Role of different LDL lowering medications on secondary prevention of atherosclerotic cardiovascular disease in patients with diabetes mellitus.

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Introduction

Heart disease is currently one of the leading causes of death among men and women in the United States today. Atherosclerotic Cardiovascular Disease (ASCVD) is one of the major contributors to this trend of cardiovascular related mortality. Hypercholesterolemia, identified via levels of low-density lipoprotein cholesterol (LDL-C), along with diabetes mellitus are direct risk factors for ASCVD. For this reason, management of LDL-C level is integral for ASCVD management.

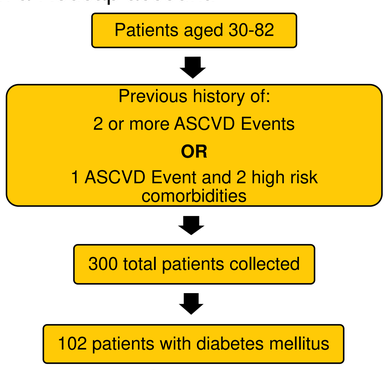
The American College of Cardiology (ACC) released new guidelines in 2018 for cholesterol management in patients with established ASCVD who are at very high risk of future ASCVD events. The new guidelines specifically highlighted two drug types in addition to maximally tolerated statin therapy. 1. Ezetimibe: a small intestine cholesterol absorption inhibitor, and 2. Evolocumab or Alirocumab: inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9). The 2013 guidelines only recommended the maximally tolerated statin therapy. The complications of diabetes mellitus reflect increased morbidity and mortality, warranting investigation into the optimal therapy for associated patients.

Objectives

The aim of this study is to determine if the use of PCSK9 inhibitors and ezetimibe in combination with statin therapy is statistically more effective than statin therapy alone in helping patients with diabetes mellitus achieve and maintain goal LDL-C levels (>50% reduction in baseline level or <70mg/dL). This will help assess if the 2018 ACC guidelines are more efficacious than the 2013 guidelines in managing patients with Diabetes Mellitus.

Methods

Data acquisition: A cohort study was done through a retrospective chart review at a large community-based cardiology practice. Inclusion criteria is shown below. Acquired data included all lipid panels, medications used, and ASCVD events between December 1st, 2013, and December 31st, 2019. Data was stored and encrypted on a Redcap account.



High risk comorbidities

- Age >65
- Hypercholesterolemia
- Arterial revascularization
- Diabetes mellitus
- Hypertension
- Chronic kidney disease
- Smoking history
- Congestive heart failure

ASCVD events are listed in **Table 1.**

Data analysis: Sub-group analysis was performed using Pearson's chi-squared and Fisher's Exact Test for categorical data and ANOVA for continuous data. A P-value of <0.05 was considered significant.

Results

Sex	
Male	42.2%
Female	57.8%
Age	
Mean	62.4
Minimum	37
Maximum	76

ASCVD Events	
Stroke	2.0%
Transient Ischemic Attack	2.9%
Coronary Artery Disease	95.1%
Angina	45.1%
Acute Coronary Syndrome	41.2%
Arterial Revascularization	77.5%
Peripheral Vascular Disease	22.5%
Aortic Aneurysm	2.9%

Table 1: Patient demographic information and prevalence of ASCVD events. N = 102

Regimen	Lipid Panels	Mean (mg/dL)	Standard Error of Mean	Interquartile Range
None	79	134.7	3.7	47
Statin	186	98.7	2.6	38
Ezetimibe	47	107.4	4.1	38
Statin + Ezetimibe	126	76.3	3.2	37
PCSK9 +/- Statin	66	48.8	4.1	32
PCSK9 & Ezetimibe +/- Statin	10	46.8	13.3	56

Table 2: LDL values from individual lipid panels for each medication regimen and descriptive statistics. N = 514

