Lipid-lowering in 'very high risk' patients undergoing coronary artery bypass surgery and its projected reduction in risk for recurrent vascular events - A Monte Carlo stepwise simulation approach.

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Running head – lipid lowering therapy after CABG

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Conflict of Interest

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Abstract

2018 AHA guidelines provide criteria to identify patients at very high-risk (VHR) for adverse vascular events and recommend an LDL-C level < 1.8 mmol/L. Data regarding the 10-year risk for adverse vascular events in CABG patients at VHR and the need for non-statin therapies in the VHR cohort are limited.

We queried a national cohort of CABG patients to answer these questions. The projected reduction of LDL-C from stepwise escalation of lipid lowering therapy (LLT) was simulated; Monte Carlo methods were used to account for patient-level heterogeneity in treatment effects. Data on preoperative statin therapy and LDL-C levels were obtained. In the first scenario, all eligible patients not at target LDL-C received high intensity statins, followed by ezetimibe and then alirocumab; alternatively, bempedoic acid was also utilized. The 10-year risk for an adverse vascular event was estimated using a validated risk score. Potential risk reduction was estimated after simulating maximal LLT. Before CABG, 8,948/27,443 patients [(median LDL-C 85 mg/dl) were VHR. In the whole cohort, 31% were receiving high intensity statins. With stepwise LLT escalation, the proportion of patients at target were 60%, 78%, 86% and 97% after high intensity statins, ezetimibe, bempedoic acid and alirocumab respectively. The projected 10-year risk to suffer a vascular event reduced by 4.6%.

A large proportion of CABG patients who are at VHR for vascular events fail to meet 2018 AHA LDL-C targets. A stepwise approach, particularly with the use of bempedoic acid, can significantly reduce the need for more expensive PCSK9 inhibitors.

Introduction

Patients undergoing coronary artery bypass grafting (CABG) often have complex multi-vessel coronary artery disease. Postoperative morbidity and mortality of patients following CABG is presently very low [1,2], but the long-term survival often depends upon freedom from recurrent adverse atherosclerotic events. In this aspect, guideline directed medical therapy (GDMT) , specifically lipid lowering therapy (LLT) forms an important component of secondary prevention after CABG [3 4]. In 2018, the American Heart Association, introduced criteria to identify patients with established atherosclerotic cardiovascular disease (ASCVD) that may have a 'very high risk' (VHR) for suffering a recurrent adverse vascular event [5] (S-table 1). The association further recommends aggressive LLT in this group of patients with the aim of lowering LDL-C < 70 mg/dl [1.8 mmol/L]. To achieve this target, after maximally tolerated statin therapy, non-statin drugs like ezetimibe (22.7% mean reduction in LDL-C reduction) and proprotein convertase subtilsin-kexin type 9 inhibitors (PCSK-9i) (48.6% mean LDL-C reduction) are recommended [6]. However, cost (at the healthcare system and patient level) remains a very important practical limitation to the widespread use of PCSK9i [7]. Therefore, further stratification of these very high patients may help by identifying those that are truly at a prohibitively high risk. The SMART (Secondary Manifestations of Arterial disease) score, is one such score, as it can predict the 10-year vascular event rate among patients with established ASCVD, and stratify patients into groups according to their risk probability [8 9].(S-table 2).

The Monte Carlo simulation approach is a practical tool which can be used to project changes in baseline values under certain specified conditions. Advantage of this approach is the ability to incorporate epistemic and aleatoric uncertainty. Prior simulation studies evaluating the need for non-statin therapies in ASCVD patients exist [10 11]. However, most have applied the

2019 European Society of Cardiology/European Atherosclerosis Society guidelines[10,11]. Significant differences exist between the 2018 AHA/ACC and 2019 ESC/EAS guidelines. The 2 guidelines differ in their criteria to determine VHR patients as well as their recommended LDL-C targets [5 12]. Moreover, limited information exists regarding the potential beneficial effect that appropriate stepwise LLT intensification may have on the risk of having a recurrent adverse vascular event in this very high cohort. Using a Monte Carlo simulation approach, we evaluated the LDL-C lowering possibility with a stepwise escalation in lipid lowering therapy.

Our aims were to:

(1) Obtain the 10-year projected risk of suffering an adverse vascular event in a 'very high risk' cohort of CABG patients.

(2) Simulate a stepwise intensification of LLT to understand the need for PCSK9i according to the 2018 AHA criteria when, more specifically, bempedoic acid is administered prior to PCSK9i therapy; and

(3) Estimate the absolute risk reduction and residual risk of an adverse vascular event that may be obtained with the stepwise LLT simulation.

