Using EMR Transactional Data for Personalized Clinical Decision Support

By

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Medical Doctor
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ABSTRACT

Collective intelligence techniques have been used to predict stock prices, customer purchasing habits, movies and books preferences for years, yet they remain unused in the medical profession. With the increasing adoption of electronic medical records, patients' medical data has grown exponentially and thus constitutes an untapped field where similar techniques could be applied. If data were collectively farmed and intelligently filtered, patient information could be added to traditional clinical decision support tools to arrive at personalized recommendations based on empiric evidence. The aim of this work is to use the collective, *de facto*, clinical experience to augment clinical guidelines thereby providing physicians with personalized clinical decision support. The pharmacological treatment of hypertension was chosen as the clinical domain in which to explore the feasibility of this approach.

Twelve-thousand-three-hundred-forty-seven hypertensive patients were seen at the Internal Medical Associates (IMA) clinic at Massachusetts General Hospital (MGH) between July 2004 and September 2009. Their relevant clinical and demographic variables, drug regimens and blood pressure measurements were collected from the clinic's electronic medical record system and a dataset was generated. Back-end application software that draws upon case-based reasoning (CBR) was constructed and used to compute similarity between an index patient and existing hypertension patients. This program returned information regarding blood pressure control status and successful drug regimens used by similar patients.

The use of EMR transactional data to provide a collective experience decision support (CEDSS) at the point-of-care using a computerized CBR approach is both technically possible and promising. Further studies are needed to evaluate the effectiveness of this method.

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INTRODUCTION

Clinical Decision Support Systems (CDSS) are tools designed to influence health care provider performance to improve quality of care and patient outcomes. While different definitions of CDSS exist, the American Medical Informatics Association (AMIA) Joint Clinical Decision Support Workgroup defines CDSS as: providing clinicians or patients with clinical knowledge and patient-related information, intelligently filtered and presented at appropriate times, to enhance patient care [1].

The desire to use computers to assist health professionals dates to 1959 when Ledley and Lusted published their work on how physicians reason about diagnosis [2]. Several decades later, various CDSS emerged that assisted physicians with computer-aided diagnosis of acute abdominal pain [3], antibiotic therapy recommendations (Mycin [4]) and differential diagnosis decision support (Dxplain [5]). More recently, CDSS have been used to enhance prescription management [6,7,53], reduce medications errors [7,8], and improve cost-effectiveness of offered treatments. [9,10]. CDSS have also been used for patient medication education activities [11], to increase preventive care reminders [54], and are widely regarded as essential tools to reduce adverse events [1,13]. Yet while there remains great potential for CDSS to change provider behavior and improve patient outcomes, recent review of the literature shows that only about half of CDSS implementations actually change health care providers behavior and a minority resulted in improved patient outcomes [13,15,16].

When you see your doctor today, he or she primarily relies on two main sources of information to guide her opinion on which tests to perform and which treatment options to choose: (1) expert consensus opinion, mainly in the form of guidelines, and (2) memory -- recall of the physician's clinical experience. Physicians probe, examine and tease out the medical history to arrive at a hypothesis or working diagnosis primarily by recalling patients with similar presentations or by remembering cases that otherwise stand out. However, both of these information sources have bias.

Not only is there variation in clinician experience but physician recall of patients they have cared for in the past is inaccurate with recent patients and patients with adverse outcomes being recalled most readily [55, 56]. Expert consensus in the form of clinical guidelines, on the other hand, do not provide recommendations for individual or special cases, but rather provide general recommendations for the population at large with a given condition.

Thus, both of these sources of information used in clinical decision making are imperfect. So it is feasible that physicians could benefit from the systems that augment memory, experience and acumen. Additionally, as the practice of medicine advances deeper into the information age, it is likely that physicians will increasingly rely on tools to help manage information in the care of their patients. This will happen both (a) because of the expanding knowledge base required to master the field of medicine and (b) the increases in time pressures of an office visit. As a result, advanced decision support tools will be necessary for physicians to efficiently practice in the future [17].

One possible solution would be to draw upon the *de facto* experience of similar clinical scenarios by tapping into the data recorded and stored within an EMR. This "collective experience" of thousands of physicians and patients could enable a computerized case-based reasoning (CBR) approach to augment traditional clinical decision support tools [18,19].

Over the last decade, electronic medical record systems have been put in place giving rise to highly granular clinical databases where day-to-day experimentations, diagnostics tests and therapeutic interventions are performed, and their outcomes recorded. This recorded transactional data could be tapped providing an additional reference source to create augmented "Collective Experience Decision Support System". The general idea is to use EMR data to discover patients whose characteristics are similar to an index patient and in a similar clinical scenario. This situational data could help predict the utility of diagnostic tests and/or interventions, as well as inform prognosis. The goal of this artificial intelligence tool would be to complement individual physician experience and expert opinion (guidelines) with the de facto prescribing habits and outcomes of practice at large. By tapping into this dataset, the actual real world

effectiveness of prescribed treatments could be used to augment and individualize evidence-based guidelines to enhance clinical decision making. Consequently, patients would be treated with therapies that have been shown to be effective in similar patients.

This notion, however, is not new. David Goldberg described "collective filtering" at Xerox PARC in 1992 when he created a system that allowed people to "tag" documents as either "interesting" or "uninteresting." The "collective" information was then used to help other people hone down the document reading task [19]. Since then, many commercial entities have taken advantage of these techniques. For example, the large online retailer Amazon, tracks the purchasing habits of all its shoppers, and when you log onto their website, Amazon uses the information of shoppers with a similar profile to suggest products you might like. Likewise, Netflix, an online movie rental service, recommends movies you might enjoy by looking into other users with a movie taste like yours. Similarly in the medical domain, by tapping the collective, a clinician trainee could be empowered with the "Collective Experience" and, in essence, take a new empiric data-driven approach to the pedagogy of medicine.

This task is theoretically feasible *today* as the experiences from decisions taken by medical experts and their outcomes are recorded in the hospital's electronic medical record systems. However, in order to deliver this goal several steps must first be achieved: (1) mine and leverage this transactional EMR data; (2) employ context-sensitive information filtering for point of care decision support and (3); present it in an actionable fashion for decision-making at the point-of-care.

The overarching goal of this thesis is to determine the feasibility of an innovative model for decision support that augments traditional guideline-based clinical decision support with the collective experience of thousands of patients (collective intelligence) to provide patient and situation specific (or personalized) clinical decision support at the point-of-care.

MOTIVATION

Clinical Decision Making and the Rationale for CDSS

The medical field is continuously changing. In the modern era, the pedagogy of medicine has evolved from a pure apprenticeship, where senior clinicians drew extensively on their personal experience and new or training clinicians turned to their senior colleagues to get definitive answers. Following this, physicians turned to evidence-based medicine (EBM), where definitive answers are based on the best evidence available from randomized clinical trials (RCTs). Clinical guidelines, best practices derived from EBM, provide general rules of thumb for medical decision making.

In essence, health care professionals rely on three principal aspects for clinical decision-making: (1) their training and personal experience; (2) clinical guidelines; and (3) the clinical scenario at hand.

While the process of becoming a physician has been an apprenticeship for centuries, there are fundamental problems with physician recall of their personal experience. It has been shown that not only is there variation in clinicians' prior experience but also in their recollection and processing of information with regard to patients they have cared for in the past with recent patients and patients with adverse outcomes being recalled most readily.

Clinical guidelines, developed to assist healthcare professionals' medical decision-making, consist of diagnostic and treatment recommendations based on medical evidence. Although they usually contain specific management directions, they are intended to be a general rule of thumb to support "best practices". They are often created by professional organizations, provide general recommendations for clinical care and are used primarily for disease or population management. While there are often very good reasons why individual patients are not on guideline recommended therapies, clinical guidelines are generally accepted as a useful tool despite their vulnerability to

biases [22]. Most importantly guidelines improve clinical outcomes. A systematic review of randomized control trials found a significant reduction in the odds of death in patients with myocardial infarction when the recommendation to use beta-blockers was followed [23]. Guidelines improve workflow efficiency and optimize value for money/lower costs [50]. For patients, guideline use provides consistent, high-quality care with proven interventions. For health care professionals, guidelines offer clear evidence-based recommendations that reduce clinical uncertainty. However, importantly guidelines are criticized for their lack of attention to individual patient characteristics and have been demeaningly referred to as "cook book medicine." Recommendations that might be good for a typical patient might not be optimal or even effective on individual or personalized basis [24]. Additionally, use of guidelines tends to increase the amount of treatments prescribed as they explicitly indicate when to treat a patient, usually discouraging professional discretion. Also, advocacy groups may use guidelines to impose their priorities encouraging resource allocation to certain topics, as guidelines are a great vehicle for promotion of group goals [25].

The last factor that goes into clinical decision-making is the clinical scenario at hand. What might be the right treatment for one patient might be inapplicable, ineffective or perhaps even dangerous to another. It is this nuance that is often overlooked in one-size-fits-all guidelines. For example, the sixth report of the JNC recommended beta blockers and thiazides to be used as first line therapy for every patient. But in reality the one-size-fits-all might not be the right path. UK physicians are currently guided to use CCB or thiazide diuretics as first line when starting to medicate hypertensive patients over 55 years of age and those of African ethnicity, whereas younger patients of other ethnic groups are recommended to be started on ACEi [26]. These subtle demographic differences yielding specific drug preferences for specific patients could be garnered from transactional EMR data to help refine the precision of clinical guidelines to a more granular level -- understanding to which patient a guideline should apply and to which it shouldn't. Patients' distinctive characteristics may be the single most important aspect to take in account when making a decision. Furthermore, recalling experiences with similar patients can be extremely helpful in approaching diagnostic or therapeutic decisions in new patients, but immediate recall is difficult.

Especially when confronted with complex cases where multiple variables are in play. For example, when choosing a medication for a patient, a clinician may remember the drug that he previously prescribed to treat a similar 60-year-old male African American patient with obesity and diabetes, however his capacity to recall the details is limited. Hence, a clinician may be able to evoke only one or a handful of similar patients. Likewise, it is not easy to remember the outcome or review the current state of those similar patients. Moreover, patients usually have more complex comorbidities than the case presented above, which makes the process even harder if not computationally impossible for the human mind.

This process, where the knowledge from previously seen similar patients is extrapolated to treat new patients is essentially CBR [18,19,19]. This methodology involves four sequential steps: *to retrieve* solutions of past cases that have a similar pattern with the new case, *to reuse* these cases by adapting them to solve the new case at hand, *to revise* the new results that occurred from the adaptation, and *to retain* the new solution in the knowledge base (Figure 1).

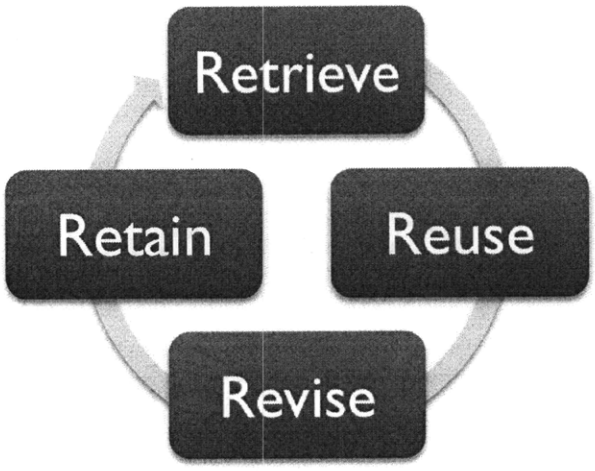

Figure 1. The case-based reasoning (CBR) cycle. Adapted from [27]. 1) Retrieve de most similar cases. 2) Reuse the cases to strive to solve a new case. 3) Revise the proposed solution. 4) Retain the new solution in the knowledge base.

Hypertension as the Clinical Scenario

One such clinical domain where this type of approach might be effective is in the treatment of hypertension. Hypertension is complex in that the underlying etiology of a common symptom, hypertension (or elevated blood pressure), differs widely amongst individuals within a large population [28]. Thus, hypertension is not a disease *per se* but rather a manifestation of a dysregulation of one or more underlying control mechanisms. Correspondingly, there are many different classes of antihypertensive medications, each targeting a unique pathophysiological pathway. Depending on the underlying physiology, one patient might have better results with a given class of drugs than another.

Essential hypertension is the form of hypertension that, by historical definition, has no identifiable cause. It accounts for 90-95% of all hypertensive patients and has a myriad of risk factors including age, gender, obesity, sedentary lifestyle, sodium and alcohol intake, and vitamin D deficiency among others. In addition to these phenotypic risk factors, genetic mutations are being discovered that predispose an individual to hypertension [45]. Indeed, we have likely not yet deciphered many more of the different underlying genetic variations that occur within the syndrome of essential hypertension.

