). None of these plans incorporates treatment with beta blocker since it has already been incorporated in the CHF CP. Thus any prospects of treatment duplication have been avoided at the knowledge synthesis and modeling levels.

We want to clarify that our approach for handling comorbidities using an ontological framework does not encompass ontology matching[36] techniques[37] (Euzenat & Shvaiko 2007)—ontology matching and alignment is not related to the problem we are investigating. Ontology alignment produces correspondences between entities belonging to two or more ontologies (Euzenat & Shvaiko 2007). The correspondence is the relation holding according to a particular matching algorithm, between entities (classes, individuals, properties or formulas) of different ontologies (Euzenat & Shvaiko 2007). It may be noted that ontology alignment techniques are required to resolve syntactic, terminological or conceptual heterogeneity when matching different ontologies (Euzenat & Shvaiko 2007). Syntactic heterogeneity occurs when two ontologies are not expressed in the same language. Terminological heterogeneity occurs when the same entities in different ontologies are referred to by different names. Conceptual heterogeneity, (also called semantic heterogeneity) occurs when the same domain is modeled differently, either by using different axioms to define the same concepts or by using entirely dissimilar concepts.

In our work, the concept and methods for ontology alignment do not apply because we are not aligning multiple ontologies; in our case we a developing a unified CP knowledge model that represents multiple CPs. In this regard, the objective of this research is to demonstrate how to resolve specific issues related to comorbid management at the

[36]Ontology matching is the process of finding relationships or correspondences between entities of different ontologies

[37] String-based techniques that match name description of entities. So that more similar the string, more likely they are to denote the same concept; Language-based techniques that consider names as words in some natural language and use morphological properties of input words to match the entities; Constraint-based techniques that use algorithms, which deal with internal constraints such as cardinality of properties to match entities; Graph-based techniques that uses graph algorithms, which consider the input ontology as labeled graphs. The similarity comparison between a pair of nodes from two ontologies is based on analysis of their position; Taxonomy-based techniques that also uses graph algorithm. But it consider only the specialization relation.

knowledge representation level using an ontological framework. Knowledge alignment in this context entails the alignment of discrete and ontologically defined care plans at the knowledge modeling level. In the realm of our approach, any potential terminological or conceptual heterogeneity has been resolved manually during the knowledge synthesis and modeling phase. For example, the term "task" is the same for all activities to be performed during the course of management of both comorbidities. Similarly, a sub-class axiom is the same, whichever comorbidity we are dealing with. Therefore, a concept "task" can be a decision making task or a non-decision making task whether we are representing CHF or AF CPG knowledge. An equivalent class axiom is also the same when representing both CPs. Therefore, for a task (in either CHF or AF CP) to be a decision making task, it is necessary that it is a task, and it is also necessary that it has at least one "has_decision_option" relationship with the concept decision option. The details of these axioms are discussed in chapter 6.

5.3.1. OTHER APPROACHES TOWARD COMORBIDITIES

One potential approach to handle comorbidities is to develop dedicated comorbid clinical practice guidelines that are based on studies that test and compare the efficacy of interventions available for the treatment of specific comorbidities. CPGs in fact are detailed reviews of the pertinent literature. They can be seen as published reports on relevant randomized control trials (RCTs) (Fortin, Dionne, Pinho, Gignac, Almiral & Lapointe. 2006). RCTs are generally recognized as the criterion standard of methodical research design for clinical studies (Fortin, Dionne, Pinho, Gignac, Almiral & Lapointe. 2006). More recently, with regards to comorbid CHF-AF, Roy et al (2009) conducted multicenter randomized comparison of rhythm control vs. rate control treatment strategies. This study concluded that in patients with CHF-AF, rhythm control therapy does not reduce the rate of death from cardiovascular causes as compared to rate control. Unlike RCTs, the purpose of our approach is not to compare the efficacy of two or more treatments to manage comorbidities, or to conclude whether one option is preferable to the other. The problem this research aims to solve is very different from the one that is solved by the Roy et al (2009) study. The research problem being investigated in this thesis is how to formally model the structural, functional and conceptual knowledge in the individual disease specific CPGs, so that they can be systematically aligned and

executed to handle comorbid management. The comorbid management plans that this application recommends are based on the CPG recommendations and are developed during the knowledge synthesis phase and formalized during the knowledge modeling phase of this research. The CPG recommendations are based on RCTs, which are reviewed by the authors of these guidelines. The evidence in the CPGs has been synthesized by the domain experts, who are the authors of these guidelines. Finally, based on this synthesized evidence, the recommendations have been provided to the clinicians. We have incorporated the best evidence from the CPGs in the CPs during the knowledge synthesis phase of this research. The purpose of the computational approach, therefore, is not to compare the two comorbid treatments in order to determine the efficacy of one treatment on other, but to recommend an appropriate task, at appropriate time, under appropriate circumstances as delineated in the CPG.

As mentioned earlier in section 5.3, with respect to an ontology based approach to handling comorbidities, another potential approach is to align multiple CPs at the knowledge execution level (Abidi & Abidi, 2009). In this scenario a unified model is not created to represent multiple CPs, instead individual CPs must be represented as independent ontological models. Multiple CPs are then merged in dynamic manner to create an adaptable CP that modulates with respect to a patient's conditions. This approach requires ontological alignment techniques (Euzenat & Shvaiko 2007) to establish linguistic, terminological and conceptual correspondences between candidates CP ontologies. This research, however, involves creating a unified ontological model in order to represent the CHF-AF CPs. Each CP has the same concepts such as Treatment, Diagnostic Concept, and Decision Option and so on. Thus a unified ontology contains concepts and axioms that are common to comorbid CPs. From the knowledge modeling perspective, we argue that it is impractical to develop two separate models to represent the same type of concepts or axioms. In our approach, alignment of the comorbid care plans is carried out in the unified model. These are dedicated plans that are developed during the knowledge synthesis phase and then represented in the ontology.

5.4. CONCLUSION

We conclude that specific, unambiguous and structured synthesis of knowledge is required to develop algorithms that can be effectively formalized and interpreted by computer systems. The content of these pathways has been synthesized with explicit and fully defined clinical terms and ranges for decision points and temporal dependencies between various tasks. We believe that such unambiguous interpretation of medical decision logic and the sequence of steps necessary to execute a care plan are absolutely essential prerequisites for computerization, alignment of the comorbidity CPs and their subsequent translation into a Clinical Decision Support System (CDSS). Our approach towards the comorbid knowledge alignment is to develop a unified ontological model that encompasses the combined knowledge of aligned CPs. This means that any potential terminological or conceptual heterogeneity that might arise as a result of comorbidity has been resolved manually during the knowledge synthesis and modeling phase of this research. Once CPs are developed, the next step is to computerize them as a formal model in the form of an ontology. However, before the CP knowledge can be formalized as ontology, this knowledge has to be conceptualized. Conceptualization involves an explicit statement of primary concepts in the domain, their relationships and constraints on these relationships. Section 6.3 presents the knowledge conceptualization phase of our methodology.

CHAPTER 6 KNOWLEDGE FORMALIZATION AND EXECUTION

6.1. KNOWLEDGE FORMALIZATION

The purpose of knowledge formalization is to generate an explicit and formally described [38] semantic structure based on the Clinical Pathway (CP) knowledge so as to (i) formalize[39] the comorbid plan alignment points and constraints (iii) instantiate the formalized model with the comorbid CPs and (ii) enable the computer applications to execute the formalized model at the point of care, thus leveraging on the principles of both the task-specific and availability heuristics. In order to build a Semantic Web based application, knowledge is expressed as an ontology in a formal language (such as OWL) so that the ontology can be unambiguously interpreted by a computer and therefore can be processed (Kim, 2002).

Knowledge formalization, which involves the development of the CP ontology, spans two essential steps. The first one is to identify the main concepts in the domain, the relationships (properties) that hold between them and restrictions on these relationships and, identifying natural language terms to refer to these concepts and relationships. The second step is to define these terms and relationships using a formal language so that it can be reasoned by computers (Stevens, Goble & Bechhofer, 2000). These two steps are discussed in the subsequent sections.

6.2. KNOWLEDGE CLASSIFICATION AND CONCEPTUALIZATION

Knowledge conceptualization involves differentiating the knowledge (the knowledge derived from the knowledge synthesis stage) in terms of task or patient specific and then conceptualizing the actionable aspect of the knowledge given in narrative Clinical Practice Guideline (CPG) in terms of explicit statements that can be used to develop the CHF and AF CP and to subsequently computerize the knowledge.

[38] Semantic structure that describes meaning of the knowledge precisely, so that the definition of terms and relationships are specified using a formal language, e.g. OWL. Precisely means that the semantics does not refer to subjective intuition, nor it is open to different interpretation by different machines. Formal semantics allows the machines to reason about the knowledge. Thus, formal semantics is a pre-requisite for reasoning support.

[39] Formally describes knowledge so that it can be interpreted by computers.

We notice that the heuristics distilled from the guidelines and other medical literature sources are mostly task-specific as compared to being patient-specific. For example consider this heuristic extracted from Canadian CPG on heart failure;

"*Beta blockade is recommended for CHF patients with (a) left ventricular ejection fraction <40%, however, those who are in New York Heart Association (NYHA) class IV should be stabilized before initiation of beta blocker, (b) for most heart failure patients with preserved systolic function, (c) for asymptomatic AF patients with left ventricular ejection fraction <40%, and (d) for symptomatic AF patients where beta blockers can be added to digoxin once patient has stabilized*".

It can be clearly seen that this heuristic is specific to a task, since it describes when a practitioner should prescribe a beta blocker. However, the practitioner still would need to interpret it to discern whether her patient's profile corresponds to any of the conditions included in the heuristic.

We note that the algorithms developed during the knowledge synthesis phase, despite presenting an unambiguous enactment of the guideline logic, are still high-level overviews and simplified idealizations of the said literature. The knowledge they express is a combination of procedural and criterion-based knowledge (with possible conditions on variables), which a practitioner is tacitly expected to modify and adapt according to an individual clinical profile. As a result, these algorithms are rigid and are not designed to be applied literally and directly (Gordon, Johnson, Waite & Veloso, 1997). This is especially true when dealing with comorbidities because these algorithms focus on single disease management. However, when dealing with comorbidities we need to execute different processes in parallel based on the presence or absence of comorbid conditions, while at the same time avoiding unnecessary duplication of tasks and preventing omission of necessary tasks and harmful events. In this scenario, the goal of knowledge conceptualization was to represent knowledge in such a form and format that it can be processed efficiently by computer applications. (Carter, 1999).

In this phase, we classified and conceptualized the knowledge along two main types—declarative knowledge and procedural knowledge (Kong, Xu & Yang, 2008):

- *Declarative knowledge* contains propositions, which are statements about the world which are either true or false, and may be connected by Boolean operators such as 'and', 'or', 'not' to form sentences. Declarative knowledge refers to the 'know what' of the domain. The declarative knowledge contains abstract terms, their relationships and their attributes.
- *Procedural knowledge* contains explicit information regarding procedures or actions to be taken, or conclusions that can be drawn from declarative knowledge. Procedural knowledge refers to the 'know how' of the domain. The procedural knowledge contains algorithmic specifications of guideline logic. It includes problem-solving knowledge used in heuristics and expert judgment.

The decision-making behavior of practitioners and role of the heuristics in clinical decision making tells us that successful incorporation of best evidence in routine practice requires, first, construction of an explicit representation of causal relationships of new knowledge necessary for understanding of the facts and, second translation of this declarative representation into well rehearsed procedural rules that can the executed during a clinical encounter (Green & Seifert, 2005). It is the *declarative knowledge* of the task domain that includes components such as the formal definition [40]of the facts involved in causal[41] relationships necessary to evaluate preconditions that are declared relevant to a specific case. The *procedural knowledge* simply specifies the subsequent action to be taken when the preconditions are matched.

From a knowledge formalization point of view, relationships between the objects (of classes) are declarative in nature, which means that they represent a relationship between objects as facts that are related to a task (Lai, 2007). A declarative hierarchy of concepts and their factual[42] relationships facilitate the abstraction of concepts and give a structured overview of knowledge elements needed to solve problems. Declarative knowledge does not, however, tell us how to compile or implement it—for this purpose, protocols need to be developed in order to make inferences from these concepts, and that's the role of

[40] Semantic or factual knowledge, e.g. History of angioedema with previous exposure to ACEI
[41] E.g. A is caused by B. In our approach we use logical relationship "A is followed by B" to represent causal relationships. Thus A and B are first declared in the ontology.
[42] Spatial, declarative

procedural knowledge. Thus, procedural knowledge has to be modeled as actions and relationships need to be formulated between facts and actions.

When we closely examine Evidence-Based Clinical Algorithms (EBCAs), we can clearly see that there is a duality between declarative and procedural knowledge. Let us consider a distilled, task-specific heuristic that we incorporated in the treatment algorithm of CHF, which states that:

"*When ACEI cannot be tolerated due to new or worsening cough, substitute Angiotensin Receptor Blocker (ARB) for Angiotensin-Converting Enzyme Inhibitor (ACEI)*"

We can easily identify declarative and procedural knowledge components in this statement. The declarative knowledge component includes 'intolerance to ACEI result in new or worsening cough', while the procedural knowledge statement is 'if intolerance to ACEI due to new or worsening cough than substitute ARB for ACEI'. The precondition that needs to be evaluated here is intolerance to ACEI.

When dealing with comorbidities, consider a statement;

"In AF patients who are asymptomatic with a left ventricular ejection fraction less than 40%, beta blocker, digoxin or a combination may be considered for control of ventricular rate"

In this case the declarative knowledge components include; 'atrial fibrillation which is asymptomatic' and 'heart failure with left ventricular ejection fraction less than 40%', the two preconditions to be evaluated by a procedural rule. Thus, the procedural knowledge statement is; 'If patient has asymptomatic atrial fibrillation and heart failure with left ventricular ejection fraction less than 40%, then consider therapy with beta blocker, digoxin or combination of two'.

We would like to point out that current clinical applications that take the procedural knowledge approach are not designed to support new knowledge[43] and the causal relationships that emerge, especially when it comes to management of concurrent

[43] I.e. Episodic knowledge, which is also a kind of declarative knowledge and is the main result of the execution of the procedural knowledge.

illnesses. When dealing with comorbidities, the execution of the rules[44] (dependencies between the tasks or processes) cannot take place in isolation of a single disease domain but rather must be executed in the presence of rules governing the behavior of the comorbid diseases. Therefore, in comorbid scenarios the newly acquired rules (newly acquired dependencies between the tasks or processes as a result of comorbid alignment) will have to interact with existing rules (dependencies between the tasks or processes with respect to single diseases) and may need to develop new rule associations. Therefore, we conclude that for handling comorbidities one type of medical knowledge may not suffice, rather knowledge conceptualization will need to identify both declarative and procedural knowledge, and their interrelationships.

Thus, during the conceptualization phase of this research, we explicitly stated the main concepts and relationships between them, and their restrictions, in order to outline the dependencies between interventions and corresponding care paths that can be represented as an OWL ontology.

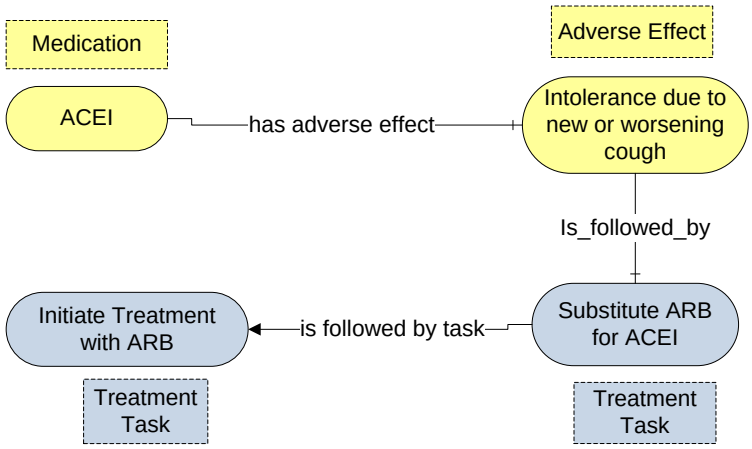

Figure 13: Conceptualization of a task-specific heuristic using declarative and procedural relationships

An example of conceptualization of CP knowledge is as follows, the task-specific heuristic "*When Angiotensin-Converting Enzyme Inhibitor (ACEI) cannot be tolerated due to new or worsening cough, substitute Angiotensin Receptor Blocker (ARB) for*

[44] Dependencies between the tasks or processes can be seen as some general rules that should always hold in a guideline. Any task in the model can be performed by a user if and only if none of the specified rules is violated. Rules constraint the model (Mulyar, N., Pesic, M., van der Aalst, W. and Peleg, M 2008)

ACEI" is conceptualized as shown in Fig. 13; Here the relationship 'has adverse effect' is a declarative (factual) relationship between two objects, which are 'ACEI' (Medication) and 'intolerance due or new or worsening cough' (Adverse Effect), the relationship 'is followed by' is a procedural relationship between a fact 'ACEI has adverse effect intolerance due to new or worsening cough' and an action 'Substitute ARB for ACEI', and 'is followed by task' is a temporal relationship depicting dependency between the actions.

The knowledge conceptualization process involved the explicit statement of primary concepts in CPs, their relationships and constraints on the relationships and it provided a vocabulary to represent the domain (Guarino, 1998).

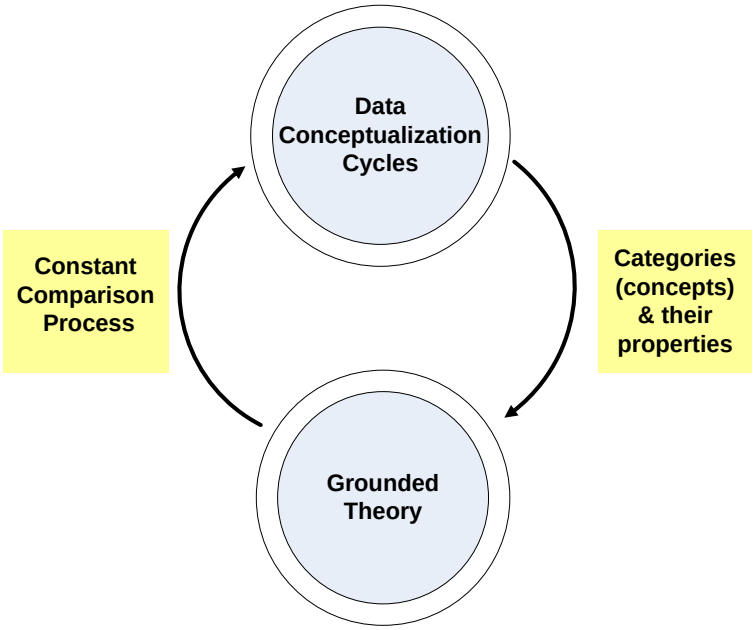

Figure 14: Concepts and Properties Generation by Constant Comparison Process using Grounded Theory

This was achieved by using Grounded Theory (Glaser, 2002), in particular a, constant comparison process for analyzing the data as seen in Fig. 14. Grounded Theory can be defined as the process for the discovery of theory from data that is systematically gathered and analyzed (Glaser, 2002). Grounded Theory is used as a research method in qualitative interpretive researches where the generation of theory is the intended goal (Mavetera & Kroeze, 2009). Grounded Theory has been successfully applied in Information Systems research to elicit concepts from rich textual data (Lamp & Milton,

2007). In order to achieve an agreed upon model (theory), we need to establish agreement about concepts that enable us to interpret the categories in such a way that they in fact represent what they are assumed to represent (Recker, 2005).

Grounded Theory offers constant comparison process (a technique for analyzing data) to generate conceptualizations from data into integrated patterns, which are denoted by categories (objects) and their properties (relationships) (Glaser, 2002). Grounded Theory suggests that the categories and the relationships are concepts that are identified by the researcher and evolve from constant comparing of data. The data analysis process of Grounded Theory can be used as one of the key methods for the conceptualization of the domain as a part of ontological analysis.

The identification of concepts and relationships was particularly relevant given that we needed to develop an ontology that would encapsulate the knowledge distilled from the guidelines. By using Grounded Theory we identified the concepts and evolved them through a constant process of comparing them with the data based on three types of coding: (a) *Open Coding* allows us to assign data to categories; (b) *Theoretical Coding* allows us to identify the relationships between the categories; and (c) *Selective Coding* ensured that all available data are associated with an emerging category and that core categories are identified to support the conceptualization of the theoretical framework. By iteratively going over the knowledge sources, we identified all the relevant concepts and their relationships, such that a theoretical saturation was achieved whereby no new categories or properties could be further identified (Lamp & Milton, 2007).

In our work a concept denotes a pattern that is cautiously discovered by the constant comparing of clinical terms (or data) in the pathway document. This pattern is then titled using a word that best captures the overall semantics of either the concept or the relationship. This is an iterative refinement process. The validity of the conceptualization process is realized, following much fitting of words, when the selected one best represents the pattern. The conceptualization will then be as valid as it will be grounded (Glaser, 2002).The conceptualization phase of the ontology engineering process requires clarification of a number of issues related to entities and their relationships. For example, whether an entity in question is an object that is persistent in time, such as, medication,

medication dose, diagnostic test, sign and symptom or whether it is a process or an action that unfolds over time, such as a diagnostic process, which includes sequential tasks such as history taking, physical exam and evaluation of test results and so on. Other considerations regarding entities include determining if a term denotes a class or an instance of class. For example, Angiotensin-Converting Enzyme Inhibitor (ACEI), Angiotensin Receptor Blocker (ARB), beta blockers and diuretics are instances of class Medication. Subsumed relationships between entities, such as sub-class and super-class relationships are also determined, for example, Diagnostic-Task is a sub-class of class Task. The conceptualization process also includes identification of unifying relationships that bind instances of an entity together to give a unique identity to an entity. For example, all instances that have a relationship called *has dose* are instances of entity treatment. Restrictions on the relationships, such as cardinality[45] constraints, and value[46]constraints, were also explicitly stated during the conceptualization phase. This process requires a multidisciplinary collaboration between the clinical and knowledge engineering disciplines (Cure, 2003).

In conclusion, we would like to point out that the knowledge conceptualization phase is a necessary step for the clarification of domain and that it requires a multidisciplinary collaboration between the clinical and knowledge engineering disciplines (Cure, 2003). Once the conceptualization of the domain is achieved the next step is to represent this conceptualization formally as ontology.

[45] Puts constraints on the number of values a property (relationship) can take, in context of a particular class description.
[46] Puts constraints on the range (range classes) of a property (relationship) can take when applied to a particular class description.

6.3. KNOWLEDGE REPRESENTATION: ONTOLOGY ENGINEERING

This phase of our research involved development/engineering[47] of an ontological model representing the comorbid Clinical Practice (CP) knowledge conceptualized in the previous phase. The key feature of the ontological model is that it exhibits constructs that are necessary for the alignment of the comorbidity CPs, depending on whether a patient has concurrent illness or not. This chapter describes the salient features of our CP ontology and its development process in order to capture all necessary concepts and strategies towards CP alignment. The ontology is built in OWL using the ontology editor Protégé.

6.3.1. ONTOLOGY EDITOR

We used Protégé 2000 as an ontology editor (also called Protégé knowledge acquisition tool) with Web Ontology Language (OWL) as the underlying representation language (Protégé Overview, n.d). Protégé has been developed by the Stanford Center for Biomedical Informatics Research at Stanford University School of Medicine. The architecture of Protégé consists of a "model" component and a "view" component (Knublauch, Fergerson, Noy & Musen, 2004). The model component is a simple and flexible metamodel[48] that can represent ontologies consisting of classes, properties, restrictions on properties and individuals. The view component of Protégé comprises the user interface with tabs (Knublauch, Fergerson, Noy & Musen, 2004). Protégé OWL uses 'Class', and 'Property[49]', tabs to create class hierarchy and the relationships between the classes, respectively. The property tab allows creation of a data type (a property that links an individual of a class to an eXtensibel Markup Language (XML) schema datatype [50]value or an RDF literal[51]), object (a property that links an individual[52] of one class to an

[47] There are two most essential features of an ontology. (1) Vocabulary, which includes terms of classes and relationships that are achieved during the knowledge conceptualization phase. (2) Definition of these terms and relationships that must be specified using a formal language, e.g., OWL (Web Ontology Language). The advantage of this formal definition is that it allows a machine to perform reasoning.
[48] Protégé metamodel itself is a Protégé ontology, with classes representing classes, properties representing properties and individuals representing individuals.
[49] Properties are binary relations on two individuals, i.e., they link two individuals together.
[50] String, Boolean, decimal, float, date, time, dateTime, gYearMonth, gYear, duration. These datatypes are used to validate element content and attribute value.

individual to another class) or annotation[53] properties (a property that is used to add information to classes, individuals or object/datatype properties, such as rdfs:label) and their sub-properties. In OWL properties are used to create restrictions, which are used to restrict the number of individuals that belong to a class. Thus, in accordance with the facilities provided in OWL, Protégé uses specific tabs to enrich the semantics of the relations through OWL property characteristics and, quantifier[54], cardinality[55] and hasValue[56] restrictions. Protégé also contains an 'Individual' tab that enables the acquisition of the knowledge of the domain in the form of instances[57] of the classes. Thus, once created, an ontology and its instances constitute a domain knowledge base. Since Protégé integrates an ontology editor and knowledge acquisition tools in a single application, it is convenient to use it for knowledge modeling purposes. It allows the exploitation of OWL reasoning capabilities through a number of descriptive logic classifiers [58]such as RACER, FaCT++ and Pellet (which we used to reason over our ontology). Given the complexity of conceptualizations of CHF and AF domains, there is a huge amount of knowledge to be built into a knowledge base. The Protégé interface is intuitive to work with and, given our previous experiences with Protégé, we believe it to be the right tool for this research.

6.3.2. ONTOLOGY ENGINEERING APPROACH

The main goal of the ontology engineering process is to develop a valid and well-representative knowledge base, which is able to incorporate the necessary semantic

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[51] There are two types of RDF literals: Plain and Datatype literals. Plain Literal is a sub-class of RDF literal that can take 1 or 2 parameters, i.e. String (the actual information contained in the literal) and Language (i.e. the language of this literal. This uses the XML:Lang attribute). Datatype literal uses datatype (by default it is XML:String) of the literal in addition to the information and language.
[52] Individuals represent objects in the domain we are interested in.
[53] Object or datatype properties can be marked as annotation property.
[54] There are two types of Quantifiers. Existential Quantifier that can be read as *at least one* or *some* (someValuesFrom in OWL), and Universal Quantifier that can be read as only (allValuesFrom in OWL).
[55] Constraints on the number of values a property (relationship) can take, in context of a particular class description
[56] Describes the set of individuals that have at least one relationship along a specified property to a specific individual
[57] Individuals are also known as instances. Individuals can be referred to as being 'instances of classes.
[58] Reasoners are also known as classifiers. DL Classifiers such as Pellet, FaCT++ or RACER are used for reasoning of an ontology, i.e. to check class consistency and taxonomy for the defined concepts. These automatically reason over the properties of the classes to classify the ontology and check inconsistencies. They check for any unexpected or implied relationships. The task of computing inferred hierarchy is also called 'classifying the ontology'.

relationships identified in the CPs of comorbid diseases, and is both scalable and stable to allow the incorporation of new knowledge (Mostowfi, & Fotouhi, 2006). Moreover, if the ontology is scalable and stable, it is feasible to make necessary changes in the model to reflect any revisions in the guidelines that may arise when new evidence becomes available. Another goal for this exercise was to construct a model that is logically consistent, which means that it is devoid of redundancies and contraindications (Uschold & Gruninger, 1996).

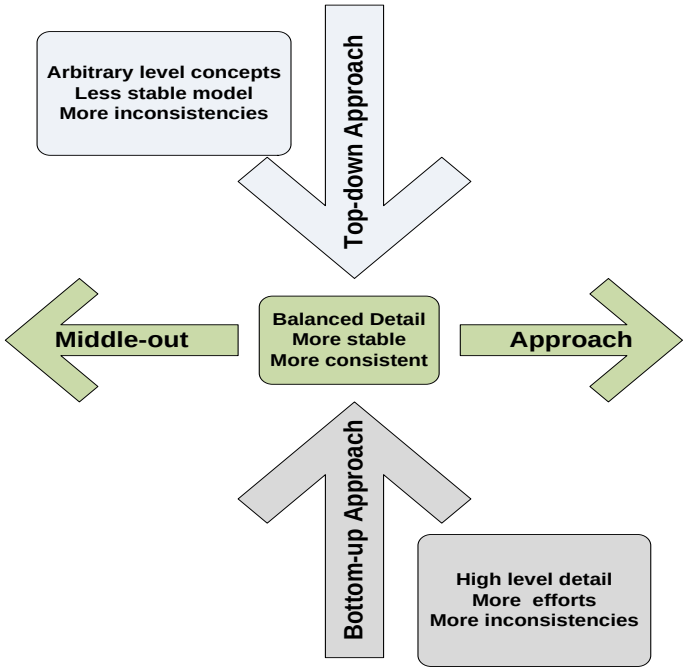


Figure 15: Approaches to Ontology Engineering

To reduce the risk consistency of the model and ensure its stability, we have adopted a "middle out" approach (Fig. 15) towards ontology engineering (Uschold & Gruninger, 1996). This approach provides a good balance in terms of level of detail. In this approach, the ontology-engineering process starts with specifying the most fundamental (or basic) terms in the domain before moving on to more abstract (or general) terms and more specific terms (Uschold & Gruninger, 1996). For example "Investigation" can be regarded as a basic term. Then, "Diagnostic Concept" is a generalization and "Chest X-ray" is a specialization. Thus, detail in the description (generalizations or specializations) of basic terms arises only as necessary.

The higher level concepts (e.g. Diagnostic Concept) in the domain are defined in terms of basic concepts (Investigation). As a result the higher level categories arise naturally. Identifying the most important concepts in a domain is associated with a shared understanding of the most important objects in a domain. Such a model is more likely to be stable and consistent and built with well grounded structure. Given the complexity of the domain, ontology engineering constructs[59] offered by the OWL DL language were applied with utmost care to avert logical inconsistency as much as possible. Single-valued [60]relations are used only when and where it is absolutely essential. Disjoint[61] constraints between classes in the ontology and cardinality[62] and value[63] restrictions on the properties are used with utmost consideration.

6.3.3. STRUCTURE OF ONTOLOGY

This section provides a detailed description of the structure of the ontology. For the purpose of clarity, class names will be written in uppercase letters with words joined using underscore. The properties (relationship between the classes) will be in lower case letters, *italicized* and the words joined by underscore. The Individuals (instances) will be capitalized. Any restrictions on the properties will be written in lower case letters and will not be italicized.

6.3.3.1. HIGHER LEVEL ONTOLOGICAL STRUCTURE

The main concepts extracted from the CPs during the knowledge conceptualization phase are represented in the ontology as a hierarchy of nine (9) highest level classes with subclasses progressively arranged at various lower levels of the hierarchy. A class in the ontology can have a number of sub-classes but only one super-class, thus exhibiting a

[59] OWL constructs such as Equality, InEquality, Property Restrictions, Property Characteristics, Cardinality Restrictions, Class Intersection, Datatypes, Boolean Combination of class expressions.
[60] A functional property, i.e., if a property is functional, for a given individual, there can be at most one individual that is related to the individual via the property.
[61] A disjoint constructor guarantee that an individual that is a member of one class cannot simultaneously be an instance of another class. OWL classes 'overlap' until they have been stated to be disjoint from each other. If certain classes are not disjoint from each other then unexpected results can arise. Accordingly, if certain classes have been incorrectly made disjoint from each other then this can also give rise to unexpected results.
[62] Constraints on the number of values a property (relationship) can take, in context of a particular class description
[63] allValuesFrom (Universal restrictions), someValuesFrom (Existential restriction). These are the local range restrictions stated on a property with respect to a class.

tree like structure. This super-class - sub-class relationship is an ‘is-a’ relationship. Each class at the top level of the hierarchy is given property (ies) that are common to all sub-classes at all lower levels of this hierarchy. However, it is possible that a sub-class of a particular class will have one or more properties that will be assigned to this particular sub-class only, in accordance with requirements in the domain, and these will be shared by its own sub-classes at lower level.

The top-level classes include (Fig. 16); PATIENT, CLINICAL_PATHWAY_ENTRY_POINT, DIAGNOSTIC_CONCEPT, MEDICATION, TASK, TREATMENT_CONSTRAINT, DECISION_OPTION, TEMPORAL_CONCEPT, and STATUS.

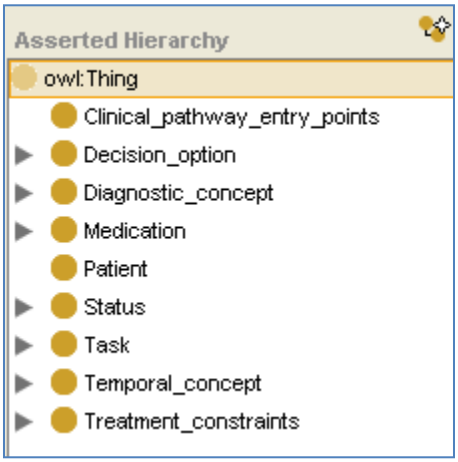


Figure 16: Top-level classes in ontology

PATIENT refers to individual patients who enter the system.

CLINICAL_PATHWAY_ENTRY_POINT refers to points in the course of the clinical pathways where a patient depending on his/her current clinical status may enter the pathway. Thus, given the complexity of the domain especially with respect to concurrent illnesses, and the fact that the workflow is long and composite, provision of multiple entry points enhances the flexibility of the application.

DIAGNOSTIC_CONCEPT refers to all the concepts related to diagnosis of CHF or AF, such as history, physical exam and tests results.

MEDICATION refers to all the medication groups involved in the treatment of CHF or/and AF, such as ACEI, BB, Diuretics, calcium channel blockers, thrombopropylaxis and digoxin.

TASK refers to all the diagnostic and therapeutic tasks that are to be performed during the execution of the CHF or/and AF pathways. These may be decision making tasks, whereby each subsequent step depends on the decision option chosen by the user, or non-decision making tasks i.e., when workflow in the pathways continues from one step to another, in sequential manner, or when tasks are executed concurrently.

TREATMENT_CONSTRAINT refers to the different kinds of constraints on the treatment of CHF or/and AF. These include, for example; identifying treatment contraindications, medication dosage, uptitration schedules and treatment monitoring.

DECISION_OPTION refers to all the decision points in the CHF and AF clinical pathways.

TEMPORAL_CONCEPT is used to represent all time annotations in the domain, for example; wait interval between two tasks or the frequency of certain actions.

STATUS refers to current clinical status of the patient.

These classes are related to one another through properties. Since OWL DL is a semantically rich formalism, the logical relations contained in the procedural rules in the pathways identified during the knowledge conceptualization exercise can be represented in the ontological form using an OWL language feature called object[64] property (Fig. 19). Object property offers the right behavior to represent task dependencies since it binds two individuals. In addition to the object type properties, some of the classes also exhibit data type properties when necessary. Furthermore, most classes also have data type properties that have RDF literals[65], such as plain textual strings[66], as property value[67]. These textual

[64] Object property link an individual to an individual.

[65] A literal is a representation of value (e.g. string value) in a source code (e.g. RDF). There are two types of RDF literals: Plain and Datatype literals. Plain Literal is a sub-class of RDF literal that can take 1 or 2 parameters, i.e. String (the actual information contained in the literal) and Language (i.e. the language of this literal. This uses the XML:Lang attribute). Datatype literal uses datatype (by default it is XML:String) of the literal in addition to the information and language.

strings include recommendations from the CPGs along with class and level of evidence to support the appropriate tasks performed at certain times. In some cases, these properties contain detailed information from the CPGs and other credible sources related to various individuals (instances) of classes to clarify the domain and provide additional relevant knowledge to the users so that they can make a more informed choice from the given options. In such cases, the sources/references for any such textual entry is always provided along with the main text.

The resulting ontology incorporates both declarative and procedural knowledge. Although many researchers favor use of declarative knowledge as the sole foundation of ontological formalization of a domain, such an approach has been unsuccessful in generating human-like logical processing for computers (Lu, Wu, Wu, Chio & Hsu, 2005). As a result we have constructed our ontology based on both declarative and procedural approaches. We believe that the main advantage of such an approach is that the resulting model is more compact and the resultant guideline knowledge representation is therefore more intuitive and insightful.

The ontology is designed as a care flow model, whereby it models the patient's induction into the care flow and his/her transition through various stages of diagnosis and treatment depending on whether he/she has a single disease or comorbidity. The care flow is maintained through a series of properties (discussed in the subsequent section) that relate these main classes and sub-classes.

6.3.3.2. HIGHER LEVEL RELATIONSHIPS

Class PATIENT is related to class CLINICAL_PATHWAY_ENTRY_POINT through an object property called *has_pathway_entry_point*, so that PATIENT is its domain and CLINICAL_ PATHWAY_ ENTRY_POINT is its range. In addition, class PATIENT also has the datatype properties, *has_name, has_address, has_date_of_birth* and *has_telephone_number* to obtain personal and demographic information about the patient. The range for *has_name* and *has_address* is string; for *has_date_of_birth* is date, and for *has_telephone_number* is integer. All these properties are declared functional.

[66] a string is, essentially, a sequence of characters (it is plain text in this case)
[67] Value (i.e. plain textual string (recommendations written in English) held by the data type properties)

This means that each of them can only have a unique value for each instance of class patient.

The class CLINICAL_PATHWAY_ENTRY_POINT is related to class TASK through an object property *has_task*. The *has_task* property has a minimum cardinality of >= 1, since every entry point in the pathway has at least one task to be performed.

The class TASK has a datatype property called *has_description* with plain textual strings as its property value. This property is included to provide the clinician the evidence from the CPGs that has been used to execute a particular task in a particular sequence. TASK has two man sub-classes; DECISION_MAKING _TASK or NON_DECISION_MAKING_TASK.

The class DECISION_MAKING _TASK is related to class DECISION_OPTION through object property *has_decsion_option* (Fig. 17). Class NON_DECISION_MAKING_TASK is related to the class TASK through the property *is_followed_by*, which represent the sequential execution of the tasks.

