Abstract

HMG-CoA reductase inhibitors, better known as statins, are used to lower the amount of cholesterol in the blood. Due to this action, popular opinion favored the idea that these medications be administered in the evening, when the liver synthesizes the most cholesterol. The paradigm has shifted, though, and new ideas on when to administer these drugs have come up. Unfortunately, there is no research supporting any new administration time and it appears that the old favored way never really had any research behind it to begin with. This has negatively impacted the healthcare field, both providers and patients alike. Providers have been left to interpret and practice based on the results of contradicting research data and patients have been receiving education that could be incorrect. And in the age of patients receiving care at multiple institutions, patients also run the risk of hearing differing information about the same topic, which can lead to confusion and decreased medication compliance. In order to fully resolve this issue, more research on the administration time of statins is needed.
The Effects of Limited Research on HMG-CoA Reductase Inhibitors on Medication Administration and Patient Education in the Inpatient Setting

“Approximately 80 million Americans have cardiovascular disease” (Montfort, 2013, np). Statins are a form of medication used to treat the plaque buildup seen in this disease process (Montfort, 2013). With this disease currently ailing so many millions of people, it is no wonder why statins are so important. Unfortunately, there is a distinct lack of research regarding the administration time of statins. The healthcare realm once thought that these medications should be administered at night but thoughts have shifted over the years, except not on one set idea and there is not enough research to back any one claim.

This has had negative impacts on the healthcare world. Hospitals and providers have been left to interpret their own variations of this differing research and consequently patients have been receiving the fallout; neighboring hospitals are educating patients differently on the same topic. With conflicting information, patient compliance to the statin therapy may, in turn, decrease adherence (Abbott, 1998).

To our knowledge, no review has addressed the negative impacts that the lack of research surrounding statins and their administration time have on patient education. Therefore, in this review, we addressed the current literature on statins and examined the benefits of patient education.

Methods
Initially, the team met to identify the research questions. The team consisted of a nursing student and nursing professor, both of which had prior experience with and background knowledge of HMG-CoA reductase inhibitors. The nursing professor was trained in proper research methods.

Secondly, research studies were found between September 2016 and February 2017. The following databases were used to conduct this review: UpToDate, CINAHL, PubMed, Elsevier and Google Scholar. The words listed below, along with synonyms, were the terms used in each database:

- Concepts relating to medications/health: statin, medication adherence, discrepancy, timing, five rights, compliance, HMG-CoA reductase inhibitors, cardiac, cardiovascular disease, lipid-lowering drugs, cholesterol, morning, evening, therapy, once daily medication

- Concepts relating to patients: patient education, safety, inpatient setting, standardized, benefits

Due to the lack of research articles addressing the research question, no study design restrictions were used in order to maximize the number of topic-relevant articles. Upon reviewing studies, we searched through reference lists to see if there were any more relevant articles that could be used. Many of these studies had already been found during the initial search.

After reviewing all of the articles, we selected the most relevant ones for our research topic. We initially started out with 14 research studies. Two of them were eliminated for redundancy. One
article was later eliminated for irrelevance. We then placed all of the studies into a chart (Table 1. in Appendix A) detailing the author, year, summary of the study with results, database accessed, and date accessed.

Upon completion of the chart, we went into the inpatient setting. We assessed the administration of statins on an orthopedic/neurosurgery unit at Hospital A for a period of 10 weeks and we assessed the nurses’ statin administration through a survey. The survey was sent to 10 nurses that were at least a Clinical Nurse II or higher. The survey was sent out once to each nurse in an individual e-mail. The survey was one question in length, seen below:

Of the once-daily statins that are ordered for your patients, do you see them ordered to be administered in the morning or at night?

From there we spoke to the Head of Pharmacy at Hospital A, who told us that statins are a nightly medication and that the computer system at Hospital A automatically categorizes them in a way so that they will always show up with the 2100 medications on a patient’s Medication Administration Record (MAR).

