Attainment of Lipid Targets Following Coronary Artery Bypass Graft Surgery: Can We Do Better?

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ABSTRACT

Objective: Patients undergoing coronary artery bypass graft (CABG) surgery remain at high cardiovascular risk; however, few studies have evaluated lipid management and attainment of lipid targets in these patients. We investigated the proportion of CABG surgery patients who attained low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (HDL-C) targets.

Methods: Data were retrospectively obtained from patients undergoing CABG surgery at an Australian tertiary hospital between February 2015 and August 2020. The most recent lipid profile was recorded (at least 3 weeks post-operatively). We studied patients with electronically available data to ensure accuracy. Target LDL-C was defined as <1.4 (54 mg/dL) and <1.8 mmol/L (70 mg/dL), and target non-HDL-C as <2.2 (85 mg/dL) and <2.6 mmol/L (100 mg/dL), as per the 2019 and 2016 European dyslipidaemia guidelines, respectively.

Results: Follow-up lipid results were available for 484 patients (median post-operative follow-up, 483 days; interquartile range, 177.5–938.75 days). The mean age was 62.7±10.5 years and 387 (80.1%) were male. At discharge, 469 (96.9%) patients were prescribed statins, 425 (90.6%) high-intensity. Ezetimibe was prescribed for 62 (12.8%) patients and a proprotein convertase subtilisin-kexin type 9 inhibitor for 1. LDL-C levels <1.4 and <1.8 mmol/L were attained in 118 (24.4%) and 231 (47.7%) patients, respectively, and non-HDL-C levels <2.2 and <2.6 mmol/L in 140 (28.9%) and 237 (49.0%) patients, respectively.

Conclusion: The use of non-statin lipid-lowering therapies was limited, and many CABG surgery patients did not attain lipid targets despite high-intensity statins. Further studies are required to optimise lipid management in this very high-risk population.

Keywords: Lipids; Statins; Coronary disease; Cardiovascular diseases
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Data Availability Statement
The data that support the findings of this study are available from the corresponding author (NSRL) upon reasonable request.

Author Contributions
Conceptualization: Lan NSR, Ali US, Yeap BB, Fegan PG, Larbalestier R, Bell DA; Data curation: Lan NSR, Ali US, Larbalestier R; Formal analysis: Lan NSR, Investigation: Lan NSR, Yeap BB, Fegan PG, Bell DA; Methodology: Lan NSR, Ali US, Yeap BB, Fegan PG, Larbalestier R, Bell DA; Project administration: Lan NSR, Larbalestier R; Supervision: Bell DA; Writing - original draft: Lan NSR; Writing - review & editing: Ali US, Yeap BB, Fegan PG, Larbalestier R, Bell DA.

INTRODUCTION
Coronary artery bypass graft (CABG) surgery is commonly performed for multi-vessel and left main coronary artery disease. However, patients who have undergone CABG surgery remain at significantly increased risk of cardiovascular disease (CVD) morbidity and mortality compared with the general population. Preventive medical therapies to address CVD risk factors following CABG surgery can reduce the risk of adverse outcomes such as myocardial infarction and death. In particular, studies have shown that lowering low-density lipoprotein cholesterol (LDL-C) with statins and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors plays a role in reducing CVD events in patients undergoing CABG surgery.

The American Heart Association (AHA) and American College of Cardiology (ACC) 2018 guidelines recommend high-intensity statin therapy for secondary prevention of CVD.

The guidelines also recommend an LDL-C threshold of ≥1.8 mmol/L (70 mg/dL) for adding non-statin LDL-C lowering therapies such as ezetimibe and PCSK9 inhibitors in very high-risk patients with CVD.

In contrast, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines recommend lipid and lipoprotein targets depending on cardiovascular risk category. Patients who have undergone CABG surgery are considered very high-risk, and thus the 2019 ESC/EAS guidelines recommend LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) targets of <1.4 mmol/L (54 mg/dL) and <2.2 mmol/L (85 mg/dL), respectively.

