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Using the Medication Cabinet to Predict Fall Risk In Elderly Adults

Jessica Lopez
University of the Pacific, j_lopez9@u.pacific.edu

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USING THE MEDICATION CABINET TO PREDICT FALL RISK IN ELDERLY
ADULTS

by

Jessica M. Lopez

A Thesis Submitted to the
Graduate School
In Partial Fulfillment of the
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College of the Pacific
Health, Exercise and Sport Sciences Department

University of the Pacific
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2017
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Jessica M. Lopez

APPROVED BY:

Thesis Advisor: Courtney D. Jensen, Ph.D.
Committee Member: Mark Van Ness, Ph.D.
Committee Member: Lewis E. Jacobsen, MD.
Department Chair: Mark Van Ness, Ph.D.
Dean of Graduate School: Thomas H. Naehr, Ph.D.
DEDICATION

This thesis is dedicated to my husband, Aldo-Chentte Ruiz. Thank you for always being my number one fan and never allowing me to give up on my ultimate goal of becoming a PT. Without your love and support throughout this master’s program, I would never have been able to accomplish as much as I did during these past two years. I can’t wait for our next adventure with PT school at Samuel Merritt University! Thank you from the bottom of my heart.
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Using the Medication Cabinet to Predict Fall Risk in Elderly Adults

Abstract

by

Jessica M. Lopez

University of the Pacific
2017

Background: In the United States, 30-60% of older adults fall each year; 10-20% of these falls result in injury, hospitalization, or even death. Better prevention of falls in this population may be facilitated by broader identification of risk factors. The use of statins has emerged as a potential risk factor, but the data provide conflicted results.

Purpose: To examine the relationship between statin use and falls among community-dwelling older adults.

Methods: We evaluated the patient registry of a Level 1 trauma center. All patients aged ≥ 50 years who were admitted for falls in 2015 were included (n=615). Many of these patients had been previously admitted for falls and many were later readmitted for falls. We analyzed predictors of both prior admission and readmission with linear regressions. Independent variables were self-reported balance problems, diagnosis of dementia, and the use of statins.
Results: On average, patients admitted for falls were 79.9 ± 9.3 years old and 28% (n=173) were taking statins. Our collection of predictors explained 14.2% of the variance in the number of prior admissions (p<0.001). In this model, the use of statins significantly predicted the number of previous fall-related admissions (95% CI: 0.07–0.50, p=0.010). This same model maintained its significance when predicting admissions for future falls (p<0.001) and the use of statins continued to predict a greater number of readmissions (95% CI: 0.04–0.36, p=0.015).

Conclusion: More than 25% of all Americans age ≥40 years are taking cholesterol-lowering medication; 93% of those medications are statins. Although evidence is conflicted, these data support the finding that statin therapy increases the risk of falls in older adults. Incorporating exercise training as a prophylactic measure: enhancing lipid profiles and decreasing the need for statins while also improving balance, coordination, and mobility, may reduce fall-related injuries.
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Chapter 1: Introduction

Atherosclerosis and atherosclerosis-associated conditions are major causes of morbidity and mortality among older adults in developed countries (Haerer, Delbaere, Bartlett, Lord, & Rowland, 2012). Elevated blood cholesterol is a primary risk factor for atherosclerotic cardiovascular disease and contributes to one in three American deaths via heart attack or stroke (Gu, Paulose-Ram, Burt, & Kit, 2015). More than 70% of adults are treated for high cholesterol with lipid-lowering prescriptions, which affect different components of one’s lipid profile (Gu et al., 2015). Lipid-lowering agents include HMB-CoA reductase inhibitors (statins), fibrates, bile acid sequestrants, or a combination of multiple medications for an increased effect on numerous lipid-profile targets. By 2012, nearly 93% percent of adults using cholesterol-lowering medication used a statin, making statins one of the most commonly used classes of drugs in the United States (Gu et al., 2015; Scott, Blizzard, Fell, & Jones, 2009). Statins inhibit endogenous cholesterol production at an early stage in the mevalonate pathway by inhibiting the enzyme HMG-CoA reductase in the liver (Golomb & Evans, 2008). Decreasing synthesis of cholesterol primarily through this pathway decreases downstream LDL synthesis and increases LDL receptor sensitivity, thereby minimizing atherosclerotic development by increasing clearance of LDLs from the blood (Stancu & Sima, 2001). Although many people treated with statins experience little or no adverse effects, there is a need for awareness of risks and benefits of statin therapy (Golomb & Evans, 2008). The best recognized and most
commonly reported adverse effects of statins include muscle pain, fatigue, weakness, and rhabdomyolysis (Stancu & Sima, 2001). It is important to consider these risks when prescribing statins to older adults with a history of falls.

Older adults have increased fall risk because of age-related muscle decline, impaired balance, comorbidities, medication use, and increased frailty. Given that statin usage and sarcopenia are both common with increased age, the association between statin use and muscle function in older adults requires clarification (Scott et al., 2009). Because 30-60% of older adults fall each year, and these falls result in injury, hospitalization or death, these falls must be further analyzed for preventive purposes (Rubenstein, 2006). Better prevention of falls in this population may be facilitated by broader identification of risk factors, and it has been postulated that statins may exacerbate age-related muscle decline, potentially increasing fall risk, but data are conflicted (Haerer et al., 2012).