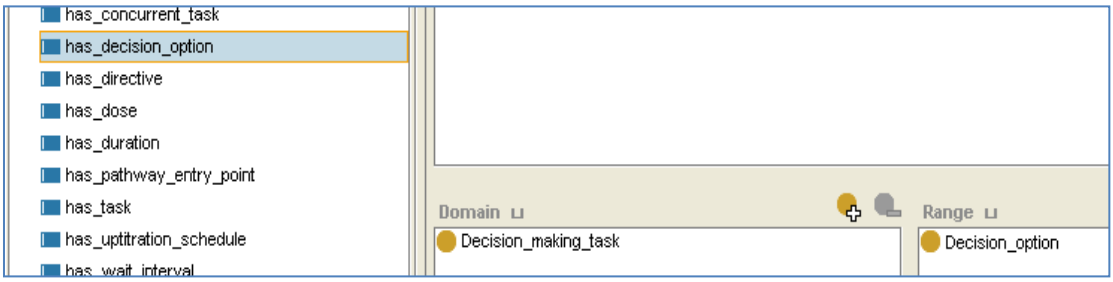


Figure 17: Object properties. Note domain and range of *has_decision_option* property

Here, it is important to note that while building this ontology we conceptualized objects on the basis of commonality of concepts and properties. However, as we built this hierarchy, additional properties were assigned specifically to concepts further down the hierarchy, as certain relations are only valid at a more specific level. Thus, a sub-class will inherit the property of its super-class, but at the same time it might have its own specific property that will be inherited by its sub-class further down the hierarchy. This is in accordance with the middle-out approach to ontology engineering that we have adopted for this phase of our methodology.

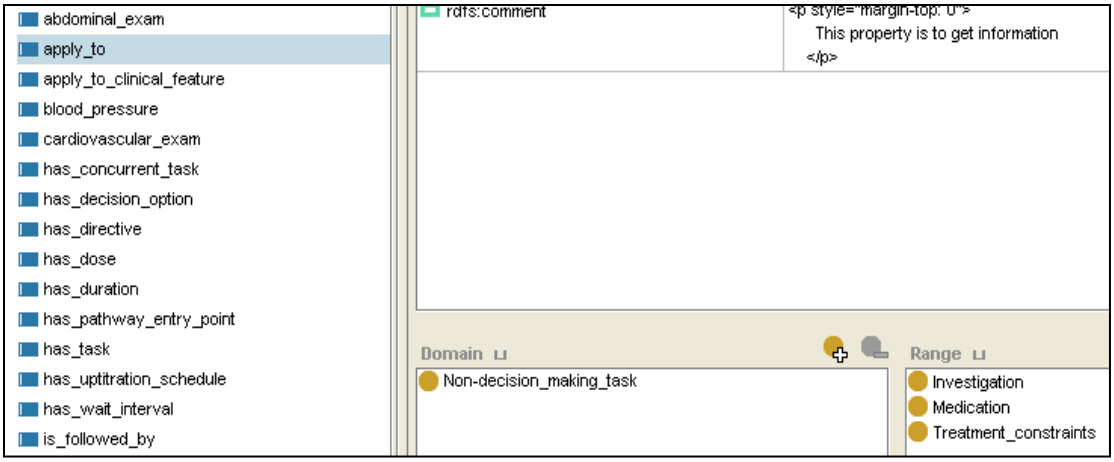


Figure 18: Object properties. Note the domain and multiple ranges for *appy_to* property

Class NON_DECISION_MAKING_TASK is related to class MEDICATION by an object property *apply_to* (Fig. 18). The property *apply_to* also relates this class to TREATMENT_ CONSTRAINT (Fig.18).

The class MEDICATION is related to the class MEDICATION_ DOSE_UPTITRATION via property *has_uptitration_schedule,* which in turn has a *has_dose* relation with the class MEDICATION_DOSE (Fig. 19). Both of these are themselves sub-classes of the class TREATMENT_CONSTRAINT. The properties *has_task, apply_to, is_followed_by, has_uptitration_schedule, has_dose* and *has_decision_option* have been given an existential quantifier (someValuesFrom) restriction (Fig. 19), which can be read as, the properties being able to have at least one value from or some values from the filler class.

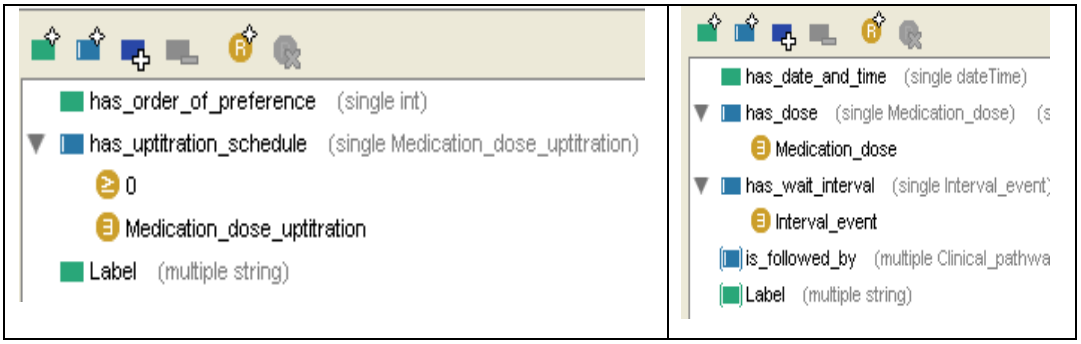


Figure 19: *has_uptitration_schedule* and *has_dose* properties relating classes MEDICATION, MEDICATION_DOSE_UPTITRATION & DOSE. Also see someValuesFrom restriction for these properties.

For example, for an object (TASK) to be a DECISION_MAKING_TASK, it is necessary for it to have at least one *has_decision_option* relationship with the class DECISION_OPTION. Thus, class DECISION_MAKING_TASK is a sub-class of all the things that have at least one DECISION_OPTION (Fig. 20).

As mentioned above, the logical relations contained in the procedural rules in the pathways identified during the knowledge conceptualization exercise can be represented in the ontological form using OWL object properties. The properties *has_pathway_entry_point*, *is_followed_by* and *has_decision_option*, in particular, are used for the purpose of capturing procedural rules in the pathways. The property *is_followed_by* denotes a sequential relationship between objects such as two TASKS, or DECISION_OPTION and a TASK, or a TREATMENT_CONSTRAINT and a TASK or, a TASK and a PATHWAY_ ENTRY_POINT, whereby a task is followed by a task, or another entry point in the pathway and a treatment constraint such as a contraindication to a treatment can also be followed by another task such as referral to the specialist. Similarly, the property *has_decision_option* (Fig. 20) controls the procedural branching statements expressing the decision logic in the pathways. The subsequent step in the ontological flow depends on the individual of class DECISION_OPTION that has been chosen by the user. This procedural rule is formalized as *is_followed_by* relationship between DECISION_OPTION and class TASK that is regarded as the range for this property.

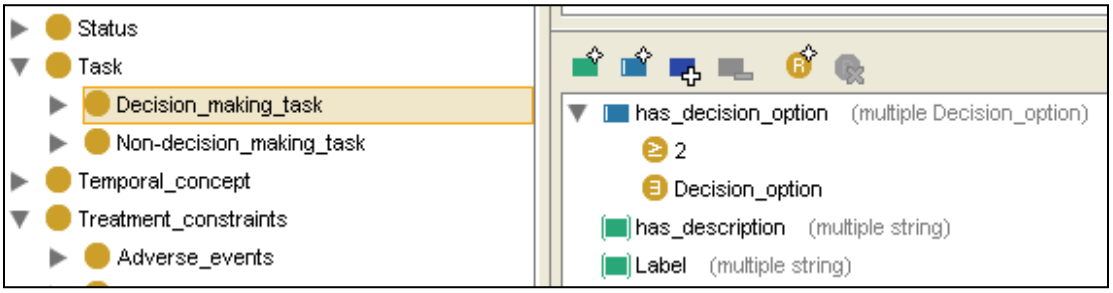


Figure 20: Domain, Range & Restrictions applied to the property *has_decision_option*

These top-level classes and their properties, and the constraint on properties, form the backbone of this extensive ontology. We believe that interpretation and representation of the hierarchy of the taxonomy in any ontology is an important modeling decision that

affects the usefulness of the ontology. Most of these classes have sub-classes related to them by the hierarchical is-a relationship, which, depending on the requirements of the domain, may or may not have their own sub-classes further down. This subsumption[68] hierarchy of classes may last up till six levels of hierarchy, resulting in over 80 classes in all. This is the basic ontological framework that is used to instantiate clinical pathways of both the comorbidities of CHF and AF.

6.3.3.3. SUPER-CLASS – SUB-CLASS HIERARCHY

Once the basic ontological model was established, the next step was to arrange the constituent concepts through a process of progressive decomposition whereby more general concepts are decomposed into more specific concepts to form a hierarchy of concepts. There are two main advantages of this approach: (i) accumulation of concepts as super-class - sub-class hierarchy helps to organize and clarify the domain concepts; (ii) more specific relationships belonging to specific sub-classes become further evident. This is extremely helpful when it comes to dealing with complex, concurrent diseases. For example, medication groups related to concurrent illness can be represented as separate sub-categories of class medication. Although all medication sub-groups may share some relationship, there are certain groups that have specific relationships that can then be clearly and unambiguously stated and formalized. This may help identification of any potential harmful events or drug interactions related to concurrent drug administration beforehand.

6.3.3.3.1. DIAGNOSTIC_CONCEPT CLASS HIERARCHY

The class DIAGNOSTIC_CONCEPT is regarded as an abstract, more generic category that subsumes more specific categories that include: CLINICAL_ASSESSMENT, PHYSICAL_EXAM, INVESTIGATION and INVESTIGATION_FINDING. These sub-classes are then decomposed into even more specific sub-classes denoting even more specific concrete concepts such as SYMPTOM, ABDOMINAL_EXAM, JVP_EXAM, PULSE_RATE, and CHEST_X-RAY_FINDING as shown in figure 21. These declarative knowledge building blocks collect the factual knowledge of the domain.

[68] Subsumption hierarchy expresses subsumption relations (sub-, super-class) between the concepts.

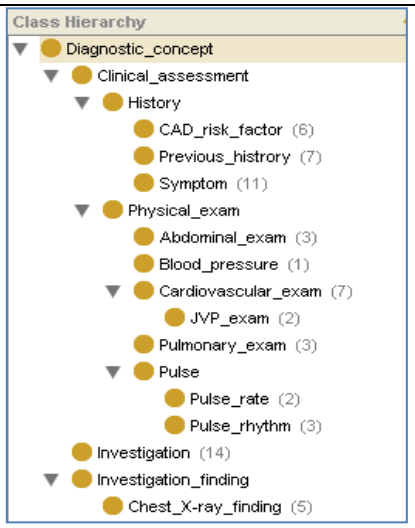


Figure 21: DIAGNOSTIC_CONCEPT class hierarchy

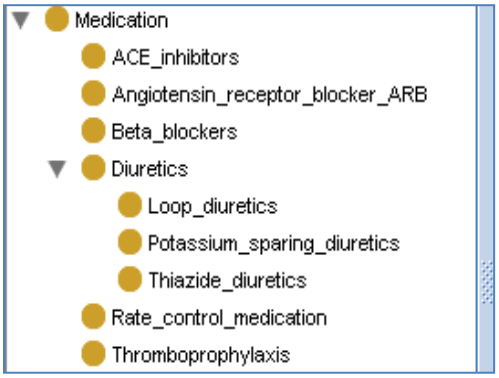


Figure 22: MEDICATION class hierarchy

6.3.3.3.2. MEDICATION CLASS HIERARCHY

The class MEDICATION has sub-classes (Fig. 22) corresponding to all the medication groups involved in the treatment of comorbid CHF and AF. Here it is important to realize that the ontology is stable enough to add more sub-classes corresponding to other medication groups involved in the treatment of other concurrent illnesses. Such additions can easily be accommodated within this framework without the need to alter any of the relationships between the classes.

6.3.3.3.3. TREATMENT_CONSTRAINT CLASS HIERARCHY

As mentioned earlier, class MEDICATION has *has_uptitration_schedule* relationships with classes MEDICATION_DOSE_UPTITRATION, which in turn has *has_dose* relation with class MEDICATION_DOSE. These two classes are sub-classes of class TREATMENT_ CONSTRAINT (Fig. 23).

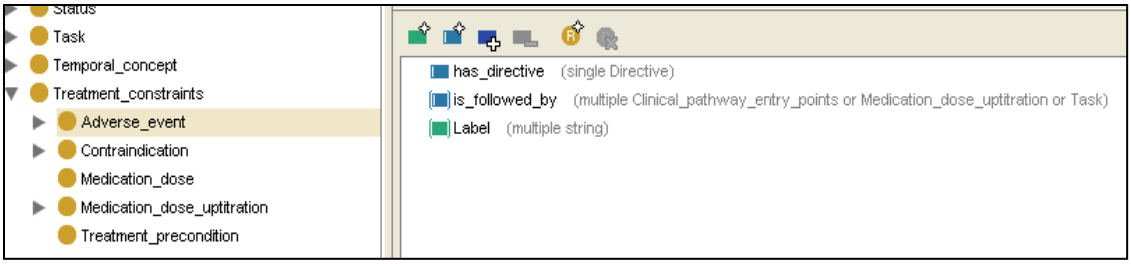


Figure 23: TREATMENT_CONTRAINT class hierarchy with Properties for sub-class ADVERSE_EVENT

As mentioned earlier, TREATMENT_CONSTRAINT represents all the constraints on the treatment and includes five main sub-classes (Fig. 23); These are ADVERSE_EVENT, which represents all the adverse events that may be caused by any kind of treatment, CONTRAINDICATION, which represents any contraindication to any treatment, MEDICATION_DOSE, which represents the dose of the medication, MEDICATION_ DOSE_ UPTITRATION, which represents the uptitration schedules for various medical treatments, and TREATMENT_PRECONDITION, which corresponds to any specific preconditions to a particular treatment that are specifically outlined in the domain. For example, signs of fluid overload that is a precondition for the diuretic administration. Here it is important to note that TREATMENT-PRECONDITION does not represent all preconditions to all the actions but only preconditions to specific treatments.

The classes ADVERSE_EVENT, CONTRAINDICATION and MEDICATION_DOSE_ UPTITRATION have sub-classes as we go down the lower levels of hierarchy. These lower level sub-classes represent individual drug groups, individual drugs or individual diseases.

The class ADVERSE_EVENT has two sub-classes: SERIOUS_ADVERSE_EVENT and NON-SERIOUS_ADVERSE_EVENT. ADVERSE_EVENT has a property called *has_directive* that relates it to class DIRECTIVE, which is a sub-class of TREATMENT_TASK. Its individuals are the directives for the patient in case he/she experiences a serious or non-serious adverse event. The property *has_directive* is given a hasValue restriction (Fig. 24), since each serious adverse event will have at least one relationship along this property to a specific individual (Advise patient to have someone

take them to emergency department or call 911). Similarly each non-serious side-effect will have at least one has directive relationship with another specific individual (Advise patient to contact family physician or proceed to ED).

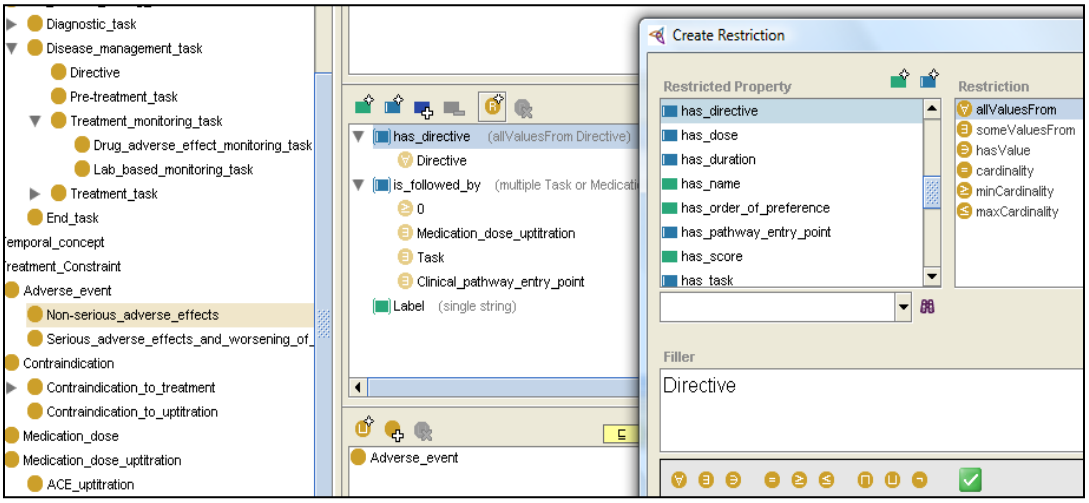


Figure 24: Property has_directive linking classes ADVERSE_EVENT and DIRECTIVE with hasValue restriction

At this point we would like to mention that, given the elaborate nature of the domain and complexity of the research problem, and for the sake of attaining clarity, explicitness and simplicity as much as possible, the instantiations[69] of the ontology by CHF and AF pathways are kept as separate files.

This does not in any way affect the basic class hierarchy, relationships between the classes or restrictions on these relationships. It can be seen in Figure 25 that the sub-classes of classes CONTRAINDICATION, MEDICATION_DOSE_UPTITRATION and TREATMENT_PRECONDITION are related to individual drugs or drug groups such as ACEI, ARB, beta blockers, digoxin, thromboprophylaxis, which are used to treat each comorbid condition. Therefore, we can add any number of treatments related to any other comorbidies, by simply adding as many drug groups as sub-classes without any risk of altering any of the class relationships.

[69] Adding instances (individuals in OWL) to the classes in the ontology. In other words adding the CP knowledge to the ontological model.

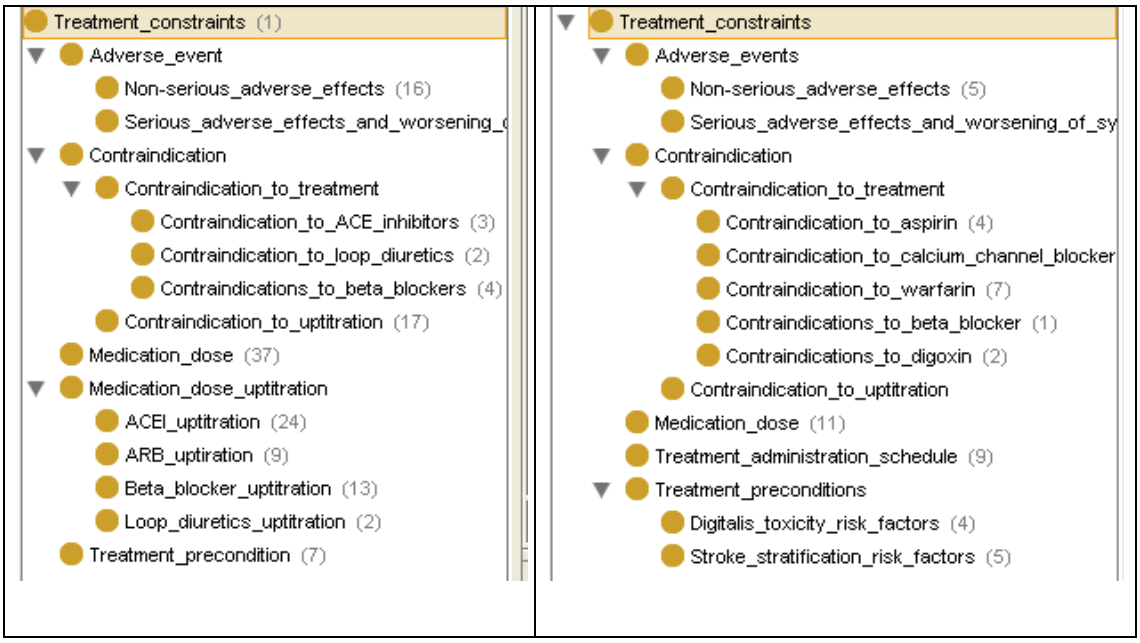


Figure 25: TREATMENT_CONSTRAINT class hierarchy for CHF and AF pathway

The class MEDICATION_DOSE_UPTITRATION is an important concept related to the drug administration for CHF, whereby medication doses are gradually increased over time to attain the maximum recommended dose. From the modeling perspective, representation of this process involves formalizing the uptitration schedules in a model (Fig. 26) so that the class MEDICATION_DOSE_UPTITRATION has relationships with several classes. These include: (i) DOSE by *has_dose* property, since each uptitration has a certain (incremented) dose; (ii) WAIT_INTERVAL by *has_wait_interval* property, since there is a specific interval before a drug can be titrated; and (iii) DECISION_MAKING_TASK by *is_followed_by* property, since after every uptitration a certain amount of monitoring has to be done. For example, whether a patient is able to tolerate a medication or not, and whether renal function and electrolytes are within normal limits or not. These monitoring tasks are represented by the class DECISION_MAKING_TASK. The next uptitration depends on the decision made at this point. This uptitration ontological model (Fig. 26) is nested within the main ontology through *has_uptitration_schedule* relationship between classes MEDICATION (domain) and MEDICATION_DOSE_UPTITRATION (range). Several independent uptitration schedules are modeled nested within the main ontology.

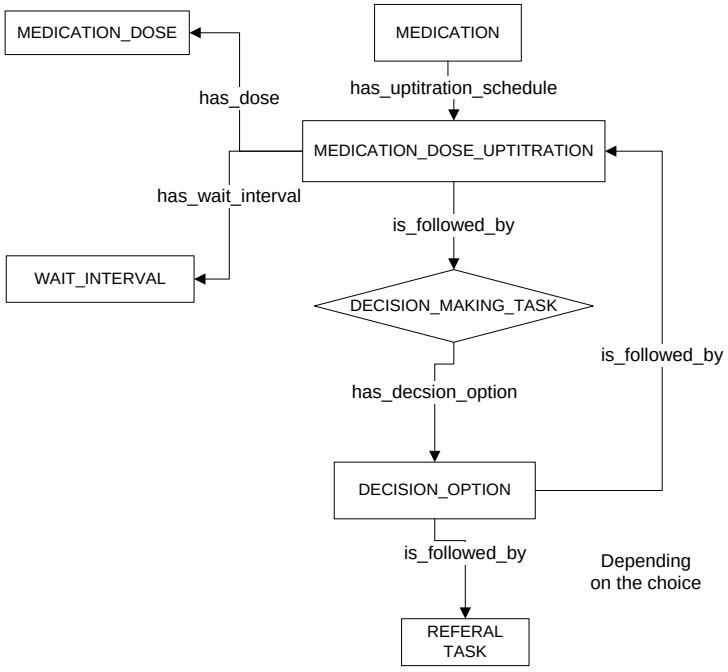


Figure 26: Classes and their property relations involve in uptitration ontology that is nested in class MEDICATION

6.3.3.3.4. TASK CLASS HIERARCHY

The class TASK has two second level sub-classes (Fig. 27); DECISION_MAKING_TASK, which represents all the decision points in the clinical workflow, and NON_DECISION_MAKING_ TASK, which refers to all the tasks which are executed sequentially or in parallel. DECISION_ MAKING_TASK is further classified as DIAGNOSTIC_DECISION_TASK (Fig. 27), which represents all the diagnostic activities where a decision had to be made before the execution of the next step and DISEASE_MANAGEMENT_DECISION_TASKS (Fig. 27), which represents all disease management activities that involve disease making. Similarly, NON_DECISION_ MAKING_ TASK is classified as DIAGNOSTIC_TASK and DISEASE_ MANAGEMENT_ TASK (Fig. 27), which represent diagnostic and management activities where no decision making is required. Thus, there is a straightforward change from one state to another state.

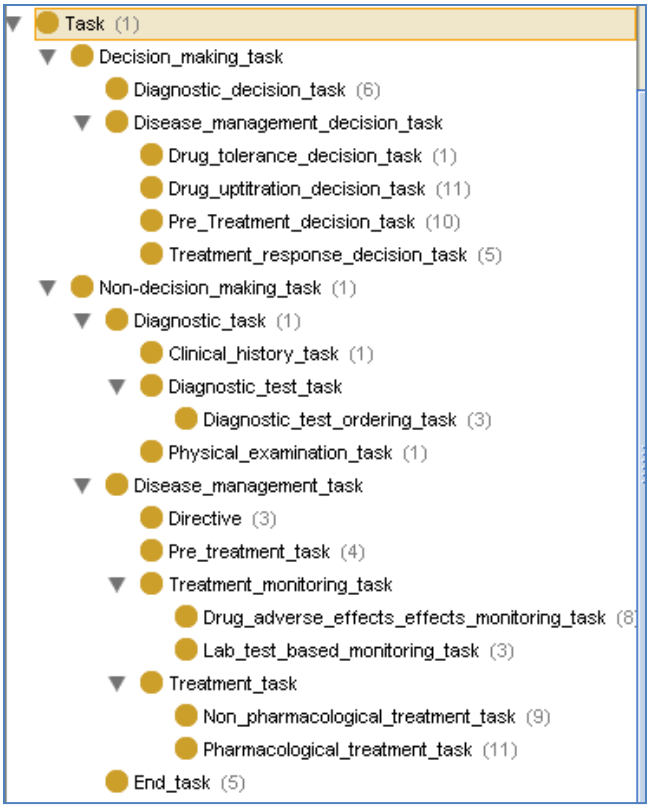


Figure 27: TASK class hierarchy

NON_DECISION_MAKING_TASK has an additional sub-class that we refer to as END_TASK, which represents all the tasks where the pathway ends, such as referrals to the specialist by the GP when management in general practice is not deemed suitable.

As can be seen in Figure 27, these sub-classes have their own sub-classes at various levels of granularity, further down the hierarchy, for the purpose of clarification and disambiguation of the domain.

The class DISEASE_MANAGEMENT_DECISION_TASK has four sub-classes (Fig. 27). PRE_TREATMENT_DECISION_TASK represents the entire set of decision making tasks to be performed before a treatment can begin, such as evaluating whether there are any contraindications to treatment or presence of electrolyte imbalance and so on. DRUG_TOLERANCE_DECISION_ TASK represents situations regarding a patient's tolerance or intolerance to certain drugs such as ACEI. DRUG_UPTITRATION _DECISION_ TASK represents all decision points related drug uptitration such as renal function and electrolyte assessment. And TREATMENT_

RESPONSE_DECISION_TASK represents all decision points related to judging the response to the treatment. For example, if symptomatic response to a particular medication such as a diuretic has been achieved or not.

The class DISEASE_MANAGEMENT_TASK also has four sub-classes (Fig. 27): DIRECTIVE represents any directive for the patient, for example, contacting physician or proceeding to emergency in case of adverse events. PRE_TREATMENT_TASK represents all activities which are to be completed before the treatment might commence. TREATMENT_ MONITORING_TASK represents monitoring patient for the occurrence of adverse drug reactions or lab based monitoring. TREATMENT_TASK represents all the tasks related to initiation or maintenance of pharmacological treatment, as well as those related to non-pharmacological management. These include advice regarding diet, compliance or medication intake.

6.3.3.3.5. DECISION_OPTION CLASS HIERARCHY

The class DECISION_OPTION has two main sub-classes (Fig. 28), DIAGNOSTIC _DECISON_OPTION and THERAPEUTIC_DECISION_OPTION, which capture all the respective instances of the diagnostic and therapeutic options available in the domain. The class DIAGNOSTIC_DECISION_OPTION has the sub-classes DIAGNOSTIC_TEST_RESULT and CLINICAL_ASSESSMENT_FINDING. In order to capture the concepts relevant to only the CHF domain, there are additional sub-classes such as CUMULATIVE_ BOSTON _CRITERIA_ SCORE and NYHA_FUNCTIONAL_CLASSIFICATION. Similarly, in the case of the AF pathways, there is STROKE_RISK_STRATIFICATION, which represents mild, moderate or high risk of stroke in an individual patient. The sub-class DIAGNOSTIC_TEST_RESULT has further sub-classes down the hierarchy; these include BLOOD_WORK_FINDING, CHEST_X-RAY_FINDING, ECG_FINDING and ECHO_FINDING. As the class names suggests, these sub-classes represent the results of specific tests identified in the domain, such as, sodium is less than 134 mEq/L, or ECG is abnormal for atrial fibrillation.

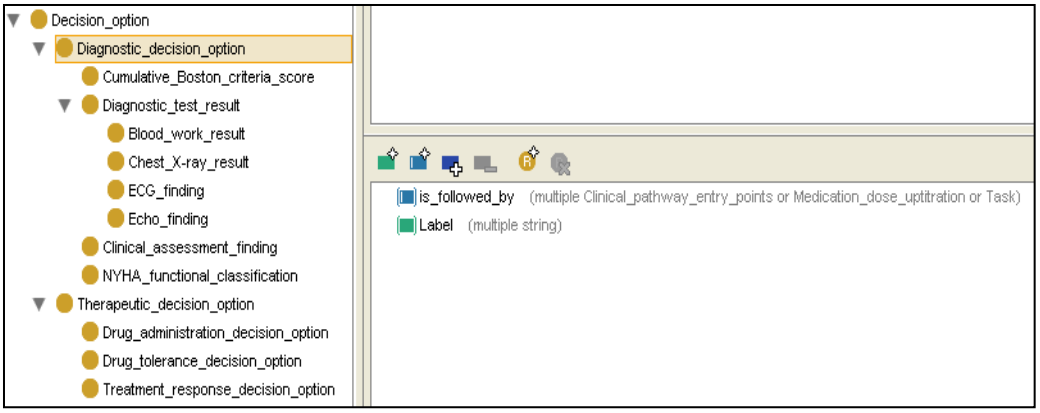


Figure 28: DIAGNOSTIC_DECISION_OPTION class hierarchy along with its properties

The class THERAPEUTIC_DECISION_OPTION has three sub-classes: DRUG_ ADMINISTRATION_DECISION_OPTION represents all the decisions relevant to the drug administration such as, whether there is any contraindication to a particular drug, or even to uptitration of a certain drug. DRUG_TOLERANCE_DECISION_OPTION represents the presence of any drug intolerance, for example, if a particular patient is intolerant to ACEI. TREATMENT_RESPONSE_DECISION_OPTION represents patient responses to a particular treatment, for example, whether acute congestion has been improved after initial loop diuretic administration.

6.3.3.3.6. TEMPORAL_CONCEPT CLASS HIERARCHY

The class TEMPORAL_CONCEPT is used to represent all time annotations[70] in the domain (Fig. 29). It has three main sub-classes: INTERVAL_EVENT, INTERVAL_DURATION and FREQUENCY_EXPRESSION. INTERVAL_EVENT represents named interval between two events, for example, wait interval between two uptitrations.

[70] Any temporal information associated with a task or a treatment, e.g. time interval between two uptitrations, or prescription of a medication say 3 times a day. (Annotation means any added information, time annotation means added information regarding time related to a task or a treatment).

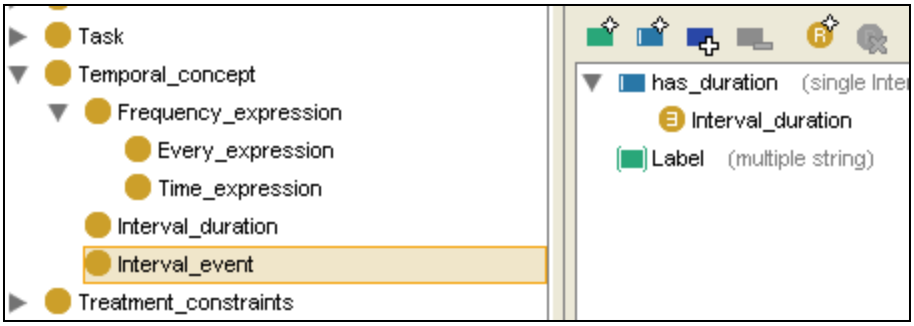


Figure 29: TEMPORAL_CLASS_HIERARCHY along with its properties

INTERVAL_DURATION represents the duration of this named interval, for example, 2 weeks. This relationship between the two classes is captured by the property *has_interval*, with class INTERVAL_EVENT as its domain and INTERVAL_DURATION as the range. The sub-class FREQUENCY_EXPRESSION is used to express the frequency of an event or action, and has two subclasses. EVERY_EXPRESSION represents time annotations with respect to frequency of any task or drug administration, for example, administration of a drug every 12 hours. TIME_EXPRESSION represents time annotation that describes a set of times for a task or a treatment, for example, follow-up is twice a month. Although, both these classes represent time frequency, EVERY_EXPRESSION represents frequency at a more fine granular level then TIME_EXPRESSION. These classes are created to represent the corresponding time annotations as they are often presented in the real medical domain.

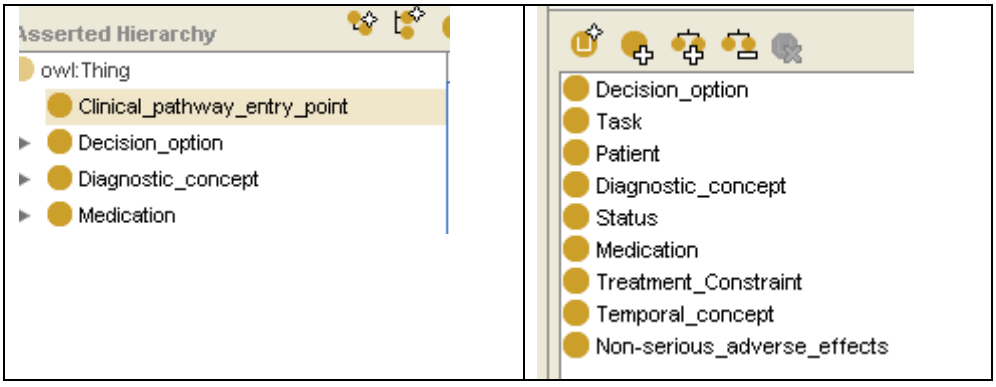


Figure 30: Class CLINICAL_PATHWAY_ENTRY_POINT disjointed with a group of classes

Finally, in order to separate a group of classes so that their individuals cannot be a member of another class in that group, we made them disjoint from one another (Fig. 30).

This is because in OWL, classes are assumed to overlap. Therefore, we cannot presume that an individual is not a member of a particular class simply because it has not been asserted to be a member of that class.

6.3.3.4. ONTOLOGY INSTANTIATION

Instantiation of an ontology involves the insertion of the domain knowledge. In order to instantiate the ontology by the CPs developed during the knowledge synthesis phase, the classes in the ontology are assigned an exhaustive list of concrete[71] concepts relevant to a particular class. These concrete concepts are abstracted from the pathways and are called 'Individuals' of a particular class (Fig. 31).

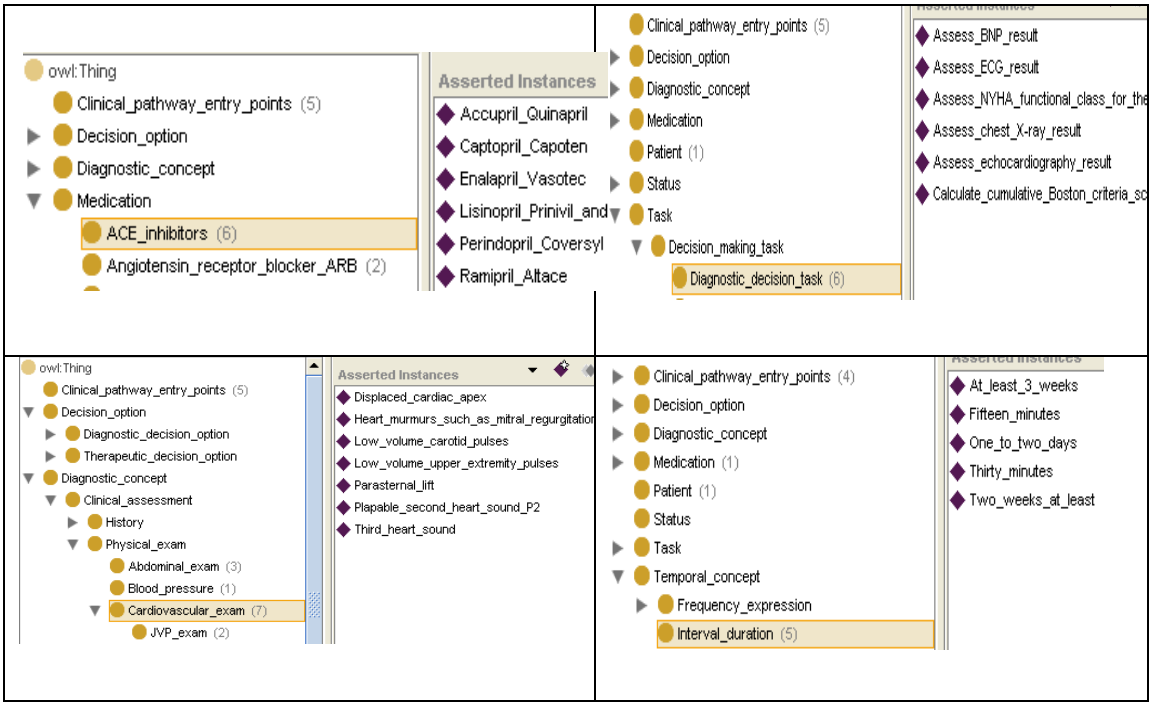


Figure 31: Classes and their individuals

For example the class CARDIOVASCULAR_EXAM has seven individuals (Fig. 29): displaced cardiac apex, heart murmurs such as mitral regurgitation murmurs, low volume carotid pulses, low volume upper extremity pulses, parasternal lift, palpable second heart sound and third heart sound. Its subclass JVP_EXAM has two individuals: (jugular

[71] Concrete concepts correspond to specific objects in the domain and are individuals (as appose to more abstract concepts, i.e., classes). For example, 'Dyspnea at rest' is a more concrete concept, because it is more specific and therefore is an individual. Diagnostic_Concept is a more abstract concept that represents 'Dyspnea at rest'.

venous pulse) Jugular Venous Pulse (JVP) elevation with more than 6cm of H_2O, and JVP elevation with more than 6cm of H_2O with peripheral pitting edema. In all, the ontology includes more than 500 individuals belonging to various classes.