The 2019 targets are more intensive than the 2016 ESC/EAS guideline targets of <1.8 mmol/L (70 mg/dL) and <2.6 mmol/L (100 mg/dL) for LDL-C and non-HDL-C, respectively, in very high-risk patients.

However, few studies in the modern era have evaluated lipid management and attainment of lipid targets in patients who have undergone CABG surgery. In light of updated guideline recommendations, the aim of this study was to determine the proportion of patients undergoing CABG surgery at an Australian hospital who had LDL-C levels above the threshold for adding non-statin lipid-lowering therapy and the proportion of patients who attained guideline-recommended LDL-C (primary) and non-HDL-C (secondary) targets.

We sought to study the subset of patients with lipid profiles available electronically through the local pathology laboratory (PathWest Laboratory Medicine) system to ensure accuracy of both lipid results and the dates when they were obtained.

MATERIALS AND METHODS
The manuscript was prepared according to ICMJE recommendations and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

1. Study cohort
A retrospective analysis of patients who underwent CABG surgery at an Australian tertiary hospital from when the hospital first opened in February 2015 until August 2020 was performed following approval by the local research governance office (GEKO Quality Activity 39504). Data for all patients undergoing CABG surgery at the hospital are collected prospectively by the cardiothoracic surgery, intensive care unit, and anaesthetic medical teams for the Australian and New Zealand Society of Cardiothoracic Surgery (ANZSCTS) database, which is subject to regular external validations to ensure accuracy and completeness of the data. The requirement for informed consent was waived because this
was a retrospective study of de-identified data. The ANZSCTS database and the definitions used for the variables collected have been previously described in detail. Variables pertaining to baseline demographics, past medical history, inpatient mortality, and 30-day mortality were extracted from the database. Patients with inpatient mortality or 30-day mortality following CABG surgery were subsequently excluded from the analysis.

Lipid profile results performed more than 3 weeks post-operatively were extracted from the PathWest Laboratory Medicine database. PathWest provides pathology services for all government hospitals in Western Australia, as well as a large network of regional laboratories. If multiple lipid profiles were available, the most recent result was used for analysis. Lipid profiles performed in the non-fasting state were included as guidelines recommend that fasting is not routinely required for lipid profile measurements. Prescriptions of statins, ezetimibe, fibrates, and PCSK9 inhibitors at the time of hospital discharge and documentation regarding history of familial hypercholesterolaemia (FH) were obtained from hospital discharge summaries. Patients are routinely prescribed high-intensity statin therapy at our institution following CABG surgery. The PCSK9 inhibitor evolocumab became subsidised by the Australian government in May 2020 for patients with symptomatic CVD with an LDL-C level >2.6 mmol/L (100 mg/dL) despite maximum tolerated statin, ezetimibe, and lifestyle therapy.

2. Definitions and outcomes
According to the AHA/ACC 2018 guidelines, the LDL-C threshold for adding non-statin LDL-C lowering therapies is ≥1.8 mmol/L (70 mg/dL). CABG surgery patients are considered very high-risk according to the ESC/EAS 2019 guidelines, where the target LDL-C and non-HDL-C levels are <1.4 mmol/L (54 mg/dL) and <2.2 mmol/L (85 mg/dL), respectively. Given that data were also collected prior to publication of the EAS/EAS 2019 guidelines, we also assessed the proportion of patients who achieved the LDL-C and non-HDL-C targets of <1.8 mmol/L (70 mg/dL) and <2.6 mmol/L (100 mg/dL), respectively, from the ESC/EAS 2016 guidelines. Non-HDL-C was calculated as total cholesterol minus HDL-C. Statin therapy was categorised as high- or moderate-intensity according to the ACC/AHA 2018 guidelines, which stipulate that atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg are considered high-intensity.

3. Statistical analysis
Statistical analyses were carried out on patients with follow-up lipid results using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and SAS software (v9.4; SAS Institute Inc., Cary, NC, USA). Descriptive results are presented as mean with standard deviation (SD), count with percent (%), or median with interquartile range (IQR). The Student’s t-test, Pearson chi-square test, and Fisher exact test were used to compare differences between groups. The Cochran-Armitage trend test was used to assess trends in the proportion attaining LDL-C targets according to lipid-lowering therapy. A two-sided p-value of <0.05 was used to define statistical significance.