Although statins have been traditionally known to have a favorable safety profile and adverse effects are rare, the uncommon effects can translate into a significant public health impact (Golomb & Evans, 2008).

Exercise has shown to enhance lipid profiles without the use of statins and may have an important role in negating the effects of statins on fall risk and sarcopenia in older adults (Trejo-Gutierrez & Fletcher, 2007).

**Research Hypothesis**

There will be a significant prediction in the number of previous admissions for falls by a diagnosis of dementia, use of statins, and self-reported balance.

There will be a significant prediction in the number of subsequent admissions for fall injuries by a diagnosis of dementia, use of statins, and self-reported poor balance.
Purpose

The purpose of this research is to examine the relationship between statin usage and previous fall admissions among older adults in a Level 1 trauma center.

Null Hypothesis

There will be no significant prediction of the number of previous admissions for falls by a diagnosis of dementia, use of statins, and self-reported poor balance.

There will be no significant prediction in the number of subsequent admissions for fall injuries by a diagnosis of dementia, use of statins, and self-reported poor balance.

Delimitations

People aged $\geq 65$ from the Level 1 trauma center

Limitations

Study is not a randomized control trial

All subjects are from a Level 1 trauma center

No information of statin dosages for each patient

Subject honesty when reporting self-reported balance
Chapter 2: Review of the Literature

Fall Occurrence, Risk Factors, and Consequences

According to the American Geriatrics Society, falls are quickly becoming the most frequent and serious problem facing the elderly as thirty percent of adults over the age of 65 and fifty percent of adults over the age of 80 fall annually while completing their activities of daily living in the community (Arnold, Sran, & Harrison, 2008; Dionyssiotis, 2012). A fall has been defined as, “an event which results in a person coming to rest inadvertently on the ground or other lower level, not as a consequence of the following: sustaining a violent blow, loss of consciousness, sudden onset of paralysis, or an epileptic seizure” (Dionyssiotis, 2012, p. 805).

The combination of high incidence of falling in older adults coupled with a higher susceptibility to injury of a fall are of great concern to this aging population and their families (Arnold et al., 2008). Falls have a proven association with reduced functionality, morbidity, premature nursing home admissions, and mortality (Dionyssiotis, 2012). As a result of these occurrences, there has been a steady increase in Emergency Department visits increasing direct and indirect costs of medical treatments to affected individuals, families, and medical providers. More specifically, Stevens, Corso, Finkelstein, & Miller (2006) reported direct medical costs totaled $0.2 billion for fatal and $19 billion for non-fatal fall related injuries among people aged 65 or older, underscoring the need for identification of risk factors and effective interventions (Stevens, Corso, Finkelstein, & Miller, 2006).
Older adults are inevitably more prone to falling due to physiological changes with age, such as osteoporosis, postural instability, gait disturbances, diminished muscle strength, poor vision and cognitive impairment, as well as the intake of multiple medications (Bunn, Dickinson, Barnett-Page, Mcinnes, & Horton, 2008). The interaction of multiple and diverse risk factors and situations may be corrected, and their interaction is modified by age, disease, and the presence of various hazards in the environment (Dionyssiotis, 2012).

The literature has structured older adult fall-risks into two broad categories: extrinsic and intrinsic factors. Extrinsic factors include environmental conditions such as poor lighting, slippery floors, and uneven surfaces (Dionyssiotis, 2012). The magnitude of the influence of these environmental factors alone is uncertain, but they frequently interact with a person’s wide range of intrinsic factors. Intrinsic factors include one’s history of falls, age, gender, solitary lifestyle, race, medical conditions, impaired mobility and gait, deconditioning/immobility, fear of falling, nutritional deficiencies, cognitive disorders, attenuated vision, and intake of various medications (Dionyssiotis, 2012). One particular intrinsic factor warranting increased attention is the intake of various medications, as emerging studies are continually identifying this as a primary predictor of a future fall. Until recently, most attention in the literature has focused on the effects of psychotropic, antiarrhythmic drugs, digoxins, diuretics, and sedatives as the predominant culprits for falls and fall-related injuries. However, more recent studies are postulating that statins, a class of cholesterol-lowering medications, may exacerbate age-related muscle decline and may be a novel predictor for fall risk in the elderly (Dionyssiotis, 2012; Haerer et al., 2012).
**Statin Overview**

Between 2003-2004, one in five adults reported using a cholesterol-lowering medication in the past 30 days to improve lipid profiles. By 2011-2012, that number had increased to one in four adults (Gu et al., 2015). Different types of cholesterol-lowering medications include: HMG-CoA reductase inhibitors (statins), bile acid sequestrants, niacins, fibrates, or PCSK6 injectable medications. Statins are currently the most effective and most commonly prescribed lipid-lowering drug on the market. They have revolutionized primary and secondary prevention of coronary atherosclerotic disease and hypercholesterolemia by strategically targeting specific components of one’s lipid profile (Abd & Jacobson, 2011; Wierzbicki, Poston, & Ferro, 2003). The CDC reported in 2011-2012, 83% of adults reported using a statin alone, 10% reported combining a statin and a nonstatin, and only 7% reported the intake of a nonstatin alone to lower cholesterol levels.

