

OUTCOMES EVALUATION OF STATIN TREATMENT IN PRIMARY
PREVENTION FOR CARDIOVASCULAR DISEASE WITH
TIME-DEPENDENT LDL-C GOAL ATTAINMENT

by

Weijia Wang

A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

in

Health System Pharmacy Administration

Department of Pharmacotherapy

The University of Utah

May 2017

Copyright © Weijia Wang 2017

All Rights Reserved

ABSTRACT

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality for adults in the United States and has caused a significant amount of spending in healthcare. The guidelines issued by the National Cholesterol Education Program Adult Panel III emphasized the importance of low-density lipoprotein (LDL) with LDL reduction. Based on patient CV risk, the guidelines identified LDL as the primary target for cholesterol-lowering therapy. The guidelines also recommended the use of statins for both primary and secondary prevention based on patient risk profile. With strong evidence of effectiveness of statins in secondary prevention, the focus was on primary prevention. Many randomized clinical trials (RCTs) conducted to evaluate the effects of statin therapy have shown that statins lower LDL-C by 19% to 47%. However, statin therapy in real-world studies has not shown the same level of LDL-C reduction as seen in RCTs.

In published studies, LDL-C goal attainment is defined as whether a patient achieves LDL-C levels based on their CVD risk, after a specific follow-up time or the end of the study. However, no studies have considered LDL-C as a modifiable risk factor that changes over time. Examining the association between LDL-C goal attainment and CVD in a time-dependent manner may provide a more accurate estimation of the association between LDL-C levels as modified by statin therapy.

The research question of this study is whether more consistent LDL-C goal attainment reduces the incidence of CV events in primary prevention patients. The

objectives of this study are to 1) identify quarterly LDL-C goal attainment per ATP-III guidelines in primary prevention patients in the real-world setting, and 2) to evaluate the relationship between the time-dependent LDL-C goal attainment and CVD outcomes.

Results from this study suggested risk reduction of CVD risk with more consistent LDL-C goal attainment, highlighting the importance of pharmacotherapy with the right intensity of medications, as well as medication adherence. The findings presented here add to the knowledge of the association between LDL-C goal attainment and CV event risk reduction.

This thesis is dedicated to
my mother Lina Zheng,
father Wenlong Wang,
grandmother Rufeng Xiao,
And
grandfather Yingjian Zheng

TABLE OF CONTENTS

ABSTRACT.....	iii
LIST OF TABLES.....	viii
LIST OF FIGURES.....	ix
ACKNOWLEDGMENTS.....	x
Chapters	
1 EXECUTIVE SUMMARY.....	1
2 LITERATURE REVIEW.....	5
2.1 Background.....	5
2.2 Approach for Lipid Control: Statin Therapy.....	6
2.3 Approach for Events Prevention: Primary Prevention.....	7
2.4 Summary.....	10
3 RESEARCH GOAL AND OBJECTIVES.....	11
4 METHODOLOGY.....	13
4.1 Study Design.....	13
4.2 Study Timeline.....	13
4.3 Data Source.....	14
4.4 Study Population.....	14
4.5 Variable Measurement.....	15
4.6 Statistical Analysis.....	18
5 RESULTS.....	20
5.1 Baseline Characteristics.....	20
5.2 Outcomes.....	23
6 DISCUSSION.....	37
Appendices	

A: CODES.....	41
B: SUMMARY OF CLINICAL TRIALS.....	47
C: TABLES AND FIGURES SUMMARY OF CLINICAL TRIALS.....	53
References.....	67

LIST OF TABLES

Tables

1 Characteristics of the Patients by LDL-C Goal Attainment.....	26
2 Quarterly Responses to LDL-C Pharmacotherapy (Goal Attainment).....	29
3 Number of Events and Incidence Rate of CV Events by LDL-C Goal Attainment...30	
4 Results of Discrete Time Logistic Model.....	31
5 Codes for Identifying Antihyperlipidemics Medications.....	42
6 Diagnose Codes.....	43
7 Codes for Identifying Antihyperlipidemics Medications.....	45
8 Relative Risk for ATP III Risk Factors Defined by ATP III.....	58
9 LDL-C Goals in Different Risk Categories.....	59
10 Primary Prevention RCTs on Evaluation of Statin Therapy.....	60
11 RCTs Results for Statin Effect on Cholesterol Lowering.....	61
12 Primary Prevention RCTs Results on Primary Endpoint.....	63
13 Number of Events and Incidence Rate of CV Events by ATP III Risk Factor.....	64
14 Meta-analysis Results in Statins Therapy in Primary Prevention.....	65
15 Summary of Studies on Suboptimal Use of Statin and Reduction of CV Events.....	66

LIST OF FIGURES

Figures

1 Flow Chart of Study Population Selection	32
2 Proportion of Patients with Goal Attainment by Baseline LDL-C Stratum	34
3 Kaplan-Meier Curve by Goal Attainment.....	35
4 Forest Plot of Discrete Time Logistic Model.....	36
5 Primary Prevention RCTs Results on Myocardial Infarction.....	54
6 Primary Prevention RCTs Results on Coronary Revascularization.....	55
7 Primary Prevention RCTs Results on Angina.....	56
8 Primary Prevention RCTs Results on Stroke.....	57

ACKNOWLEDGMENTS

I would like to extend my sincere gratitude to Dr. Carrie McAdam-Marx, my supervisor, for her extensive guidance and support over time. I also want to thank Mark Munger and Jaewhan Kim for serving on my thesis committee.

This project would not have been possible without the generous support of the Department of Pharmacotherapy, University of Utah's Research Assistant Scholarship. Thanks to General Electric for access to the Centricity Electronic Medical Record Database.

CHAPTER 1

EXECUTIVE SUMMARY

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality for adults in the United States and has caused a significant amount of spending in healthcare [1]. In 2011, the hospitalization incidence rate for CVD was 2,983 events per 100,000 person-years among the Medicare population, which paid roughly \$16 billion for hospitalization cost associated with CVD diagnoses [2, 3]. The Framingham Heart Study (FHS) in 1998 identified risk factors for CVD including elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL), family premature history of CVD, and hypertension [4]. Among these risk factors, elevated LDL-C is a leading cause of CV events, as shown in animal laboratory models, epidemiological studies, as well as clinical trials [5]. Based on evidence found in the FHS, guidelines issued by the National Cholesterol Education Program Adult Panel III (ATP III) emphasized the importance of LDL with LDL reduction. The ATP III guidelines identified LDL as the primary target for cholesterol-lowering therapy. It recommended the use of statins for both primary and secondary prevention based on patient risk profile [5].

In 2014, the American College of Cardiology and the American Heart Association (ACC/AHA) together with the National Heart, Lung, and Blood Institute updated guidelines on treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [6]. The emphasis of ACC/AHA guidelines was in the identification of patients

by statin benefit group aimed at effective use of statins to reduce cardiovascular morbidity and mortality risk rather than focusing specifically on LDL reduction. These statin benefit groups include both primary and secondary prevention populations. This change triggered much debate among physicians, pharmacists, and other healthcare practitioners [7-9].

This thesis, which was developed and executed under ATP III guidelines, evaluates CV event risk, controlling for LDL goal attainments. The ATP III guidelines discussed two different clinical approaches to CVD risk management: primary and secondary prevention. A Cochrane review found significant reduction in a pooled analysis of CVD and stroke in statin therapy in primary prevention, when analyzing 14 randomized clinical trials (RCTs) [10]. Several meta-analyses on RCTs also found a significant risk reduction in CVD [11-13]. These studies are discussed in greater detail in the following chapter. While prior events may be the largest predictor, we would ultimately like to prevent patients from having any CV event. Thus, this study will focus on CVD primary prevention.

Many RCTs conducted to evaluate the effects of statin therapy have shown that statins lower LDL-C by 19% to 47% [14-18]. However, statin therapy in real-world studies has not shown the same level of LDL-C reduction as seen in RCTs [19]. A recent study that included 146,064 patients from a national registry found <70% patients attained the LDL-C goal [20]. Among a group of 2045 post-myocardial infarction patients with hypercholesterolemia, 43.4% who were treated with a statin failed to achieve the optimal LDL-C goal set by ATP III [21]. Suboptimal treatment was found to double the risk of myocardial infarction (MI) or coronary heart disease (CHD)

death compared with optimal treatment. The possible explanations of the gap between RCTs and the real-world setting maybe the difference in study cohorts. RCTs have specifically defined inclusion and exclusion criteria versus nondiscriminative perspective of real-world setting. Undocumented social activity, cost, lack of motivation, non-controlled medication adherence as well as loss of information when switching healthcare providers all contributed to the less desirable LDL-C reduction seen in real-world studies.

In published studies, LDL-C goal attainment is defined as whether a patient achieves LDL-C levels based on their CVD risk, after a specific follow-up time or the end of the study. However, no studies have considered LDL-C as a modifiable risk factor that changes over time. Examining the association between LDL-C goal attainment and CVD in a time-dependent manner may provide a more accurate estimation of the association between LDL-C levels as modified by statin therapy.

The research question of this study is whether more consistent LDL-C goal attainment reduces the incidence of CV events in primary prevention patients. The objectives of this study are to 1) identify quarterly LDL-C goal attainment per ATP-III guidelines in primary prevention patients in the real-world setting, and 2) to evaluate the relationship between the time-dependent LDL-C goal attainment and CVD outcomes.

This study has found a positive association between more severe ATP III risk and less LDL-C goal attainment in the primary prevention real-world setting. It also found a significant association between the risk of CV events and LDL-C goal attainment; notably, that failure to attain or maintain LDL-C goal at any time during the follow-up period increased the likelihood of a CV event occurrence by 30%.

Results from this study suggested risk reduction of CVD risk with more consistent

LDL-C goal attainment, highlighting the importance of pharmacotherapy with the right intensity of medications, as well as medication adherence. The findings presented here add to the knowledge of the association between LDL-C goal attainment and CV event risk reduction. While guidelines are now less specific about specific LDL-C goals, this study nonetheless is consistent with the rationale for treating patients at risk for CVD with an appropriate intensity of medications per their CV risk.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

Cardiovascular disease (CVD) is a set of diseases and disorders that involves the heart and blood vessels. CVD includes ten categories, with the five most common diseases being coronary heart disease (CHD), cerebrovascular disease, peripheral heart disease, rheumatic heart disease, and heart failure. According to the report, an estimated 17 million American adults had CVD in 2008, which was 7% of the total U.S. adult population [1]. In 2011, the hospitalization incidence rate for CVD was 2,983 events per 100,000 person-years among the Medicare population, which paid roughly \$16 billion for the hospitalization cost associated with CVD diagnoses [3].

There are many risk factors associated with CVD, including family history, ethnicity, age, tobacco exposure, high blood pressure, high cholesterol, obesity, physical inactivity, and diabetes. However, Low-density lipoprotein (LDL-C), a modifiable risk factor, was the main concern [22]. LDL-C is among the major groups of lipoproteins. It contains a single apolipoprotein B-100 molecule that keeps LDL-C soluble in blood, which allows it to transport cholesterol [23].

A range of observational and RCT studies published over several decades based on animal, pathological, clinical, and genetics have established a causal role of elevated LDL-C in the development of CVD [24]. Thus, the Adult Treatment Panel (ATP III)

guidelines identified elevated LDL-C as a primary target for CVD risk reduction. It also proposes LDL-C <100 mg/dL as the optimal level, 100-129 mg/dL as near optimal, 130-159 mg/dL as borderline high, 160-189 mg/dL as high, and ≥ 190 mg/dL as very high [5].

In addition to LDL-C, ATP III also defined risk factors such as low high-density lipoprotein (HDL) level (<40 mg/dL), hypertension (blood pressure $\geq 140/90$ mmHg), cigarette smoking, family history of premature CVD, and age (men ≥ 45 years, women ≥ 55 years) for developing CV events [5].

2.2 Approach for Lipid Control: Statin Therapy

Clinically, therapeutic lifestyle change (TLC) and drug therapy have been adopted to reduce risks for developing CVD [4]. According to ATP III guidelines, physicians should consider drug therapy when patients 1) have one ATP III risk factor with LDL-C > 190 mg/dL; or 2) have two or more ATP III risk factors and $< 20\%$ 10-year risk with LDL-C > 130 mg/dL; or 3) have previous CV events or CVD equivalents with LDL-C > 100 mg/dL.