RESULTS
Of 1,676 patients who underwent CABG surgery and met the study criteria, 484 (28.9%) had follow-up plasma lipid profiles. Their baseline characteristics are presented in Table 1. Their mean age was 62.7±10.5 years and 387 (80%) were male. Venous bypass grafts were used in
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Table 1. Baseline characteristics and lipid medications at discharge for patients with follow-up lipid profile results

| Characteristics                                    | Value (n=484) |
|----------------------------------------------------|---------------|
| Age (yr)                                           | 62.7±10.5     |
| Sex (male)                                         | 387 (80.0)    |
| Indigenous                                         | 90 (18.6)     |
| Dyslipidaemia history                              | 382 (78.9)    |
| Familial hypercholesterolaemia documented          | 3 (0.6)       |
| Hypertension history                               | 360 (74.4)    |
| Diabetes history                                   | 259 (53.5)    |
| Smoking history                                    | 335 (69.2)    |
| Prior myocardial infarction                        | 303 (62.6)    |
| NSTEMI                                             | 252 (52.1)    |
| STEMI                                              | 51 (10.5)     |
| Body mass index (kg/m²)                            | 29.5±5.4      |
| Surgery at age <60 years                           | 185 (38.2)    |
| Elective (non-urgent) surgery                      | 226 (46.7)    |
| Arterial graft used                                | 457 (94.4)    |
| Vein graft used                                    | 431 (89.0)    |
| Concomitant valve or aortic procedure              | 69 (14.3)     |
| Statin (any)                                       | 469 (96.9)    |
| High-intensity                                     | 425 (87.8)    |
| Moderate-intensity                                 | 39 (8.1)      |
| Statin only                                        | 387 (80.0)    |
| Ezetimibe only                                     | 2 (0.4)       |
| Fibrate only                                       | 1 (0.2)       |
| Statin plus ezetimibe                              | 57 (11.8)     |
| High-intensity statin plus ezetimibe               | 46 (9.5)      |
| Statin plus fibrate                                | 24 (5.0)      |
| Statin plus ezetimibe plus fibrate                 | 1 (0.2)       |
| Ezetimibe plus fibrate                             | 1 (0.2)       |
| PCSK9 inhibitor plus ezetimibe                     | 1 (0.2)*      |
| No lipid-lowering medications                      | 10 (2.1)      |

Data are presented as mean±standard deviation or count (percent).

NSTEMI, non-ST-segment elevation myocardial infarction; PCSK9, proprotein convertase subtilisin-kexin type 9; STEMI, ST-segment elevation myocardial infarction.

*This patient was not prescribed a statin due to a history of statin intolerance.

431 (89.0%) and arterial grafts in 457 (94.4%). A history of dyslipidaemia was documented for 382 (78.9%) patients. FH was documented in the discharge summary of 3 (0.6%) patients, and CABG surgery was performed at an age <60 years in 185 (38.2%) patients. Lipid-lowering medications prescribed at discharge from the hospital following CABG surgery are also presented in Table 1. At discharge, 469 (96.9%) patients were prescribed statin therapy, of which 425 (90.6%) received high-intensity therapy. Overall, ezetimibe was prescribed for 62 (12.8%) patients, of whom 58 (93.5%) received ezetimibe in combination with a statin. One (0.2%) patient was discharged on a PCSK9 inhibitor, which was prescribed in combination with ezetimibe due to a history of statin intolerance.