Hypertension or high blood pressure refers to the increased pressure resulting from the flow of blood and the resistance of the arterial walls. The consequences of a chronically elevated blood pressure have been well known for decades. The JNC has released guidelines to help the medical community [29].

Hypertension is defined as:

- *Systolic blood pressure ≥ 140 mmHg or/and*
- *Diastolic blood pressure ≥ 90 mmHg or/and*
- *Taking antihypertensive medicine or/and*
- *Having been told at least twice by a physician or other health professional that one has high blood pressure*

It is clear to the medical community that the goal for treatment of hypertension is to keep patient's blood pressure measurements under 140/90 mmHg. Unfortunately, this target goal has still not been achieved.

Given its asymptomatic nature, hypertension (a.k.a. "The silent killer") slowly damages target organs for years before symptoms develop. Thus, it shortens life expectancy and is a precursor to multiple disease conditions such as: kidney failure, dementia, coronary artery disease, heart failure, retinopathy, stroke, arteriosclerosis, atherosclerosis and others.

To explore and test our model, we focused on the pharmacological treatment of

hypertension. We selected this domain for several reasons:

1) Hypertension places an enormous burden on the American Health care system. Hypertension is highly prevalent disease, affecting 1 in 3 adults in the United States, and is the most common primary care diagnosis in the U.S. Hypertension was estimated to result in nearly $73.4 billion in 2009 in health care costs with a death toll of 57,356 in 2005 [29,30].

2) The pharmacological treatment of hypertension is complex with a wide array of treatment choices. Most often, clinically, physicians do not distinguish types of hypertension rather treating incident cases of hypertension as essential hypertension without exploring the underlying pathophysiological cause in detail. When antihypertensives are prescribed their efficacy is often uncertain, hence most recent clinical guidelines note that the end (blood pressure control) is more important than the means (type of medication used).

3) Current control of hypertension is suboptimal. A prospective study from University of Texas Southwestern Medical Center showed that only one in three of the patients taking antihypertensives were controlled to goal. The numbers are lower in another study of 4,814 patients with hypertension and diabetes with only 26.3% at the JNCs target blood pressures [31,31].

4) The treatment goals of hypertension are clearly defined, with a measurable and readily available target (BP < 140/90).

In essence, hypertension provides an ideal condition on which to apply a computerized CBR model. Our specific aims:

Aim 1) Explore techniques to develop a model characterizing patients with existing transactional electronic medical record data.

Aim 2) Use the model generated in specific aim 1 to build a decision support system framework using collective experience (CEDSS).

Aim 3) Use the CEDSS to predict a successful drug regimen for hypertension based on a specific patient's phenotypic disease profile.

Shortliffe sets forth three requirements for excellent decision-making: accurate data, pertinent knowledge, and appropriate problem-solving skills [33]. We tried to achieve these by: (1) creating a precise dataset of patient's phenotypes; (2) using this dataset to find similar patients based on current treatment guidelines demonstrated to be effective [34]; and (3) looking for successful drug regimens in those patients.

MATERIALS AND METHODS

The Laboratory of Computer Science (LCS) at Massachusetts General Hospital (MGH) developed and maintains an electronic medical record (EMR) system, Oncall, for clinical use at MGH. OnCall facilitates creation of problem-based structured clinical notes. Rather than creating and saving flat or unstructured notes, notes in Oncall are comprised of a variety of sections: reason for visit, problem, medications, allergies and a dedicated section for each problem. Each of these entities in Oncall has an associated concept name. *OnCall* classifies and stores data using COSTAR (Computer Stored Ambulatory Record) codes [34]. This coding system granularly stores symptoms, signs, diseases and medications using unique identifiers.

Microsoft SQL Sever 2005 databases were used. Data extraction was performed using Microsoft SQL Server Management Studio 9.0 in collaboration with software engineers and database experts. Eclipse Platform 3.3.2 with Pydev 1.4.7.2843 were used to write code in Python™, a high-level programming language. For demonstration purposes ActivePython 2.6.2.2 was used in the terminal of a MacBook Pro running Mac OS X 10.6.2 (10C540) Darwin Kernel 10.2.0 and Matplotlib 0.99.1 was used to display data elements.

Develop a model characterizing patients using existing transactional electronic medical record data.

We identified patients who had an active code of hypertension (MHAB1) and were also patients of the Internal Medicine Associates (IMA) clinic between 7/1/2004 and 9/29/2009. We used all the following identifiers to help classify our medical notes: heart failure, post-myocardial infarction, proteinuric chronic renal failure, high coronary disease risk, diabetes mellitus, angina pectoris, atrial fibrillation, atrial flutter, benign prostatic hypertrophy, essential tremor, hyperthyroidism, migraine, Osteoporosis, Raynaud's syndrome, angioedema, bronchospastic disease, depression, liver disease, pregnancy, second or third degree heart block (see Table 1).

Patients' current and past medications used to treat their hypertension were also collected. To simplify our model, medications were classified into drug-families by mechanism of action (e.g. beta blocker for propranolol). We gathered data for medications from nine different drug families including: thiazides diuretics, non-thiazides diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), beta blockers (BB), adrenergic receptor agonists (AA), adrenergic receptor blockers (AB), calcium channel blockers (CCB), and vasodilators (Appendix A). We created a binary data matrix utilizing drug family names as columns and patients' medical record number (MRN) as rows. We gathered the prescribing status of antihypertensive drugs and group them under their drug family on each patient included. We assigned a value of 1 when a patient was taking a medication corresponding to a certain drug family, and a value of 0 when he was not taking it (Figure 2).

MRN	Thiazides	Non-Thiazides	ACEi	ARB	AB	BB	CCB	AA	Vasodilator
Patient 1	1	0	1	0	0	0	0	0	0
Patient 2	0	0	0	0	0	1	0	0	0
Patient...	...	...	...	...	...	...	...	...	...

Figure 2. Columns: Type (by drug family) of antihypertensive taken (1) or not taken (0) by individual patients (Rows). The table shows: Patient 1, who is taking a double drug regimen including a thiazide diuretic and ACEi. Patient 2, who is taking a beta blocker as single drug regimen.

Attempted Methods

Initially, to narrow down our feature space, we attempted to directly find variables that predicted the success or failure of a certain drug treatment. At that time, the plan was to create a logistic regression model for each family of drugs (e.g. model 1 (beta blockers), model 2 (ACEi), etc.) and use these regression models to discriminate between patients who succeed or failed a certain drug regimen. Although some heuristics were used to mine the first set of variables, specific caution was taken to avoid bias selection. Therefore, at first, several hundred variables were collected with the inclusion of several clinical findings unrelated to the treatment of hypertension. Some examples that appeared to be significant from this heuristic/regression included: allergies, level of physical activity, presence of specific types of headaches, neurodegenerative diseases, cardiac diseases, rheumatologic disorders, psychiatric disorders and the status of other clinical findings. Next, this patient's dataset was loaded into Weka 3-6-1 and feature selection algorithms (e.g. CfsSubsetEval, InfoGainAttributeEval) were run. This feature selection process yielded medication knowledge linkages that seemed to indicate clear causality or known prescribing indications. For example, having an ACEi was found to be associated with people who had taken ACEi at one time. Being a diabetic was also found to be associated with ACEi, a common indication for ACEi use. Similarly, having a history of a myocardial infarction was found to be associated with the use of BB, another compelling indication. In the end using this approach would result in decision support for indications or clear associations. While this in itself might be valuable in another context, this would not help us in discovering a model for patient similarity.

We then attempted to use the results of this exercise to find a logistic regression model with good discrimination (using area under the curve, AUC) and calibration (using Hosmer-Lemeshow, HL) for each family of drugs. For this, the original dataset was divided in subsets that contained only those patients who succeed or failed taking a certain drug class (one dataset was created for patients who took or were taking BB, another dataset for patients who tool or were taking ACEi, etc.). Hence, each regression model could be trained and tested with data pertaining to a specific drug

family and drug families that would work for a given patient could be predicted. Two regression models were created, one for ACEi and one for BB. Dependent variables were drugs families being predicted (ACEi or BB) and independent variables were those clinical findings found to be associated with the outcome. 10-fold cross-validation was used to train both models (2/3 of the original dataset) and then they were tested on unseen data (1/3 of the original dataset). Unfortunately, after attempting several different models, adequate discrimination power was not achieved. The receiver operator characteristics (ROC) curves from both models were close to randomness on unseen data. Similar results were obtained when running other classifiers such as: Naïve Bayes, Bayesian or Neural Networks. None of these approaches were successful enough to warrant further exploration.

Redefining the feature space

Current indications for individualizing antihypertensive therapy that are part of The Seventh Report of the Joint National Committee (JNC) [29] were used as the new variables to describe a patient's profile. Each indication was matched with its homologous *OnCall* COSTAR code (Table 1). To adjust for demographic factors variables found to be an influential factor in hypertension such as gender, race and age were included in the creation of a patient vector [36]. Since high coronary risk (one of JNCs indications) has no homologous COSTAR code in OnCall, a high coronary risk score was developed. A patient was considered to have high coronary risk score when either: (1) the patient had a history of coronary artery disease; or (2) the patient had at least two of the following three problems: diabetes, smoking or obesity.

Patient's status for every JNC indication was obtained and a binary matrix was created with JNC indications as columns (from now on referred to as variables or attributes) and patients as rows (represented with their medical record number). Cells were assigned a value of 1 when an attribute was present and 0 when an attribute was absent (Figure 3).

MRN	GENDER	CHF	MI	CRI	DM	AP	AFIB	...
Patient 1	1	1	1	0	1	0	0	...
Patient 2	0	0	0	1	1	0	0	...
Patient ...	...	...	...	...	...	...	...	...

Figure 3. Columns: comorbid indications (from JNC VII report) to account for when prescribing antihypertensives. Rows: patients in the dataset. Cells are binary, a value of 1 reflects the presence of the disease and a value of 0 the absence. The table shows: Patient 1, a male with congestive heart insufficiency, a history of myocardial infarction and diabetes. Patient 2, a female with chronic renal insufficiency and diabetes.

A SQL query was used to mine the final dataset generating a single matrix containing: drug regimen, blood pressure measurements and comorbid indications for individualizing antihypertensive therapy from the JNC VII for every patient. The resulting data was saved and exported as a comma separated values (.CSV) dataset file for later use.

Using the model to build a collective experience decision support system (CEDSS) framework.

Collaborative Filtering techniques were used to discover which antihypertensives were suitable for a specific index patient based on the previously described dataset. This dataset combines the JNC 7 considerations for individualizing antihypertensive therapy (expert generated) and the experience of hundreds of physicians whose prescriptions were stored in the OnCall database.

In order to find which patient profiles matched an index patient, two different algorithms that measure similarities were used. The first, cosine similarity, draws on trigonometric functions to measure the cosine of the angle between two vectors. Hence, when representing a patient's profile from our dataset as a vector, we can measure the cosine of the angle formed between other patients in the dataset and the index patient profile of interest, also represented as a vector (Figures 4,5,6). The second algorithm used, computes the Euclidian distance between two points. Here, a patient's profile is represented as a point in the Euclidian space. The distance between the point corresponding to the index patient and the points corresponding to the other

patient's profiles are measure (Figure 7).

The dataset previously exported as .CSV was imported into Python™ using the native *csv.DictReader* function. The dataset was imported as a Python™ dictionary data structure. This data type is a hash table that pairs keys with values. Therefore, for each patient in the dataset, the variable names (column names) became the dictionary keys and their values became the dictionary values. The dataset, now in a Python™ dictionary format, was fed to the above-mentioned similarity algorithms. Euclidian distance was measured using Segaran's algorithm and NumPy extension (a Python™ library with high-level mathematical functions) was used to compute the dot product and norm of the vectors to calculate cosine similarity. Segaran's ranking algorithm was used to order the resulting matches that were most similar [37,38]. All the results shown in this thesis were obtained using the cosine similarity algorithm.

$$\cos(\vec{x},\vec{y}) \equiv \frac{\sum_{i=1}^{n} x_i y_i}{\sqrt{\sum_{i=1}^{n} x_i^2}\sqrt{\sum_{i=1}^{n} y_i^2}}$$

Figure 4. Cosine similarity formula.