Statins are typically classified by their chemical structure, which largely determines their mechanism of action and length of duration in the body. The most commonly known statins include Atorvastatin (brand: Lipitor), Fluvastatin (Lescol, Lescol XL), Lovastatin (Mevacor, Altoprev for long-acting), Pravastatin (Pravachol), Simvastatin (Zocor), Rosuvastatin (Crestor), and Pitavastatin (Livalo) (Stancu & Sima, 2001). Cervastatin (Baycol, Lipobay) was previously on the pharmaceutical market from Bayer A.G., but was removed in 2001 after thirty-one patients died by acute renal failure caused by rhabdomyolysis in the United States (Stancu & Sima, 2001) and an additional twenty-one deaths worldwide (Furberg & Pitt, 2001). Additionally, there were 385
nonfatal cases reported among the estimated 700,000 users in the United States, most of which required hospitalization (Furberg & Pitt, 2001).

Statins target hepatocytes and competitively inhibit HMG-CoA reductase, a key enzyme in the cholesterol-forming physiological pathway converting HMG-CoA into mevalonate (Stancu & Sima, 2001). Primary targets of the drug include minimized low-density lipoprotein cholesterol (LDL-C), decreased triglyceride levels, and/or increased high-density lipoprotein cholesterol levels (HDL-C) (Wierzbicki et al., 2003) which contribute to the downstream formation of cholesterol and other physiological byproducts.

**Cholesterol Synthesis**

The synthesis of cholesterol is vital for the maintenance and structural integrity of various organ systems, cellular membranes, and is a precursor to produce other downstream products such as bile acids, steroid hormones, and vitamin D.

Cholesterol synthesis is often simplified into a series of three primary steps: the formation of mevalonate, the formation of isopentyl pyrophosphate, and the formation of cholesterol. Synthesis begins with the oxidation of fatty acids or pyruvate into acetyl-CoA and is then transported into the cytoplasm. It is further metabolized in the cytoplasm, endoplasmic reticulum and the peroxisomes of the cell. Two Acetyl-CoA molecules are acted on by Thiolase, an intracellular enzyme, in order to form Acetoacetyl CoA. HMG-CoA synthase acts on Acetoacetyl-CoA to form B-hydroxyl-B-methyl-glutaryl. B-hydroxyl-B-methyl-glutaryl is catalyzed by HMG-CoA reductase to form the 6-carbon Mevalonate compound. We will revisit HMG-CoA reductase in further detail.
in upcoming sections, as it is a common target for various cholesterol-lowering medications.

The next phase of the cholesterol synthesis pathway involves the conversion of the 6-carbon Mevalonate compound into a 5-carbon Isopentyl pyrophosphate compound. Mevalonate undergoes a series of three kinase reactions, adding a phosphate to the subsequent compound from an ATP molecule. The final reaction after three kinase reactions is a decarboxylase reaction involving the removal of a carbon dioxide molecule. The final removal of the carbon dioxide forms the 5-carbon Isopentyl pyrophosphate molecule, which is later synthesized into a 27-carbon downstream cholesterol.

Isopentyl pyrophosphate undergoes a series of reactions combining carbon molecules to eventually form the 27-carbon cholesterol molecule. Isopentyl pyrophosphate isomerase acts upon isopentyl pyrophosphate to form a 5-carbon Dimethyl pyrophosphate. This 5-carbon molecule combines with an additional 5-carbon Isopentyl pyrophosphate to form the 10-carbon Geranyl pyrophosphate molecule. Geranyl pyrophosphate combines with another Isopentyl pyrophosphate molecule to form a 15-carbon Farnesyl pyrophosphate. Farnesyl pyrophosphate can continue moving downstream in the cholesterol synthesis pathway, or has the potential for conversion into dolicohols or ubiquinone (CoQ_{10}) for other intracellular functions (Wierzbicki et al., 2003). Two 15-carbon Farnesyl pyrophosphates continue through the cholesterol synthesis pathway in the endoplasmic reticulum to form a 30-carbon Squalene molecule. The enzyme Squalene synthase helps in the formation of the 30-carbon Squalene molecule. Similar to HMG-CoA reductase, Squalene synthase is also a common target for cholesterol-lowering medications.
Squalene is further metabolized in the endoplasmic reticulum or in nearby peroxisomes to form the 30-carbon Lanosterol molecule. Lanosterol is then transformed through a series of nineteen additional reactions to form the final 27-carbon cholesterol molecule for a variety of future uses.

Figure 1 adapted from Wierzbicki et al. (2003) describes the compartmentalization and simplified biochemistry of cholesterol synthesis. Common drug targets are shown in bold italics.

Figure 1: Compartmentation and Simplified Biochemistry of Cholesterol Synthesis.
The Role of Statins in Cholesterol Synthesis

The beneficial effects of HMG-CoA reductase inhibitors (statins) are attributed to their ability to reduce endogenous cholesterol production in the liver by competitively inhibiting the primary enzyme involved, HMG-CoA reductase (Stancu & Sima, 2001). Inhibiting this enzyme at an early stage in the mevalonate pathway produces pleiotropic effects, as cholesterol is not the only product in this pathway. These effects, while often beneficial in lowering LDL-C levels, together may contribute to adverse effects to unregulated downstream targets. For instance, Golomb and Evans (2008) highlight the need for cholesterol in the production of sex steroids, corticosteroids, bile acids, and vitamin D, which are indirectly affected by statin therapy (Golomb & Evans, 2008). Furthermore, cholesterol intermediates formed in the mevalonate pathway are also affected, as ubiquinone (CoQ10), heme-A, and isoprenylated protein production are hindered. These molecules have pivotal roles in cellular biology and human physiology, and may be of potential relevance in the conversation about statins and their adverse effects, specifically muscle weakness and myopathy in the elderly population (Stancu & Sima, 2001).

