

AUTOMATING DISEASE MANAGEMENT USING
ANSWER SET PROGRAMMING: HEART FAILURE

by

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DISSERTATION

Presented to the Faculty of
The University of Texas at Dallas
in Partial Fulfillment
of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY IN
COMPUTER SCIENCE

THE UNIVERSITY OF TEXAS AT DALLAS

December 2017

ACKNOWLEDGMENTS

This dissertation comes into being thanks to many individuals. Dr. Gopal Gupta, my supervisor, not only introduced me to both logic programming and answer set programming, but also provided me with unfailing support. Dr. Lakshman Tamil, my co-supervisor, showed me the prospect of future medicine. I thank Dr. Alpesh Amin, Dr. Sandeep Das and Dr. Daniel Cheeran for their help in providing the valuable data and answering my questions regarding medicines. I extend my gratitude to Dr. Michael Skinner, who facilitated the collaboration with the University of Texas Southwestern Medical Center. I also thank my fellow researchers, Dr. Kyle Marple and Elmer Salazar, for the fruitful discussions. I also would like to express my appreciation to Douglas Hyde, Norma Richardson and Alphonse Coleman who took care of all the paperwork with tremendous patience. I want to thank Dr. Shyam Karrah for his advice on my graduation plan. I thank Dr. Balakrishnan Prabhakaran for his guidance on my graduate studies. I thank David Allen who through his wonderful books taught me how to handle the endless details of life. I feel deeply grateful to Eckhart Tolle, whose spiritual teaching help me find the inner peace. Finally, I would not be what I am today without my dear father and mother's selfless love.

October 2017

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Management of chronic diseases such as heart failure (HF), diabetes and chronic obstructive pulmonary disease is a major health care problem. A standard approach that the medical community has devised to manage widely prevalent chronic diseases such as heart failure is to have a committee of experts develop guidelines that all physicians should follow. These guidelines typically consist of a series of complex rules that make recommendations based on a patient's information. Due to their complexity, often the guidelines are either ignored or not complied with at all, which can result in poor medical practices. It is not even clear whether it is humanly possible to follow these clinical guidelines due to their length and complexity. In the case of heart failure management, the guidelines run nearly 80 pages. In this dissertation we describe a physician advisory system that codes the entire set of clinical practice guidelines for heart failure management using answer set programming (ASP). ASP is a form of declarative programming geared toward solving NP-hard search problems. Our approach is based on developing reasoning templates that we call knowledge patterns and using these patterns to systematically code the clinical guideline for HF management as ASP rules. Use of the knowledge patterns greatly facilitates the development of the physician advisory system. Given a patient's medical information, the system generates a set of

guideline-compliant recommendations just as a human physician would. The system works even in the presence of incomplete information. Abductive reasoning is also implemented in the system to find missing symptoms and conditions that the patient must exhibit in order for a treatment prescribed by a physician to work effectively. The physician advisory system is validated by using data of representative patients with heart failure.

TABLE OF CONTENTS

| | |
|--|-----|
| ACKNOWLEDGMENTS | iv |
| ABSTRACT | v |
| LIST OF FIGURES | xi |
| LIST OF TABLES | xii |
| CHAPTER 1 INTRODUCTION | 1 |
| 1.1 Overview | 1 |
| 1.2 Structure of the Dissertation | 4 |
| CHAPTER 2 BACKGROUND | 6 |
| 2.1 Overview | 6 |
| 2.2 Problem Description | 6 |
| 2.3 Literature Review | 8 |
| 2.4 Answer Set Programming | 12 |
| 2.4.1 Negation as Failure | 13 |
| 2.4.2 Gelfond-Lifschitz Transformation | 15 |
| 2.5 Goal-directed Execution of Answer Set Programs | 16 |
| CHAPTER 3 PHYSICIAN ADVISORY SYSTEM DESCRIPTION | 18 |
| 3.1 Overview | 18 |
| 3.2 Guideline for the Management of Heart Failure | 18 |
| 3.3 System Description | 21 |
| CHAPTER 4 KNOWLEDGE PATTERNS | 31 |
| 4.1 Overview | 31 |
| 4.2 Literature Review | 31 |
| 4.3 Knowledge Patterns | 32 |
| 4.3.1 Aggressive Reasoning | 33 |
| 4.3.2 Conservative Reasoning | 35 |
| 4.3.3 Anti-recommendation | 36 |
| 4.3.4 Preference | 38 |
| 4.3.5 Concomitant Choice | 39 |

| | | |
|--|--|----|
| 4.3.6 | Indispensable Choice | 41 |
| 4.3.7 | Incompatible Choice | 43 |
| CHAPTER 5 PHYSICIAN ADVISORY SYSTEM VALIDATION | | 46 |
| 5.1 | Overview | 46 |
| 5.2 | Case studies | 46 |
| 5.2.1 | Case One - Profile | 47 |
| 5.2.2 | Case One - Input for the Physician Advisory System | 48 |
| 5.2.3 | Case One - Experimental Result | 49 |
| 5.2.4 | Case Two - Profile | 51 |
| 5.2.5 | Case Two - Input for the Physician Advisory System | 51 |
| 5.2.6 | Case Two - Experimental Result | 52 |
| 5.2.7 | Case Three - Profile | 54 |
| 5.2.8 | Case Three - Input for the Physician Advisory System | 54 |
| 5.2.9 | Case Three - Experimental Result | 55 |
| 5.2.10 | Case Four - Profile | 56 |
| 5.2.11 | Case Four - Input for the Physician Advisory System | 56 |
| 5.2.12 | Case Four - Experimental Result | 58 |
| 5.2.13 | Case Five - Profile | 58 |
| 5.2.14 | Case Five - Input for the Physician Advisory System | 59 |
| 5.2.15 | Case Five - Experimental Result | 61 |
| 5.2.16 | Case Six - Profile | 62 |
| 5.2.17 | Case Six - Input for the Physician Advisory System | 62 |
| 5.2.18 | Case Six - Experimental Result | 64 |
| 5.2.19 | Case Seven - Profile | 65 |
| 5.2.20 | Case Seven - Input for the Physician Advisory System | 66 |
| 5.2.21 | Case Seven - Experimental Result | 67 |
| 5.2.22 | Case Eight - Profile | 69 |
| 5.2.23 | Case Eight - Input for the Physician Advisory System | 70 |
| 5.2.24 | Case Eight - Experimental Result | 71 |

| | | |
|---|---|-----|
| 5.2.25 | Case Nine - Profile | 72 |
| 5.2.26 | Case Nine - Input for the Physician Advisory System | 73 |
| 5.2.27 | Case Nine - Experimental Result | 74 |
| 5.2.28 | Case Ten - Profile | 75 |
| 5.2.29 | Case Ten - Input for the Physician Advisory System | 76 |
| 5.2.30 | Case Ten - Experimental Result | 77 |
| 5.3 | Summary of the Experimental Results | 78 |
| CHAPTER 6 IMPLEMENTATION OF ABDUCTIVE REASONING | | 80 |
| 6.1 | Overview | 80 |
| 6.2 | Introduction to Abductive Reasoning | 80 |
| 6.3 | The s(ASP) Predicate Answer Set Programming System | 81 |
| 6.4 | Abductive Reasoning in Answer Set Programming | 83 |
| 6.5 | Application of Abductive Reasoning in Physician Advisory System | 86 |
| 6.6 | Related Work | 92 |
| CHAPTER 7 CONCLUSION | | 94 |
| 7.1 | Contributions | 94 |
| 7.2 | Future work | 95 |
| APPENDIX PATIENT'S PROFILE | | 97 |
| A.1 | Case One | 97 |
| A.1.1 | Chief Complaint | 97 |
| A.1.2 | History of Present Illness | 97 |
| A.1.3 | Past Medical History | 98 |
| A.1.4 | Family History | 100 |
| A.1.5 | Social History | 100 |
| A.1.6 | Allergies | 100 |
| A.1.7 | Medication Intolerance | 100 |
| A.1.8 | Review of Systems | 100 |
| A.1.9 | Patient Reported | 101 |
| A.1.10 | Physical Exam | 102 |

| | |
|---|-----|
| A.1.11 Additional Diagnostics/Labs | 103 |
| A.1.12 Pertinent Data/Labs Reviewed | 103 |
| A.1.13 Impression | 103 |
| REFERENCES | 105 |
| BIOGRAPHICAL SKETCH | 110 |
| CURRICULUM VITAE | |

LIST OF FIGURES

| | | |
|------|--|----|
| 2.1 | Ground Normal Logic Program | 12 |
| 2.2 | An Example of Answer Set Program K | 13 |
| 2.3 | A Stable Model of Program K | 13 |
| 2.4 | A Model (not stable) of Program K | 13 |
| 3.1 | The Architecture of Physician Advisory System | 26 |
| 3.2 | Representation of a patient’s information in physician-advisory system for HF management | 27 |
| 3.3 | Representation of a patient’s information in GUI | 28 |
| 3.4 | Recommendations produced by the physician advisory system | 29 |
| 3.5 | Recommendation shown in user interface | 30 |
| 4.1 | Knowledge Pattern for Aggressive Reasoning | 34 |
| 4.2 | Knowledge Pattern for Conservative Reasoning | 35 |
| 4.3 | Knowledge Pattern for Anti-recommendation | 37 |
| 4.4 | Knowledge Pattern for Preference | 38 |
| 4.5 | Example for Preference Pattern | 39 |
| 4.6 | Knowledge Pattern for Concomitant Choice | 40 |
| 4.7 | Example for Concomitant Choice Pattern | 40 |
| 4.8 | Knowledge Pattern for Indispensable Choice | 42 |
| 4.9 | Example for Indispensable Choice Pattern | 42 |
| 4.10 | Knowledge Pattern for Incompatible Choice | 44 |
| 4.11 | Example for Incompatible Choice Pattern | 45 |
| 6.1 | Representation of the simulated patient’s information in the physician advisory system for HF management | 87 |
| 6.2 | Abducibles for one patient | 89 |
| 6.3 | Results of abductive reasoning | 91 |

LIST OF TABLES

| | | |
|------|--|-----|
| 3.1 | Input of the Physician Advisory System for HF Management | 22 |
| 3.2 | Output of the Physician-Advisory System for HF Management | 22 |
| 5.1 | Physician Advisory System's Recommendations for Case One | 50 |
| 5.2 | Physician Advisory System's Recommendations for Case Two | 53 |
| 5.3 | Physician Advisory System's Recommendations for Case Three | 55 |
| 5.4 | Physician Advisory System's Recommendations for Case Four | 59 |
| 5.5 | Physician Advisory System's Recommendations for Case Five | 61 |
| 5.6 | Physician Advisory System's Recommendations for Case Six | 64 |
| 5.7 | Physician Advisory System's Recommendations for Case Seven | 68 |
| 5.8 | Physician Advisory System's Recommendations for Case Eight | 72 |
| 5.9 | Physician Advisory System's Recommendations for Case Nine | 74 |
| 5.10 | Physician Advisory System's Recommendations for Case Ten | 77 |
| 5.11 | The number of total/questioned treatment recommendations given by physician advisory system | 79 |
| 6.1 | Results of abductive reasoning for 10 representative cases | 92 |
| 6.2 | Running time of the physician advisory system | 92 |
| A.1 | Most recent labs completed | 104 |

CHAPTER 1

INTRODUCTION

1.1 Overview

Chronic diseases are health conditions that persist for a long time that can neither be prevented by vaccines nor cured by medications but can only be managed. In America alone there are more than 133 million people who suffer from one or more chronic diseases (Wu and Green, 2000). Chronic diseases are responsible for 81% of hospitalizations, 91% of prescriptions filled and 76% of all physician visits. The top five chronic conditions are: heart diseases, cancers, stroke, chronic obstructive pulmonary disease and diabetes. Chronic diseases have been a major consumer of health care funds. In 2010, more than a trillion dollars went into the treatment of chronic disease (Centers for Disease Control and Prevention, 2016). The successful management of chronic disease has two indispensable components: (i) self-management by the patients and (ii) management by physicians while adhering to clinical practice guidelines. The failure of either of the components can lead to the failure of the whole enterprise of the management of chronic diseases.

Our work on chronic disease management started several years ago with the building of a telemedicine-based chronic disease management system designed to facilitate the self-management of chronic diseases by patients (Monteiro et al., 2011). The chronic care platform was put to the test to see whether it could successfully prevent patients from going to an emergency room or being readmitted to a hospital within 30 days of discharge after the original heart failure (HF) episode. These patients were provided with the chronic care platform and peripheral devices. The vital sign data were automatically uploaded to a server where it was available for processing and viewing. Working remotely, the case nurse was able to manage twelve patients discharged from Texas Methodist Hospital and prevent all of them from being readmitted within 30 days (Baldwin et al., 2013).

This dissertation focuses on the second component of disease management, which is assisting physicians in adhering to the clinical practice guidelines. Heart failure (HF) is the first chronic disease for which we have built a tool to assist physicians in disease management. Heart failure is the inability of the heart to keep up with the demands of the body. As a result, an inadequate amount of blood is supplied to the human body and/or pressures in the heart can rise. This can cause congestion of blood in the lungs, abdomen, leg, etc. All of this culminates in symptoms of exercise intolerance. Half of the patients diagnosed with heart failure die within five years. In the U.S. there are about 5.7 million people currently living with heart failure (Go et al., 2013).

Optimal management of HF requires adherence to the clinical practice guideline, which is the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines for the Management of Heart Failure (Yancy et al., 2013). This guideline was created by a multidisciplinary committee of experts and was based on thorough reviews of best available clinical evidence on the management of heart failure. It represents a consensus among experts on the appropriate treatment and management of heart failure.

Although evidence-based guidelines should be the basis for all disease management, physicians' adherence to those clinical guidelines is poor (Cabana et al., 1999). The major reasons for the failure of guideline implementation are lack of awareness, lack of familiarity, lack of motivation and external barriers. Even when the guidelines are readily accessible, the physicians are not familiar with enough of the guidelines to apply their rules correctly. In all surveys of physicians conducted, the lack of familiarity was more common than the lack of awareness (Cabana et al., 1999). One of the reasons for the lack of familiarity is that the guidelines can be quite complex, as in the case of heart failure management. For example, more than 100 variables have been associated with mortality and re-hospitalization related to heart failure. In the 2013 ACCF/AHA Guideline for the Management of Heart Failure (referred to as the 2013 Guideline in the rest of the dissertation), the variables range from

simple information like age and sex to sophisticated data like the patterns in electrocardiogram and history of HF-related symptoms and conditions.

To overcome the difficulties that physicians face in implementing the clinical practice guidelines, we developed a physician advisory system that automates the 2013 Guideline. Given a patient’s information, the physician advisory system is able to generate all guideline-compliant treatments for the patient with heart failure. The system relies on answer set programming (ASP) (Gelfond and Lifschitz, 1988) for coding the rules in the guideline. ASP is a form of declarative programming oriented towards difficult search problems (Lifschitz, 2008). It is powerful in knowledge-intensive applications since sophisticated reasoning mechanisms like non-monotonic reasoning, default reasoning, counterfactual reasoning and abductive reasoning can be elegantly modeled by it. The core idea of ASP is to describe problem specification using a non-monotonic logic program (Eiter et al., 2009). A non-monotonic program has the property that new information may invalidate earlier conclusions that were drawn in lack of complete knowledge. The logic program can be fed into an ASP solver and then solutions to such a logic program will be computed by ASP solvers and presented as the so-called answer sets. ASP’s ability to perform non-monotonic reasoning is powered by a formalism called Negation as Failure (NAF) (Clark, 1978). NAF is a non-monotonic inference rule used to derive *not p* from failure to derive *p*. Note that *not p* is different from $\neg p$ of the logical negation of *p*.

We developed reasoning templates called knowledge patterns to facilitate the development of the physician advisory system. These knowledge patterns are quite general and can be used as solid building blocks for systematically translating the complex rules to ASP code. The complexity of the rules stems from the fact that the recommendation/contraindication of one treatment impacts the recommendation of other treatments. It is likely not possible to correctly code the entire set of rules in the 2013 Guideline without a systematic approach. By making use of knowledge patterns, we were able to code each rule and ensure that the

conglomerate of the ASP code faithfully represents the meaning of the whole set of rules in the guideline.

Abductive reasoning is also realized in our physician advisory system. Abductive reasoning is a form of reasoning that is concerned with the generation and evaluation of explanatory hypotheses. In other words, abductive reasoning leads from the observed facts to a proposed explanation of those facts. We deployed abductive reasoning to find missing symptoms and conditions that a heart failure patient must exhibit in order for a treatment prescribed by a physician to work effectively. If a physician does not make an appropriate recommendation or makes a non-adherent treatment recommendation, the physician advisory system will advise the physician about symptoms and conditions that must be in effect for that recommendation to apply. While abductive reasoning can be implemented under the stable model semantics (Gelfond and Lifschitz, 1988), it is difficult to identify the minimum set of abducibles if we adopt a SAT-solver-based approach. To overcome this difficulty, we used s(ASP) (a Predicate Answer Set Programming System) (Marple et al., 2017), which computes the stable model of normal logic programs via coinductive selective linear definite clause resolution (Co-SLD resolution). One ramification of s(ASP)'s top-down execution strategy is that the answer set produced by s(ASP) may be partial. The partial answer set contains the predicates that are necessary to establish the query. In the context of abductive reasoning, partial answer set is the minimum set of abducibles without extraneous predicates.

1.2 Structure of the Dissertation

Chapter 2 provides background information necessary to understand the remainder of the dissertation. Answer set programming and its goal-directed execution are discussed. We also give a description of the problem domain, chronic disease management.

Chapter 3 describes the physician advisory system for heart failure management. The development methodology, the system architecture and implementation are presented.

Chapter 4 introduces the knowledge patterns we identified in the rules of clinical practice guideline. Each knowledge pattern and its code template in ASP is presented in detail.

Chapter 5 presents the validation of the physician advisory system. Ten representative cases are used to validate the efficacy of the system. The case profiles, the system's input and output for each case are shown with discussions.

Chapter 6 illustrates the realization of abductive reasoning in the physician advisory system. The underlying predicate answer set programming system called s(ASP) is presented. The application of abductive reasoning in ten representative cases is also covered.