When initiating drug therapy, available medications include: HMG-CoA reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibric acids. ATP III guidelines recommend that statins be considered the first-line for cholesterol-lowering treatment because statins are the most effective agents and are generally well tolerated [25].

In 2014, American College of Cardiology and American Heart Association together with National Heart, Lung, and Blood Institute published new guideline [6]. Although it continued to stress the significance of initiating cholesterol-lowering therapy with statins to reduce CV risk, it shifted the focus onto patient risk versus LDL-C levels,

which is a notable departure from previous guidelines. However, this research was conducted during a timeframe in which providers would have been following ATP III guidelines and based on the notion that even if LDL-C was not necessarily the strongest predictor, it is still relevant to CVD outcomes.

2.3 Approach for Events Prevention: Primary Prevention

While prior events may be the largest predictor, we would ultimately like to prevent a patient from having any CV event. In clinical practice, primary prevention is to prevent patient from have a CV event. This practice denotes efforts to prevent or delay occurrence of disease which would result in a CV event by modifying risk factors. Many RCTs have focused on CVD primary prevention through lipid lowering including: the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) [17], the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) [14], the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [26], the Collaborative Atorvastatin Diabetes Study (CARDS) [15], and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS) [27].

2.3.1 RCTs on Lipid Control

According to results from these trials, significant LDL-C absolute reduction was observed with statin therapy, ranging from 18.5% to 47.2% [14, 17, 26, 27]. Significant reduction in HDL, total cholesterol (TC), and triglycerides (TG) was also noted throughout all primary prevention studies mentioned above.

2.3.2 RCTs on Primary Endpoint

In addition to lipid control, the five RCTs mentioned above also reported CV event outcomes. The results revealed that statin therapy significantly reduced the risk of a major CV event when considered as a composite primary endpoint. Strong evidence was also seen in statin treatments in individual studies, with statistically significant reductions in major CV events ranging from 33% to 44% [14-17, 27].

Specific outcomes such as MI, coronary revascularization, angina, and stroke were also reported as individual components of the composite primary endpoints. Although results differed slightly in particular outcomes, beneficial effects of statins in terms of CVD risk reductions were observed across all individual outcomes in the majority of RCTs. For example, in MI, the hazard ratios were 0.52 [95% CI: 0.29-0.94], 0.46 [95% CI: 0.30-0.70], and 0.60 [95% CI: 0.43-0.83] for MEGA, JUPITER, and AFCAPS, respectively.

2.3.3 Cochrane Review

In a recent Cochrane systemic review, researchers included 14 trials (covering MEGA, AFCAPS, ASPEN, and CARDS), which recruited 34,272 participants and observed outcomes ranging from 1-5.3 years, amounting to approximately 113,000 patient-years [28].

The review found no evidence of reduction in total mortality (all-cause mortality), fatal CV events, or non-fatal CV events. However, statistically significant effects were observed in a pooled analysis of fatal or non-fatal stroke events and revascularization. When combining CVD and stroke, a significant reduction was also maintained with a hazard ratio of 0.78 [95% CI: 0.66-0.87]. The pooled reductions in both TC and LDL

were parallel to results seen in individual trials [28].

2.3.4 Meta Analysis

Numerous meta-analyses have been published, examining the effects of statins seen in a variety of RCTs. To date, five studies focused exclusively on primary prevention [11-13, 29, 30]. All studies detected around 30% reduction in major coronary heart disease. In major cerebrovascular disease, four of the five studies showed more than 20% reduction that was significant [10-12, 30] while one showed 14% reduction that was not significant [13]. Three studies found no effect of statin therapy in reducing all-cause mortality events [11-13], while two observed 16% and 12% significant reduction in all-cause mortality [30]. There was no effect of statin therapy in reducing CVD fatal events from the Cochrane Review and Brugts et al. while Choudhry et al. detected 23% significant reduction in CVD mortality [10, 30]

2.3.5 Gap between RCTs and the Real-world Setting

The five aforementioned primary prevention RCTs used restrictive inclusion and exclusion criteria that may affect the external validity of these trials. JUPITER and AFCAPS excluded patients with type 2 diabetes [26, 27]. JUPITER also excluded patients with blood pressure higher than 190/100 mmHg, while AFCAPS excluded patients with ‘uncontrolled hypertension’ and those whose weight was 50% more than desired limit for the height. MEGA excluded poorly controlled hypertension and diabetes patients [31]. ASPEN excluded patients with HbA1C > 10%, blood pressure higher than 160/100 mmHg, and patients with BMI > 35 kg/m². [14] Therefore, the external validity of clinical trials was reduced due to the exclusion of patients with high blood pressure, obesity, and diabetes. However, this could be improved by an observational study that

aims to reflect real-world practice.

2.4 Summary

CVD is prevalent in US adult population, and benefits of statin therapy in LDL-C lowering toward primary CVD risk reductions are seen in clinical trials. LDL-C goal attainment reported as LDL-C changes from baseline to either an intermediate follow-up or end of pharmacotherapy program is an important factor for physicians. Physicians could benefit from an observational study that focuses on the impact of CVD by LDL-C goal attainment over time. These data are, however, missing in current literature. Therefore, this study is designed to answer the question of how LDL-C goal attainment over time affects the incidence of the CV events in the real-world setting.

CHAPTER 3

RESEARCH GOAL AND OBJECTIVES

The goal of this study is to evaluate the relationship between statin therapy for primary prevention and CVD outcomes in the real-world setting. To accomplish this goal, the following study objectives were addressed:

- Identify and describe a cohort of patients with the first statin prescription order, defined as the index date, and no previous CVD prior to the index date treated in the real-world setting
- Identify and describe the incidence of CV events with stratification by proportion of time at the LDL-C goal
- Evaluate the relationship between LDL-C goal attainment, defined using a threshold from the ATP III guideline, as a time-dependent variable using a Cox's proportional hazard model.

The rationale of this study is as follows. When a patient is prescribed statins, it is expected to lower the patient's LDL-C. There are reasons that a patient may have suboptimal LDL-C response and failure to attain a goal with treatment, such as comorbidities including hypertension, diabetes, and obesity [32]. It has been well established that suboptimal LDL-C response will increase risk of CVD [8]. What remains unknown in primary prevention is how the incidence of CV events changes with different degrees of goal attainment to statin therapy in the real-world setting. A real-

world study that focuses on the relationship between LDL-C response to statin therapy as measured by goal attainment and CV event outcomes in primary prevention could provide information on the difference in incidence of CV events by LDL-C goal attainment. With this information, physicians could assess patient CVD risk given the patient's response to statin therapy relative to LDL goals. Physicians could also counsel patients on the implications of suboptimal LDL-C goal attainment when addressing medication compliance issues, especially when patients do not fully understand their risk for a CV event in primary prevention.

In addition, data on the relationship between CVD risk and LDL-C goal attainment over time in the real-world setting are also lacking, and more informative than only considering time-static or average LDL-C level. A patient's LDL-C levels change over time. Rather than computing an average of all available LDL-C records over a defined follow-up period, considering all LDL-C values over a follow-up period would help assess the association between time at or above the LDL-C goal and CVD risk. This could provide essential information to physicians about the importance of consistently keeping LDL-C at or below a goal over time, or conversely, the risk associated with periods of time when LDL-C is above the goal.

CHAPTER 4

METHODOLOGY

4.1 Study Design

A retrospective cohort study for the period from January 1996 to December 2010 among patients in an Electronic Medical Record (EMR) database without prior history of cardiovascular disease with a first-time statin prescription order was conducted.

4.2 Study Timeline

Based on General Electric EMR (GE EMR) data, patients who met the inclusion criteria from January 1996 to December 2010 were identified. The date of the first statin prescription order was defined as the index date. Patients were followed for a year and one extra month prior to the index date to confirm they were treatment naïve and that they were primary prevention patients, and for 900 days post index date to assess LDL-C and outcomes. The reason for this 395 days is that the EMR database only captures prescriptions, but not dispensing as seen in the claims database. Situations might arise when patients refill early in December and wait until the end of January to see the physician again. The phantom that the patient was not taking any medications in the exclusion or inclusion list could be revealed by requiring one extra month for treatment naïve confirmation.

Patients were followed until 1) the first occurrence of a CV event, or 2) the end of

the study without a CV event (December 2010), or 3) the end of the patient's EMR activity. A CV event was defined as an ischemic heart disease event including MI [ICD-9 410-412] and angina [ICD-9 413-414]), or a cerebrovascular disease event [ICD-9 430-438].

4.3 Data Source

This proposed study used data from the GE Centricity EMR research database (GE Healthcare, Waukesha, WI). The GE EMR, a de-identified, HIPAA-compliant database, was comprised of longitudinal patient data and includes, but was not limited to, demographic information, vital signs, laboratory orders and results, medication list entries and prescribed medications, and diagnoses or problems. Medical record data were submitted by over 100 physician practice sites located in 42 states who participate in the Medical Quality Information Consortium (MQIC). Consortium members represent a variety of practice types including solo practices, group practice, community clinics, academic medical centers, and large integrated delivery networks, all representing ambulatory care settings. Currently, the EMR includes data on over 15 million patients.

4.4 Study Population

To be eligible for study inclusion, patients need to be at least 18 years old, initiated on statin therapy that includes atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or pitavastatin (Appendix A). The date of the first statin prescription order was defined as the index date. To help establish the intention for patients to stay on statin therapy, another statin prescription must have been documented in the EMR from 30-days to 365-days post index date.

Patients with record of antihyperlipidemia treatment prior to the index date

including statins, bile acid sequestrants, fibrin, niacin, or ezetimibe per prescription order or medication list entries in this period were excluded.

Patients were excluded if they had a previous diagnosis of ischemic heart disease [ICD-9 410-414] (including acute myocardial infarction, other acute and sub-acute forms of ischemic heart disease, old myocardial infarction, angina pectoris, and others forms of chronic ischemic heart disease), cerebrovascular disease [ICD-9 430-438] (including subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified intracranial hemorrhage, occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, transient cerebral ischemia, acute but ill-defined cerebrovascular disease, other and ill-defined cerebrovascular disease, and late effects of cerebrovascular disease), or peripheral vascular disease [ICD-9 443]. In addition, patients with the following diagnosis throughout the study time were excluded: hepatic dysfunction [aspartate or alanine aminotransferase levels 3 times the upper limit of normal (aspartate: female 6-34 U/L, male 8-40 U/L; alanine: 5-60 U/L)], and rhabdomyolysis [ICD-9 728.88].

4.5 Variable Measurement

4.5.1 Primary Independent Variable

The primary independent variable was LDL-C goal attainment treated as a time-dependent variable. To identify goal attainment, all documented LDL-C levels during the 900-day follow-up period were captured and were used to estimate LDL-C levels at quarterly intervals. Quarter LDL-C goal attainments were evaluated against ATP III guidelines with a binary result: At-Goal or Not-At-Goal based on patient's risk profile. For quarters without LDL-C measures, the missing observations were filled using the last observation carried forward (LOCF) technique.

Those whose LDL-C levels were at goal for 80-100% of the quarterly readings during their follow-up period were assigned to Goal I, those whose LDL-C levels were at goal for 79-50% of the period were assigned to Goal II, and those whose LDL-C levels were at goal for <50% of the period were assigned to Goal III. The risk factors include HDL <40 mg/dL, blood pressure \geq 140/90 mmHg, and men \geq 45 years or women \geq 55 years old. If a patient has 0-1 risk factor, LDL-C \leq 160 mg/dL is the optimal level; if a patient has 2+ risk factors, LDL \leq 130 mg/dL is the optimal level and \leq 100 mg/dL for a patient with CHD Equivalent.

4.5.2 Outcomes Measurement

The primary outcome of interest in this study was the occurrence of composite endpoint of MI [ICD-9 410-414], Angina [ICD-9 413-414]), or cerebrovascular disease event [ICD-9 430-438] occurring from the index date to the end of the study period. The secondary outcomes of interest were the occurrence of MI, Angina, and cerebrovascular disease.

4.5.3 Other Independent Variables

Other independent variables were identified to describe the patient cohort, and to control for characteristics that might influence outcomes or otherwise introduce bias to the findings as described below.

4.5.3.1 Baseline Characteristics Description

Baseline characteristics included age as of index date (continuous; and 19-44, 45-54, 55-64, 65-74, 75+), sex, race (White, Black, Hispanic, other, unknown), region (Northeast, South, Midwest, West), and insurance.