Although multiple clinical trials have documented the relative safety and efficacy of statin medications in reducing fatal and non-fatal coronary heart disease, strokes, and overall mortality, there is emerging evidence that targeting the formation of certain lipids or cholesterol may negatively affect other physiological pathways, potentially leading to increased risk of various detrimental effects to one’s health. Wierzbiki et al. (2003) note the principal side effects of statins are gastrointestinal disturbances, abnormal liver transaminases, and myalgia-myositis (Scott et al., 2009; Wierzbicki et al., 2003). Of the
known statin-induced toxicities, muscle adverse effects are the most reported problem both in the literature and by patients (Golomb & Evans, 2008).

Although statin-induced myopathy is the most recognized adverse effect of the drug, reported measures have been inconsistent and perhaps underreported in epidemiological studies and in randomized control trials. This inconsistency may be due to the absence of a consensus in the definition of statin-induced muscle events, hindering the estimation of their true incidence (Abd & Jacobson, 2011). Statin-induced myopathy is the generalized term for four separate muscle adverse effects: myopathy, myalgia, myositis, and rhabdomyolysis. These terms and their objective parameters have been defined inconsistently between the American College of Cardiology (ACC), American Heart Association (AHA), National Heart, Lung, and Blood Institute (NHLBI), and the National Lipid Association (NLA), making reporting of these adverse events unstandardized and potentially inaccurate. Table 1 adapted from Abd & Jacobson (2011) demonstrates the inconsistencies in definitions between these four terms (Abd & Jacobson, 2011). A more accurate and widely accepted definition of these conditions and corresponding chemical markers is warranted in order to best identify and treat this clinical problem. Doing so may provide further transparency and analysis between randomized control trials regarding statin-induced myopathy and the predictors for potential falls.
Table 1. Proposed Definitions for Statin-Related Myopathy.

<table>
<thead>
<tr>
<th>Clinical entity</th>
<th>ACC/AHA/NHLBI 2002</th>
<th>NLA 2006</th>
<th>FDA</th>
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<tr>
<td>Myopathy</td>
<td>General term referring to any disease of muscles</td>
<td>Complaints of myalgia (muscle pain or soreness), weakness, and/or cramps, plus elevation in serum CK &gt; 10 × ULN</td>
<td>CK ≥ 10 × ULN</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Muscle ache or weakness without CK elevation</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle symptoms with increased CK</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Muscle symptoms associated with marked CK elevations, typically substantially &gt; 10 × ULN and with creatinine elevation (usually with brown urine and urinary myoglobin)</td>
<td>CK &gt; 10,000 IU/L or CK &gt; 10 × ULN plus an elevation in serum creatinine or medical intervention with i.v. hydration</td>
<td>CK &gt; 50 × ULN and evidence of organ damage, such as renal compromise</td>
</tr>
</tbody>
</table>

Adapted with permission from Joy et al. [54].

Proposed Mechanisms of Statin-Induced Myopathy

Recent clinical reports have confirmed suspicions that statins frequently produce muscle symptoms. For instance, Parker & Thompson (2012) analyzed 7924 patients treated with high dose statins and found that 11% developed muscle symptoms, 4% had symptoms severe enough to interfere with daily activities, and 0.4% were actually confined to bed with their symptoms (Parker & Thompson, 2012). In another report by Abd & Jacobson, researchers found that 10-15% of statin users also developed these muscle effects ranging from mild myalgia to more severe muscle symptoms involving elevated creatine kinase levels (Abd & Jacobson, 2011).

The exact mechanisms of statin-induced myopathy have not yet been confirmed, but studies suggest the multi-branched effects of statins and their numerous targets in the cholesterol-forming pathway may be of significant impact. Abd et al. (2011) summarize some of the leading theories including isoprenoid depletion, inhibition of ubiquinone
synthesis (CoQ₁₀), decreased or altered sarcolemmal membrane cholesterol, disturbed calcium metabolism, or autoimmune phenomena.

By inhibiting the formation of mevalonate through competitive binding of statins to the HMG-CoA reductase enzyme, mevalonate production is decreased and downstream lipids are also minimized during production. Isoprenoids are one type of specific lipid byproducts produced through the HMG-CoA reductase pathway in cholesterol synthesis and serve as attachments for a variety of intracellular signaling molecules (Liao, 2002). The two most important subclasses of isoprenoids formed through this pathway are farnesyl pyrophosphate (F-PP) and geranylgeranyl pyrophosphate (GG-PP) which are attached to proteins by the process of protein prenylation, a post-translational process at the terminal end of mRNA (Abd & Jacobson, 2011). Statins reduce protein prenylation, promoting downstream alternative modifications to small GTPases (Rho, Ras, Rac) and lamin proteins. This modification may lead to downstream vacuolation of myofibers, degeneration and swelling of organelles, increased susceptibility to mechanical stress, and eventually cell death (Abd & Jacobson, 2011).