Chapter 7 gives the conclusions and points out the future work related to the dissertation. The contributions of this dissertation are also reviewed.

Appendix A presents the original medical profile for case No.1, which is one of the ten representative cases we used in our research.

CHAPTER 2

BACKGROUND

2.1 Overview

This chapter covers the background knowledge of this dissertation. The relevant areas include heart failure management, expert system, logic programming, answer set programming and knowledge representation. To understand this dissertation, it is necessary to grasp the concepts discussed in this chapter. The remainder of this chapter is organized as follows. Section 2.2 describes the problem this dissertation is trying to solve. Section 2.3 gives a review of past approaches to automated reasoning and knowledge representation. Section 2.4 introduces the syntax of answer set programming. Two important concepts in answer set programming, negation as failure and Gelfond-Lifschitz transformation are also presented. Section 2.5 discusses the goal-directed execution strategy of answer set programming, which is the corner stone of the implementation of abductive reasoning in chapter 6.

2.2 Problem Description

Chronic diseases are health conditions that persist for a long time can neither be prevented by vaccines nor be cured by medications but can only be managed. In U.S. alone there are more than 133 million people who suffer from one or more chronic diseases (Wu and Green, 2000). The U.S. patients with chronic diseases account for 81% of hospital admissions, 91% of prescriptions filled and 76% of all physician visits (Anderson, 2010). The top five chronic conditions are: heart disease, cancer, stroke, chronic obstructive pulmonary disease and diabetes. In 2010, 68% of the healthcare spending was for treatment of chronic diseases (Centers for Disease Control and Prevention, 2016).

Heart failure (HF) is the inability of the heart to keep up with the demands of the body. As a result, an inadequate amount of blood is supplied to the human body and/or pressure

in the heart can rise. This can lead to congestion of blood in the lungs, abdomen, legs, etc. All of this culminates in symptoms of exercise intolerance. Half of the people diagnosed with HF die within five years. In 2013, U.S. has about 5.7 million people living with HF (Go et al., 2013).

Optimal management of HF requires adherence to evidence-based clinical practice guidelines (Cabana et al., 1999). American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Guidelines for the Management of Heart Failure have been created by a multi-disciplinary committee of experts and are based on thorough review of best available clinical evidence on the management of heart failure. They represent a consensus among experts on the appropriate treatment and management of heart failure. (Jacobs et al., 2013).

Although evidence-based guidelines should be the basis for all disease management, physicians' adherence to those guidelines is poor (Cabana et al., 1999). The major reasons for the failure of guideline implementation are lack of awareness, lack of familiarity, lack of motivation and external barriers. For 78% of clinical practice guidelines, more than 10% of the physicians are not aware of their existence. In all surveys conducted with physicians, the lack of familiarity is more common than the lack of awareness. In other words, the physicians are not familiar enough with the guidelines to apply them correctly even when the guidelines are readily accessible.

One of the reasons for the lack of familiarity is that the guidelines can be quite complex, as in the case of HF management. For example, more than 100 variables have been associated with mortality and re-hospitalization related to heart failure. In the 2013 ACCF/AHA Guideline for the Management of Heart Failure, the variables range from simple information like age and sex to sophisticated data like the patterns in electrocardiogram and history of HF-related symptoms and diseases. The rules for treatment recommendation in the guideline look like the following:

“Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.”

“In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics.”

With more than 60 rules like the ones above, giving correct recommendations becomes an error-prone task for even the most experienced physicians (Group, 2006).

2.3 Literature Review

There have been many approaches for building knowledge-based system. The goal is to enable machine to reason given a knowledge base (Buchanan et al., 1984).

OPS5 (Forgy, 1981) is a member of the class of programming languages known as production systems. It is deployed mainly in applications for artificial intelligence, expert systems, and cognitive psychology. A production system is a program composed entirely of conditional statements called productions. The production is similar to the IF-Then statement in conventional programming languages. For example, a production that contains n conditions C_1 through C_n and m actions A_1 through A_m means when C_1 through C_n are all true, actions A_1 through A_m should be executed. The method of reasoning in OPS5 is called forward chaining (Abraham, 2005). Forward chaining starts with the available facts and use inference rules to extract more data until a goal is reached. In the case of OPS5, the inference engine using forward chaining searches the productions until it finds one where the conditions are satisfied. Once such a production is found, the inference engine performs the actions specified in that production.

One limitation with production systems is the absence of definition of how one statement can contradict another (McCabe, 1993). This is to say the production system formalism has no semantics. One can not tell what the production rules mean in terms of truth values since the semantic notions are not explicitly defined.

Prolog (Clocksin and Mellish, 2003) is one of the first logic programming languages (Gelfond, 1990). It has been used for theorem proving, expert system and automated planning, etc. In Prolog, program logic is expressed in terms of relations, which are defined by clauses. The computations is initiated by a query. The execution strategy of Prolog is called backward chaining (Darden, 2002). Backward chaining starts with a list of goals and search the rules for evidence that supports the goals. Depth-first search strategy is usually employed in backward chaining. In the case of Prolog, this strategy is implemented by SLD resolution (Gallier and Raatz, 1986). SLD resolution defines a search tree in which the initial goal clause is associated with the root of the tree. For every definite clause in the program whose positive literal unifies with the selected literal in the goal clause, there is a child node associated with the goal clause obtained by SLD resolution. A leaf node represents a success if its associated goal clause is empty. Prolog is well-suited for tasks that benefit from rule-based logical queries.

IBM Watson for Oncology (WFO) (SP et al., 2016) is a system able to extract structured data from text files using natural language processing (NLP). It utilizes NLP and machine learning (ML) to learn knowledge from huge amounts of unstructured data. WFO has been trained to interpret cancer patients' clinical information and identify individualized treatment options. About 200 medical journals, 250 textbooks, about 15 million pages of text and more than 10,000 oncology cases were used to train IBM Watson for Oncology. IBM Watson for Oncology is able to interpret cancer patients' clinical information and identify individualized, evidence-based treatment options. In a case study conducted in Manipal Hospital, 638 breast cancer cases were analyzed to evaluate concordance of WFO treatment recommendations with Manipal multidisciplinary tumor board (MMDT). The degree of concordance was 73% overall and it varied depending on the type of breast cancer. Treatment recommendations from WFO were concordant with MMDT in nearly 80% of the time in non-metastatic and only 45% in metastatic disease. In cases of triple negative

breast cancer, WFO agreed with the physicians 68% of the time, but in HER2/neu-negative cases, it matched the physicians' recommendation only 35% of the time. For an artificial intelligent system dealing with medical care, the fact that its accuracy can only be as high as 80% and can reach as low as 35% is not satisfactory at all. One reason for the low degree of concordance is some diseases have more treatment options and variables for consideration, as in the case of HER2/neu-negative breast cancer. To further improve systems which automate disease management, some human thinking capacity may be necessary.

An expert system is intended to embody the knowledge of a human domain expert and to solve problems in that domain (Giarratano and Riley, 1998). It is designed to mimic the decision-making ability of a human expert. A typical expert system contains a fact base, a rule base and an inference engine. The fact base provides the expert system with the problem descriptions which are usually declarative statements about the case in question. The rule base is the embodiment of domain knowledge in the form of conditional statements. The combination of the fact base and rule base is the knowledge base of expert system. The inference engine is the implementation of the mechanism by which the fact base is related to the rule base. Different techniques are used in the realization of the inference engine. Those techniques include but are not limited to rule-based reasoning, case-based reasoning and fuzzy logic. Expert systems have been used in many areas such as automobiles, agriculture, medicine, education and finance, etc.

Although the performance of expert system in their specialized domain is truly impressive, none of the expert systems possess the ability of commonsense reasoning (McCarthy, 1984). The implication of the lack of commonsense reasoning ability is that it is difficult to extend expert system beyond the scope in which the system is supposed to function. MYCIN (Shortliffe, 2012), a system for advising physicians on treating bacterial infections of the blood and meningitis, is a good example to illustrate the strengths and weaknesses of expert system. MYCIN first asks basic facts about the patient such as name, age and gender.

Then MYCIN asks about more sophisticated subjects like suspected sites of infection, presence of specific symptoms and some others. After getting the relevant information, MYCIN recommends a certain course of antibiotics. MYCIN's program is written in a formalism called production system, which is quite suitable for coding a large amount of information about the diagnosis and treatment of bacterial infections. MYCIN outperformed members of Stanford medical school faculty when used in its intended manner. However, MYCIN was never being put to use in production environment. One reason for that given by human experts is MYCIN's inability to stay updated to date with respect to new discoveries in the field. For instance, MYCIN could do nothing about Legionella bacteria since it was understood after MYCIN was developed. Another limitation of MYCIN is the lack of commonsense reasoning capability. MYCIN would readily recommend two weeks of tetracycline to a patient who has Cholerae Vibrio in his intestines. The problem is that this recommendation alone would not save the patient's life if no measure is being taken to treat diarrhea. It is clear that the capability of performing commonsense reasoning is necessary for expert system to be useful even in a narrow domain. However, representing common sense knowledge in formal terms has proved to be not an easy task.

A large number of software systems have been designed to address chronic disease management. Chronic disease management systems generally can be classified to seven categories (Jantos and Holmes, 2006): accessibility, care management, point-of-care functions, decision support, patient self-management, population management and reporting. Telemedicine is the kind of system that combines telecommunication and information technology to provide clinical healthcare from a distance (Norris, 2002). Hygeiatel is a representative of telemedicien system (Monteiro et al., 2011). Patients are provided with chronic care platform and peripheral devices such as a weighing scale, blood pressure meter, gluco-meter and pulse oximeter. The patients measure their vital signs on a regular basis and answered questionnaires about their health condition. Based on the data gathered from the devices

and patients, nurses and doctors were able to manage the patients remotely. For example, a rule-based system (Seto et al., 2012) was developed to generate automated alerts and patient instructions aiming at increased self-care and improved clinical management. The system relies on both tele-monitoring data and clinical rule set. The tele-monitoring data are patient’s weight, blood pressure, heart rate and symptoms. The rule set was developed with input from heart failure experts. Semi-structured interviews with physicians were conducted to validate and refine the rule set.

The software systems of the kinds mentioned above clearly lack reasoning capabilities since they focus either on information retrieval or emergency alert. As far as we know, there have been no system that is designed to automatically advise physicians based on clinical practice guidelines.

2.4 Answer Set Programming

Answer set programming (ASP) is a form of declarative programming for solving difficult search problems, which are primarily NP-hard (Lifschitz, 2008). ASP is well-suited for knowledge-intensive applications since it realizes nonmonotonic reasoning (Brewka, 1991).

A rule in ASP program follows the form in Figure 2.1

$$p \text{ :- } q_1, \dots, q_m, \text{ not } r_1, \dots, \text{ not } r_n.$$

Figure 2.1. Ground Normal Logic Program

where $m \geq 0$ and $n \geq 0$. Each of p and q_i ($\forall i \leq m$) is a literal; each $\text{not } r_j$ ($\forall j \leq n$) is a literal of Negation as Failure (NAF). A negative condition $\text{not } r_i$ is shown to hold by showing that the positive condition r_i fails to hold. It is read declaratively as a logical implication: p if q_1 and ...and q_m and $\text{not } r_1$ and ...and $\text{not } r_n$.

ASP reduces search problems to computing stable models of a normal logic program. Consider the logic program K in Figure 2.2:


```

p.
r :- p, q.
s :- p, not q.

```

Figure 2.2. An Example of Answer Set Program K

```

p ← true
q ← false
r ← false
s ← true

```

Figure 2.3. A Stable Model of Program K

```

p ← true
q ← true
r ← true
s ← false

```

Figure 2.4. A Model (not stable) of Program K

We say that the truth assignment in Figure 2.3 is a stable model of the logic program K. A stable model of a logic program represents the behavior of SLDNF (Van Gelder et al., 1991) resolution. For logic program K, the query p will first succeed because p is a fact; the query r will fail because one of its subgoals, the query q will fail; the query s will succeed because both of its subgoals p and $not\ q$ succeed.

Logic program has other models such as the one in Figure 2.4. This model is not *stable* since it does not represent the behavior of SLDNF resolution.

2.4.1 Negation as Failure

Negation as Failure is a non-monotonic inference rule in logic programming. It derives $not\ p$ from failure to prove p . Note that $not\ p$ is different from classical negation $\neg p$. For example, a school bus may cross railway tracks if there is no approaching train. Using classical negation to express this rule looks like:

```

cross :- ¬train.

```

It means it is okay to cross the railway if we know explicitly that no train is approaching.

Had we used negation as failure, the rule would be:

cross :- *not train*.

It says it is okay to cross the railway tracks in the absence of information about an approaching train.

An example adapted from (Dung and Mancarella, 2002) can illustrate the expressiveness of negation as failure. Suppose there is a person doing his household work. He has two ways of washing the clothes. One is hand washing and the other machine washing. If there is washing powder in the house, then machine washing can take place. If not, then he can acquire washing powder by either buying it in a shop or by borrowing it from a neighbor. These logic can be represented by following rules:

machine_wash :- *powder*

powder :- *buy_powder*

powder :- *borrow_powder*

Of course, hand washing is not desirable and will be considered only when there is no washing powder in the house. The naive representation of this rule is to use classical negation:

hand_wash :- \neg *powder*

However, this is not the correct way to capture the reasoning process. What this person really means is that he hand-washes the clothes if there is no way to acquire the washing powder. The above naive implementation will suggest hand washing while there are ways to get machine powder. With negation as failure, the reasoning process can be represented as:

hand_wash :- *not powder*

The rule above says hand washing would be allowed only if there is no way to acquire washing powder. Clearly, negation as failure is a better way to represent human reasoning process in some cases.

2.4.2 Gelfond-Lifschitz Transformation

Given a ground normal logic program K in Figure 2.1 and a set of ground terms I , the reduct of K relative to I is the set of rules without negation obtained by:

- I. Deleting all rules in K which have *not* L in their body where L is any literal in I .
- II. Deleting all the remaining NAF-literals from the bodies of the remaining rules.

We say I is a *stable model* or an *answer set* of K if I is the least fixed point of the reduct of K relative to I .

Consider the answer set program K in Figure 2.2. Let's check that $\{p, s\}$ is a stable model of program K by using Gelfond-Lifschitz Transformation (GL Transformation). The reduct of program K relative to $\{p, s\}$ is:

```
p.  
r :- p, q.  
s :- p.
```

The least fixed point of the program above is $\{p, s\}$, which proves that $\{p, s\}$ is indeed a stable model of program K . On the other hand, $\{p, q, r\}$ is not a stable model of program K . This can be verified by following the GL Transformation. The reduct of program K relative to $\{p, q, r\}$ is:

```
p.  
r :- p, q.
```

The least fixed point of the program above is $\{p\}$, which is different from $\{p, q, r\}$. Thus $\{p, q, r\}$ is not a stable model of program K .

2.5 Goal-directed Execution of Answer Set Programs

Goal-directed ASP systems are able to compute stable models of normal logic programs. Given an answer set program and a query goal, a goal-directed ASP system will systematically enumerate all answer sets that contain the propositions/predicates in the query goal. This enumeration utilizes Coinductive SLD resolution (or Co-SLD resolution) (Simon et al., 2006), which systematically computes elements of the greatest fixed point (GFP) of a program via backtracking (Marple et al., 2012). Specifically, Co-SLD resolution expands SLD-resolution by storing each succeeding call in a set called coinductive hypothesis set (CHS). Candidate partial models are generated and then tested to ensure that no constraint is violated. This testing is implemented by non-monotonic reasoning check (NMR check). A logic program P is executed with a query Q as follows: First, the NMR check relative to P is created. Then the body of the NMR check is appended to Q . Next, each goal G in Q is executed in order. G is checked against the CHS (Marple et al., 2017):

- G succeeds if the CHS contains an exact match for G .
- G fails if the CHS contains an exact match for *not* G .
- G is constrained against any CHS entry which unifies with *not* G if there is no exact match in the CHS.

If G goes through the above processes without succeeding or failing, the call stack is checked for any cycle containing G :

- G succeeds if G is an exact match for an entry in the call stack with even and non-zero number of negations.
- G succeeds if G constructively unifies with an entry in the call stack with even and non-zero number of negations.

- G fails if G is an exact match for an entry in the call stack without any negation.

If G passes the above processes without succeeding or failing, G is expanded using the rules in program P. G is added to the CHS if G succeeds. The query Q succeeds if every goal in Q succeeds. The content in the CHS is a partial stable model for program P.

One ramification of the top-down execution strategy of a goal-directed ASP system is that the answer set can be partial (Marple et al., 2012). Consider the following program:

```
p :- not q.  
q :- not p.  
r :- not s.  
s :- not r.
```

Using a goal-directed ASP system, the query `?- q` will produce `{q, not p}` as the partial answer set because the rules containing `r` and `s` are independent of the rules for `p` and `q`. Had the query been `?- q, s`, the system would give `{q, not p, s, not r}` as the result. Thus the partial answer set the system produces is determined by the query it is given. The partial answer set essentially contains the propositions that are necessary to establish the query.

CHAPTER 3

PHYSICIAN ADVISORY SYSTEM DESCRIPTION ¹

3.1 Overview

This chapter gives the description of the physician advisory system for heart failure management. First, the guideline for the management of heart failure, which provides the underlying rules for the physician advisory system, is introduced. The architecture of the system is then illustrated. The input and output of the system are listed in detail. Four underlying principles in building the system are discussed. An simplified example of a heart failure patient is used to demonstrate the usage of the system.

3.2 Guideline for the Management of Heart Failure

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) have jointly developed and published clinical practice guideline since the early 1980s. The ACCF/AHA Task Force is responsible for developing, updating and reviewing practice guidelines for cardiovascular diseases and procedures. Evidence-based, patient-centric treatment recommendations are developed by committees that review and evaluate all available evidence. The recommendations are listed in ACCF/AHA Class of Recommendation (COR) and Level of Evidence (LOE) scheme.

The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm.

COR is summarized as follows:

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- Class I recommendation: the treatment is effective and should be performed.
- Class IIa recommendation: the treatment can be useful and is probably recommended.
- Class IIb recommendation: the treatment's usefulness is uncertain and it might be considered.
- Class III recommendation: the treatment is harmful or unhelpful and should be not administrated.