METHODS

The Veteran Health Affairs is largest integrated health care system in the United States, providing care to approximately 9 million Veterans [13]. The VA Surgical Quality Initiative Project (VASQIP), the primary source for this study, contains perioperative clinical information regarding patients that receive surgery in the VA system. Laboratory results, clinical characteristics and preoperative prescription information can be obtained from other data sources within the central computing infrastructure and linked together for each patient. The study was

approved by the Louis Stokes Cleveland VAMC institutional review committee: IRB# CY-045 and individual patient consent was waived.

From patients that underwent CABG (January 2010 – September 2019) we initially identified 27,443 who received primary isolated CABG and had a non-missing LDL-C level prior to surgery. Among these, 8,948 (32.6%) patients that were defined as very high-risk according to the 2018 AHA/ACC criteria were the subject of this study (S-figure 1). Demographics like age, sex, self-reported race and preoperative clinical characteristics for all patients were obtained. The International Classification of Diseases, 9th and 10th edition codes were used to identify clinical comorbidities when these were not directly available from the database.

Ongoing LLT was defined as a prescription fill within 120 days prior to the surgery. Patients were defined as not receiving any LLT if they did not have a documented prescription for a statin, ezetimibe or PCSK9i drug within 120 days of surgery. Using the type and dose of statin therapy and the AHA/ACC guidelines on statin dosing, statin therapy was classified as either low/moderate or high intensity[14]. Based on their LLT prior to CABG, patients were grouped as follows: (1) no LLT (2) low or moderate intensity statin therapy (3) high intensity statin therapy (4) high intensity statins + ezetimibe therapy and (5) only ezetimibe therapy. None were receiving PCSK9i therapy prior to surgery.

The LDL-C level within 120 days prior to the surgical procedure was also obtained. When multiple results were available, the result closest to the surgery date was chosen. For patients that were not on LLT, these readings were their untreated LDL-C levels. For patients receiving LLT at the time of surgery, untreated LDL-C levels were calculated using the extrapolation methods recommended by the ESC / EAS [10]. At each step in the simulation

pathway, the LDL-C from the prior step and the expected reduction in LDL-C, modeled as a β distribution, were used to obtain the new projected LDL-C level. The β distribution for the projected LDL-C reduction for each LLT was calculated using data provided by Cannon et al. [6] (S-table 3). These values have been implemented and validated in prior analyses [10,11].

Data Analyses:

LLT escalation was simulated in a stepwise manner. For each step, a Monte Carlo model was run (with 10,000 simulations) to simulate the heterogeneity in the projected LDL-C reduction. To model high-intensity statin therapy, rosuvastatin 40mg was used, as among statins, this therapy provides the maximal LDL-C reduction [6]. Among available PCSK9 inhibitors, alirocumab 75mg biweekly, was chosen to model the simulation as, alirocumab is the PCSK9i of choice in the VA healthcare system. At each step, the proportion of patients with LDL-C < 70 mg/dl [1.8 mmol/L] i.e., at target were calculated. The 95% confidence intervals for these target proportions were obtained by non-parametric bootstrap. Patients above target entered the next step of LLT intensification. Statin intolerance among statin naïve was modeled at 15%.

The following scenarios were simulated:

(1) Baseline scenario: In this scenario, all eligible patients with LDL-C > 70 mg/dl [1.8 mol/L] prior to surgery and not on high intensity statin therapy, were simulated to receive high intensity statin therapy. Statin intolerance (15%) was accounted for in this model. After high intensity statin therapy, patients received 10 mg ezetimibe, and finally, those that still had LDL-C levels > 70 mg/dl [1.8 mmol/L] were simulated to receive 75mg biweekly alirocumab.

(2) Adding bempedoic acid prior to alirocumab: In this situation, after adding high intensity statins and ezetimibe, 180 mg bempedoic acid was simulated in patients with LDL-C > 70 mg/dl [1.8 mmol/L]. Alirocumab 75mg biweekly was then added as the final step in this pathway.