The median follow-up from day of CABG surgery to the latest available lipid profile result was 483 days (IQR, 177.5–938.75 days) and the lipid profile was performed ≥30 days postoperatively for 473 (97.7%) patients. Apolipoprotein B was measured in 28 (5.8%) patients. At follow-up, mean LDL-C levels (follow-up: 1.92±0.90 mmol/L [74.6±35.0 mg/dL] versus baseline: 2.57±1.18 mmol/L [99.3±45.6 mg/dL], p<0.001) and non-HDL-C levels (follow-up: 2.76±1.05 mmol/L [107.4±41.4 mg/dL] versus baseline: 3.53±1.38 mmol/L [137.0±53.0 mg/dL], p<0.001) were significantly lower than at baseline, as presented in Table 2. LDL levels ≥1.8 mmol/L (70 mg/dL) were present in 205 (53.0%) of the 387 patients prescribed a statin without a non-statin lipid-lowering agent.
The proportions of patients attaining lipid targets at follow-up are presented in Table 3. Overall, the target LDL-C levels of <1.4 mmol/L (54 mg/dL) and <1.8 mmol/L (70 mg/dL) were attained in 118 (24.4%) and 231 (47.7%) patients respectively and the non-HDL-C targets of <2.2 mmol/L (85 mg/dL) and <2.6 mmol/L (100 mg/dL) were attained in 140 (28.9%) and 237 (49.0%) patients respectively. Compared with patients discharged on high-intensity statin therapy only, or moderate- or low-intensity statin therapy with or without ezetimibe, patients discharged on high-intensity statin therapy plus ezetimibe were more likely to attain the LDL-C target levels of <1.4 mmol/L (54 mg/dL) \( (p\text{ for trend}=0.020) \) and <1.8 mmol/L (70 mg/dL) \( (p\text{ for trend}<0.001) \), as presented in Fig. 1. The proportion of patients with a ≥50% reduction in LDL-C levels from their pre-operative baseline status to the follow-up lipid profile analysis was 98 (20.2%). The proportion of patients attaining lipid targets according to year of CABG surgery was not significantly different, as presented in Supplementary Table 1.

### Table 2. Lipid profile at baseline and follow-up

| Lipid profile component | Baseline | Follow-up | p-value |
|-------------------------|----------|-----------|---------|
| LDL-C (mmol/L)          | 2.57±1.18| 1.92±0.90 | <0.001  |
| LDL-C (mg/dL)           | 99.3±45.6| 74.6±35.0 |         |
| Non-HDL-C (mmol/L)      | 3.53±1.38| 2.76±1.05 | <0.001  |
| Non-HDL-C (mg/dL)       | 137.0±53.0| 107.4±41.4|         |

Data are presented as mean±standard deviation.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

### Table 3. Attainment of lipid targets at follow-up based on therapy at discharge

| Therapy | AHA/ACC 2018 Guideline | ESC/EAS 2019 Guideline | ESC/EAS 2016 Guideline |
|---------|-------------------------|------------------------|------------------------|
|         | Overall (n=484)         | High-intensity statin plus ezetimibe (n=46) | High-intensity statin only (n=379) | Moderate- or low-intensity statin with or without ezetimibe (n=44) | Ezetimibe only (n=3) |
|         | LDL ≥1.8 mmol/L (70 mg/dL) threshold | LDL-C <1.4 mmol/L (54 mg/dL) | Non-HDL-C <2.2 mmol/L (85 mg/dL) | LDL-C <1.8 mmol/L (70 mg/dL) | Non-HDL-C <2.6 mmol/L (100 mg/dL) |
|         | 253 (52.3) | 118 (24.4) | 140 (28.9) | 231 (47.7) | 237 (49.0) |

Data are presented as count (percent).

AHA/ACC, American Heart Association/American College of Cardiology; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

The proportions of patients attaining lipid targets at follow-up are presented in Table 3. Overall, the target LDL-C levels of <1.4 mmol/L (54 mg/dL) and <1.8 mmol/L (70 mg/dL) were attained in 118 (24.4%) and 231 (47.7%) patients respectively and the non-HDL-C targets of <2.2 mmol/L (85 mg/dL) and <2.6 mmol/L (100 mg/dL) were attained in 140 (28.9%) and 237 (49.0%) patients respectively. Compared with patients discharged on high-intensity statin therapy only, or moderate- or low-intensity statin therapy with or without ezetimibe, patients discharged on high-intensity statin therapy plus ezetimibe were more likely to attain the LDL-C target levels of <1.4 mmol/L (54 mg/dL) \( (p\text{ for trend}=0.020) \) and <1.8 mmol/L (70 mg/dL) \( (p\text{ for trend}<0.001) \), as presented in Fig. 1. The proportion of patients with a ≥50% reduction in LDL-C levels from their pre-operative baseline status to the follow-up lipid profile analysis was 98 (20.2%). The proportion of patients attaining lipid targets according to year of CABG surgery was not significantly different, as presented in Supplementary Table 1.