The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity and consistency of data from clinical trials and other sources. The definitions of LOE are listed as follows:

- Level of Evidence A: Multiple populations are evaluated. Data are derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Limited populations are evaluated. Data are derived from a single randomized trial or nonrandomized studies.
- Level of Evidence C: Very limited populations are evaluated. Only consensus opinion of experts, case studies, or standard of care are available.

The 2013 ACCF/AHA Guideline for the Management of Heart Failure contains a range of acceptable approaches to the management of heart failure. An extensive evidence review was conducted through October 2011 and includes selected other references through April 2013. This thorough review of clinical evidence on heart failure management has resulted in the guideline that assists clinicians in selecting the best management strategy for an individual patient with heart failure. Experts in heart failure are selected by the ACCF and AHA to examine data and write guidelines.

The guideline is based on four progressive stages of heart failure. Stage A includes patients who are at risk of heart failure but are asymptomatic. Stage B describes asymptomatic patient with structural heart disease; it includes New York Heart Association (NYHA) class I, in which ordinary physical activity does not lead to symptoms of heart failure. Stage C includes patients with structural heart disease who have prior or current symptoms of heart failure; it includes NYHA class I, II (slight limitation of physical activity), III (marked limitation of physical activity) and IV (unable to carry on any physical activity without symptoms of heart failure, or symptoms of heart failure at rest). Stage D describes patients with refractory heart failure who require specialized interventions; it includes NYHA class IV. Treatment recommendations at each stage are aimed at reducing risk factors (stage A), treating structural heart disease (stage B) and reducing morbidity and mortality (stages C and D) (Yancy et al., 2013).

In 2016, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines issued 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure (Yancy et al., 2016). This update reassesses guideline recommendations on the basis of recently published data.

Although evidence-based guidelines should be the basis for all disease management, physicians' adherence to those guidelines is poor (Cabana et al., 1999). The major reasons for the failure of guideline implementation are lack of awareness, lack of familiarity, lack of motivation and external barriers. For 78% of clinical practice guidelines, more than 10% of the physicians are not aware of their existence. In all surveys conducted with physicians, the lack of familiarity is more common than the lack of awareness. In other words, the physicians are not familiar enough with the guidelines to apply them correctly even when the guidelines are readily accessible.

One of the reasons behind the lack of familiarity is that the guidelines can be quite complex, as in the case of heart failure management. More than 100 variables have been associated with mortality and re-hospitalization related to heart failure. In the 2013 ACCF/AHA

Guideline for the Management of Heart Failure, the variables range from straightforward information like age and sex to sophisticated data like the patterns in electrocardiogram and history of HF-relevant symptoms and conditions. Let us look at one rule from the guideline:

Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.

With more than 60 rules like the one above, giving guideline-compliant recommendations becomes an error-prone task for even the most experienced and best-intentioned physicians (Group, 2006). What makes things trickier is the fast growing rate of knowledge base in medicine. For instance, the doubling rate of medical knowledge is about one year. It is difficult for healthcare providers to keep up with the latest development of medical knowledge even more so for them to actually adopt the newly-confirmed best practices.

3.3 System Description

The physician advisory system for heart failure management consists of the rule database and a fact table. The rule database covers all the knowledge in the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al., 2013). The fact table contains the relevant information of the patient with heart failure. The patient's information mainly includes 5 pieces of demographics information, 8 measurements and 25 types of HF-related diseases and symptoms. The physician advisory system is able to generate all guideline-compliant treatments for the patient. These treatments are 11 pharmaceutical treatments, 9 management objectives and 4 device/surgery therapies. The medical rules can also be executed by CLASP system (Gebser et al., 2014) since they are grounded. Note that SAT-based ASP systems such as CLASP don't distinguish between treatment that are in the same model but are independent of each other. Table 3.1 and Table 3.2 display the inputs and outputs of the physician advisory system for heart failure management, respectively.

Table 3.1. Input of the Physician Advisory System for HF Management

| | |
|-----------------------|--|
| Demographics | gender; age; race |
| Measurements | weight; creatinine; potassium; left bundle branch block; non-left bundle branch block; QRS duration; ejection fraction NYHA class; ACCF/AHA stage; sinus rhythm; |
| Diseases and Symptoms | sleep apnea, acute coronary syndrome; myocardial infarction; diabetes; stroke; fluid retention; angioedema; ischemic attack; thromboembolism; elevated plasma natriuretic peptide level; asymptomatic ischemic cardiomyopathy; atrial fibrillation; myocardial ischemia; lipid disorders; acute profound hemodynamic compromise; obesity; angina; threatened end organ dysfunction; ischemic heart disease; structural cardiac abnormalities; atrioventricular block; hypertension; dilated cardiomyopathy; volume overload coronary artery disease; |
| Miscellany | expectation of survival; pregnancy; history of standard neurohumoral antagonist therapy; risk of cardioembolic stroke; ischemic etiology of HF; eligibility of mechanical circulatory support; dependence of continuous parenteral inotropic; requirement of ventricular pacing history of cardiovascular hospitalization; eligibility of significant ventricular pacing; |

Table 3.2. Output of the Physician-Advisory System for HF Management

| | |
|---------------------------|--|
| Pharmaceutical Treatments | ACE inhibitors; ARBs; Beta blockers; statin; diuretics; aldosterone receptor antagonists; digoxin; inotropes; anticoagulations; Omega-3 fatty acids; hydralazine and isosorbide dinitrate; |
| Management Objectives | systolic blood pressure control; diastolic blood pressure control; obesity control; diabetes control; tobacco avoidance; cardiotoxic agents avoidance; atrial fibrillation control; sodium restriction; water restriction; |
| Device/Surgery Therapies | implantable cardioverter-defibrillator; cardiac resynchronization therapy; mechanical circulatory support; coronary revascularization |

The physician advisory system was built based on two core concepts: recommendation and contraindication. A recommendation is can be translated into action or activity that can be implemented and measured. A contraindication is a specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the person. Certain facts were taken into consideration during the development of the physician advisory system. These facts are:

- Multiple rules can trigger a *recommendation*.
- Multiple rules can lead to a *contraindication*.
- A *recommendation* of a treatment can't be made if at least one *contraindication* for that treatment is present.
- A *recommendation/contraindication* can impact the *recommendation/contraindication* of other treatments.

Fact #1: Multiple rules can trigger a *recommendation*. An instance of this fact can be found in the following two rules recommending Implantable Cardioverter Defibrillator (ICD):

“Class I: ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of 35% or less and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for more than 1 year.”

“Class I: ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.”

Fact #2: Multiple rules can lead to a *contraindication*. An instance of this fact can be found in the following two rules forbidding ACE inhibitors:

“Patients should not be given an ACE inhibitor if they have experienced life-threatening adverse reactions (ie, angioedema) during previous medication exposure or if they are pregnant or plan to become pregnant.”

“Class III: Routine combined use of an ACE inhibitor, ARB and aldosterone antagonist is potentially harmful for patients with HFrEF.”

Fact #3: A *recommendation* of a treatment can't be made if at least one *contraindication* for that treatment is present.

Fact #4: A *recommendation/contraindication* can impact the other treatments. An instance of this fact can be found in the following rule recommending ARBs:

“Class I: ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality.”

The guideline rules are fairly complex and require the use of negation as failure, non-monotonic reasoning with incomplete information. A fairly common situation in medicine is that a drug can only be recommended if its use is not contraindicated. Contraindicated is naturally modeled by negation as failure. The ability of answer set programming to model defaults, exceptions, preferences, etc., makes it ideally suited for coding clinical practice guidelines. Not surprisingly, the program for the physician advisory system is unstratified. Both odd and even loop over negation occur in the program of the physician advisory system. As an example, the indispensable choice knowledge pattern (Chen et al., 2016) used in our system contains an even loop. Consider the following rule from ACCF/AHA stage C (Yancy et al., 2013):

In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics.

The pattern describes a case in which if a choice is made, some other choices must also be made; if those choices can't be made, then the first choice is revoked. Note that Prolog conventions are followed (variables begin with an upper case letter).

```
recommendation(beta_blockers, class_1) :-  
    not absent_indispensable_choice(beta_blockers),  
    not rejection(beta_blockers), evidence(accf_stage_c),
```

```
diagnosis(hf_with_reduced_ef).
```

```
absent_indispensable_choice(beta_blockers) :-  
    not recommendation(diuretics, class_1),  
    diagnosis(hf_with_reduced_ef), evidence(accf_stage_c),  
    current_or_recent_history_of_fluid_retention.
```

```
recommendation(diuretics, class_1) :-  
    recommendation(beta_blockers, class_1),  
    diagnosis(hf_with_reduced_ef),  
    not rejection(diuretics), evidence(accf_stage_c),  
    current_or_recent_history_of_fluid_retention.
```

Consider a case in which we have a patient who has heart failure with reduced ejection fraction (HFrEF) and is in ACCF/AHA stage C. According to the guideline, our system would recommend the use of beta blockers. However, if we add the information that the patient has a history of fluid retention, then the system would try to add diuretics. However, if diuretics are contraindicated for any reason, then the system will not recommend beta blockers either.

The architecture of the physician advisory system is shown in Figure 3.1.

To illustrate how the physician advisory system works, consider a female heart failure patient who is in ACCF/AHA stage C, belongs to NYHA class III and has been diagnosed as myocardial ischemia, atrial fibrillation, coronary artery disease. She also suffers from sleep apnea, fluid retention and hypertension. Her left ventricular ejection fraction (LVEF) is 35%. There is evidence that she has ischemic etiology of heart failure. Her electrocardiogram (ECG) has sinus rhythm and a left bundle branch block (LBBB) pattern with a QRS duration of 180ms. The blood test says her creatinine is 1.8 mg/dL and potassium is 4.9 mEq/L. She

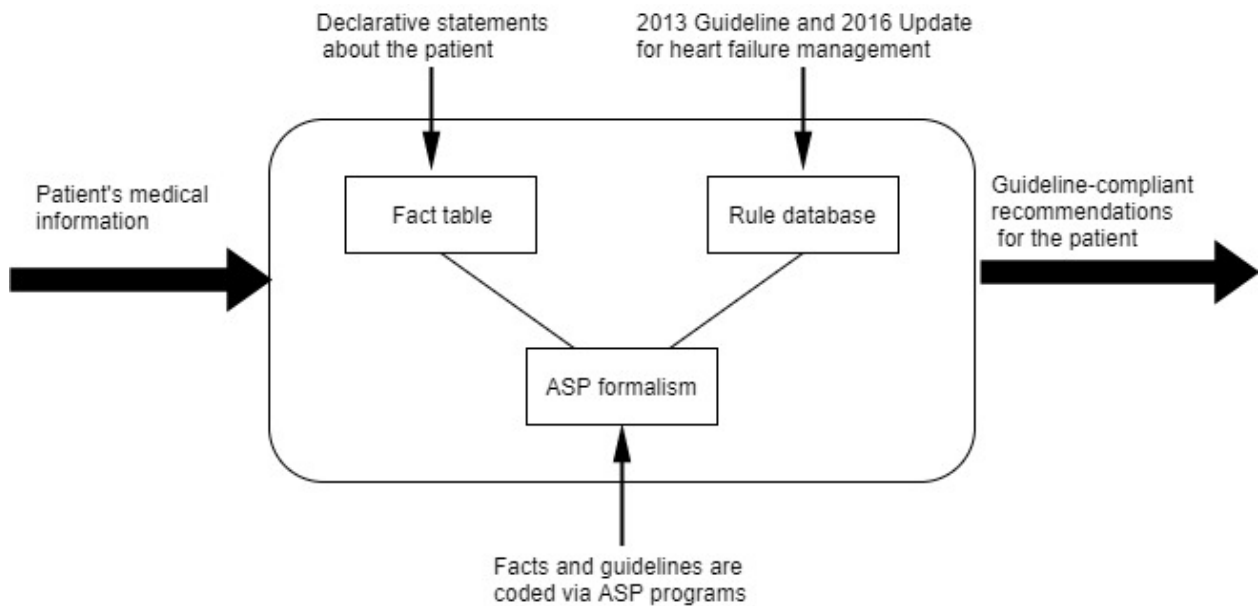


Figure 3.1. The Architecture of Physician Advisory System

has a history of stroke. It has been 40 days since the acute myocardial infarction happened to her. Her doctor assessed that her expectation of survival is about 3 years.

This patient's information is coded as the facts shown in Figure 3.2

Figure 3.3 shows this patient's information in the user interface of the physician advisory system we have developed.

With the patient's information above available, we can then run the physician advisory system to get all applicable recommendations for this patient. Note that since this patient is in ACCF stage C, measures listed as Class I recommendations for her in stages A and B are also recommended where appropriate. To save some space, we only list the answer set for stage C. Figure 3.4 displays the answer set produced by the physician advisory system, which utilizes CLASP (Gebser et al., 2014).

With the user interface, the recommendations are listed in a drop box, as is shown in Figure 3.5.

```

%doctor's assessments
accf_stage(c).
nyha_class(3).
expectation_of_survival(3).

%demographics of the patient
gender(female).
age(78).

%measurements from the lab
hf_with_reduced_ef.
measurement(creatinine, 1.8).
measurement(potassium, 4.9).
measurement(lvef, 0.35).
measurement(lbbb, 180).
measurement(sinus_rhythm).

%history of the patient
diagnosis(myocardial_ischemia).
diagnosis(atrial_fibrillation).
diagnosis(coronary_artery_disease).
diagnosis(hypertension).
evidence(ischemic_etiology_of_hf).
evidence(sleep_apnea).
evidence(fluid_retention).
history(mi, recent).
history(stroke).
history(cardiovascular_hospitalization).
post_mi(40).

```

Figure 3.2. Representation of a patient's information in physician-advisory system for HF management

| | |
|---------------------|--|
| Evidence | The NYHA class is III |
| | The ACCF stage is C |
| | The gender is female |
| | The ECG indicates sinus rhythm |
| | Fluid retention |
| | Sleep apnea |
| | Ischemic etiology of heart failure |
| Measurements | The expectation of meaningful survival is 3 years |
| | The left ventricular ejection fraction is 35% |
| | The creatinine level is 1.8 mg/dL |
| | The potassium level is 4.9 mEq/L |
| | Left bundle branch block with a QRS duration of 180ms |
| | 40 days post-MI |
| | 78 years old |
| History | History of myocardial infarction |
| | History of stroke |
| | This patient has a history of cardiovascular hospitalization |
| Diagnosis | Coronary artery disease |
| | Hypertension |
| | Heart failure with reduced ejection fraction |
| | Atrial fibrillation |
| | Myocardial ischemia |

Figure 3.3. Representation of a patient's information in GUI


```

{ treatment(ivabradine) treatment(ace_inhibitors) treatment(icd) treatment(crt)
treatment(beta_blockers) treatment(diuretics) treatment(arni) treatment(arbs)
treatment(statins) treatment(aldosterone_antagonist) treatment(digoxin)
treatment(hydralazine_and_isosorbide_dinitrate) treatment(omega3_fatty_acids)
treatment(anticoagulation) treatment(continuous_intravenous_inotropic_support)
treatment(short_term_continuous_intravenous_inotropic_support)
treatment(long_term_continuous_intravenous_inotropic_support)
treatment(blood_pressure_control) treatment(systolic_blood_pressure_control)
treatment(diastolic_blood_pressure_control) treatment(obesity_control)
treatment(obesity_avoidance) treatment(diabetes_control)
treatment(diabetes_avoidance) treatment(tobacco_use_avoidance)
treatment(cardiotoxic_agents_avoidance) treatment(coronary_revascularization)
treatment(atrial_fibrillation_management) treatment(sodium_restriction)
treatment(fluid_restriction) treatment(mechanical_circulatory_support)
treatment(continuous_positive_airway_pressure) recommendation_class(class_1)
recommendation_class(class_2a) recommendation_class(class_2b) measurement(survival,3)
evidence(accf_stage_c) evidence(nyha_class_3) diagnosis(hf_with_reduced_ef)
evidence(female) measurement(age,78) measurement(creatinine,18) measurement(potassium,49)
diagnosis(myocardial_ischemia) diagnosis(atrial_fibrillation) history(mi)
diagnosis(coronary_artery_disease) diagnosis(hypertension) evidence(sleep_apnea)
evidence(ischemic_etiology_of_hf) history(cardiovascular_hospitalization) history(stroke)
evidence(fluid_retention) measurement(mi,40) measurement(lvef,35) measurement(lbbb,180)
evidence(sinus_rhythm) lvef_less_than_40 diagnosis(ischemic_heart_disease)
history(hf_with_reduced_ef) history(nyha_class_3) history(fluid_retention)
history(myocardial_ischemia) history(atrial_fibrillation) history(coronary_artery_disease)
history(hypertension) history(ischemic_heart_disease) history(accf_stage_c)
history(female) history(ischemic_etiology_of_hf) history(sleep_apnea)
history(sinus_rhythm) lvef_less_than_35 age_greater_than_75 creatinine_less_than_25
creatinine_less_than_20 potassium_less_than_50 mi_post_40_days survival_year_greater_than_1
lbbb_qrs_greater_than_150 nyha_class_2_to_4 nyha_class_2_to_3
nyha_class_3_to_4 current_or_recent_history_of_fluid_retention
history_of_mi_or_acs safe_condition_for_aldosterone_antagonists_male_creatinine
safe_condition_for_aldosterone_antagonists_female_creatinine
safe_condition_for_aldosterone_antagonists_potassium
contraindication(blood_pressure_control) contraindication(aldosterone_antagonist)
contraindication(hydralazine_and_isosorbide_dinitrate)
cardioembolic_source rejection(blood_pressure_control) rejection(aldosterone_antagonist)
rejection(hydralazine_and_isosorbide_dinitrate)
recommendation(diuretics,class_1) recommendation(beta_blockers,class_1)
recommendation(ace_inhibitors,class_1) recommendation(sodium_restriction,class_2a)
recommendation(continuous_positive_airway_pressure,class_2a) recommendation(crt,class_1)}
recommendation(digoxin,class_2a) recommendation(anticoagulation,class_1)
recommendation(omega3_fatty_acids,class_2a) recommendation(icd,class_1)

```

Figure 3.4. Recommendations produced by the physician advisory system

Recommendations

The image shows a user interface for medical recommendations. At the top, there is a dropdown menu currently set to "Stage C Recommendations". Below this, the recommendations are organized into three sections, each with a blue header bar:

- Stage C Recommendations**
 - Diuretics(class I)
 - Beta blockers (class I)
 - Valsartan/sacubitril (class I)
 - Sodium restriction (class IIa)
 - Continuous positive airway pressure(class IIa)
 - Digoxin(class IIa)
 - Anticoagulant agents(class I)
 - Omega-3 polyunsaturated fatty acid supplementation(class IIa)
 - Implantable Cardioverter Defibrillator(class I)
 - Cardiac Resynchronization Therapy (class I)
- Stage B Recommendations**
 - Statins(class I)
 - Diuretics(class I)
 - Beta blockers (class I)
 - Angiotensin-converting-enzyme inhibitor(class I)
- Stage A Recommendations**
 - Blood pressure control(class I)
 - Obesity avoidance(class I)
 - Diabetes avoidance(class I)

The interface includes a vertical scrollbar on the right side of the list, indicating that there are more items than can be seen at once.