Coefficients for each variable included in the SMART score were obtained from the appendix of the manuscript outlining model development [8]. The clinical SMART score contains the following variables – age, sex, smoking status, systolic blood pressure, presence of diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm, years since diagnosis of ASCVD, total cholesterol (mmol/lit), HDL-cholesterol (mmol/lit), eGFR (ml/min/m^2) and hs-CRP (mg/dl). Information regarding years since diagnosis of ASCVD, systolic blood pressure and hs-CRP were not available in our database. Hence, these values were imputed by using a random sampling algorithm from the summary statistics presented in the SMART score manuscript [8]. Missing data was present for total cholesterol (10%) and HDL-cholesterol (9%). Mean imputation was used to fill missing information. All other variables used in the model were complete. In a large individual patient level meta-analysis, the Cholesterol Treatment Trialists (CTT) collaborators reported a 12% risk reduction per 1 mmol/L of LDL-C change[15]. Therefore, using the simulated mmol/ lit LDL-C reduction, a projected hazard ratio was calculated for each patient. The logarithm of this hazard ratio was then included in the SMART regression model and the projected residual risk for an adverse vascular event at 10 years was calculated for that individual was calculated.

Statistical analyses were performed using R 4.0.2 (The R Foundation for Statistical Computing, Austria). Statistical code is available at the corresponding authors Github account (https://github.com/svd09). The appendix contains further information regarding statistical analyses performed.

Results

We studied 8,948 patients (January 2010 – September 2019) undergoing CABG and identified as very high risk as per the 2018 AHA/ACC criteria. In this very high-risk cohort, 2,408 (27%) were included as they had at least 2 major criteria, while all other patients had at least 1 major and 2 minor criteria. The median age of the very high-risk cohort was 66 (IQR: 62 – 71) years and 948/8,948 (11.1%) were >70 years old at surgery. The prevalence of diabetes mellitus, hypertension, and peripheral vascular disease was 49%, 94% and 58% respectively (Table 1).

Preoperatively, the median LDL-C level was 86 (66 – 115) mg/dl [2.2 (IQR: 1.7 – 2.9) mmol/L]. LDL-C < 70 mg/dl [1.8 mmol/L], 70 – 100 mg/dl [1.8 – 2.6 mmol/L] and > 100 mg/dl [2.6 mmol/L] were present in 29%, 37% and 34% respectively. Prior to surgery, in the very high-risk group, 70% were receiving LLT; 40% and 30% were receiving low/moderate intensity statin and high intensity statin therapy respectively (Figure 1). Only 1% of patients were receiving ezetimibe therapy prior to surgery. Compared to patients not on LLT, those receiving LLT had a significantly lower median LDL-C level (81 vs 103 mg/dl; $p < 0.001$) [2 vs 2.6 mmol/L].

Prior to surgery, from the LDL-C levels observed in our data, 29.5% (95% CI: 28.6 – 30.5%) of patients had an LDL-C < 70 mg/dl [1.8 mmol/L]. The remaining 70.5% were, therefore, eligible for a stepwise intensification of their LLT (S-table 4). Among statin-naïve patients, those simulated as statin intolerant did not receive any statin therapy. The remaining patients were simulated to receive 40mg rosuvastatin 40 mg. After adding rosuvastatin therapy, the overall anticipated median LDL-C for the entire cohort will be 64 (IQR: 48, 87) mg/dl [1.6 (IQR: 1.2, 2.2) mmol/L]. At the end of this step, 77%, 13%, and 1% will be receiving high

intensity statins, moderate/low intensity statin, and ezetimibe therapy respectively. After simulating treatment with 10 mg ezetimibe for those patients with LDL-C > 70 mg/dl [1.8 mmol/L], 76.1% are expected to attain target. The overall estimated LDL-C will now reduce to a median level of 59 (IQR: 46 – 69) mg/dl [1.5 (IQR: 1.2, 1.7) mmol/L]. In this simulation, after rosuvastatin and ezetimibe therapy, 23.9% of patients will still be projected to be above target LDL-C; they were therefore simulated to receive 75mg biweekly alirocumab. At the end of this simulation, from the whole cohort, we expect 94% to attain the target LDL-C. (Figure 2). Overall, in this simulated scenario, 41% received only high intensity statins. Ezetimibe and alirocumab therapy were added in 15% and 21% patients respectively. (Figure 3).

In the second scenario, after the initial steps of simulating 40mg rosuvastatin and 10mg ezetimibe therapy, 180mg bempedoic acid was added to those not reaching the target LDL-C level. Therefore, 21.4% of patients were simulated to receive 180mg bempedoic acid. After this step, we project the median LDL-C concentration will be 57 (IQR: 46 – 66) mg/dl [1.4 (IQR: 1.2, 1.7) mmol/L] and the percentage of patients expected to reach the target will increase from 78.6% to 86.8%. In this scenario, after simulating treatment with 75mg biweekly alirocumab, we expect that 97.4% patients will reach the target (Figure 4). Overall, in this scenario, 42% and 14% received high intensity and low/moderate intensity statins respectively; however, 21% were projected to need triple drug therapy with rosuvastatin, ezetimibe and bempedoic acid (Figure 5).