4.5.3.2 Clinical Characteristics Description

Clinical characteristics were captured from 365-day prior to 90-day post index date for laboratory/biometric values based on ICD-9 codes in Appendix A.

The clinical characteristics included HbA1C (continuous & $< 7.0/\geq 7.0\%$ /not available), BMI (continuous & $< 25.0, 25.0-29.9, 30.0-34.9, 35.0-39.9, \geq 40$ kg/m²/not available), weight (continuous/not available), SBP (continuous & $< 130/\geq 130$ mmHg /not available), DBP (continuous & $< 80/\geq 80$ mmHg /not available), lipid values (LDL-C [continuous & $\geq 100/< 100$ mg/dL/not available], HDL-C [continuous & $\geq 40/< 40$ mg/dL/not available], TC [continuous & $\geq 200/< 200$ mg/dL/not available] and TG [continuous & $\geq 150/< 150$ mg/dL/not available]), ATP III risk factors, and comorbidities (hypertension). Baseline LDL-C was defined as the closet LDL-C value to the index date. Patients were required to have at least one baseline LDL-C and two follow-up readings. One of the follow-up LDL-C readings must have been recorded at the 0-180 day period and another at the 181-900 day period to ensure patients were actively monitored.

4.5.3.3 Additional Drug Treatment Description

Since additional antihyperlipidemia and antihypertensive drug treatment may affect LDL-C, it was imperative to stratify study population by additional drug treatments. The prescription orders of antihyperlipidemia agents, including bile acid sequestrants, fibric acid derivatives, nicotinic acid derivatives, and combinations of above drugs, as well as antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors, α -blockers, angiotensin ii receptor, β -blockers, calcium channel blockers, aldosterone receptor antagonists, thiazides, vasodilators, and combinations of the above drugs, were described with stratification by LDL-C goal groups (Appendix A).

4.6 Statistical Analysis

Descriptive statistics were used to describe baseline demographic and clinical characteristics. The independent t-test and χ^2 test were used to detect the differences in all baseline and clinical characteristics for continuous and categorical variables, respectively, with stratification of number of ATP III risk factors. Tukey's honest significance difference test was used to draw the pairwise comparisons among primary independent variables.

The incidences of the composite endpoints were identified from 90-day to 900-day post index date. The incidence was reported as events per 100 person-years. Individual endpoints of MI, angina, and cerebrovascular disease were also reported.

A survival analysis using the discrete time logistic model was performed to estimate the treatment effects of independent variables. LDL-C goal attainment was included as a time-dependent exposure variable. In this model, time was treated as non-continuous. Each patient would have observations starting from the index date until censorship or event occurred, thus creating a series of monthly observations by every subject. Therefore, it was necessary to treat each patient as a cluster in order to obtain the robust standard errors. In addition to the time-dependent LDL goal attainment variable, the model also controlled for baseline demographic and clinical characteristics as covariates. An odds ratio estimate was interpreted as the odds of experiencing a CV event from one quarter to the next with having attained LDL-C goal as compared to not, while holding all other covariates constant. Finally, model diagnostics were performed with the Deviance and Pearson statistics and Hosmer-and-Lemeshow Goodness-of-Fit tests.

All statistical tests were performed at a significant level of 0.05 using SAS[®] 9.4.

The protocol for this study was presented to the University of Utah Institutional Review Board for approval prior to commencing data analysis.

CHAPTER 5

RESULTS

5.1 Baseline Characteristics

Between January 1996 and December 2010, a total of 954,022 patients with two statin prescriptions were identified in the GE Centricity[®] Electronic Medical Record research database. Of these, 142,459 had no previous history of CVD from 395 days prior to and 900 days post index date activity. After excluding those with less than one LDL-C record during 0-180 days and 181-900 days post index date from the total sampling, 52,126 patients were included in the final study cohort (Figure 1).

5.1.1 LDL-C Goal Attainment

Of the total study population, 31,502 (60.4%) had LDL-C goal attained for 80-100% of the follow-up period (Goal I, LDL-C levels were at goal for 80~100% of the quarterly readings during their follow-up period), 12,140 (23.3%) for 79-50% of the period (Goal II, LDL-C levels were at goal for 79-50% of the period), and 8,478 (16.3%) for <50% of the period (Goal III, LDL-C levels were at goal for <50% of the period).

When stratifying the cohort by risk-specific LDL-C goal attainment, in the group with 0-1 ATP III risk factor, there were more patients who had the most time at goal (Goal I, 52.0%) than those who had the least time at goal (Goal III, 12.6%); in the group with CHD Equivalent risk factor, there were more Goal III (55.7%) than Goal I (14.6%)

patients. Patients with higher percent of goal attainment time tended to be younger female Caucasians, living in the northeastern United States (hereafter referred to as ‘the Northeast’) and insured by commercial plans. There were statistically significant differences across goal attainment groups among all baseline demographic parameters (Table 1).

5.1.2 Baseline Demographic Characteristics

Mean (standard deviation [SD]) age of the population was 57.0 (\pm 11.2) years; over half of the cohort 30,054 (57.7%) were women. The largest proportion of patients were between the ages of 55 and 64 years (29.1%), Caucasians (38.3%), living in the southeastern United States (hereafter referred to as ‘the South’) (34.5%), and insured (36.6%). The baseline characteristics are shown in Table 2.

5.1.3 Baseline Clinical Characteristics

There were statistically significant differences in mean values among all baseline clinical characteristics when comparing stepwise among risk-specific LDL-C goal attainment groups (Table 2).

5.1.3.1 Baseline Lipid

Mean baseline LDL-C was 154.6 (\pm 35.9) mg/dL and it ranged from 150 mg/dL for the Goal I to 166 mg/dL for the Goal III ($P < 0.001$). Baseline LDL-C values were significantly associated with greater goal attainment. The highest proportion of Goal I patients (33.5%) had baseline LDL-C 130-159 mg/dL, the highest proportion of Goal II and Goal III patients (33.0%, 32.4%) had baseline LDL-C 160-189 mg/dL ($P < 0.001$). The proportion of patients with goal attainment by baseline LDL-C stratum is shown in

Figure 2.

5.1.3.2 Baseline HDL-C, TC, and TG

Mean baseline HDL-C was 50.9 (± 13.6) mg/dL. Mean baseline TC was 221.3 (± 36.9) mg/dL. Mean baseline TG was 158.0 (± 81.6) mg/dL, noting that 44% of the patients did not have TG records.

5.1.3.3 Baseline HbA1C and Type 2 Diabetes Mellitus

Mean baseline HbA1C, when documented (n=16,096, 30.9%), was 7.0 (± 1.5) % with a range from 5.8 (± 0.5) % to 7.4 (± 1.5) %. Prevalence of baseline type 2 diabetes mellitus differed by LDL-C goal groups (P<0.001), with 14.1% of patient having diabetes in Goal I, 33.3% in Goal II, versus 54.1% in Goal III.

5.1.3.4 Baseline BMI

Mean BMI was 30.8 (± 6.7) kg/m², 64.9% were overweight (BMI \geq 25.0 kg/m²), and there were statistically significant differences in BMI among LDL-C goal groups (P<0.001).

5.1.3.5 Baseline Hypertension

There were 27,563 (52.9%) patients with hypertension at baseline indicated by blood pressure, diagnosis of hypertension, or treated with at least one antihypertensive agent. The mean systolic blood pressure (SBP), when documented (n=50,804, 97.5%), was 130.9 (± 13.5) mmHg and the mean diastolic blood pressure (DBP) was 78.8 (± 7.8) mmHg. Prevalence of hypertension varied by LDL-C goal groups (P<0.001), with 41.9% in Goal I, 61.9% in Goal II, and 56.2% in Goal III.

5.1.4 Pharmacotherapy Characteristics

About 2% of the patients were treated with additional antihyperlipidemia medications. Of these, the top 2 classes were prescribed intestinal cholesterol absorption inhibitors (n=344, 35.5%) and fibric acid derivatives (n=305, 31.5%). About 88% of patients were treated with antihypertensive medications. Of these, 11,839 (25.8%) patients were prescribed ACE inhibitors, followed by β -blockers (n=8,749, 19.1%). There were relatively similar numbers of patients prescribed thiazides (n=6,805, 14.9%), combined antihypertensive treatments (6,468, 14.2%), and calcium channel blockers (n=5,987, 13.1%).

5.2 Outcomes

5.2.1 Event Rates

In total, 2,019 composite CV events occurred among 52,126 patients during a median of 2.5 years (30 months) follow-up period. The overall incidence rate was 1.61 composite events per 100 person-years, ranging from 1.50 for Goal I patients, 1.72 for Goal II patients, to 1.88 for Goal III events per 100 person-years (Table 3).

When considering CV events by type, there were 424 MI events, 306 new cases of Angina and 1,289 Cerebrovascular events. The incidence rate ranged from 0.309 cases per 100 person-years of Goal I in MI to 1.15 cases per 100 person-years of Goal III in Cerebrovascular events.

The Kaplan-Meier curve was plotted by LDL-C goal group shown in Figure 3. There were statistically significant differences in survival probability of composite CV events among LDL-C goal attainment group ($p < 0.001$). Compared to Goal III patients, Goal I and Goal II patients had a higher survival rate.

5.2.2 Survival Analysis: Discrete Time Logistic Model

The result from the discrete time logistic model with LDL-C goal attainment as the time-dependent exposure was shown in Table 4 and Figure 5. The odds of experiencing composite CV events were 2.6 times for a failure at LDL-C goal in a quarter as compared to goal attainment at the same time (OR=2.6, 95% CI: [2.0-3.1], $p<0.001$), after adjusting for demographic characteristics including age, gender, race, region, insurance type, and clinical characteristics including hypertension, HDL, and ATP III risk groups.

When comparing patients with ≤ 1 ATP III risk factor, those with ≥ 2 ATP III risk factors had a higher risk of experiencing CV events (OR=1.9, 95% CI: [1.7-2.2], $p<0.0001$), and those with ATP III equivalency risk factors had the highest CVD risk level (OR=3.0, 95% CI:[2.5-3.5], $p<0.0001$).

Age was associated with CVD risk. The odds ratio was 2.7 (95% CI: [2.4-3.1], $p<0.0001$) for those ≥ 65 years old vs. < 65 years old.

Compared to males, female patients had 1.1 (95% CI: [1.0-1.2], $p=0.1$) times greater odds of experiencing a CV event, although this was not statistically significant. African American patients had 1.1 (95% CI: [0.8-1.4], $p=0.6$) times greater odds of experiencing a CV event than Caucasian patients, although race was not a statistically significant predictor of outcomes. Compared to patients from the Northeast, the odds of experiencing CV events for patients residing in the South and Midwest were 1.2 (95% CI:[1.1-1.4], $p=0.006$) and 1.2 (95% CI:[1.0-1.4], $p=0.0027$) times higher, respectively. Patients covered by Medicare had 1.4 times higher odds of a CV event than those covered by commercial insurance plans (OR=1.4, 95% CI:[1.2-1.7], $p<0.0001$).

Comorbid conditions were associated with CVD risks. Hypertension was associated with 1.3 (95% CI: [1.2-1.5], $P < 0.001$) times risk of CVD, compared to no-hypertension.