More recent research has noted a relationship between statin therapy and serum Ubiquinone (CoQ₁₀) levels. CoQ₁₀ is an key component of oxidative phosphorylation and ATP production in the mitochondria (Abd & Jacobson, 2011). As statins inhibit mevalonate production, the synthesis of the precursor of CoQ₁₀ is also minimized. Inhibiting the synthesis of CoQ₁₀ has been suggested to compromise the function of mitochondrial respiration and may impair energy production and ultimately induce myopathy, but data are conflicted.
Reduced cholesterol levels from statin therapy may also cause alterations in myocyte membrane cholesterol by adversely modifying their physical properties, such as the integrity and fluidity of the conjoined phospholipids, and destabilizing membranes (Abd & Jacobson, 2011).

Calcium is a critical component in regulating skeletal muscle function. The regulation and uptake of calcium is regulated through L-type calcium channels on intracellular membranes and RYR receptors found on the sarcoplasmic reticulum (Abd & Jacobson, 2011). In studies looking into muscle biopsies of patients with myopathy, researchers found increased expression of RYR receptors and structural changes in the T-tubule structure of the sarcoplasmic reticulum. It has been postulated therefore that statin therapy may alter calcium handling such that calcium leaking from the mitochondria may impair SR calcium cycling and increases resting cytosolic calcium (Parker & Thompson, 2012).

More research is warranted on the effect of statins on patients with certain autoimmune disorders such as polymyositis, lupus, and myasthenia gravis. The mechanism regarding this statin-induced aggravation has yet to be confirmed but may include the upregulation of MHC-1 expression and antigen presentation in muscle fibers (Abd & Jacobson, 2011). As a result, statins have been reported to cause severe immune-mediated necrotizing myopathy to this population.

The mechanism by which statins produce myopathic symptoms is unclear, but numerous hypotheses have been proposed on the mechanisms of statin-induced myopathy. Decreased sacroplasmic reticular cholesterol, reduced production of CoQ\textsubscript{10} required for mitochondrial electron transport, decreased production of prenylated
proteins, changes in fat metabolism, increased uptake of cholesterol, failure to replace 
damaged muscle protein via the ubiquitin pathway, disruption of calcium metabolism in 
the skeletal muscle and inhibition of various protein synthesis have all been suggested as 
possible mediators (Krishnan & Thompson, 2010).

**Statins and Fall-Risk**

As emerging studies continue to identify the molecular mechanisms for statin-
induced myopathy on a molecular scale, it is also important to take note of the 
consequences of these molecular changes to the general population on a larger scale. 
Evidence for an association between statins and increased fall-risk is inconsistent 
throughout the literature. A systematic review by Krishnan and Thompson (2010) 
document that there are few studies examining the effect of statins on muscle strength 
and capacity. In addition, of the available clinical trials, muscle strength was often 
measured by crude or poorly described techniques (Krishnan & Thompson, 2010).

When examining the literature to determine if a relationship exists between statin-
therapy and fall-risk, the data are conflicted. In current clinical practice, physicians often 
monitor patients taking statins by monitoring their creatine kinase levels, a commonly 
referenced chemical marker to determine the scope of one’s muscle damage from 
metabolizing a statin medication. If creatine kinase levels are within normal limits, 
patients are encouraged to continue with statin therapy (Mohaupt et al., 2009). Phillips et 
al. (2002) was the first to examine the effects of statin-induced myopathy in patients with 
normal creatine kinase levels. Philips et al., however, highlight that some patients who 
develop muscle symptoms while receiving statin therapy have demonstrated weakness in 
hip abductors and hip flexors without rising serum levels of creatine kinase, further
highlighting the importance of a need for an improved myopathy definition and testing parameters to analyze statin-induced adverse effects (Phillips et al., 2002).

The relationship between statin-induced myopathy and skeletal muscle strength is also conflicted in the literature. Scott et al. (2009) employed a prospective cohort design to examine the effects of statin therapy on muscle function and muscle mass for people aged 50-79 years (Scott et al., 2009). At a 2.6 year follow up, statin users had a significantly lower mean leg strength than non-statin users at follow up, and muscle strength and quality decreased significantly in those who reported statin use at baseline and follow up when compared to all other patients (Parker & Thompson, 2012; Scott et al., 2009). Dobkin (2005) found similar results in subjects three to twelve months after taking a statin. Subjects experienced difficulty walking and rising from a chair after starting statin therapy (Dobkin, 2005).

Alternatively, emerging studies reveal conflicting evidence between fall-risk and statin therapy and suggest there is no adverse effect of the medication. Contrary to Dobkin (2005), Agnostini et al. (2007) found statin use to be associated with slightly improved performance in timed standing tests among community-dwelling males (Agostini et al., 2007). These subjects had been taking the medications for at least one year before enrollment, suggesting they may have tolerated the medication beforehand. Similarly, Ashfield et al. (2010) found no association of statin use with handgrip with a dynamometer, a predictor of increased falls, fractures, and morbidity in elderly populations (Ashfield et al., 2010; Krishnan & Thompson, 2010).

Variations in the literature may be attributed to a lack of a consensuses in a clinical definition and chemical markers for statin-induced myopathic symptoms,
inconsistencies in functional tests used among trials, sample sizes, sex, and comorbidities of subject populations (Haerer et al., 2012). Differences seen in clinical trials may be due to the fact that healthy participants were used as subject for most clinical trials and are less likely to report occasional mild side effects of the medications (Abd & Jacobson, 2011). It is also important to note that clinical trials often exclude subjects with a high risk of developing statin myopathy (such as those with previous myopathy, or those taking medications that may interact with statins) in clinical trials (Abd & Jacobson, 2011). It is important to highlight that most previous studies have included a limited range of muscle strength tests, and few have examined the precise relationship between statin use and prospectively measured falls (Haerer et al., 2012).