Instantiating an ontology with assertions from the textual documents can be very laborious. Moreover, since we are required to analyze and extract knowledge triples from multiple source documents (comorbid CHF and AF pathways), it is inevitable that duplicated and contradictory information will be extracted. Handling such complex information proved to be extremely challenging during the instantiation of the ontology. As a result, for the sake of clarity and simplicity, the instantiation of the CHF and AF pathways were kept separately, as separate files. This instantiation approach enabled us to distinguish conflicting information, and to verify it. In addition, it also helped us manually to identify duplicate assertions in the knowledge base, so that redundancies were avoided during the modeling exercise. Since the pathways are based on evidence-based practice guidelines, evidence related to the prescribed tasks or decision points in the workflow is provided as links to graded recommendations and references (Fig. 30). For example, 'Initiate treatment with ACE inhibitors' is the individual of class PHARMOCOLOGICAL_TREATMENT_TASK and has a datatype property *has_description*, which has plain textual strings as property and is instantiated with the recommendation and grade of evidence from the CPG regarding the prescription of Angiotensin-Converting Enzyme Inhibitor (ACEI), as shown in Fig. 32.

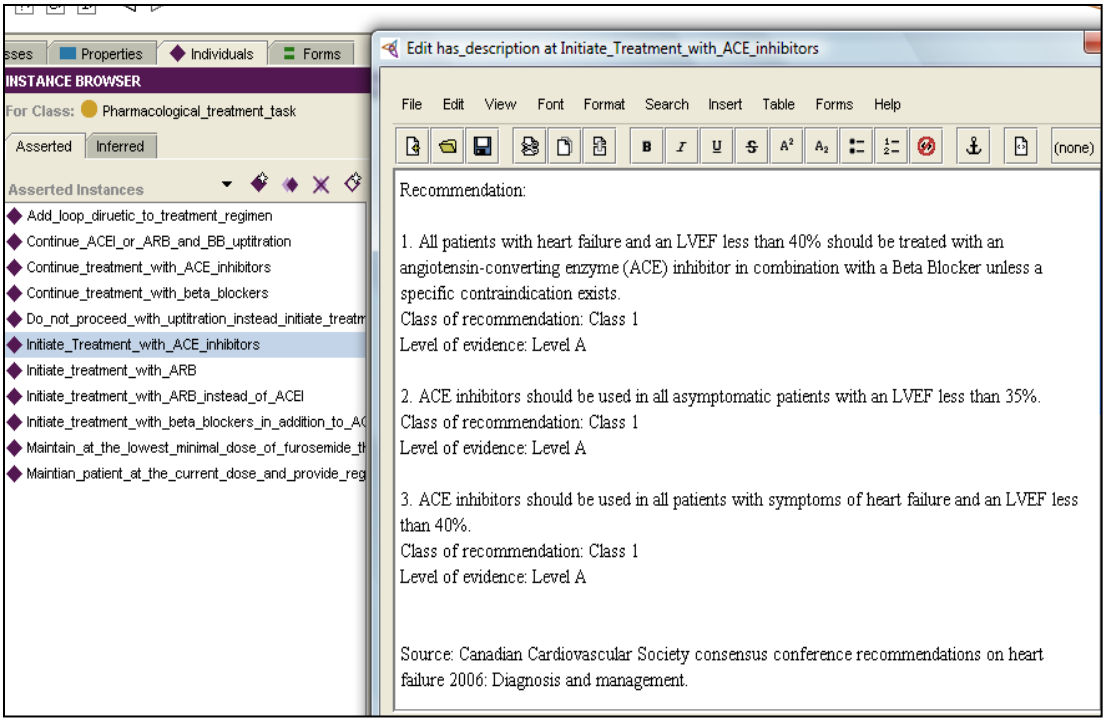


Figure 32: Recommendation from the CPG supporting a task along with class of recommendation and level of evidence

In addition to the evidence from the CPG, other task-related information that might be helpful for the GP to understand the task at hand, or to make an appropriate decision, is also provided in relation to a specific task. For example; 'Assess NYHA functional class for the patient' is an individual of class DIAGNOSTIC_DECISION_TASK. Its property *has_description* contain detailed information regarding NYHA functional classification, as shown in the Fig. 33, along with the source of this information. We believe that this information can be extremely valuable for a GP while deciding which of the NYHA classes her patient is more likely to be in, given the patient's symptoms?

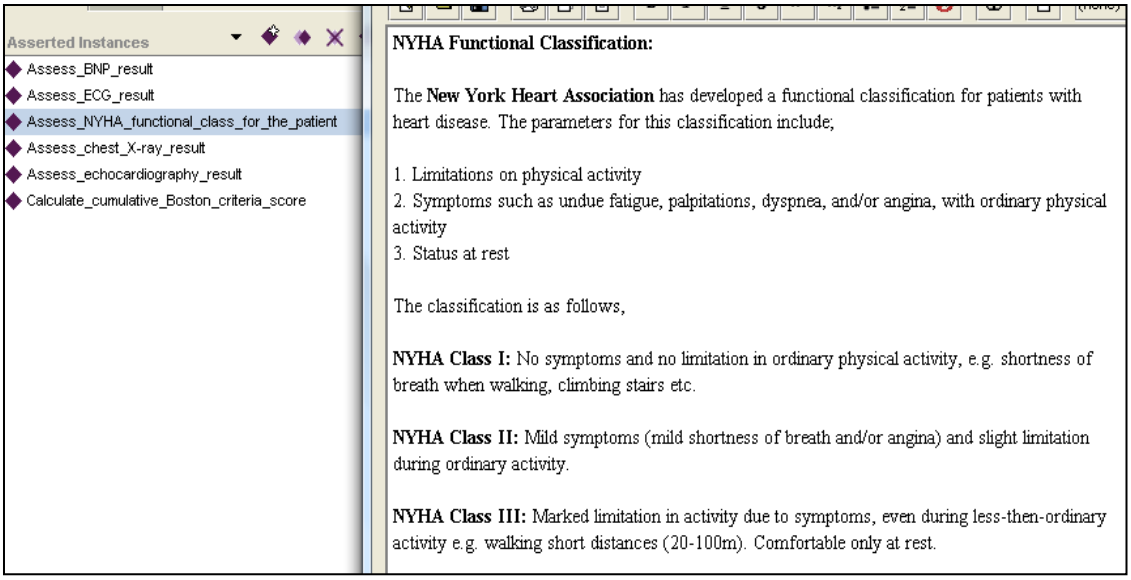


Figure 33: Description of NYHA functional classification as filler of *has_description* property of individual 'Assess NYHA functional class for the patient' of class TASK

6.4. ONTOLOGY BASED KNOWLEDGE ALIGNMENT

The requirements in handling comorbidities in a decision support and care planning framework are: (i) clinical tasks such as diagnostic tests, therapies, or examinations, are not replicated (ii) common comorbid care activities are identified, (iii) temporal relationships between the activities in the context of comorbidities are clearly identified and followed, (iv) preconditions for specific tasks in the context of comorbidities are explicitly stated, (v) potential risks and harmful events while aligning the comorbid processes are affirmed; (vi) care coordination is achieved given that the comorbidities may involve various specialties.

In the knowledge synthesis phase, we managed to identify and explicitly state most of the above constraints and highlighted the core domain and operational concepts in the CP ontology. Next, we proceeded to align the CHF and AF CP to handle comorbid CHF-AF, thus resulting in the development of specific comorbid management care plans that are formally[72] represented in terms of an OWL-based CP ontology. These plans can be executed in response to both CHF and AF related preconditions.

As mentioned earlier, class CLINICAL_ENTRY_POINT is instantiated by a number of plans to be executed at various points during the patient care process. The specific plans to be triggered during the execution of the clinical pathways will depend on whether a patient does or does not have a co-morbid illness. Thus there are discrete care plans that are valid only when a patient has either CHF or AF, and then there are other plans that are valid when a patient has a concurrent illness.

There are five such plans for the diagnosis and management of CHF (Fig. 34), which are to be executed sequentially.

[72] Codified formally using OWL, so that can be interpreted by computers.

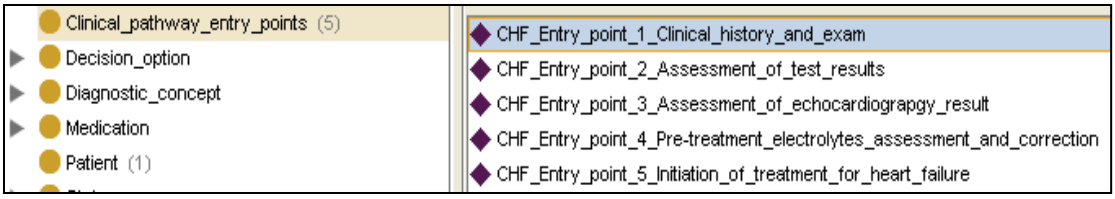


Figure 34: Entry points in the CHF pathways modeled as instantiations of class CLINICAL_PATHWAY_ENTRY_POINT

The AF care planning includes four plans as seen in figure 35.

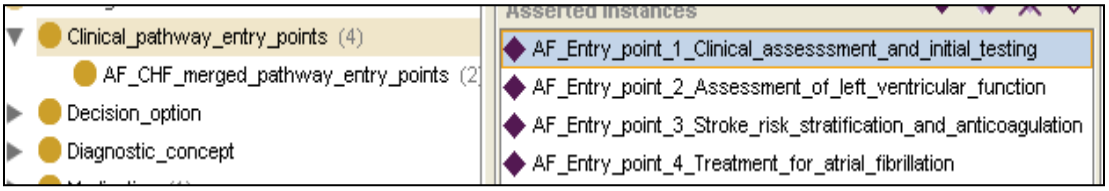


Figure 35: Entry points in the AF pathways modeled as instantiations of class CLINICAL_PATHWAY_ENTRY_POINT

Two plans are to be executed when a patient has concomitant CHF and AF (Fig. 36).

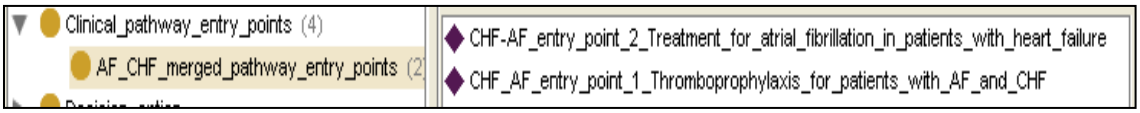


Figure 36: Comorbid Entry points modeled as instantiations of class CLINICAL_PATHWAY_ENTRY_POINT

From the GP perspective, the basic treatment of CHF remains the same even if the patient has concurrent AF, which is the prescription of Angiotensin-Converting Enzyme Inhibitor (ACEI) and beta blockers along with assessment and correction of electrolyte imbalance. From the perspective of electronic care planning, this means that in addition to execution of these CHF treatment plans, after assessing the patient for any specific contraindications and risk, the treatment plans of concurrent AF (anti-thromoembolism or digoxin administration) should be synchronized. In addition, the patient with CHF and AF is also at high risk of thromboembolism. Therefore, it is appropriate to ensure the safety of antithromboembolic treatment before such treatment can be started. Thus, from the electronic care planning point of view, in such a case, the execution of first four care plans are triggered; CHF entry point1- clinical history and exam; CHF entry point 2- assessment of test results; CHF entry point 3- assessment of echocardiography result; and CHF entry point 4- pre-treatment electrolyte assessment and correction for the CHF is

carried on as usual, in a sequential order. The two common care plans, 'CHF-AF entry point 1- Thromboprophylaxis' for patients with AF and CHF, and 'CHF-AF entry point 2- Treatment for atrial fibrillation for patient with heart failure' is electronically aligned with the 'CHF entry point 5- Initiation for the treatment of heart failure'. This synchronization occurs during the execution of the pathways as follows:

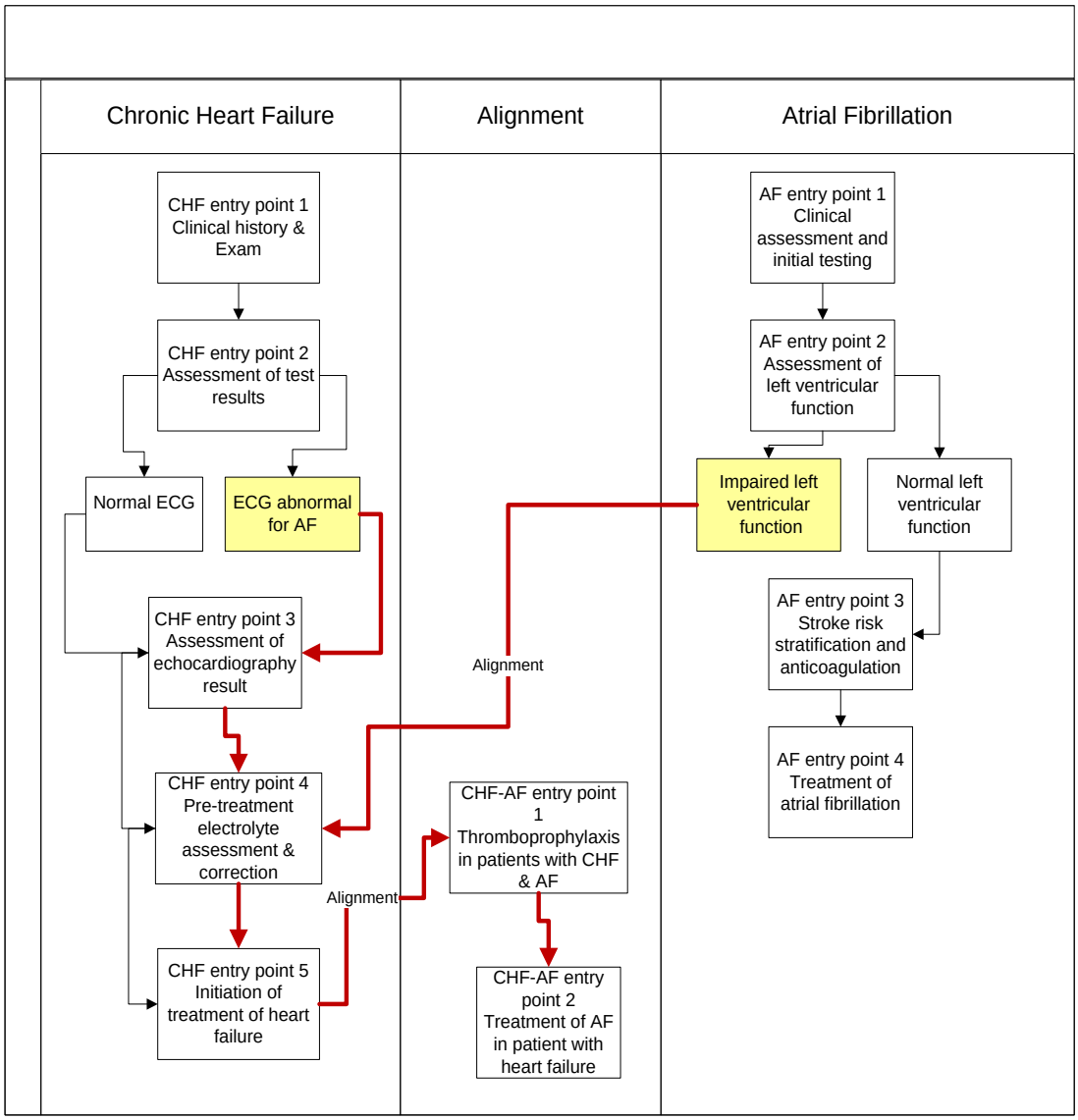


Figure 37: Aligning CHF and AF plans. The red arrows indicate the temporal relations between the plans while alignment

The execution of the AF pathway begins with the 'AF entry point 1- Clinical assessment and initial testing'. The subsequent plan is 'AF entry-point 2- assessment of left ventricular function', through echocardiography. The normal left ventricular function

results in the execution of the next two entry points in sequential manner. If, however, left ventricular systolic dysfunction (LVSD) is identified during the execution of AF entry point 2, then it is necessary to ensure that CHF care plans are executed in addition to AF plans (Fig. 37).

Synchronization of the two pathways takes place in such a way that the last two care plans from the CHF pathways, 'CHF entry point 4 - Pre-treatment electrolytes correction and assessment' and 'CHF entry point 5 - initiation of the treatment of heart failure' are executed and synchronized with the comorbid plans that include, 'CHF-AF entry point 1- Thromboprophylaxis' for patients with AF and CHF, and 'CHF-AF entry point 2- Treatment for atrial fibrillation for patient with heart failure' (Fig. 37).

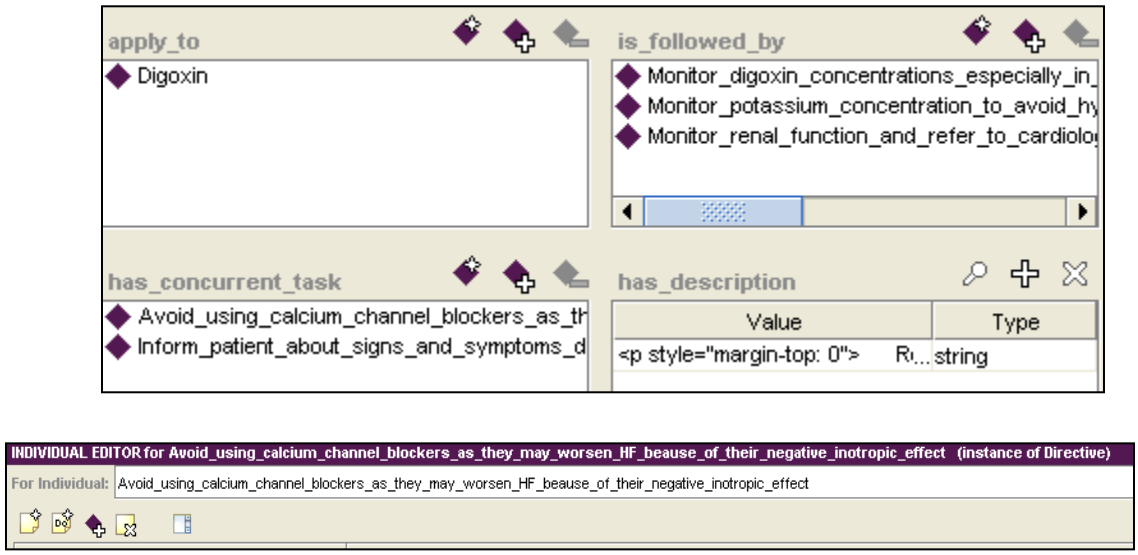


Figure 38: Modeling of directives regarding potentially harmful treatments while aligning comorbid plans

It is important to note that the synchronization of these care plans takes place irrespective of the side where the comorbidity is diagnosed, i.e. whether during the execution of the CHF CP or that of AF CP, thereby preventing duplication of activities. Thus, there are four plans which are executed whenever comorbid CHF and AF is detected:

i. CHF entry point 4- Pre-treatment electrolyte assessment and correction
ii. CHF entry point 5- Initiation of treatment of heart failure
iii. CHF-AF entry point 1- Thromboprophylaxis in patients with CHF and AF
iv. CHF-AF entry point 2- Treatment of AF in patient with heart failure

However, not every AF medication can be prescribed when there is concomitant CHF. For example; calcium channel blockers can further deteriorate left ventricular function, and should therefore be given with much caution, or better yet avoided in this setting. Thus the AF treatment plan for the patients with comorbid CHF is adjusted to include information regarding potentially harmful treatment in addition to AF treatment, for example digoxin (Fig. 38). The addition of such information (regarding potentially harmful treatments for patients with comorbidity) as instance (individual) of class DIRECTIVE makes sure that the potential problems associated with the concomitant administration of comorbidity treatments are uncovered beforehand and are thus avoided.

6.4.1. AUTOMATED CARE PLANING FOR COMORBID CHF AND AF

Modeling of this strategy for synchronization of the treatment plans involves sequential relationships between four main classes: PRE-TREATMENT_DECISION_TASK, DRUG_ADMINISTRATION_DECISION_TASK, PHARMACOLOGICAL_DECSION_TASK and TREATMENT (Fig. 39). This also includes three main properties: *has_decsion_option, is_followed_by,* and *apply_to,* which relate these classes forming a compact model evaluating preconditions such as signs of fluid overload or presence of any risks to comorbid treatments ahead of all prescriptions (Fig. 39). These preconditions are modeled as instances of PRE-TREATMENT_DECSION_TASK. For example, 'Determine any contraindication to ACEI', Determine any contraindications to Digoxin', or 'Determine any risk factors of digitalis toxicity' are responsible for checking the presence of any contraindication or serious risk associated with any medication, and 'Determine presence of any signs of fluid over load' is responsible to check if the patient needs treatment with diuretics. PRE-TREATMENT_DECSION_TASK is related to class DECISION_OPTION through property *has_decision_option*. The instances of class DECISION_OPTION include Boolean or other types of options available to the physician to choose from, for example, ACEI is not contraindicated' or 'No risk factors associated for digitalis toxicity' or ' 'ACEI is contraindicated due to' and 'digitalis toxicity risk factors are present such as'. These last two instances of class DECISION_OPTION are related through the property *apply_to_clinical_feature* to CONTRAINDICATION that is a sub-class of

TREATMENT _CONSTRAINT. It may be noted that the specific clinical features associated with ACEI contraindications might include renal artery stenosis, outflow tract obstruction or severe aortic stenosis; and those for digitalis toxicity might include concomitant use of certain drugs, or elderly patients who might have hypokalemia.

The presence of potential contraindications and associated serious risk factors to all the medications prescribed are thus checked sequentially before the system proceeds to the next treatment (Fig. 40). Taking into account that the main target users for this application are GPs, not many alternate treatments are provided. Thus, if during the pathway execution, whether that of CHF or comorbid CHF and AF, a CONTRAINDICATION to beta blockers such as 'severe reactive airway disease', or to ACEI such as 'renal artery stenosis', is selected, then the system will direct the GP to 'refer the patient to the specialist', which is an individual of the class END_TASK (Fig. 40). There will be no further treatment plans for this patient, including execution of any comorbid AF management plan. There are two reasons for this. First, the management of patient with such complications is safer under the care of a specialist. Second, and more importantly, any treatment regimen that is an alternate to basic treatments are beyond the scope of this project, including any dose adjustments due to the presence of complications. However, there is one exception to this rule, i.e., 'history of angioedema with no other contraindication' that is modeled as an instance of the class DRUG_ADMINISTRATION_DECISION_OPTION and is related to the individual 'initiate treatment with ARB instead of ACEI' through the relation *is_followed_by*. Thus, in such case, the ARB is administered instead of ACEI.

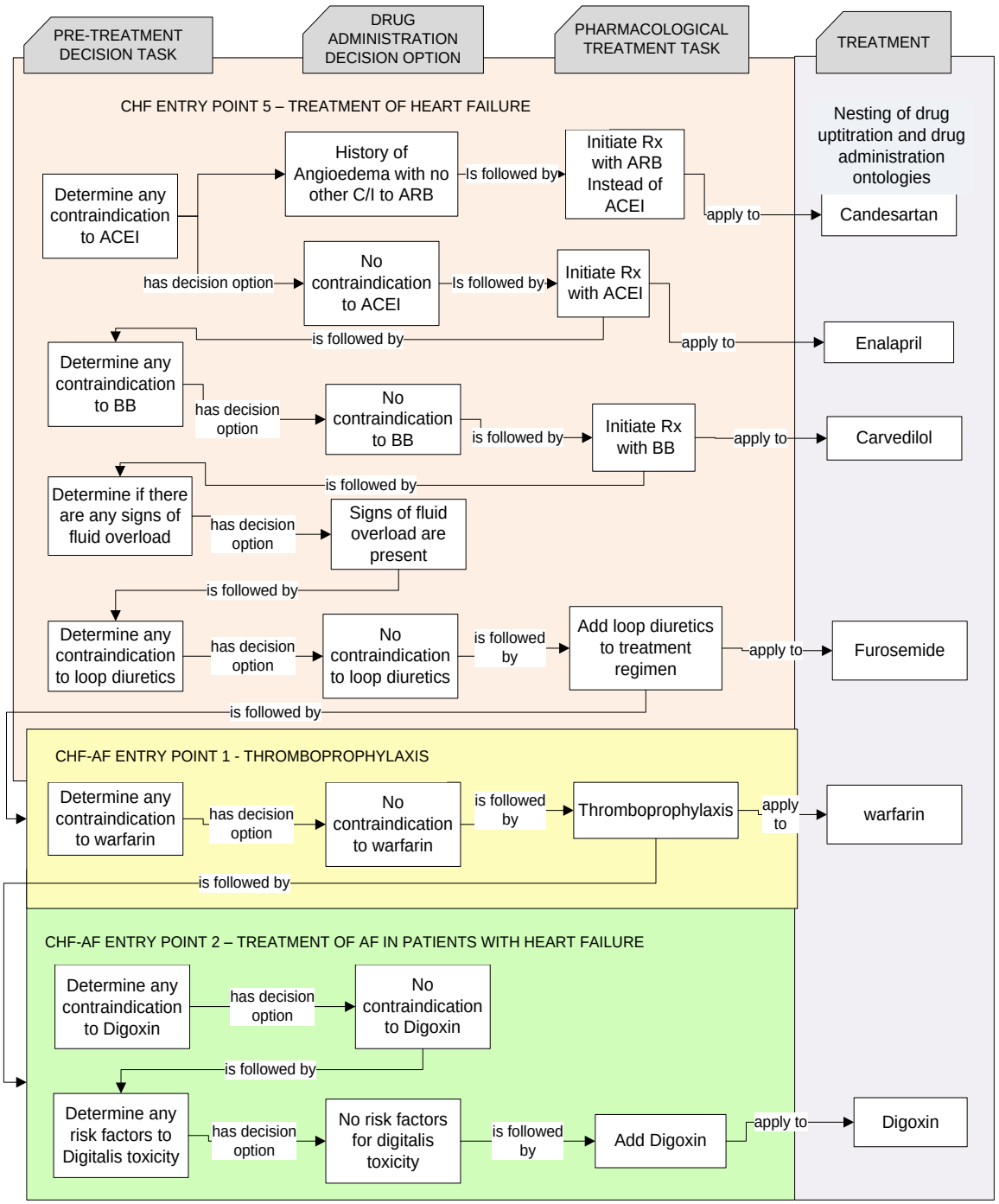


Figure 39: Alignment of entry points and their tasks for management of comorbid CHF and AF

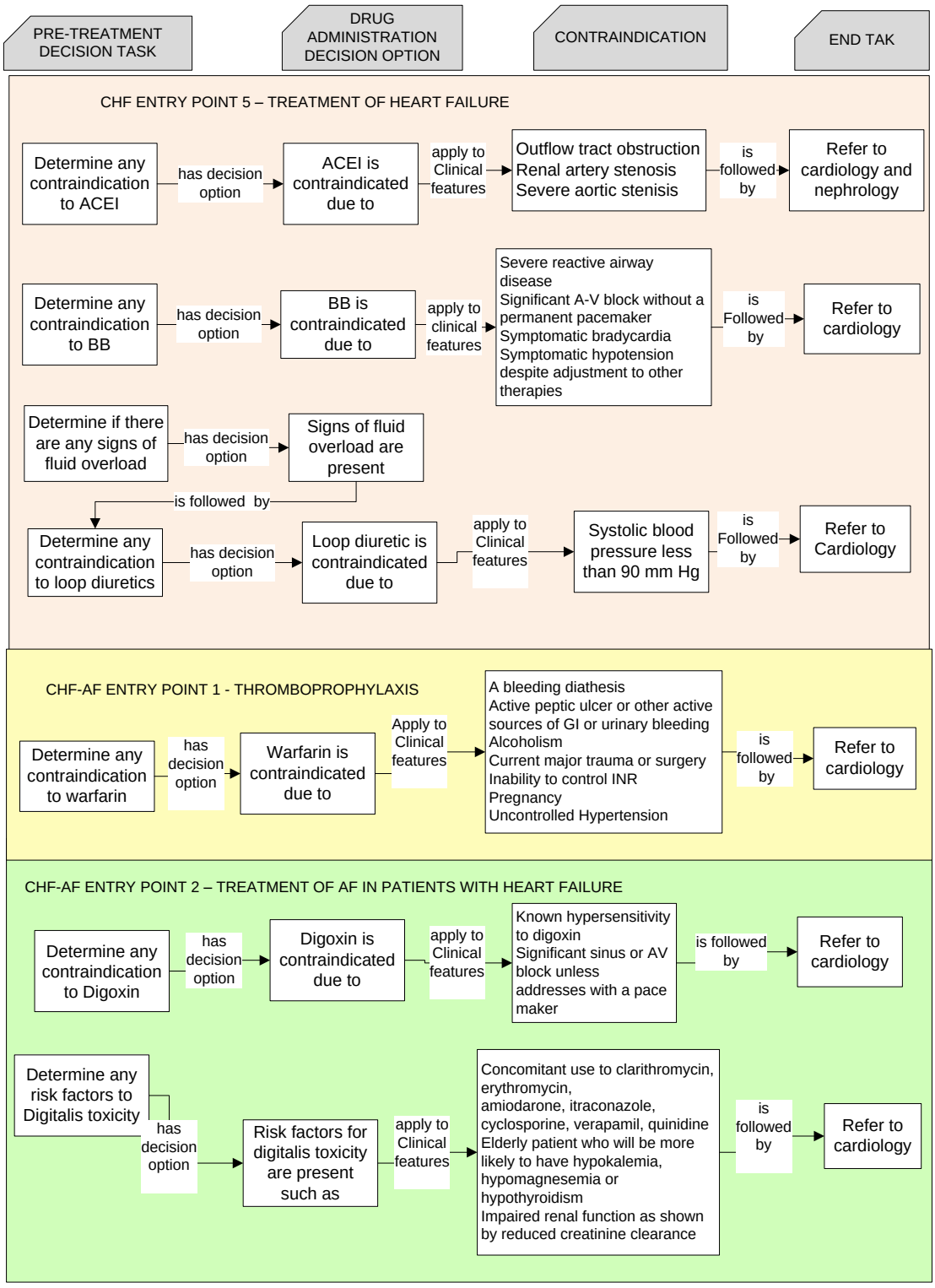


Figure 40: Sequential checking of the safety of drug prescription during comorbidity treatment

6.4.2. NESTING OF COMORBID DRUG ADMINISTRATION AND UPTITRATION ONTOLOGIES

In the CP ontology we modeled various checks and balances before the initiation of the treatment and have included numerous safety features once the treatment has commenced. According to the Canadian CPG, and ACC/AHA 2005 guideline for the diagnosis and management of chronic heart failure, ACEI and BB should be prescribed to all CHF patients (in our case NYHA class I and NYHA class II), and additional diuretic administration is also required if there are signs of fluid overload. Furthermore, patients with comorbid AF will require treatment with digoxin and thromboembolic therapy. This means that there are multitudes of therapy-related constraints that are to be addressed:

- Checking the presence of contraindications and potential risk factors before each drug is administered
- Sequence in which these contraindications are checked so that the drugs can be prescribed in that sequence
- Uptitration of drugs since, once prescribed, most CHF treatment drugs are gradually uptitrated over weeks
- Checking various clinical parameters before any dose enhancement or after drug administration
- Informing the patient about side-effects and the appropriate response in case they experience these side effects
- Judging response to treatment and what to do in the absence of an appropriate response
- Nesting of these uptitrations and drug administration schedules with all the above constraints within each prescription

Addressing these complex issues regarding the comorbidity treatment proved to be a modeling challenge. In order to solve this problem, we converted this complicated predicament into a complex, but well-organized and logically constructed model. This involved prescription of all drugs sequentially, starting from Angiotensin-Converting Enzyme Inhibitor (ACEI), checking any contraindications and then prescribing the drug.

If a contraindication to any of the drug groups in the sequence is detected then the next step is the referral step and the ontology execution ends.

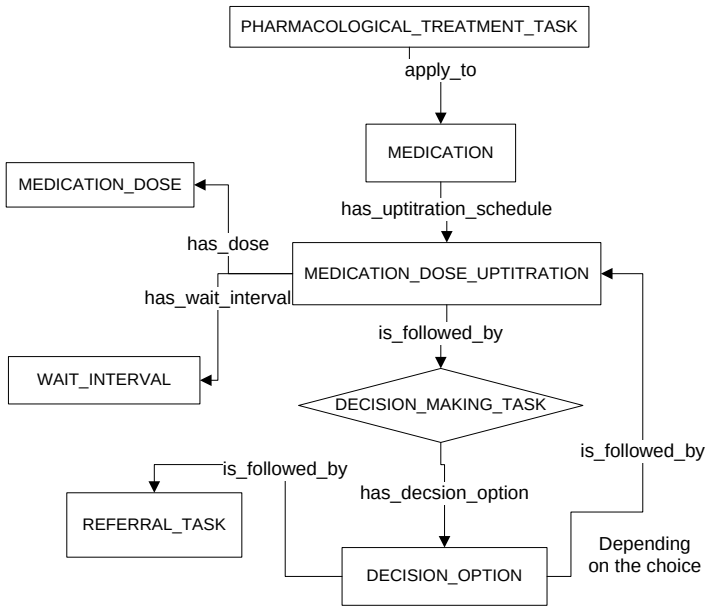


Figure 41: Classes and properties involved in dose uptitration of CHF medication

Once a drug has been safely prescribed, its uptitration and administration schedule is modeled by an ontology, nested within the class MEDICATION. The execution of this sub-ontology continues separately but within the main ontology, while the next step on the main ontology is determining the contraindication of the next drug, for example, beta blocker after ACEI has been prescribed. If all is well, this cycle continues till the medication for the treatment of comorbid AF is prescribed with a nested drug administration schedule. The issues related to the drug administration or uptitration, such as parameters that are to be monitored, information regarding side effects and what to do in such cases, and the schedules of uptitration, are all handled in the sub-ontology. This demanded the nesting of these schedules, which at the knowledge modeling level is achieved through relationships between the classes PHARMOCOLOGICAL_TREATMENT_TASK, MEDICATION, MEDICATION_DOSE_UPTITRATION, MEDICATION_DOSE and DRUG_UPTITRATION_DECISION_TASK (Fig. 41). Also, the time intervals between the two dose titrations are captured through the class WAIT_INTERVAL. These classes are related through the properties *has_uptitration_schedule, is_followed_by* and

has_decison_option capturing procedural rules in the uptitration schedules, while properties *apply_to* and *has_dose* capture the declarative information. The property *has_wait_interval* capture temporal information related to titration of the drug (Fig. 41).

s. Thus Carvedilol initial administration begins the Carvedilol titration schedule (Fig. 43).

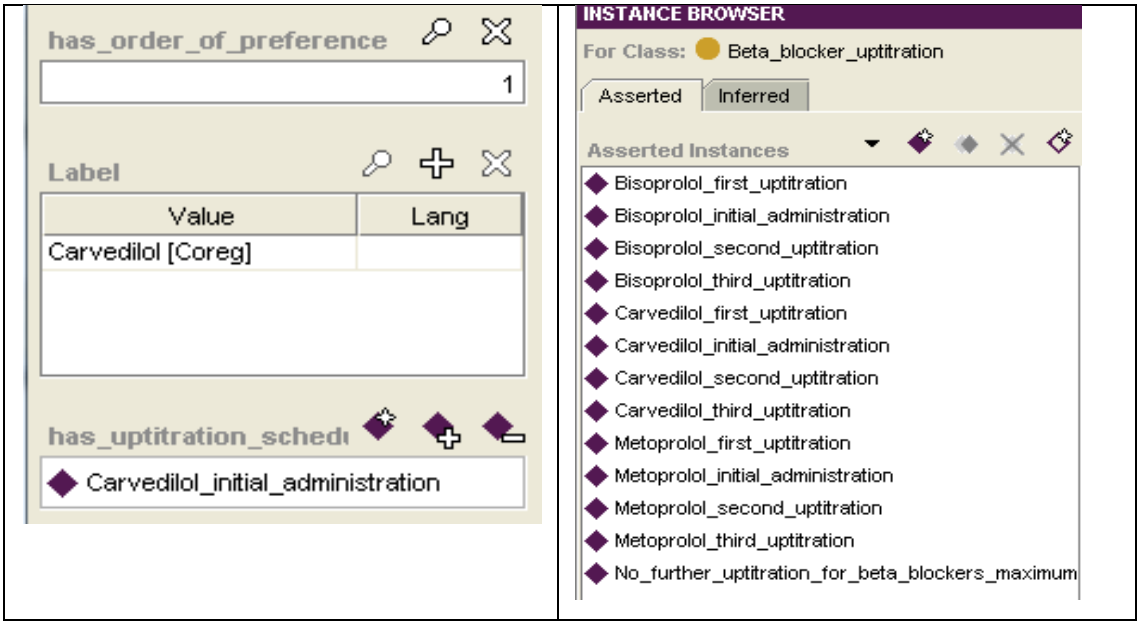


Figure 42: Modeling of beta blocker order of preference and uptitration schedules

To explain the relationships between individuals of these classes we take an example of uptitration of beta blockers. The individual 'initiate treatment with beta blocker' of class PHARMACOLOGICAL_TREATMENT_TASK has *apply_to* relation with Carvedilol, Bisoprolol, and Metoprolol, all of which are individuals of class MEDICATION. In accordance to the Capital Health uptitration protocols provided to us by the domain experts, all the medications in various medication groups have given order of preference through a functional data type property *has_order_of_preference*. As seen in Fig. 42, Carvedolol has order of preference 1, since it is the most preferred Beta Blocker (BB) according to the protocol. Each medication in a BB drug group then follows its own individual uptitration or administration schedule as prescribed in the protocol.