Table 1

Quarterly Responses to LDL-C Pharmacotherapy (Goal Attainment)

Proportion of Duration Not-At-Goal	Number of Patients (Percentage, %)			No. of Patients	Cumulative Percentage, %*
	0~1	2+	CVD/CVD Equivalency		
0%	4,601 (58.74)	10,540 (37.76)	4,601 (16.48)	31,537	38.64
<10%	1,769 (8.71)	2,554 (9.15)	1,769 (6.33)	6,754	46.92
10-20%	2,579 (8.86)	3,315 (11.87)	2,579 (9.24)	8,367	57.17
20-30%	2,263 (6.36)	2,488 (8.91)	2,263 (8.10)	6,527	65.17
30-40%	2,281 (5.25)	2,260 (8.09)	2,281 (8.17)	6,007	72.53
40-50%	2,157 (3.61)	1,870 (6.70)	2,157 (7.72)	5,037	78.7
50-60%	2,039 (2.43)	1,544 (5.53)	2,039 (7.30)	4,264	83.93
60-70%	1,820 (2.18)	1,217 (4.36)	1,820 (6.52)	3,648	88.4
70-80%	1,517 (1.56)	1,051 (3.76)	1,517 (5.43)	3,005	92.08
80-90%	1,428 (1.13)	838 (3.00)	1,428 (5.11)	2,583	95.25
90-99.9%	588 (0.36)	233 (0.83)	588 (2.10)	924	96.38
100%	1,943 (0.74)	803 (2.87)	1,943 (6.96)	2,955	100

* The cumulative percentage values might not add up from left, due to round up

Table 2

Characteristics of the Patients by LDL-C Goal Attainment

Demographics/Baseline Parameter (Unit)	Goal I* (N=31,502)	Goal II (N=12,140)	Goal III (N=8,478)	P-value
Risk Factor				
0~1	16,389 (52.0)	3,397 (28.0)	1,072 (12.6)	<0.001
2+	10,529 (33.4)	4,600 (37.9)	2,687 (31.7)	
CHD/CHD Equivalent	4,584 (14.6)	4,143 (34.1)	4,719 (55.7)	
Age Mean (SD), years	57 (11)	57 (11)	56 (11)	
>65	8,697 (27.6)	3,133 (25.8)	2,120 (25.0)	<0.001
≤65	22,805 (72.4)	9,007 (74.2)	6,358 (75.0)	
Sex				
Female	13,511 (42.9)	5,081 (41.9)	3,479 (41.0)	0.0041
Male	17,991 (57.1)	7,059 (58.1)	4,999 (59.0)	
Race				
Caucasian	12,338 (39.2)	4,595 (37.9)	3,024 (35.7)	<0.001
African American	1,031 (3.3)	621 (5.1)	696 (8.2)	
Hispanic	360 (1.1)	304 (2.5)	258 (3.0)	
Other	475 (1.5)	268 (2.2)	161 (1.9)	
Unknown	17,298 (54.9)	6,352 (52.3)	4,339 (51.2)	

Table 2 continued

Demographics/Baseline Parameter (Unit)	Goal I* (N=31,502)	Goal II (N=12,140)	Goal III (N=8,478)	P-value
Region				
Northeast	9,554 (30.3)	3,998 (32.9)	2,731 (32.2)	<0.001
South	9,841 (31.2)	3,806 (31.4)	2,753 (32.5)	
Midwest	6,904 (21.9)	2,296 (18.9)	1,526 (18.0)	
West	5,150 (16.3)	2,017 (16.6)	1,447 (17.1)	
Unknown	53 (0.2)	23 (0.2)	21 (0.2)	
Insurance				
Commercial	11,643 (37.0)	4,416 (36.4)	3,002 (35.4)	<0.001
Medicare	9,122 (29.0)	3,431 (28.3)	2,363 (27.9)	
Medicaid	160 (0.5)	82 (0.7)	89 (1.0)	
Other	162 (0.5)	85 (0.7)	99 (1.2)	
Unknown	10,415 (33.1)	4,126 (34.0)	2,925 (34.5)	
BMI, Mean (SD), kg/m²	30.27(6.4)	31.17(6.7)	32.26(7.2)	<0.001
<25	4,634 (14.7)	1,431 (11.8)	787 (9.3)	<0.001
25-29.9	9,274 (29.4)	3,357 (27.7)	2,067 (24.4)	
30-34.9	6,067 (19.3)	2,531 (20.8)	1,827 (21.5)	
35-39.9	2,691 (8.5)	1,257 (10.4)	981 (11.6)	
40+	1,941 (6.2)	960 (7.9)	871 (10.3)	

Table 2 continued

Demographics/Baseline Parameter (Unit)	Goal I* (N=31,502)	Goal II (N=12,140)	Goal III (N=8,478)	P-value
BMI, Mean (SD), kg/m ²				
Unknown	6,895 (21.9)	2,604 (21.4)	1,945 (22.9)	
Baseline LDL-C, mg/dL	150 (35)	159 (35)	166 (36)	<0.001
<100	2,858 (9.1)	603 (5.0)	241 (2.8)	<0.001
100-129	5,178 (16.4)	1,682 (13.9)	931 (11.0)	
130-159	10,545 (33.5)	3,644 (30.0)	2,507 (29.6)	
160-189	9,507 (30.2)	4,005 (33.0)	2,751 (32.4)	
>190	3,414 (10.8)	2,206 (18.2)	2,048 (24.2)	
Diabetes Mellitus				
Diabetic	4,438 (14.1)	4,037 (33.3)	4,585 (54.1)	<0.001
Hypertension				
Hypertensive	13,189 (41.9)	6,818 (56.2)	5,252 (61.9)	<0.001
SBP				
Mean (SD)	129.76 (13)	131.72 (13)	133.59 (14)	<0.001
DBP				
Mean (SD)	78.31 (7.8)	79.18 (7.8)	79.98 (7.9)	<0.001
HDL				
Mean (SD)	51.85 (14)	50.10 (13)	48.78 (13)	<0.001

* Goal I: 80~100% of the follow-up period; Goal II: 79-50% of the period; Goal III: <50% of the period.

Table 3

Number of Events and Incidence Rate of CV Events by LDL-C Goal Attainment*

Goal Group	N	Person Years	Composite		MI	Angina	Cerebrovascular
Goal I	1,136	75,936	1.496	Case	232	142	762
				Incidence Rate	0.309	0.189	1.008
Goal II	501	29,179	1.717	Case	114	92	295
				Incidence Rate	0.396	0.319	1.016
Goal III	382	20,287	1.883	Case	78	72	232
				Incidence Rate	0.389	0.359	1.149
Total	2,019	12,540	1.610	Case	424	306	1,289
				Incidence Rate	0.342	0.247	1.033

* events per 100 person years

Table 4

Results of Discrete Time Logistic Model

Parameters	Odds Ratio	95% Confidence Interval		P Value
LDL-C, time-dependent [¶]				
At-Goal vs. Not-At-Goal	2.606	1.954	3.058	<.0001
No. of ATP III Risk Factors				
2~3 vs. 0~1	1.917	1.702	2.159	<.0001
CVD/CVD Equivalent vs. 0~1	2.993	2.543	3.523	<.0001
Age, years				
>65 vs. ≤65	2.721	2.394	3.093	<.0001
Female vs. Male	1.089	0.977	1.214	0.1125
Race				
African American vs. Caucasian	1.061	0.823	1.366	0.6486
Unknown vs. Caucasian	1.159	1.033	1.301	0.0121
Region				
South vs. Northeast	1.197	1.053	1.360	0.0060
Midwest vs. Northeast	1.189	1.020	1.386	0.0027
Insurance				
Commercial vs. Medicare	1.443	1.226	1.698	<.0001
Hypertension				
Yes vs. No	1.338	1.182	1.516	<.0001

[¶] The LDL-C was the time-dependent variable. Patients' LDL-C was measured quarterly, the status of being at-goal or not-at-goal was determined according to ATP-III guidelines.

* P-value was calculated using Tukey HSD test, to compare differences among categories within each characteristics group; i.e., Caucasian, Black, Hispanic, and other races were compared and the resulting p-value was reported here.