The possible adverse effects of statins coupled with age-related declines supports the need for further investigation on the relationship between fall-risk and statin use, especially among older adults. The aims of this study therefore, were to investigate the relationship between statin usage and previous fall-related emergency department admissions among older adults.
Chapter 3: Methodology

This chapter will provide discussion regarding the research design and experimental procedures taken to answer the research question of the study. Subject population, instrumentation, assessment measures, experimental interventions, and ethical concerns will be presented and further discussed in the upcoming sections.

Data Acquisition and Management

All data concerning patient demographics, diagnoses, associated injuries, self-report problems, and medications were exported from the institution’s trauma registry. We examined all patients who were admitted to the emergency room with a mechanism of injury of a fall and were discharged from the emergency room with no codable injuries. A database was composed of patient medical numbers, age, sex, type of injury, discharge diagnosis, home medications, associated medical conditions, number of falls known, number of return emergency room visits, self-reporting of poor balance, lightheadedness, visual impairment, any cognitive struggles, fall risk score documented by nursing, known reason for fall, and any other medical conditions documented from the patient’s history.

Subjects

We retrospectively analyzed the patient registry of an ACS-verified Level 1 Trauma Center. All patients aged ≥ 65 years who were admitted for a fall-related injury in 2015 were included (n=615). Demographic data (age, sex) diagnoses (e.g., dementia, hypertension, etc.) associated injuries (e.g., head trauma, laceration, etc.), self-report
problems (e.g., poor balance), and medications exported. Many of these patients had been previously admitted for falls and many were later readmitted for falls. We recorded the total number of previous admissions and return admissions. The medication of interest was statins; we compared the number of previous falls of patients using statins to that of patients not using statins. We then compared the number of subsequent falls between patients using and not using statins.

**Statistical analysis.** All statistical tests were conducted using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). Descriptive statistics (percentages, means, and standard deviations) of the sample population were calculated. Group means were compared with independent sample t-tests. Differences in categorical data were measured with chi-square tests. Linear regression analyses tested the effects of statins, dementia, and self-reported balance measurements on 1) the number of previous admissions for falls, and 2) the number of subsequent admissions for falls. Significance was set at $p>0.05$. Predictors that did not meet significance were removed from the model.
Chapter 4: Draft of Manuscript

Title

Using the Medication Cabinet to Predict Fall Risk in Older Adults

Abstract

Background. In the United States, 30-60% of older adults fall each year; 10-20% of these falls result in injury, hospitalization, or death. Better prevention of falls in this population may be facilitated by broader identification of risk factors. The use of statins has emerged as a potential risk factor, but the data are conflicted. Purpose. To examine the relationship between statin use and falls among community-dwelling older adults.

Methods. The patient registry of a Level 1 trauma center was evaluated. All patients aged ≥ 50 years who were admitted for falls in 2015 were included (n=615). Many of these patients had been previously admitted for falls and many were later readmitted for falls. We analyzed predictors of both prior admission and readmission with linear regression. Independent variables were self-reported balance problems, diagnosis of dementia, and the use of statins. Results. On average, patients admitted for falls were 79.9 ± 9.3 years old and 28% (n=173) were taking statins. Our collection of predictors explained 14.2% of the variance in the number of prior admissions (p<0.001). In this model, the use of statins significantly predicted the number of previous fall-related admissions (95% CI: 0.07–0.50, p=0.010). This same model maintained significance when predicting admissions for future falls (p<0.001) and the use of statins continued to
predict a greater number of readmissions (95% CI: 0.04–0.36, p=0.015). **Conclusion.** Statin medication therapy increases the risk for falls in patients over 65 years old. This finding is significant since more than 25% of all Americans age ≥ 40 years are taking cholesterol-lowering medication, and 93% of those medications are statins. Exercise training should be considered as a prophylactic measure as it improves lipid profiles and may also improve balance, coordination, and mobility, may reduce fall-related injuries.

**Introduction**

Atherosclerosis and atherosclerosis-associated conditions are major causes of morbidity and mortality among older adults in developed countries (Haerer et al., 2012). Elevated blood cholesterol is a primary risk factor for atherosclerotic cardiovascular disease and contributes to one in three American deaths via heart attack or stroke (Gu et al., 2015). More than 70% of adults are treated for high cholesterol with lipid-lowering prescriptions, which affect different components of one’s lipid profile (Gu et al., 2015). By 2012, nearly 93% percent of adults using cholesterol-lowering medication used a statin, making statins one of the most commonly used classes of drugs in the United States (Gu et al., 2015; Scott et al., 2009). Although many people treated with statins experience little or no adverse effects, there is a need for awareness of risks and benefits of statin therapy (Golomb & Evans, 2008). The best recognized and most commonly reported adverse effects of statins include muscle pain, fatigue, weakness, and rhabdomyolysis (Stancu & Sima, 2001). Although statin-induced myopathy is the most recognized adverse effect of the drug, reported measures have been inconsistent and perhaps underreported in epidemiological studies and in randomized control trials. This inconsistency may be due to the absence of a consensus in the definition of statin-induced
muscle events, hindering the estimation of their true incidence (Abd & Jacobson, 2011). It is important to consider these risks when prescribing statins to older adults with a history of falls. Given that statin usage and sarcopenia are both common with increased age, the association between statin use and muscle function in older adults requires clarification (Scott et al., 2009). Because 30-60% of older adults fall each year, and these falls result in injury, hospitalization or death, these falls must be further analyzed for preventive purposes (Rubenstein, 2006). Better prevention of falls in this population may be facilitated by broader identification of risk factors, and it has been postulated that statins may exacerbate age-related muscle decline, potentially increasing fall risk, but data are conflicted (Haerer et al., 2012).