We then spoke informally to a few nurses on the Heart Unit at Hospital A, who told us that statins are administered randomly on their unit and that it is more common for patients to have them administered in the morning rather than at night. We tried to get in touch with the nursing informatics officer at Hospital A, but achieved no response.
After re-evaluating all of our conflicting data from Hospital A, we decided to approach the topic from another angle. About three weeks later, we met with the Patient Education committee for the health system of Hospital A. It was there that we got the idea to look up the policies on statin administration at Hospital A.

We were also granted the permission to look up the policy on statins at another hospital, Hospital B, to compare the two policies. Hospital A and Hospital B are within 40 miles of each other. These two hospitals are not within the same health system.

Results

This review includes 11 research based studies and data from two hospitals.

Medication discrepancies are best defined as differences in documented medication regimens between care settings i.e. at home, outpatient setting, inpatient setting (Quelennec, Beretz, Paya, Blickle, Gourieux, Andres, Michel, 2013). This poses a threat to patient safety and optimal patient outcomes because, as the patient’s standard medication regimen is not assessed, sub or supra-therapeutic doses of medications could be administered to the patient (Stitt, Elliott, Thompson, 2011).

Cardiovascular drugs are among the top three most frequently documented medications involved in medication discrepancies (Quelennec, et. al., 2013). Moreover, statins were found to be the most common medications out of these cardiovascular drugs involved in these reported
medication discrepancies (Quelennec, et. al., 2013). “For over 40 years, statins have been used as a means of both primary and secondary cardiovascular disease treatment” (Sirtori, 2014, p.10). “Statins, or HMG-CoA Reductase inhibitors, work by blocking a step in the cholesterol synthesis pathway, which significantly lowers production of cholesterol, lowers the hepatic-cholesterol concentration, and leads to the increased expression of LDL-receptors in the liver membranes yielding a higher uptake of cholesterol from the blood (Sirtori, 2014, p. 7)”. Research has also shown that statins “stabilize cholesterol plaques in the vasculature by dissolving cholesterol crystals, which lessens the chance of an adverse cardiac event, such as a myocardial infarction or stroke” (Abela, Vedre, Janoudi, Huang, Durga, Tamhane, 2010, p. 1710).

It is important to administer statins at the right time and at the same time daily in order to achieve the maximal lipid lowering effect (Kamal, 2011). In previous years, it was thought that all statins were to be administered in the evening (Wallace, Chinn, Rubin, 2003). This is based on the idea that statin administration should coincide with liver synthesis; the “liver synthesizes the most cholesterol when dietary intake is at its lowest, which, for most people, is during their sleep” (Wallace, et. al., 2003).

The FDA, however, promotes administering statins based on the length of their individual half-lives (Kamal, 2011). As cholesterol is synthesized in the early morning hours, the FDA recommends that statins with a shorter half-life be taken in the evening (Kamal, 2011). “Statins with a shorter half-life include: lovastatin, simvastatin, and fluvasstatin” (Kamal, 2011, p. 3). “For statins with a longer half-life, atorvastatin, pravastatin, and rosuvastatin, the FDA recommends day time administration” (Kamal, 2011, p. 3).
The results have been varied amongst the studies that have researched the effectiveness of administering statins at different times based on the length of their half-lives. Despite its longer half-life, Zhu, Zhou, Yan, and Yeng (2008) listed pravastatin as a medication to “always be administered in the evening when treating hypercholesterolemia” (p. 1562). When compared side by side, the lipid lowering effect of the statins with the longer half-lives was not more significant when administered in the morning as opposed to the evening (Plakogiannis & Cohen, 2007).

Of significant importance to note is that, in at least one study, daily adherence to the medication was higher when clients were on an evening regimen versus a morning regimen, regardless of the statin itself (Calvo, Lopez, Hermida, Ayala, Covelo, Rodriguez, Romero, Fontao, Soler, 2005). Adherence to cardiovascular treatment is necessary to retain a healthy lifestyle. “Non-adherence to statins has been associated with worsening hypertension, diabetes, myocardial infarction and stroke” (Frishman, 2007, p. 257).