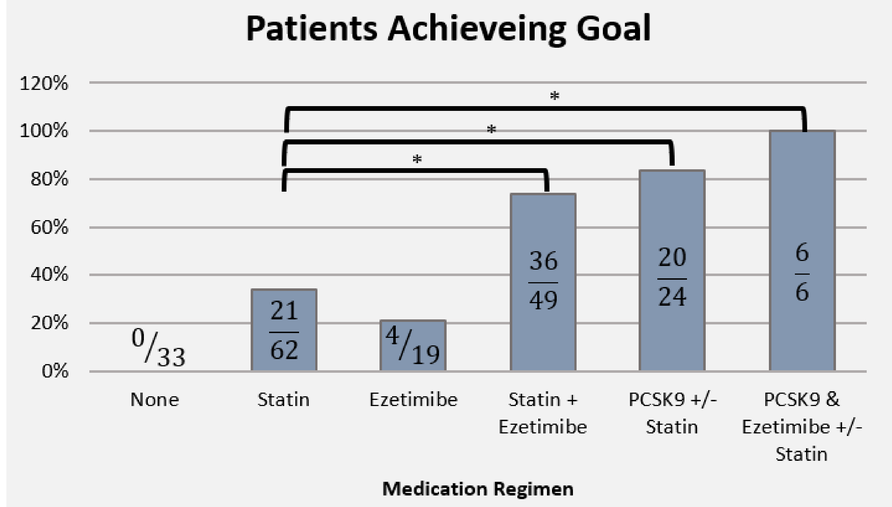


Figure 1: Percentage of patients that achieved goal at some point on each regimen. Patients were accounted for multiple times if they achieved goal on multiple regimens.

*Fisher's Exact Test shows a significant difference in the ability to achieve goal between Statin vs. Statin + Ezetimibe (P < .001), Statin vs. PCSK9 +/- Statin (P < .001) and Statin vs. PCSK9 & Ezetimibe +/- Statin (P = .003). There is no significant difference between PCSK9 +/- Statin vs. Statin + Ezetimibe (P = .395).

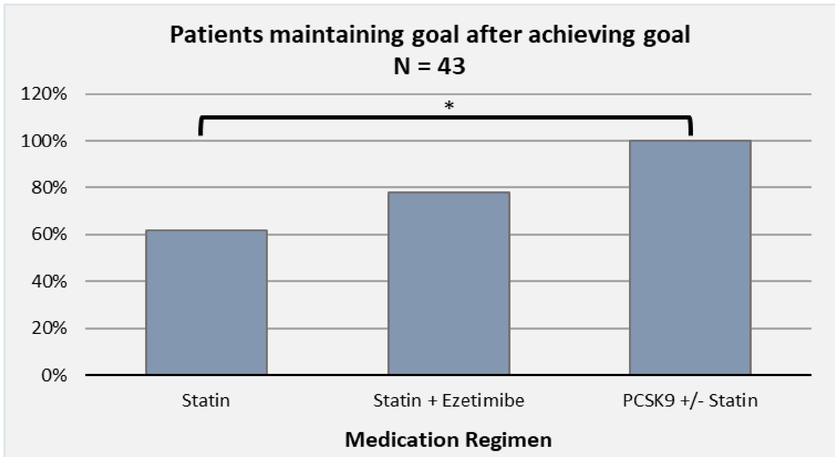


Figure 2: Percentage of Patients that achieved AND maintained goal on each regimen. The regimens "Ezetimibe" and "PCSK9 & Ezetimibe +/- Statin" were excluded based on sample size. Patients were included if they met goal and continued the same regimen in the subsequent lipid panel.

*Fisher's Exact Test shows a significant difference in the ability to achieve AND maintain goal at the subsequent lipid panel between Statin vs. PCSK9 +/- Statin (P = .039). There is no significant difference between Statin + Ezetimibe vs. PCSK9 +/- Statin (P = .130) and Statin vs. Statin + Ezetimibe (P = .433).

Discussion

- In summary, our analysis demonstrated that both Statin + Ezetimibe and PCSK9 inhibitor combination regimens were more effective that statin therapy in achieving goal, however only PCSK9 inhibitors showed a greater ability to achieve and maintain goal for diabetic patients at very high risk for ASCVD events.
- When looking at the results, only 83.3% of patients who tried PCSK9 inhibitors were able to achieve goal, yet all of those that achieved goal were able to maintain it. This implies that PCSK9 inhibitors could be a superior long term adjunct treatment option for diabetic patients than ezetimibe, especially among those that show a response early on in treatment.
- **Overall, patients with diabetes mellitus are inherently at a heightened risk for adverse cardiovascular events. Our results show that statin therapy alone may be insufficient for a large proportion of patients, and there should be heightened consideration for diabetics under the umbrella of very high risk to be treated with combination therapy of Statin and ezetimibe or a PCSK9 inhibitor in accordance with the 2018 ACC guidelines.**
- Some limitations in this study must be noted. Primarily, this is a retrospective chart review so we can only establish correlation, not causation. Additionally, there are many factors that play a role in LDL value outside of medication regimen that could affect results. In the analysis for **Figure 2**, it is worth noting that patients were excluded if they discontinued the regimen after achieving goal. This could be due to multiple factors such as intolerance or expense, with the latter being key problem for PCSK9 inhibitor therapy. More research should be done to see how those common problems affect treatment and outcomes in diabetic patients.