Methods

**Subjects.** We retrospectively analyzed the patient registry of an ACS-verified Level 1 Trauma Center. All patients aged ≥65 years who were admitted for a fall-related injury in 2015 were included (n=615). Demographic data (age, sex) diagnoses (e.g., dementia, hypertension, etc.) associated injuries (e.g., head trauma, laceration, etc.), self-report problems (e.g., poor balance), and medications exported. Many of these patients had been previously admitted for falls and many were later readmitted for falls. We recorded the total number of previous admissions and return admissions. The medication of interest was statins; we compared the number of previous falls of patients using statins to that of patients not using statins. We then compared the number of subsequent falls between patients using and not using statins.

**Statistical Analysis.** All statistical tests were conducted using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). Descriptive statistics
(percentages, means, and standard deviations) of the sample population were calculated. Group means were compared with independent sample t-tests. Differences in categorical data were measured with chi-square tests. Linear regression analyses tested the effects of statins, dementia, and self-reported balance measurements on 1) the number of previous admissions for falls, and 2) the number of subsequent admissions for falls. Significance was set at p>0.05. Predictors that did not meet significance were removed from the model.

Results

On average, patients admitted for falls were 79.9 ± 9.3 years old and 28% (n=173) were taking statins. There was no difference in age between patients taking statins and those not taking statins, but there is a small difference in sex (Table 2).
Table 2. Demographic Data, Number of Falls, and Diagnoses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statin</th>
<th>Non-Statin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80.1 ± 8.4</td>
<td>79.8 ± 9.6</td>
<td>0.765</td>
</tr>
<tr>
<td>Sex</td>
<td>65.9% female</td>
<td>74.2% female</td>
<td>0.039</td>
</tr>
<tr>
<td>Number of previous falls</td>
<td>2.1 ± 1.4</td>
<td>1.9 ± 1.3</td>
<td>0.039</td>
</tr>
<tr>
<td>Number of subsequent falls</td>
<td>0.7 ± 0.9</td>
<td>0.5 ± 0.9</td>
<td>0.045</td>
</tr>
<tr>
<td>Dementia/Alzheimer's</td>
<td>1.2%</td>
<td>2.5%</td>
<td>0.302</td>
</tr>
<tr>
<td>Injury or Trauma to Head</td>
<td>50.3%</td>
<td>46.8%</td>
<td>0.440</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>8.7%</td>
<td>6.8%</td>
<td>0.420</td>
</tr>
</tbody>
</table>

**Model 1.** Predictors of previous admissions for fall-related injuries: The stepwise regression model that best predicted number of previous admissions for falls included: a diagnosis of dementia, self-reported poor balance during a visit, and use of statins. This collection of predictors explained 14.2% of the variance in the number of previous admissions (R²=0.142, standard error of the estimate=1.215, F=33.80, P<0.001). With all other variables held constant, administering statin therapy to a patient predicted a significant increase in the number of previous admissions for fall-related injuries (95% CI: 0.07–0.50, p=0.010).
Model 2. Predictors of subsequent admissions for fall-related injuries: The stepwise regression model that best predicted the number of subsequent admission for fall injuries included: A diagnosis for dementia, self-reported poor balance during visit, and use of statins. This collection of predictors explained 9.0% of the variance in the number of subsequent falls ($R^2=0.092$, standard error of the estimate =0.902, $F=20.726$, $P<0.001$). The use of statins predicted a greater number of readmissions for fall-related injuries (95% CI: 0.04–0.36, $p=0.015$).

Table 3. Linear Regression Analysis Predicting Number of Previous Admissions for Falls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized $\beta$</th>
<th>95% confidence interval</th>
<th>$t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia</td>
<td>1.246 falls</td>
<td>0.946 falls to 1.547 falls</td>
<td>8.148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-reported poor balance</td>
<td>1.335 falls</td>
<td>0.744 falls to 1.927 falls</td>
<td>4.432</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of statins</td>
<td>0.284 falls</td>
<td>0.070 falls to 0.499 falls</td>
<td>2.601</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table 4. Linear Regression Analysis Predicting Number of Return Emergency Room Visits.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized β</th>
<th>95% confidence interval</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia</td>
<td>0.748 falls</td>
<td>0.525 falls to 0.971 falls</td>
<td>6.591</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-reported poor balance</td>
<td>0.657 falls</td>
<td>0.217 falls to 1.096 falls</td>
<td>2.936</td>
<td>0.003</td>
</tr>
<tr>
<td>Use of Statins</td>
<td>0.197 falls</td>
<td>0.038 falls to 0.358 falls</td>
<td>2.429</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Discussion

More than 30% of people over 65 years of age fall each year and in half of these cases, falls are recurrent (Dionyssiotis, 2012). The combination of high incidence of falling in older adults coupled with a higher susceptibility to injury of a fall are of great concern to this aging population and their families (Arnold et al., 2008). Falls have a proven association with reduced functionality, morbidity, premature nursing home admissions, and mortality (Dionyssiotis, 2012). As a result of these occurrences, there has been a steady increase in Emergency Department visits which increases direct and indirect costs of medical treatments to individual fallers, families, and medical providers, underscoring the need for identification of broader risk factors and effective interventions (Stevens et al., 2006). Older adults are inevitably more prone to falling due to physiological changes with age, such as osteoporosis, postural instability, gait disturbances, diminished muscle strength, poor vision and cognitive impairment, as well as the intake of multiple medications (Bunn et al., 2008).