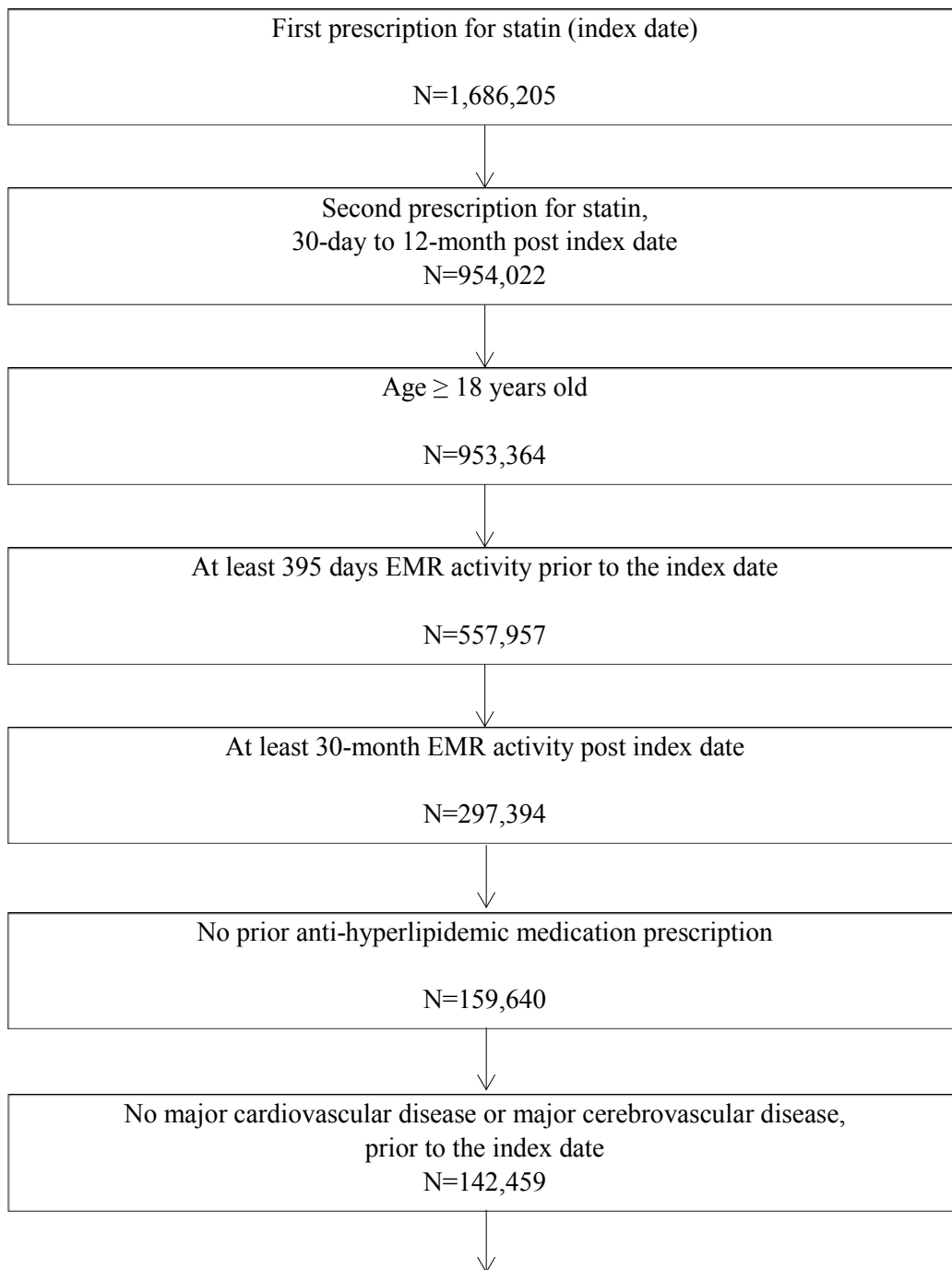


Figure 1 Flow Chart of Study Population Selection

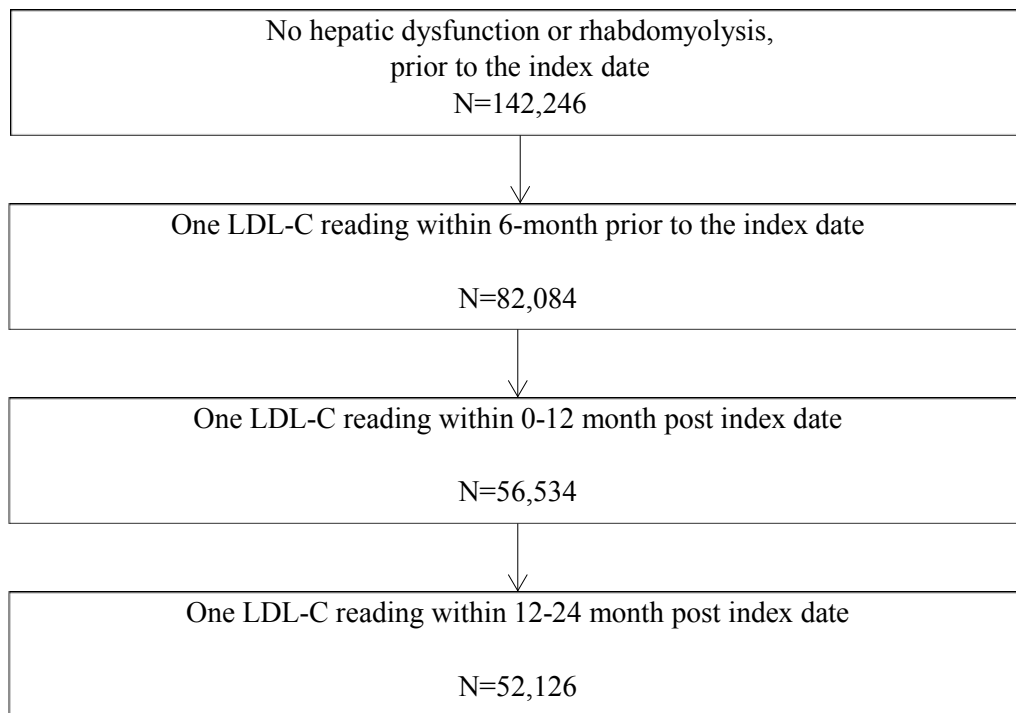


Figure 1 Continued

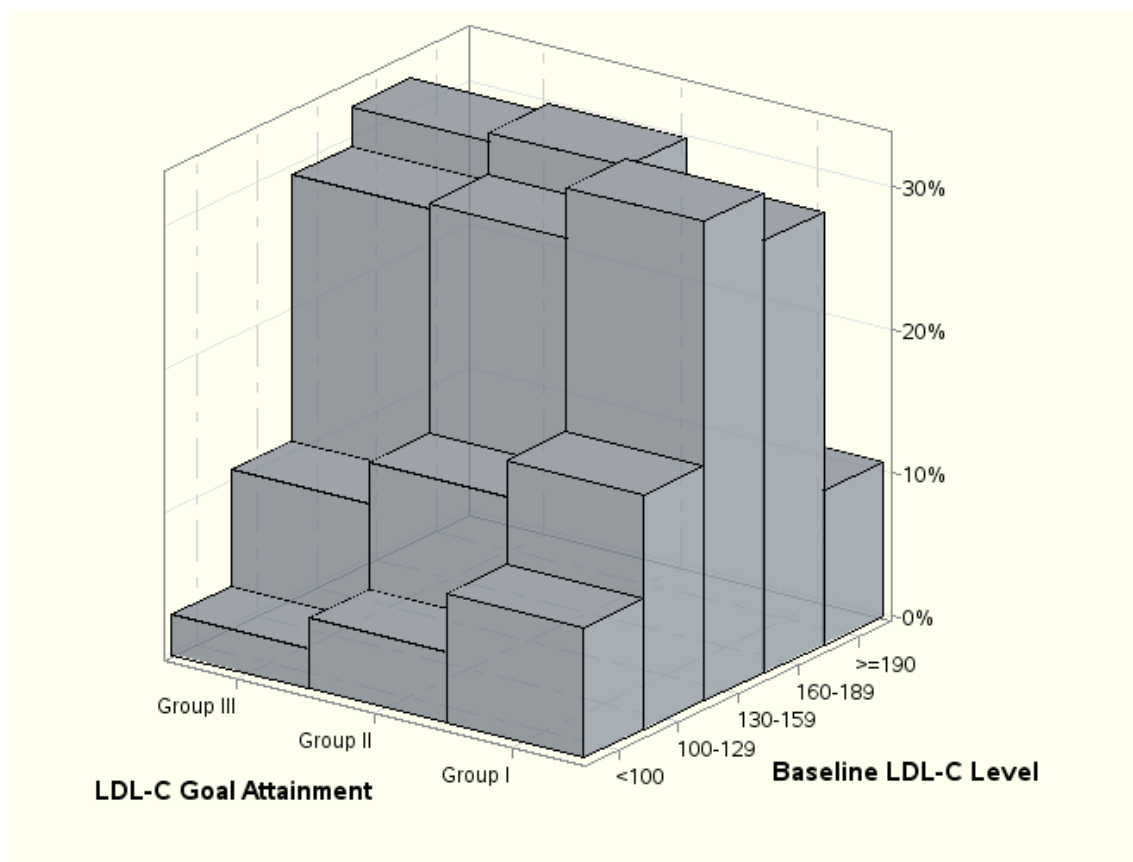


Figure 2 Proportion of Patients with Goal Attainment by Baseline LDL-C Stratum

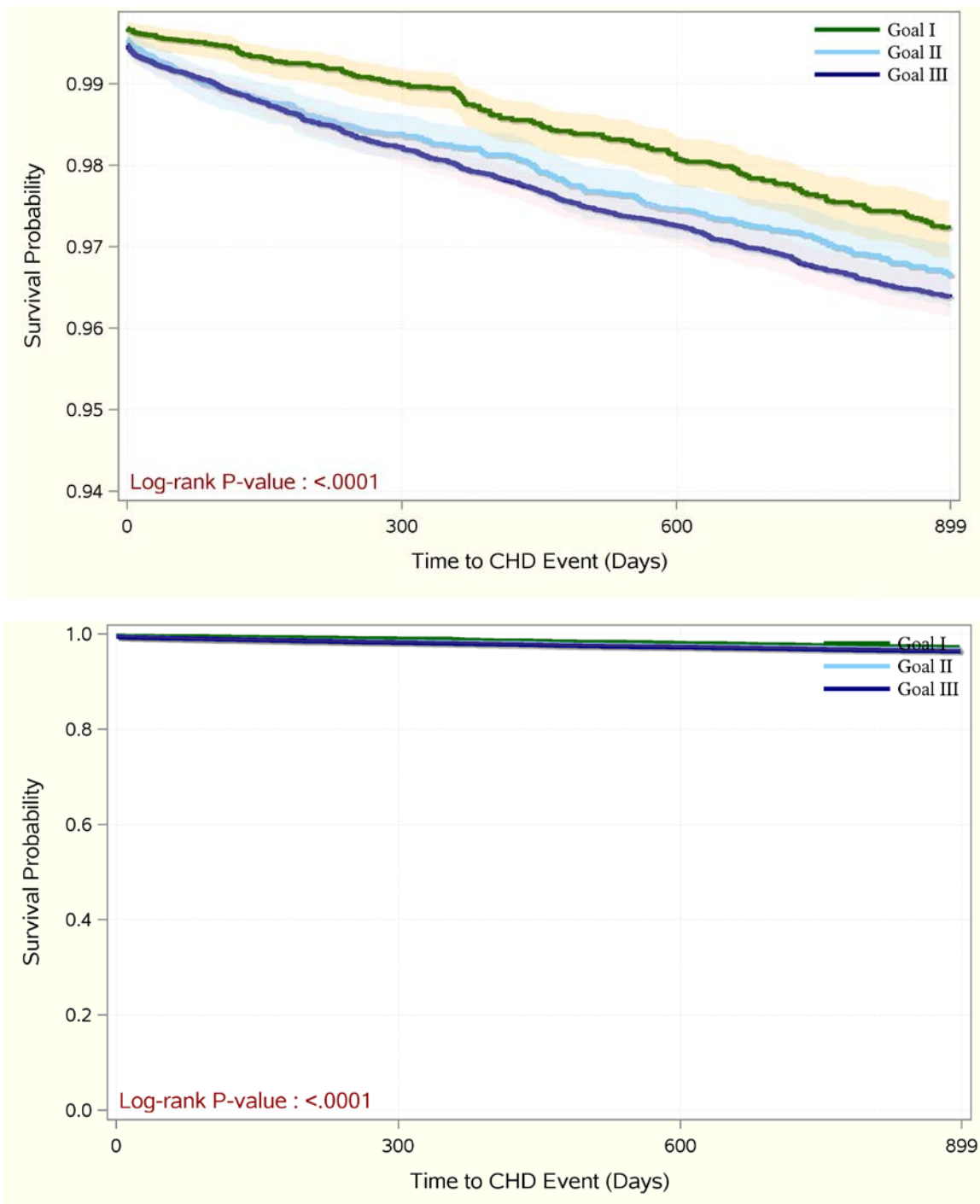


Figure 3 Kaplan-Meier Curve by Goal Attainment

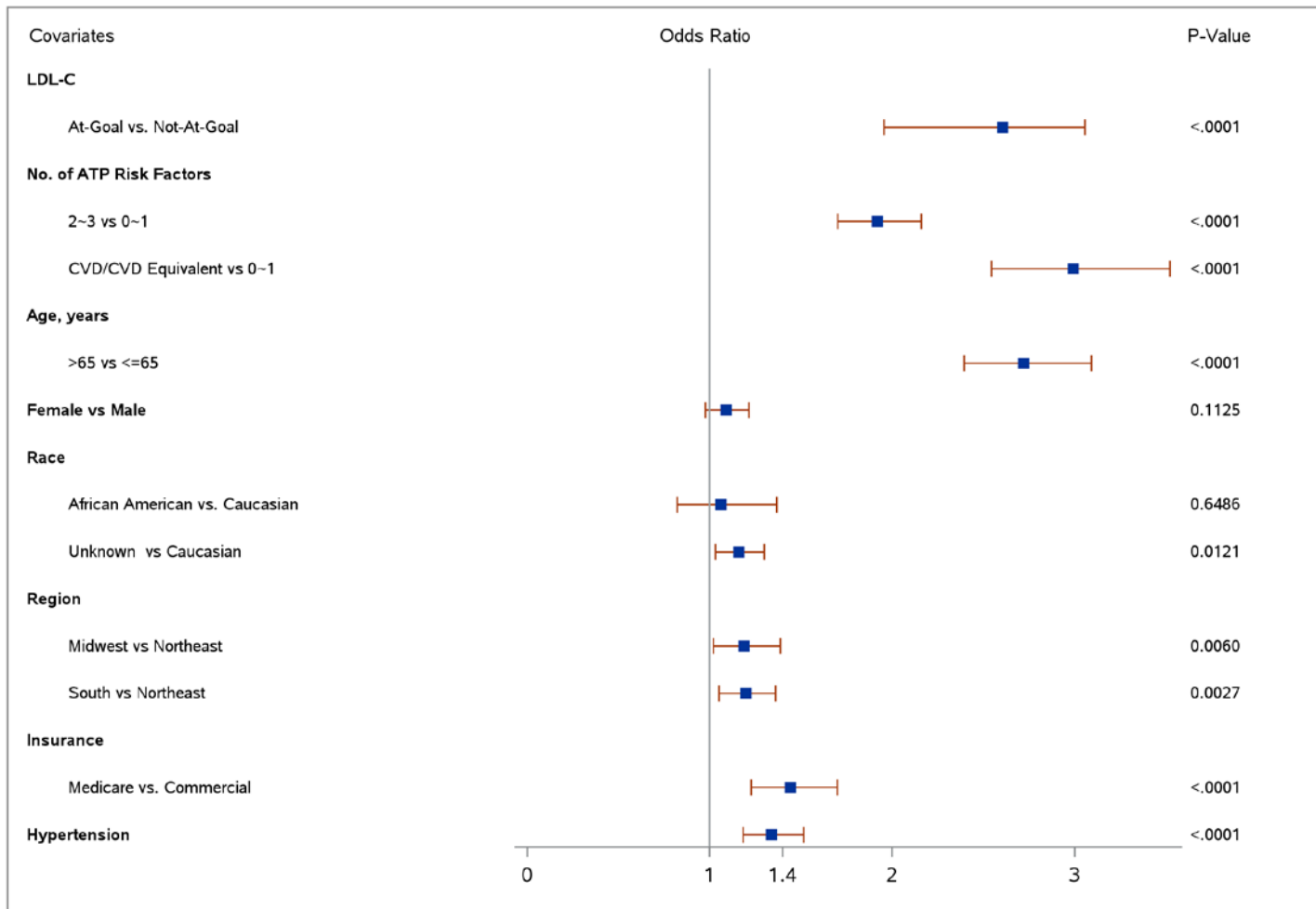


Figure 4 Forest Plot of Discrete Time Logistic Model

CHAPTER 6

DISCUSSION

This study of 52,126 patients in a nationwide EMR database between 1996 - 2010, found a significant association between the risk of CV events and LDL-C goal attainment. Notably, the study found that the likelihood of a CV event due to patients failing to attain or maintain LDL-C goal at any time during the follow-up period was 2.6 times compared to those achieving goals. The other factors with a significant association with CVD risk from highest to lowest in strength were ATP III risk group, age, hypertension, race, and region. These results suggested risk reduction of CVD risk with more consistent LDL-C goal attainment.