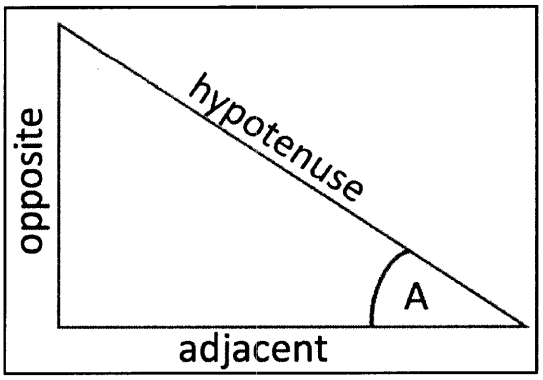

Figure 5. Cosine similarity draws on the trigonometric cosine function to correlate the angles a triangle to the length of its sides. The cosine of angle 'A', is the ratio of the adjacent side to the hypotenuse of the triangle.

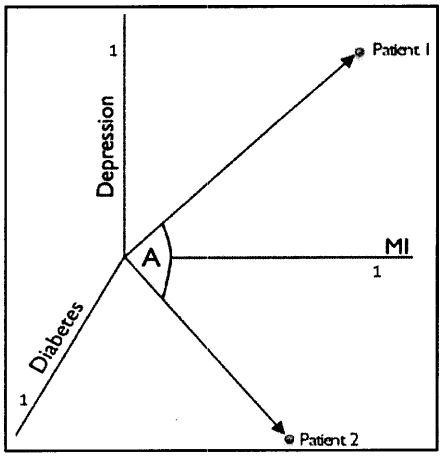

Figure 6. Shows two patients (patient 1 and patient 2) represented as vectors (using their disease profile). For practical purposes, the feature space is simplified and reduced to three binary dimensions: depression, myocardial infarction (MI), and diabetes. Calculating the cosine of angle 'A' would return the cosine similarity between patient's 1 and 2. Notice that Patient 1 and 2 are similar in that both have had a MI.

$$d(p,q) = \sqrt{(p_1 - q_1)^2 + (p_2 - q_2)^2 + \ldots + (p_n - q_n)^2} = \sqrt{\sum_{i=1}^{n} (p_i - q_i)^2}$$

Figure 7. Euclidean distance formula.

Defining success

We defined a successful drug regimen as the one that is maintained for at least 6 consecutive months and keeps blood pressure measurements under 140/90 mmHg. Only patients with systolic pressures under 140 mmHg *and* diastolic pressures under 90 mmHg were classified as controlled.

Two more separate Python™ dictionaries were created: One containing the actual drug regimens taken by each patient in the dataset, and the other containing the average systolic and diastolic blood pressure measurements recorded after the last drug activity (medication start, renew, or dose change).

In summary, three distinct hash tables were created. The first one included all patient significant variables (from the JNC VII indications) and was used to find similarity

between patients using both methods described above. Once similar patients were found, the remaining two hash tables were used to retrieve these patients' most current drug regimens and their average blood pressure measurements. Resulting data was aligned and reported.

RESULTS

Data description

Twelve-thousand-three-hundred-forty-seven patients with hypertension followed at MGH IMA clinic between July 2004 and September 2009 were found. The vast majority of these patients were treated with antihypertensive medications. Multiple drug regimens were more commonly used than single drug regimens. The mostly used single regimen was ACEi and the most taken multiple drug regimen was a combination of thiazides and ACEi. Figures 8 to 16 detail demographics and drug regimens used by patients in this dataset.

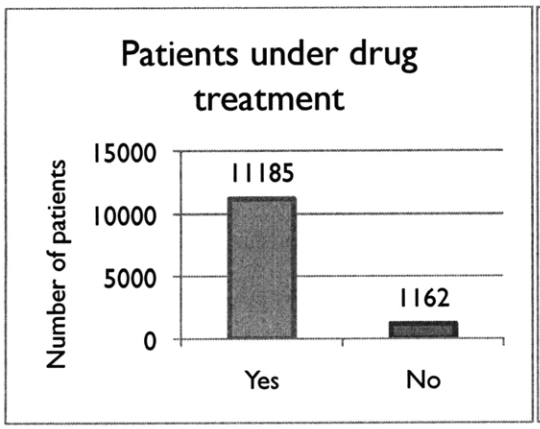

Figure 8. Number of patients with and without pharmacological treatment.

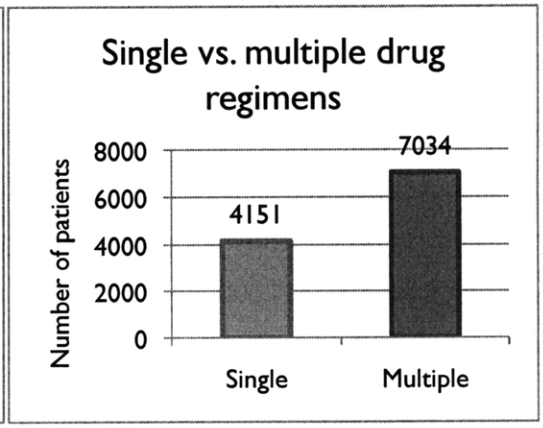

Figure 9. Number of patients using single and multiple drug regimes

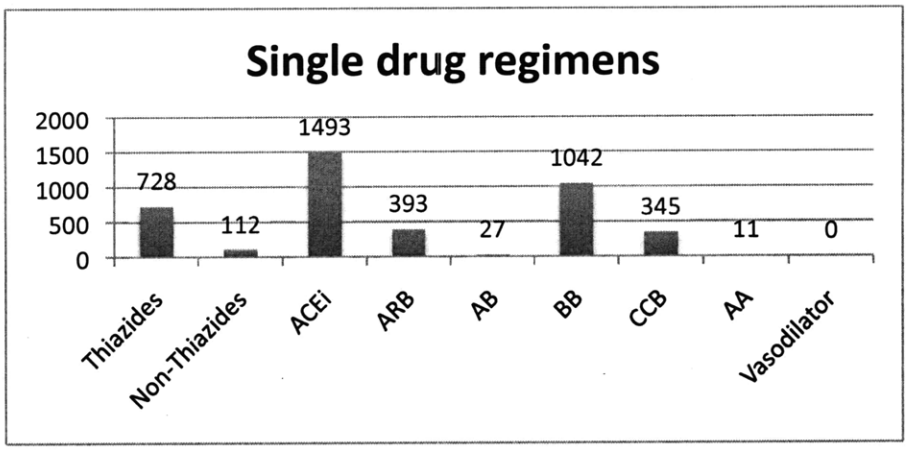

Figure 10. Single drugs regimens by number of patients taking them.

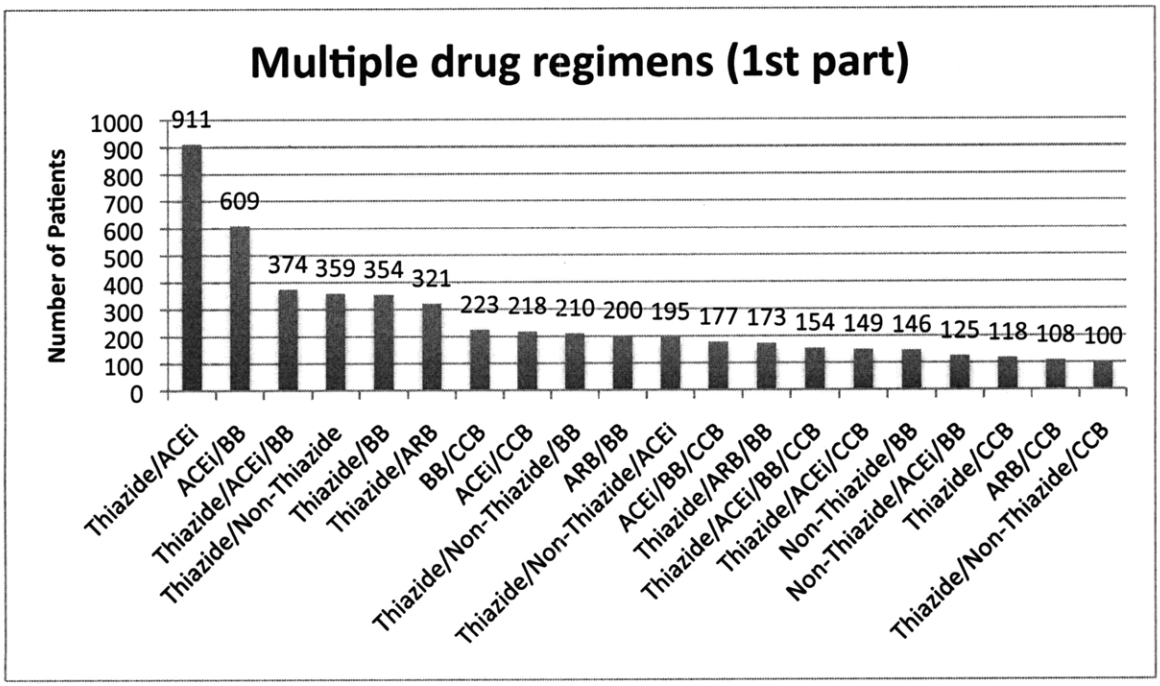

Figure 11. Multiple drug regimens by number of patients taking them (continued in next figure).

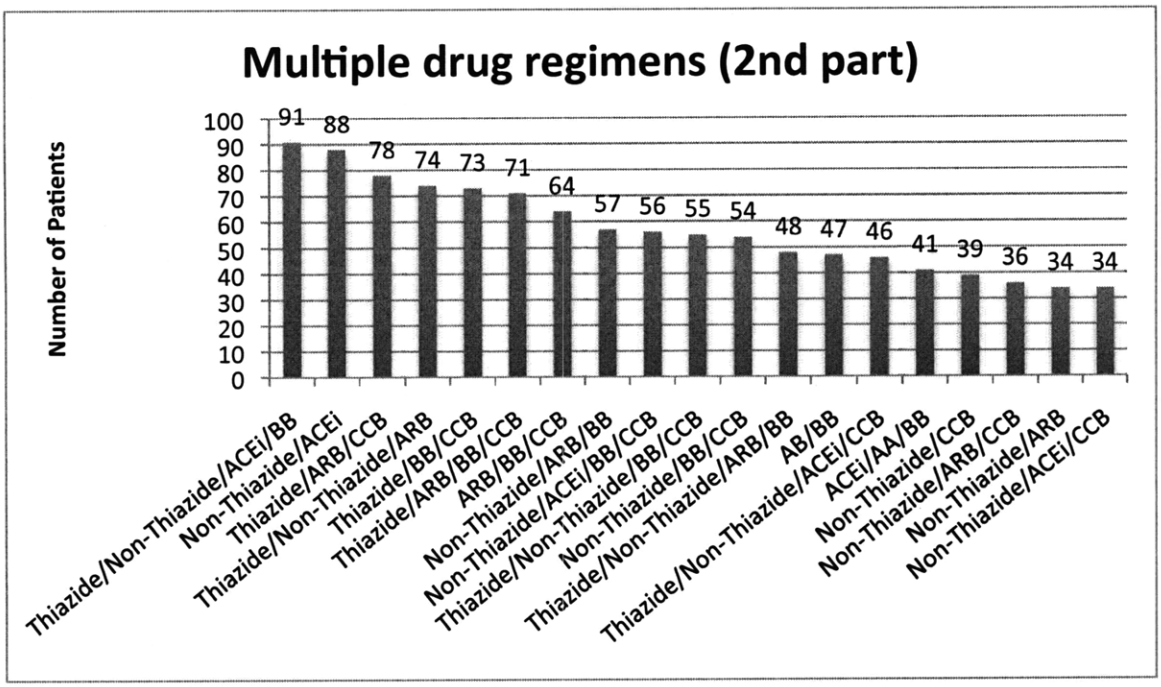

Figure 12. Multiple drug regimens by number of patients taking them (the 724 patients not shown were taking other less frequent multiple drug regimens).