Figure 3.5. Recommendation shown in user interface

CHAPTER 4

KNOWLEDGE PATTERNS ¹

4.1 Overview

This chapter discusses the knowledge patterns that we identified during the development of the physician advisory system. The incentive for developing the knowledge patterns is to enable developers to code each rule individually and build a knowledge-based system that faithfully represent the meaning of the knowledge base. Each knowledge pattern can be seen as a reasoning template that capture the essence of a type of reasoning process of human mind. We first present the related work of knowledge patterns. Next we discuss in detail each knowledge pattern with two examples, one from the guideline for the management of heart failure and the other from a different application domain.

4.2 Literature Review

A method was developed to identify and extract cause-effect information, which are available in medical abstracts (Khoo et al., 2000). A set of graphical patterns were defined to express the causal relations in sentences. Specifically, these patterns point out which part of the sentence represents the cause and which part represents the effect. For each target sentence in textual documents, a syntactic parse tree is generated and then matched with the graphical causality patterns. When a match is identified, the cause, the effect and the modality can be extracted and put into cause-effect templates.

Clark et al. (Clark et al., 2004) proposed a knowledge engineering technique based on the knowledge patterns. Knowledge patterns are general templates representing recurring

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theories and their transformations. A knowledge pattern can be transformed from a general theory into a specific one. The motivation behind knowledge patterns is to overcome the limitation of inheritance in traditional knowledge engineering. Inheritance is problematic when a general theory can be applied in multiple ways or when some of the properties in a general theory are transferred to specific domains. The knowledge patterns make use of morphism to address the issue with multiple applications of theories. They can also selectively transfer information by hiding irrelevant relations with respect to knowledge base. The advantages of knowledge patterns include modularization of knowledge base, reuse of general theories and separation of a general theory from a specific domain.

Marshman (Marshman, 2007) studied lexical knowledge patterns that indicate conceptual relations of cause-effect and association in specialized medical texts. Knowledge patterns, composed of a lexical marker that represents a relation between two concepts can be compiled to help identify information in knowledge base. The data were gathered from two corpora, English and French, to reveal similarities and differences between the data in the two languages. A number of lexical markers of cause-effect and association relations were identified. These markers can be promising candidates for semi-automatic knowledge-rich contexts extraction tools.

4.3 Knowledge Patterns

The ACCF/AHA Guideline for the Management of Heart Failure has very complex rules. Such complexity has been part of the reason behind physician’s poor compliance with the clinical guidelines (Cabana et al., 1999). For instance, one rule in the guideline look like this (Yancy et al., 2013):

“Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II—IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma

natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/ 1.73 m^2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency”

The methodology we adopted when we were building the physician advisory system was to identify a set of knowledge patterns that represent the logical relations between treatment recommendations. We believe that human uses common and straightforward reasoning form when trying to reason with a set of rules and principles. In other words, those rules and principles always follow some patterns which are cognitively-friendly. These knowledge patterns are quite general and serve as solid building blocks for systematically translating the specifications written in English to ASP. The knowledge-based system developers can simply plug specific items into the knowledge patterns. With the knowledge patterns, we were able to code each rule individually and the conglomerate of the encoding of rules faithfully represent the meaning of the whole guideline.

Next we present the knowledge patterns we identified and developed from the guideline for heart failure management. We will start from straightforward patterns, which make possible for more complicated ones. These patterns are presented at a high level and non-essential details are ignored. They are quite generic and can be easily applied to domains other than medicine. Apart from the examples of the medical application, one extra example from a different application domain is given for each of the knowledge patterns.

4.3.1 Aggressive Reasoning

The aggressive reasoning pattern can be stated as “take an action (e.g., recommend treatment) if there is a reason; no evidence of danger means there is no danger in taking that action”. The aggressive reasoning pattern is coded as in Figure 4.1

The code in Figure 4.1 makes use of negation as failure to encode the concept of contraindication. A contraindication is a specific situation in which a drug, procedure, or surgery

```

#1 recommendation(Choice) :- preconditions(Choice),
#2     not contraindication(Choice).
#3 contraindication(Choice) :- dangers(Choice).

```

Figure 4.1. Knowledge Pattern for Aggressive Reasoning

should not be used because it may be harmful to the person. Line #1 specifies that the preconditions should be met for the treatment choice. Line #2 uses negation as failure to ensure that there is no explicit evidence for the contraindication of the treatment choice. Line #3 is the place where the contents of the contraindication are defined.

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF.”

The rule above is realized in the physician advisory system as shown below. The meaning of the code is that to recommend Digoxin with Class of Recommendation I to a patient, he/she must have been diagnosed with heart failure with reduced ejection fraction and in ACCF stage C, and Digoxin must not be contraindicated for him/her. A patient is considered intolerant of Digoxin if he/she has developed atrioventricular block.

```

recommendation(digoxin, class_2a) :- not contraindication(digoxin),
    accf_stage(c), hf_with_reduced_ef.
contraindication(digoxin) :- evidence(atrioventricular_block).

```

Another example for the aggressive reasoning pattern can be found in the Texas Driver Handbook (Texas Department of Public Safety, 2017):

“A steady green light means the driver can proceed on a green light if it is safe to do so. You may drive straight ahead or turn unless prohibited by another sign or signal. Watch for cars and pedestrians in the intersection. Be aware of reckless drivers who may race across the intersection to beat a red light.”

The rule above can be realized by the following code:

```

proceed :- green_light,
not unsafe.

unsafe :- prohibiting_sign.
unsafe :- prohibiting_signal.
unsafe :- cars_in_the_intersection.
unsafe :- pedestrians_in_the_intersection.

```

4.3.2 Conservative Reasoning

Conservative reasoning knowledge pattern is stated as “A reason for a recommendation is not enough; evidence that the recommendation is not harmful must be available”. The conservative reasoning knowledge pattern is coded as in Figure 4.2.

```

#1 recommendation(Choice) :- preconditions(Choice),
#2     not contraindication(Choice).
#3 contraindication(Choice) :- not -dangers(Choice).

```

Figure 4.2. Knowledge Pattern for Conservative Reasoning

The code in Figure 4.2 is similar to the code for aggressive reasoning knowledge pattern. The only difference lies in the line #3, which uses a combination of classical negation and negation as failure to explain the contraindication of a treatment choice. This coding pattern requires evidence of the absence of danger. Without such evidence, the choice would be considered contraindicated. Note that the “-” operator indicates classical negation.

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“In patients with structural cardiac abnormalities, including LV hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.”

The rule above is realized in the physician advisory system as shown below. The meaning of the code is that to recommend blood pressure control with Class of Recommendation I to a patient, he/she must be in ACCF stage b and have been diagnosed with structural cardiac abnormalities. Additionally, the proof must be there that this patient does have the history of myocardial infarction or the history of acute coronary syndrome. Otherwise, blood pressure control is considered a contraindication for him/her.

```
recommendation(blood_pressure_control, class_1):-  
    accf_stage(b), diagnosis(structural_cardiac_abnormalities),  
    not contraindication(blood_pressure_control).  
contraindication(blood_pressure_control):- not -history(mi).  
contraindication(blood_pressure_control):- not -history(acs).
```

Another example for the conservative reasoning pattern can be found in “The 12 Golden Rules for Safe Gun Handling” (Magtech Ammunition Company, Inc., 2017):

“Be sure the barrel is clear of obstructions before loading and shooting.”

The above rule can be realized by the following code:

```
loading_and_shooting :- other_conditions_for_loading_and_shooting,  
not danger.  
danger :- not -obstruction_in_barrel.
```

4.3.3 Anti-recommendation

The anti-recommendation knowledge pattern is stated as “a choice can be prohibited if evidence of danger can be found”. This knowledge pattern is coded as in Figure 4.3

The code in Figure 4.3 specifies the conditions under which a choice will be ruled out (i.e., contraindicated). Note that for a choice to be made, both aggressive reasoning and conservative reasoning require that the contraindication of the choice be false.


```
#1 contraindication(choice) :- dangers(Choice).
```

Figure 4.3. Knowledge Pattern for Anti-recommendation

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source.”

The rule above is realized in the physician advisory system as shown below. The meaning of the code is that anticoagulants are contraindicated if the patient does not have cardioembolic source, atrial fibrillation or history of thromboembolism. Though not shown in the code, cardioembolic source includes history of hypertension, diagnosis of diabetes, history of stroke, history of ischemic attack or being of age greater than 75.

```
contraindication(anticoagulation) :- not cardioembolic_source,  
    not diagnosis(af), not history(thromboembolism),  
    hf_with_reduced_ef.
```

Another example for the anti-recommendation pattern can be found in the article “how to tell if raw chicken has gone bad” (Mooney, 2017):

“There are a few signs that can help identify whether chicken is safe to eat or if it should be tossed in the trash: ”

- Is it gray?
- Does it stink?
- Is it slimy?

The rule above can be realized by the following code:

```
toss_the_chicken :- chicken_is_bad.  
chicken_is_bad :- chicken_is_gray.  
chicken_is_bad :- chicken_stink.  
chicken_is_bad :- chicken_is_slimy.
```

4.3.4 Preference

The preference pattern is stated as “use the second-line choice when the first-line choice is not available”. This pattern is coded as in Figure 4.4

```
#1 recommendation(First_choice) :- conditions_for_both_choices,  
#2     not contraindication(First_choice).  
#3 recommendation(Second_choice) :- conditions_for_both_choices,  
#4     contraindication(First_choice),  
#5     not contraindication(Second_choice).
```

Figure 4.4. Knowledge Pattern for Preference

This code chooses the treatment recommendation in the second choice only when the conditions are satisfied, the first choice is contraindicated, and there is no evidence preventing the use of second choice. Line #1 and #2 specify that first choice should be made when its conditions are met and there is no evidence of contraindication of it. Line #3 – #5 means that taking the second choice if the conditions for the first choice are met, the first choice is contraindicated and the second choice is not contraindicated.

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“ARBs are recommended in patients with HF_{rEF} with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality.”

The rule above is realized in the physician advisory system as in Figure 4.5. The meaning of the code is that ACE inhibitors are recommended to a patient with heart failure with reduced ejection fraction in ACCF stage C and ACE inhibitors are contraindicated. If ACE inhibitors are contraindicated, ARBs are recommended in place of ACE inhibitors.

Note that the preference knowledge pattern applies not only to two choices but as many choices as needed. The pattern can be easily expanded to third choice, fourth choice, etc. Another example for the preference pattern can be found in “veterans’ preference” (U.S. Office of Personnel Management, 2017):

```

recommendation(ace_inhibitors, class_1) :-
    not contraindication(ace_inhibitors),
    accf_stage(c), hf_with_reduced_ef.
recommendation(arbs, class_1) :- contraindication(ace_inhibitors),
    not contraindication(arbs),
    not taboo_choice(arbs),
    accf_stage(c), hf_with_reduced_ef.

```

Figure 4.5. Example for Preference Pattern

“Veterans’ Preference gives eligible veterans preference in appointment over many other applicants. Veterans’ preference applies, to virtually all new appointments in both the competitive and excepted service.

There are basically three types of preference eligibles, disabled (10 point preference eligible), non-disabled (5 point preference eligible) and sole survivorship preference (0 point preference eligible).”

The rule above can be realized by the following code:

```

hire(Applicant) :- qualified(Applicant), ten_point_preference(Applicant),
not unavailable(Applicant).
hire(Applicant) :- qualified(Applicant), five_point_preference(Applicant),
not unavailable(Applicant).
hire(Applicant) :- qualified(Applicant), zero_point_preference(Applicant),
not unavailable(Applicant).

```

4.3.5 Concomitant Choice

The concomitant choice pattern is stated as “if a choice is made, some other choices are automatically in effect unless they are prohibited.” This pattern is coded as in Figure 4.6.

The above code makes sure that a concomitant choice appears in all stable models containing the trigger choice, provided the concomitant choice is not prohibited. The trigger choice is always recommended along with the concomitant choice unless the concomitant choice is contraindicated. An even loop over negation is formed through line #1, #3, #4, #5, #7 and #8.

```

#1 recommendation(Trigger_choice) :- preconditions(Trigger_choice),
#2     not contraindication(Trigger_choice),
#3     not skip_concomitant_choice(Trigger_choice).
#4 skip_concomitant_choice(Trigger_choice) :-
#5     not recommendation(Concomitant_choice),
#6     not contraindication(Concomitant_choice).
#7 recommendation(Concomitant_choice) :-
#8     recommendation(Trigger_choice),
#9     not contraindication(Concomitant_choice).

```

Figure 4.6. Knowledge Pattern for Concomitant Choice

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“Diuretics should generally be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist. Few patients with HF will be able to maintain target weight without the use of diuretics.”

The rule above is realized in the physician advisory system as in Figure 4.7. The meaning of the code is that for a patient with heart failure with reduced ejection fraction and ACCF stage C, ACE inhibitors and diuretics should be recommended to him/her. However, if diuretics are contraindicated for the patient, ACE inhibitors should still be recommended to him/her. Simply speaking, prescribing diuretics is the concomitant choice for recommending ACE inhibitors, which is the trigger choice.

```

recommendation(ace_inhibitors, class_1) :- accf_stage(c),
    not skip_concomitant_choice(ace_inhibitors),
    not contraindication(ace_inhibitors), hf_with_reduced_ef.
skip_concomitant_treatment(ace_inhibitors) :-
    hf_with_reduced_ef, not recommendation(diuretics, class_1),
    not contraindication(diuretics).
recommendation(diuretics, class_1) :-
    hf_with_reduced_ef, not contraindication(diuretics),
    recommendation(ace_inhibitors, class_1).

```

Figure 4.7. Example for Concomitant Choice Pattern

Another example for the concomitant choice pattern can be found in the recipe for iced-coffee frapp recipe (OPRAH.COM, 2017):

Ingredients for ice-coffee frappe:

- 1 1/2 cups double-strength coffee
- 1/2 cup low-fat milk
- 2 Tbsp. sugar
- 1 1/2 cups ice
- Whipped cream (optional)

The rule above can be realized by the following code:

```
make(ice-coffee-frappe) :- choose(coffee), choose(milk), choose(sugar),
not skip_concomitant_choice.
skip_concomitant_choice :- not choose(whipped_cream),
not unavailable(whipped_cream).
choose(whipped_cream) :- make(ice-coffee-frappe),
not unavailable(whipped_cream).
```

4.3.6 Indispensable Choice

The indispensable choice pattern is stated as “if a choice is made, some other choices must also be made; if those choices can’t be made, then the first choice is revoked”. This pattern is coded as in Figure 4.8.

The code above makes sure that the trigger choice will always appear with the indispensable choice. If for some reason the indispensable choice cannot be made, then the trigger choice cannot be made either. In other words, choosing trigger choice forces indispensable choice.

An example of this knowledge pattern can be found in (Yancy et al., 2013):

```

#1 recommendation(Trigger_choice) :- preconditions(Trigger_choice),
#2     not contraindication(Trigger_choice)
#3     not absent_indispensable_choice(Trigger_choice).
#4 absent_indispensable_choice(Trigger_choice) :-
#5     not recommendation(Indispensable_choice).
#6 recommendation(Indispensable_choice) :- recommendation(Trigger_choice),
#7     not contraindication(Indispensable_choice).

```

Figure 4.8. Knowledge Pattern for Indispensable Choice

“In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics”.

The rule above is realized in the physician advisory system as in Figure 4.9. The meaning of this code is that for a patient with heart failure with reduced ejection fraction and ACCF stage C, beta blockers should always be recommended to him/her along with diuretics. If diuretics can not be recommended to the patient due to contraindication or any other reason, beta blockers are not supposed to be on the list of recommendations either. Simply speaking, prescribing diuretics is the indispensable choice for recommending beta blockers, which is the trigger choice.

```

recommendation(beta_blockers, class_1) :-
    not skip_concomitant_choice(beta_blockers),
    not absent_indispensable_choice(beta_blockers),
    not contraindication(beta_blockers), accf_stage(c), hf_with_reduced_ef.
absent_indispensable_choice(beta_blockers) :-
    not recommendation(diuretics, class_1), hf_with_reduced_ef,
    accf_stage(c), current_or_recent_history_of_fluid_retention.
recommendation(diuretics, class_1) :-
    recommendation(beta_blockers, class_1),
    not contraindication(diuretics), accf_stage(c), hf_with_reduced_ef,
    current_or_recent_history_of_fluid_retention.

```

Figure 4.9. Example for Indispensable Choice Pattern

Another example for the indispensable choice pattern can be found in the definition of a valid contract (FORBES.COM, 2017):

“All that is necessary for most contracts to be legally valid are the following two elements:”

- All parties are in agreement.
- Some of value has been exchanged, such as cash, services or goods for something else of value.

The rule above can be realized by the following code:

```
contract :- content, not invalidity.  
invalidity :- not agreement_among_all_parties.  
invalidity :- not exchange_of_values.  
agreement_among_all_parties :- contract.  
exchange_of_values :- contract.
```

4.3.7 Incompatible Choice

The incompatibility pattern is stated as “some choices cannot be in effect at the same time”.