To achieve this nesting, class MEDICATION is related to class MEDICATION_DOSE_UPTITRATION through property *has_uptitration_schedule*. Individuals of MEDICATION_DOSE_UPTITRATION include titration schedules

beginning from initial administration till the last uptitration as prescribed in the protocol MEDICATION_DOSE_UPTITRATION has relation *has_dose* with class MEDICATION_DOSE, so that 'Carvedilol initial administration' *has_dose* 3.125mg bid PO. Since the protocol advises that certain parameters and any contraindications to the following uptitrations should be checked before any dose increments, class MEDICATION_DOSE_UPTITRATION is linked to DRUG_UPTITRATION_DECSION_MAKING_TASK (a sub-class of DECISION_MAKING_TASK) through the property *is_followed_by*, thereby capturing relevant decision logics and procedural rules pertinent to these dose increments. In this case the subsequent task is, 'identify any contraindication to BB first uptitration'. DRUG_UPTITRATION_DECSION_MAKING_TASK is related to the class DRUG_ADMINISTRATION_DECISION_OPTION a sub-class of DECISION_OPTION via property *has_decision_option*, the instances of which are Boolean decision options that are: whether further uptitration is contraindicated or it is not. DECSION_OPTION has two relation with two different classes. These include *apply_to_clinical_features* with class CONTRAINDICATION_TO_UPTITRATION and *is_followed_by* with MEDICATION_DOSE_UPTITRATION.

Thus, if the option is no contraindication, then the next step in the ontology is the subsequent upitration, which in this case is 'Carvedilol first uptitration' (Fig. 43) and the whole cycle is repeated till the path leads to final dose increment, which is the optimal dose as per protocol. Once the optimal dose is achieved, it is maintained and appropriate patient education material is included in the ontology. On the other hand, if there is any contraindication to titration, the specific clinical feature(s) causing this contraindication can be accessed or checked through the list of contraindications which are instances of the class CONTRAINDICATION_TO_UPTITRATION and linked through property *apply_to_clinical_features*. Presence of any of these contraindications will lead to an instance of the class DIRECTIVE through property *has_directive,* which states 'Do not proceed with uptitration and refer to cardiologist'.

In order to maintain an acceptable interval between uptitrations, the class MEDICATION_DOSE_UPTITRATION has *has_wait_interval* relation with the class

INTERVAL_EVENT, which in turn is related to INTERVAL_DURATION property *has_duration.* Individuals of INTERVAL_EVENT include named intervals between two events, for example, 'interval between initial administration and first uptitration', while those of INTERVAL_DURATION include actual durations of these named intervals, for example, 'two weeks' (Fig. 43). Thus, the uptitration ontology specifies the interval between two uptitrations and the duration of this interval so that the dose increase can take place at safe intervals as per protocol.

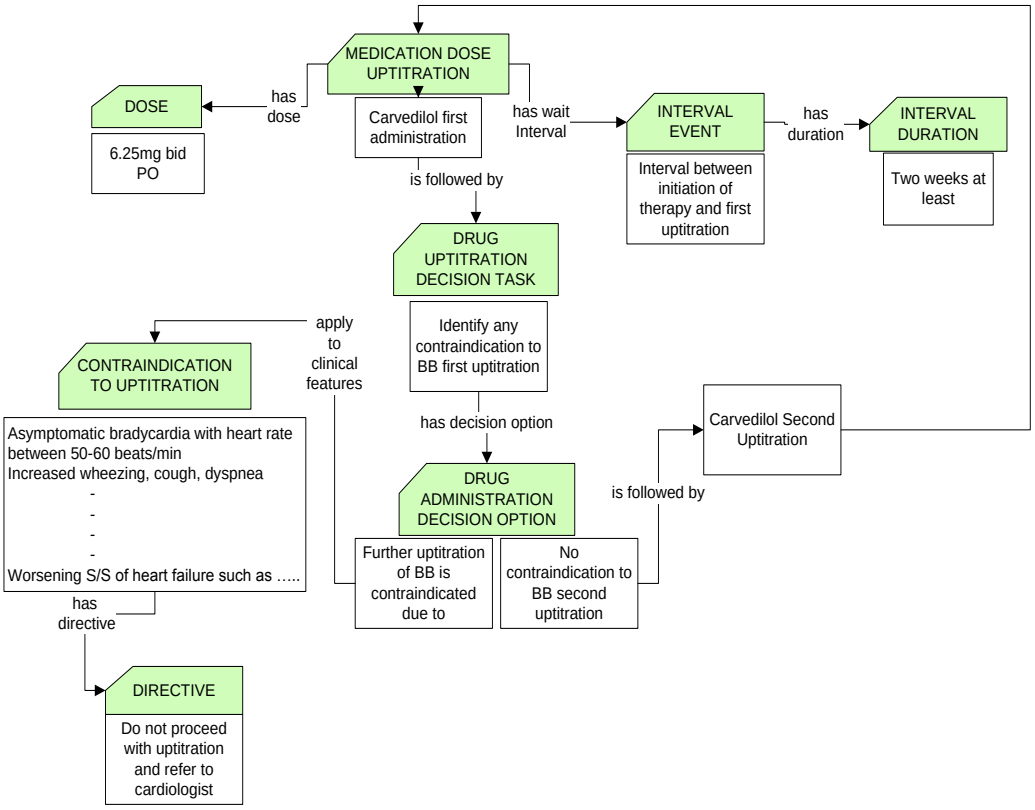


Figure 43: shows progress from first to second uptitration of Carvedilol withstanding all the necessary constraints

The same relationships are utilized for the administration of other drugs such as those for the treatment of AF, for example, digoxin. These schedules include more relevant sub-classes of the same classes with similar relationships, constraints and safety measures. Thus, the presence of potential dangers is checked at various levels as necessary to allow safe and effective drug administration.

Having aligned the care processes for CHF and AF at the knowledge level, we next demonstrate the execution of the aligned CPs through a computerized decision support system.

6.5. COMORBID CLINICAL PATHWAY KNOWLEDGE EXECUTION

Once the task-specific heuristics in the CPs are formalized as an ontology and the plan alignment strategy of these heuristics has been ascertained, the next step is execution of the CPs while automatically synchronizing the care plans when concurrent AF or CHF are identified. By execution, we mean that the comorbid ontology is rendered in such a format that the CPs can be executed with patient data. The execution of a CP involves traversal through its workflow formalized as an ontology, where each state contain two elements: (i) actions performed whilst satisfying relevant constrains; and (ii) potential next state (Danyal, Abidi & Abidi, 2009). In order to execute the ontology, the services of a computer programmer were employed. It needs to be emphasized that the programming and any written description of this programming is not the work of the researcher. In order to explain the execution of the pathways, the excerpts from the report (with some changes) written by the programmer at our request have been added to this thesis by his permission.

6.5.1. CLIENT-SERVER PROGRAMMING MODEL

In order to ensure the portability of the application, the programmer adhered to the client-server programming model (Fig 44), which dictates that the server acts as the central storage and computing hub, while the client merely displays and sends data coming and going to the server. Utilizing this model for this program allowed the user interface to be light and quick loading, with no additional components to be download and installed.

The server part is programmed in Java, and runs as a Java Servlet, which is a memory resident (or constantly running program) that waits for client connections. The client was programmed using the Google Web Toolkit that simplifies creating web application clients. The clients are programmed using Java and Google Web Toolkit automatically compiles the Java code into JavaScript. This is significant because other frameworks rely on externally downloaded components, such as Flash, to create rich and interactive web applications, whereas Google Web Toolkit does not. This translates into speed and ease of deployment.

The ontologies were provided as .owl files to the programmer. This means that the domain knowledge is represented in Web Ontology language (OWL). In order to read

and manipulate these .owl files, the Protégé-OWL programming library was utilized on the server. This library provides easy access to the domain information structures through conventional Java classes and methods. The main structures that are important in this application are Resources, Properties, and Property-Values. Potential property-values can come from a pre-specified range, or can be a type of Resource. This facility of the OWL is used in the ontology to model the temporal relations in the CP flow-charts. Thus, from the execution perspective this means that the user can be presented with a property along with the possible ranges the property-value can take on at the client side of the program. The user can then choose the desired property-value at the client side, which is then sent back to the server (Fig. 44). If the property value is of type Resource (from object property's range), then this new Resource's (Range class) properties are fetched and displayed to the user along with their corresponding property value ranges and the cycle goes on as per procedural rules in ontology.

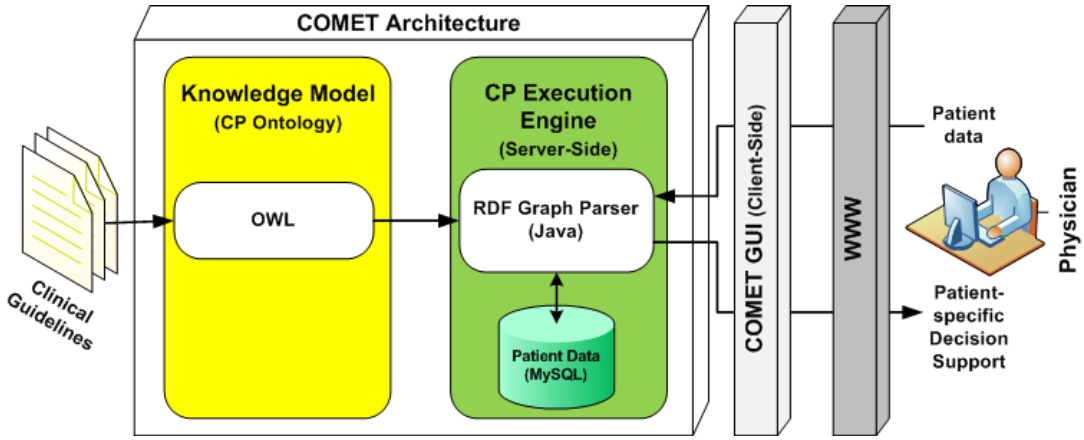


Figure 44: Architecture of COMET

6.5.1.1. ROLE OF THE CLIENT

The client visualizes and enables the navigation of the ontology by presenting the properties of the current resource to the user (Fig. 44). The user then selects the desired property-values and sends those back to the server until the next task is 'Pathway Ends' in the ontology. The execution of the CP ontology begins with the user searching for a particular instance of the Resource PATIENT, for example, 'P12345' through the client interface. The server receives this request. If found, the Resource P12345 is set as the

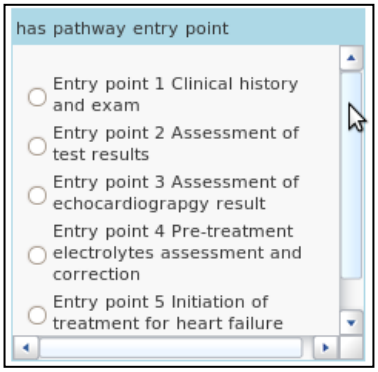
current node, and the server begins parsing the properties of P12345 (instance of class PATIENT). The resource PATIENT has been modeled to have five properties

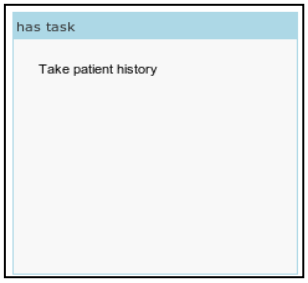
- *has_name*
- *has_address*
- *has_date_of_birth*
- *has_telephone_number*
- *has_pathway_entry_point*

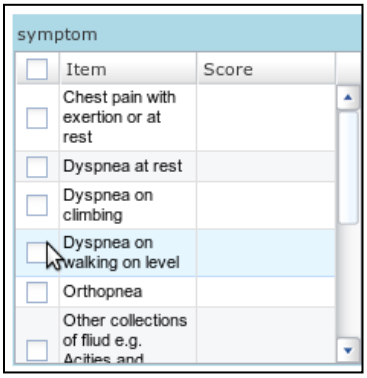
Since P12345 is an instance of the resource PATIENT, then P12345 inherits these properties as well. The server then looks up the type of the property value and sets it either as Literal or Resource. If the type is Literal, as in case of the first four properties, nothing more needs to be done for them, since they require input of patient demographic information every time a new patient is added to the system. However, if the type is found to be Resource, then the range or allowable resources for that property are looked up and attached to that property. The last property, *has_pathway_entry_point*, is of type Resource. The allowable property values for this Resource are in the case of CHF pathways, as follows:

- Entry point 1 Clinical history and exam
- Entry point 2 Assessment of test results
- Entry point 3 Assessment of echocardiography result
- Entry point 4 Pre-treatment electrolytes assessment and correction
- Entry point 5 Initiation of treatment for heart failure

These values from the range classes are attached to the property *has_pathway_entry_point*. This property, along with four other properties, is then sent back to the client for processing. Once the client receives the list of properties, it begins parsing them in accordance to their values. In case the property value is of type Literal, the property name is displayed with an empty text box below it. The user may then enter an appropriate value in the text field, for example, name of the patient and his address. If, however, the property value is of type Resource, a special meta-data file further describing the rendering of property and the attached property-value ranges is used. The ranges of property values are divided into three categories: No-Choice, Single-Choice and Multi-Choice (Fig.44).







a. Rendering of a property where the property-value ranges are of type Single-Choice	**b.** Rendering of a property where the property-value ranges are of type No-Choice	**c.** Rendering of a property where the property-value ranges are of type Multi-Choice

Figure 45: Single-Choice, No-Choice and Multi-Choice Property-Values selection in CDSS

- Ranges of type ***Single-Choice*** (Fig. 45, a) mean that, in the context of this ontology, it only makes sense to choose one of potentially many choices. The property-value ranges of *has_pathway_entery_point* are of this type. This type of property and its associated property-value ranges are rendered using Radio Selection where the user can only have one active selection at any given time.
- Property-value ranges of type ***No-Choice*** (Fig. 45, b) are those for which there is only a single item in the range. In this case, the property is rendered along with the single property-value below it. The user is not given any other options. The property *has_task* is of this type. The sole property-range is allowable for this property.
- Lastly, ***Multi-Choice*** (Fig. 45, c) property-value ranges are those for which it is permissible for a property to have more than one property-value. A Check List represents the property-value ranges of this property. The checklist allows the user to check more than one property-value for each property. One such example is the *symptoms* property.

Once appropriate selection for each property has been made, the "Save & Continue" button is clicked. The user interface then collects all the properties, along with the user

selection of each respective property-value, and sends them back to the server for processing.

6.5.1.2. ROLE OF THE SERVER

Once the server receives the properties along with the property-values selected by the user, it begins to process them by running through each property and retrieving the user-selected property values and storing them in the ontology (Fig. 44). At this point in the program's execution, the "current node" is still the instance P12345 of the resource PATEINT, and all the property-values selected by the user have been saved. The server then brings up a meta-data file that describes which properties lead to the "next node". These properties are chosen by the ontology designer (the researcher herself) to reflect the path the user must follow. Once the property of the "current node" is identified as the one that leads to the next node, its value is retrieved. This property-value by definition is a Resource. This property-value thus becomes the "current node". The server now fetches the properties of this "current node". As per ongoing example, the property *has_pathway_entry_point* is property that leads to the "next node". If the user selects 'Entry point 1-Clinical history and exam' as the property-value for that node, then the server would fetch the Resource 'Entry point 1-Clinical history and exam' and set it as the "current node". The properties of this node as per ontology now would be:

- *has_date_and_time*
- *has_task*

This process repeats until the ontology pathway comes to an end. This happens when none of the properties of the "current node" are denoted as "next node".

6.5.1.3. AUTOMATED DECISION SUPPORT

One of the main purposes of the execution step is to provide decision support based on user input and selection. For example, the Resource 'Assess Chest X-ray Result' has property *has_decsion_option* that has two potential property values; 'Chest X-ray is abnormal' or 'Chest X-ray is normal'. The next step and the subsequent path executed in this case would be based on user assessment of the X-ray finding. However, in certain cases the subsequent path is decided automatically by the program, once it has collected

enough information. For example, Class CUMULATIVE_BOSTON_CRITERIA_SCORE, a sub-class of DIAGNOSTIC_CONCEPT has been given a property *has_rule_1*, with value ranges that include 'Entry Point 3 – Assessment of echocardiography result' or 'Consider alternate diagnosis and refer'.

Table 3: Property-values for *has_decsion_option* property, evaluation of which will automatically trigger the 'Entry point 3_ Assessment of echocardiography result' path

Resource	Property	Property-Value
Assess_BNP_result	has_decision_option	BNP_is_abnormal
Assess_ECG_result	has_decision_option	ECG_abnormal_for_atrial_fibrillation
Assess_ECG_result	has_decision_option	ECG_is_abnormal
Assess_chest_X-ray_result	has_decision_option	X-ray_is_abnormal
Calculate_cumulative_Boston_criteria_score	has_decision_option	Between_5_and_7_points
Calculate_cumulative_Boston_criteria_score	has_decision_option	Equal_to_or_more_than_8_point

The correct path to be taken in this instance depends on the combination of various test results that were collected as Property-Values of the properties listed in Table 3. These values are selected earlier, sequentially, during the ontology execution. If any of these Property-Values are found to have been selected by the user then the execution of the pathway moves along 'Entry Point 3 – Assessment of echocardiography result' and the path that follows. On the other hand if decision options other than these ones are selected for all the relevant Property-Values, then next step is 'Consider alternate diagnosis and refer'. During execution of the ontology, the server watches the incoming property values selected by the user. If any of them matches the Property-Value outlined in table 3, then the application automatically sets the Property-Values of the property has_rule_1 to the Resource 'Entry Point 3 – Assessment of echocardiography results'.

6.5.1.4. SYNCHRONIZATION OF COMORBID PLANS

The point during the CHF care flow where presence of concurrent AF is revealed is test result of ECG. When the user encounters the Resource 'Assess ECG result' which has a property *has_decision_option*, there are three possible Property-values: 'ECG is normal', 'ECG is abnormal for atrial fibrillation' (whereby any abnormality indicative of AF is

detected on ECG) and 'ECG is abnormal' (any other abnormality of ECG). If the property-value 'ECG is abnormal for atrial fibrillation' is selected by the user then the AF care plans are triggered (Fig. 46). Even if the patient has been found to have ECG evidence of AF, they must undergo further testing such as echocardiography to assess LVSD.

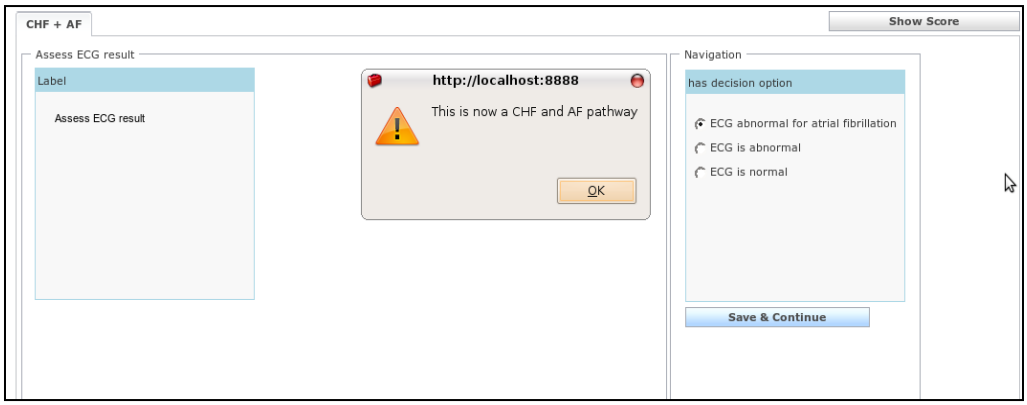


Figure 46: Choosing the property-value 'ECG abnormal for atrial fibrillation' will trigger the *A*F pathway later on in the program execution

Also, for CHF patients who have concurrent AF, all the treatment plans for CHF must be executed in addition to specific AF plans. Therefore, when the patient selects the Resource 'ECG is abnormal for atrial fibrillation', this information is recorded by the application and an alert is provided mentioning: 'This is now a CHF and AF pathway' (Fig. 46). The AF treatment plans are then automatically triggered at the appropriate time in the application, where a separate tab indicating AF plans is opened so that the user can begin traversing the AF paths through this tab.

6.5.2. COMET(Co-morbidity Ontological Modeling & ExecuTion): DECISION SUPPORT SYSTEM FOR DIAGNOSIS AND MANAGEMENT OF CHF AND AF

In COMET, presently the execution and alignment of the pathways for decision support purposes originate from the CHF side. This means that the entire CHF pathway and the part of AF pathway which has to be triggered when a CHF patient has concurrent AF can be executed with patient data. The CP can be traversed concurrently, displaying patient

states indicting the actions to be performed given the patient data and the potential next state. The part of the AF pathway that is necessary for the management of patients who have only AF has already been formalized in the ontology and will be executed in the future. Thus, a GP can logon to the system through the CHF screen right now and will be able to logon from the AF screen in the future. If, from the CHF side, the presence of comorbid AF is detected then the comorbid AF plans will be aligned and executed in accordance to the appropriate constraints and sequence as identified during the knowledge synthesis phase.

COMET is a web-based application designed to visualize and navigate two CHF and AF CPs. The aim of this application is threefold:

- To visualize the CPs using a user-friendly interface
- To assist GPs in care planning and decision support for patients with single disease or comorbid CHF and AF
- To be a deployable application with minimal effort on any modern web browser, thereby ensuring its portability and accessibility

After entering demographic information and date in the COMET system, the clinician can either select any of the entry points on the screen, with the assumption that all the previous care plans have been executed or begin with the very first plan and go sequentially through the remaining plans depending on a patient's progress. Selection of an entry point generates a series of screens depicting directives regarding the next tasks and the related information as well as decision points with pertinent options in drop down menus that can be selected by the user. In some cases, various combinations of user inputs are used to produce an output, for example, CHF diagnosis through combinations of input regarding signs and symptoms, ECG, X-ray and B-type natriuretic peptide (BNP). If comorbidity is identified during the initial assessment and testing (for example, assessment of ECG), this information is retained till the appropriate time, such as, execution of treatment plans when the comorbid plans are aligned after all preconditions has been satisfied. The screen will show a tab proclaiming presence of the comorbidity and comorbidity plans will be executed in appropriate sequence. Once a drug has been prescribed, its uptitration or administration schedules are accessed through a separate tab

on the next screen and lead to a series of screens, which are separate from the main sets of screens, which continue with the prescription of the ensuing necessary treatment. However, if there is any serious risk during the execution of any of these plans at any point, the COMET system will issue an alert suggesting that the patient should be referred to a specialist.

CHAPTER 7 EVALUATION OF THE COMET SYSTEM

In this chapter we present the evaluation of this research and the relevant results. Three different evaluations were performed:

i. Evaluation of the modeling of the knowledge: This involved evaluating the CP ontology, which is used to encode the comorbid CPs for logical consistency.
ii. Evaluation of the functionality of COMET: This involved evaluating the ability of COMET to provide decision support for CHF, AF and comorbid CHF-AF. This is an internal evaluation based on case scenarios.
iii. Evaluation of the correctness of the content of COMET from the perspective of users—i.e. health professionals. This is an external validation whereby domain experts interacted with COMET and provide their assessment.

7.1. EVALUATION OF ONTOLOGY

The evaluation of the ontology was carried out before the knowledge execution phase of this research. The ontology was evaluated in accordance to the criteria suggested by Gomez-Perez (Gomez-Perez, 2000), which include the three Cs: Consistency, Completeness and Conciseness. These three Cs are necessary to check the correctness of the ontological definitions, meaning that whether the ontological definitions are adequate and correct given the domain, what can be inferred from these definitions and are these inferences correct (Gomez-Perez, 2000).

7.1.1. EVALUATION OF ONTOLOGY FOR CONSISTENCY

An ontology can be regarded as logically consistent if it is satisfiable, which means that it does not contain contradictory information (Gomez-Perez, 2000). In order to evaluate the consistency of the CP ontology we performed subsumption tests to establish concept satisfiability and consistency. The consistency of an ontology is checked on the basis of description[73] of the class so that a reasoner can check whether it is possible for a class to have any instances. A class is regarded as inconsistent if it cannot have any instances. We used an open source DL reasoner called Pellet (Pellet: The Open Source Reasoner. n.d.). Fig. 47 illustrates the results of the subsumption tests performed on our ontology. The

[73] Formal definition of a class, i.e. a class that has at least one set of necessary and sufficient conditions. An individual who satisfies this definition can belong to a class.

results indicate that are no inconsistencies in the ontology. Therefore it was concluded that the ontology is consistent and satisfiable.

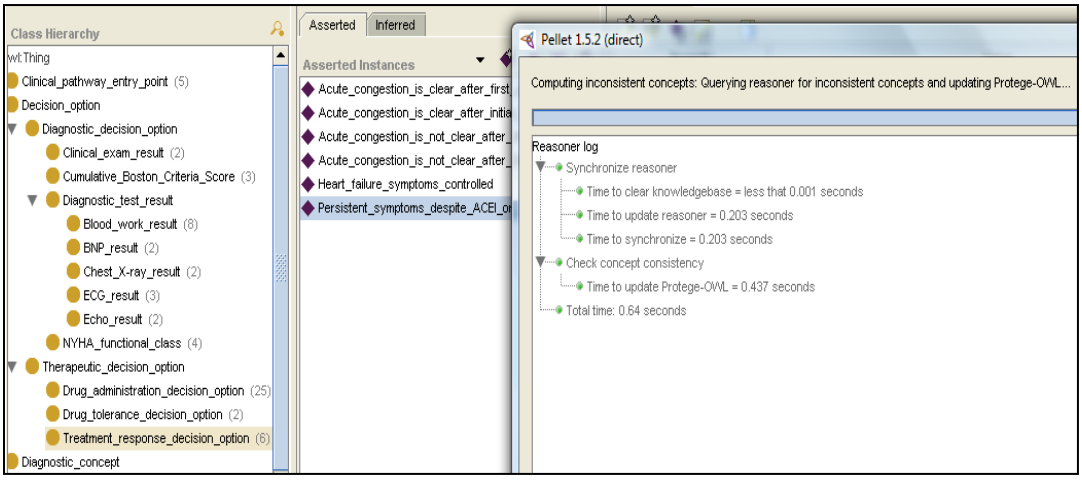


Figure 47: Ontology evaluation for logical consistency using the reasoner Pellet. The results showed no inconsistent classes

7.1.2. EVALUATION OF ONTOLOGY FOR COMPLETENESS

An ontology is complete "if and only if all the knowledge that is supposed to be in the ontology is explicitly stated in it, or can be inferred" (Gomez-Perez, 2000). This is a challenging situation as in an open-world closure (semantic web purports open world semantics) it is not entirely possible to prove the completeness of an ontology. This is because it is difficult to establish that the ontology is not missing any knowledge. Therefore, ontology completeness is established by deducing the incompleteness of an ontology by proving incompleteness of its definitions, i.e., the inability to define adequately the necessary domain knowledge for which the ontology has been constructed (Gomez-Perez, 2000). In order to evaluate the ontology for completeness, we instantiated the ontology with the clinical pathways for CHF and AF, developed during the knowledge synthesis phase of this research. We found that the ontological definitions in terms of structural criteria such as necessary and sufficient conditions of a predicate, domain and range of relations, generalization and specialization of classes, have adequate representational capacity to capture comorbid domain and procedural concepts. This is established by the ability of the CP ontology to adequately instantiate all the domain concepts and relations formalized in the two CPs with their comorbid constraints.

7.1.3. EVALUATION OF ONTOLOGY FOR CONCISENESS

An ontology is considered to be concise if it does not store any unnecessary or useless definitions—i.e. it is devoid of redundancies in its definitions. For example redundancies of *subclass_of* relations can take place between two classes when they have more than one *subclass_of* relations between them (Gomez-Perez, 2000).

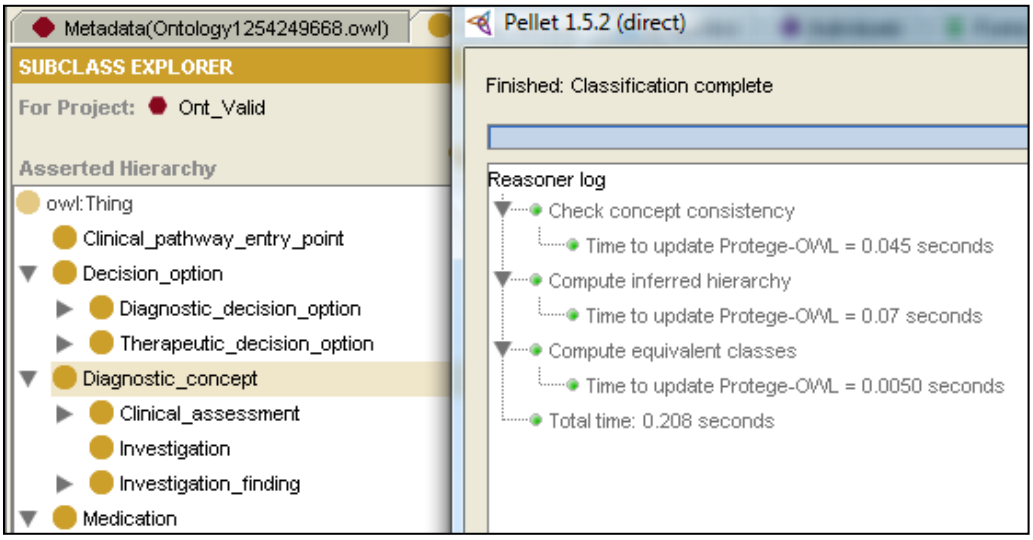


Figure 48: Reasoner (Pellet) log for classification and computation of inferred hierarchy

To establish the conciseness of our CP ontology, we used a Descriptive Logic (DL) reasoner—i.e. Pellet—to compute the inferred class hierarchy and to identify redundant arcs between the classes (Fig. 48). Our classification tests did not show any redundant arcs in the ontology, therefore it is concluded that the asserted hierarchy is similar to the inferred hierarchy, as shown in Fig. 49.

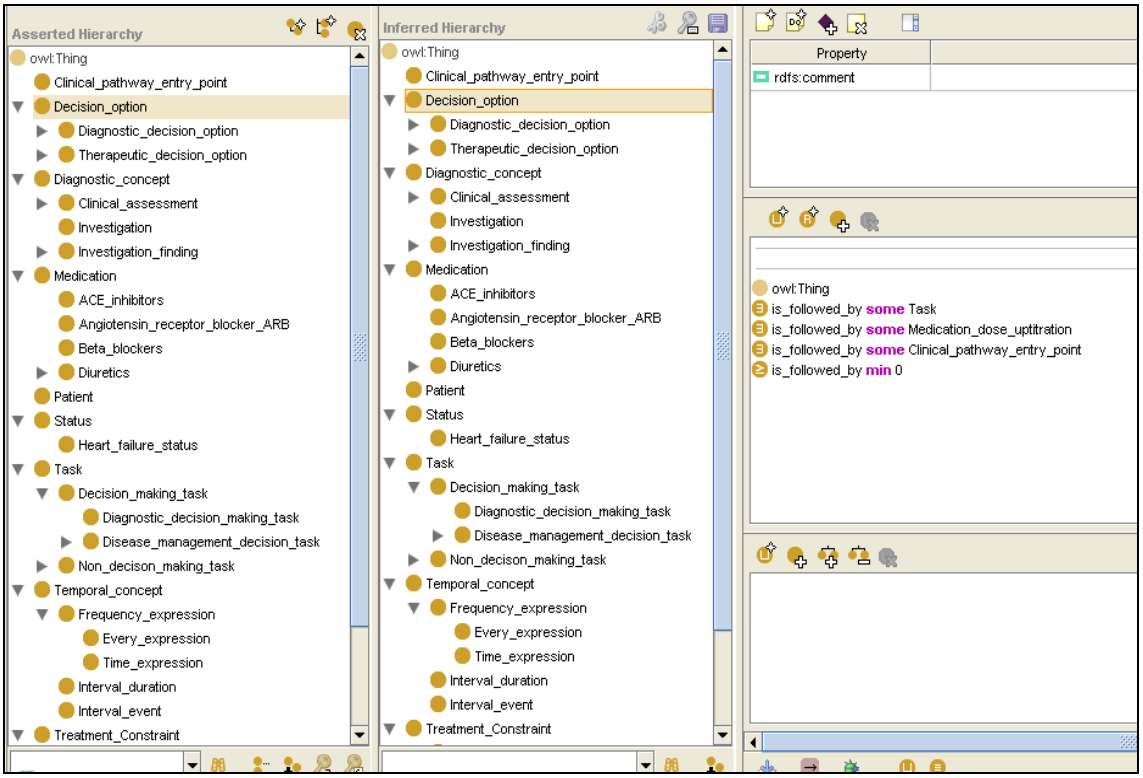


Figure 49: Asserted and inferred class hierarchy. Inferred hierarchy computed by running tests by Pellet. Note that both hierarchies came out be same

In conclusion, from a knowledge modeling perspective we established that the CP ontology is consistent, complete and concise.

7.2. INTERNAL VALIDATION – COMET IN ACTION

This evaluation concerns the functionality of the COMET system to handle both single and comorbid disease scenarios. These care scenarios were created by the author based on the available medical literature and the CPGs. The scenarios depicted patient data and constraints related to single disease (CHF) and comorbid CHF- AF. The evaluation involved comparing the output of COMET at every phase with the expected output as per the known knowledge about single disease or comorbid disease management—i.e. whether execution of COMET with patient data follows the work flow patterns, i.e. branching and synchronization of comorbid care activities as formulated in the CPs. Execution of the CPs based on the data in the scenarios showed that the prescription of the management plans and the sequence of these prescriptions are in accordance with the intended output. Below, we present the scenarios and their output at different phases of

the execution of the pathways. Since our application is meant for care planning in addition to decision support, we have created multi-step scenarios so that we can input the data in each entry point and compare the resultant output with the expected output. The scenarios are written in Italics.

7.2.1. SINGLE DISEASE SCENARIO

A 74-year-old woman with a history of rheumatic fever while in her 20s, presented to her GP with complaints of increasing shortness of breath (dyspnea) upon exertion, such as climbing uphill and walking on the level. She also noted that the swelling in her ankles is getting worse. She feels that in past week her appetite has decreased considerably, with some nausea and vomiting, and tenderness in the right upper quadrant of the abdomen. Her blood pressure is 110/70 mmHg. On exam, she has low volume carotid and upper extremity pulses that are regular with a rate of 100bpm. In addition, her jugular veins are considerably distended, with JVP elevated more than 6cm of H_2O along with a large pulsatile liver. She also has a moderate degree of ascites. Auscultation of the heart reveals a low-pitched, rumbling systolic murmer. In addition, she also has an extra S3 heart sound. Given her symptoms, the GP has placed her in NYHA class II.

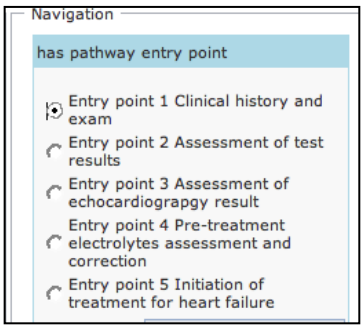


Figure 50: Five entry points in the CHF pathways. The GP selects entry point 1

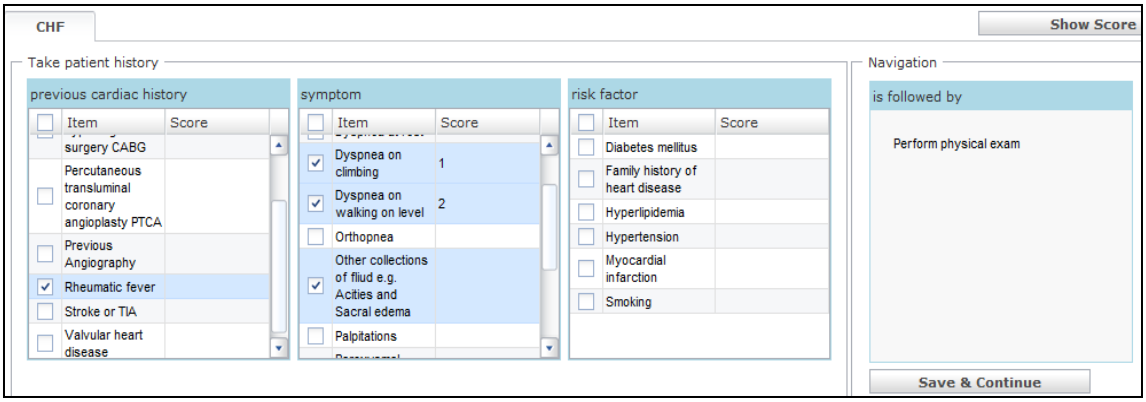


Figure 51: Selecting relevant previous cardiac history, symptoms and CAD risk factors from the menu, and displaying the next step: 'Perform physical exam'. Note that Boston criteria points are also displayed

After logging in to the system and entering the demographic information, the GP selects the first entry point to navigate the pathway (Fig. 50). This is 'Clinical history and exam'. Here the GP enters the necessary information collected during history taking and physical exam by selecting the relevant signs and symptoms, as shown in the figures 51, 52 & 53.