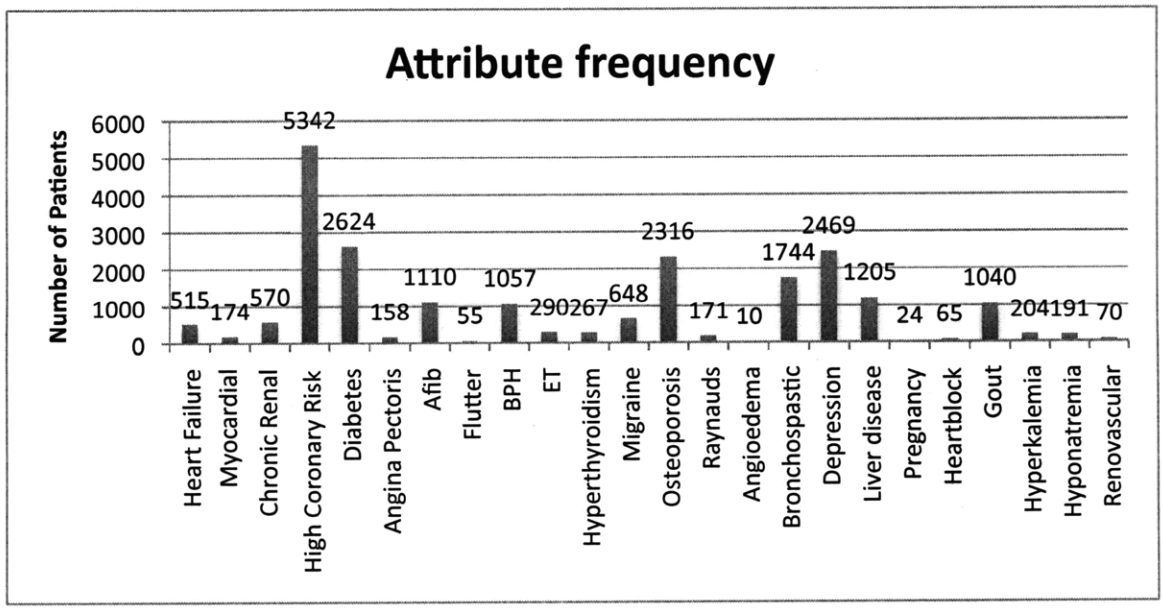

Figure 13. Profiles (by attribute frequency) of the cohort of patients with hypertension used.

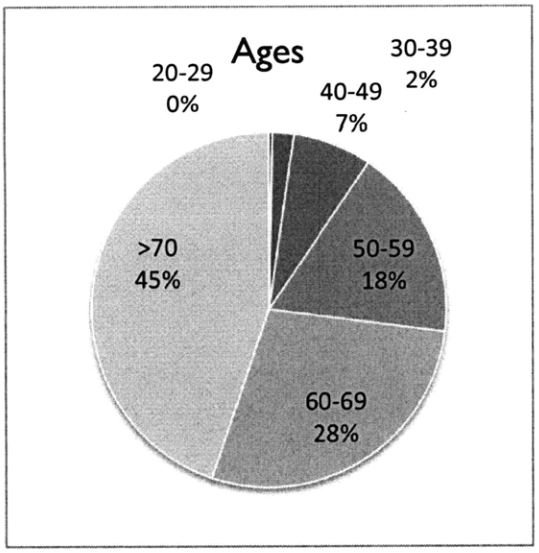

Figure 14. Cohort ages as percentages.

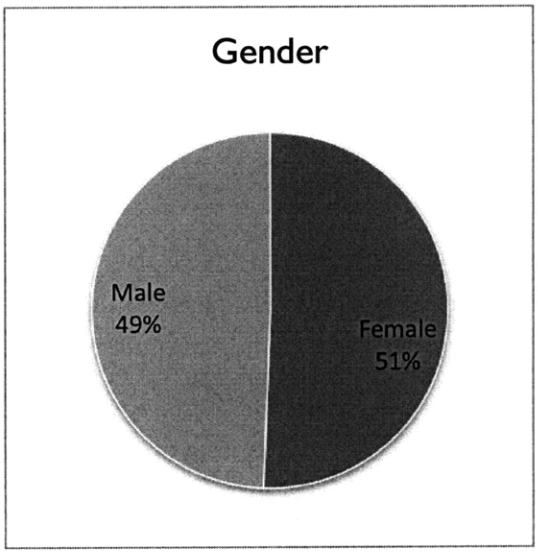

Figure 15. Cohort gender as percentages.

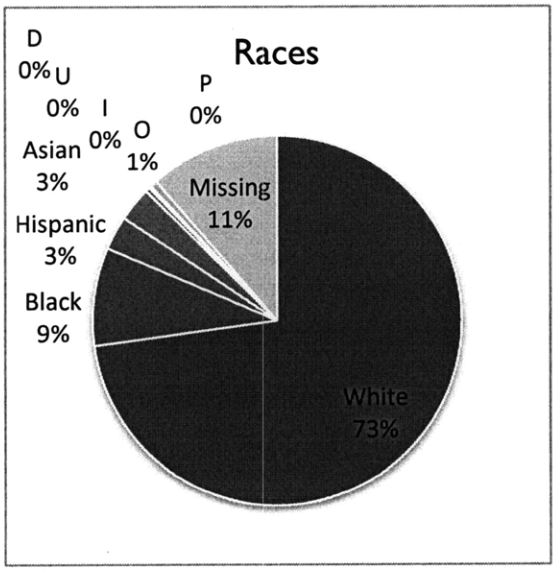

Figure 16. Cohort races as percentages.

Using the CEDSS in the clinical domain of hypertension towards predicting a successful drug regimen based on a patient's phenotypic disease profile.

A Python™ back-end application that computes similarity among patients using a given set of attributes was built. The application takes a patient's MGH medical record

number and returns data visualizations in Portable Network Graphics (PNG) format.

To exemplify the application's output, two different patients seen at the IMA clinic and known to have hypertension were selected.

Patient A

Patient A is a 75-year-old white male with past medical history significant for alcohol abuse, degenerative joint disease and erectile dysfunction. He is obese and an active smoker and has high coronary risk. Figure 17 shows results based on patients that were more than 80% similar to patient A.

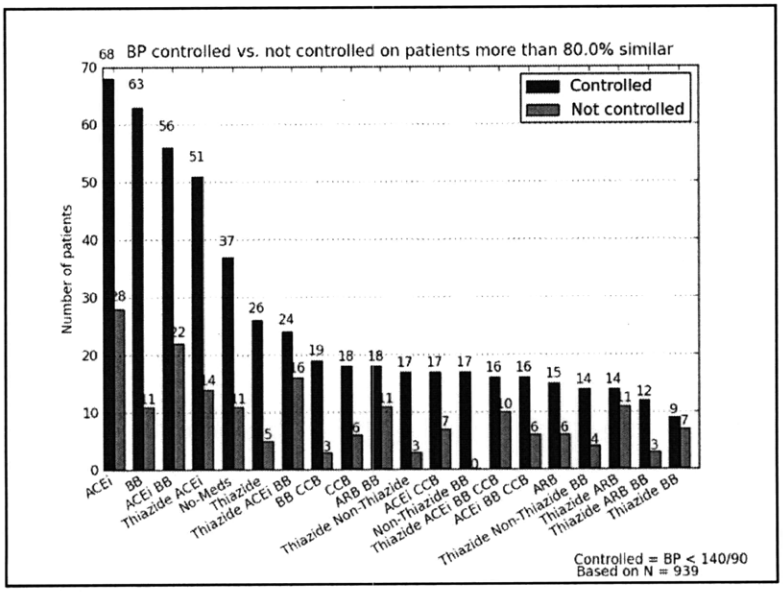

Figure 17. Pharmacological regimens recommend to patient A when looking for 80% or more similar patients. A total of 939 similar patients were found (N). The chart displays up to the first 20 most used regimens that controlled the blood pressure on these patients. The frequency of controlled patients (blue) is paired with the frequency of patients not controlled (red) under each drug regimen.

The chart allows comparing similar patients by drug regimens and blood pressure status (controlled vs. not controlled). Regimens are ordered by frequency of use. Given that there are some patients with hypertension that are taking no medications, "No-Meds" also appears as a suggested treatment regimen. For this specific

example, 939 patients (or 7.6% of the population at large) were more than 80% similarity to index patient A. This large similar patient population is explained by the fact that patient A is quite typical in this cohort: He is older than 70 (45% of the cohort), his race is white (73% of the cohort) and from his comorbid state, the only significant factor to account for when computing disease similarity to prescribe a drug regimen is that he has a high coronary risk (found in almost 50% of the cohort). Consequently, in such typical cases, tighter collective filtering must be applied for any meaningful use. Figures 18 to 21 show the results obtained when looking into patients that were more than 85%, 90%, 95% and 100% similar to patient A.

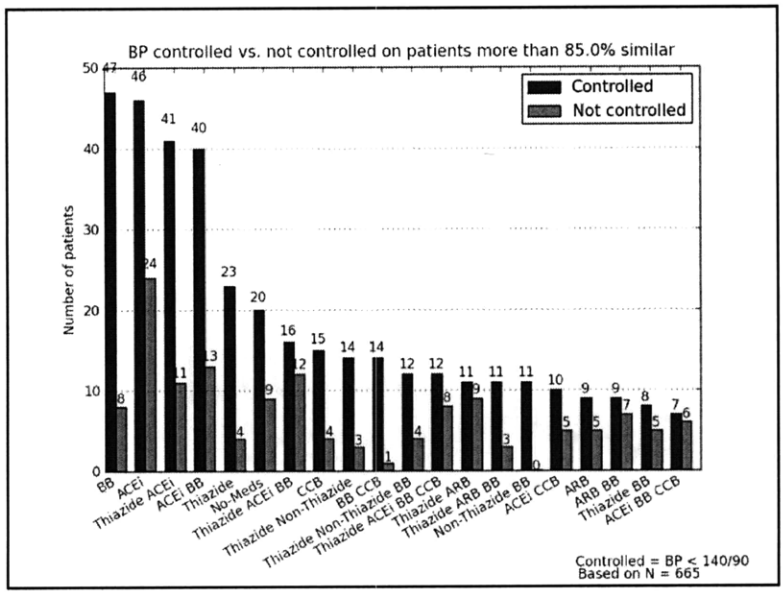

Figure 18. Pharmacological regimens recommend to patient A when looking for 85% or more similar patients. Notice a decrease in the amount of similar patients found (N=665)

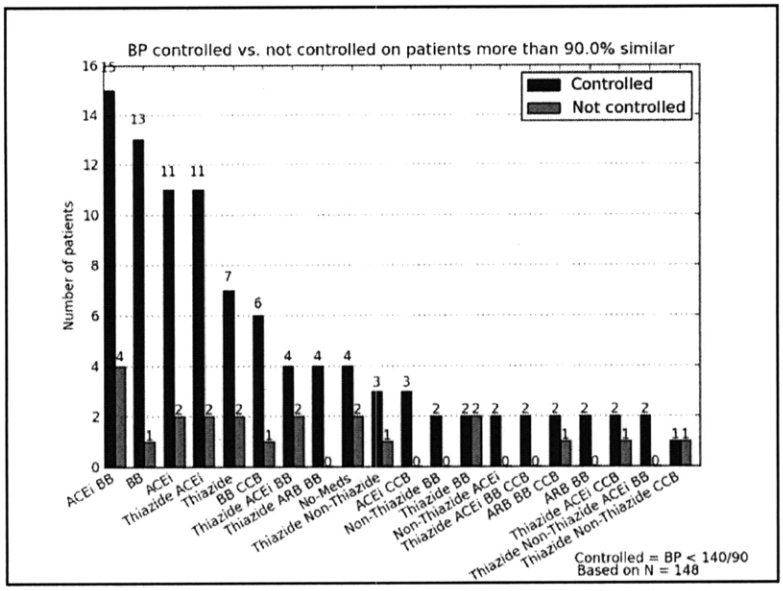

Figure 19. Pharmacological regimens recommend to patient A when looking for 90% or more similar patients. Notice another decrease in the amount of similar patients found (N=148)

We observe that as the model is tuned with varying similarity sensitivities, the accuracy and power of the recommendations varies. The recommendations with 80% similarity or more are based on 939 patients while the ones with 100% similarity are based on 148 patients. Naturally, as the demand of recommendations based on higher percentage similarity increases, we will find less patients meeting the criteria. There is a clear trade off between percentage similarity and the number of patients on which the recommendations are based. Interestingly, the order of recommended treatments also varies as the percentage similarity changes. The most frequent recommended regimen (left side of the chart) when looking into 80% similarity or more was ACEi; it later became BB with 85% similarity or more and finally became ACEi combined with BB with 90% similarity or more. Another interesting finding is that when looking into percentage ratios of the suggested regimens and weighting these by the number of patients (N) using those regimens, BB is consistently the best single recommendation for patient A (Figures 22 and 23). Incidentally, when we looked back into the medical record, we corroborated that in fact patient A takes 50 mg per day of toprol XL, a beta blocker, and his last documented blood pressure measurement shows that he is controlled (his blood pressure was 138/86 on 6/16/2009).