Medication intake has warranted increased attention, as emerging studies are continually identifying this as a significant predictor for a future fall. Most attention has
focused on the effects of psychotropic, antiarrhythmic, digoxins, diuretics, and sedatives as the predominant culprits for falls and fall-related injuries. However, more recent studies are postulating that statins, a class of cholesterol-lowering medications, may exacerbate age-related muscle decline and may be a novel predictor for fall risk in the elderly (Dionyssiotis, 2012; Haerer et al., 2012).

More than 25% of Americans age ≥ 40 years are taking cholesterol-lowering medication; 93% of those medications are statins (Gu et al., 2015). Although multiple clinical trials have documented the relative safety and efficacy of statin medications in reducing fatal and non-fatal coronary heart disease, strokes, and overall mortality, there is emerging evidence that targeting the formation of certain lipids or cholesterol with statins may be pleiotropic, potentially leading to increased risk of detrimental effects to one’s health. Of the known statin-induced toxicities, muscle adverse effects are the most reported problem both in the literature and by patients (Golomb & Evans, 2008) and may be a contributor to increased fall risk with statin therapy.

Our data support the finding that statin therapy increases the risk of falls in older adults, although evidence is conflicted. Patients are prescribed statins as a means to combat unfavorable lipid profiles and prevent atherosclerotic cardiovascular disease. Patients and physicians should be made aware that while there are benefits of statin therapy, there are adverse effects to these medications that may cause an increase for fall-risk in this population. It may also be appropriate to emphasize alternative treatments to statin therapy such as lifestyle modifications, diet, and implementation of an exercise regimen, as a fall-related injury may accelerate the path towards a life-threatening fall-related injury or death. Identifying patients who present with our collection of predictors
and suggesting an improvement in their dietary habits, medication use, or referral to balance may be appropriate to minimize risk for a future fall. Exercise may function as a prophylactic measure, enhancing lipid profiles and decreasing the need for statins while also improving balance, coordination, and mobility, reducing the risk of fall-related injuries (Arnold et al., 2008; Trejo-Gutierrez & Fletcher, 2007).
REFERENCES


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doi:10.1097/MOL.0b013e32833c1edf


APPENDIX A. SPSS LINEAR REGRESSION OUTPUTS FOR MODEL 1

## Model Summary

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.377&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.142</td>
<td>.138</td>
<td>1.215</td>
</tr>
</tbody>
</table>

<sup>a</sup> Predictors: (Constant), Dementia, Statins, SelfReport_PoorBalance_NotAsked

## ANOVA<sup>a</sup>

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Regression</td>
<td>3</td>
<td>49.910</td>
<td>33.800</td>
<td>.000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Residual</td>
<td>611</td>
<td>1.477</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1051.935</td>
<td>614</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Dependent Variable: Num_of_Previous_Falls

<sup>b</sup> Predictors: (Constant), Dementia, Statins, SelfReport_PoorBalance_NotAsked

## Coefficients<sup>a</sup>

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td>t</td>
<td>Lower Bound</td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>1.654</td>
<td>.061</td>
<td>26.963</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>.284</td>
<td>.109</td>
<td>.098</td>
<td>2.601</td>
</tr>
<tr>
<td></td>
<td>SelfReport_PoorBalance_NotAsked</td>
<td>1.335</td>
<td>.301</td>
<td>.167</td>
<td>4.432</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>1.246</td>
<td>.153</td>
<td>.308</td>
<td>8.148</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dependent Variable: Num_of_Previous_Falls

**Independent variables:** Diagnosis of dementia, self-reported poor balance during visit, and use of statins.

**Dependent variable:** The number of previous admissions for falls.
APPENDIX B. SPSS LINEAR REGRESSION OUTPUTS FOR MODEL 2

Model Summary

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.304a</td>
<td>.092</td>
<td>.088</td>
<td>.902</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), Dementia, Statins, SelfReport_PoorBalance_NotAsked

ANOVA

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Regression</td>
<td>3</td>
<td>16.852</td>
<td>20.726</td>
<td>.000b</td>
</tr>
<tr>
<td></td>
<td>Residual</td>
<td>611</td>
<td>.813</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>614</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Dependent Variable: Num_Return_ER_Visits
b. Predictors: (Constant), Dementia, Statins, SelfReport_PoorBalance_NotAsked

Coefficients

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>.363</td>
<td>.046</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>.197</td>
<td>.081</td>
</tr>
<tr>
<td></td>
<td>SelfReport_PoorBalance_NotAsked</td>
<td>.657</td>
<td>.224</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>.748</td>
<td>.114</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Num_Return_ER_Visits

Independent variables: Diagnosis of dementia, self-reported poor balance during visit, and use of statins.

Dependent variable: The number of subsequent admissions for fall injuries.