Compared to patients in the derivation of the SMART study cohort, our patients were older, with a higher prevalence of peripheral vascular disease. The prevalence of diabetes mellitus was higher in our cohort, while the rate of active smoking was comparable. Preoperatively, the median 10-year risk was 29% (IQR: 21% – 40%) (Figure 6). Overall, 56% of patients were in the very high (30% to < 40%) or extremely high-risk category (> 40%), while

19% were in the low (< 10%) or moderate (10% to < 20%) risk category (Table 2). After simulating maximal LLT and calculating the projected LDL-C levels, we can anticipate that the proportion of patients in the low or moderate risk category may increase from 19% to 36%, while those in the very high or extremely high-risk category may reduce from 56% to 34%. We project that, with a maximal LLT, in our cohort, we may observe a median absolute risk reduction of 4.6 % (IQR: 0.1% - 8.2%). However, even after maximal LLT, we estimate that the median residual risk in our cohort for suffering an adverse vascular event over 10 years will be 23.9 % (16.7% – 34.7%).

Discussion

The 2018 guidelines from the AHA/ACC recommend that patients at 'very high risk' of suffering an adverse vascular event receive intensified LLT to achieve a target LDL-C concentration < 70 mg/dl [1.8 mmol/L]; in many patients, this cut-off is challenging to achieve using only statins. They, therefore, recommend an incremental approach of high intensity statins followed by non-statin drugs like ezetimibe and PCSK9i. We observed that, in a nationally representative cohort of CABG patients, almost one-third fit the 2018 AHA/ACC criteria of 'very high risk'. Simulating a stepwise approach to LLT intensification and Monte Carlo methods to model the heterogeneity in treatment effects, we project that, in our cohort, 24% of patients would need incremental alirocumab therapy to reach the recommended target LDL-C. After treating with maximally tolerated statin therapy and ezetimibe therapy, however, if 180mg bempedoic acid were added, this may reduce the need for PCSK9i therapy by almost 8%. In patients deemed to be 'very high risk' by the 2018 AHA/ACC criteria, we observed a wide range of SMART scores. In fact, according to the SMART model, 1/5th patients were in the low- risk category. If all patients were to receive maximally tolerated LLT, we project a 5% median

absolute reduction in patients SMART scores. However, even with this simulated maximal reduction in LDL-C levels, we still project a substantial residual risk for adverse vascular events in our cohort.

In our cohort of CABG patients, approximately 30% was identified as VHR according to the 2018 AHA criteria. The incidence of VHR ranges between approximately 50 – 60% in prior studies[16 17], while 57% and 64% from the REACH and SMART fit the 'very high risk' criteria [18]. The lower incidence of VHR observed in our data could be as our cohort consists of only male CABG patients, which may introduce a selection bias. A recent study reported that the 2018 AHA/ACC criteria, themselves, have a poor discriminative ability in identifying patients at 'true' high risk for atherosclerotic vascular disease [18]. However, our study and many others clearly demonstrate that targeted lipid lowering therapy is not being used by many high-risk patients. In our group, approximately 30% patients were not receiving any LLT. From those receiving any LLT, only 44% were on high intensity statin therapy (Table 1). In a cohort of privately insured patients, Colantonio et al. observed that 80% were receiving statin therapy; however, only 35% were on high intensity statin dosing [16]. An et al. reported similar findings, with high intensity statins being prescribed in 21 – 34% patients in the VHR cohort [17]. In the SMART and REACH registries, 66% and 70% of patients respectively were receiving statin therapy. In a cohort of patients from Sweden, among 25,466 patients with myocardial infarction, only 20% of patients prior to admission were receiving LLT, while 85% were subsequently discharged with LLT. Other studies also report high rates of needing PCSK9i therapy to meet the 2019 ESC/EAS lipid guidelines[10 11]. In our simulation, there would be a reduction in the need for PCSK9i by 8 – 10% by using bempedoic acid after ezetimibe therapy. Till date, bempedoic acid has been studied in phase 3 trials on patients with ASCVD and had demonstrated substantial reduction in LDL-C

concentrations over a 52 week period [19 20 21]. However, a trial examining cardiovascular outcomes with bempedoic acid therapy is ongoing [22]. The annual cost of bempedoic acid therapy in Germany is € 1722.50 [23], which is less than half the cost of alirocumab therapy. Therefore, the potential use of bempedoic acid may provide a more cost-effective way of reducing LDL-C levels in very high-risk patients. Therefore, our study demonstrates that the prior use of bempedoic acid may provide financial savings to both the patient and healthcare system.