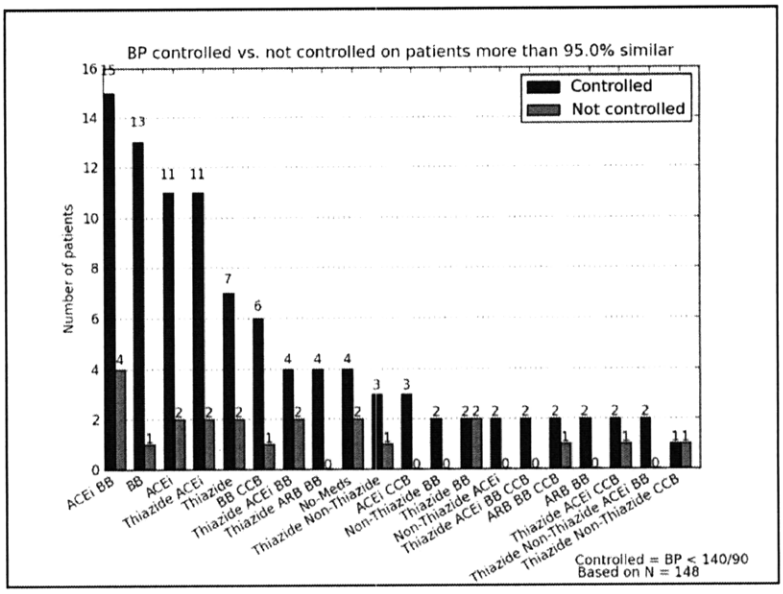

Figure 20. Pharmacological regimens recommend to patient A when looking for 95% or more similar patients. Notice that the amount of similar patients found is the same as when we looked for 90% similarity (N=148).

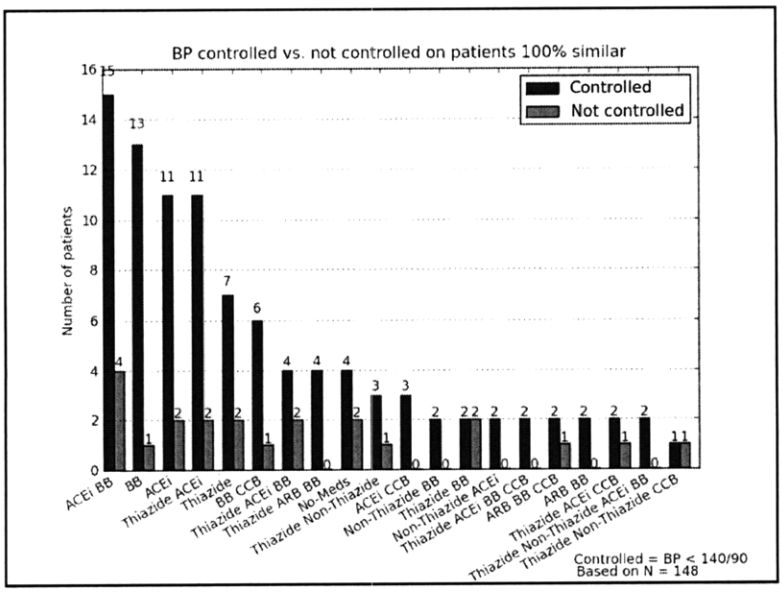

Figure 21. Pharmacological regimens recommend to patient A when looking for 95% or more similar patients. Notice that the amount of similar patients found is the same as when we looked for 90% and 95% similarity (N=148).

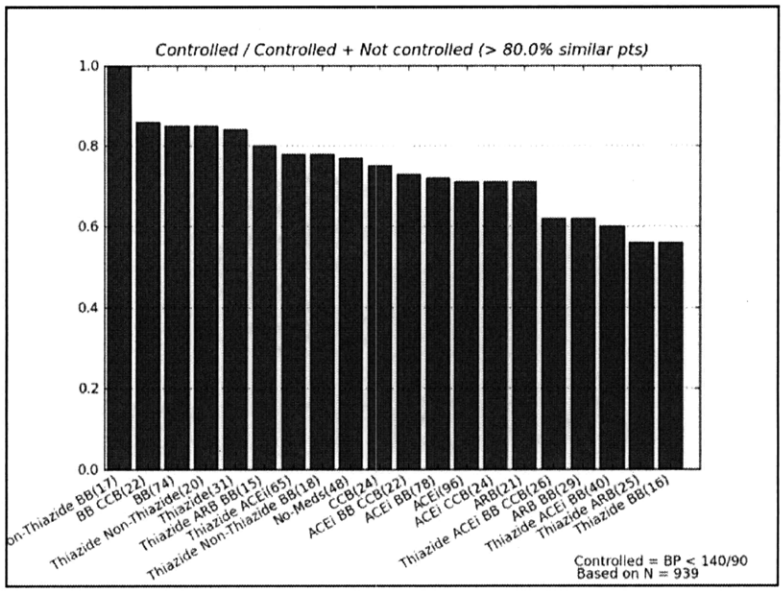

Figure 22. Percentage ratio of recommended regimens for patient A based on patients that were more than 80% similar. The number between parentheses within each recommended regimen indicates the amount of patients controlled by that regimen (weight). Notice that BB is the single regimen with better ratio and weight.

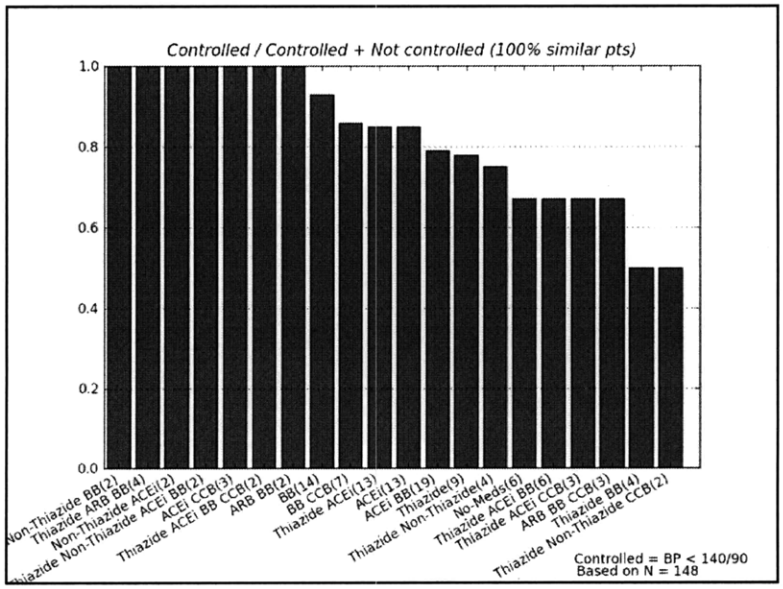

Figure 23. Percentage ratio of recommended regimens for patient A based on patients that were 100% similar. The number between parentheses within each recommended regimen indicates the amount of patients controlled by that regimen (weight). Notice that BB is the single regimen with better ratio and weight.

Patient B

Patient B carries a more complex comorbid state and therefore constitutes a good contrasting example. He is a 60-year-old white male with a significant medical history. He is status post myocardial infarction and has heart failure, chronic renal failure (s/p renal transplant), type I diabetes mellitus, osteoporosis, bronchospastic disease (asthma) and liver disease (hepatitis B). Since he has a history of coronary artery disease, he also classifies as having high coronary risk. As a result, his disease profile is (fortunately) not easy to match (Figure 24).

However, when we attempted to discover patients that were 80% similar to patient B we found only two patient matches. Thus, in order to have more medication recommendations from which to choose, we were required to decrease similarity sensitivity (patients displayed by the application are less similar to the index patient) with a resulting tradeoff in accuracy of recommendations. Figures 25 to 28 show the results obtained when we looked into patients that were more than 75%, 70%, 65% and 60% similar to patient B.

As expected, even though only 2 patients were initially similar to patient B, this number jumped to 887 when we decreased the demand for similarity to 60%. Again, different single and multiple drug regimens were recommended. However, when we looked into the percentage ratios of the suggested regimens weighted by the number of patients taking the regimen, thiazide combined with an ACEi and ACEi combined with a BB were the best recommendation for patient B.

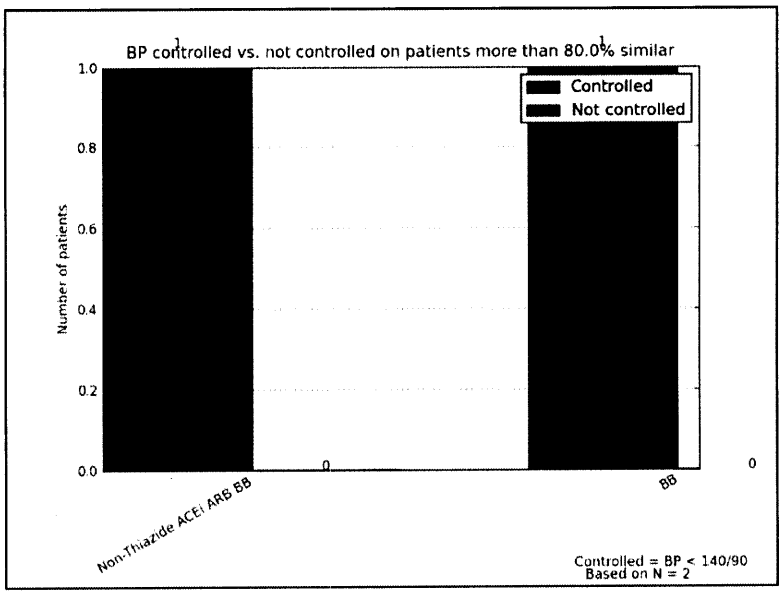

Figure 24. Pharmacological regimens recommend to patient B when looking for 80% or more similar patients. 2 similar patients were found (N).

While these are valid recommendations, the IMA EMR reports that patient B was receiving a triple drug regimen. His blood pressure was controlled using 20 mg of lisinopril (ACEi) per day, 150 mg of irbesartan (ARB) per day and metoprolol tartrate (BB) 25 mg every 8 hours (his blood pressure was 103/81 on 11/26/2009). Interestingly, one of the two recommendations initially given to patient B (a non-thiazide combined with ACEi, ARB and BB with 80% similarity) was very close to his actual regimen.

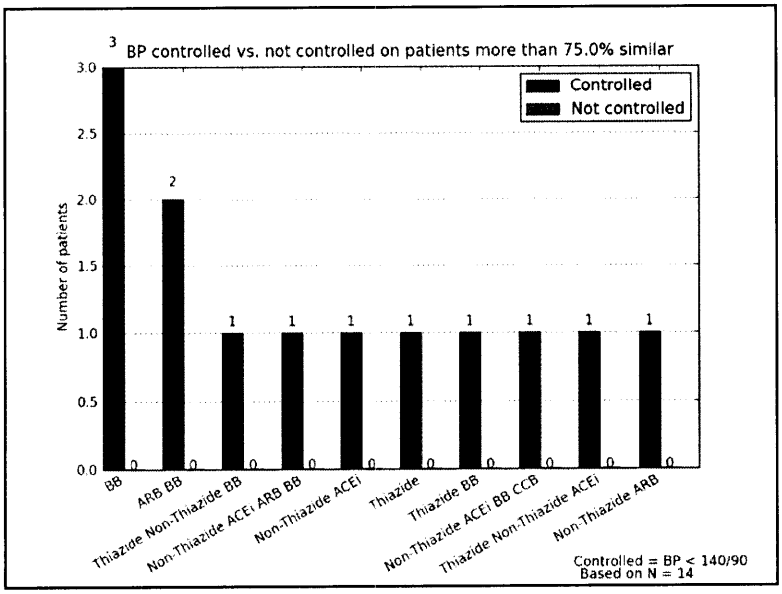

Figure 25. Pharmacological regimens recommend to patient B when looking for 75% or more similar patients. Notice an increase in the amount of similar patients found (N=14).

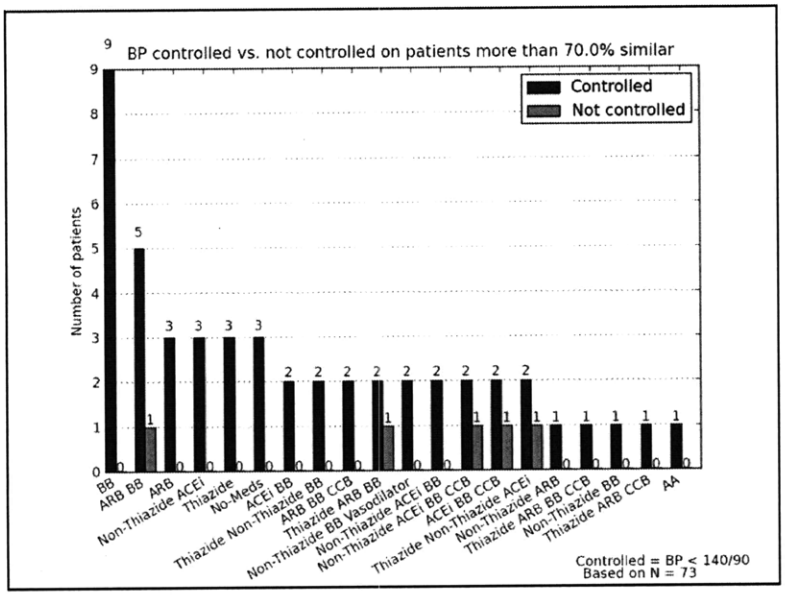

Figure 26. Pharmacological regimens recommend to patient B when looking for 70% or more similar patients. Notice another increase in the amount of similar patients found (N=73).