This study contributes to the literature by evaluating the real-world effects of LDL-C levels on CVD risks per risk-based targets in patients treated with a statin. The increase in CVD risk with goal attainment failure accentuated the importance of consistency in maintaining LDL-C goal status and suggested that LDL-C reduction should be the life-long primary target of cholesterol therapy for patient's identified at high risk for CVD [4]. Recently, the American College of Cardiology and American Heart Association together with the National Heart, Lung, and Blood Institute published new guidelines, which focus on risk-based treatment intensity versus specific LDL-C targets. The results presented here serve as evidence that while guidelines may now be less specific about LDL-C goals, reduction in LDL with statin treatment with a statin of

appropriate intensity per CV-risk remains relevant in primary prevention of CV events. Since ATP III, we have seen rises in prescriptions of statins in primary prevention [40]. However, as observed in this study, more than half (60%-85%) of the patients failed to maintain the LDL-C goal for at least 10% of the follow-up period, meaning that prescribing statins does not alone guarantee stable and consistent reduction in LDL-C levels. In addition to prescribing appropriate doses and statin potency, patient adherence to the long-term pharmacotherapy and non-adherence is also key to LDL-C goal attainment. Therefore, increasing in the overall utilization of statins does not assure an improvement in primary prevention outcomes across a population, and more systematic efforts in medication adherence improvement, disease, and wellness education should also be undertaken. These efforts could come as a collaboration of healthcare providers and payers, and studies have found that such patient-centered care management programs improve both clinical and economic outcomes [33].

The target population who were prescribed statins for primary prevention has been estimated in the tens of millions in the United States. A strength of this study is that it evaluates LDL-C reduction after statin therapy in a real-world setting using data from a large, national EMR database. With these data, the findings were not limited to a specific region or insurance type, and patients were not excluded due to poor control of comorbid conditions. Thus, this observational study demonstrates the effectiveness in the real-world setting, offering greater external validity than randomized clinical trials [34, 35].

Prevalence of diagnosed baseline hypertension (52.9%) in this study was low, which was not usually observed in clinics. However, this may represent under-reporting

of hypertension in the EMR as the percentage of patients commonly treated with antihypertensive medications was considerably higher (74.9%). While the reason for use of antihypertensive medications was not captured, this treatment rate is more consistent with what would be expected in this cohort [36].

In the early phase of this research, another stratifying algorithm which grouped patients by their first-goal-failure time (early failure/late failure/no failure) was used. This approach led to the realization that a first-goal-failure was not sensitive enough in classifying the exposure to elevated LDL-C. Thus, a time-dependent approach was adopted for this project.

This study contributes to quantification of time-variant LDL-C goal attainment and risk of CVD in a real-world setting, but it comes with several limitations. First, while a large national dataset, it is not nationally representative, and the population is skewed to patients with health insurance, and who are younger, non-African Americans. Second, the study includes patients with a minimum follow-up period and monitored by their provider more consistently, which might lead to better health outcomes. Finally, data for several factors that can influence CVD risk, including reliable smoking and alcohol consumption data, as well as diet and exercise information, are not captured in this EMR database. Further, pharmacy dispensing data are not available in EMR datasets, which limited our ability to control for medication adherence as a potential confounder. If a prescription order for a drug was not captured from the database or it was not in the medication list, it was assumed that there was no treatment, which could cause potential misclassification. Also, if baseline characteristics such as race, region, and insurance type were not reported, it was categorized as unknown/missing, which challenged the interpretation of results for

these characteristics. However, other than race, which is ubiquitously underreported in secondary datasets, missing data generally accounted for a small proportion of records of data obtained from the EMR database.

In conclusion, this study found that failure to attain LDL-C goal at any time during the follow-up period increased the likelihood of CV event occurrence. Future studies, such as evaluation of real-world treatment outcomes under the new ACC/AHA guidelines, or a study that controls for adherence to isolate if failure to attain or maintain LDL-C goal is treatment inertia, are warranted.

APPENDIX A

CODES

Table 5
Codes for Identifying Antihyperlipidemics Medications

GPI subclass for Index Date Prescription (Statins)	Generic name
HMG COA Reductase Inhibitors	Atorvastatin Calcium
HMG COA Reductase Inhibitors	Fluvastatin Sodium
HMG COA Reductase Inhibitors	Lovastatin
HMG COA Reductase Inhibitors	Pravastatin Sodium
HMG COA Reductase Inhibitors	Rosuvastatin Calcium
HMG COA Reductase Inhibitors	Simvastatin
HMG COA Reductase Inhibitors	Pitavastatin

Table 6
Diagnose Codes

Diagnoses	Codes	Description
Ischemic Heart Disease (MI)	410.x	Acute myocardial infarction
	411.x	Other acute and subacute forms of ischemic heart disease
	412.x	Old myocardial infarction
Ischemic Heart Disease (Angina)	413.x	Angina pectoris
Ischemic Heart Disease (Other forms)	414.x	Other forms of chronic ischemic heart disease
Cerebrovascular Disease	430.x	Subarachnoid hemorrhage
	431.x	Intracerebral hemorrhage
	432.x	Other and unspecified intracranial hemorrhage
	433.x	Occlusion and stenosis of precerebral arteries without infarct
	434.x	Occlusion of cerebral arteries without infarct
	436.x	Acute, but ill-defined, cerebrovascular disease
	437.x	Other and ill-defined cerebrovascular disease
Peripheral Vascular Disease	438.x	Late effects of cerebrovascular disease
	443.x	Other peripheral vascular disease

Table 6 continued

Diagnoses	Codes	Description
Non-coronary forms of atherosclerotic disease (Abdominal aortic aneurysm)	441.3x	Abdominal aneurysm ruptured
	441.4x	Abdominal aneurysm without rupture
Diagnoses	Codes	Description
Non-coronary forms of atherosclerotic disease (Abdominal aortic aneurysm)	442.x	Other aneurysm
Non-coronary forms of atherosclerotic disease (Carotid artery disease)	433.1x	Occlusion and stenosis of carotid artery
Hypertension	401.xx	Essential hypertension
	402.xx	Hypertensive heart disease
	404.xx	Hypertensive heart and kidney disease
	405.x	Secondary hypertension
Rhabdomyolysis	728.88	Rhabdomyolysis

Table 7

Codes for Identifying Antihyperlipidemics Medications

GPI subclass for Post Index Date Prescription	Generic name
Non-Statins	
Antihyperlipidemics - misc.	Omega-3-acid ethyl esters
	Policosanol
Bile Acid Sequestrants	Cholestyramine
	Cholestyramine Light
	Colesevelam HCL
	Colestipol HCL
Fibric Acid Derivatives	Choline Fenofibrate
	Fenofibrate
	Fenofibrate Micronized
	Fenofibric Acid
	Gemfibrozil
Intestinal Cholesterol Absorption Inhibitors	Ezetimibe
Nicotinic Acid Derivatives	Niacin
Combinations	Generic name
Antihyperlipidemics	Ezetimibe-Simvastatin

Table 7 continued

GPI subclass for Post Index Date Prescription	Generic name
HMG COA Reductase Inhibitors	Niacin-Lovastatin
	Aspirin Buffered-Pravastatin
	Misc Nat HMG COA Reduct. Inhib.
	Niacin-Simvastatin

APPENDIX B

SUMMARY OF CLINICAL TRIALS

MEGA

The MEGA study initiated 10-20mg/d pravastatin to patients aged 40-70 years old, who met the inclusion criteria: TC 220-270 mg/dL, bodyweight > 40 kg[10]. A total of 7,832 patients were enrolled and followed up for a mean of 5.3 years. A total of 3,866 patients were enrolled in the case arm and 3,966 in the control arm. In the pravastatin group, 95% patients were compliance with medication at year 1, 90% at year 5, and 89% at year 9. Primary endpoint was CVD which included MI (HR=0.67, 95% CI [0.49, 0.91], P=0.01), sudden cardiac death (HR=0.51, 95% CI [0.18, 1.50], P=0.21), angina (HR=0.83, 95% CI [0.56, 1.23], P=0.35), coronary revascularization (HR=0.60, 95% CI [0.41, 0.89], P=0.01). Significant reductions in TC, LDL-C were noted in the case arm compared with the control arm. TC decreased by 12% in the pravastatin group at year 5 compared with 3% in the placebo group; LDL: -19% vs. -5%; TG: -13% vs. -10%; HDL: 7% vs. 5%. This study showed that low doses of pravastatin can reduce the risk of MI, with small to moderate reductions in TC and LDL-C concentration. This study also showed no statistically significant difference in sudden cardiac death, angina, as well as coronary revascularization between two groups.

ASPEN

ASPEN enrolled patients aged 40-75 years old, who had type 2 diabetes, and met serum lipid inclusion criteria[7]. Exclusion criteria included type 1 diabetes; myocardial infarction, interventional procedure, or episodes of unstable angina ≤ 3 months before screening; HbA1C >10%; active liver disease or hepatic dysfunction; severe renal dysfunction or nephrotic syndrome; congestive heart failure treated with digoxin; creatine phosphokinase $\geq 3 \times$ the upper limit of normal; blood pressure >160/100 mmHg; BMI >35

kg/m²; abuse of alcohol and/or drugs; and placebo run-in compliance rate <80%. There were 959 patients recruited in the atorvastatin group, and 946 in the placebo group. After a 4-year follow-up, 100 patients developed primary composite endpoint events (MI, stroke, sudden cardiac death, heart failure, arrhythmic non-sudden CV death, revascularization, coronary artery bypass grafting, resuscitated cardiac arrest, worsening or unstable angina hospitalization) in the case arm, and 102 in the control arm, with hazard ratio of 0.9 (95% CI [0.73, 1.12], P=0.341). As for the secondary endpoint all-cause mortality, there were 44 events out of 959 in the case arm compared with 41 events out of 946 in the control arm, with a hazard ratio of 1.06 (95% CI [0.69, 1.62], P>0.05). The results indicated that no statistically significant difference lied between atorvastatin and placebo groups in terms of composite endpoint as well as all-cause mortality. Significant mean percent reductions from baseline were observed for LDL-C, TC, and TG in the atorvastatin group compared with the placebo group.

JUPITER

The results of JUPITER were so far the most promising on primary prevention in statin therapy[41]. The study enrolled 17,802 people with LDL-C less than 130 mg/dL and high-sensitivity C-reactive protein (hsCRP) larger than 2.0 mg/L, and issued 20 mg daily rosuvastatin to patients randomly selected in control group. Exclusion criteria were: current use of statin or other lipid-lowering therapies, including fibrates, niacin, and bile-acid sequestrants; known hypersensitivity to statin therapy; current use of postmenopausal oral hormone therapy; current use of immune-suppressants; active liver disease or elevated liver enzymes; creatine kinase [CK] >3 times ULN; diabetes mellitus (fasting serum glucose >126 mg/dL, or use of insulin or oral hypoglycemic agent);

uncontrolled hypertension (systolic or diastolic blood pressure >190 or 100 mm Hg, respectively); history of cancer, except non-malignant skin cancer, within the past 5 years; uncontrolled hypothyroidism; chronic inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease; history of alcohol or drug abuse within the past year; and serious medical or psychological conditions that may compromise successful study participation. Terminated over a median of 1.9 years of follow-up, which was previously scheduled around 5 years, JUPITER found a 46.8% and 45.8% decrease in LDL for women and men, respectively, and 20% all-cause mortality reduction. The primary endpoint, which was a combined outcome of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV events, showed a hazard ratio of 0.56 (95% CI [0.46, 0.69], $P < 0.001$). The secondary endpoint which was all-cause mortality showed statistically significant (HR=0.8, 95% CI [0.66, 0.96], $P = 0.02$).

However, the efficacy and effectiveness of JUPITER was criticized immediately after the results were released. Yusuf et al. pointed out that JUPITER Independent Data and Safety Monitoring Board (IDSMB) terminated the trial after 1.9 years median follow-up which exaggerated its findings since given a longer follow-up time, the early effects of the benefits seen in JUPITER would diminish [42]. After re-examining the clinical outcomes in JUPITER, de Lorgeril et al. found cardiovascular mortality (fatal stroke plus fatal MI) to be identical between the control and placebo groups (12 vs. 12)[43]. Therefore, they concluded that “JUPITER dataset appears biased” and “should have led to the continuation of the trial rather than to its premature ending”. Kaul et al. also questioned the early moratorium by citing results from a study done by Bassler et al.,

which compared 91 truncated with 424 matched nontruncated RCTs, and found the pooled ratio of relative risks as 0.71(95% CI [0.65, 0.77]) suggesting that early truncation of clinical trials could be premature[44]. Kaul also cited two other trials for supporting the idea that early benefits seen in truncated trials would disappear later on final evaluation [45].