The health system for Hospital A did not have a preference for the administration time of their statins. According to the survey sent out via e-mail to 10 nurses on an orthopedic/neurosurgery unit at Hospital A, the administration time of daily statins varies. 4 nurses stated that they see the orders for once-daily statins to be administered at night. 3 nurses stated that they see the orders for once-daily statins to be administered in the morning. 2 nurses stated that they see the orders for once-daily statins to be administered both in the morning and at night, depending on the ordering provider. One nurse did not respond to the survey.
The health system for Hospital B prefers to administer their statins with in the evening, but according to their policy on statin administration, they will alter their inpatient medication administration time if the manufacturer of the medication recommends an administration time.

Patient education is the transfer of information from healthcare provider to patient (Abbott, 1998). With a patient population that is growing more knowledgeable of their treatment and with patients receiving care at multiple facilities now, it is important to find out their baseline understanding of their care, as they may already have their own ideas of how things should be done (Abbott, 1998).

**Discussion**

It is interesting to note the dates of the studies in this literature review. The older studies, those around the early 2000s, claim that statins are more effective when taken at night. Towards the new decade, minds have shifted. During 2011, as seen in Kamal’s study, the FDA sponsored taking statins based on its half-life. Before that, though, it seems that the healthcare world started questioning the nightly statin administration time, most likely between 2005 and 2010, as seen by the 2007 Plakogiannis study on half-lives and the 2008 Zhu study regarding pravastatin. So it seems that a whole new slew of research on the administration time of statins came to light during this time, but none of it was conclusive. This had an interesting effect on the healthcare setting, which are starting to play out now.
Take for instance, Hospital A. We have concluded that there is no set time for statin administration at Hospital A, despite the Head of Pharmacy’s claims. The nurses there administer their statins either at 0900 or 2100. Their patient education handouts regarding statins, though, say to “take regularly.” The nurses at Hospital B administer all of their statins at 2100. Their patient education handout regarding statins says to “take nightly.” This poses a potential problem. Since these two hospitals are within 40 miles of each other, it is highly likely that patients may receive treatment at both hospitals at some point in their life. If a patient is taking their statin nightly and goes in for treatment at Hospital A, they run the risk of being administered their medication at 0900. This medication discrepancy can affect adherence to the treatment due to confusion (Calvo et.al, 2005). The same goes for the patient taking a statin in the morning and going in for treatment at Hospital B.

The data supporting Hospital A’s patient education handouts are from 2016. The data supporting Hospital B’s patient education handouts range from 2003-2007. Both materials were copyrighted in 2017.

Due to the lack of conclusive research we have on the administration of statins, healthcare providers have not been able to carry out their treatment plans in the most effective manner. The more the provider knows, the more they can educate the patient and the more likely the patient will adhere to the treatment regimen (Abbott, 1998).

**Limitations**
Limitations of this study include a lack of research on the topic. In general there are few studies addressing the administration time of statins and those that do address the administration time of statins contradict one another. The majority of these studies were also from the early 2000’s and could have held outdated information but due to the lack of research on this topic, there was no way to know what was and what was not outdated. We also only looked into the policies of two hospitals. Moreover, these two hospitals were in the same region. At both institutions, despite having access to the hospital-wide policies on statin administration, we only had access to see how the policies were implemented on one unit at each hospital.

**Recommendations**

Moving forward we recommend that statins be researched further in order to eliminate some of the discrepancies currently going on right now in the healthcare world. We also recommend that hospitals in close proximity work together as much as possible to not provide different patient medication experiences and different patient education materials in order to promote compliance, safety, and patient satisfaction.

**Conclusion**

This review has discussed various articles in regards to HMG-CoA reductase inhibitors, or statins, and the current lack of and contradictory research there is when it comes to the optimal time to administer these medications. Due to the research that is out there, healthcare
organizations and providers have struggled finding the best way to educate patients on statins, and policies on these medications have been shown to vary from institution to institution, even amongst institutions in close proximity, which can have negative impacts on patient medication compliance. The results of this study should encourage researchers to continue looking into statins and their therapeutic administration time.
References