This pattern is coded as in Figure 4.10.

The above code makes sure that incompatible choices will not be made together. Note that we did not use a simple constraint to implement this pattern. A constraint would kill all stable models if each of the choices in question can be made. Our implementation, on the other hand, will produce partial answer sets supporting the query, thanks to the goal-driven mechanism of s(ASP) (Marple et al., 2016).

An example of this knowledge pattern can be found in (Yancy et al., 2013):

“Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.”

The rule above is realized in the physician advisory system as in Figure 4.11. The meaning of the code is that for a patient diagnosed with heart failure with reduced ejection fraction

```

taboo_choice(Choice_1) :-
    recommendation(Choice_2),
    ...,
    recommendation(Choice_n).
taboo_choice(Choice_2) :-
    recommendation(Choice_1),
    recommendation(Choice_3),
    ....
    recommendation(Choice_n).
...
taboo_choice(Choice_n) :-
    recommendation(Choice_1),
    recommendation(Choice_2),
    ....
    recommendation(Choice_n-1).

recommendation(Choice_1) :-
    conditions_for_choice_1,
    not contraindication(Choice_1),
    not taboo_choice(Choice_1).
recommendation(Choice_2) :-
    conditions_for_choice_2,
    not contraindication(Choice_2),
    not taboo_choice(Choice_2).
...
recommendation(Choice_n) :-
    conditions_for_choice_n,
    not contraindication(Choice_n),
    not taboo_choice(Choice_n).

```

Figure 4.10. Knowledge Pattern for Incompatible Choice

and ACCF stage C can never be given an ACE inhibitor, ARB and aldosterone antagonist at the same time. However, such a patient can still be given one or two out of the three pharmaceutical treatments.

Another example the incompatible choice pattern can be found in the driving law of the state of California (California Legislative Information, 2017):

“V.C. Sec. 23152(b) - it is a misdemeanor to drive with .08% or more of alcohol in your blood.”

The rule above can be realized by the following code:

```

taboo_choice(alcohol) :- driving.
taboo_choice(driving) :- alcohol.
driving :- preconditions(driving), not taboo_choice(driving).
alcohol :- preconditions(alcohol), not taboo_choice(alcohol).

```



```

taboo_choice(ace_inhibitors) :- hf_with_reduced_ef,
    recommendation(arbs, class_1),
    recommendation(aldosterone_antagonist, class_1).
taboo_choice(arbs) :- hf_with_reduced_ef,
    recommendation(ace_inhibitors, class_1),
    recommendation(aldosterone_antagonist, class_1).
taboo_choice(aldosterone_antagonist) :- hf_with_reduced_ef,
    recommendation(arbs, class_1), recommendation(ace_inhibitors, class_1).
recommendation(ace_inhibitors, class_1) :- accf_stage(c),
    hf_with_reduced_ef, not skip_concomitant_choice(ace_inhibitors),
    not taboo_choice(ace_inhibitors), not contraindication(ace_inhibitors).
recommendation(arbs, class_1) :- contraindication(ace_inhibitors),
    not contraindication(arbs), not taboo_choice(arbs),
    accf_stage(c), hf_with_reduced_ef.
recommendation(aldosterone_antagonist, class_1) :-
    conditions_for_aldosterone_antagonist_class_1,
    not skip_concomitant_choice(aldosterone_antagonist),
    not contraindication(aldosterone_antagonist),
    not taboo_choice(aldosterone_antagonist).

```

Figure 4.11. Example for Incompatible Choice Pattern

CHAPTER 5

PHYSICIAN ADVISORY SYSTEM VALIDATION

5.1 Overview

This chapter covers the validation of the physician advisory system. The system was put to test with ten representative patients with heart failure. The data source and structure are described. The system input and experimental result for each case are presented in detail. The summary of the validation is also provided. The case study was carried out in collaboration with The University of Texas Southwestern Medical Center.

5.2 Case studies

To validate the efficacy of the physician advisory system for heart failure management, we ran the system using data of 10 representative patients with heart failure. The patients' profiles were provided by the University of Texas Southwestern (UTSW) Medical Center. The methodology is to let the physician advisory system give its recommendations independently for those patients and compare the system's recommendations with the ones from cardiologists. The input data for the system were extracted from the patient's profile by the developers of the system. Note that although the system developers had limited knowledge of clinical medicine, they were familiar with the 2013 ACCF/AHA Guideline for the Management of Heart Failure (2013 Guideline) and the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure (2016 Update), which provided the rule set for the physician advisory system. With the help from the cardiologists of UTSW, questions and doubts with respect to medical knowledge were addressed. Thus, the system developers were able to extract useful information from a patient's profile. The relevant information was then coded as an answer set program that the physician advisory system could execute.

The representative patients consisted of 4 females and 6 males. The youngest patient was 32 and the eldest 73. Among them were 6 African Americans and 4 Caucasians.

All HF-related information in the patient's profile was coded using one of five categories: diagnosis, history, evidence, contraindication and measurement. We were aware that comorbidities such as myocardial infarction (MI) and diabetes mellitus (DM) play significant roles in the management of heart failure. However, they have dedicated clinical practice guidelines which have not been included in the physician advisory system. In this dissertation, we limit the validation of the physician advisory system to the context of the 2013 Guideline and 2016 Update.

Next we present the experimental results for the ten cases. For each case, the HF-related information and the corresponding ASP code are presented. The system-generated recommendations are listed in a table. A cardiologist-affirmed recommendation is marked with "Y" and otherwise "N".

The original raw medical records of the ten representative can be found in the Appendix A for those who are interested.

5.2.1 Case One - Profile

The patient has a chief complaint as heart failure with reduced ejection fraction. She is a 60 year old African American female. She is in ACCF/AHA stage D and NYHA Class IIIb. She has been diagnosed with dilated nonischemic cardiomyopathy and diabetes mellitus type 2. Her left ventricular ejection fraction is 16%. She is not a candidate for CRT-D. ACE inhibitor (captopril) causes cough. Carvedilol dose higher than 6.25 mg bid causes overt fatigue and hypo-tension with systolic B/P in the 80's. She would have headache with isodil. She has a narrow QRS of 110 ms. She has chest pain with increased fluid. Her blood pressure is 108/73 mmHg. Her N-terminal pro-BNP is 5051 pg/mL. The potassium level in serum is 3.0 mmol/L. The creatinine level is 1.49 mg/dL. The estimated glomerular filtration rate is 44 mL/min/1.73 m^2 . She has hemodynamic profile B.

5.2.2 Case One - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_3).
evidence(accf_stage_d).
```

```
%demographics of the patient
measurement(age,60).
evidence(african_american).
evidence(female).
```

```
%measurements from lab
measurement(potassium, 3).
measurement(creatinine, 1.5).
measurement(glomerular_filtration_rate, 44).
measurement(heart_rate, 97).
measurement(nt_pro_bnp, 5051).
measurement(lvef, 16).
measurement(non_lbbb, 110).
```

```
%history of the patient
diagnosis(hf_with_reduced_ef).
diagnosis(dilated_cardiomyopathy).
diagnosis(diabetes).
```

```
evidence(angina).
history(ace_inhibitors).
history(beta_blockers).

%contraindications
contraindication(crt).
contraindication(ace_inhibitors).
```

5.2.3 Case One - Experimental Result

Table 5.1 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.2.

Except for beta blockers, angiotensin II receptor blockers and aldosterone antagonists, all other recommendations made by the physician advisory systems were positively confirmed by cardiologists. Our system made a recommendation for beta blockers according to the rule below:

“Use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (Level of Evidence: A)”

Since there is no evidence showing the patient’s intolerance of beta blockers, the system recommended it. After some discussions with our cardiologist collaborators, we found that one important rule regarding the trials of beta blockers was not included by the physician advisory system. In reality, most of the beta blockers trials take patients with hemodynamically stable HF. Clinically, cardiologists would not initiate beta blockers for patient who is “wet”. Being “wet” means having some sort of congestion such as orthopnea, pulmonary rales, edema, etc. The guideline does very briefly mention that beta blockers should be

Table 5.1. Physician Advisory System’s Recommendations for Case One

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Diabetes control (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | N |
| Stage C | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | N |
| Aldosterone antagonists (Class I) | N |
| Sodium restriction (Class IIa) | Y |
| Angiotensin II receptor blockers (Class I) | N |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Combination of hydralazine and isosorbide dinitrate (Class I) | Y |
| Stage D | |
| fluid restriction (Class IIa) | Y |
| long term continuous intravenous inotropic support (Class IIb) | Y |

prescribed to all patients with *stable* HFReF. However, the system developers failed to appreciate the significance of word "stable" due to their insensitivity to medical terms. This example shows that it is an intricate job to systemically code human knowledge in a given area. On the other hand, it is very easy to incorporate the human expert’s feedback into the system thanks to the expressiveness of ASP.

Angiotensin II receptor blockers (ARBs) and aldosterone antagonists were recommended by the physician advisory system but not the cardiologists. Both of the two drugs had been stopped due to renal failure of this patient. However, those facts were not on the patient’s profile and the system could not reason with the consideration of them. Omega 3 fatty acids are of class IIa recommendations and are not part of routine heart failure care.

5.2.4 Case Two - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. He is a 32 year old white male. He is in ACCF/AHA stage C and NYHA class I. He has a history of dilated ischemic and cocaine induced cardiomyopathy. He also has nonischemic dilated cardiomyopathy. The additional co-morbidities include hyperlipidemia and chest pain. Lisinopril or Atorvastatin cause rash. His blood pressure is 107/56 mmHg. He has hemodynamic Profile A. His N-terminal pro-BNP is 701 pg/mL. The potassium level in serum is 4 mmol/L and creatinine 1.41 mg/dL. The estimated glomerular filtration rate is 55 mL/min/1.73 m^2 .

5.2.5 Case Two - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(accf_stage_c).
evidence(nyha_class_1).

%demographics of the patient
measurement(age,32).
evidence(white).
evidence(male).

%measurements from lab
evidence(elevated_plasma_natriuretic_peptide_level).
measurement(potassium, 4).
measurement(creatinine, 1.4).
```

```

measurement(glomerular_filtration_rate, 55).
measurement(heart_rate, 71).

%history of the patient
diagnosis(dilated_cardiomyopathy).
diagnosis(ischemic_heart_disease).
evidence(ischemic_etiology_of_hf).
diagnosis(coronary_artery_disease).
diagnosis(lipid_disorders).
evidence(angina).
history(mi).
cardioembolic_source.
history(ace_inhibitors).
history(beta_blockers).
diagnosis(hf_with_reduced_ef).

```

5.2.6 Case Two - Experimental Result

Table 5.2 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.5.

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. We also studied the list of recommendations made by the physicians who had been taking care of this patient and found some discrepancies between their prescriptions and the system's. Aspirin showed up in the physician's recommendation list but was not recommended by the physician advisory system. The cardiologists prescribed it according to the rules in the guideline of myocardial infarction management.

Table 5.2. Physician Advisory System’s Recommendations for Case Two

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes avoidance (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ACE inhibitors (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| ACE inhibitors (Class I) | Y |
| Beta blockers (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |

Since our system contained only the rules from the guideline of heart failure management, it could not recommend Aspirin. Another recommendation ignored by the system is prasugrel. The cardiologists agreed that there was no reason to prescribe prasugrel to this patient. Thus prasugrel is not a reasonable choice in this case. Candesartan (ARB) was recommended by the physician as an alternative to ACE inhibitors. However, there is no sign that ACE inhibitors are contraindicated. According to the guideline (Yancy et al., 2013), ACE inhibitors should serve as the first choice for patient who has heart failure with reduced ejection fraction; ARBs can be considered only when ACE inhibitors are contraindicated. So the recommendation of candesartan (ARB) is not guideline-compliant. Actually, the knowledge about ACE inhibitors and ARB is coded through a knowledge pattern called “preference” which is illustrated in section 4.3.4. Digoxin (Class IIa) was recommended by the physician advisory system but not by the cardiologists. The cardiologists claimed that recommendations of class IIa are more of personal preference and thus not mandatory.

5.2.7 Case Three - Profile

This patient has a chief complaint as nonischemic cardiomyopathy. She is a 58 year old white female. She is in ACCF/AHA stage and NYHA class I. She also has a history of non-ischemic dilated cardiomyopathy. The additional co-morbidities include hyperlipidemia, hyperglycemia, pleural effusion, anemia, depression, elevated liver enzymes, rheumatoid arthritis, alcohol abuse and tobacco use. Left heart cardiac catheterization revealed no coronary artery disease. Her ejection fraction is of 15% to 20 %. She has been diagnosed with hypertension. She has a history of tobacco use. She has Hemodynamic Profile A, warm and dry.

5.2.8 Case Three - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(accf_stage_c).
evidence(nyha_class_1).

%demographics of the patient
evidence(female).
measurements(age,58).
evidence(caucasian).

%measurements from lab
diagnosis(hf_with_reduced_ef).
measurement(lvef, 20).
measurement(heart_rate, 85).
```

```

%history of the patient
diagnosis(dilated_cardiomyopathy).
diagnosis(lipid_disorders).
-history(coronary_artery_disease).
history(hypertension).
history(ace_inhibitors).
history(beta_blockers).

```

5.2.9 Case Three - Experimental Result

Table 5.3 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.8.

Table 5.3. Physician Advisory System's Recommendations for Case Three

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes avoidance (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ACE inhibitors (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| ACE inhibitors (Class I) | Y |
| Beta blockers (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | N |

Except for digoxin, all treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Since digoxin is an ACCF/AHA Class IIa recommendation, it depends on physician's discretion to prescribe this drug. In this case, cardiologists would not initiate digoxin for her since she is in NYHA class I, which means she is quite stable.

The cardiologists did not give any recommendation for treating hyperlipidemia in this patient. On the other hand, the system recommended lipid disorders control with ACCF/AHA Class I based on the following rule:

“Class I - Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF. (Level of Evidence: A)”

The cardiologists confirmed that the prescription of lipid disorders control is a reasonable supplement to the recommendations for the patient.

5.2.10 Case Four - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. He is a 44 year old African American male. He is at ACCF/AHA stage D and NYHA class IIIb. He has a history of nonischemic cardiomyopathy. He has been diagnosed with mild coronary artery disease, dyslipidemia, hypertension, chronic renal failure, obstructive sleep apnea, morbid obesity. His left ventricular ejection fraction is of 15-20%. He would have headache with bidil. His N-terminal pro-BNP is 598 pg/mL. The potassium level in serum is 3.5 mmol/L. The creatinine level is 2.07 mg/dL. The estimated glomerular filtration rate is 42 mL/min/1.73 m^2 . He has Hemodynamic Profile A. He does not have episodes of atrial tachycardia/atrial fibrillation.

5.2.11 Case Four - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(accf_stage_d).
evidence(nyha_class_3).

%demographics of the patient
evidence(male).
measurement(age,44).
evidence(african_american).

%measurements from lab
measurement(lvef, 20).
measurement(potassium, 3.5).
measurement(creatinine, 2).
evidence(elevated_plasma_natriuretic_peptide_level).
measurement(glomerular_filtration_rate, 42).
measurement(heart_rate, 75).

%history of the patient
diagnosis(hf_with_reduced_ef).
diagnosis(dilated_cardiomyopathy).
diagnosis(coronary_artery_disease).
diagnosis(lipid_disorders).
diagnosis(hypertension).
evidence(sleep_apnea).
diagnosis(obesity).
-diagnosis(atrial_fibrillation).
```

```
history(ace_inhibitors).
```

```
history(beta_blockers).
```

```
%medication intolerance
```

```
contraindication(hydralazine_and_isosorbide_dinitrate).
```

5.2.12 Case Four - Experimental Result

Table 5.4 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.11.

Except for digoxin, all treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. The cardiologists did not recommend digoxin to this patient due to his chronic renal failure. We were not able to identify relevant rules regarding renal failure and digoxin in the guideline of heart failure management. Thus the physician advisory system did not contain the logic that digoxin should not be prescribed to a patient if he/she has renal failure. This piece of medical knowledge must be general so the dedicated guideline for heart failure management does not include it. However, given relevant rules of general medical knowledge, the physician advisory system would be able to incorporate them in the form of ASP code.

Aldosterone antagonists and continuous airway pressure are on the list of the recommendations by the physician advisory system. The cardiologists agreed that they are both reasonable recommendations which should have been prescribed by the physicians.

5.2.13 Case Five - Profile

This patient has a chief complaint as ischemic cardiomyopathy. He is a 73 year old white male. He is in ACCF/AHA stage D and NYHA class IIIb-IV. He has a history of myocardial

Table 5.4. Physician Advisory System’s Recommendations for Case Four

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes avoidance (Class I) | Y |
| Obesity control (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Continuous positive airway pressure (Class IIa) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Aldosterone antagonist (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | N |
| Omega 3 fatty acids (Class IIa) | Y |
| Stage D | |
| fluid restriction (Class IIa) | Y |
| long term continuous intravenous inotropic support (Class IIb) | Y |

infarction and stroke. He has been diagnosed with coronary artery disease, dyslipidemia, atrial fibrillation, angina, hypertension, diabetes mellitus type 2 and sleep apnea. His left ventricular ejection fraction is 35%. His blood pressure is 160/92 mmHg and pulse 72 beats per minute. He has Hemodynamic Profile B, warm and wet.

5.2.14 Case Five - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_3).
```

```
evidence(nyha_class_4).
evidence(accf_stage_d).

%demographics of the patient
measurement(age,73).
evidence(caucasian).
evidence(male).

%measurements
measurement(lvef, 35).
measurement(heart_rate, 72).