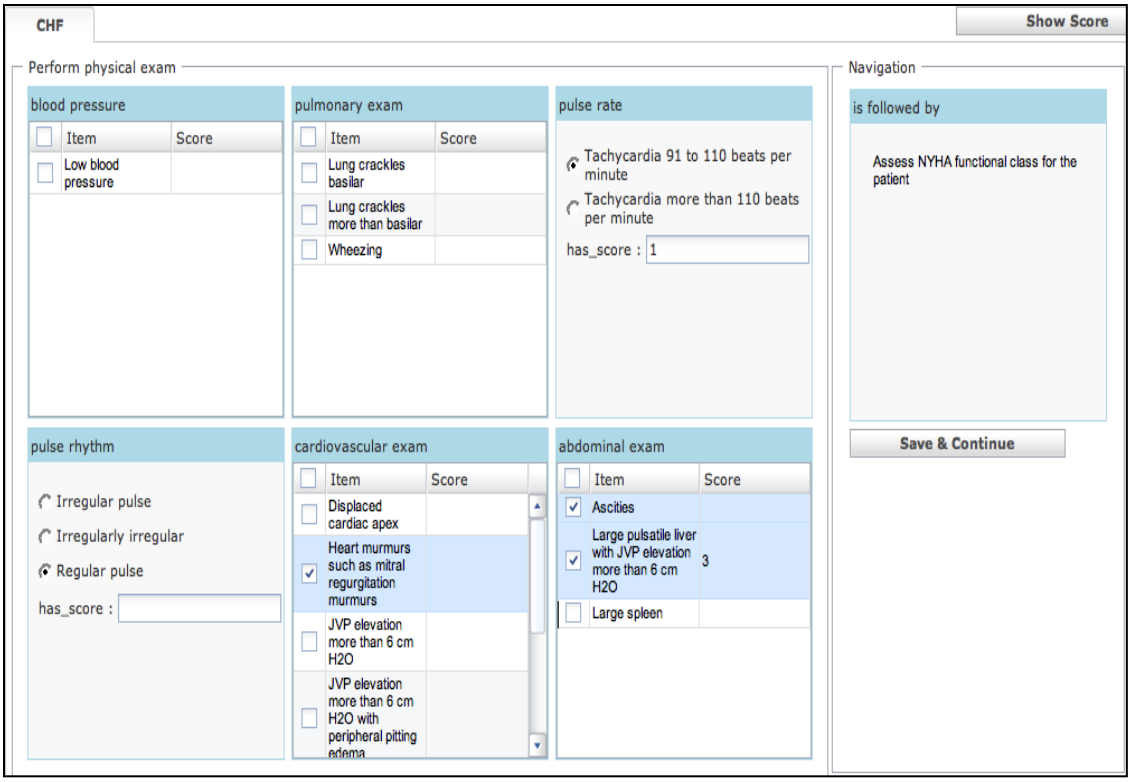


Figure 52: Selecting relevant signs. Note the scores attached to the signs are displayed along with the next step i.e. 'assess NYHA class functional class for the patient'

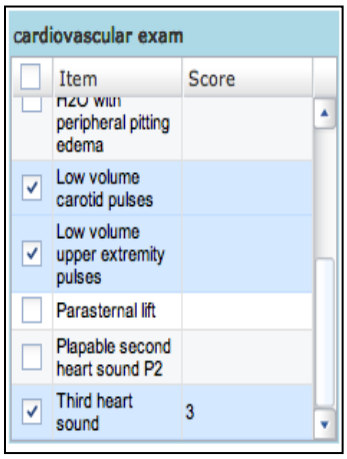


Figure 53: Selecting the relevant signs on cardiovascular exam (note the scores)

On the basis of clinical presentation, the GP has decided that her patient falls into NYHA class II and she selects the New York Heart Association (NYHA) class II option from the drop down menu in the following window (Fig. 54). It is to be noted that in case the patient's symptoms are more severe and consistent with NYHA class III or IV, COMET will not allow the GP to proceed any further and instead will recommend immediate

referral to the specialist. To assist the GP's decision-making process, COMET displays the description of NYHA classification as well as the source of this description (Fig. 54).

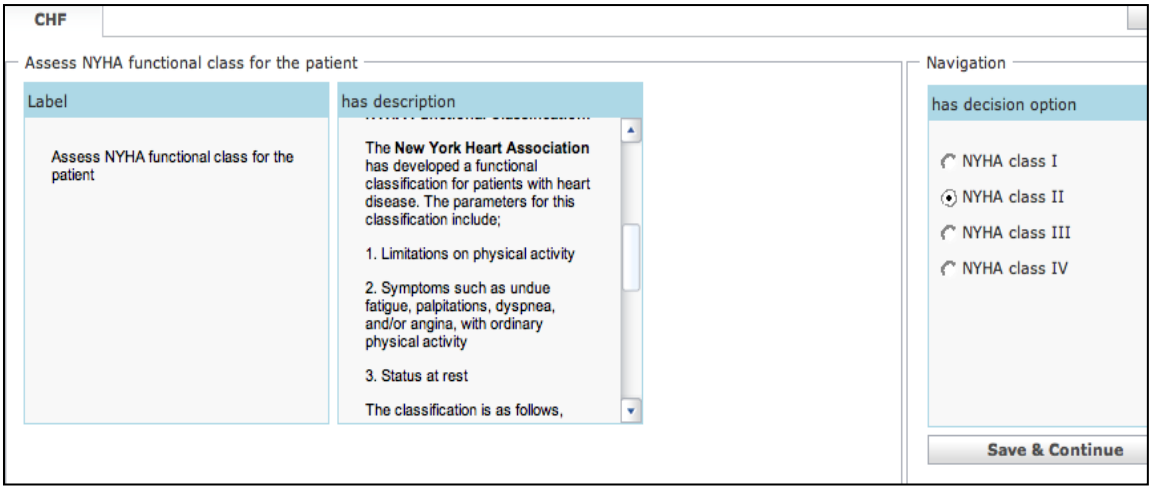


Figure 54: Selecting NYHA class. Note the description of NYHA classification in a separate window

Once the NYHA class II has been selected, COMET recommends some tests in order to exclude heart failure as the possible diagnosis. These tests include, in addition to routine blood chemistry (such as Na, K, creatinine and so on), a chest X-ray, ECG and B-type natriuretic peptide (BNP). If any of these tests along with cumulated Boston criteria score is unable to rule out heart failure, then COMET advises the GP to perform an echocardiography, an expensive test, to confirm the diagnosis and assess left ventricular function.

Once the test results are back, the GP assesses the findings and enters the data in entry point 2, i.e. 'Assessment of tests results'. The chest X-ray reveals cardiomegaly with a cardiothoracic ratio >50% and upper zone redistribution. The ECG appears to be normal but BNP is elevated. These finding are entered into the system in a sequential manner. In addition, routine blood chemistry showed that Na is 128mEq/L; K is 5.8 mmol/L; urea is 9mmol/L; and creatinine is within normal range.

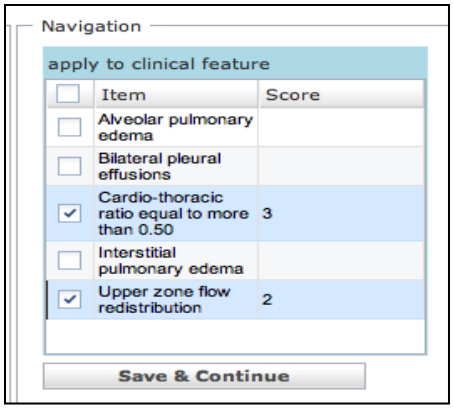


Figure 55: Assessment of chest X-ray result. Note the display of scores as the relevant findings are selected

Figure 56: Assessment of ECG result

Once all the assessment has been carried out and test findings are evaluated (Fig. 55, 56, 57), COMET then prompts the GP to calculate a cumulative Boston criteria score by aggregating scores assigned to various features in three categories: history, physical exam and chest X-ray findings. It should be noted that for an aggregate score, no more than 4 points are allowed from each category. Currently this aggregation of scores is not automated in COMET but can be achieved through additional programming—it is not a modeling issue but a programming issue and will be considered in the future. In this particular case, we can see that the patient has 2 points in the first category, which is history. In the physical exam category, she has 7 points in all. However, since a maximum of 4 points are allowed in all three categories, we can only take a maximum of 4 points in this category. Finally, in the category of chest X-ray, the patient has a total of 5 points from which only 4 can be taken for an aggregate score. Thus, this patient has a cumulative score of more than 8 points.

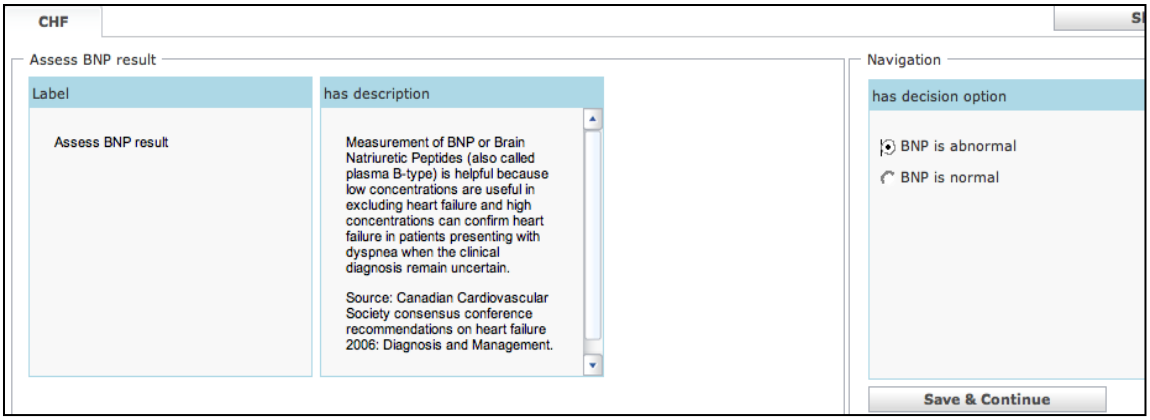


Figure 57: Assessment of BNP result. The description regarding the BNP and source of its description is also displayed

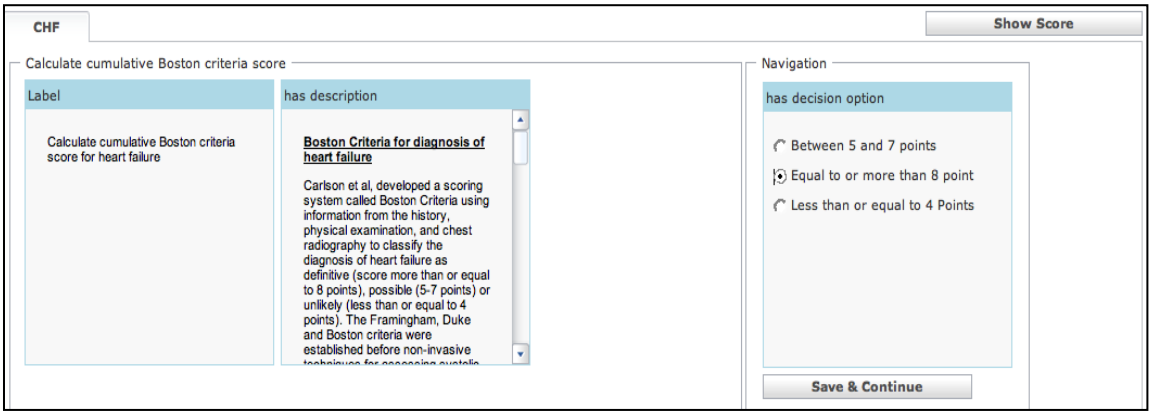


Figure 58: Selecting 'equal to or more than 8 point' option. Note the description of the of Boston Criteria along with its sources is also provided at the same screen

This means that based on patient's signs and symptoms and chest X-ray findings, the diagnosis of heart failure is classified as 'definite'. Thus, based on (B-type natriuretic peptide) BNP (Fig. 57) and Boston criteria score, heart failure cannot be ruled out in this patient. Therefore, when the GP selects the appropriate range for Boston criteria cumulative score in the drop down menu on the screen (Fig. 58) the system reaches the entry point 3. This should prompt a recommendation for echocardiography. In this case, the system does recommend echocardiography for confirmation of the diagnosis and the assessment of left ventricular function (Fig. 59).

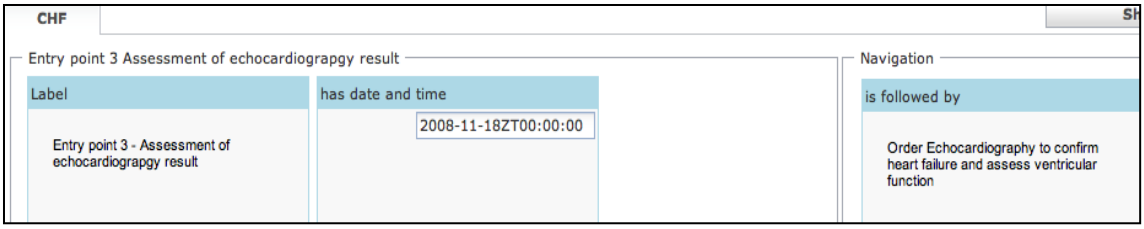


Figure 59: Boston criteria score more than or equal to 8 leads to the entry point 3, with first task involving ordering echocardiography for assessment of ventricular function

As mentioned earlier, COMET is not designed to produce a list of differential diagnoses. Therefore, for patients who have a cumulative Boston score of less than or equal to 4 with normal ECG and (B-type natriuretic peptide) BNP, echocardiography is not recommended, and the GP is urged to reassess the patient.

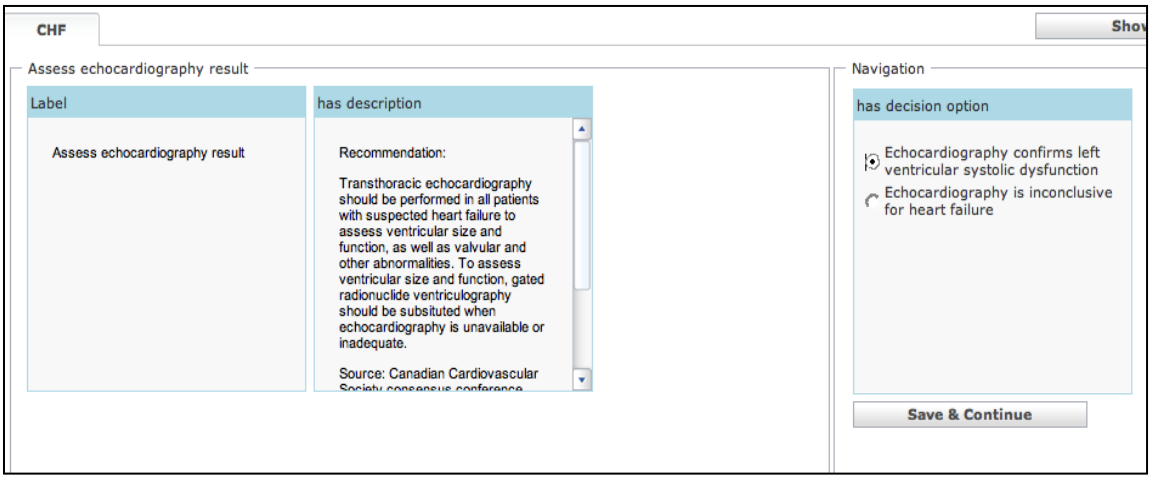


Figure 60: Assessment of echo result, along with relevant recommendation from CPG its source, and strength of the evidence

Since echocardiography showed evidence of left ventricular systolic dysfunction, the diagnosis of heart failure is confirmed (Fig. 60). COMET now proceeds to recommend the initiation of treatment. However, before treatment can be commenced, it is important to evaluate and correct the routine blood chemistry results. The application now leads the GP to entry point 4, which is, evaluation and correction of the routine blood chemistry results (Fig. 61).

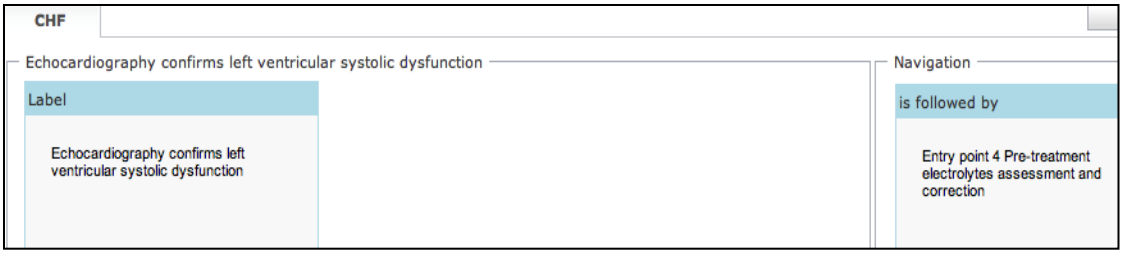


Figure 61: Once LVSD is confirmed by echo, the application leads to entry point 4

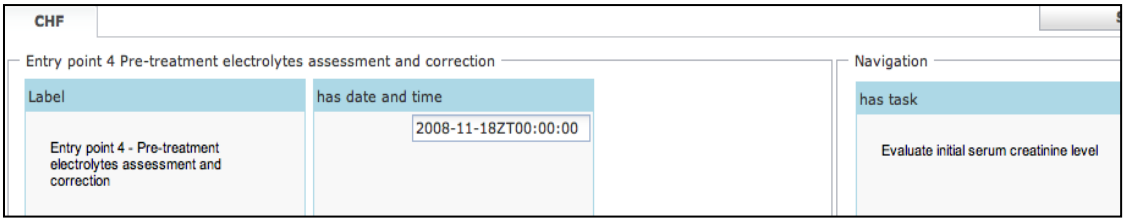


Figure 62: First step in entry point 4; 'Evaluate serum creatinine

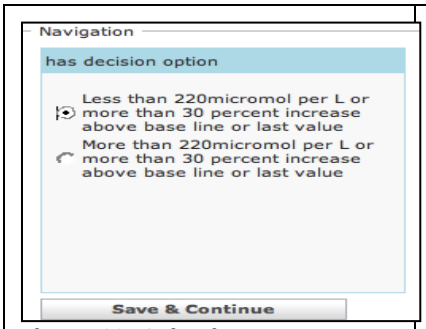


Figure 63: Selecting serum creatinine value that applies to the patient

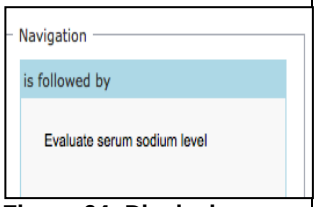


Figure 64: Displaying next task; 'evaluate serum sodium level'

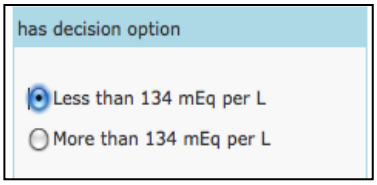


Figure 65: and selecting relevant value

Once the entry point 4 is launched, COMET allows the GP to select the value ranges for the blood chemistry results. The first one is serum creatinine (Fig. 62). Since it is within normal range i.e. less than 220 micromol/L (Fig. 63), COMET directs the GP to the next page that allows her to select Na level (Fig. 64). If the patient would have had a creatinine level above the normal range, COMET would have recommended referral since such high a level indicates serious renal impairment. The Na level for this patient is 128 mEq/L, which is below the normal level. Therefore the GP selects the value 'Less than 134 mEq/L' (Fig. 65). The sodium level needs to be within normal range before drug treatment can begin. As a result, COMET recommends some corrective measures, such as free water restriction and subsequent recheck of the Na level, as seen in figure 66.

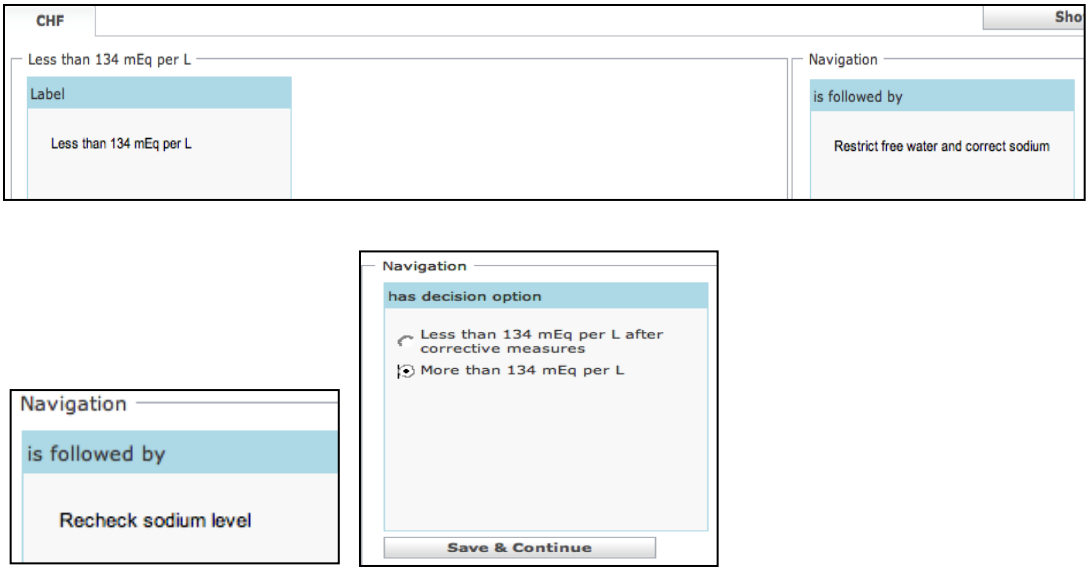


Figure 66: Series of screen giving advice regarding measures to be taken given the sodium level and selection of relevant value on recheck

Once the corrective measures are taken and serum sodium is rechecked, the result showed that it is now 135mEq/L, within normal range.

The GP now selects the appropriate option from the Na level window (more than 134mEq/L) after the recheck Na recommendation (Fig. 66). This leads to the next essential inquiry related to blood chemistry, which is serum K level (Fig. 67).

Figure 67: Advice regarding evaluation of serum potassium

This patient has a serum K higher than normal, i.e., 5.8 mmol/L. Thus, the GP selects the relevant option (more than 5.5 mmol/L) as seen in Fig. 68.

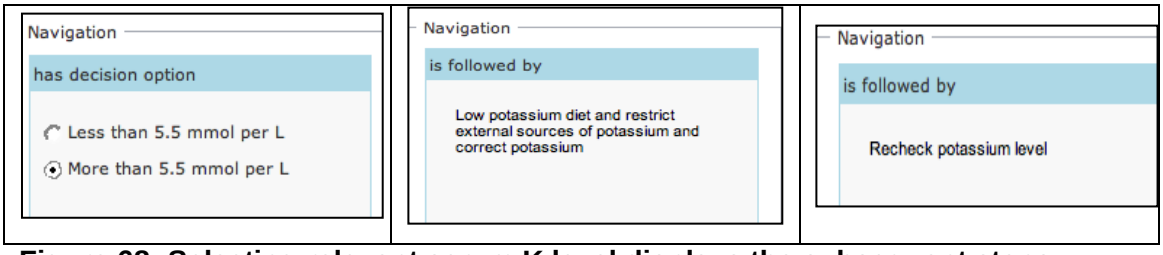


Figure 68: Selecting relevant serum K level displays the subsequent steps

Selection of this leads COMET to recommend low potassium diet and restrict external sources of potassium and subsequently recheck the potassium (Fig. 68).

After taking the appropriate measures to correct the serum potassium level, the GP rechecks the potassium and the potassium is now 5.4 mmol/L, i.e. within the normal range.

On recheck, the GP then selects the 'Less than 5.5 mmol/L' option for K level (Fig. 69)

Figure 69: Selecting relevant K level on recheck

COMET then advises the GP to determine systolic blood pressure. *On exam, it was determined that the systolic blood pressure for the patient is 110 mmHg.* The application provides two options for selection at this point; systolic B.P is more than 90mmHg and Systolic B.P is less than 90 mmHg. Since systolic B.P is more than 90 mmHg, the GP selects this option (Fig. 70).

Figure 70: Selecting systolic blood pressure after advice regarding determining B.P

Selection of this option will lead to the entry point 5 - initiation of heart failure therapy (Fig. 71). This is because, after all the checks and balances, the application decides that it is safe to initiate drug treatment. If this patient had low Na or high K on recheck, despite all corrective measures or systolic B.P less than 90 mmHg, COMET would have recommended referral to the specialist since such complicated situations require more

complex measures and monitoring, which might not be suitable for the general practice setting.

Figure 71: Next step: entry point 5 – initiation of treatment for heart failure

Entry point 5 begins with inquiries regarding the presence of any contraindications to the medications. These inquires are made in a linear fashion, so that uptitration of a drug deemed safe starts in a separate tab and the system does not wait for the uptitration to finish before safety of another drug is evaluated. Contraindications to uptitration are also evaluated and, if detected during uptitration of any drug, the pathway execution stops and recommendation is made for referral.

Once the GP launches entry point 5, COMET advises the GP to determine any contraindications to ACEI (Fig. 72). If she suspects the presence of contraindications to Angiotensin Converting Enzyme Inhibitor (ACEI) and selects the appropriate option, then a list of related clinical features is displayed that a GP can select. Selection of any of these options results in advice regarding referral.

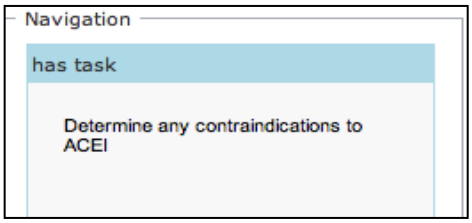


Figure 72: First step in entry point 5: determine any contraindication to ACEI

In addition to specific contraindications to ACEI, COMET also provides an option regarding history of angioedema with previous exposure to ACEI. Selection of this option will result in the launching of Angiotensin Receptor Blockers (ARB) therapy and uptitration instead of that of ACEI (Fig. 73).

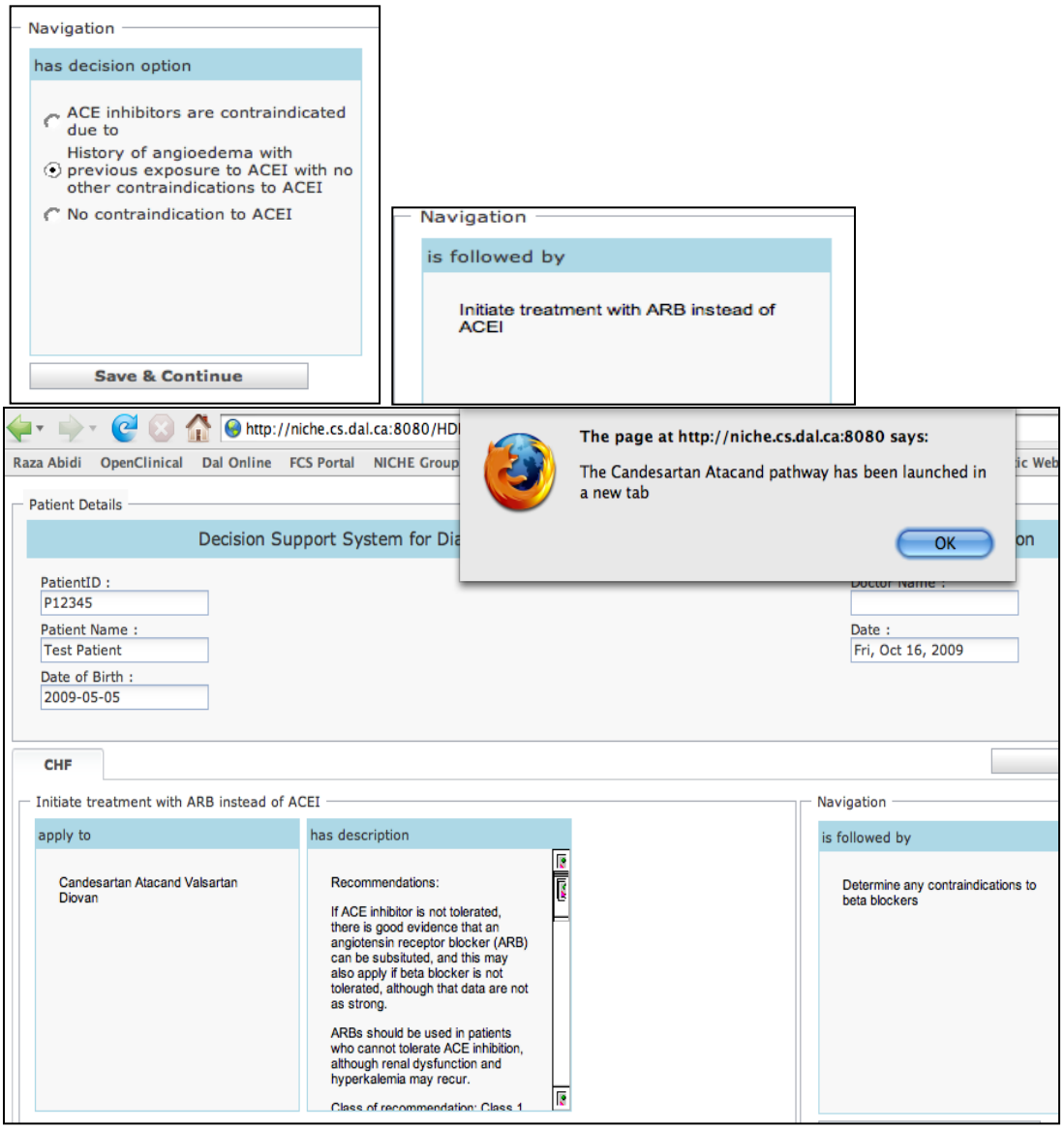


Figure 73: Sequence of screens depicting management steps if a patient has history of angioedema, ARB pathway is initiated instead of ACEI

Since this patient does not have any such history, the GP selects the last option: 'no contraindication to ACEI' (Fig. 74). Note that the recommendations supporting this prescription along with strength of evidence is also displayed with the advice.

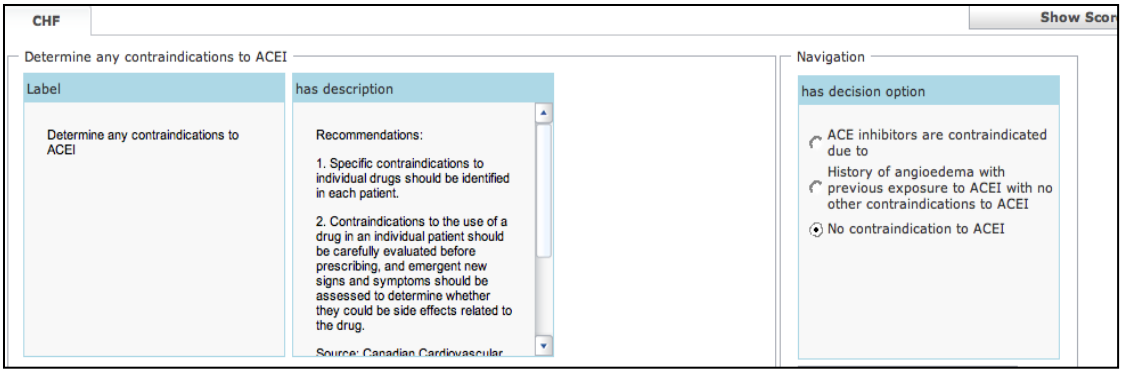


Figure 74: Selecting appropriate decision option for this patient who does not have any contraindication to ACEI. Note supporting CPG recommendation along with source and strength of evidence

The resultant advice is to 'initiate treatment with ACEI' (Fig. 75). Once the GP clicks the save & continue button, two things happen on the next screen. First, a window pops up indicating that

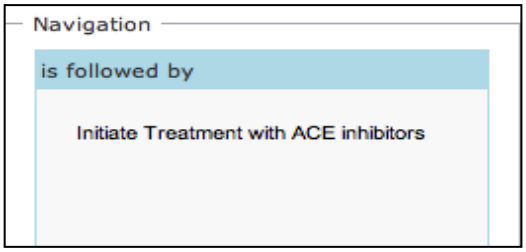


Figure 75: Advice regarding initiation of ACEI treatment

the uptitration pathway for Enalapril (an ACEI) has been launched in a new tab. Secondly, COMET inquires about any contraindication to beta blockers, another heart failure medication prescribed in addition to ACEI as recommended by the CPGs (Fig. 76). Thus, COMET does not wait to complete the entire ACEI uptitration before other treatment such as BB is prescribed, since in reality both Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Beta Blockers (BBs) are often prescribed simultaneously and are uptitrated and monitored for any adverse events.

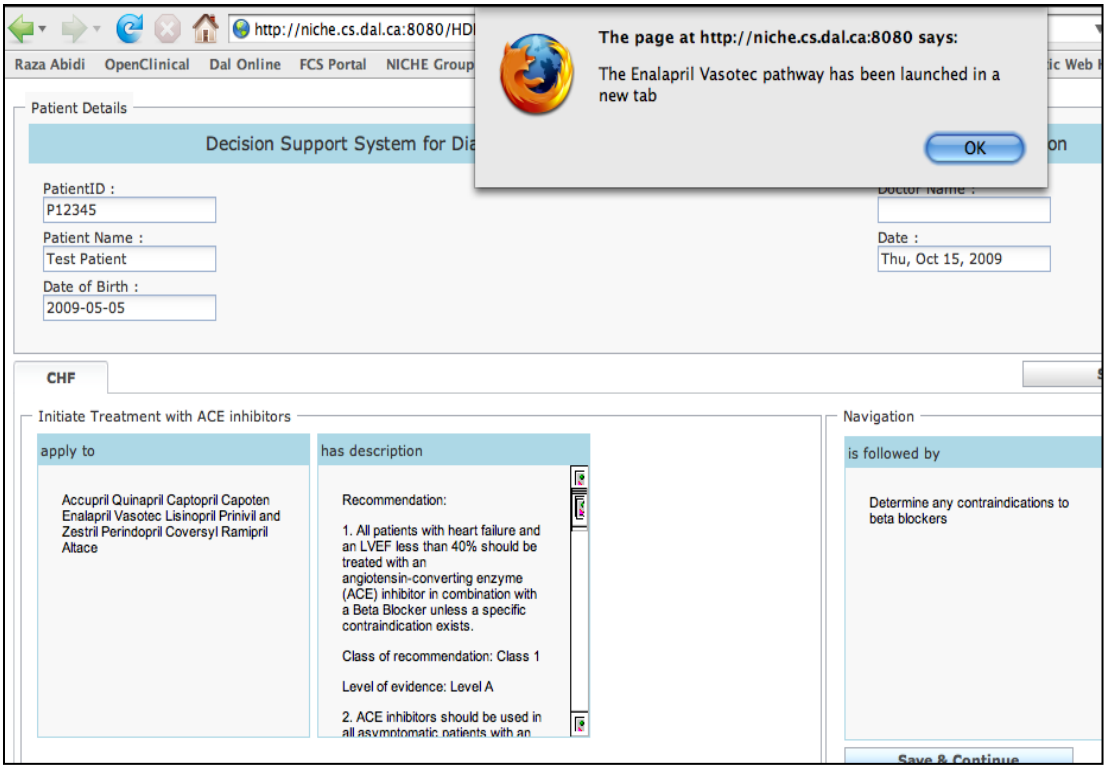


Figure 76: Initiation of Enalapril pathway, followed by advice to determine any contraindication to BB. Also, note the supporting CPG recommendation

Enalapril pathways will begin when the GP clicks the Enalapril tab (Fig. 77). At the present time uptitration of other medications in the ACEI group has not been executed yet, although use of these has been modeled in the ontology. We hope to execute these uptitration algorithms in the future so that a GP can select any one of the medications in the ACEI group.

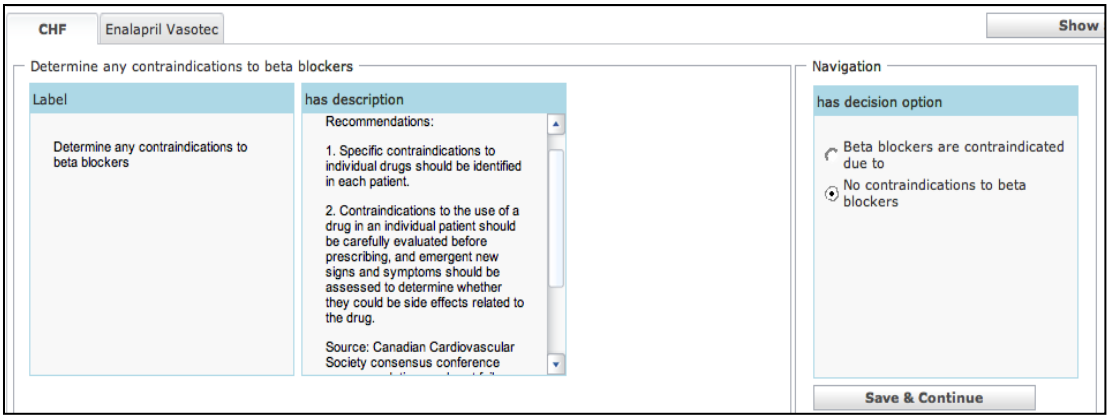


Figure 77: Determining appropriateness of BB administration in the patient. Also note supporting CPG recommendation. (Also see the Enalapril Tab in the upper left corner).

As noted in the case of ACEI, if the GP suspects the presence of any contraindications to Beta Blocker (BB) and selects the appropriate option, this lead to a list of clinical features, the presence of any one of which prompts referral. However, this patient does not have any contraindication to BB (Fig. 77). Thus, the GP selects the option 'no contraindication to beta blocker' (Fig. 77).

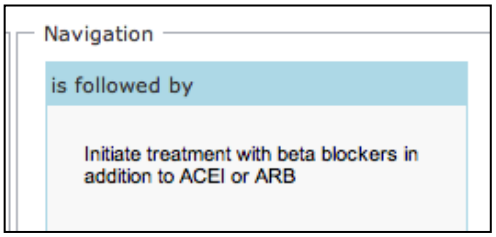


Figure 78: Advice regarding initiation of BB therapy

As a result, COMET advises the GP to 'initiate treatment with beta blockers' (Fig. 78).

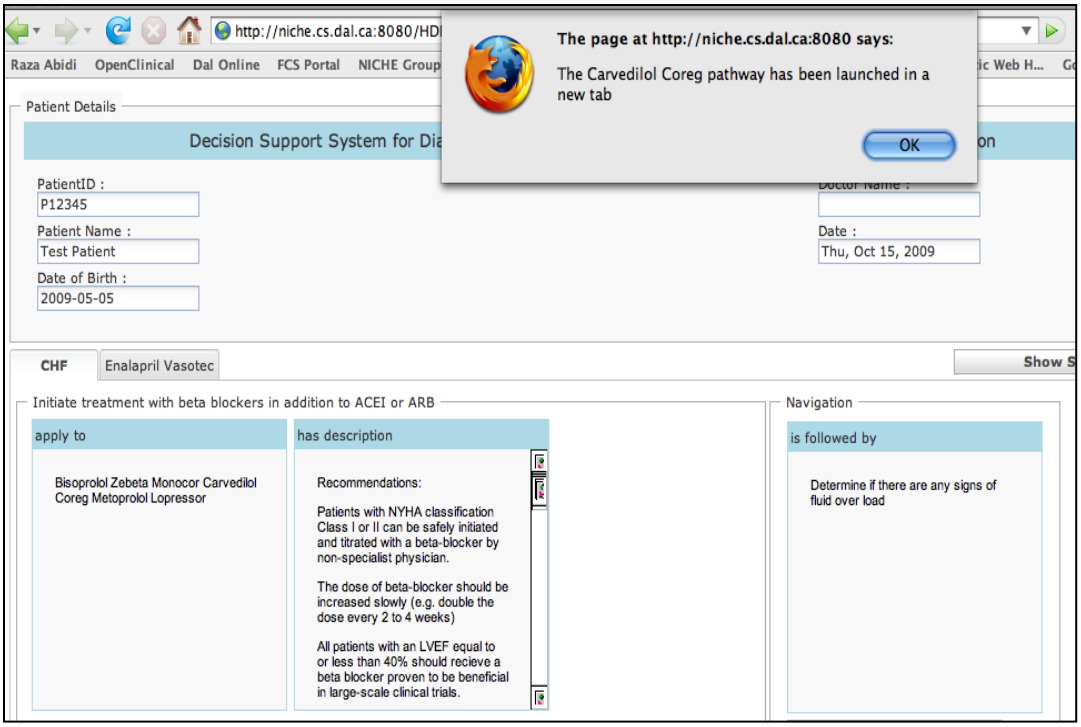


Figure 79: Launching of Carvedilol (BB) pathway

At this time, when the GP hits the save & continue button, another window pops up indicating that the uptitration pathway of carvedilol a beta blocker has been launched in a new tab (Fig. 79). Thus, a new tab appears at the next screen, which when clicked by the GP results in carvedilol uptitration execution. So now the GP has to follow two separate uptitrations simultaneously in two separate tabs leading to separate sets of screen. The main screen, however, continues with inquiries and recommendations regarding prescription of treatments for CHF. COMET advices the GP to determine if there are any signs of fluid overload.