Although all patients in our cohort were deemed very high risk by the 2018 AHA/ACC criteria, using the SMART score, we still observed a wide range of estimated 10-year risk rates (Table 2). Van den Berg et al. reported that the discriminatory ability of the 2018 AHA/ACC criteria to determine a recurrent vascular event is limited [18]. When the 2018 AHA/ACC criteria were externally validated in the REACH and SMART cohorts, the c-statistic observed was 0.53 and 0.54 respectively [18], suggesting minimal discriminatory ability. In our cohort of very high-risk patients, the 10-year risk of recurrent events was < 30% in half the patients. Studies have demonstrated that, at least in the United States, at present, the widespread use of PCSK9i drugs is not generally cost effective [24]. Therefore, along with the 2018 AHA criteria, we recommend physicians use a scoring system which may provide improved risk stratification. This would allow a more targeted and cost-effective approach, wherein, costly non statin drugs can be preferentially prescribed to patients at highest risk for future adverse vascular events.

The strengths of this study are the use of a large national cohort of CABG patients, reflecting a varied population, modeling the heterogeneity in the individual response to LLT with Monte Carlo methods, reliable data regarding baseline LDL-C concentrations and the availability of accurate information regarding statin therapy prior to surgery. Our study also has some limitations. As our data are from the Veteran Affairs healthcare system, patients are almost all

males. This limits generalizability of our results to women. In the calculation of the SMART score, missing data were imputed. However, we performed sensitivity analyses to evaluate the impact of such simulations on the overall results.

In conclusion, from a national database, we observed that a sizeable proportion of CABG patients fit the 2018 AHA/ACC very high-risk criteria. Lipid lowering therapy remains suboptimal with many patients having LDL-C concentrations > 70 mg/dl, the recommended target for such high-risk patients. The simulated need for PCSK9 inhibitor therapy was substantial at 21%; however, this can be reduced by 8% using bempedoic acid, emphasizing the increasing need for use of multiple lipid-lowering drugs in many patients with prior CABG. We further observed that, in our cohort, simulating maximal lipid lowering therapy may reduce the risk of recurrent events by approximately 5% from baseline. Finally, applying a well validated scoring model to our cohort, we observed a wide variation in the estimated risk rate for recurrent vascular events, suggesting a need to re-evaluate the approach to identifying high risk patients advocated by the 2018 AHA/ACC guidelines.

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Author Contribution Statement

SD – study concept & design, statistical analysis, writing manuscript

PU – statistical analysis, study design, critical revisions to manuscript

AMS – study design, writing manuscript

SA – writing manuscript, critical revisions to manuscript

YE – critical revisions to manuscript

JR – critical revisions to manuscript

BC – critical revisions to manuscript

NH – statistical analysis, study design, critical revisions to manuscript

DM – study design, critical revisions to manuscript

MR – critical revisions to manuscript

NS – study design, critical revisions to manuscript

JP – study design, critical revisions to manuscript

Figure Legends:

Figure 1 – Prior to CABG, 30 % were not on LLT, while 30 % and 39 % were receiving high-intensity and low/moderate intensity statin therapy respectively. *Abbreviations: eze – ezetimibe, lmis – low/moderate intensity statin therapy, his – high intensity statin therapy*

Figure 2 – Flowchart of the stepwise simulated escalation of LLT to achieve a target LDL-C level < 1.8 mmol/lit (70 mg/dl).

** High intensity statin modeled is Rosuvastatin 40 mg*

Figure 3: (A) Distribution of projected LDL-C levels at the end of the simulation algorithm in *figure 2*. (B) After complete simulation, proportion of patients requiring 75mg bi-weekly alirocumab to attain LDL-C levels < 1.8 mmol/Lit is depicted in blue. *Abbreviations: ali – alirocumab, eze – ezetimibe, lmis – low/moderate intensity statin therapy, his – high intensity statin therapy*

Figure 4 – Flowchart of the stepwise simulated escalation of LLT to achieve a target LDL-C level < 1.8 mmol/lit (70 mg/dl).

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Figure 6. A histogram of SMART scores from our cohort at baseline (A) and then after simulating treatment with maximal LLT (B). After simulating treatment with maximal LLT, the percentage of patients in the very high risk (SMART score: 30 – 40%) and extremely high risk (SMART score > 40%) reduced from 56% to 34%. The median SMART score (red line) correspondingly reduced from 29% to 24%. *Red line – median SMART score, black dotted line – SMART score of 30%.*

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