%history of the patient
diagnosis(ischemic_heart_disease).
evidence(ischemic_etiology_of_hf).
diagnosis(lipid_disorders).
diagnosis(atrial_fibrillation).
evidence(angina).
diagnosis(hypertension).
diagnosis(diabetes).
history(stroke).
evidence(sleep_apnea).
measurement(mi,8030).
history(ace_inhibitors).
history(beta_blockers).
```


%contraindications

contraindication(continuous_positive_airway_pressure).

5.2.15 Case Five - Experimental Result

Table 5.5 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.14.

Table 5.5. Physician Advisory System's Recommendations for Case Five

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes control (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Blood pressure control (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Statins (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Continuous positive airway pressure (Class IIa) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Aldosterone antagonist (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Anticoagulation (Class I) | Y |
| Stage D | |
| fluid restriction (Class IIa) | Y |
| long term continuous intravenous inotropic support (Class IIb) | Y |

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Additionally, the system did cover Diuretics, Angiotensin Receptor-Nepriylsin Inhibitor (ARNI) and continuous positive airway pressure (CPAP) which had been missed by the physicians. Giving diuretics to volume overload is extremely straightforward decision nobody would miss it could be just bad documentation. That being said, either bad documentation or oversight can result in dire consequences in heart failure management. It is obvious that the kind of problem is compounded by transferring of heart failure patient from one physician to another.

Sleep apnea is normally not managed by cardiologists so CPAP is not on the list of cardiologist's recommendations.

5.2.16 Case Six - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. She is a 66 year old African American female. She is in ACCF/AHA stage D and NYHA class IV. She has a history of ischemic cardiomyopathy, myocardial infarction and hyperlipidemia. She has been diagnosed with coronary artery disease, diabetes and hypertension. Her left ventricular ejection fraction is of 10%. Her blood pressure is 107/65 mmHg and pulse 87 beats per minute. Her N-terminal pro-BNP is 7998 pg/mL. Her potassium level in serum is 2.9 mmol/L and creatinine 1.54 mg/dL. Her estimated glomerular filtration rate is 40 mL/min/1.73 m^2 .

5.2.17 Case Six - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_4).
evidence(nyha_class_3).
```

```
evidence(accf_stage_d).
```

```
%demographics of the patient
```

```
measurement(age,66).
```

```
evidence(african_american).
```

```
evidence(female).
```

```
%measurements from lab
```

```
measurement(lvef, 10).
```

```
evidence(elevated_plasma_natriuretic_peptide_level).
```

```
measurement(potassium, 2.9).
```

```
measurement(creatinine, 1.5).
```

```
measurement(glomerular_filtration_rate, 40).
```

```
measurement(heart_rate, 87).
```

```
%history of the patient
```

```
diagnosis(hf_with_reduced_ef).
```

```
diagnosis(ischemic_heart_disease).
```

```
evidence(ischemic_etiology_of_hf).
```

```
diagnosis(diabetes).
```

```
diagnosis(hypertension).
```

```
diagnosis(lipid_disorders).
```

```
measurement(mi,7300).
```

```
history(ace_inhibitors).
```

```
history(beta_blockers).
```

5.2.18 Case Six - Experimental Result

Table 5.6 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.17.

Table 5.6. Physician Advisory System's Recommendations for Case Six

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes control (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Blood pressure control (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Statins (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Aldosterone antagonist (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Combination of hydralazine and isosorbide dinitrate (Class I) | Y |
| Stage D | |
| fluid restriction (Class IIa) | Y |
| long term continuous intravenous inotropic support (Class IIb) | Y |

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Additionally, ARNI, aldosterone antagonists, sodium restriction are good catches by the system.

The condition for the recommendation of ARNI is specified by the following rule:

“Class I - In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.”

Note that ARNI is newly-introduced drug in the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure (Yancy et al., 2016). By using the anti-recommendation knowledge pattern described in 4.3.3 and negation as failure, the rule above is elegantly coded as follows:

```
recommendation(arni, class_1):-  
    evidence(accf_stage_c),  
    nyha_class_2_to_3,  
    not contraindication(ace_inhibitors),  
    not rejection(arni).
```

```
recommendation(arni, class_1):-  
    evidence(accf_stage_c),  
    nyha_class_2_to_3,  
    not contraindication(arbs),  
    not rejection(arni).
```

5.2.19 Case Seven - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. She is a 41 year old African American female. She is in ACCF/AHA stage C and NYHA class III-IV. She has very aggressive coronary artery disease and ischemic cardiomyopathy. She has a history of prior myocardial infraction with her first MI at the age of 27. She also has hypertension and diabetes mellitus type 1. Her left ventricular ejection fraction is 39%. He

pulse is 85 beats per minute. Her N-terminal pro-BNP is 620 pg/mL. Her potassium level in serum is 4.0 mmol/L and creatinine 1.03 mg/dL. Her estimated glomerular filtration rate is greater than 60 mL/min/1.73 m². She has Hemodynamic Profile A, warm and dry. She does not have episodes of atrial tachycardia/atrial fibrillation.

5.2.20 Case Seven - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_3).
evidence(nyha_class_4).
evidence(accf_stage_c).

%demographics of the patient
measurement(age,41).
evidence(african_american).
evidence(female).

%measurements from lab
measurement(lvef, 39).
measurement(heart_rate, 85).
evidence(elevated_plasma_natriuretic_peptide_level).
measurement(potassium, 4).
measurement(creatinine, 1).
safe_condition_for_aldosterone_antagonists_GFR.

%history of the patient
```

```
diagnosis(lipid_disorders).
diagnosis(diabetes).
diagnosis(hypertension).
history(mi).
evidence(ischemic_etiology_of_hf).
diagnosis(coronary_artery_disease).
diagnosis(hf_with_reduced_ef).
-history(atrial_fibrillation).
history(ace_inhibitors).
history(beta_blockers).
```

5.2.21 Case Seven - Experimental Result

Table 5.7 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.20.

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. One thing worth mentioning is that the system recommended the combination of hydralazine and isosorbide dinitrate (BiDil) based on the following rule:

“Class I - The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated.”

An ambiguity that arises with the introduction of ARNI in the 2016 Update on the heart failure management guideline (Yancy et al., 2016) is that it is not clear if BiDil should be prescribed to a patient when ARNI replaces ACE inhibitors. After consulting with the cardiologists, they decided it is a reasonable choice to recommend BiDil in the case where ARNI replaces ACE inhibitors.

Table 5.7. Physician Advisory System’s Recommendations for Case Seven

| Recommendation | Feedback |
|---|-----------------|
| Stage A | |
| Lipid disorders control (Class I) | Y |
| Diabetes control (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Blood pressure control (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Statins (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Combination of hydralazine and isosorbide dinitrate (Class I) | Y |

Note that a similar issue happens when taking ARBs, which is a substitute for ACE inhibitors, into consideration with the rule above. We resolved this issue by communicating with the cardiologists. The conclusion is that BiDil should be recommended when ARB replaces ACE inhibitors.

The code for recommendation BiDil is as follows:

```
recommendation(hydralazine_and_isosorbide_dinitrate, class_1):-
    not rejection(hydralazine_and_isosorbide_dinitrate),
    evidence(accf_stage_c),
    nyha_class_3_to_4,
    diagnosis(hf_with_reduced_ef),
```



```
evidence(african_american),
recommendation(ace_inhibitors, class_1),
recommendation(beta_blockers, class_1).
```

```
recommendation(hydralazine_and_isosorbide_dinitrate, class_1):-
  not_rejection(hydralazine_and_isosorbide_dinitrate),
  evidence(accf_stage_c),
  nyha_class_3_to_4,
  diagnosis(hf_with_reduced_ef),
  evidence(african_american),
  recommendation(arni, class_1),
  recommendation(beta_blockers, class_1).
```

```
recommendation(hydralazine_and_isosorbide_dinitrate, class_1):-
  not_rejection(hydralazine_and_isosorbide_dinitrate),
  evidence(accf_stage_c),
  nyha_class_3_to_4,
  diagnosis(hf_with_reduced_ef),
  evidence(african_american),
  recommendation(arbs, class_1),
  recommendation(beta_blockers, class_1).
```

5.2.22 Case Eight - Profile

This patient has chief complaint as heart failure with reduced fraction. He is a 70 year old white male. He is in ACCF/AHA stage C and NYHA class II. He has a history of myocardial

infarction, dyspnea, angina and atrial fibrillation. He has been diagnosed with dilated ischemic cardiomyopathy, coronary artery disease, diabetes mellitus type 2, hypertension and hyperlipidemia. He has positive test result for ischemia by symptoms with paced rhythm. His left ventricular ejection fraction is of 37%. His pulse is 77 beats per minute and blood pressure 110/63 mmHg. He does not have apnea. His creatinine level in serum is 1.5 mg/dL and potassium level 5.3 mmol/L. He has Hemodynamic Profile A, warm and dry.

5.2.23 Case Eight - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_2).
evidence(accf_stage_c).

%demographics of the patient
measurement(age,70).
evidence(caucasian).
evidence(male).

%measurements
measurement(lvef, 37).
measurement(sinus_rhythm).
measurement(heart_rate, 77).
measurement(creatinine, 1.5).
measurement(potassium, 5.3).

%history of the patient
```

diagnosis(hf_with_reduced_ef).
measurement(mi,9855).
evidence(angina).
diagnosis(dilated_cardiomyopathy).
diagnosis(ischemic_heart_disease).
evidence(ischemic_etiology_of_hf).
diagnosis(myocardial_ischemia).
diagnosis(diabetes).
history(hypertension).
diagnosis(atrial_fibrillation).
history(ace_inhibitors).
history(beta_blockers).

5.2.24 Case Eight - Experimental Result

Table 5.8 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.23.

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Note that aldosterone antagonist is not recommended by the system but by the physicians. In fact, aldosterone antagonists were considered not a safe choice by the physician advisory system due to the following rule:

“Class III - Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate $< 30 \text{ mL/min/1.73 } m^2$), and/or potassium greater than 5.0 mEq/L.”

Table 5.8. Physician Advisory System’s Recommendations for Case Eight

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Diabetes control (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Statins (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Anticoagulation (Class I) | Y |

The patient has a potassium level of 5.3 mmol/L which is greater than the threshold for safety (for potassium, one millimole is equivalent to one milliequivalent). Clearly, aldosterone antagonists should not be prescribe to him due to the risk of hyperkalemia.

5.2.25 Case Nine - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. He is a 50 year old African American male. He is in ACCF/AHA stage D and NYHA class IIIb. He has a history of nonischemic dilated cardiomyopathy, hypertension, dyslipidemia and cardiovascular hospitalization. He does not have apnea. His pulse is 85 beats per minute. He has Hemodynamic Profile B, warm and wet. He is not a candidate for an aldosterone antagonist due to hyperkalemia and end stage renal disease.

5.2.26 Case Nine - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_3).
evidence(accf_stage_d).
```

```
%demographics of the patient
measurement(age,50).
evidence(african_american).
evidence(male).
```

```
%measurements from lab
measurement(lvef, 31).
measurement(heart_rate, 85).
```

```
%history of the patient
diagnosis(hf_with_reduced_ef).
diagnosis(dilated_cardiomyopathy).
diagnosis(hypertension).
diagnosis(lipid_disorders).
-diagnosis(myocardial_ischemia).
-diagnosis(ischemic_heart_disease).
-evidence(ischemic_etiology_of_hf).
evidence(angina).
-evidence(sleep_apnea).
```

```
history(ace_inhibitors).
```

```
history(beta_blockers).
```

```
%contraindications
```

```
contraindication(aldosterone_antagonist).
```

5.2.27 Case Nine - Experimental Result

Table 5.9 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.26.

Table 5.9. Physician Advisory System's Recommendations for Case Nine

| Recommendation | Feedback |
|--|-----------------|
| Stage A | |
| Blood pressure control (Class I) | Y |
| Diabetes avoidance (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Stage C | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Combination of hydralazine and isosorbide dinitrate (Class I) | Y |
| Stage D | |
| fluid restriction (Class IIa) | Y |
| long term continuous intravenous inotropic support (Class IIb) | Y |

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Diuretics were missed by the physicians but covered by the system. The rule involved in the recommendation process is:

“Diuretics should be generally combined with an ACE inhibitor, beta blocker, and aldosterone antagonist. Few patients with HF will be able to maintain target weight without the use of diuretics.”

Since the patient was given beta blockers, diuretics were recommended as the “concomitant choice” for beta blockers. In section 4.3.5, the concomitant choice knowledge pattern is discussed in detail.

It is worth mentioning that our cardiologist collaborators were not in agreement with our interpretation of the above rule. Although they concurred that diuretics should be prescribed to this patient, it was not because of this rule. They claimed that the above rule should not be interpreted as a directive. Clinically, there are no additive benefit of diuretics when someone is on an ACE inhibitor. Diuretics are commonly used in those with heart failure to control symptoms of fluid retention/congestion. Despite the objections of cardiologists, we kept this rule in the physician advisory system since we wanted the system to reflect the guideline as faithfully as possible.

5.2.28 Case Ten - Profile

This patient has a chief complaint as heart failure with reduced ejection fraction. He is a 46 year old African American male. He is in ACCF/AHA stage C and NYHA class III. He has been diagnosed with hypertension, dilated nonischemic cardiomyopathy, atrial fibrillation, obstructive and sleep apnea. Bidil causes severe headaches for him. Altace causes persistent cough in the setting of a PCWP of 3 mmHg per RHC. His left ventricular ejection fraction is of 34%. His pulse is 98 beats per minute. His N-terminal pro-BNP is 184 pg/mL. The potassium level in serum is 5.6 mmol/L and creatinine 0.54 mg/dL. His estimated glomerular filtration rate is greater than 60 mL/min/1.73 m².

5.2.29 Case Ten - Input for the Physician Advisory System

The above medical information can be coded as follows:

```
%doctor's assessments
evidence(nyha_class_3).
evidence(accf_stage_c).
```

```
%demographics of the patient
measurement(age,46).
evidence(african_american).
evidence(male).
```

```
%measurements from lab
measurement(lvef, 34).
measurement(heart_rate, 77).
measurement(potassium, 5.6).
measurement(creatinine, 5).
safe_condition_for_aldosterone_antagonists_GFR.
```

```
%history of the patient
diagnosis(hf_with_reduced_ef).
diagnosis(hypertension).
diagnosis(dilated_cardiomyopathy).
diagnosis(atrial_fibrillation).
evidence(sleep_apnea).
history(ace_inhibitors).
```



```
history(beta_blockers).
```

```
%contraindications
```

```
contraindication(hydralazine_and_isosorbide_dinitrate).
```

5.2.30 Case Ten - Experimental Result

Table 5.10 displays all the recommendations given by the physician advisory system for the patient whose information is available in Section 5.2.29.

Table 5.10. Physician Advisory System's Recommendations for Case Ten

| Recommendation | Feedback |
|---|-----------------|
| Stage A | |
| Blood pressure control (Class I) | Y |
| Diabetes avoidance (Class I) | Y |
| Obesity avoidance (Class I) | Y |
| Tobacco avoidance (Class I) | Y |
| Cardiotoxic agents avoidance (Class I) | Y |
| Stage B | |
| Diuretics (Class I) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Stage C | |
| Diuretics (Class) | Y |
| Beta blockers (Class I) | Y |
| ARNI (Class I) | Y |
| Sodium restriction (Class IIa) | Y |
| Continuous positive airway pressure (Class IIa) | Y |
| Digoxin (Class IIa) | Y |
| Omega 3 fatty acids (Class IIa) | Y |
| Anticoagulation (Class I) | Y |

All treatment recommendations made by the physician advisory system were positively confirmed by the cardiologists. Diuretics and ARNI were covered by the system but were missed by the physicians.

Like case #8 in section 5.2.24, aldosterone antagonists were on the list of physician's recommendations despite the fact that the patient's potassium level is 5.6 mEq/L which is greater than the safety value that is 5.0 mEq/L.

Note that one of the cardiologist collaborators claimed that he would not initiate ARNI unless the patient is stable on an ACE inhibitor or ARB at maximum target dose. In this case, the patient was already taking ramipril, which is an ACE inhibitor, with the target dose. Having ARNI on the recommendation list happened to be correct considering that the physician advisory system did not incorporate dosage management of pharmaceutical treatments. This example shows that dosage management is an important aspect in automating disease management and should be the next functionality to be added to the system.

5.3 Summary of the Experimental Results

The summary of the experimental results for the ten cases is shown in Table 5.11. For each case, both the total number of system-generated recommendations and the number of cardiologist-questioned recommendations (in parenthesis) are shown. Out of 155 treatment recommendations made by the physician advisory system, 150 were affirmed by the cardiologists from the University of Texas Southwestern Medical Center. And they also confirmed that there was no treatment missed by the system for all ten cases.

Throughout the ten cases, the causes of the discordant recommendations are:

1. Failure to understand the guideline
2. Insufficient system input due to poor medical documentation
3. "Hidden" personal rules of cardiologists

Table 5.11. The number of total/questioned treatment recommendations given by physician advisory system

| | Stage A | Stage B | Stage C | Stage D |
|---------|---------|---------|---------|---------|
| Case 1 | 4 | 2(1) | 8(2) | 2 |
| Case 2 | 5 | 3 | 5 | N/A |
| Case 3 | 5 | 3 | 5(1) | N/A |
| Case 4 | 5 | 3 | 8(1) | 2 |
| Case 5 | 6 | 4 | 8 | 2 |
| Case 6 | 6 | 4 | 7 | 2 |
| Case 7 | 6 | 4 | 6 | N/A |
| Case 8 | 4 | 4 | 7 | N/A |
| Case 9 | 6 | 3 | 6 | 2 |
| Case 10 | 5 | 3 | 8 | N/A |

The first and third issues can be addressed with more investigations and feedback. The second one, however, concerns the data infrastructure and documentation practice in medical community, which are out of reach of this dissertation. That being said, thanks to the use of ASP formalism, the physician advisory system still gives the most reasonable guideline-compliant recommendations with whatever information is available.

CHAPTER 6

IMPLEMENTATION OF ABDUCTIVE REASONING ¹

6.1 Overview

This chapter describes the implementation of abductive reasoning using answer set programming. The introduction of abduction is given both formally and informally. The *s*(ASP) Predicate Answer Set Programming System, on which we implement abductive reasoning in the domain of heart failure management, is also described. The formal definition of abductive reasoning is given. The application of abductive reasoning on heart failure management is illustrated through an example.

6.2 Introduction to Abductive Reasoning

The term *abduction* refers to a form of reasoning that is concerned with the generation and evaluation of explanatory hypotheses. Abductive reasoning leads from facts to a proposed explanation of those facts. Abductive reasoning takes the following form (Harman, 1965):

The fact *B* is observed.

But if *A* were true, *B* would be a matter of course.

Thus, there is reason to suspect that *A* is true.

In the above form, *B* can be either a particular event or an empirical generalization. *A* serves an explanatory hypothesis and *B* follows from *A* combined with relevant background knowledge. Note that *A* is not necessarily true, but plausible and worthy of further validation.

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An example of abductive reasoning is: “When it rains, the grass gets wet. The grass is wet, it must have rained.” Note that unlike deduction and induction, abduction can produce unsound results. However, it is still useful as a heuristic.

6.3 The $s(\text{ASP})$ Predicate Answer Set Programming System

$s(\text{ASP})$ is a goal-driven predicate answer set programming system (Marple et al., 2016, 2017). It computes stable models of normal logic program in the presence of predicates. $s(\text{ASP})$ completely removes the need to ground input programs. Therefore, $s(\text{ASP})$ programs can utilize lists, terms and complex data structures, all of which are unavailable in traditional ASP solvers. $s(\text{ASP})$ makes use of several techniques:

- **Extended Herbrand Universe:** The Herbrand universe (Chang and Lee, 1997) is extended to be a superset of the standard countably infinite Herbrand universe.
- **Coinduction:** $s(\text{ASP})$ relies on positive and negative coinduction (Gupta et al., 2007) to detect even and odd cycles through negation.
- **Dual Rules:** Dual rules are rules for the negation of a predicate which will succeed whenever a call to the original predicate would fail under negation as failure. They are used to ensure that appropriate variables are bound to appropriate values.
- **Constructive Negation:** $s(\text{ASP})$ uses unification algorithm to allow for negatively constrained variables. For each unbound variable $s(\text{ASP})$ keeps track of values the variable cannot be bound to.

$s(\text{ASP})$ has several advantages compared to SAT-based ASP solvers:

1. $s(\text{ASP})$ is able to execute normal logic program with general predicates (Min, 2009) that do not have finite grounding. Thus the issue of explosive size of ground terms in traditional ASP solver is avoided.

2. ASP programs can be elegantly extended to constraints (Jaffar and Lassez, 1987) and probabilities (De Raedt et al., 2007).
3. Parallel execution strategies can be used on ASP program (Gupta et al., 2001).
4. Abductive reasoning can be realized with great ease (?).
5. s(ASP) produces partial answer set which is relevant to the query. Most of the time, users are interested in only a part of the whole answer set. Traditional ASP approaches make it hard to isolate solutions from the entire model.
6. s(ASP) allows reasoning with real numbers while SAT-based solvers don't.

Consider an example from (Baral, 2003). Suppose we have rules deciding the interview eligibility of students. We will interview her if she has high GPA. However, if she does not, she is still worth an interview if she has fair GPA and some special talents. We won't interview her if she has neither high GPA nor special talents. If we still can't decide her interview eligibility after applying the rules above, we will interview her. Using s(ASP), these strategies can be coded into the following logic program:

```

eligible(X):- highGPA(X).
eligible(X):- special(X), fairGPA(X).
-eligible(X):- -special(X), -highGPA(X).
interview(X):- not eligible(X), not -eligible(X).

```

Given some facts about John:

```

fairGPA(john).
-highGPA(john).

```

We pose a query to s(ASP):

?-interview(john).

s(ASP) return the following partial answer set:

{interview(john), not -eligible(john), not -special(john),
not eligible(john), not highGPA(john), not special(john)}

6.4 Abductive Reasoning in Answer Set Programming

Given an answer set program P and a query goal G , a goal-directed ASP system for executing answer set programs will systematically enumerate all answer sets that contain the propositions/predicates in Q . This strategy adopts Coinductive SLD resolution (Co-SLD resolution), which systematically computes elements of the greatest fixed point (GFP) of a program via backtracking (Marple et al., 2012).

The Galliwasp system (Marple and Gupta, 2012) was the first efficient implementation of the goal-directed method. It is essentially an implementation of A-Prolog (Baral, 2003) that uses grounded normal logic programs as input. Galliwasp uses coinduction (Gupta et al., 2007) to find partial answer sets containing a given query. The s(ASP) predicate ASP system operates in a manner similar to Galliwasp in that rules are classified according to negation and executed in a goal-directed manner. However, s(ASP) completely removes the need to ground input programs.

Formally, abduction is a form of reasoning where, given the premise $P \Rightarrow Q$, and the observation Q , one surmises (*abduces*) that P holds (Kakas et al., 1992). More generally, given a theory T , an observation O , and a set of abducibles A , then E is an explanation of O (where $E \subset A$) if:

1. $T \cup E \models O$
2. $T \cup E$ is consistent

Generally, A consists of a set of propositions such that if $p \in A$, then there is no rule in T with p as its head. We assume the theory T to be an answer set program. Under a goal-directed execution regime, an ASP system can be extended with abduction by simply adding the following rule:

```
p :- not _not_p.
_not_p :- not p.
```

for every $p \in A$. Posing the observation O as a query to this extended answer set program will yield all the explanations as part of a (partial) answer set. The reason why this works is simple: rules of the form above have two answer sets, one in which p is false and another in which p is true. These settings (along with assignments to other propositions) may make the observation O succeed. As an example, consider the program below:

```
p :- a, not q.
q :- a, b.
q :- c.
```

and the abducibles $\{a, b, c\}$. If we add the clauses below to program above:

```
a :- not _not_a.      b :- not _not_b.
_not_a :- not a.     _not_b :- not b.
c :- not _not_c.
_not_c :- not c.
```

then the query (observation) $?- p$ will succeed, producing the answer set $\{p, \text{not } q, a, \text{not } b, \text{not } c\}$ and abducibles $\{a, \text{not } b, \text{not } c\}$. First, $_not_a$, $_not_b$ and $_not_c$ are not included in the answer set as they are auxiliary predicates introduced for convenience. Note that $s(\text{ASP})$ omits from output the predicates starting with an underscore ('_'). Second,

in goal-directed execution, as noted earlier, since the models generated may be partial, propositions/predicates that are known to be true, as well as propositions/predicates known to be false, are shown explicitly in the (partial) answer set.

It should also be noted that abductive reasoning is more precise under goal-directed execution. Other execution strategies, most of which are based around SAT-solvers (e.g., the CLASP system (Gebser et al., 2014)), compute the entire stable model, which can produce confusing answers where it is not clear as to which of the abducibles are involved in the explanation. Consider the example program above. Suppose we extend the set of abducibles to include a new proposition `{d}` and add the two customary rules involving `d` and `not_d`. For observation `{p}`, if we use a traditional ASP solver, now we will get two answer sets: `{p, not q, a, not b, not c, d}` and `{p, not q, a, not b, not c, not d}`. These two answer sets essentially are extensions of the single answer set produced by the goal-directed method, however, this answer set has to be replicated twice—once for including `{d}` and once for including `{not d}`. Thus, if there are irrelevant abducibles, then for a given observation, the number of answer sets will proliferate exponentially. Considerable analysis will be required to extract the true abducibles. The goal-directed execution method does not suffer from this problem, as it only explores the space of knowledge that is relevant to the observation. Thus, only relevant propositions/predicates are abduced.

Abductive reasoning is supported by the s(ASP) system, where the abducibles predicates are specified as follows:

```
#abducible goal(X).
```

This declaration means that the specified goal may be abduced when failure of the query would otherwise occur during execution. Specifically, s(ASP) creates the following rules for the declaration statement above:

```
goal(X) :- not _neggoal(X), abducible(goal(X)).
_neggoal(X) :- not goal(X).
abducible(goal(X)) :- not _negabducible(goal(X)).
_negabducible(goal(X)) :- not abducible(goal(X)).
```

6.5 Application of Abductive Reasoning in Physician Advisory System

A physician may give prescriptions using his/her intuitions based on incomplete information about a patient. In such a case, the physician's recommendation can be run in the s(ASP) system in the abductive mode where the physician's recommendation is posed as a query. The system will then tell the physician, via abduction, any symptoms, conditions, or required evidence that must be present for the recommendation to be correct. The physician can then work on ascertaining the presence of those symptoms, conditions, etc., or revise their recommendation if those symptoms/conditions are not present. The fact that the physician advisory system succeeds in producing abducibles means the original recommendation given by physicians is guideline-compliant if the abduced symptoms/conditions/evidence were to be present. On the other hand, if the query representing the physician's recommendation fails, then it means that the physician's recommendation is incorrect with respect to the guidelines, and should be rejected or carefully re-evaluated.

Our intention is to help improve compliance with the clinical practice guidelines via abductive reasoning. This is achieved as follows: all guideline-compliant treatment recommendations are first generated in a single answer set with the help of the CLASP system (Gebser et al., 2014). Any treatment recommendation made by a doctor that is not among the recommendations made by CLASP system is considered a non-guideline-compliant treatment recommendation. A non-guideline-compliant treatment recommendation made by a physician is posed as an observation and fed as a query to s(ASP) system, which is then run in

```

%doctor's assessments
evidence(accf_stage_c).
evidence(nyha_class_3).

%demographics of the patient
evidence(female).
evidence(age, 60).

%history of the patient
diagnosis(hf_with_reduced_ef).
diagnosis(dilated_cardiomyopathy).
diagnosis(diabetes).
evidence(angina).
evidence(elevated_plasma_natriuretic_peptide_level).
history(standard_neurohumoral_antagonist_therapy).

%measurements from the lab
measurement(potassium, 3.0).
measurement(creatinine, 1.49).
measurement(lvef, 0.16).
measurement(non_lbbb, 110).
measurement(glomerular_filtration_rate, 44).

%contraindications
contraindication(crt).
contraindication(ace_inhibitors).

```

Figure 6.1. Representation of the simulated patient's information in the physician advisory system for HF management

the abductive mode to discover the necessary evidence that must be available for the given treatment to be applicable.

Figure 6.1 displays the information of one patient with heart failure. The data is provided by the University of Texas Southwestern Medical Center. Her doctor prescribed (recommended) the isordil/hydralazine to this patient. However, we know that the recommendation of isordil/hydralazine is not reasonable for this patient under the guidelines once we run CLASP system on the data.

Since isordil/hydralazine is highly effective in treating HF in African Americans, we want to make sure that we did not miss any vital information regarding their recommendation.

The applicable rules for this class I recommendation of isordil/hydralazine is reproduced below (Yancy et al., 2013):

“Class I : The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV EFrEF receiving optimal therapy with ACE inhibitors and beta blockers , unless contraindicated.”

“The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HFrEF in patients who have no prior use of standard neurohumoral antagonist therapy and should not be substituted for ACE inhibitor or ARB therapy in patients who are tolerating therapy without difficulty.”

Next we declare all possible abducibles which are not shown in the patient’s profile. Note that this step can be automated using simple string matching. Figure 6.2 shows all the abducibles for this case.

Abducibles involving numeric values are declared as textual propositions, e.g., “lvef_less_than_30”, “mi_post_40_days”, etc. The corresponding auxiliary rules are also introduced. For example:

```
lvef_less_than_30:- measurement(lvef, Data), Data =< 30.  
mi_post_40_days:- measurement(mi, Data), Data >= 40.
```

The declaration of abducibles should be placed after facts and rules in s(ASP) since we only want to abduce what are not facts and deducibles. This arrangement guarantees that whatever s(ASP) abduces leads us to overlooked or missed evidence which is necessary to justify the treatment recommendation in question.

Next we pose the following query (the observation) to the s(ASP) system with the abductive reasoning flag set:

```
recommendation(hydralazine_and_isosorbide_dinitrate, class_1)
```

With the abducibles declared, s(ASP) will abduce them when failure of the query would otherwise occur. In this case, s(ASP) returns false as the result, which means there is truly

```

#abducible survival_year_greater_than_1.
#abducible survival_year_less_than_1.
#abducible survival_year_less_than_2_and_greater_than_1.
#abducible evidence(sinus_rhythm).
#abducible contraindication(ivabradine).
#abducible contraindication(icd).
#abducible contraindication(beta_blockers).
#abducible contraindication(diuretics).
#abducible contraindication(arni).
#abducible contraindication(arbs).
#abducible contraindication(statins).
#abducible contraindication(aldosterone_antagonist).
#abducible contraindication(hydralazine_and_isosorbide_dinitrate).
#abducible contraindication(digoxin).
#abducible contraindication(anticoagulation).
#abducible contraindication(omega3_fatty_acids).
#abducible contraindication(continuous_positive_airway_pressure).
#abducible evidence(fluid_retention).
#abducible history(fluid_retention).
#abducible history(mi).
#abducible mi_post_40_days.
#abducible mi_within_7_days.
#abducible history(acs).
#abducible diagnosis(ischemic_heart_disease).
#abducible history(ischemic_heart_disease).
#abducible diagnosis(coronary_artery_disease).
#abducible history(coronary_artery_disease).
#abducible diagnosis(hypertension).
#abducible history(hypertension).
#abducible diagnosis(lipid_disorders).
#abducible diagnosis(obesity).
#abducible diagnosis(structural_cardiac_abnormalities).
#abducible diagnosis(asymptomatic_ischemic_cardiomyopathy).
#abducible evidence(sleep_apnea).
#abducible history(angioedema).
#abducible evidence(atrioventricular_block).
#abducible diagnosis(atrial_fibrillation).
#abducible history(thromboembolism).
#abducible history(stroke).
#abducible history(ischemic_attack).
#abducible evidence(volume_overload).
#abducible diagnosis(myocardial_ischemia).
#abducible evidence(ischemic_etiology_of_hf).
#abducible evidence(threatened_end_organ_dysfunction).
#abducible evidence(acute_profound_hemodynamic_compromise).
#abducible history(cardiovascular_hospitalization).
#abducible evidence(cardiovascular_hospitalization).
#abducible evidence(requirement_ventricular_pacing).
#abducible evidence(premise_near_100_percent_ventricular_pacing).
#abducible evidence(requirement_greater_than_40_percent_ventricular_pacing).
#abducible evidence(mechanical_circulatory_support_eligibility).
#abducible evidence(cardiac_transplantation_eligibility).
#abducible evidence(dependence_on_continuous_parenteral_inotropic).
#abducible evidence(refractory_to_gdmt).
#abducible evidence(pregnancy).
#abducible evidence(maximum_dose_ace_inhibitors).
#abducible evidence(maximum_dose_arbs).
#abducible evidence(maximum_dose_beta_blockers).

```

Figure 6.2. Abducibles for one patient

nothing we can do to make class I recommendation of isordil/hydralazine, given the patient's data.

Next we want to know if it is possible to make class IIa recommendation of isordil/hydralazine. The relevant rules in the guideline (Yancy et al., 2013) regarding the class IIa recommendation of isordil/hydralazine are shown below:

“Class IIa : A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.”

We pose the following query (the observation) to s(ASP) running in the abductive mode:

```
recommendation(hydralazine_and_isosorbide_dinitrate, class_2a)
```

One of the answer sets produced by s(ASP) is displayed in Figure 6.3. Two things are abduced by the system: 1) the contraindication of ARB and 2) the history of angioedema. It can be seen from Figure 6.1 that both of the abducibles are not in the patient's profile. With some medical knowledge, we know that the history of angioedema is an indication for the contraindication of ACE inhibitors, which is listed in the fact sheet. Isordil/hydralazine would be a reasonable class IIa recommendation once we confirm the intolerance of ARB for the patient. In this case, the patient's profile says nothing about her intolerance of ARB. Thus, the physician could look for this piece of information elsewhere to ensure that she does not miss useful data regarding the recommendation of isordil/hydralazine. Once she has done that, she will have the justification for the original recommendation of isordil/hydralazine.

Experiments were done on a set of ten representative patients. For these ten patients, we had detailed patient data, as well as physician's recommendations. Table 6.1 displays the experimental results for seven of these patients. The remaining three patients are not shown in the table because the physician's prescriptions (recommendations) for them are compliant with the clinical practice guidelines. Thus there is no need to perform abductive reasoning