The patient has increased dyspnea, swelling in the ankle and raised JVP.

The GP selects the option that 'signs of fluid overload are present', and in the subsequent screen the clinical signs related to fluid over load are listed. The GP then selects the appropriate signs as noted during the physical exam (Fig. 80); COMET responds by recommending treatment with diuretics for the fluid overload.

Figure 80: Selecting clinical features related to fluid overload

Just like the prescription of the rest of the medications, the prescription of loop diuretics begins by prompting the GP to rule out any contraindications (Fig. 81).

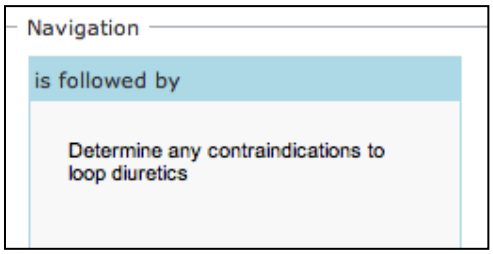


Figure 81: Advice regarding determining appropriateness to loop diuretics

According to the Capital Health protocol for diuretics uptitration, the main contraindication to loop diuretics is a systolic blood pressure less than 90 mmHg.

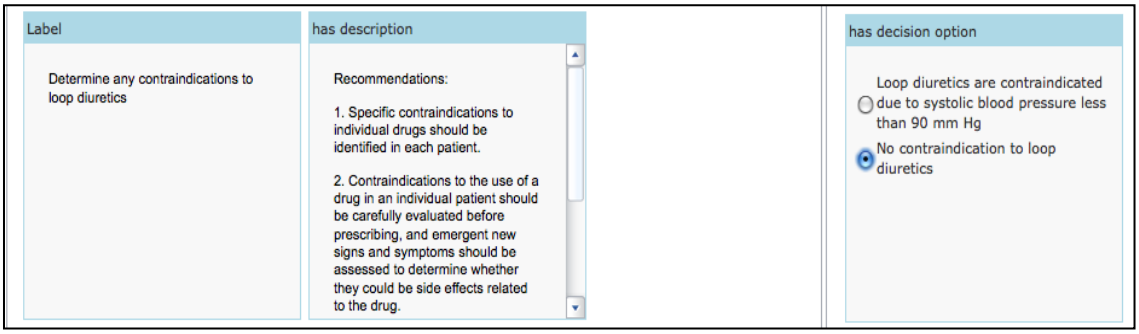


Figure 82: Determining any contraindication to loop diuretic

Since this patient's systolic blood pressure is 110 mmHg, diuretics can be prescribed to her.

Therefore, the GP selects the option that the patient does not have any contraindication to loop diuretics (Fig. 82). COMET then advices the GP to evaluate whether any caution is needed with respect to treatment with loop diuretics (Fig. 83).

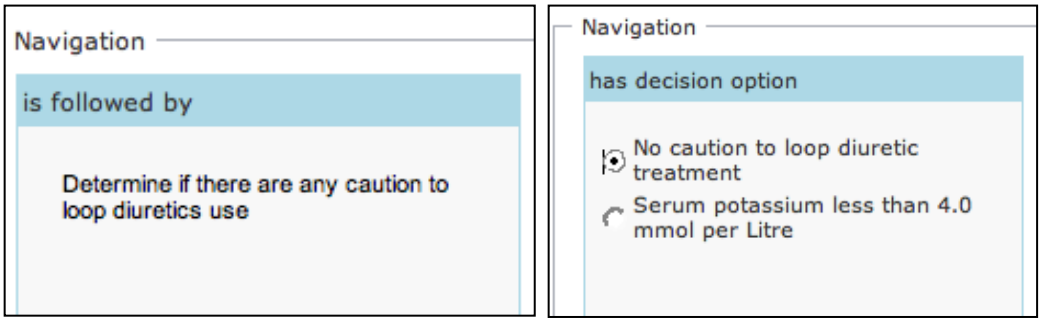


Figure 83: Determining any caution to loop diuretic. If serum K is less than 4.0 mmol/L, then application advises the GP to refer the patient to specialist to determine appropriateness and dose to K supplement and diuretic dose adjustment

According to Capital Health protocols, loop diuretics must be prescribed with caution in patients with a serum potassium less than 4.0mmmol/L.

However, the patient's initial serum potassium, while higher at the initial presentation but brought to a value of 5.4mmol/L by appropriate measures before the onset of therapy.

Therefore, the GP selects 'no caution to loop diuretic treatment' (Fig. 83). COMET then recommends treatment with loop diuretics (Fig. 84).

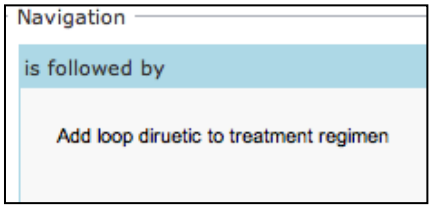


Figure 84: Advice for adding loop diuretic to the treatment regimen

The loop diuretics administration and dose increment is not a lengthy algorithm like that of Angiotensin-Converting Enzyme Inhibitor (ACEI), Angiotensin Receptor Blocker (ARB) or Beta Blocker (BB), and it is the last medication administrated in the treatment of CHF in this application. Therefore, its administration is executed in the main set of screens instead of a separate tab.

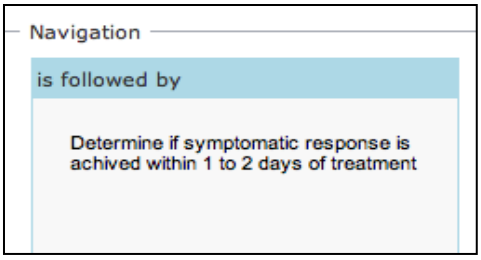


Figure 85: Prompting the GP to determine if symptomatic response is achieved within 1-2 days of treatment

Once the GP has prescribed loop diuretics, COMET prompts the GP to determine if a symptomatic response is achieved within 1 to 2 days of treatment (Fig. 85).

On examination, the GP decides that congestion has cleared by the initial dose of loop diuretics.

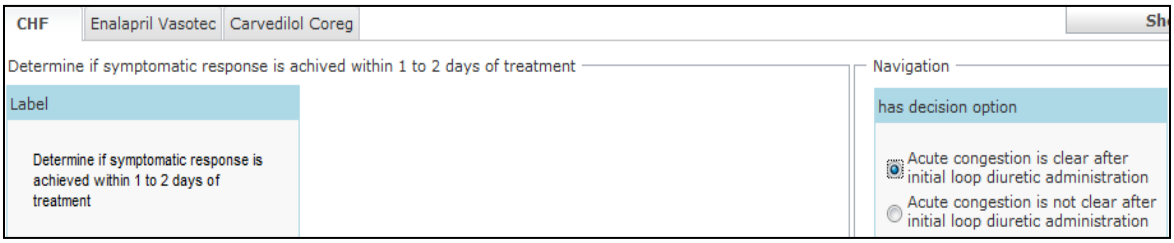


Figure 86: Selecting option 'acute congestion is clear '

Thus, the GP selects the option that states that 'acute congestion is clear after initial loop diuretic administration' (Fig. 86). This option is followed by patient education, in particular advice regarding the loop diuretics timing, spacing and dose adjustment and compliance and adherence of ACE/ARB and beta blockers (Fig. 87, 88).

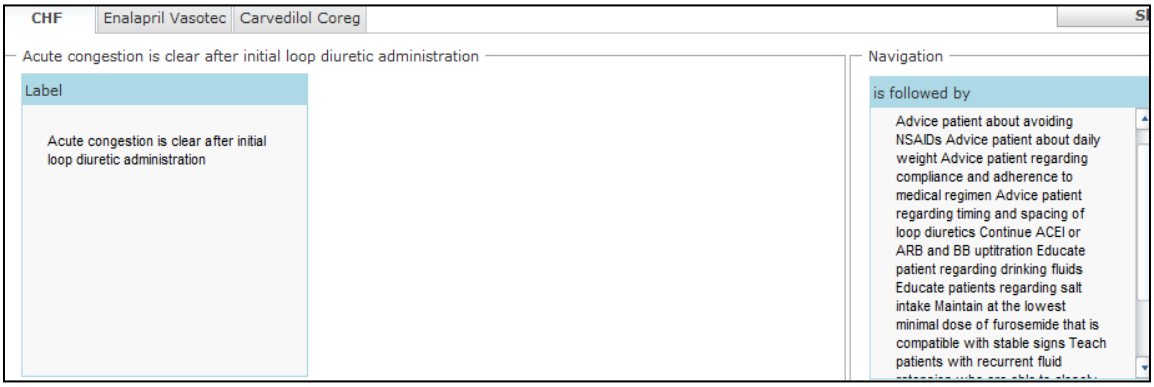


Figure 87: Patient education and advice after loop diuretic administration and clearing of acute congestion

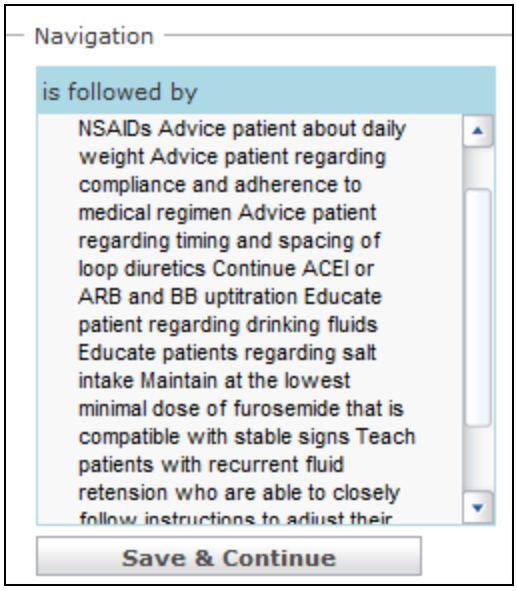


Figure 88: Patient education and advice

Other patient education material regarding salt and fluid intake, daily weight, intake of non-steriodal anti-inflammatory drugs and timing and spacing of medications is also displayed. (Fig. 88, 89, 90). The GP promptly offers this advice, thus successfully and safely managing the care for this patient.

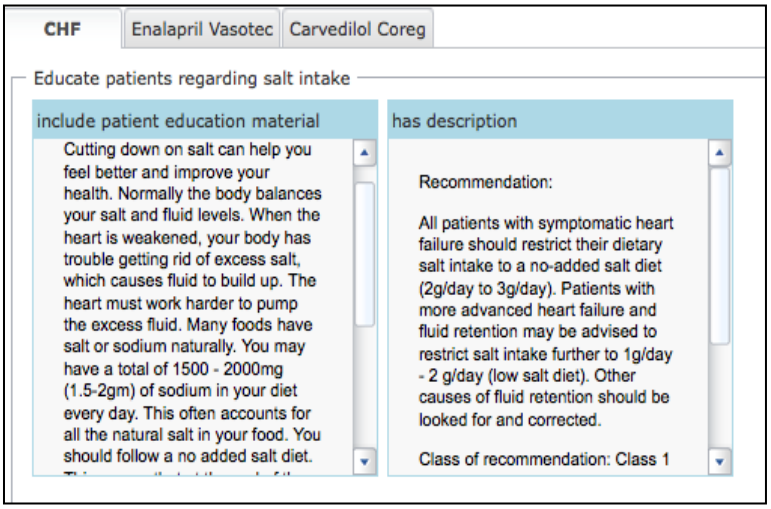


Figure 89: Screen depicting patient education material regarding salt intake along with supporting recommendation from the CPG

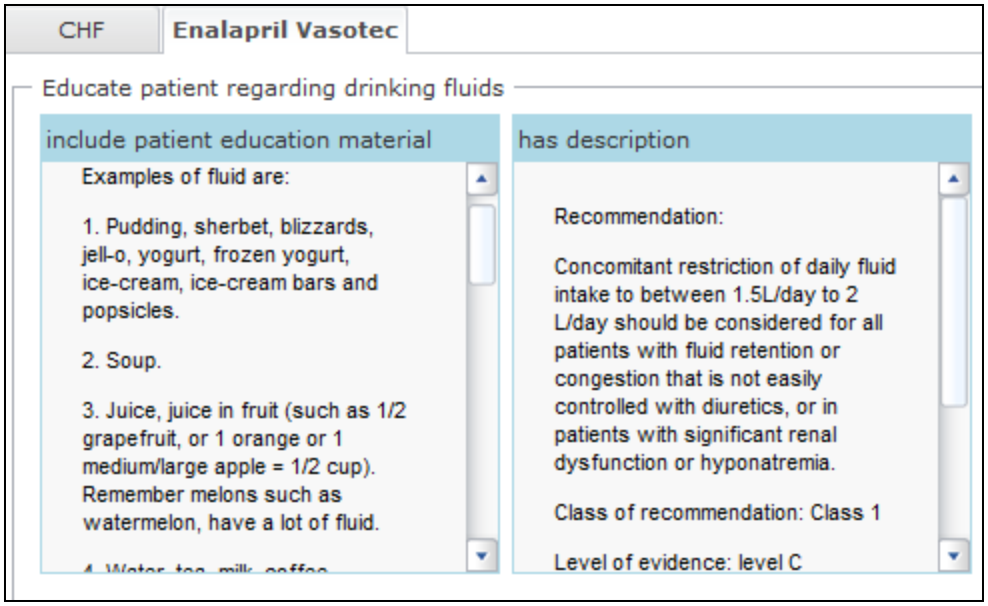


Figure 90: Patient education material regarding drinking fluids

As mentioned earlier, once prescribed, the uptitration of ACEI and BB continues in separate tabs in the main screen. Therefore, COMET allows a GP to trace the uptitration schedules along with the patient's progress with respect to each prescription and, if any contraindication or adverse situation arises during any stage of these titrations, COMET stops and recommends that this patient should be referred to a specialist.

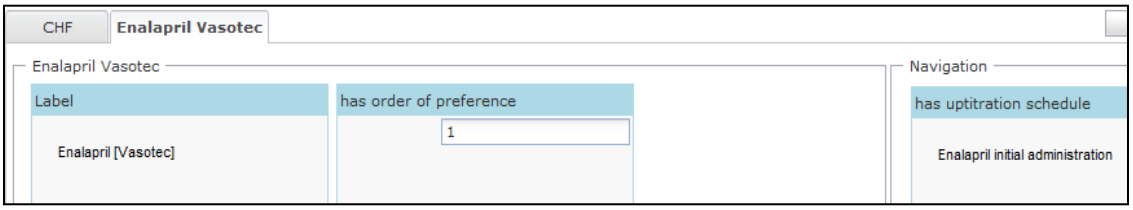


Figure 91: Commencement of Enalapril (ACEI) uptitration

Thus, as when the GP hits the 'Enalapril Vasotec' tab, its uptitration is commenced (Fig. 91). This screen also depicts the order of preference of ACEI, which in this case is 1, which according to the protocol it is most preferred[74] ACEI. Once the GP hits the save button, the next screen displays the details of initial Enalapril administration (Fig. 92).

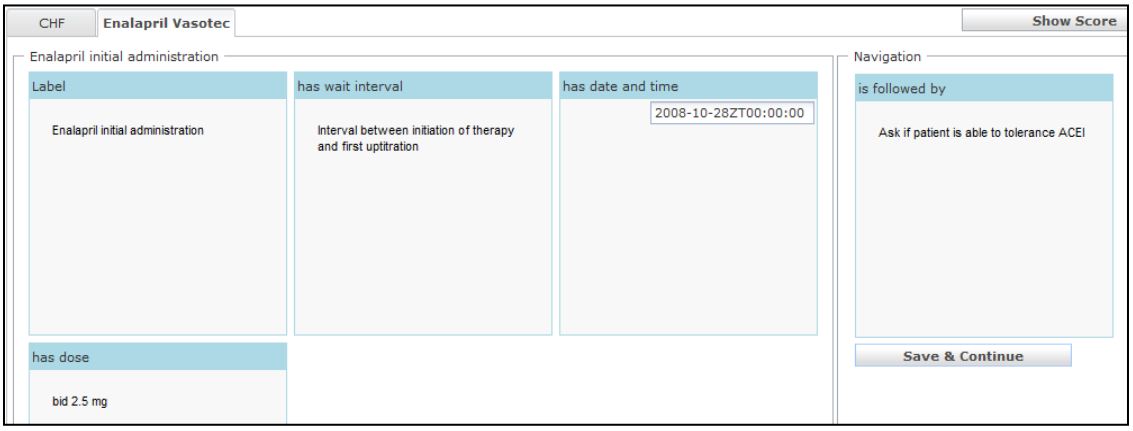


Figure 92: Details of Enalapril (ACEI) initial administration

These include the dosage (2.5 mg, b.i.d), interval between initiation of the therapy and the first uptitration (which is two weeks), and what to do after initial Enalapril administration, which in this case is to ask the patient if he is able to tolerate an ACEI (Fig. 92)

The patient is tolerant to ACEI.

Therefore, the GP selects the appropriate option (Fig. 93). The next screen displays the advice regarding the assessment of renal function and electrolytes and thereby identifies any possible contraindications to the first uptitration (Fig. 94). All this is carried out in the two week interval between the initial administration and first uptitration of the drug.

After performing the necessary physical exam and lab tests, the GP decides that there are no contraindications to first uptitration.

[74] The Capital Health Interdisciplinary Protocol for ACEI uptitration provides a list of ACEI in the order of preference: 1.Enalapril, 2.Ramipril, 3.Perindopril, 4.Accupril, 5.Lisinopril, 6.Captopril. It does not however, mentions any criteria for this preference order.

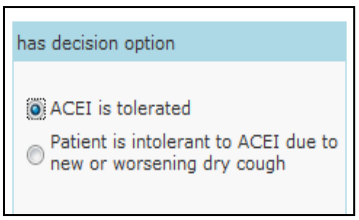


Figure 93: Decision options regarding tolerance to ACEI

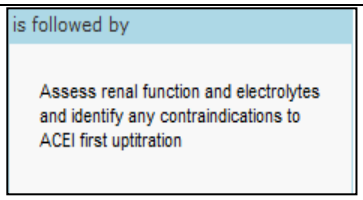


Figure 94: advice regarding assessment of renal function and electrolytes and identifying contraindications to first uptitration

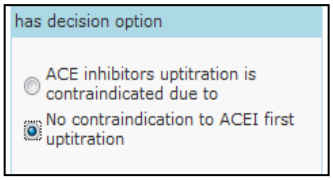


Figure 95: decision options to regarding contraindications to ACEI first uptitration

Therefore, the GP selects the relevant option (Fig. 95). This leads to the next screen recommending Enalapril (ACEI) first uptitration (Fig. 96).

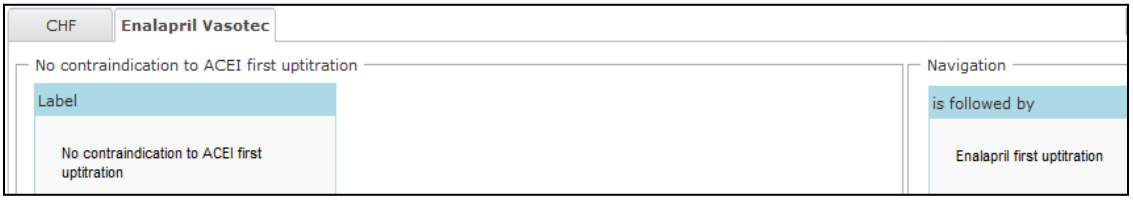


Figure 96: COMET recommends ACEI first uptitration

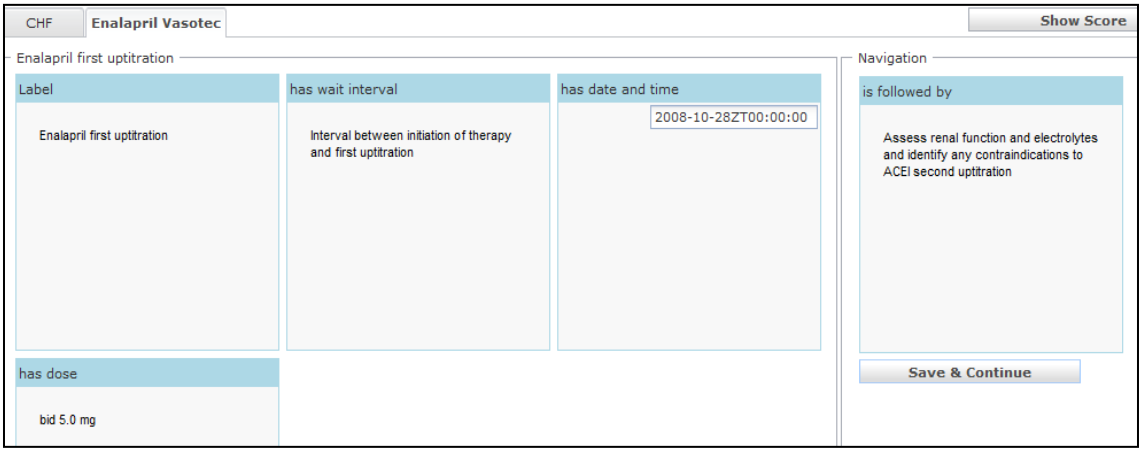


Figure 97: Screen depicting the details regarding Enalapril (ACEI) first uptitration

Once the GP hits the save & continue button, the screen containing the details regarding Enalapril first uptitration pops up (Fig. 97). This screen depicts the dosage, which is now 5.0 mg b.i.d (more than previous dose), the interval between this and the next uptitration, (second uptitration) and what to do after this particular dosage of Enalapril has been prescribed. This time, in accordance with the protocols, COMET recommends the GP to only assess renal function, electrolytes and the contraindications to Angiotensin-Converting Enzyme Inhibitor (ACEI) second uptitration (Fig. 97), since the application

already knows that the patient is able to tolerate the medication. This cycle goes on until the highest dosage of the medication in the protocol has been prescribed safely.

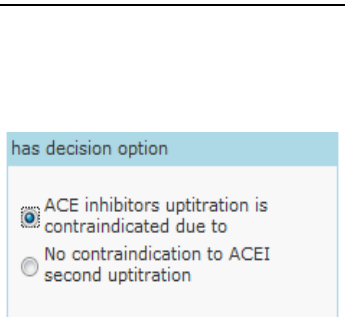


Figure 98: Selecting decision option that ACEI uptitration is contraindicated

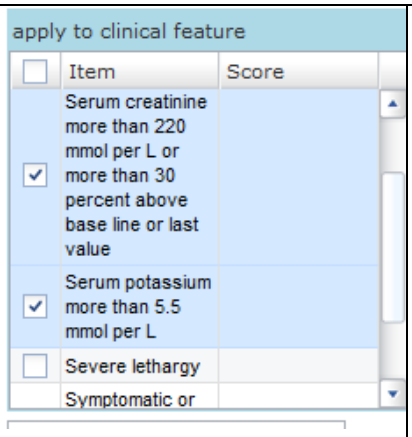


Figure 99: Next screen displays the possible causes of contraindications that can be selected

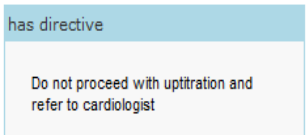


Figure 100: The following screen alerts that GP not to proceed with uptitration and refer the patient to the cardiologist

Suppose that at any point during the uptitration process, the GP finds out that it might not be safe to continue with the titration, she can then select the relevant option before titrating (Fig. 98). This leads to the next screen, which depicts the possible contraindications to uptitration that she may select (Fig. 99). This selection will issue an advice, alerting the GP not to continue with titration and refer the patient to a cardiologist (Fig. 100).

The uptitration of BB blocker is also carried out in similar fashion. Once the GP hits

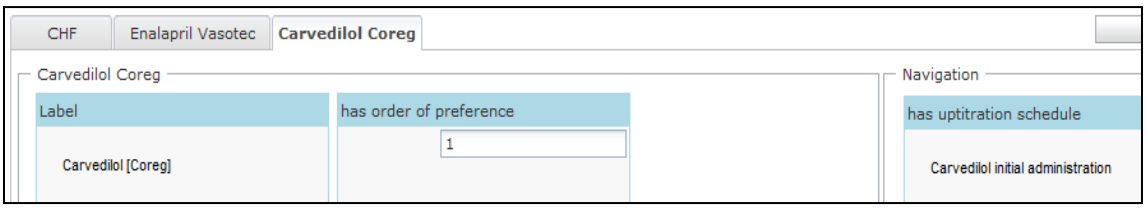


Figure 101: Commencement of Carvedilol (BB) uptitration

Carvedilol Coreg button, its uptitration schedule commences (Fig. 101). The next screen depicts all the necessary information regarding initial administration and what to do next (Fig. 102), which is to identify any contraindications to the first uptitration (Fig. 102). This cycle is similar to that described for the ACEI uptitration and continues until a

maximum BB dosage has been safely prescribed (Fig. 103).

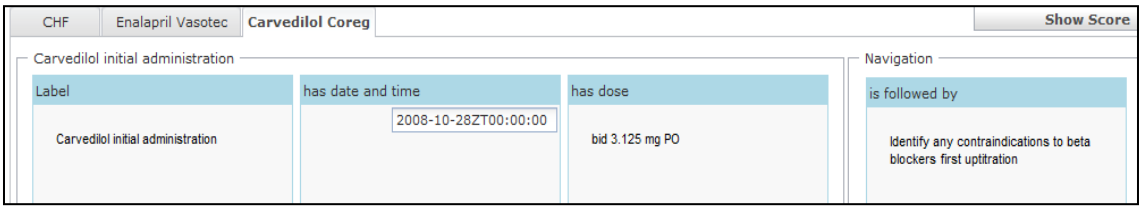


Figure 102: Details relevant to Carvedilol initial administration

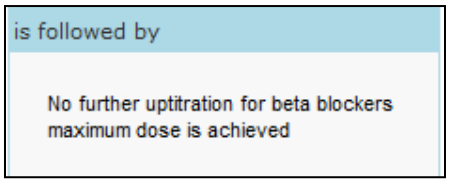


Figure 103: Message informing the GP that maximum dose of BB has been achieved and there is no need for any further titration

Similar to what we have described for the ACEI uptitration schedule, if the GP figures out that further uptitration at any point is not safe, she can then select the relevant option (Fig. 104). This

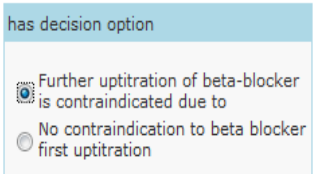


Figure 104: Selecting decision option that BB uptitration is contraindicated

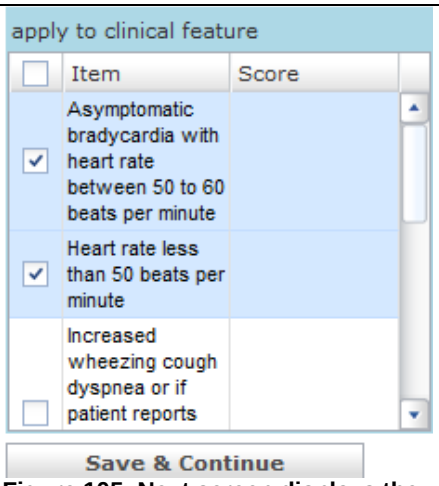


Figure 105: Next screen displays the possible causes of contraindications that can be selected

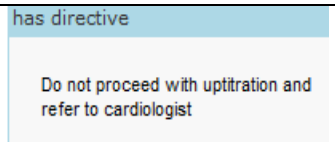


Figure 106: The following screen alerts that GP not to proceed with uptitration and refer the patient to the cardiologist

will lead to the list of the possible contraindications to BB uptitration (Fig. 105). She can select the features from this list that apply to her patient. This will alert the GP to withheld the titration of the medication and refer the patient to the cardiologist (Fig. 106).

The GP can visit the main screen at any time by clicking the CHF button next to the Enalapril and Cardevilol buttons. She can enter any of the two pathways by clicking the relevant tab (Enalapril or Cardevilol). This allows the GP to monitor the treatments that are running parallel at the same time.

In conclusion, we have shown that COMET is able to execute the CHF CP with the patient data, showing various states in the workflow and depicting actions to be performed given the patient data or outcome of the previous step as well as the potential next step. We will like to point out that the execution of the COMET is in accordance to the CP formulated during the knowledge synthesis phase.

7.2.2. COMORBID CHF-AF SCENARIO

Suppose this patient complains of palpitations in addition to the above clinical features. On examination, the pulse is irregularly irregular. The rest of the findings related to CHF are the same as mentioned above. The ECG shows findings consistent with AF, and an echocardiography confirms that the patient has CHF.

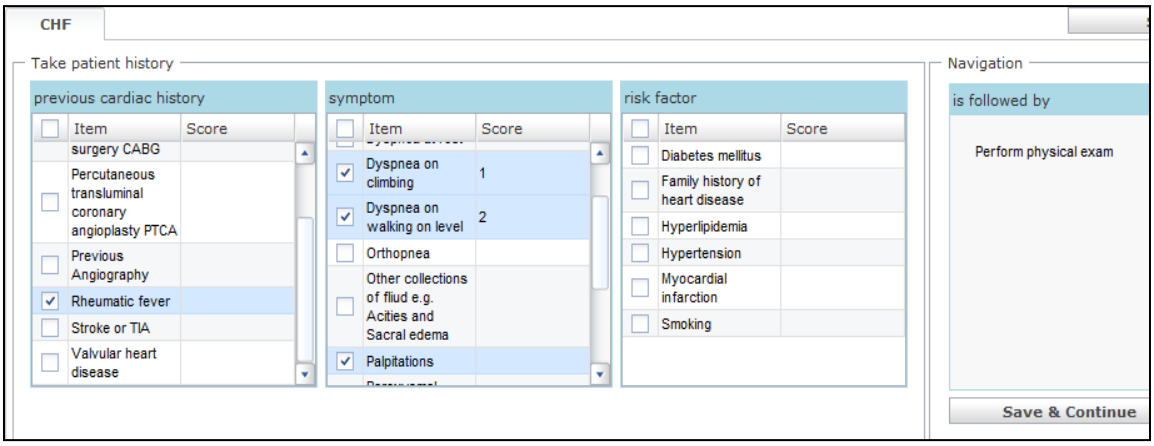


Figure 107: Selecting features relevant to the patient's history, note 'palpitation' has been selected

The GP begins with entry point 1, and selects the items corresponding to the patient's history, which in this case includes an additional symptom of palpitations (Fig. 107). The

next step is the physical exam. Here, the GP select signs that are similar to the ones in the previous case except that for pulse, which in this case is irregularly irregular (Fig. 108).

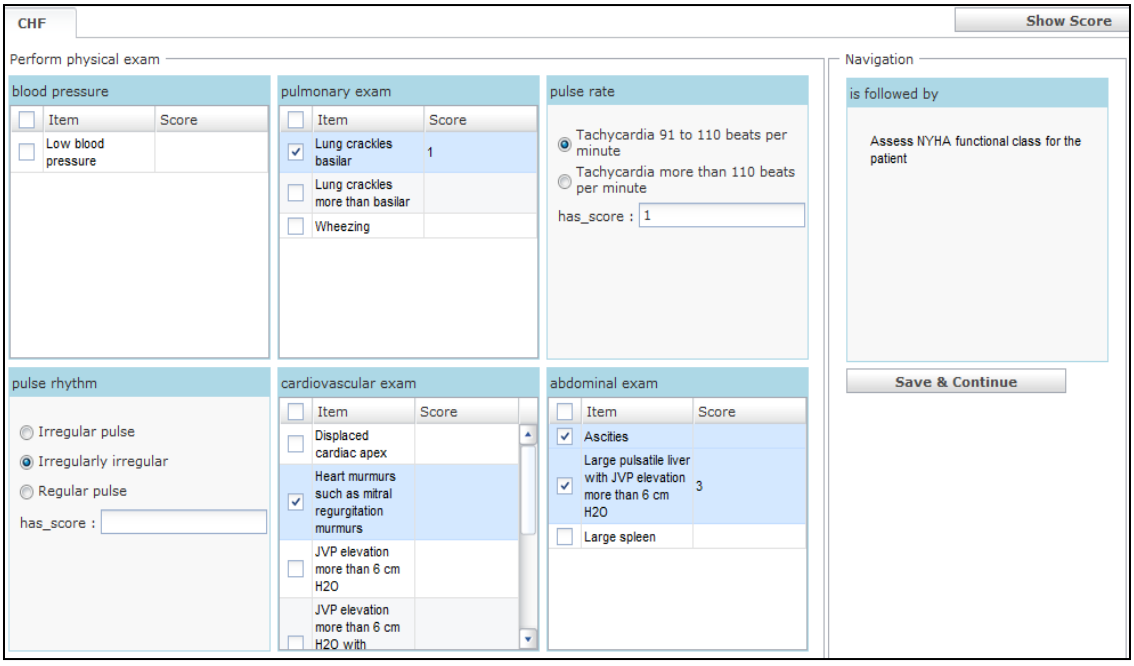


Figure 108: Selecting features relevant to patient's signs, note selection for pulse is irregularly irregular

The subsequent steps in entry point 1, such as assessment of New York Heart Association (NYHA) class and ordering of routine blood tests, X-ray, ECG and B-type Natriuretic Peptide (BNP) are carried out in same manner as mentioned in the single disease scenario. In entry point 2, although BNP is abnormal for CHF, this test does not provide any information with respect to AF. After BNP, COMET the application prompts the GP to assess the ECG result. Since the ECG in this scenario has findings consistent with AF, the GP selects 'ECG is abnormal for atrial fibrillation' (Fig. 109).

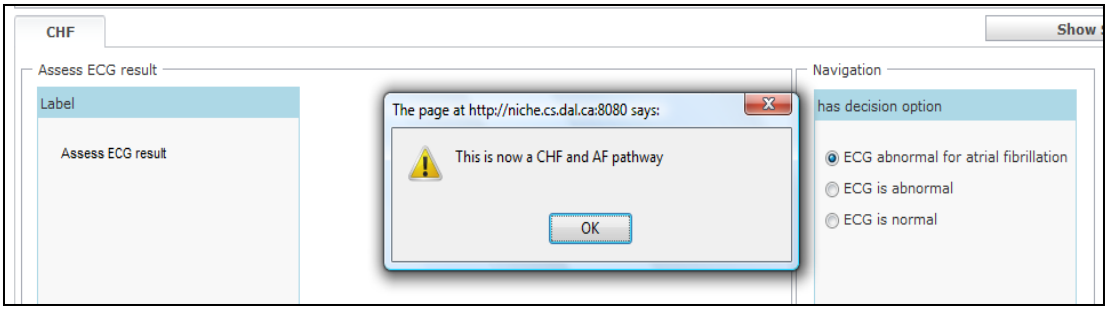


Figure 109: As soon as the GP selects the option 'ECG abnormal for atrial fibrillation', a window pops up confirming that 'this is now a CHF and AF pathway'

This confirms that the patient has AF. As a result, a window pops up letting the GP know that this pathway is now a comorbid pathway, i.e., for both CHF and AF (Fig. 109). Since other causes of dyspnea and other related signs and symptoms are yet to be ruled out and (Left Ventricular Systolic Dysfunction) LVSD is yet to be confirmed using echocardiography, the remaining steps in the pathway, which is now regarded as a comorbid pathway, remain the same. The X-ray findings are assessed and the Boston score is accumulated, which as in the previous case is more than 8. Since AF is confirmed by ECG and the CHF cannot be ruled out by the other tests, COMET leads to the entry point 3, which involves the assessment of the Left Ventricular Systolic Dysfunction (LVSD) by echocardiography. The echocardiography confirms LVSD. Thus it is confirmed that this patient has concurrent CHF and AF.

The management algorithm continues as before for the entire entry point 4, since the patient would still be prescribed CHF treatment, and it remains essential to evaluate the creatinine level and the electrolytes, and to make sure that the B.P is more than 90 mmHg before any additional treatment can be started. Thus, entry point 4 in comorbid pathway will remain the same as in CHF pathway.

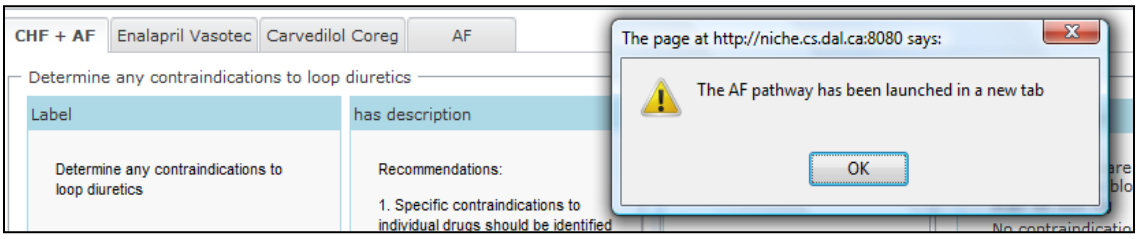


Figure 110: Launching of comorbid AF plan in a separate tab, after CHF medication prescription

Entry point 5 is the one in which medications are prescribed to the patient. Since this is a comorbid pathway, the medication for the treatment of CHF and AF are concomitantly prescribed to the patient. The advice begins with evaluation of CHF medications and their prescription in sequential manner as mentioned in section 6.2.1.