CARDS

In CARDS, there were overall 2,838 patients aged 40–75 years old, randomized to atorvastatin 10 mg daily (n=1428) or placebo (n=1410)[8]. Patient inclusion criteria were no documented previous history of cardiovascular disease, LDL-C \leq 160.07 mg/dL, fasting TG \leq 603 mg/dL, and at least one of the following: type 2 diabetes, retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of the following: acute coronary heart disease events, coronary revascularization, or stroke. Since the early stopping rule for efficacy was met, the trial was terminated 2 years earlier. With a median follow-up of 3.9 years, the relative reduction rate for at least one major CV event was 0.63 (95% CI [0.48, 0.83], p=0.001), and for stroke was 0.52 (95% CI [0.31, 0.89], p=0.001). There was a 40% decrease in LDL-C level, 26% decrease in HDL-cholesterol level, 19% decrease in TG level, and 1% increase in TC level with p-value all less than 0.01. However, there was no statistically significant difference in the all-cause mortality rate between statin and placebo groups.

AFCAPS

A total of 6,605 patients with average TC and LDL-C and below-average HDL-C were recruited in AFCAPS. Exclusion criteria were hypertension, secondary

hyperlipidemia, type 1 or 2 diabetes. After an average follow-up of 5.2 years, lovastatin reduced the incidence of major coronary events (HR=0.63, 95% CI [0.50, 0.79], P<0.001), MI (HR=0.6, 95% CI [0.43, 0.83], P=0.002), unstable angina (HR=0.68; 95% CI [0.49, 0.95], P=0.02), coronary revascularization procedures (HR=0.67, 95% CI [0.52, 0.85], P=0.001), coronary events (HR=0.75, 95% CI [0.61, 0.92], P=0.006), and cardiovascular events (HR=0.75, 95% CI [0.62, 0.91], P=0.003). Lovastatin (20-40 mg daily) reduced LDL-C by 25% to 115 mg/dL and increased HDL-C by 6% to 39 mg/dL. There were totally 80 deaths in case cohort and 77 deaths in control cohort, with hazard ratio of 1.04 (95% CI [0.76, 1.42], P>0.05). AFCAPS did not reveal a trend of difference in mortality between case and control arms either.

APPENDIX C

TABLES AND FIGURES SUMMARY OF CLINICAL TRIALS

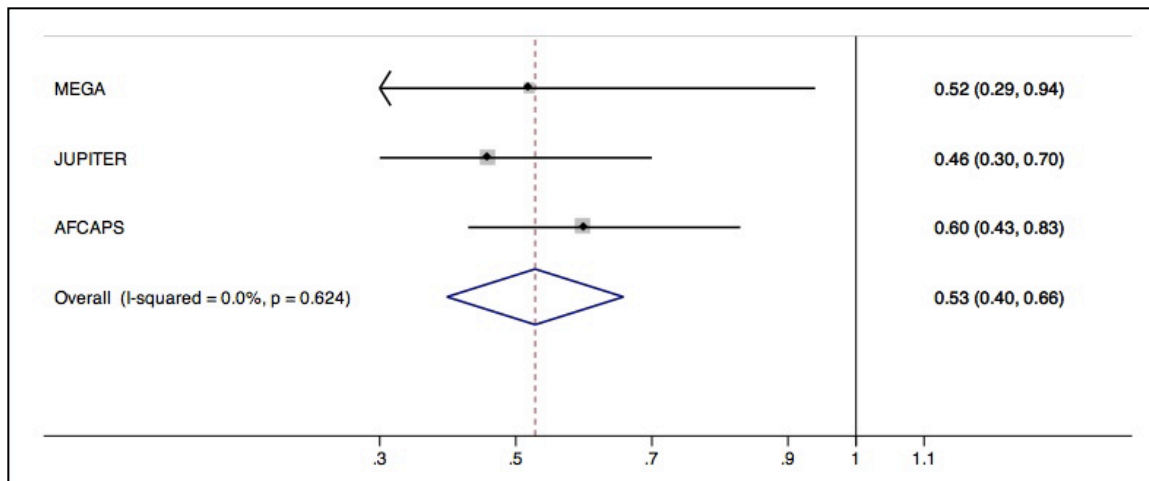


Figure 5 Primary Prevention RCTs Results on Myocardial Infarction

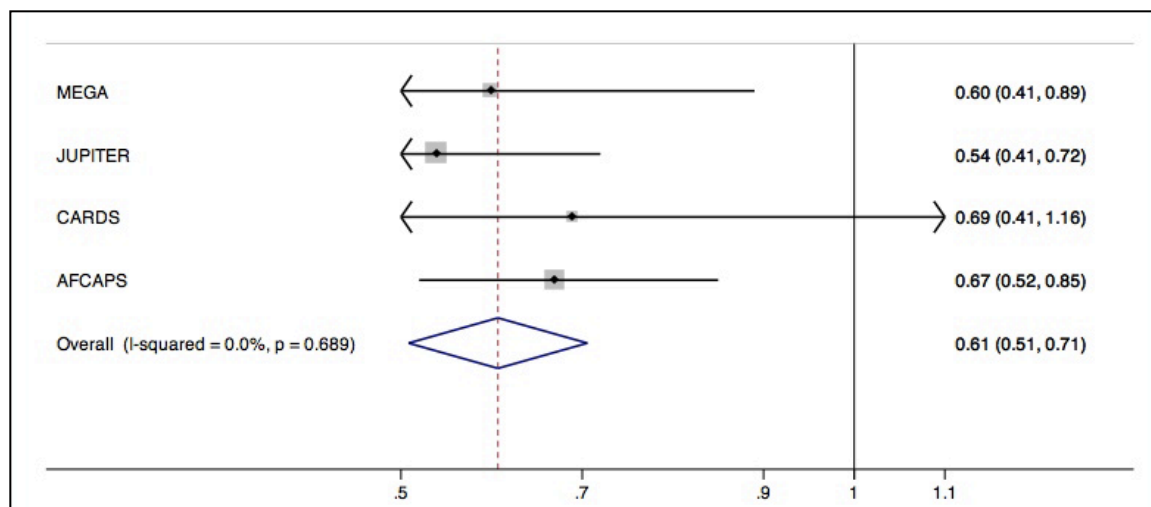


Figure 6 Primary Prevention RCTs Results on Coronary Revascularization

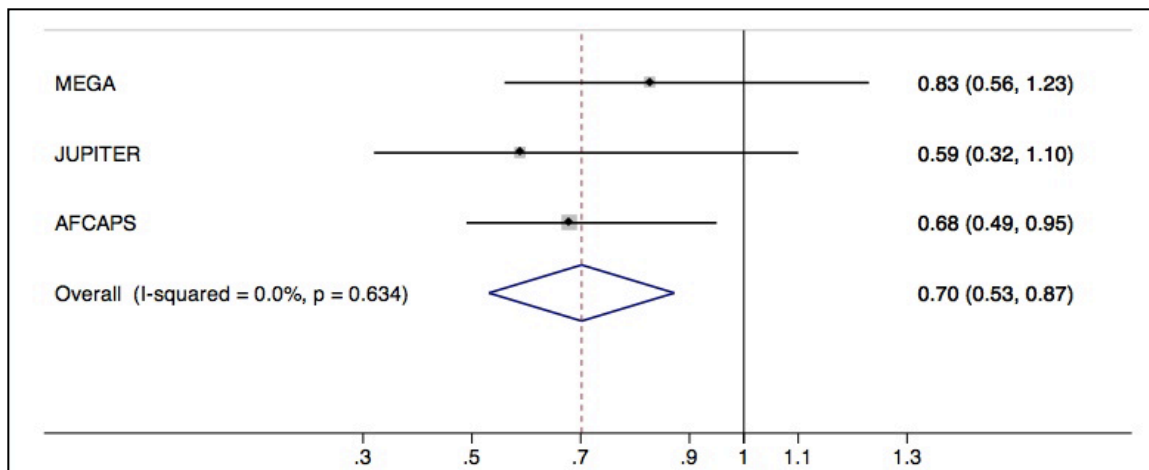


Figure 7 Primary Prevention RCTs Results on Angina

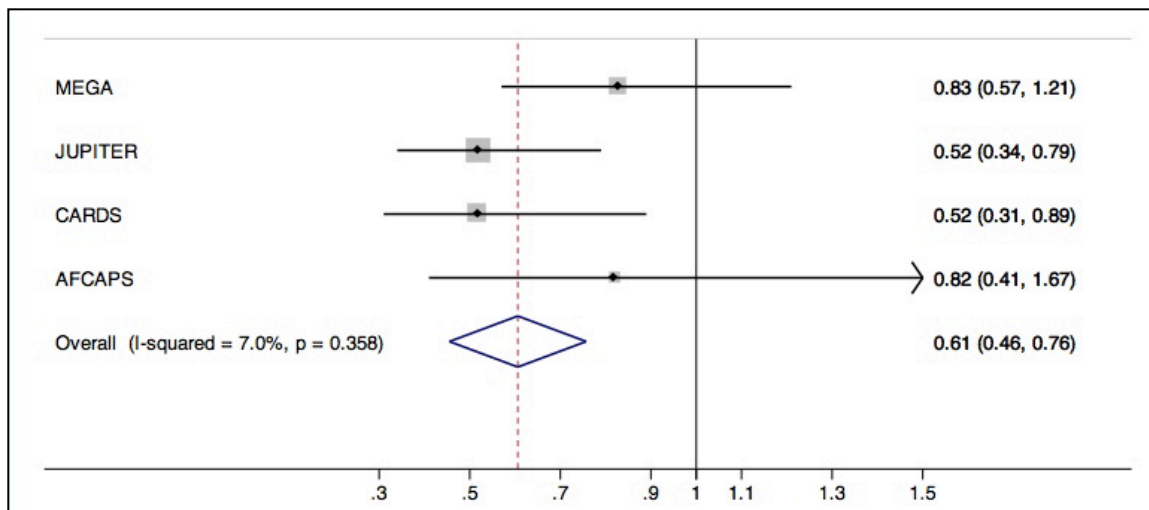


Figure 8 Primary Prevention RCTs Results on Stroke

Table 8

Relative Risk for ATP III Risk Factors Defined by ATP III

	Men			Women		
	Relative Risk	95% CI	P-value	Relative Risk	95% CI	P-value
Age (y)	1.05	1.04,1.06	<0.001	1.04	1.03,1.06	<0.001
Blood Pressure						
Normal	1.00			1.00		
Stage I	1.73	1.32,2.26	<0.001	1.34	0.88,2.05	
Stage II	1.92	1.42, 2.59	<0.001	2.19	1.46, 3.27	<0.001
Cigarette use (y/n)	1.71	1.39-2.10	<0.001	1.49	1.13-1.97	<0.01
LDL-C, mg/dL						
<130	1.00			1.00		
130-159	1.19	0.91-1.54	≥0.05	1.24	0.84-1.81	≥0.05
≥160	1.74	1.36-2.24	<0.001	1.68	1.17-2.40	<0.01
HDL-C, mg/dL						
<35	1.46	1.15-1.85	<0.01	2.08	1.33-3.25	<0.01
35-39	1.00			1.00		
≥40	0.61	0.41-0.91	<0.05	0.64	0.47-0.87	<0.01

Table 9

LDL-C Goals in Different Risk Categories

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CVD or CVD Risk Equivalents*	<100 mg/dL	≥100 mg/dL	≥130 mg/dL
2+ ATP III Risk Factors	<130 mg/dL	≥130 mg/dL	≥130 mg/dL or ≥160 mg/dL†
0-1 ATP III Risk Factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL

* CVD risk equivalents include: other clinical forms of atherosclerotic disease (Peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease), diabetes, and multiple risk factors. Source: ATP III report, *Circulation*, July 13, 2004.