**Fig. 1.** Attainment of LDL-C targets at follow-up.

1.4 mmol/L equates to 54 mg/dL, 1.8 mmol/L equates to 70 mg/dL.

LDL-C, low-density lipoprotein cholesterol.
After an overall median follow-up of 1,254 days (IQR, 772–1,597 days) from the day of CABG surgery, 38 (7.9%) deaths were recorded. As presented in Table 4, there were no significant differences in LDL-C levels at follow-up, the proportion of patients who attained LDL-C targets at follow-up, and the proportion of patients who received statin plus ezetimibe prescriptions at discharge between those who died and those who were alive at time of follow-up.

**DISCUSSION**

The major finding of this study is that a large proportion of patients who underwent CABG surgery could potentially benefit from the addition of non-statin lipid-lowering therapies, as they are not attaining lipid targets despite the majority being prescribed high-intensity statins at discharge. These results are important, since studies have demonstrated that patients who have undergone CABG surgery derive greater absolute benefits from PCSK9 inhibitor therapy. Although LDL-C and non-HDL-C levels were significantly lower at follow-up in our study, approximately 50% of patients attained the previous ESC/EAS 2016 guideline lipid targets. More importantly, only 25%–30% of patients in our study attained the lipid targets from the more recent ESC/EAS 2019 guideline, which utilises lower lipid targets and indicates a more intensive approach to lipid-lowering in modern practice due to evidence from PCSK9 inhibitor trials, where low LDL-C concentrations were achieved safely.

Our data provide important support to the relatively few real-world studies that have investigated whether patients undergoing CABG surgery attain lipid targets. Similar to our study, a recent study from Israel found that only 44% of CABG surgery patients attained LDL-C levels <1.8 mmol/L (70 mg/dL) at follow-up. In that study, a lack of attainment of lipid targets was independently associated with decreased survival; however, we did not find a significant association between the attainment of LDL-C targets and all-cause mortality in our study. Another study from the Middle East found that only 29% and 59.3% of CABG surgery patients attained LDL-C targets of <1.4 mmol/L (54 mg/dL) and <1.8 mmol/L (70 mg/dL) respectively. Data from large registry studies in primary and secondary prevention cohorts in Europe have also shown that the ESC/EAS 2016 and 2019 guideline targets were attained in fewer than half and one-fifth of patients prescribed statin therapy, respectively. Thus, despite the relative paucity of publications, it is evident that there remains an important gap in secondary prevention of CVD for CABG surgery patients. Additionally, reductions in lipid levels may also reduce venous graft failure, which is an important consideration as most patients in our study had vein grafts.
Given the results of our study, it is important to identify and address the reasons for suboptimal lipid management. Such reasons may include medication non-adherence, statin intolerance, undertreatment, insufficient efficacy, uncertainties regarding guideline recommendations, and medication cost. As such, the use of non-statin lipid-lowering therapies may be required, and we identified many patients who were above the AHA/ACC 2018 guideline threshold for addition of such therapies. This is further supported by our data showing that a higher proportion of patients attained lipid targets when more intensive statin therapy was combined with ezetimibe. Evidence from large observational studies suggests that even with optimisation of statin and ezetimibe therapy, the use of PCSK9 inhibitors may be needed to attain lipid targets in a significant number of individuals with CVD (up to 50% of individuals in one study of individuals with recent myocardial infarction).\textsuperscript{19,21} Despite over 85% of patients in our study being prescribed high-intensity statin therapy following CABG surgery, only 20% of patients achieved ≥50% reduction in LDL-C levels from their pre-operative status to their follow-up lipid profile. This is presumably because many patients awaiting CABG surgery are already treated with lipid-lowering therapy; thus, their pre-operative lipid profile may not necessarily reflect pre-treatment levels. However, statin non-adherence and undertreatment remain possible explanations for less than anticipated reductions in LDL-C. Future work should therefore aim to develop strategies to assist in implementing guideline recommendations in this very high-risk population to achieve lipid targets.\textsuperscript{14}