After COMET has evaluated the safety of CHF medications and prescribed them, it launches the comorbid AF plans that are modeled separately in the ontology in a separate tab (Fig. 110). Clicking the AF tab on the screen begins the comorbid AF plan in a separate pathway (Fig. 110). There are two concurrent treatments prescribed along with the CHF treatments when CHF and AF comorbidity is identified. The first is thromboprophylaxis (Fig. 111) and the second is treatment with digoxin. The guidelines recommend warfarin as thromboprophylaxis for patients with concurrent CHF and AF. Therefore, the first comorbid AF plan begins with prompting the GP to identify whether the patient might have any contraindication to warfarin therapy (Fig. 111).

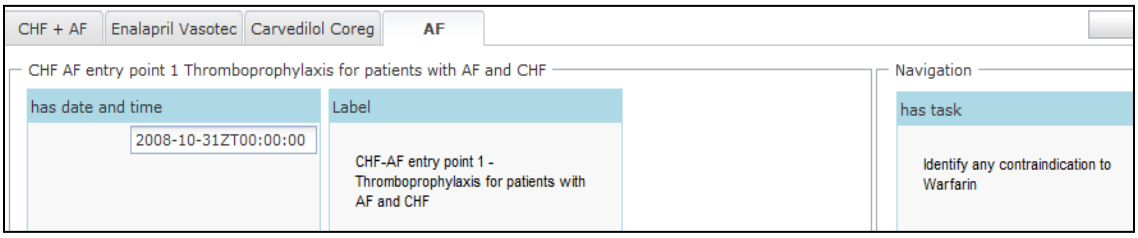


Figure 111: Clicking the AF tab leads to thromboprophylaxis plan, which prompt the GP to identify any contraindications to warfarin administration

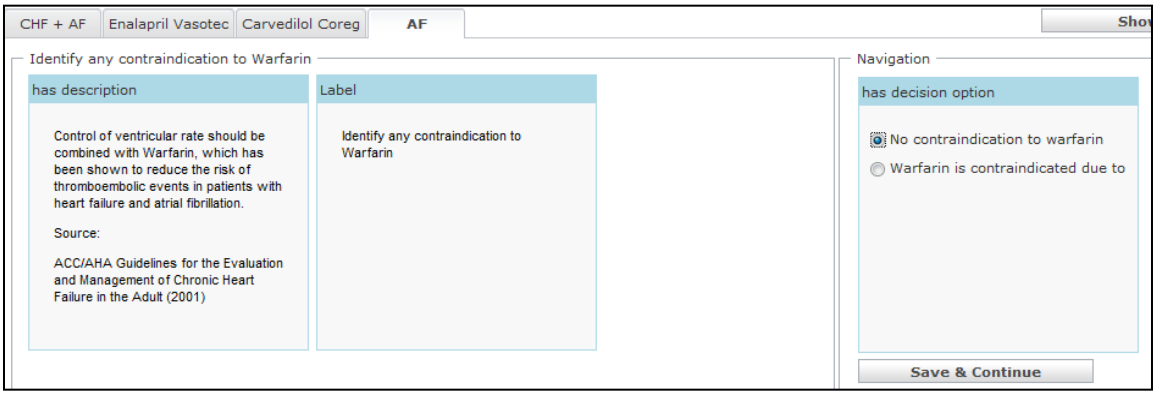


Figure 112: Selecting option regarding contraindication to warfarin. Also note supporting information and the source from the guideline

The patient has no contraindications to warfarin therapy, therefore the GP selects the corresponding option on the screen (Fig. 112). This lead to prescription of warfarin and the

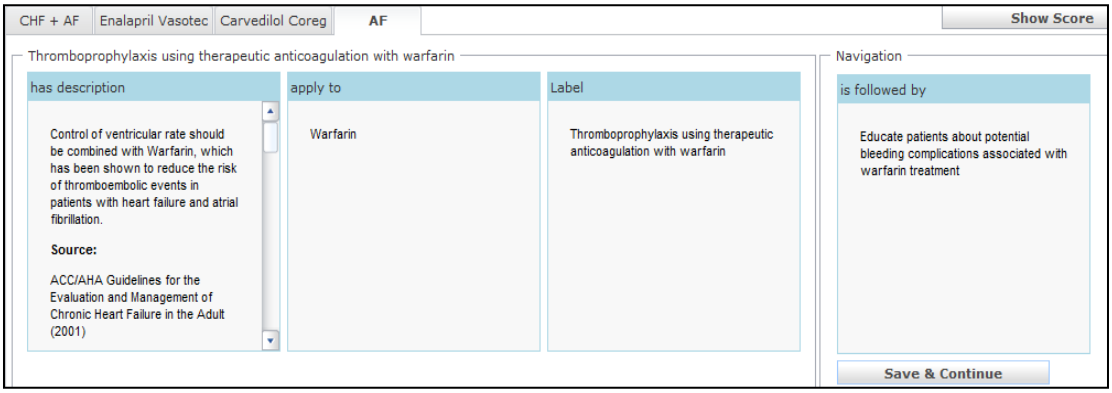


Figure 113: Prescription of warfarin and details regarding this prescription

subsequent screens provide supporting information from the guideline (Fig. 113), and necessary steps regarding educating the patient about potential bleeding complications associated with warfarin treatment (Fig. 114).

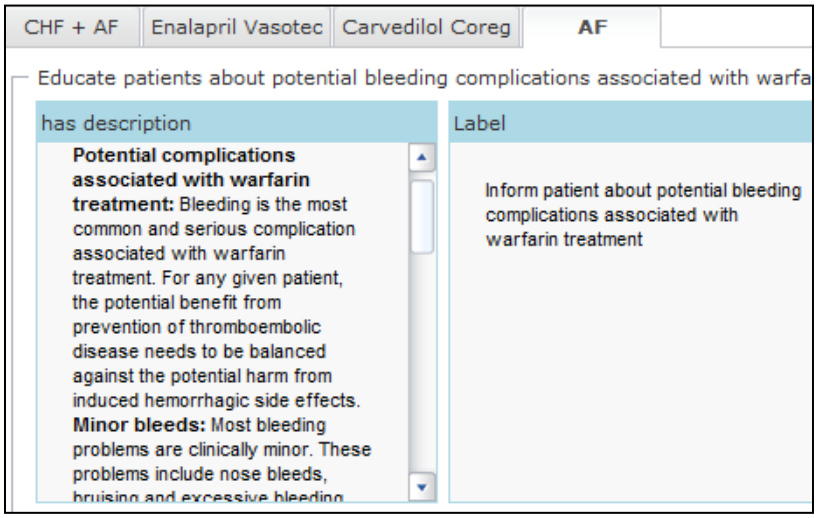


Figure 114: Patient education material regarding potential bleeding complications associated with warfarin treatment

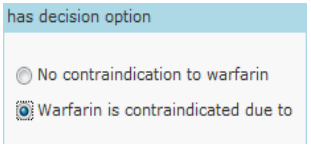


Figure 115: Selecting option 'warfarin is contraindicated'

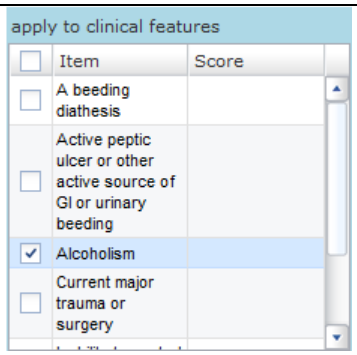


Figure 116: A list of possible contraindications to warfarin are displayed

Figure 117: Selection of any of the options from the list results in referral

Suppose this patient has a history of alcoholism, which is a contraindication for thromboprophylaxis. In such a case, the GP will have to select the option stating that 'warfarin is contraindicated due to' (Fig. 115). This will lead to the following screen depicting a list of potential contraindications associated with warfarin therapy (Fig. 116). The GP will then select 'Alcoholism' from the list (Fig. 116) and the subsequent message will be regarding referral to a specialist (Fig. 117), and the further execution of the comorbid paths will stop.

The next plan is digoxin treatment (Fig. 118), which begins by inquiring about the presence of any contraindications to digoxin.

The GP is not sure if there might be any contraindication to digoxin .

Therefore, the GP selects the option that states that 'digoxin is contraindicated due to' (Fig. 119).

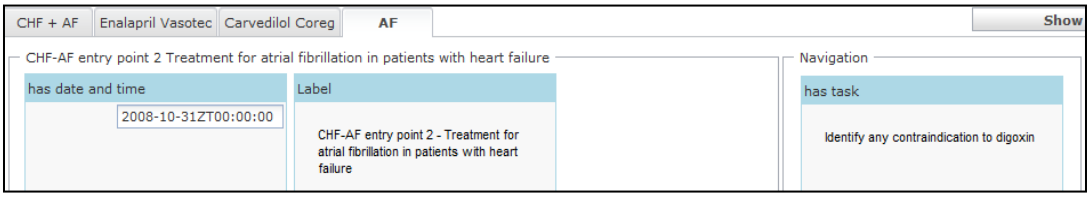


Figure 118: Digoxin treatment plan, depicting inquires regarding contraindication to digoxin

This selection leads the GP to the next screen that provides the list of possible contraindications (Fig. 120). If the GP chooses any one of these contraindications, the subsequent advice is regarding the referral (Fig. 121).

The GP checks the list and realizes that her patient has none of these conditions.

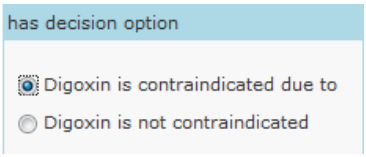


Figure 119: Selecting option 'Digoxin is contraindicated due to'

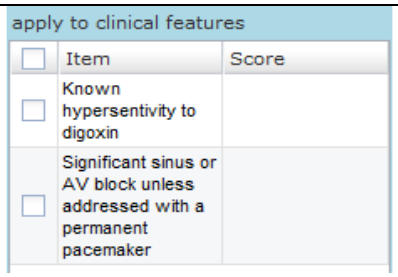


Figure 120: list of contraindications to digoxin

Figure 121: Advice regarding referral

Therefore, the GP goes back and chooses the option stating that 'digoxin is not contraindicated' (Fig. 122). The following screen directs the GP to check for any risk factors associated with

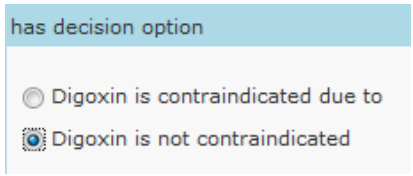


Figure 122: Choosing the option ' Digoxin is not contraindicated

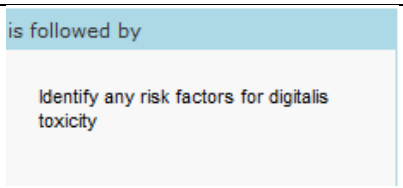


Figure 123: The following task directs the GP to identify risk factors for digitalis toxicity

digitalis toxicity (Fig. 123). Again, suppose that the GP is unsure about what digitalis toxicity risk factors are and whether her patient might have any of them. The GP therefore selects the option suggesting 'risk factors for digoxin toxicity are present such as' (Fig. 124), which displays a list of clinical features consistent with digitalis toxicity (Fig. 125). If she chooses any of the features on the list, the next advice is for specialist referral (Fig. 126).

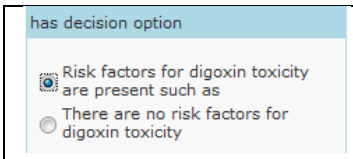


Figure 124: Choosing option 'Risk factors for digoxin toxicity are present such as'

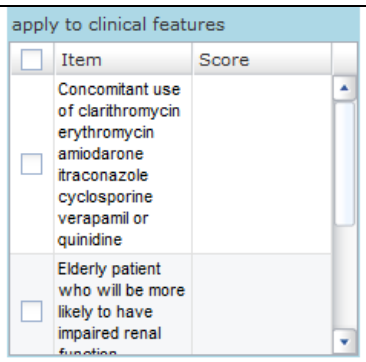


Figure 125: list of clinical features associated with digitalis toxicity

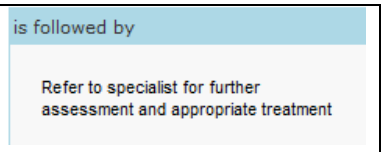


Figure 126: Advice regarding referral if a risk factor is selected

However, after going through the list she conclude that her patient does not have any of the risk factors associated with digitalis toxicity. Therefore, she goes back and selects the option 'There are no risk factors for digoxin toxicity' (Fig. 127). This screen also provides information about

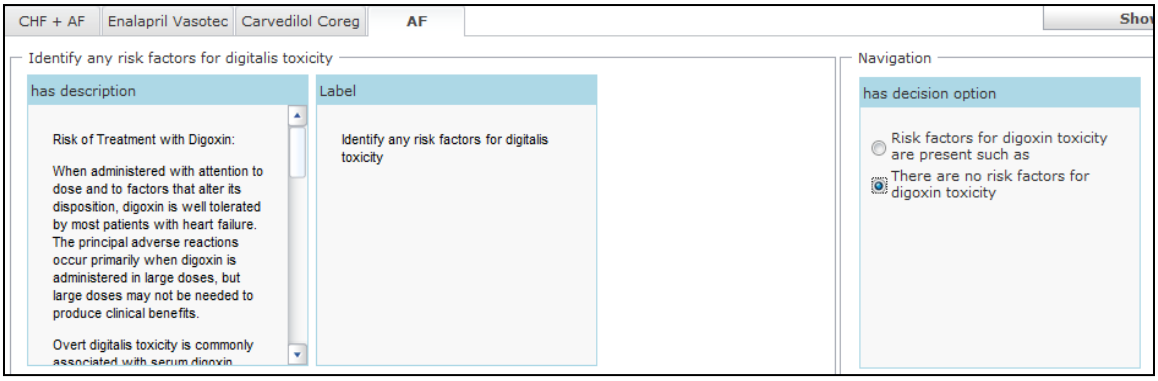


Figure 127: Selecting the option 'There are no risk factors for digoxin toxicity'. Also note the supporting text providing information regarding risk of treatment with digoxin along with the source of this information

risks associated with treatment with digoxin and the sources of this information (Fig. 127). Next, the COMET system advises the GP to add digoxin to the treatment regimen (Fig. 128). The subsequent screen provides the details regarding digoxin administration along with the recommendation supporting this prescription, the strength of evidence and the source of supporting evidence (Fig. 129). The next step is to monitor concentrations of digoxin (Fig. 129).

Figure 128: Advice regarding adding digoxin to the treatment regimen along with evidence from the CPG

Figure 129: Details regarding digoxin prescription. Note that the supporting recommendation the strength of evidence and source of recommendation is also displayed

This is followed by additional advice regarding monitoring of the potassium concentration (Fig. 130), to avoid hypokalemia, and the monitoring of renal function (Fig. 131). In the event that renal function is abnormal, COMET advises the GP to refer the patient to a cardiologist.

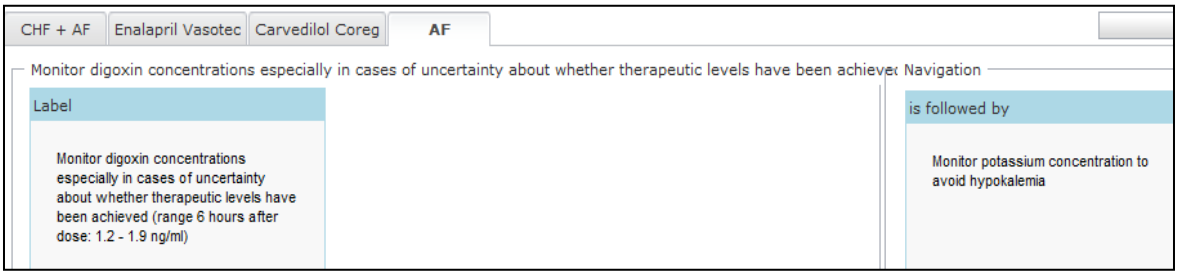


Figure 130: Advice regarding monitoring of potassium concentration to avoid hypokalemia

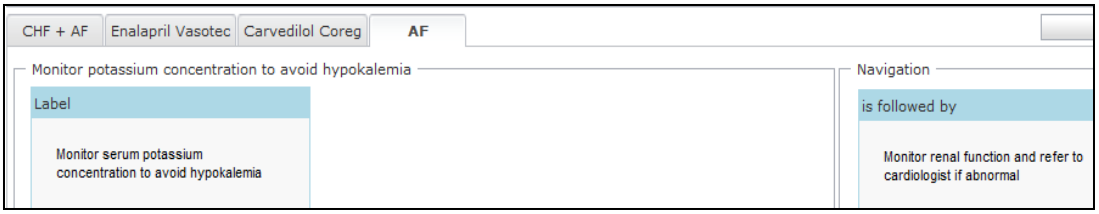


Figure 131: Advice regarding monitoring of renal function

The pathway ends at this point. The system provides education material for the patient as mentioned above. The plans of ACEIs, beta blockers, diuretics and digoxin along with thromboprophylaxis, given patient's clinical features, are executed more or less concurrently whilst ensuring patient safety by advising the GP to monitor the patient for associated treatment risks, contraindications, adverse events and tests results.

In conclusion, our internal validation to test the functionality of COMET has concluded that it is able to handle single disease and comorbid scenarios, including with varying combinations of clinical features that a patient may have during the course of diagnosis and management of CHF and comorbid CHF/AF. We noted that the output of COMET at every phase coincides with the knowledge formalized in the CPs. Therefore, the internal validation was deemed as a success.

7.3. EXTERNAL VALIDATION

In the last evaluation, we performed an external validation of COMET for the correctness of medical content. This evaluation involved three domain experts—one cardiologist and two GPs working in Halifax. Our external evaluation entailed three separate testing sessions with the domain experts. In these testing sessions, we walked the experts through the main features of COMET—i.e. showing its knowledge, features and functionality—for the management of CHF and comorbid CHF-AF. The sessions were interview style and informal, in which the experts provided their feedback to medical content in COMET and to some extent, its functionality. The testing results and the responses of the domain experts are presented as follows;

7.3.1. DOMAIN EXPERT No. 1 – CARDIOLOGIST

The first session was with Dr. Jafna Cox, who is a Professor in the Department of Medicine, Division of Cardiology, at Dalhousie University. After reviewing the entire CP

and its representation in terms of the CP ontology, Dr. Cox suggested the following updates to medical content in COMET:

With respect to 'CHF entry point 2 – Assessment of test results', Dr. Cox suggested that it would be beneficial to add optimal cut-off points for BNP test, rather than just mentioning that B-type Natriuretic Peptide (BNP) is abnormal or normal (for CHF). He suggested that in the future, precise cut off value can be acquired from a lab where the BNP test is conducted and added to the CP, so that it can be displayed in COMET.

With respect to 'CHF entry point 3 –Assessment of echocardiography', Dr. Cox advised that it is better to add another decision option to the echocardiography test results. This option is related to diagnosis of diastolic heart failure. In Dr. Cox's opinion, since there are no evidence-based treatments available for the management of diastolic heart failure, it is best managed in the specialist care setting. Therefore, once identified by the GP, such patients should be referred to the specialist, sooner rather than later. Given the scalable nature of the CP ontology, we implemented this update promptly through instantiation, without any need to alter the structure of the model in any way. As shown in Fig. 132, another individual 'Echocardiography confirms diastolic heart failure' was added to the class ECHO_RESULT, which is a sub-class of DIAGNOSTIC_TEST_RESULT.

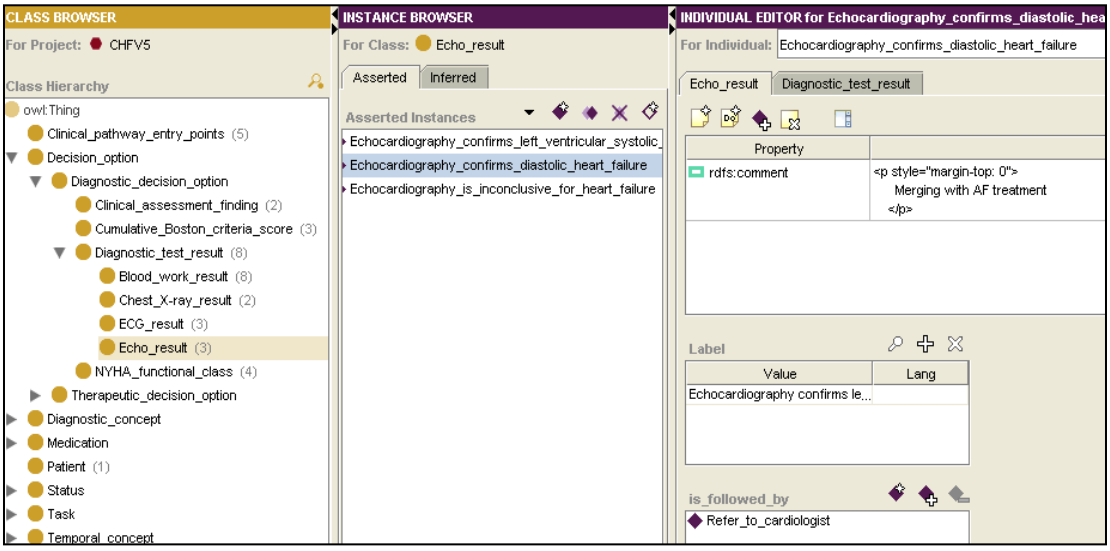


Figure 132: Adding individual "Echocardiography confirms diastolic heart failure' to the class ECHO_RESULT. Also see the following step, which is "Refer to cardiologist"

In accordance to the relationships formalized in the ontology, this individual is linked with the individual, "Refer to cardiologist" (Fig. 132).

With respect to 'CHF entry point 4 – Pre-treatment electrolytes assessment and correction', it was recommended that any abnormality of serum potassium should be checked before that of sodium. Dr Cox also emphasized that any abnormality of electrolytes should be corrected simultaneously and not sequentially as currently performed in the COMET.

Again, the recommendation was readily implemented within the CP ontology by simply reversing the sequence of individuals representing assessment of the electrolytes, so that checking of potassium is performed before that of sodium (shown in Fig. 133, 134). The concurrent correction of electrolytes however is not a modeling issue but a programming issue, as it requires the handling of concurrent processes. In an earlier version of the ontology, these two tasks were represented at the same level so that they can be executed concurrently. However, on the request of the programmer, they were later arranged sequentially since he found it very difficult to execute them concurrently. This issue will be resolved in updated version of COMET.

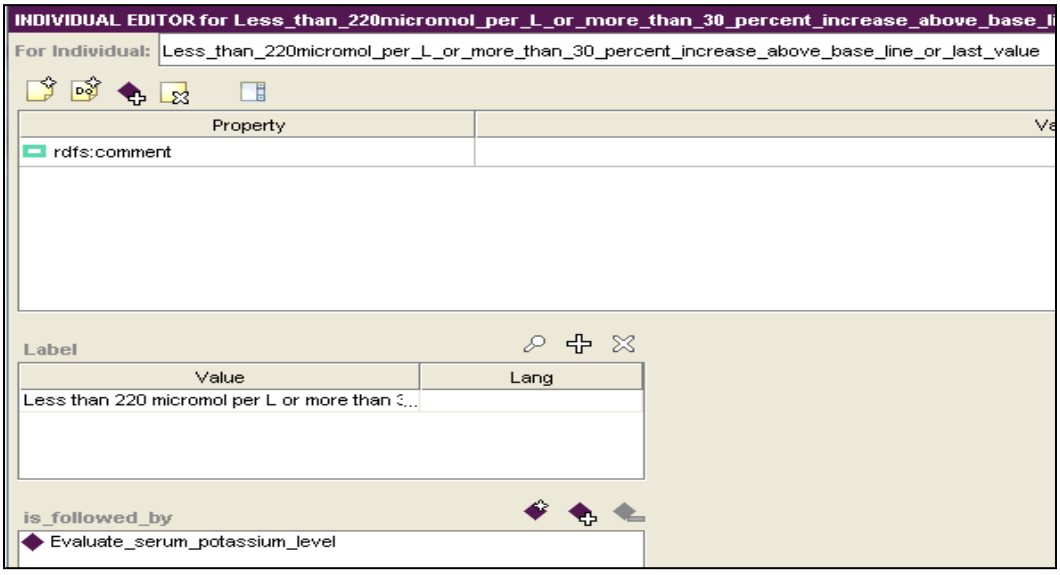


Figure 133: If serum creatinine is < 220 micromol/L then next step is to 'evaluate serum potassium' instead of sodium

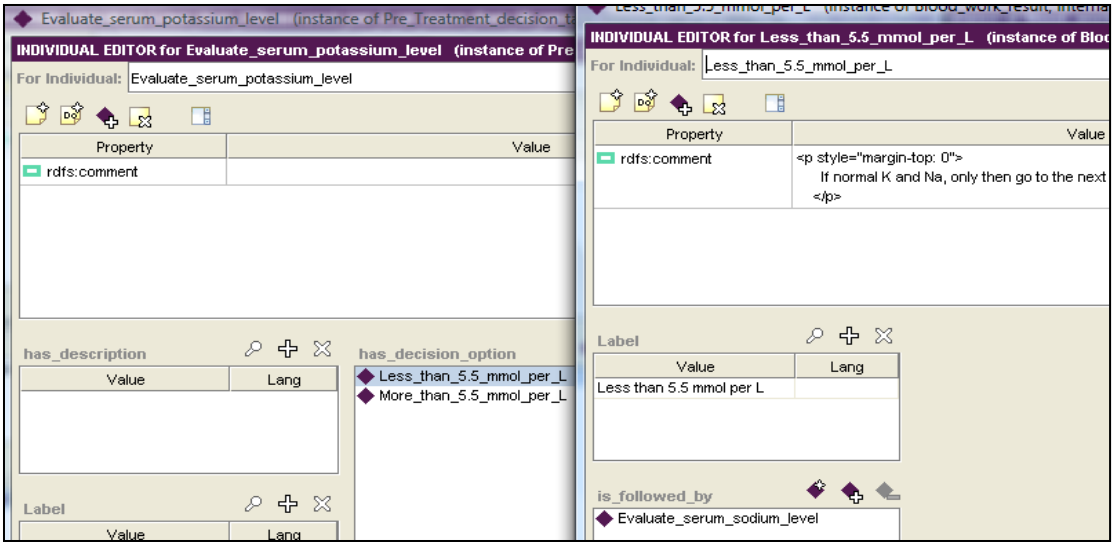


Figure 134: If serum potassium < 5.5 mmol/L then the next step is to 'evaluate serum sodium'

The cutoff value for serum creatinine in the CPs and in the COMET presently is 220mmmol/L. This means that any value 'greater than 220mmol/L or greater than 30% increase above baseline or last value' is regarded as abnormal and patient should be referred for the specialist assessment. This value has been extracted from Capital Health Interdisciplinary Protocols for the ACEI Uptitration. However, this cutoff value has been used only in the context of ACEI uptitration in the protocol. This means that if serum creatinine is greater than 220mmol/L or greater than 30% increase above baseline or last value, further uptitration is contraindicated and the patient should be referred to the cardiologist. In Dr. Cox's opinion, this value does not reflect the correct cutoff value with respect to initiation of the treatment. Furthermore, Dr. Cox also proposed that the units for measurement of other blood parameters such as serum potassium and sodium as well as their normal limits should be consistent with those used in the local labs. In the next version of COMET, we plan to acquire the correct values and units for creatinine, sodium and potassium from the labs and incorporate them in COMET.

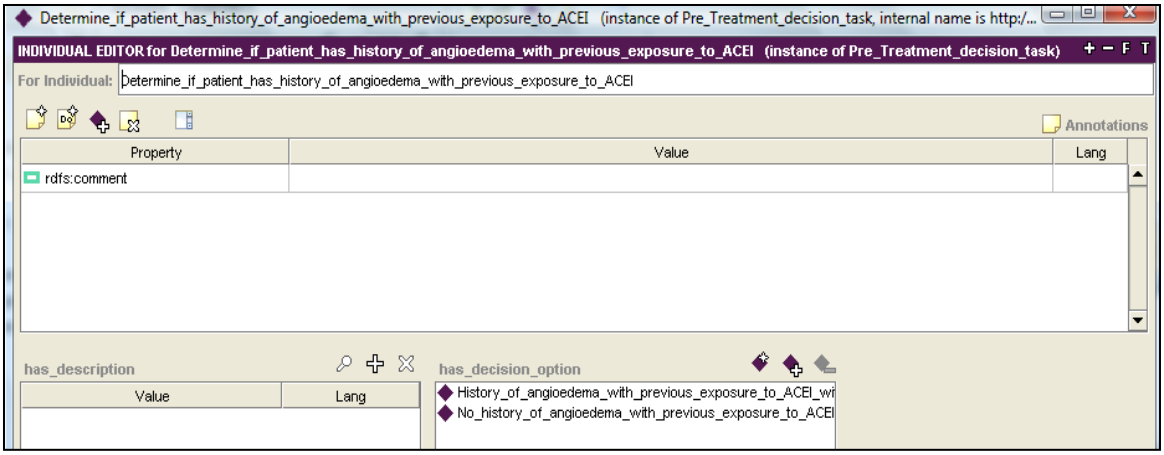


Figure 135: Adding 'Determine if patient has history of angioedema with previous exposure to ACEI' as an individual of class PRE_TREATMENT_DECISION_TASK, with two decision options 'History of angioedema' and 'No history of angioedema'

With respect to 'CHF entry point 5 – Initiation of treatment for CHF', Dr. Cox advised that a history of angioedema should be the first logic branch (not the second as we currently have) since it is an immediate and potentially fatal side-effect of the ACEI exposure and should be evaluated immediately. We were able to implement this recommendation by adding another individual "Determine if patient has history of angioedema" to the class PRE_TREATMENT_ DECISION_TASK (Fig. 135). This individual has two decision options, "History of angioedema with previous exposure to ACEI" and, "No history of angioedema" (Fig. 136)

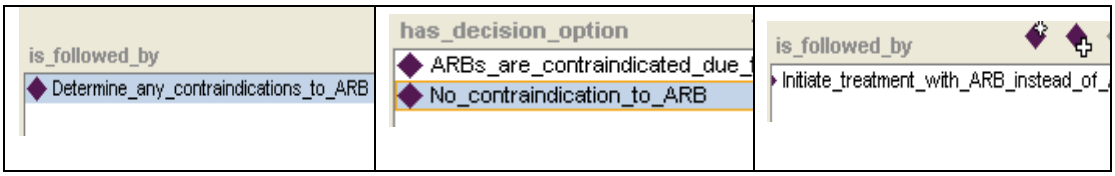


Figure 136: Incase Patient has history of angioedema, the next step is to determine presence of contraindications to ARB and to start the treatment with ARB instead to ACEI if there are none

In case the patient has a previous history of angioedema, then the next step (Fig. 136) is to determine the presence of any contraindications to Angiotensin Receptor Blocker (ARB) such as bilateral renal artery stenosis and severe aortic stenosis. If these contraindications are present, the subsequent step is specialist referral. If there are no contraindications to ARB treatment then the following step is to initiate treatment with

ARB instead of ACEI. This will launch the ARB uptitration schedule (as seen in the ontology and the COMET).

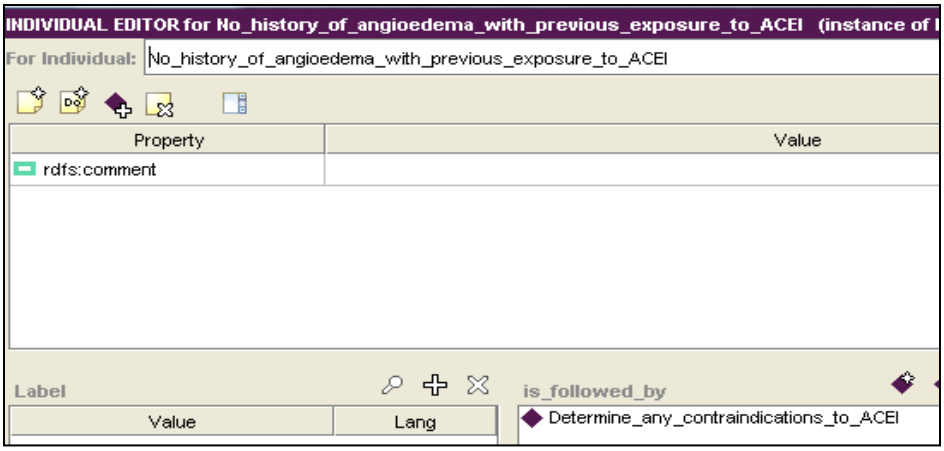


Figure 137: If there is no history of angioedema, then the next step is to determine any contraindication to ACEI

If, however, there is no history of angioedema then the next step is to determine other contraindications to ACEI as shown in Fig. 137 and as seen presently in the COMET. In the absence of any contraindication, ACEI is recommended and its uptitraion begins. The execution of the plan from this point forward is same as currently seen in the COMET.

Dr. Cox also mentioned that a useful feature with respect to general practice will be to add tabs (just like we have for Enalapril and Candesartan in the current version) for all the drugs available in Nova Scotia in ACEI and ARB groups, their uptitration schedules and information regarding their insurance coverage and pricing. Presently, the uptitration schedules of 6 drugs in ACEI group and two drugs in ARB group (as provided in the protocols) have been formalized in the ontology. Although one schedule in each group has been executed in COMET, we plan to execute the rest of the schedules in the next version of COMET with the addition of pricing and insurance information.

With respect to treatment with loop diuretics, Dr. Cox suggested that if acute congestion is not cleared within 1 to 2 days of diuretic administration, the patient should be referred to the cardiologist immediately. The GP should not attempt to further uptitrate the diuretic as is currently the case in COMET.

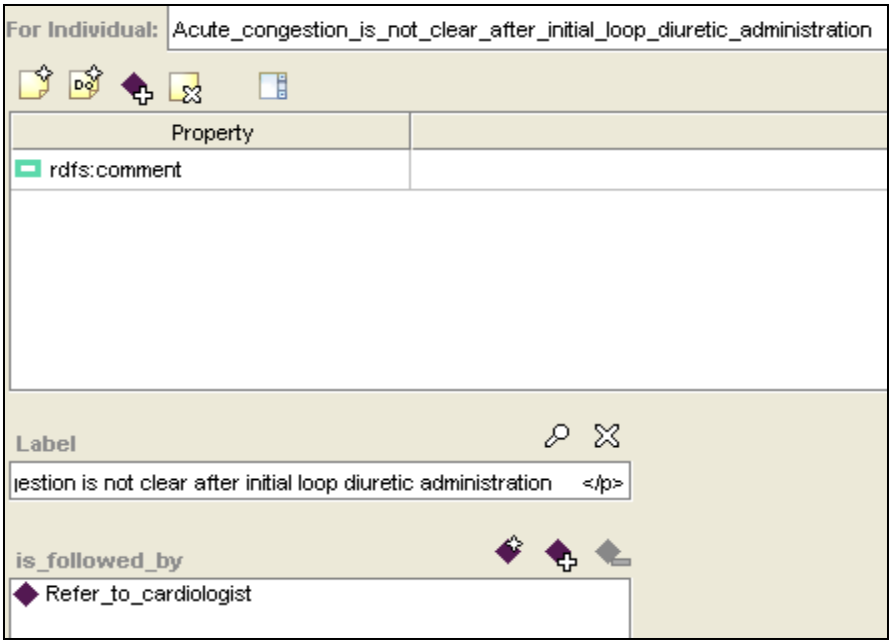


Figure 138: The individual 'Acute congestion is not clear after initial loop diuretic administration' *is_followed_by* 'Refer to cardiologist'

In order to incorporate this suggestion, we removed the loop diuretic uptitration schedule from the ontology. The diuretic treatment is modeled in the ontology as follows: The individual 'Add loop diuretic to treatment regimen' (of class PHARMACOLOGICAL_TREATMENT_TASK) has '*is_followed_by*' relationship with 'Determine if symptomatic response is achieved within 1 to 2 days of treatment' an individual of class DECISION_MAKING_TASK. This task in turn has two DECISION_OPTIONS, 'Acute congestion is clear after initial loop diuretic treatment' and 'Acute congestion is not clear after initial loop diuretic treatment'. The former '*is_followed_by*' patient education regarding diuretic dose adjustment and treatment compliance, while the latter currently '*is_followed_by*' diuretic dose uptitration. In accordance with the advice of the domain expert, the loop diuretic uptitration was replaced by an individual 'refer to cardiologist' (of class END_TASK). This means that the individual 'Acute congestion is not clear after initial loop diuretic treatment' '*is_followed_by*' 'refer to cardiologist' (Fig. 138).

With respect to treatment of comorbid CHF-AF, Dr. Cox had some concerns regarding treatment with Digoxin. In his opinion, the automatic addition of Digoxin to beta blocker might not be appropriate in all or even most patients with NYHA class I and II

symptoms. According to Dr. Cox, Digoxin is a weak rate control agent. It is, however, more appropriate for patients with NYHA class III and IV symptoms, who are promptly referred to the cardiologist by COMET. He mentioned that treatment with the beta blockers along with thromboprophylaxis should be enough for this group of patients. Additionally, the program should dissuade the GPs from use of nondihydropyridine calcium channel blockers for patients with left ventricular systolic dysfunction.

Our approach towards knowledge modeling and alignment was able to handle these concerns without any need to alter the structure of the ontology. It may be recalled from our previous discussion on ontology based knowledge alignment (section 6.4) that we have formalized single disease and comorbid diagnosis and treatment processes as discrete plans. The specific plans to be triggered during the execution of the clinical pathways will depend on whether a patient does or does not have a comorbid illness. The benefit of this approach is that we can add another plan as long as it has been defined in the ontology in terms of its preconditions and post-conditions. Also, we can remove a plan if it is not desired, without jeopardizing the integrity of other plans. Therefore, in this case we simply removed the 'CHF-AF Entry Point 2 - Treatment with Digoxin' from the ontology. Any patient with comorbid CHF-AF would already be receiving treatment with beta blockers. The alignment of the CPs will result in the synchronization of 'CHF-AF entry point 1- Thromboprophylaxis', as currently expressed in the COMET. Caution against using calcium channel blockers for a patient with comorbid CHF-AF is already present in the ontology as an individual "Avoid using calcium channel blockers as they may worsen heart failure because of their negative inotropic effect", of class DIRECTIVE (a sub-class of NON_DECISION_ MAKING_ TASK).