† Depends on 10-year risk based on Framingham Study, electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

Table 10

Primary Prevention RCTs on Evaluation of Statin Therapy

Author	Title	Study No.	Intervention	Control	Follow-up	Exclusion Criteria	Compliance Rate
Kyoichi et al, 2006	MEGA	7,832	Pravastatin	Diet	5.3	Indication of secondary prevention	>89%
Knopp et al, 2006	ASPEN	1,905	Atorvastatin	Placebo	4.3	BP>160/100, BMI>35, run-in compliance rate <80%	>80%
Mora et al, 2010	JUPITER	17,802	Rosuvastatin	Placebo	1.9	Type 2 diabetes, BP>190/100	>80%
Helen et al, 2004	CARDS	2,838	Atorvastatin	Placebo	4.0	Indication of secondary prevention	>80%
Downs et al, 1998	AFCAPS	6,605	Lovastatin	Placebo	5.2	Type 2 diabetes, weight more than 50% greater than the desirable limit for height	NA

Table 11
RCTs Results for Statin Effect on Cholesterol Lowering

Trials	Baseline		At 12 months		Change		Change Percentage		
JUPITER	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	
	LDL	108.0	108.0	55.0	110.0	-51.0	4.0	-47.2%	3.7%
	HDL	49.0	49.0	52.0	50.0	3.0	1.0	6.1%	2.0%
	TG	118.0	118.0	99.0	119.0	-17.0	-1.0	-14.4%	-0.9%
MEGA	Pravastatin	Diet	Pravastatin	Diet	Pravastatin	Diet	Pravastatin	Diet	
	LDL	156.6	156.6	127.6	153.5	-29	-3.1	-18.5%	-2.0%
	HDL	57.6	57.6	60.3	58.4	2.7	0.8	4.7%	1.4%
	TG	128.2	128.2	109.9	117.8	-18.3	-10.4	-14.3%	-8.1%
	TC	242.4	242.4	213.4	239.3	-29.0	-3.1	-12.0%	-1.3%
ASPEN*	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo	
	LDL	114	114	79.3	113.5	-34.8	-0.6	-30.5%	-0.5%
	HDL	48	47	48.9	46.8	0.9	-0.2	1.9%	-0.3%
	TG	145	144.5	138.2	155.0	-6.8	10.5	-4.7%	7.2%
	TC	195	195	156.4	192.3	-38.6	-2.7	-19.8%	-1.4%

Table 11 continued

Trials	Baseline		At 12 months		Change		Change Percentage	
	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
AFCAPS								
LDL	92.0	158.4	115	156	-23.0	2.4	-25.0%	1.5%
HDL	41.5	38.5	39	38	2.5	0.5	6.0%	1.2%
TG	124.3	159.3	143	163	-18.7	-3.7	-15.0%	-2.3%
TC	155.4	230.1	184	228	-28.6	2.1	-18.4%	0.9%
CARDS								
LDL	117.5	116.8	71.9	119.9	-45.6	3.1	-38.8%	2.7%
HDL	53.7	54.9	53.0	53.0	-0.7	-1.9	-1.3%	-3.5%
TG	173.6	171.8	143.3	169.1	-33.0	2.6	-19.0%	1.5%
TC	207.2	206.9	159.3	204.2	-53.7	2.7	-25.9%	1.3%

* ASPEN only provided data on year 4

Table 12

Primary Prevention RCTs Results on Primary Endpoint

Title	Events for Primary Endpoint		Hazard Ratio	95% CI		P-value
	Statin	Placebo				
MEGA	66	101	0.67	0.49	0.91	0.01
ASPEN	100	102	0.90	0.73	1.12	0.34
JUPITER	142	251	0.56	0.46	0.69	<0.001
CARDS	83	127	0.63	0.48	0.83	0.001
AFCAPS	116	183	0.63	0.50	0.79	<0.001

Table 13

Number of Events and Incidence Rate of CV Events by ATP III Risk Factor

ATP III Risk FactorEvent/Rate*	MI	Anigna	Cerebrovascular	Composite
0~1	55 0.109	60 0.119	259 0.510	374 0.734
2+	110 0.260	97 0.229	528 1.237	735 1.713
CVD/CVD Equivalent	259 0.833	150 0.482	503 1.604	912 2.892
Total	424 0.342	307 0.248	1,290 1.033	2,021 1.61

* Rate was calculated as number of events per 100 person-years

Table 14

Meta-analysis Results in Statins Therapy in Primary Prevention

Title	Major Coronary		Major Cerebrovascular		All-cause mortality		CVD mortality	
	Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value
Pignone et al	0.70	<0.05	NA	NA	0.94	>0.05	0.71	<0.05
Choudhry et al	0.71	<0.05	0.86	0.02	0.92	>0.05	0.77	<0.05
Brugts et al	0.70	<0.05	0.81	<0.05	0.88	<0.05	0.88	>0.05
Ray et al	NA	NA	NA	NA	0.91	>0.05	NA	NA
Cochrane Review	0.72	<0.05	0.78	<0.05	0.84	<0.05	0.78	>0.05

Table 15

Summary of Studies on Suboptimal Use of Statin and Reduction of CV Events

Title	Population	Comparator	Follow-up ¹	End points	Risk Reduction	
					Rate ²	95% CI
Perreault et al, 2007	20,543	PDC ³ ≥90% vs. <90%	1.6 years	Non-fatal coronary artery disease event ⁴	0.81	0.67, 0.97
Perreault et al, 2009	115,290	MPR ⁵ ≥80% vs. <20%	6 months- 6.5 years	Coronary artery disease event ⁶	0.82	0.77, 0.87
Perreault et al, 2009	112,092	MPR ≥80% vs. <20%	2.95 years	Cerebrovascular disease ⁷	0.74	0.65, 0.84

¹ Mean follow-up was reported here.

² Risk reduction was compared between case and control after one-year statin therapy treatment.

³ Proportion of Days Covered, defined as the number of days medication was supplied divided by the observation time interval.

⁴ Non-fatal coronary artery disease was defined as a composite end-point of nonfatal myocardial infarction or angina; a revascularization procedure, angioplasty, coronary artery bypass graft; or initiation of treatment with a nitrate drug.

⁵ Medication Possession Ratio, defined as number of day's supply of medication filled divided by the length of follow-up (from the beginning of first fill through the end of last fill).

⁶ Coronary artery disease was defined as myocardial infarction, angina, coronary procedure, use of nitrate drug or death.

REFERENCES

1. Roger, V.L., et al., *Heart Disease and Stroke Statistics--2011 Update: A Report from the American Heart Association*. Circulation, 2010. **123**(4): e18-e209.
2. Krumholz, H.M., et al., *Mortality, Hospitalizations, and Expenditures for the Medicare Population Aged 65 Years or Older, 1999-2013*. JAMA, 2015. **314**(4): p. 355-65.
3. Krumholz, H.M., S.L. Normand, and Y. Wang, *Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011*. Circulation, 2014. **130**(12): p. 966-75.
4. Wilson, P.W., et al., *Prediction of coronary heart disease using risk factor categories*. Circulation, 1998. **97**(18): p. 1837-47.
5. Panel, T.R.o.t.N.C.E.P.N.E., *Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)*. JAMA, 2001. **285**(19): p. 2486-97.
6. Stone, N.J., et al., *2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*. J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2889-934.
7. Yeboah, J., et al., *Implications of the new American College of Cardiology/American Heart Association cholesterol guidelines for primary atherosclerotic cardiovascular disease event prevention in a multi ethnic cohort: Multi-Ethnic Study of Atherosclerosis (MESA)*. Am Heart J, 2015. **169**(3): p. 387-395 e3.
8. Fihn, S.D., et al., *2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons*. J Thorac Cardiovasc Surg, 2015. **149**(3): p. e5-23.

9. Adhyaru, B.B. and T.A. Jacobson, *New cholesterol guidelines for the management of atherosclerotic cardiovascular disease risk: a comparison of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines with the 2014 National Lipid Association recommendations for patient-centered management of dyslipidemia*. *Cardiol Clin*, 2015. **33**(2): p. 181-96.
10. Taylor F, W.K., Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S, *Statins for the primary prevention of cardiovascular disease (Review)*. *Cochrane Database of Systematic Reviews*, 2013(1). Art. No.: CD004816.
11. Pignone, M., C. Phillips, and C. Mulrow, *Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials*. *BMJ*, 2000. **321**(7267): p. 983-6.
12. Thavendiranathan, P., et al., *Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials*. *Arch Intern Med*, 2006. **166**(21): p. 2307-13.
13. Ray, K.K., et al., *Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants*. *Arch Intern Med*, 2010. **170**(12): p. 1024-31.
14. Knopp, R.H., et al., *Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN)*. *Diabetes Care*, 2006. **29**(7): p. 1478-85.
15. Colhoun, H.M., et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial*. *Lancet*, 2004. **364**(9435): p. 685-96.
16. Ridker, P.M., et al., *Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein*. *N Engl J Med*, 2008. **359**(21): p. 2195-207.
17. Mizuno, K., et al., *Usefulness of pravastatin in primary prevention of cardiovascular events in women: analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study)*. *Circulation*, 2008. **117**(4): p. 494-502.
18. Furberg, C.D., et al., *Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group*. *Circulation*, 1994. **90**(4): p. 1679-87.
19. Ohsfeldt, R.L., et al., *Statin cost-effectiveness comparisons using real-world effectiveness data: formulary implications*. *Value Health*, 2008. **11**(7): p. 1061-9.

20. Spinler, S.A., et al., *Frequency of Attainment of Low-Density Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol Goals in Cardiovascular Clinical Practice (from the National Cardiovascular Data Registry PINNACLE Registry)*. Am J Cardiol, 2015. **116**(4): p. 547-553.
21. Baessler, A., et al., *Failure to achieve recommended LDL cholesterol levels by suboptimal statin therapy relates to elevated cardiac event rates*. Int J Cardiol, 2005. **101**(2): p. 293-8.
22. Brubaker, P.H., L.A. Kaminsky, and M.H. Whaley, *Coronary artery disease : essentials of prevention and rehabilitation programs*. 2002, Champaign, IL. ; Leeds: Human Kinetics. xi, 364 p.
23. Emerging Risk Factors, C., et al., *Major lipids, apolipoproteins, and risk of vascular disease*. JAMA, 2009. **302**(18): p. 1993-2000.
24. Ehrman, J.K., *ACSM's resource manual for Guidelines for exercise testing and prescription*. 6th ed. 2010, Philadelphia, Pa. ; London: Lippincott Williams & Wilkins. xxiv, 868 p.
25. Law, M.R., N.J. Wald, and A.R. Rudnicka, *Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis*. BMJ, 2003. **326**(7404): p. 1423.
26. Ridker, P.M., *Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial*. Circulation, 2003. **108**(19): p. 2292-7.
27. Downs, J.R., et al., *Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study*. JAMA, 1998. **279**(20): p. 1615-22.
28. Riche, D.M. and K.S. McClendon, *Role of statins for the primary prevention of cardiovascular disease in patients with type 2 diabetes mellitus*. Am J Health Syst Pharm, 2007. **64**(15): p. 1603-10.
29. Ebrahim, S., et al., *Multiple risk factor interventions for primary prevention of coronary heart disease*. Cochrane Database Syst Rev, 2011. **1**: p. CD001561.
30. Brugts, J.J., et al., *The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials*. BMJ, 2009. **338**: p. b2376.

31. Nakamura, H., et al., *Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial*. Lancet, 2006. **368**(9542): p. 1155-63.
32. Bates, T.R., V.M. Connaughton, and G.F. Watts, *Non-adherence to statin therapy: a major challenge for preventive cardiology*. Expert opinion on pharmacotherapy, 2009. **10**(18): p. 2973-85.
33. McAdam-Marx, C., et al., *The effect of a diabetes collaborative care management program on clinical and economic outcomes in patients with type 2 diabetes*. J Manag Care Spec Pharm, 2015. **21**(6): p. 452-68.
34. Garrison, L.P., Jr., et al., *Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report*. Value Health, 2007. **10**(5): p. 326-35.
35. Black, N., *Why we need observational studies to evaluate the effectiveness of health care*. BMJ, 1996. **312**(7040): p. 1215-8.
36. Wong, N.D., et al., *Global cardiovascular risk associated with hypertension and extent of treatment and control according to risk group*. Am J Hypertens, 2012. **25**(5): p. 561-7.