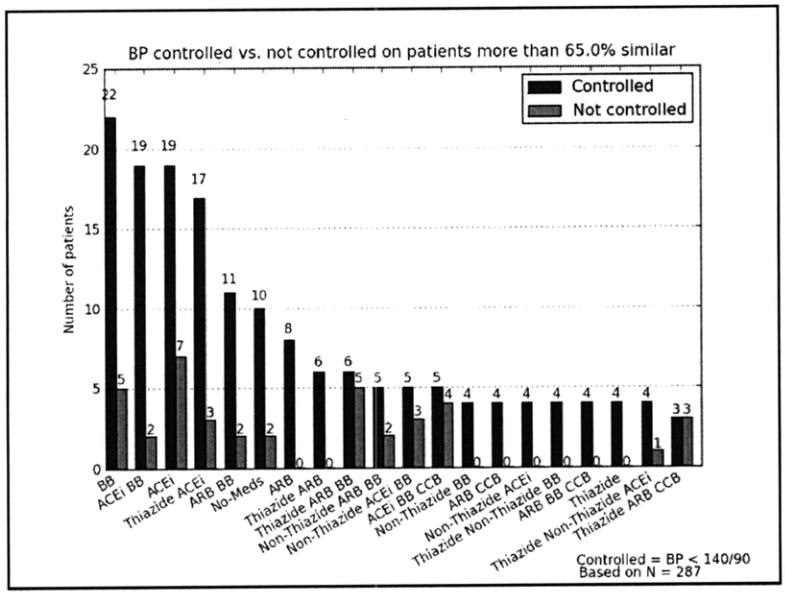

Figure 27. Pharmacological regimens recommend to patient B when looking for 65% or more similar patients. Notice another increase in the amount of similar patients found (N=287).

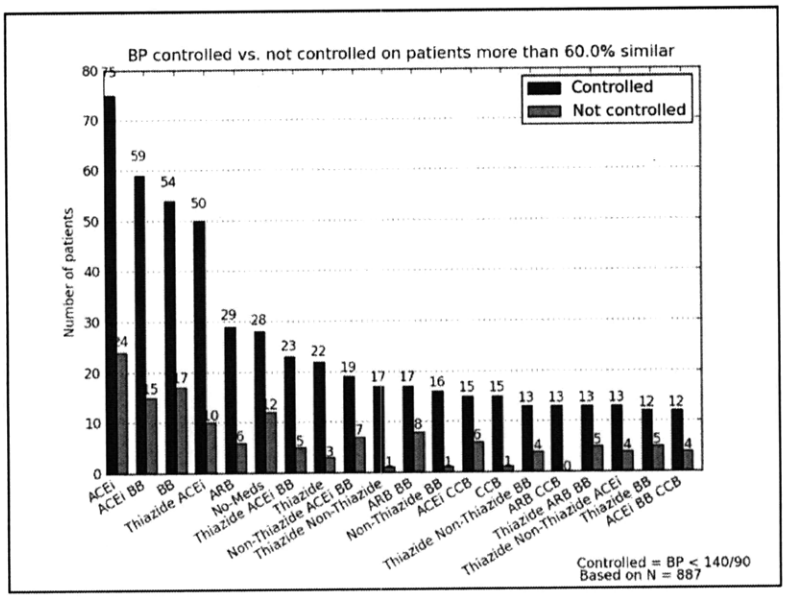

Figure 28. Pharmacological regimens recommend to patient B when looking for 65% or more similar patients. Notice another increase in the amount of similar patients found (N=887).

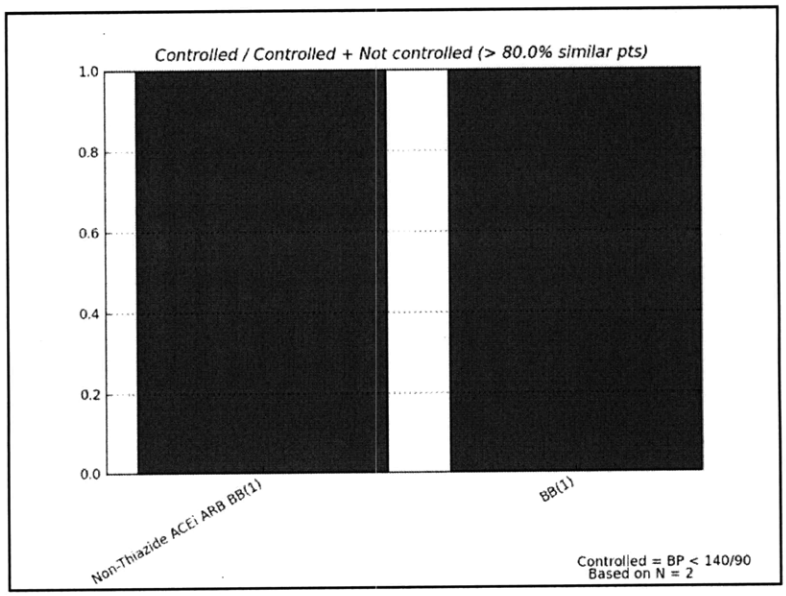

Figure 29. Percentage ratio of recommended regimens for patient B based on patients that were more than 80% similar. The number between parentheses within each recommended regimen indicates the amount of patients controlled by that regimen (weight). Notice the regimen on the left (non-thiazide, ACEi, ARB, and BB) which is very close to the actual regimen taken by the patient.

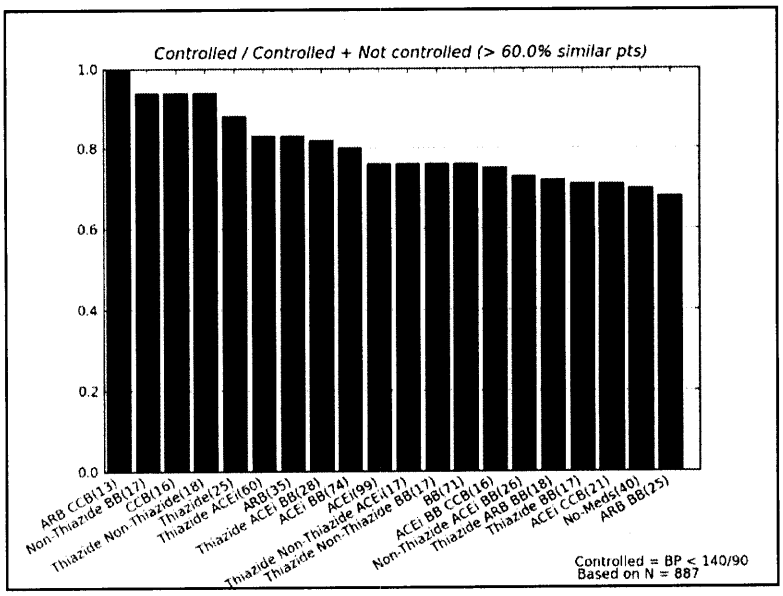

Figure 30. Percentage ratio of recommended regimens for patient B based on patients that are more than 60% similar. The number between parentheses within each recommended regimen indicates the amount of patients controlled by that regimen (weight). When accounting for both (ratio and weights), thiazide with ACEi and ACEi with BB are the best recommendations for this patient.

Providing Clinical Rationale

According to Teach and Shortliffe, health care professionals will often reject a system that offers advice without providing the clinical rationale, even if it has impressive diagnostic accuracy and an ability to provide reliable treatment plans [14].

Results given for patient B where corroborated manually. On OnCall, we selected the patient who was most similar to patient B (when using more than 80% similarity) to learn which attributes were found to be similar by the algorithm. The most similar patient found, Patient C, is a 65 year-old white male whose mayor problems are: heart failure, diabetes mellitus, hypertension, a history of anterior wall myocardial infarction, coronary artery disease (and thus high coronary risk) and presumably chronic obstructive lung disease. While not a perfect match, patient C is the most similar to patient B with 85.28% cosine similarity.

Accordingly we designed this application to provide clinicians with the rationale

behind recommendations. By selecting a particular regimen, a chart is displayed detailing the disease profiles observed on similar patients who are well controlled on that particular regimen. In addition, diseases percentages from the entire patient cohort are shown as a reference. Figures 31 and 32 are disease profile charts of two possible different regimens considered for patient B when looking into patients more than 60% similar.

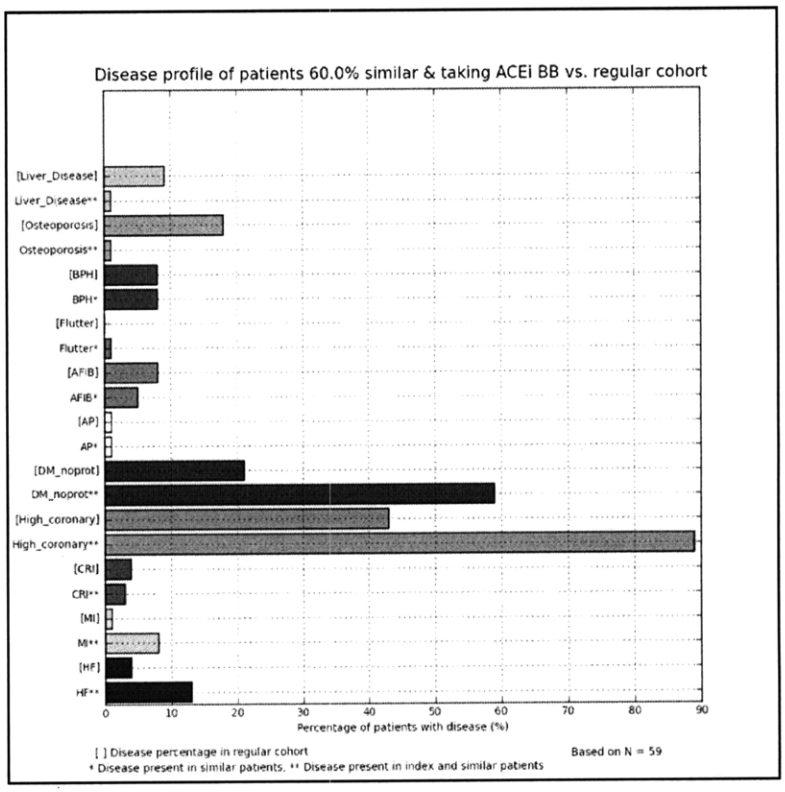

Figure 31. Percentages of comobordities present in a group of similar patients taking a certain drug regimen. In this case ACEi and BB. On the vertical axes, each disease state is represented with a different color. Two horizontal bars are showed for each disease present in the group. The first bar is a reference of the disease percentage present in the entire cohort (between square brackets). The second bar (with the same color) is the actual percentage of disease in the group taking the regimen (ACEi and BB in this case). Notice that the disease name in the second bar is tag by one star (*) when the disease is present on similar patients or a double star (**) when the disease is present in both, similar patients and the index patient.

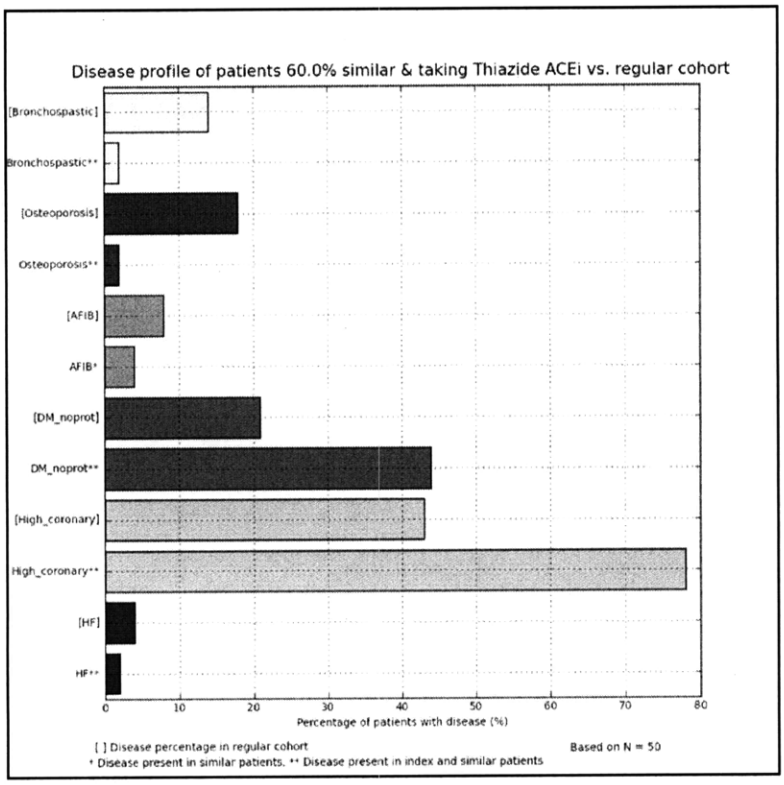

Figure 32. Percentages of comobordities present in a group of similar patients taking a certain drug regimen. In this case thiazide and ACEi. On the vertical axes, each disease state is represented with a different color. Two horizontal bars are showed for each disease present in the group. The first bar is a reference of the disease percentage present in the entire cohort (between square brackets). The second bar (with the same color) is the actual percentage of disease in the group taking the regimen (thiazide and ACEi in this case). Notice that the disease name in the second bar is tag by one star (*) when the disease is present on similar patients or a double star (**) when the disease is present in both, similar patients and the index patient.