7.3.2. DOMAIN EXPERT No. 2 – GENERAL PHYSICIAN

Our second evaluation session was with Dr. David Zitner, who is a general physician and professor of medical informatics at Dalhousie University. The feedback provided by Dr. Zitner is as follows:

Dr. Zitner mentioned that when COMET recommends the ordering of routine blood tests during CHF entry point 1, certain tests such as HbA1c (glycosylated hemoglobin) and thyroid-stimulating hormone should also be added to the list. We were able to add these two tests to the individual list of class INVESTIGATION in the ontology, so that they can be displayed along with rest of the routine tests (Fig. 139).

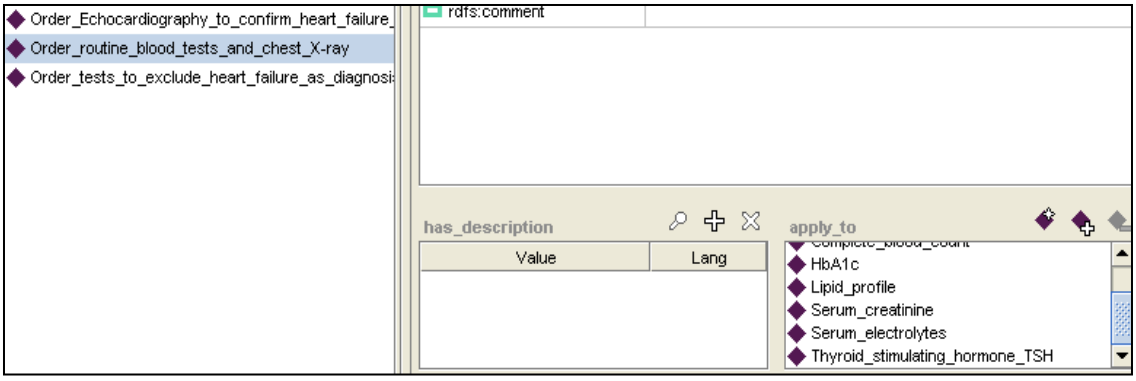


Figure 139: Individuals HbA1C and thyroid-stimulating hormone have been added to class INVESTIGATION and are displayed along with other routine blood tests

With regards to CHF entry point 3, Dr. Zitner also advised that the corrective measures for the electrolyte imbalance (for potassium and sodium) need to be taken concurrently and not sequentially, as can currently be seen in COMET. As mentioned earlier, this is a programming issue and not a modeling issue which we plan to resolve in the next version of COMET.

Dr. Zitner did not have any more comments regarding the correctness of medical knowledge in COMET. However, he did comment that given the vast knowledge about the disease encoded within COMET and a built-in mechanism to execute the knowledge with patient data, COMET will be a particularly useful for medical educational purposes as they can simulate clinical cases and both test their knowledge and find out the evidence-based recommendations.

7.3.3. DOMAIN EXPERT No. 3 – GENERAL PHYSICIAN

Our third evaluation session was with Dr. Craig St. Peters who is a general physician at Parkland Medical Clinical in Halifax. With regards to the modeled knowledge, Dr. St. Peters had only one comment, which was with respect to CHF entry point 3. Like other domain experts, he also suggested that correction of electrolytes should be concurrent.

This means that a GP should not have to wait to correct one parameter (potassium) before going to the next one (sodium).

Dr. St Peters currently has CHF and CHF-AF patients in his care. However, these patients were diagnosed and treated in the specialist care. He pointed out that if he has even a slight suspicion of heart failure or atrial fibrillation (based on sign and symptoms and some tests such as X-ray in case of CHF), he refers the patients to the specialist. According to St. Peter's, for his patients who are suspected of having CHF or CHF-AF, even echocardiography is performed by a cardiologist. Once diagnosed, treated and stabilized, they are referred back to the GP clinic, where he is responsible for the follow-up. He said that he would like to be able to identify patients with milder symptoms and diagnose and treat them. Unfortunately, currently there are no protocols in place to guide him through these processes. In general, Dr. St. Peters felt that an application like COMET can be very beneficial in general practice, whereby a GP is able to identify low risk patients and can take appropriate steps for diagnosis and treatment. In particular, he was pleased to see additional task-specific information displayed with each recommended tasks such as assessment of B-type Natriuretic Peptide (BNP) or using NYHA functional classification for identifying low risk patients. He mentioned that presence of such information in the workflow could be very beneficial when making decisions. For example, he has never recommended the BNP test in his practice. Availability of information regarding purpose and use of BNP, such as the one displayed in COMET can be helpful in such clinical decision making.

Dr. St. Peters also made some suggestions regarding the usability of COMET. He suggested that since his clinic uses an EMR, COMET would be more useful if it is integrated with the EMR, so that the data can directly enter into the application from the EMR and the recommendations or subsequent steps are promptly displayed. This will make sure that COMET is seamlessly integrated in the workflow and a GP does not have to enter data at two different interfaces. The issue of integration of COMET and EMR is discussed in detail in section 8.4. Another feature Dr. St. Peters wanted to see in COMET was to have a summary of all the previous visits that can be accessed in a subsequent visit. We understand the usefulness of such a feature and this will be added in the updated

version of COMET in future. Dr. St. Peters also mentioned that COMET is easy to understand and use. He did not have any other concerns regarding the medical content in the application.

In general, reactions among the domain experts who tested COMET were unanimous that this application could help in the decision-making process with respect to diagnosis and treatment of CHF and CHF-AF. We noticed that we got more critique with respect to medical content of the application from the cardiologist, then any of the GPs. However, both the GPs agreed that such an application once updated and fully evaluated can be very beneficial from educational as well as clinical perspective. It should be noted that we were able to deal with most of the concerns with regards to medical content of COMET expressed by domain experts at knowledge modeling level.

7.4. EVALUATION OF UPDATED ONTOLOGY FOR CONSISTENCY AND CONCISENESS

We anticipate that the updates carried out in the ontology after the external validation did not in any way alter the structure of the ontology. This is because all the updates were handled at the instantiation level and the classes and their relationships remained unaltered. Nevertheless, the ontology was again evaluated for the consistency and conciseness in order to make sure that it still is semantically consistent.

Subsumption tests to establish concept satisfiability and consistency were again performed using the Pellet reasoner. The result as shown in Fig. 139 indicated that there are no inconsistencies in the updated ontological model.

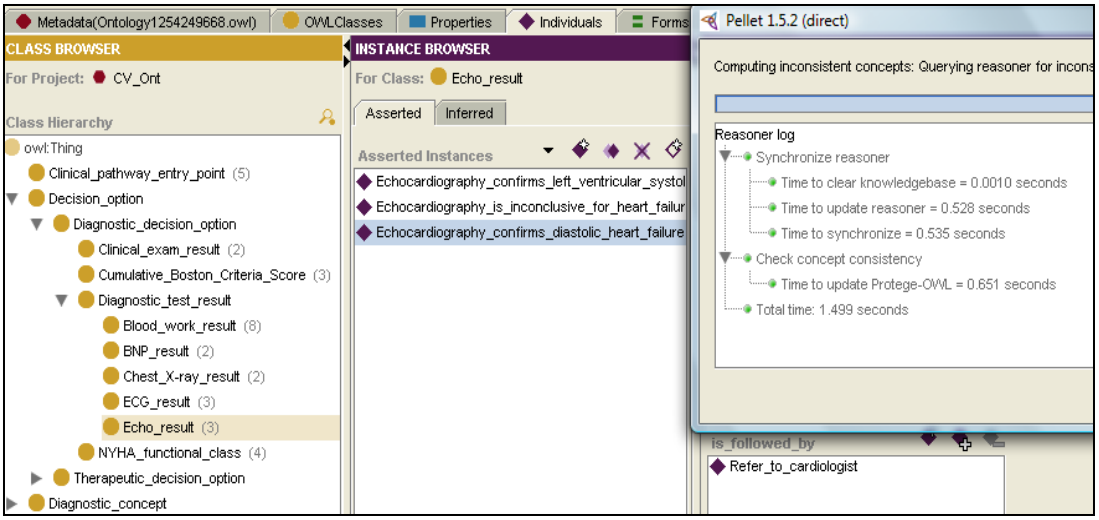


Figure 140: Evaluation of updated ontology for logical consistency using the reasoner Pellet. The result showed no inconsistent classes once updates were done after the external evaluation

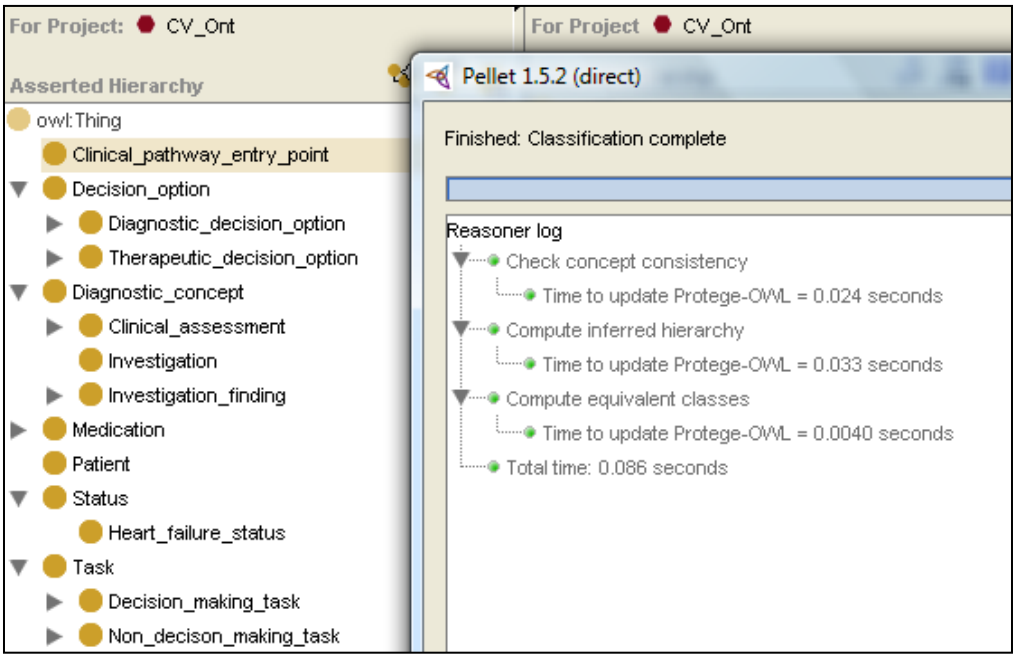


Figure 141: Pellet log for taxonomy classification and computation of inferred hierarchy of the updated ontology

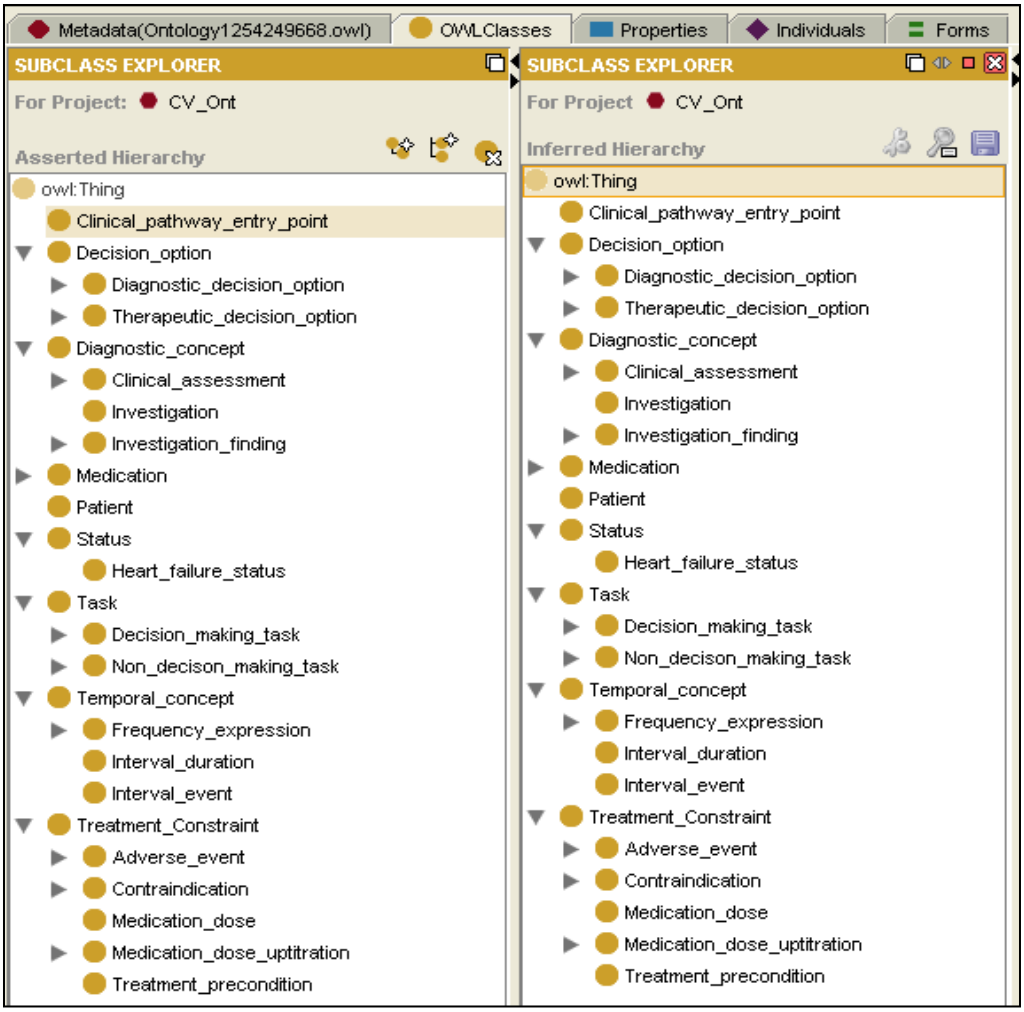


Figure 142: Asserted and inferred class hierarchy of the updated ontology. Note that there are no redundant arcs pointed out by the pellet after running the tests

Pellet was also used to establish the conciseness of the updated ontology. The conciseness was checked by computing the inferred class hierarchy and by identifying the redundant arcs in the updated model. The results as shown in Fig. 141 and 142 indicate that asserted hierarchy is still similar to the inferred hierarchy and the tests do not show any redundant arcs in the updated ontology.

Our evaluation demonstrates the robustness of our CP ontology, as it was able to incorporate most of the suggested updates without the need to alter the structure of the ontology. The fact that the changes were handled at the knowledge model level means that the knowledge model (CP ontology) is scalable and thus there is no need to alter the program that is used to execute the ontology. We believe that the flexibility of our

knowledge modeling approach allows for new knowledge about single disease or comorbidities to be incorporated within the knowledge model.

CHAPTER 8 CONCLUSION

8.1. CONCLUSION AND DISCUSSION

The coexistence of CHF and AF is responsible for significant morbidity, mortality, impairment of quality of life and hence increases the burden of illness (Wang, T.J et al. 2003). One approach to reduce the burden of illness is to engage general practitioners in the management of CHF, together with its co-morbidities such as AF, since GPs are the first point of care. In Canada, about 50% of CHF cases are treated by GPs (Canadian Heart Failure Network, n.d). However, there are challenges in the diagnosis of CHF given that many of its clinical features are not organ-specific (Watson, Gibbs & Lip, 2000). Furthermore, concurrent presence of AF complicates the management of either condition as the choice of treatment depends on individual factors of each disease as it manifests in the patient (Lip, Beevers, Singh & Watson, 1995). A Canadian study has shown a significant care gap in management of the cardiovascular diseases (Tremblay, Drouin, Parker, Monette, Cote & Reid, 2004). EBCAs such as CPGs and CPs have the potential to close this gap (Brush, Radford & Krumholz, 2005). They can by assisting GPs to undertake complex diagnostic and management scenarios resulting from concomitance of CHF and AF.

The Canadian Cardiovascular Society has developed CPGs for management of CHF and AF. The problems with these paper-based CPG, from a decision support perspective, are (a) they do not provide temporal/procedural information that is necessary to handle the care processes related to co-morbidities; and (b) clinically useful task-specific heuristics are designed around a peculiar clinical scenario and not around a specific patient, hence they are less useful if a particular patient has co-morbidities. Given that the available knowledge resources do not adequately cover the overall clinical requirements for handling the patient's co-morbidities (Starfield, 2006; Boyd, Darer, Boult, Fried, Bult & Wu 2005; Dawes, 2010); health professionals are required to refer to the individual CPG for the co-morbid diseases to guide their actions.

We posit that one approach to incorporate EBCAs in the handling of comorbid diseases is to (a) computerize paper-based EBCAs and then (b) systematically *align* the computerized EBCAs of the co-morbid diseases to generate an evidence-based

knowledge resource. The eventual benefit of alignment of multiple disease-specific EBCAs will be the optimization of the care process in terms of: (a) avoiding duplication of intervention tasks, resources and diagnostic tests; (b) re-using results of common activities; (c) ensuring that different clinical activities, across different EBCAs, are clinically compatible and their simultaneous application does not comprise patient safety; and (d) standardization of care across multiple institutions. In this thesis, we pursued the alignment of multiple EBCAs to generate a knowledge model that can provide recommendations to discharge the care of comorbid diseases.

Although a large volume of EBCAs exist for a range of clinical conditions, our research into the clinical decision making behavior of clinicians and the current clinical use of EBCAs indicate that the critical impediment to the effective use of any guideline is their lack of integration into the routine workflow of patient care (Brush, Radford & Krumholz, 2005). This is largely due to the fact that EBCAs are paper-based, and hence are difficult to be incorporated within the decision-making process at the point-of-care (Ma, Monti & Stafford, 2006; Bloom, de Pouvourville, Chhatre, Jayadevappa & Weinberg, 2004; Crim, C. 2000; Cabana et al, 2000; Brand, Newcomer & Freiburger & Tian, 1995). In instances, where EBCAs have been computerized the simplicity of the knowledge representation schemes have led to the inability to capture the full scope and complexity of the medical knowledge. For example, most of the current clinical applications are mere reminder-generating systems, invoking simple rules such as drug interaction checking, offering some specific treatment recommendations or health maintenance reminders and so forth. Such simplistic approaches are inadequate to deal with the intricate scenarios associated with the management of complex, chronic diseases such as CHF. This is even more so when comorbid conditions are present such as CHF together with AF. Chronic disease guidelines, such as those of CHF, are extremely complicated. They require professional interpretation and a great deal of disambiguation for successful application of their heuristics to clinical practice. For this reason they are very difficult to electronically implement. Alignment of a comorbid CPGs to an already complex chronic disease guideline requires additional disambiguation and formalization exercise and more precise definitions of the relationships between the comorbid plans and the data, which itself has to be more complete.

From our research, we conclude that knowledge modeling using ontologies and EBCA alignment through the mapping of ontologically-defined concepts pertaining to a single-disease EBCA is a viable option for developing a knowledge model to handle comorbid diseases. Semantic web ontologies allow the modeling of alignments between two semantically-defined EBCAs, in keeping with clinical pragmatic relations between the co-morbid diseases. Our experience indicates that temporal and functional relations between the care processes across the co-morbidity EBCAs, and preconditions derived from them to trigger these comorbid processes, need to be explicitly stated before this knowledge can be formalized as an ontology. The ontology should be created using both the declarative and procedural approach thereby generating more intuitive and insightful logical processing for the CP knowledge. In this way, care processes that are common to the management of comorbidities can be safely handled by modeling them as a set of discreet care plans, and these care plans can be executed when a comorbidity is detected. We believe that this approach is well-organized and generic enough to allow the addition of more related co-morbidities in the future, whilst maintaining tasks pragmatics and ensuring patient safety.

The key knowledge translation activity is that the GPs are able to access COMET through the web—this means that GPs do not need to be concerned about knowledge updates and system maintenance, yet they can access the computerized EBCAs at the point-of-care to manage patients suspected of having CHF, AF or concurrent CHF and AF. COMET is designed to *assist* a GP and to offer her clinical advice for a patient suspected of having CHF, AF or concurrent CHF and AF. We want to stress that this application is not designed to generate a list of differential diagnoses but rather to engage a GP with moderately high suspicion of CHF or AF in a given patient, to verify her suspicions against a clinical pattern in accordance with the best evidence.

Although COMET is designed for evidence based care planning, management advice and decision support, we want to emphasize that this application should be regarded as a resource that can aid a GP in point-of-care management of CHF and AF. It is therefore important that a GP, as a user of COMET, should have a reasonable working knowledge

of heart failure and atrial fibrillation and some understanding of the relationship between the two comorbidities in order to interpret certain output terms and phrases. Although, a significant effort has been expended in COMET to disambiguate the states and modifiers during the knowledge synthesis phase, there are few outputs that are incorporated in the application with the assumption that a GP should be able to interpret them using her own knowledge and judgment. Examples of these outputs are, "consider anticoagulation or aspirin", "consider alternate diagnosis and refer", or "maintain serum potassium at 4 mmol/L or more during treatment". Such statements however, are the exception rather than a rule since, in most cases, the outputs are explicit statements that are supported by the evidence-based recommendations, which are displayed on the screen for informed decision making. Interactions with COMET are facilitated by an intuitive input mechanism that comprises a number of drop-down menus that are accompanied by additional information to guide the GP. For example, if the GP is required to enter patient's NYHA class, the screen will display necessary information regarding the NYHA functional classification, such as symptoms belonging to each class. This information can then help the GP to determine which of the four NYHA classes her patient's symptoms fall into and, accordingly, which tab from the drop down menu she should select.

We recognize that a patient with CHF and AF can present with additional comorbidities, diverse underlying risk factors, and various responses to treatment. At this stage, the COMET system can offer tailored care planning for a limited number of these elements that were carefully identified, studied and modeled. Our approach was guided by the consideration that in order to provide patient-specific care plans it is required to relate the patient's profile to the medical knowledge and recommendations provided by COMET. This can be achieved through a closed-world outlook—i.e. by setting an initial boundary around the knowledge to be computerized and the medical conditions that can handled by the computerized knowledge. This purports (i) a sound and scalable knowledge model; and (ii) an efficient knowledge execution engine that works seamlessly with the modeled knowledge. There is a correlation between the increase of the elements of the disease that can be handled by COMET and the complexity of the knowledge model and the execution engine. Therefore, at this point, we have not taken into account some

underlying conditions such as ischemic heart disease, or actions other than referral for any unexpected response to the treatment. Having said that, we believe that our modeling and comorbid plan alignment approach is both scalable and robust enough to be able to incorporate additional factors for patient-specific advice and care planning for patients with a more complex clinical history, presentation and treatment response.

8.2. COMPLEXITY AND LIMITATIONS OF THIS APPROACH

Our approach towards the comorbidity knowledge alignment is based on developing a unified ontological model that can represent CHF, AF and CHF-AF treatment plans using OWL constructs. A key element of our comorbid CPs computerization approach is the a priori resolution of: (a) potential terminological or conceptual heterogeneity; (b) relationships between the concepts; and (c) preconditions used to trigger the comorbid plans. This implies that the knowledge synthesis stage is quite complex and central to the overall exercise and it prepares the knowledge for it to be computerized. In this regard, we are developing a deterministic knowledge model, represented as a formal ontology that leverages both the existing domain knowledge and the tacit knowledge of the knowledge modeler. Much as this approach involves the disambiguation, synthesis and modeling of knowledge. We note a few potential limitations associated with this approach as follows:

1. The addition of new knowledge is only possible at the knowledge synthesis level—i.e. new knowledge can only be assimilated by taking into account the existing knowledge. In this case, at the knowledge synthesis level the knowledge engineer will need to ensure the potential clinical/pragmatic interactions the new knowledge may have with existing knowledge, and will be required to subsequently align the new and existing knowledge. Establishing interactions between knowledge objects (i.e. CP care plans) is a complex activity, but it is essential to ensure the validity of the final knowledge model. In this case, within the COMET framework if a new comorbidity is to be added we will have to start from step 1 of the framework (shown in Fig. 1), which is the knowledge acquisition (knowledge identification and synthesis) phase. New comorbid plans

would have to be developed, disambiguated and then defined using the existing ontological framework.

2. The knowledge modeling approach is deterministic as opposed to being self-adaptive/self-learning. This implies that if a new comorbid CP is to be included, the knowledge must be expressed in the terms of the axioms and relationships formalized in the existing model. New comorbid CPs cannot be directly entered in the CP ontology without identifying the tasks dependencies and the single disease-comorbid plan dependencies. Such dependencies would have to be categorized and established during the knowledge synthesis phase.

3. We realize that this is work in progress. Although, a great number of updates in accordance to the domain expert's responses have already been incorporated in the instantiation of the ontology, there is yet a lot to do before COMET is ready for a clinical study. As mention in section 7.3.1, the normal limits, cutoff values and units of measurements for various blood parameters (sodium, potassium and creatinine) have to be consistent with those used in the local labs. Also assessment of these tests currently is sequential, which is not clinically correct. In future version, concurrent assessment of the electrolytes and subsequent recommendations for the corrective measures will be incorporated in COMET. The calculation of Boston criteria scores is manual in the current version of COMET. This means that the GP will have to keep track of all the scores and will have to compute them at the end of assessment. The computation of the scores has to be automated in the future.

4. We recognize that the CPs developed were based on the CPGs and the advice of the cardiologists in the Nova Scotia, and the GPs were not included in the knowledge synthesis phase of this research. The medical CPs developed and applied in this research are used as exemplar CP to demonstrate the efficacy of the knowledge modeling solution and to provide a real clinical perspective to this research, so that the knowledge modeling research has a clear clinical focus and purpose. Nevertheless, COMET has been evaluated with two GPs, both of whom have shown a great deal of interest in any future work on COMET. We have

demonstrated during our external evaluation that the model is robust and is able to handle the updates in the medical knowledge. We plan to seek input from the GPs in the future, in particular with regards to the usability of COMET.

On the other hand, the benefits of our approach for CP alignment at the knowledge modeling level approach are:

1. Updates to a CPG can be readily incorporated within the knowledge model, thus ensuring that whenever a CPG is updated it can be readily computerized and operationalized at the point-of-care. Since the CP model is developed using the OWL language which is an extensible language, it is possible to form new terms by combining existing ones through concepts constructors, such as: unionOf, intersectionOf and complementOf. If there is a need to add a new concept in the ontology we can combine the existing concepts to form a new concept. Thus, from a concept instantiation perspective the knowledge model is extensible to incorporate new concepts or relationships in the domain which may arise due to update of the evidence.

2. Updates to existing knowledge in the CP model can be achieved through the *instantiation* of new concepts within the ontology. This has been demonstrated in section 7.3, whereby the ontology was able to handle the updates suggested by the domain experts. We recognize that a CPG is revised whenever new evidence emerges. With respect to the 2009 update to the Canadian Cardiovascular Society Consensus Conference guidelines on heart failure (Howlett et al. 2009), the 2009 update includes best practices for the diagnosis and management of right–sided heart failure, myocarditis and device therapy. Given the scope of this research, the only relevant review is about the rhythm vs. rate control of atrial fibrillation in heart failure. The recommendation provided in this respect states that, "In patients with stable heart failure and atrial fibrillation (AF), rate control is an acceptable management strategy and routine rhythm control is not required (class I, level B)" (Howlett et al. 2009, p. 100). Note that the target population for COMET is patients with NYHA class I and II symptoms, who are regarded as having stable

heart failure. The AF treatment for patients with comorbid CHF (which according to 2009 update is rate control) is already incorporated in our CPs as advised by Dr. Jafna Cox. Therefore, the knowledge related to this recommendation in the 2009 update is already present in the CPs and the ontology. This means that despite the fact that the 2009 update has been released; there was no need for any update in the ontology. If there would have been any changes in the domain knowledge required we could have done so as discussed in section 7.3. The other topics in the 2009 update are about right sided-heart failure, myocarditis and device therapy which are beyond the scope of this research. This research only deals with diagnosis and treatment of CHF involving left ventricular systolic dysfunction and AF.

3. The interactions between the medical concepts, both within a CP and across CPs, can be examined in a simulation-like framework to identify the role of patient data and care plan outcomes for a given clinical scenario.

4. The medical concepts are abstracted at a higher level of plans, tasks, treatments, diagnostic concepts and decision options. This allows interoperability of concepts leading to the potential alignment of multiple CPs to handle comorbidities.

8.3. CONTRIBUTIONS

This research addresses the development of a knowledge management framework to align multiple CPs to provide decision support for comorbid diseases. To achieve the above, this thesis covers three related topics:

i. The development of Clinical Pathways (CPs) for handling CHF, AF and co-morbid CHF-AF. This involved acquisition of clinically useful task-specific heuristics from the CPGs, through the processes of selection, interpretation and augmentation of guideline statements and logic. The heuristics are then temporally organized resulting in CHF and AF CPs.

ii. The modeling of the CHF and AF CPs and the derived CHF-AF CP in terms of a semantically-rich ontology that describes the CHF and AF diagnostic and treatment concepts and their interrelationships in a formal language. To handle

co-morbidities, we presented a novel modeling approach that establishes temporal and procedural alignments between the clinical processes across the individual CHF and AF CPs to realize a unified ontological model of the CHF-AF CPs.

iii. The development of a clinical decision support system that leverages the CP knowledge modeled through a CP ontology to guide GPs in the diagnosis and treatment of CHF, AF and comorbid CHF-AF in a primary care setting.

From a knowledge modeling and technology perspective, the development of a decision support and care planning framework, especially for complex and comorbid diseases such as CHF and AF, remains a challenging exercise. This is largely due to the diversity, complexity and richness of the medical knowledge involved in clinical decision making for handling the chronic diseases of CHF, AF and their comorbidities. Although there have been previous attempts to computerize CPG for the management of heart failure, these attempts were deemed as inadequate to handle any comorbidities, concurrent therapies or the timing of administration and gradual uptitration of medications (Leslie, S.J. & Denvir, M.A. 2007). This research is an attempt to address the prevailing knowledge modeling and knowledge translation gap that is limiting our ability to handle co-morbidities in a decision support framework. In our research, we extensively studied the complexities associated with the management of CHF, AF and comorbid CHF-AF, and proposed a novel and comprehensive knowledge management framework that provides both a methodology and a set of technical methods to synthesize, model, operationalize and translate paper-based EBCA into a computerized decision support system that can handle both single and comorbid diseases. We believe the following are some of the salient contributions of this research:

i. We proposed a knowledge management methodology to manage and model healthcare knowledge so that it can be used as a knowledge-base for a clinical decision support system. In this regard, we elicited the steps to synthesize medical knowledge dispersed across multiple CPGs and protocols in order to identify and derive a set of task-specific heuristics for managing a specific disease (in our case CHF, AF and comorbid CHF-AF) given specific preconditions and patient

parameters. In this exercise, we outlined the steps necessary to identify the heuristics that are valid to comorbid disease management. We provided an in-depth description of the processes involved in the disambiguation of the knowledge derived from the CPGs and presented an approach to disambiguate any implicit constraints derived from combining comorbid processes. The key feature of this contribution is that we demonstrated our methodology in action whereby we illustrated how diverse sources of medical knowledge can be synthesized to formulate the CPs for CHF and AF.

ii. We developed a knowledge modeling approach that facilitates the computerization of paper-based CP to an executable format. Although, knowledge modeling approaches for handling single diseases exist (Sutton & Fox, 2003; Boxwala, 2004; Miksch, 1999), there are no knowledge modeling approaches focusing on the formalization of medical knowledge in such a way to deal with comorbid diseases. In this research, we developed a knowledge modeling approach to model the knowledge from different CPs to develop a unified co-morbid knowledge model that can be applied to handle comorbidities. The application of our knowledge modeling approach led to the development of an elaborate CP ontology that formalizes the knowledge encapsulated within the synthesized medical knowledge about CHF and AF management. This thesis contributes an executable CP ontology—built using Protégé Owl—that features nine highest level classes with over 80 subclasses arranged at various lower levels. By using ontologies to model healthcare knowledge, we have developed a more sustainable knowledge models that can handle broad additions and updates to ensure that the knowledge is relevant and current.

iii. From a practical standpoint, the CP ontology is instantiated with CPs for CHF, AF and comorbid CHF-AF. We believe that by modeling healthcare knowledge using well-understood and semantically-defined constructs we are better positioned to pursue the alignment of CPs.

iv. We proposed a new CP alignment approach, based on knowledge modeling, together with a demonstration of its ability to formalize comorbid care processes, in keeping with their implicit medical and pragmatic constraints. The key feature

of our CP alignment approach is that it establishes temporal and procedural alignments between the clinical processes across the individual CHF and AF CPGs to realize a unified ontological model of the CHF-AF CPs. To achieve the alignment of CPs to handle comorbidities, at the knowledge modeling level we developed a range of unique ontological constructs that allow the systematic mapping between different CPs, whilst ensuring medical and pragmatic constraints. Therefore, we believe that this thesis contributes to the broader challenge of how to model healthcare knowledge to handle comorbidities whilst ensuring patient-centeredness and patient safety. Our CP alignment approach is generic and can be applied to other comorbid diseases as well.

v. We developed a prototype clinical decision support system—COMET (Co-morbidity Ontological Modeling & ExecuTion) system—that can operationalize our comorbid knowledge model to provide clinical decision support and comorbid care planning. COMET demonstrates the translation of medical knowledge, modeled in terms of our CP ontology, to point-of-care clinical practices to assist in the handling of four patient care scenarios: (i) patient starts with CHF; (ii) patient starts with AF; (iii) patient develops a co-morbidity of either AF or CHF; and (iv) patient has both CHF and AF. Therefore, we believe that this research completes the entire knowledge translation cycle of knowledge identification, synthesis and application.

In summary, we believe that the knowledge management framework developed in this thesis addresses the research problem posed at the onset of this project. We have successfully demonstrated how to formally model the structural, functional and conceptual knowledge encapsulated within individual disease-specific CP so that one can systematically align and execute multiple CPs to handle comorbid diseases, whilst maintaining the integrity of medical knowledge, task pragmatics, coordination of care and patient safely.

Being a health informatics thesis, we have successfully developed and evaluated a functional technical solution to handle comorbidities through the alignment of ontologically-modeled CPs.

Finally, we will like to highlight that the research contributed in an interdisciplinary area—that is health and informatics. The researcher successfully maintained the interdisciplinary nature of the research project and in addressing the research problem applied her knowledge of (a) medicine to formulate the CHF, AF and CHF-AF CPs, and (b) informatics, in particular semantic web and ontologies, to model the medical knowledge so that it can be executed to provide decision support for handling CHF, AF and comorbid CHF-AF.

8.4. FUTURE PERSPECTIVES

At present, COMET allows the GP to log on to the CHF screen. Our immediate next step is to develop the AF screen, allowing execution of the AF pathway and synchronization with the comorbid CHF plans, once presence of comorbid CHF is identified during the execution of the AF pathway.

In this research, we have taken into account two comorbid CPGs to provide care planning and decision support via the COMET system. However, in practice, a practitioner may be required to consult more than two CPGs for more tailored advice and care planning. For example, a heart failure patient might have hypertension or coronary artery disease in addition to AF. This means that other comorbidities need to be added into the application. Our approach involves various phases for systematic disambiguation and formalization of the comorbid knowledge. These phases are explicitly able to state any implicit constraints and relationships between the processes that might arise as result of alignment of the care plans. We therefore believe that this approach is well-organized, logical and generic enough to allow the addition of more related comorbidities in the future while maintaining task pragmatics and ensuring patient safety.

Another potential future course of this research is integration of COMET with electronic medical records. Since one of the main purposes of the computerization of guidelines is to provide point-of –care decision support and care-planning, it would be extremely useful to draw data directly from the EMR to trigger the COMET and to store outputs directly into the EMR for future references. As governmental support for implementation of EMR across Canada increases, we can see more and more potential for innovative applications like COMET. Integration of COMET with the Electronic Medical Record

(EMR) will save the GPs precious time as they would not need to enter data that already exists in the EMR. This will also reduce the potential for data entry errors. This line of research requires semantic interoperability, which involves mapping of patient data items and clinical concepts that are derived from the CPGs to the entries in the EMR (Boxwala et al. 2004). Semantic interoperability is achieved when either the two applications share the same, mutually understood vocabulary, or by creating mappings between their different vocabularies. We believe that our Semantic Web approach for comorbid pathways modeling and execution is a step forward towards achieving this mapping. Semantic Web technologies such as Resource Descriptive Framework (RDF) and Web Ontology Language (OWL) can be used to enable the semantic mapping required to solve such interoperability problems. RDF/OWL uses constructs such as exact logical equivalence, which can be used to specify that a concept is equivalent to another concept or a property is equivalent to another relation. Similarly, disjoint constructs can specify differences between concepts. In addition, other OWL/RDF constructs, such as SameAs, SubClassOf, and SubPropertyOf, can also be used for mapping purposes.

COMET can only be deployed in a GP clinic once its safety, functionality and efficacy have been evaluated. However, such an evaluation has to be carried out iteratively at various stages of maturity of the COMET, before it is clinically ready to be used in a GP clinic. The first stage is the validation of the medical knowledge encoded in the application in terms of correctness, reliability and validity in accordance with the evidence based guidelines, by a panel of domain experts. This is needed to ensure that our interpretations and the concepts, tasks, relationships and workflow patterns are clinically correct and result in safe, relevant, reliable and valid advice.

Although, interface design is not one of the goals of this research, we nevertheless understand the importance of a user-friendly interface. We believe that an interface dealing with the complex issue of comorbid care-planning and decision support should be appropriately constructed so that the tabs, questions, drop-down menus, data entry fields and clinical advice are intuitive, user-friendly and allow correct interpretation by users. Thus the user-friendliness and clinical appropriateness of the current interface need to be evaluated and updated if necessary.

The second phase of appraisal will involve the evaluation of the clinical efficacy of the fully operational COMET system by a panel of GPs. Such efficacy testing should not just rest on evaluation reports from clinicians but on measurable effects of COMET on clinical practices and performance or on patient outcomes. Such an endeavor is one of our long term goals and will require a great deal of involvement of GPs.

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