FH is a dominantly inherited disorder leading to elevated LDL-C levels and premature CVD. The prevalence of FH is approximately 1:250 people in the general population, but it is substantially more common in patients with premature CVD, with estimates of between 15% and 25% depending on the study.\textsuperscript{22} Although 38.2% of patients in our study had CABG surgery performed at an age <60 years, FH was documented in only 3 patients. FH is a condition that remains under-recognised worldwide, and patients undergoing CABG surgery may represent a unique cohort where screening can be opportunistically performed due to the higher prevalence compared to the general population.\textsuperscript{23} Testing for FH is important because detecting index cases has implications for lipid management, genetic testing, and family screening.\textsuperscript{23} At our institution, screening for FH is not routinely performed in the cardiac or cardiothoracic units, and this is another important modifiable gap in lipid care for the prevention of CVD.\textsuperscript{24}

The establishment of a new cardiometabolic speciality, with integration into inpatient cardiothoracic units, cardiac units, and outpatient clinics, could potentially bridge the gap in lipid management and FH detection.\textsuperscript{25,26} Cardiometabolic services can assist in providing a more comprehensive approach to managing complex lipid and lipoprotein disorders, such as facilitating the initiation of preventative therapies (e.g., PCSK9 inhibitors or newer therapies that are under development or currently undergoing CVD outcome trials, such as inclisiran or therapies targeting lipoprotein[a])).\textsuperscript{25,26} In addition, the cardiometabolic speciality can help support a more comprehensive patient-centred approach to cardiovascular risk reduction. Collaboration between cardiometabolic and cardiothoracic services may provide a solution for optimising lipid care before and after CABG surgery.

The limitations of our study include its retrospective and single-centre design. Lipid profile results were extracted from a single laboratory database. However, the laboratory we used is the provider for all tertiary hospitals and many non-tertiary hospitals in Western Australia, which would capture most follow-up measurements. Three private laboratories operate in Western Australia, and we had data on 28.9% of patients. It is possible that our data may...
not be representative of the entire CABG surgery cohort due to the nature of this selection, as patients self-elected to have their blood tests performed at PathWest. However, our findings are comparable to other international studies in this field. The period of our audit was not covered entirely by the ESC/EAS 2019 guidelines, and lipid targets were therefore applied retrospectively. Due to the retrospective nature of this study, which relied on a review of medical records, we did not have complete data on adherence, medication intolerance, or changes to lipid-lowering medications at follow-up. In addition, patients may not be routinely followed-up in the hospital; thus, data on medication use and changes may not be available. Furthermore, the proportion of patients attaining target apolipoprotein B levels was not studied, as this was not routinely measured in practice as demonstrated by our data. Despite strong evidence that more intensive LDL-C lowering is associated with reduced risk of cardiovascular mortality in individuals with CVD, we did not demonstrate such a relationship in our study, likely due to limitations in the length of follow-up, sample size, and the inclusion of non-cardiovascular causes of death. The key strength of this study is the analysis of real-world data from a unique population with little research in this area and a moderate sample size.

In conclusion, there is a significant gap in lipid management for patients undergoing CABG surgery. Although high-intensity statin therapy is prescribed for the majority of patients, the addition of non-statin LDL-C lowering therapies, such as ezetimibe and PCSK9 inhibitors, is required to attain contemporary lipid targets. Further research is needed to identify barriers to treatment and to optimise lipid management in this very high-risk population to reduce morbidity and mortality. This may be best coordinated by a multidisciplinary cardiometabolic service.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Attainment of LDL-C targets according to year of surgery

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