Predictive Ability for Randomly Chosen Patients

To determine the application's predictive ability, 10 different randomly chosen patients with controlled blood pressure were tested using the application. Each patient was tested using a population of at least 100 patients (allowing for variation in similarity percentage). Accuracy was calculated by factoring: (1) the percentage of blood pressure control (with respect to other predicted regimens) and (2) the number of similar patients on that regimen. Predictive rankings were calculated. Table 2 shows the results

of this study.

Patient ID	Number of similar patients evaluated (Min n = 100) (% similarity)	Actual regimen predicted within the first 5 regimens?	Prediction Place	Actual regimen
D	103 (90%)	No	8th	Thiazide,ACEi,BB
E	119 (75%)	Yes	3rd	BB, ACEi, Thiazide
F	311 (67%)	Yes	1st	ACEi
G	195 (91%)	Yes	4th	CCB,ACEi
H	148 (100%)	Yes	1st	ACEi,BB
I	142 (85%)	No	-	BB,CCB,ACEi
J	122 (70%)	Yes	2nd	Thiazide,ACEi
K	103 (90%)	Yes	3rd	BB
L	137 (90%)	Yes	5th	Thiazide,Non-Thiazide,ACEi
M	205 (80%)	Yes	1st	Thiazide

Table 2. Results from 10 randomly tested patients.

DISCUSSION

Strengths and limitations

This work shows that using a computerized case-based reasoning (CBR) approach to treat patients based on the outcomes of similar patients successfully treated in the past is technically feasible. We developed a model that characterizes patients using EMR transactional data and a framework that finds similarities among a large pool of patients to predict successful drug regimens for the treatment of hypertension. The data used by this framework represents both clinical guidelines currently used by the medical community and the collective prescribing habits and outcomes of similar patients. In this way we arrive at recommendations that are both evidence-based *and* personalized. The complexities of a large multidimensional dataset are clearly and graphically summarized with charts that could be easily presented as point of care decision support. These interfaces also enable physicians to understand the clinical rationale and explore the underlying data.

On the other hand, this work is proof of concept and has room for improvement. First, only medication class was used as a variable; predictions using medication dosing is not yet not supported. Therefore, comparisons between high vs. low doses of a same drug are not yet possible. For example, a patient's hypertension might not be controlled with a low dose of a particular medication, a higher dose might be successful without the use of a different class.

Additionally, the application does not yet take the current pharmacological state of an index patient into account. Thus every patient is though as a 'new' patient regardless of current or previously prescribed medications. Also, due to the very nature of CBR, recommendation power is positively influenced by a large patient pool. Therefore complex patients remain a predictive challenge without a change in similarity sensitivity and a corresponding drop in accuracy. A logical workaround to this problem is to increase the size of the dataset with the inclusion of data from additional settings (clinics, hospitals, regions, etc.) thereby adding to the number of similarly unique patients. Also, for the examples shown here, arbitrary similarity percentages were

selected (from 60% to 100%). We would prefer recommendations to be based on the percentage that minimize patient's clustering error. As future work, a rigorous a dataset cluster analysis could be performed where the percentage similarity that returns the least mean squared error could be use by the application. Also, features used to compute patients' similarity were equally weighted. In next iterations, assigning variable feature weights based on merit or importance should be explored.

In the real world, a patient may not be immediately entitled to use every antihypertensive drug available, yet insurance formulary information is not currently part of the application. There are hundred of possibilities, but health insurance companies cover only a portion of these within their drug formulary. Therefore, for practical purposes accounting for a patient's insurance must be addressed in the future.

Patient medication adherence plays an important role as to which medications are actually effective [39], but adherence is not yet captured in this model. Adherence is not the only factor however as physician's unfortunately often fail to intensify treatment when needed [40]. Such decision support tools could help with physician recognition of undertreatment and regardless of regimen used [41].

More complete and accurate blood pressure measurements would also help to refine this system. Currently only blood pressure measurements recorded in OnCall were used. Nearly one third of these data points had missing or incorrectly formatted data. Patients with missing or incorrectly formatted data were discarded reducing the number of similar patients on whom to base the recommendations. We foresee many ways to solve this problem. One simple solution would be to improving the reliability EMR entry interface with more structured data fields and data validation. Patients themselves could contribute by reporting home blood pressure monitoring via personal health records (PHR) like Google Health™, Microsoft HealthVault™ or iHealthSpace™ [48,49] increasing the accuracy and robustness of the outcome (blood pressure control in this case).

Future work

Specialized populations with tighter JNC control requirements could also benefit from this system, such as diabetic or chronic renally impaired patients with treatment

goals of 130/80 mmHg (rather than 140/90 mmHg). Similarly, if an index patient is a stage two hypertensive (> 160/100 mmHg), the application could only recommend treatment regimens based on two or more drugs [50].

Ultimately to prove true utility, this approach should be evaluated in a prospective randomized controlled trial. While there might be many ways to perform this trial, one thought would be differentially display CEDSS recommendations at the point of antihypertensive prescribing. We hypothesize that such an approach might result in quicker time to blood pressure control, fewer and less severe adverse events, fewer number of drug changes and/or number of dose changes required to achieve control.

Once this approach is proven sound, it could scale to other disease treatment areas such as type 2 diabetes mellitus [41], hypercholesterolemia [42] and depression [43].

Finally, data in CEDSS models are not restricted to phenotypic data. Mendelian monogenic causes of hypertension such as Bartter's, Gitelman's syndrome or pseudohypoaldosteronism have been known and identified for years. More recently this year, genome-wide association studies (GWAS) have discovered a number of loci linked with the more complex type of high blood pressure known as essential hypertension [45]. But, more salient to the efforts of this thesis, GWAS efforts are now being employed to discover alleles associated with response to antihypertensives. A study from Tuner, for example, found a region in chromosome 12q15 influences the response to thiazides [46] and genetic factors are being studied relating to atenolol (BB) and hydrochlorothiaide (thiazide) effectiveness [47]. These results are expected in 2010.

Understanding the causes of essential hypertension as well as the reasons behind the variability in response to antihypertensives is imperative to accomplish the goal of tailored therapies. It seems to be the path towards Christensen's vision of precision medicine [51]. Here, the underlying cause of disease (e.g. hypertension) is known and thus a targeted effective treatment could be developed. Ultimately, a rules-based system (instead of an expert system) can make the diagnosis and choose the treatment. However, the road to this realization could be long, and leveraging medical databases to

enhance the use of guidelines with the empiric evidence seems to be a good solution for the present. Until more genes and SNPs related to the response to antihypertensives are discovered and new drugs that target known molecular pathways responsible for essential hypertension are develop, augmenting clinical guidelines with *de facto* collective clinical experience for personalized clinical decision support looks like a viable solution. Meanwhile, as these molecular markers become available to the medical community, they could be included in the set of attributes of those applications like this one to continue enhancing the empirical treatment.

Summary

Implementing a collective experience decision support system using EMR transactional data is not only feasible but also provides a valuable utility for existing health care data towards our goal of providing high quality, dependable care. To reach this goal, collective data was farmed and intelligently filtered to provide empiric evidence at the point-of-care. Although preliminary results are encouraging, further studies are needed to evaluate the effectiveness of this method.

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Table I

Indication	Antihypertensive drugs	COSTAR code
Compelling indications (major improvement in outcome independent of blood pressure)		
Systolic Heart failure	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*	MLSY1, MLSY1-A, MLSY1-B, MLSY1-C, MLSY1-D, MLNS3, MLSN3,
Post-myocardial infarction	ACE inhibitor, beta blocker, aldosterone antagonist	MLQM1, MLQM1-2, MLQM1-A, MLQM1-AB, MLQM1-AE, MLQM1-B, MLQM1-BC, MLQM1-C, MLQM1-CB, MLQM1-CD, MLQM1-CE, MLQM1-D, MLQM1-E, MLQM1-EA, MLQM1-EF, MLQM1-F, MLQM1-FE, MLQM1-G, MLQM1-GE, MLQM1-H, MLQM1-I
Proteinuric chronic renal failure	ACE inhibitor and/or ARB	TLAA5, TLAE5, TLPA5-1, TLPC2, AND TGPG1
High coronary disease risk	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)	2 of the following: Age>65, Current smoker, DM, Hypercholesterolemia, Obesity OR CAD
Diabetes mellitus (no proteinuria)	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)	EHAT2, EHAT2-A, EHAT2-B, EHAT2-C, EHAT2-D, EHAT2-E, EHAT2-EG, EHAT2-F, EHAT2-G, EHAT2-H, EHAT2-I, EHAT2-J, ELAC7, ELBB1, ELBB1, ELBJ2 AND NO TGPG1, Proteinuria
Angina pectoris	Beta blocker, calcium channel blocker	MLPE4, MLDQ6,MLPV6, JJAD5, MLPM5, KJHL4, MLDH5
Atrial fibrillation rate	Beta blocker,	MHEN3, MHEN3-1,

control	nondihydropyridine calcium channel blocker	MHEN3-2, MLBR1
Atrial flutter rate control	ABeta blocker, nondihydropyridine calcium channel blocker	MHEW4, MHEW4-1
Likely to have a favorable effect on symptoms in comorbid conditions		
Benign prostatic hypertrophy	Alpha blocker	SKDA3, SKDA3-B
Essential tremor	Beta blocker (noncardioselective)	WLAP9, WLAP9-1, WLAP9-2
Hyperthyroidism	Beta blocker	EHCK6, EHCK6-1, EHCK6-A, EHCK6-B
Migraine	Beta blocker, calcium channel blocker	WHAZ5,WHAZ5-1, WHAZ5-2, WHAZ5-A, WHAZ5-B, WHAZ5-C, WLAB6
Osteoporosis	Thiazide diuretic	VLLB7, VLLB7-1,VLLB7-2, VLLB7-3,VLLB7-4, VLLB7-A
Perioperative hypertension	Beta blocker	No costar representation
Raynaud's syndrome	Dihydropyridine calcium channel blocker	NHAD1, NHAD1-1
Contraindications		
Angioedema	ACE inhibitor	GLDC9, GLDC9-1, GLDC9-2, GLDC9-3, GLDC9-4, GLDC9-5
Bronchospastic disease	Beta blocker	LJAH5, LJCD3, LHAZ1, LJEZ1-3, LKNW1, LKNW1-A, LKNW1-B, LKNW1-C, LKNW1-D
Depression	Reserpine	YJSD3, YJSL4, YJSN1, YJSN1-A, YJSN1-C, YJSN1-CA, YJSN1-D, YJSN1-E, YJSN1-F, YJSN1-G, YJSN1-H, YJSN1-J, YJSN1-Z, YJSW2, YLAB2-J, YLAF3, YLAF5, YLAI2
Liver disease	Methyldopa	DJBW8, DJBW8-1,DJCY1, EHAB3, EHAB3-1, EHAJ4, ELAB5, QJAA1, QJAP8, QJCH9, QJNB1, QJPG1, QJPX3, QJQH7, QJQM1, QJQM1-2,

		QJQM1-3, QKAA6, QKBK3, QKGA8, QKGC5, QKGC5-A, QKGC5-B, QKGC5-H, QKNA1, QLAB2, QLBY1, QLEM4, QLJB3, QLJB3-A, QLJT2, QLJZ6, WLLH1-A
Pregnancy	ACE inhibitor, ARB (includes women likely to become pregnant)	RMAY1, RMAN3, RLRP6
Second or third degree heart block	Beta blocker, non-dihydropyridine calcium channel blocker	MHLB7, MHLB7-1, MHLF1, MHLL5, MHLL5-A, MHLL5-B, MHLL5-C, MLAX9
May have adverse effect on comorbid conditions		
Depression	Beta blocker, central alpha agonist	Described above
Gout	Diuretic	VJJW2, VJJW2-1,VJJW2-2, VJJW2-3, TLQW7
Hyperkalemia	Aldosterone antagonist, ACE inhibitor, ARB	CLVM4
Hyponatremia	Thiazide diuretic	CLVX2
Renovascular disease	ACE inhibitor or ARB	MHAB1-A, NLHB1-B, NLKV2, NLKV2-1