```

{ abducible(contraindication(arbs)),
  abducible(history(angioedema)), history(angioedema),
  contraindication(ace_inhibitors), contraindication(arbs),
  diagnosis(hf_with_reduced_ef), evidence(accf_stage_c),
  history(standard_neurohumoral_antagonist_therapy),
  recommendation(hydralazine_and_isosorbide_dinitrate,class_2a),
  treatment(hydralazine_and_isosorbide_dinitrate),
  not contraindication(hydralazine_and_isosorbide_dinitrate),
  not rejection(hydralazine_and_isosorbide_dinitrate) }

```

Figure 6.3. Results of abductive reasoning

for them. The first column of the table presents the patient number. The second column shows the non-guideline-compliant treatment recommendations given by physicians. The third column displays the abducibles (symptoms, conditions, etc.) produced by the s(ASP) system. These abducibles must be verified by the physicians before the recommendations shown in the second column can be regarded as compliant with the guidelines.

It is worth nothing that for patients No.4, No.8 and No.10, the system produced a failure (i.e., it failed to abduce anything). This means that the original recommendation made by the physician in each of these cases was incorrect. In the case No.4, the patient data shows no sign of atrial fibrillation or cardioembolic source, which makes anticoagulants unhelpful. The relevant rule is as following:

“Class III No Benefit : Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source. ”

For case No.8 and No.10, the latest lab results say their potassium level is greater than 5.0 mEq/L, which makes aldosterone antagonists harmful to them. The rule is as following:

‘Class III Harm : Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/ 1.73 m^2), and/or potassium greater than 5.0 mEq/L.’

Table 6.1. Results of abductive reasoning for 10 representative cases

| Patient Number | Non-guideline-compliant recommendations | Abducibles |
|-----------------------|--|---|
| No.1 | isordil/hydralazine (class IIa) | contraindication(arbs). history(angioedema). |
| No.4 | anticoagulants (class I) | None found |
| No.5 | ICD (class I) | survival_year_greater_than_1. |
| No.6 | isordil/hydralazine (class IIa) | contraindication(arbs). history(angioedema). |
| No.7 | aldosterone antagonists (class I) | evidence(recent_mi). |
| No.8 | aldosterone antagonists (class I) | None found |
| No.10 | aldosterone antagonists (class I) | None found |

Table 6.2. Running time of the physician advisory system

| Patient Number | Obtaining recommendations (CLASP) | Computing abducibles (s(ASP)) |
|-----------------------|--|--------------------------------------|
| No.1 | 0.021s | 3.451s |
| No.2 | 0.021s | N/A |
| No.3 | 0.020s | N/A |
| No.4 | 0.020s | 0.965s |
| No.5 | 0.020s | 3.440s |
| No.6 | 0.021s | 3.041s |
| No.7 | 0.020s | 3.053s |
| No.8 | 0.021s | 0.291s |
| No.9 | 0.020s | N/A |
| No.10 | 0.020s | 0.214s |

Table 6.2 presents the running time of the physician advisory system to obtain all applicable treatment recommendations using CLASP and performing abductive reasoning via s(ASP) for ten representative cases. As can be seen, the execution times are quite acceptable.

6.6 Related Work

There has been some work on applying abduction within logic programming as well as ASP (Satoh and Iwayama, 1991; Inoue, 1991; Kakas et al., 1992; Mcilraith, 1998; Baral, 2003).

Chesani et al. (Chesani et al., 2007) describe an approach to perform the conformance verification of careflow process executions. The approach translates clinicians workflow into a formal language based on computational logic and abductive logic programming. A graphical language was developed to specify careflow models. Given a set of events that have taken place, expectations are generated which can be compared with the actual participants behavior. If a participant does not behave as expected with respect to the model, a violation will be raised by the procedure.

Temporal logic is used to identify ways a treatment can be non-compliant with clinical guidelines (Groot et al., 2009). One of possible reasons for a non-compliant treatment is relevant findings are missing in patient data. Those missing relevant parameters in records can be found using the proposed critiquing method.

PROforma (Fox et al., 1998) is a knowledge representation language that is based on classical predicate calculus augmented by first-order logic. In PROforma, an application such as a protocol or clinical guideline is modeled as a plan made up of one or more tasks. PROforma is able to recognize clinical problems and identify possible solutions to them. It can also assess the strengths and weaknesses of alternative solutions, yielding a preference order on the set of alternatives.

Spiotta et al. (Spiotta et al., 2015) propose an approach for analyzing conformance of ASP execution traces for patient treatment with respect to clinical guidelines and basic medical knowledge. Basic medical knowledge may be used to justify deviations from the application of guidelines.

The above approaches, including ours, capture clinical expertise in a form which can be directly applied by one agent (such as a machine) on behalf of another (such as an expert physician). However, our system does not require complete information when performing abductive reasoning, thanks to use of negation as failure and ASP. The ability to perform reasoning with incomplete information is highly valuable in a real world setting.

CHAPTER 7

CONCLUSION

7.1 Contributions

In this dissertation, we presented a physician advisory system that generates guideline-compliant treatment recommendations for heart failure patient. This system completely automates the entire set of guidelines for heart failure management developed by the American College of Cardiology Foundation and American Heart Association. The input to the system is patient’s information, including demographics, history, daily symptoms, risks and measurements. When queried for a treatment recommendation, the physician advisory system is able to give recommendations according the clinical practice guideline just as a physician would.

Answer set programming is used as a crucial technique in the implementation of the physician advisory system. The system is designed for running on top of the s(ASP) system, a goal-directed predicate ASP system that can be thought as Prolog extended with negation as failure based on the stable model semantics. Because of the goal-directed nature of the s(ASP) system, only the particular treatment applicable to the patient are reported by the system. With minor changes, the physician advisory system also works with the traditional SAT-based implementations such as CLASP (Gebser et al., 2014).

Knowledge patterns are derived from the rules in the 2013 Guideline to serve as reasoning templates. They prove to be solid building blocks for the development of the physician advisory system. By adopting the knowledge patterns, the developers of the system were able to code each rule individually without compromising the correctness of the whole system. The knowledge patterns are generic enough to be deployed in various application domains.

Abductive reasoning is realized in the physician advisory system to help physicians improve their treatment recommendations. In practice, physicians often need to give treatment

plans under the constraint of limited time and information. Considering the complexity of the rules in clinical guidelines, it is an error-prone task for even the most experienced physicians to give completely guideline-compliant recommendations. The abductive reasoning provides all the missing conditions and symptoms the patient must exhibit in order for a treatment prescribed by the physician to work. We show how physician advisory system, quipped with abductive reasoning capability, helps to ensure the compliance with the 2013 Guideline. The successful implementation of abductive reasoning in the physician advisory system highlights a major advantage of goal-directed ASP system such as s(ASP). Our work is the first real-life application of abduction with ASP technology in the very important area of medicine.

The validation of the physician advisory system was done with ten representative patients with heart failure. The data were provided by the cardiologists from University of Texas Southwestern Medical Center. They also helped to verify the correctness of the recommendations produced by the physician advisory system. The experimental results show that the physician advisory system is able to generate guideline-compliant recommendations for all ten cases. Thus the meaning of the clinical guideline for heart failure management is successfully captured by ASP code.

7.2 Future work

The ways to further extend our work include but not limited to:

- Extending the system to cover the clinical guidelines of other co-morbid diseases: heart failure is usually accompanied by other diseases such as myocardial infarction, diabetes mellitus, etc.
- Field trial: conducting a field trial for a large number of patients to validate the physician advisory system with statistical significance.

- Integrating with electronic medical records (EMR) system and telemedicine platform: an adapter may be needed to enable the physician advisory system to recognize vocabularies of other system which use different medical terms than the 2013 Guideline.
- Incorporating dosage management into the system: the physicians follow a set of quantitative rules which dictate the initial daily doses and maximum total daily doses for pharmacological treatments.

APPENDIX

PATIENT'S PROFILE

A.1 Case One

A.1.1 Chief Complaint

HFrEF

A.1.2 History of Present Illness

The patient is a 60 year old African American female with a history of dilated nonischemic cardiomyopathy/NICM with New York Heart Association class IIIb symptoms who has been followed in our Heart Failure Disease Management program since ***¹. Additional comorbidities include diabetes mellitus type 2, hypothyroidism, history of thyroid and uterine cancer. The patient's most recent transthoracic echocardiogram completed on *** reveals a LVEF of 16%. The patient has a single lead ICD and not a candidate for CRT-D with a narrow QRS of 110 ms on ***.

Today patient endorses: (+ is positive and - is negative). Additional review of system below.

- General: (-) fevers, (-) chills, (-) sweats, (-) nausea, (-) vomiting, (-) diarrhea, (-) anorexia, (-) unintentional weight loss. Appetite is fair.
- Activity: Patient can walk 100 feet before developing symptoms
- Arrhythmia: (+) palpitations, (+) dizziness - intermittent with position changes, (-) fainting, (-) presyncope or (-) syncope.

¹date information was censored to preserve patient anonymity

- HF symptoms: (+) chest pain - with increased fluid, (+) orthopnea - sleeps on 5 pillows, (+) PND, (+) bendopnea, (+) DOE, (+) fatigue, (+) activity limitations, (+) cough - intermittent and dry, (-) shortness of breath at rest, (+) lower extremity edema, (+) abdominal swelling.
- Weight: Down 8 pounds since discharge.
- Heme: No bleeding issues.

A.1.3 Past Medical History

Dilated Nonischemic Cardiomyopathy diagnosed *** - denied orthotopic heart transplant on *** due to financial means and noncompliance.

Transthoracic echocardiogram completed *** at an outside facility reveals LA (1.9-4.0cm): 4.6, LVdia(3.5-6.0): 7.1, LVsys(2.1-4.0): 6.6, RA: normal, RVDd (0.9 -2.6): 2.7, LVEF: 15 to 20%, MR: mild to moderate, TR: mild, AR: none, PR: none, RVSP: normal. LV is severely dilated. Normal LV wall thickness. LVSF is severely reduced. LVEF of 15 to 20%. Severe global hypokinesis of LV. RV is normal in size and function. Mild to moderate MR. Mild TR.

Transthoracic echocardiogram completed *** reveals IVSD (0.7 - 1.1) 1.0, LA (1.9-4.0cm): 4.5, LVdia (3.5-6.0): 7.1, LVsys (2.1-4.0): 6.7, RA (2.9-4.5): moderatel dilated, RVDd (0.9 -2.6): 4.3, LVEF: 16%, MR: moderate, TR: mild, AR: none, PR: trace, RVSP: 35 mmHg. There is no comparison study available. Four-chamber enlargement. Midlly depressed RV systolic function. Severely depressed LV systolic function. Single-plane LVEF 16%. Global severe hypokinesis. Dilated mitral annulus with moderate regurgitation. Mild tricuspid regurgitation. RVSP 35mmHg above mean RA pressure. Dilated IVC with flow reversal in hepatic vein consistent with markedly elevated RA pressure > 20. Small pericardial effusion. There is a catheter/pacemaker lead seen in the right atrium.

Transthoracic echocardiogram completed *** reveals IVSD (0.7 - 1.1) 0.86, LA (1.9-4.0cm): mildly dilated, LVdia (3.5-6.0): 8.3, LVsys (2.1-4.0): 7.5, RA (2.9-4.5): mildly dilated, RVDd (0.9 -2.6): 5.1, LVEF: 14%, MR: mild, TR: moderate, AR: trace, PR: Mild to moderate, RVSP: 32 mmHg. Impression: The left ventricle is severely dilated. Left ventricular systolic function is severely reduced. LVEF 14% by Simpsons SP. The septum is akinetic with hypokinetic lateral wall. Near akinesis elsewhere. The right ventricle is mildly dilated. The right ventricular systolic function is mild to moderately reduced. There is a pacemaker lead in the right ventricle. The transmitral spectral Doppler flow pattern is suggestive of pseudonormalization. There is mild mitral regurgitation. There is moderate tricuspid regurgitation. RVSP 32 mmHg above RA pressure. IVC dilated with reduced collapse, suggests elevated CVP. Small pericardial effusion. There are no echocardiographic indications of cardiac tamponade. Compared to previous study, LV is further dilated.

Diabetes Mellitus Type II with HgbA1C of 9.6% on ***. Followed by endocrinology.

Hypothyroidism related to thyroidectomy for cancer in ***.

History of Thyroid Cancer diagnosed in ***, s/p thyroidectomy.

History of Uterine Cancer s/p hysterectomy.

History of Salivary Cancer.

Dyspepsia.

Right Internal Jugular Thrombus related to Swan Ganz catheter previously treated with Xarelto (Xarelto stopped March 2015 during hospitalization).

Mild Restrictive Lung disease.

Non-proliferative Diabetic Retinopathy - moderate.

Endometriosis s/p hysterectomy.

H. Pylori diagnosed *** and treated with amoxicillin, clarithromycin and nexium x 14 days.

Single lead ICD.

Status post Thyroidectomy related to cancer in ***.

Status post Hysterectomy related to uterine cancer in ***.

FNA of the thyroid on ***.

A.1.4 Family History

Positive for family history of CAD in family members less than 60 years of age. Father - HF, MI, HTN, hyperlipidemia, CVA, DM. Mother - HF, Sudden Death, HTN, DM, hyperlipidemia, MI at 63 (cause of death). Brother with DM.

A.1.5 Social History

Tobacco: 160 pack/years, quit ***. Alcohol: denies. Intravenous drug abuse: denies. Marital Status: widowed, with 3 children.

A.1.6 Allergies

NKDA

A.1.7 Medication Intolerance

Carvedilol dose higher than 6.25 mg bid causes overt fatigue and hypotension with systolic B/P in the 80's. Ace inhibitor (captopril) causes cough. HAs with isordil.

A.1.8 Review of Systems

Answers for ROS submitted by the patient with further investigation by provider with additional questions during visit as above - Patient advised to follow-up with PCP or internal medicine/family practice for noncardiac symptoms.

A.1.9 Patient Reported

- Constitutional: Positive for weight loss, weight gain and fatigue. Negative for fever, chills, diaphoresis, night sweats, hot flashes and general weakness.
- HENT: Positive for trouble swallowing and headaches. Negative for nasal congestion, ear discharge, ear pain, hearing loss, oral lesions, nosebleeds, sore throat, tinnitus and loss of smell.
- Eyes: Negative for blurred vision, double vision, photophobia, pain, discharge and redness.
- Respiratory: Positive for cough, sputum production and shortness of breath. Negative for snoring, hemoptysis, wheezing, stridor and pain when breathing.
- Cardiovascular: Positive for chest pain, palpitations, orthopnea and leg swelling. Negative for PND.
- Gastrointestinal: Positive for constipation and appetite change. Negative for heartburn, nausea, vomiting, abdominal pain, diarrhea, blood in stool, melena and bowel incontinence.
- Genitourinary: Positive for nocturia. Negative for dysuria, urgency, hematuria, penile discharge, vaginal discharge, frequency, bladder incontinence, sexual dysfunction and female genitourinary complaint. Musculoskeletal: Negative for back pain, falls, joint pain, myalgias and neck pain.
- Skin: Positive for itching and rash. Negative for change in mole, hair loss and breast concerns.
- Neurological: Positive for dizziness. Negative for tremors, sensory change, speech change, seizures, loss of consciousness and generalized weakness.

- Endo/Heme/Allergies: Negative for environmental allergies, cold intolerance, heat intolerance, polydipsia, seasonal allergies and easy bruising/bleeding.
- Psychiatric/Behavioral: Positive for anxiety and insomnia. Negative for depression, suicidal ideas, hallucinations, memory loss and substance abuse.

A.1.10 Physical Exam

- Constitutional: Well developed, well nourished, alert and oriented in no apparent distress at rest. Denies fevers, chills, or night sweats.
- Vital signs: BP 108/73 mmHg. Pulse 97. Temp(Src) 36.6 C (97.9 F) (Temporal Artery). Resp 18. Ht 5' 7.5" (1.715 m). Wt 180 lb 6.4 oz (81.829 kg). BMI 27.82 kg/m². SpO₂ 99%.
- Eyes: conjunctiva pink, moist; sclera clear w/o lesions; eyelids soft, nontender, w/o lesions, drainage or discharge.
- Neck: supple w/o masses, full ROM; trachea straight, midline. No thyromegaly or lymphadenopathy. JVP is elevated 1/2 way up from the clavicle at 45 degrees.
- Resp/Chest: chest wall symmetrical; no kyphosis or anomalies noted; respiratory effort normal, respirations regular, even, nonlabored w/o nasal flaring; anterior/posterior thoracic expansion/retraction equal bilaterally; No use of accessory muscles or stridor. No apnea, no tachypnea and no bradypnea. Patient has no decreased breath sounds, no wheezes, no rhonchi, no rales. Auscultation reveals clear lung sounds anterior and posterior bilaterally.
- CV: apical pulse regular rate and rhythm, S1, S2, +S3 w/ SEM 2/6; no rubs or gallops. PMI is displaced.

- GI/Abdomen: Soft, no masses noted, nontender, nondistended, symmetrical contour, soft, positive bowel sounds x 4 quadrants. + hepatojugular reflux at 45 degrees; no hepatomegaly, liver edge nonpalpable with deep inspiration at right costal border.
- Musculoskeletal: Posture erect, no deformities noted, Gait coordinated, smooth and steady, No cyanosis, clubbing, or weakness noted.
- Ext/Skin: warm, dry, intact; 1+ lower extremity edema noted bilaterally to the knees. No clubbing, cyanosis, or stasis dermatitis skin changes noted.
- Psychiatric: Appropriate mood, behavior and affect. Oriented to person, place, and time. Good insight into healthcare treatment and plan. Thought process intact.

A.1.11 Additional Diagnostics/Labs

EKG completed *** with a QRS of 110 ms which does not meet the criteria for upgrade to CRT-D.

A.1.12 Pertinent Data/Labs Reviewed

See the Table A.1.

A.1.13 Impression

Dilated Nonischemic Cardiomyopathy diagnosed September 2012, normal coronaries at that time by reports, NYHA Class IIIb, Hemodynamic Profile B, warm and wet.

Table A.1. Most recent labs completed

| | *** | *** |
|-----------------------|----------|----------|
| N-TERMINAL PRO-BNP | 4617 (H) | 5051 (H) |
| SODIUM | 137 | 141 |
| POTASSIUM, BLD | 4.7 | 3.0 (L) |
| CHLORIDE | 93 (L) | 93 (L) |
| CO2 | 31 | 30 |
| ANION GAP | 13 | 18 (H) |
| BUN | 46 (H) | 43 (H) |
| CREATININE | 1.53 (H) | 1.49 (H) |
| eGFR AFRICAN AMERICAN | 43 (L) | 44 (L) |
| BUN/CREAT RATIO | 30.1 (H) | 28.9 (H) |
| CALCIUM | 9.7 | 9.3 |
| MAGNESIUM | 2.4 | 2.3 |
| GLUCOSE | 184 (H) | 72 |
| WBC | 4.38 | |
| RBC | 3.92 | |
| HEMOGLOBIN | 10.7 (L) | |
| HEMATOCRIT | 34.7 | |
| PLATELETS | 114 (L) | |
| DIGOXIN LVL | | 0.5 (L) |

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BIOGRAPHICAL SKETCH

Zhuo Chen was born on December 3, 1987 in Chongqing, China. He was exposed to a personal computer the first time when he was an elementary school student. It was an Intel 80486 at his uncle's home that intrigued him. He showed interest in algorithm at Chongqing No.8 Secondary School and won the first prize twice in National Olympiad in Informatics in Provinces in 2004 and 2005. Zhuo received his Bachelor of Engineering in Software Engineering from Huazhong University of Science and Technology, Wuhan, China in 2010.

He worked as an application developer for Bank of Communications for one year and a half. During that time, he built a mission-critical system which processed citizens' social information for account creation. The system receives data from government, supports transactions for tellers and communicates with the headquarters of the bank. It took him three months to develop the system and it has been in production since 2011.

In 2013, he went to the U.S. to pursue the doctoral degree in computer science at The University of Texas at Dallas. Zhuo was introduced to logic programming and answer set programming, which powered the physician advisory system he built. The system generates guideline-compliant treatment recommendations for a patient with heart failure. Several papers related to the system were published. He received the master's degree in computer science in the spring of 2017.

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