## Appendix A

Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Article Title</th>
<th>Year</th>
<th>Database Used</th>
<th>Accessed</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace, A., Chinn, D., Rubin, G.</td>
<td>Taking simvastatin in the morning compared with in the evening: a randomized control trial</td>
<td>2003</td>
<td>CINAHL</td>
<td>2-Sep-16</td>
<td>Simvastatin has been proven most effective when taken at night. Atorvastatin has no difference when taken at night or in am, possibly due to its longer half life.</td>
</tr>
<tr>
<td>Calvo, C., Lopez, J., Hermida, R., Ayala, D., Covelo, M., Rodriguez, M., Romero, M., Fontao, M., Soler, R.</td>
<td>Administration Time-Dependent Efficacy of Statins in Hyperlipidemic Patients With Essential Hypertension</td>
<td>2005</td>
<td>GoogleScholar</td>
<td>2-Sep-16</td>
<td>When taken at night, statins are more effective than when taken at lunch or morning. Therapeutic compliance also increases when taken at night.</td>
</tr>
<tr>
<td>Kamal, S.</td>
<td>Effects of single-dose morning and evening administration of pravastatin on antioxidant markers in cholesterol-fed rabbits</td>
<td>2011</td>
<td>PubMed</td>
<td>7-Sep-16</td>
<td>t has been stated that statins with a longer half life are more effective when given in the morning. Although pravastatin has a longer half life, it is more effective when given at night.</td>
</tr>
<tr>
<td>Frishman, W.</td>
<td>Importance of medication adherence in cardiovascular disease and the value of once-daily treatment regimens</td>
<td>2007</td>
<td>PubMed</td>
<td>3-Oct-16</td>
<td>Adherence to statin therapy is critical in preventing poor outcomes. The number of daily doses has a positive relationship with adherence.</td>
</tr>
<tr>
<td>Zhu, L., Zhou, Q., Yan, F., Zeng, S.</td>
<td>Optimal time to take once-daily oral medications in clinical practice</td>
<td>2008</td>
<td>CINAHL</td>
<td>3-Oct-16</td>
<td>Statins with shorter half lives are more effective when given at night. Pravastatin should always be administered at night.</td>
</tr>
<tr>
<td>Abela, G., Vedre, A., Janoudi, A., Huang, R., Durga, S., Tamhane U.</td>
<td>Effects of Stains on Cholesterol Crystallization and Atherosclerotic Plaque Stabilization</td>
<td>2011</td>
<td>CINAHL</td>
<td>3-Oct-16</td>
<td>Stains are proven to dissolve crystals in human plaques. It also changes the shape of the plaque (less pointed more blunt). These things together prevent plaque rupture.</td>
</tr>
<tr>
<td>Stitt, D., Elliott, D., Thompson, S.</td>
<td>Medication Discrepancies Identified at Time of Hospital Discharge in a Geriatric Population</td>
<td>2011</td>
<td>CINAHL</td>
<td>3-Oct-16</td>
<td>Medication discrepancies are related to the number of medications prescribed. They occur frequently in the elderly population. Reconciliation programs have started to pop up in 78% of hospitals</td>
</tr>
<tr>
<td>Quelennec, B., Beretz, L., Paya, D., Blickle, JF., Gourieux, B., Andres, E., Michel, B.</td>
<td>Potential clinical impact of medication discrepancy at hospital admission</td>
<td>2013</td>
<td>CINAHL</td>
<td>3-Oct-16</td>
<td>Cardiovascular agents are among the most common drugs where medication discrepancies occur. One of the most common discrepancies was incorrect frequency of med admin.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td>Year</td>
<td>Database</td>
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<tr>
<td>Plakogiannis, R., Cohen, H.</td>
<td>Optimal Low-Density Lipoprotein Cholesterol Lowering— Morning Versus Evening Statin Administration</td>
<td>2007</td>
<td>PubMed</td>
<td>5-Oct-16</td>
<td>Simavastatin is more effective when given in the morning. Lovastatin, Pravastatin and Rouvastatin showed an increase in lowered LDL levels when taken at night.</td>
</tr>
<tr>
<td>Abbott, S</td>
<td>The Benefits of Patient Education</td>
<td>1998</td>
<td>PubMed</td>
<td>1-Feb-17</td>
<td>It is up to the nurse to ensure that patient education is carried out appropriately. Educating patients fully comes with many benefits such as increased patient satisfaction and increased medication compliance.</td>
</tr>
</tbody>
</table>