Appendix A

Drug Family	Generic Name	Commercial Name	COSTAR
AA	methyldopa	methyldopa	MTJC1
AA	methyldopa	aldomet	MTJC1-1
AA	methyldopa	methyldopa tablets	MTJC1-T
AA	clonidine	clonidine	MTBP1
AA	clonidine	catapres	MTBP1-1
AA	clonidine	catapres TTS patch	MTBP1-2
AA	clonidine patch	clonidine patch	MTBP1-3
AA	clonidine tablets	clonidine tablets	MTBP1-T
AA	guanfacine hydrochloride	guanfacine hydrochloride	MTBV5
AA	guanfacine	tenex	MTBV5-1
AB	doxazosin	doxazosin	MTBK7
AB	doxazosin	cardura	MTBK7-1
AB	doxazosin	cardura XL	MTFP8-1
AB	terazosin	terazosin	MTBE3
AB	terazosin	hytrin	MTBE3-1
AB	prazosin	prazosin	MTVG1
AB	prazosin	minipress	MTVG1-1
BB	carvedilol	carvedilol	MTDL9
BB	carvedilol	coreg	MTDL9-1
BB	carvedilol	carvedilol ER	MTGP4
BB	carvedilol cr	coreg CR	MTGP4-1
BB	labetalol hcl	labetalol hcl	NSPG8
BB	labetalol	tandrate	NSPG8-1
BB	labetalol	normodyne	NSPG8-2
BB	labetalol	labetalol tablets	NSPG8-T
BB	acebutolol	acebutolol hydrochloride (sectral capsules)	MTBM4
BB	acebutolol	acebutolol	MTBM4-1
BB	acebutolol hydrochloride	sectral	MTBM4-2
BB	atenolol	atenolol	MTAZ3
BB	atenolol	tenormin	MTAZ3-1
BB	atenolol	atenolol tablets	MTAZ3-T
BB	bisoprolol	bisoprolol	MTEB7
BB	bisoprolol	zebeta	MTEB7-1
BB	betaxolol	betaxolol	HTPD2
BB	betaxolol	kerlone	HTPD2-2
BB	nebivolol	nebivolol	MTGV8
BB	nebivolol	bystolic	MTGV8-1
BB	carteolol hydrochloride	cartrol	MTCF9
BB	carteolol	cartrol	MTCF9-1
BB	nadolol	nadolol	NSAF4

BB	nadolol	corgard	NSAF4-A
BB	pindolol	pindolol	MTAG4
BB	pindolol	visken	MTAG4-1
BB	pindolol	pindolol tablets	MTAG4-T
BB	metoprolol succinate	metoprolol	MSNJ6
BB	metoprolol succinate	metoprolol ER	MSNJ6-1
BB	metoprolol tartrate	metoprolol	NSPL2
BB	metoprolol tartrate	lopressor	NSPL2-1
BB	metoprolol tartrate	lopressor	NSPL2-L
BB	propranolol	propranolol	MSPB1
BB	propranolol	inderal	MSPB1-1
BB	propranolol	betachron	MSPB1-2
BB	propranolol	inderal la	MSPB1-3
BB	propranolol	inderal la	MSPB1-4
BB	propranolol	innopran xl	MSPB1-5
BB	propranolol	propranolol tablets	MSPB1-T
BB	propranolol	inderal tablets	MSPB1-1T
BB	timolol	timolol	HTNF3
BB	timolol	blocadren	HTNF3-1
BB	timolol	timolol maleate tablets	HTNF3-T
BB	penbutolol sulfate	penbutolol	MTCQ7
BB	penbutolol sulfate	levatol	MTCQ7-1
ACEi	quinapril	quinapril	MTCY8
ACEi	quinapril	accupril	MTCY8-1
ACEi	ramipril	ramipril	MTCC2
ACEi	ramipril	altace	MTCC2-1
ACEi	benazepril	benazepril	MTBA9
ACEi	benazepril hydrochloride	lotensin	MTBA9-1
ACEi	enalapril maleate	enalapril maleate	MTAJ1
ACEi	enalapril	vasotec	MTAJ1-1
ACEi	enalapril maleate tablets	enalapril maleate tablets	MTAJ1-T
ACEi	enalapril maleate (vasotec) tablets	enalapril maleate (vasotec) tablets	MTAJ1-1T
ACEi	fosinopril	fosinopril	MTCK3
ACEi	fosinopril	monopril	MTCK3-1
ACEi	lisinopril	lisinopril	MTAV9
ACEi	lisinopril	zestril	MTAV9-1
ACEi	lisinopril	prinivil	MTAV9-2
ACEi	captopril	captopril	NSPB4
ACEi	captopril	capoten	NSPB4-1
ACEi	captopril	captopril tablets	NSPB4-T
ACEi	trandolapril	trandolapril	NSBZ9
ACEi	trandolapril	mavik	NSBZ9-1
ACEi	moexipril HCl	moexipril HCl	MTEN2
ACEi	moexipril hydrochloride	univasc	MTEN2-1
ACEi	perindopril	perindopril	MTER9
ACEi	perindopril	aceon	MTER9-1
ARB	candesartan	candesartan	MTED4

ARB	candesartan	atacand	MTED4-1
ARB	irbesartan	irbesartan	MTDW7
ARB	irbesartan	avapro	MTDW7-1
ARB	olmesartan	olmesartan	MTFT2
ARB	olmesartan	benicar	MTFT2-1
ARB	losartan	losartan	MTDY4
ARB	losartan	cozaar	MTDY4-1
ARB	valsartan	valsartan	MTDD8
ARB	valsartan	diovan	MTDD8-1
ARB	telmisartan	telmisartan	MTEJ8
ARB	telmisartan	micardis	MTEJ8-1
ARB	eprosartan mesylate	teveten	MTFL1-1
CCB	nifedipine	nifedipine	NSAN5
CCB	nifedipine	procardia	NSAN5-1
CCB	nifedipine	adalat	NSAN5-2
CCB	nifedipine	nifedipine extended release	NSAT9
CCB	nifedipine	procardia XL	NSAT9-1
CCB	nifedipine er	adalat cc	NSAT9-2
CCB	nifedipine	nifedical xl	NSAT9-3
CCB	nifedipine	nifediac CC	NSAT9-4
CCB	nifedipine	nifedipine ER	NSAT9-5
CCB	amlodipine besylate	amlodipine besylate	MTDH2
CCB	amlodipine	norvasc	MTDH2-1
CCB	verapamil	verapamil	NSAW6
CCB	verapamil	isoptin	NSAW6-1
CCB	verapamil	isoptin tablets	NSAW6-1T
CCB	verapamil	calan	NSAW6-2
CCB	verapamil	verapamil (calan) tablets	NSAW6-2T
CCB	verapamil	verelan pm	NSAW6-3
CCB	verapamil	verapamil tablets	NSAW6-T
CCB	verapamil	verapamil SR	NSBW2
CCB	verapamil hydrochloride	verapamil hydrochloride, SR ER tablets	NSBW2-T
CCB	verapamil	calan sr	NSBW2-1
CCB	verapamil	calan sr tablets	NSBW2-1T
CCB	verapamil	isoptin sr	NSBW2-2
CCB	verapamil	covera hs	NSBW2-3
CCB	verapamil	verelan	NSBW2-4
CCB	verapamil	verapamil hydrochloride exten rel capsules	MSNT4
CCB	verapamil	verelan	MSNT4-1
CCB	verapamil	verelan pm	MSNT4-2
CCB	verapamil	covera hs	MSNT4-3
CCB	diltiazem	diltiazem extended release	NSBB6
CCB	diltiazem	cardizem CD	NSBB6-1
CCB	diltiazem	tiazac	NSBB6-2
CCB	diltiazem	diltiazem SR	NSBD3

CCB	diltiazem	cardizem D	NSBD3-1
CCB	diltiazem	dilacor XR	NSBD3-2
CCB	diltiazem	cardizem sr	NSBD3-3
CCB	diltiazem	cartia XT	NSBD3-4
CCB	diltiazem	diltiazem	NSAD7
CCB	diltiazem	cardizem	NSAD7-1
CCB	diltiazem	cardizem tablets	NSAD7-1T
CCB	diltiazem	diltiazem CD	NSAD7-2
CCB	diltiazem	diltiazem CD tablets	NSAD7-2T
CCB	diltiazem	diltiazem tablets	NSAD7-T
CCB	diltiazem	diltiazem HCl	MTDN6
CCB	diltiazem	tiazac	MTDN6-1
CCB	isradipine	isradipine	MTCA5
CCB	isradipine	dynacirc	MTCA5-1
CCB	isradipine	dynacirc CR	MTCA5-2
CCB	felodipine	felodipine	NSBL4
CCB	felodipine	plendil	NSBL4-1
CCB	nicardipine	nicardipine	NSAY3
CCB	nicardipine	cardene	NSAY3-1
CCB	nicardipine	cardene sr	NSAY3-2
CCB	nisoldipine	nisoldipine	MTEL5
CCB	nisoldipine	sular	MTEL5-1
CCB	nimodipine	nimodipine	NSQG4
CCB	nimodipine	nimotop	NSQG4-1
CCB	bepridil	bepridil	MSMN4
CCB	bepridil	vascor	MSMN4-1
Non-Thiazide	spironolactone	spironolactone	TTJQ1
Non-Thiazide	spironolactone	aldactone	TTJQ1-1
Non-Thiazide	spironolactone	spironolactone tablets	TTJQ1-T
Non-Thiazide	amiloride HCl	amiloride HCl	TTJN4
Non-Thiazide	amiloride HCl	midamor	TTJN4-1
Non-Thiazide	amiloride HCl	amiloride HCl tablets	TTJN4-T
Non-Thiazide	torsemide	torsemide	TTAV4
Non-Thiazide	torsemide	demadex	TTAV4-1
Non-Thiazide	triamterene	triamterene	TTKW1
Non-Thiazide	triamterene	dyrenium	TTKW1-1
Non-Thiazide	triamterene	triamterene tablets	TTKW1-T
Non-Thiazide	furosemide	furosemide	TTGE1
Non-Thiazide	furosemide	lasix	TTGE1-1
Non-Thiazide	furosemide	furosemide tablets	TTGE1-T
Non-Thiazide	eplerenone	eplerenone	MTFB3
Non-Thiazide	eplerenone	inspra	MTFB3-1
Non-Thiazide	aliskiren	aliskiren	MTGX5
Non-Thiazide	aliskiren	tekturna	MTGX5-1
Thiazide	bendroflumethiazide	bendroflumethiazide	MTNX4
Thiazide	bendroflumethiazide	naturetin	MTNX4-1
Thiazide	chlorothiazide	chlorothiazide	TTAX1

Thiazide	chlorothiazide	diuril	TTAX1-1
Thiazide	chlorothiazide	chlorothiazide tablets	TTAX1-T
Thiazide	chlorthalidone	chlorthalidone	TTBC1
Thiazide	chlorthalidone	hygroton	TTBC1-1
Thiazide	chlorthalidone tablets	chlorthalidone tablets	TTBC1-T
Thiazide	methyclothiazide	methyclothiazide	TTCW6
Thiazide	methyclothiazide	aquatensin	TTCW6-1
Thiazide	methyclothiazide	enduron	TTCW6-2
Thiazide	methyclothiazide	methyclothiazide tablets	TTCW6-T
Thiazide	hydrochlorothiazide	hydrochlorothiazide	TTAK6
Thiazide	hydrochlorothiazide	hydrodiuril	TTAK6-1
Thiazide	hydrochlorothiazide	esidrix	TTAK6-2
Thiazide	hydrochlorothiazide	oretic	TTAK6-3
Thiazide	hydrochlorothiazide	hydrozide	TTAK6-5
Thiazide	hydrochlorothiazide	microzide	TTAK6-8
Thiazide	hydrochlorothiazide tablets	hydrochlorothiazide tablets	TTAK6-T
Thiazide	indapamide	indapamide	TTAE2
Thiazide	indapamide	lozol	TTAE2-1
Vasodilator	hydralazine	hydralazine	MTHX1
Vasodilator	hydralazine	apresoline	MTHX1-1
Vasodilator	hydralazine	hydralazine tablets	MTHX1-T
Vasodilator	hydralazine and isosorbide dinitrate	bidil	NSRM4-1