Adherence to Guideline Medication Recommendations to Prevent Atherosclerotic Cardiovascular Disease Progression Among Adults With Prior Myocardial Infarction

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Introduction

With improvements in acute care, most patients with a myocardial infarction (MI) now survive the index event but remain at risk of recurrent events, thereby making secondary prevention therapies critical. Prior studies have examined in-patient and discharge medications after MI, but few have examined postdischarge treatment. For secondary prevention medications, adherence over time can markedly reduce the risk of recurrent MI, heart failure, and cardiovascular death. We describe the use of evidence-based therapies for secondary prevention in a large contemporary US cohort of patients with prior MI and elevated levels of low-density lipoprotein (LDL) cholesterol.

Methods

The Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (Gould) trial (ClinicalTrials.gov identifier NCT02993120) is a US-based prospective cohort study of patients with atherosclerotic cardiovascular disease (coronary artery, cerebrovascular, or peripheral artery disease) and either LDL cholesterol levels greater than or equal to 70 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or taking a proprotein convertase subtilisin/kexin type 9 inhibitor. Consecutive eligible patients were approached for enrollment between 2016 and 2018 from 119 sites (46% cardiology, 45% primary care, and 9% other) and were followed-up for 2 years. The baseline data were used for the current analysis.

Each participating site obtained institutional review board approval. All patients provided written informed consent. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patient data were obtained through medical record abstraction at the enrollment visit to the treating physician. Optimal medical therapy was defined as antiplatelet or anticoagulant (including P2Y12 if MI occurred <1 year ago), high-intensity statin or β-blocker (if MI occurred <3 years ago), and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker if the patient had diabetes. Patient factors and medications were compared between those for whom MI occurred less than 1 year ago vs those whose MI occurred 1 year ago or longer using a χ² test for proportions and a Kruskal-Wallis test for continuous variables. SAS statistical software version 9.4 (SAS Institute) was used for all data calculations. Statistical significance was defined as 2-sided P < .05. Data were analyzed from May 2019 to February 2020.

Results

Among 1564 patients with atherosclerotic cardiovascular disease and prior MI (259 [16.6%] occurring <1 year ago), the median age was 67 years (interquartile range, 59-73 years), 1055 (67.5%) were men, 589 (37.7%) had diabetes, and the median LDL cholesterol level was 90 mg/dL (interquartile range, 78-113 mg/dL) (Table 1). Among the patients, 1361 (87.0%) used statins, 758 (48.5%) were taking high-intensity statins, and 1475 (94.3%) were taking an antiplatelet agent or anticoagulant. Among

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Table 1. Characteristics of Patients With Prior MI

| Characteristic                        | Patients, No. (%) | MI <1 y ago (n = 259) | MI ≥1 y ago (n = 1305) | P value |
|--------------------------------------|-------------------|-----------------------|------------------------|---------|
| Total (N = 1564)                      |                   |                       |                        |         |
| MI<1yago (n = 259)                   |                   |                       |                        |         |
| MI≥1yago (n = 1305)                  |                   |                       |                        |         |
| Age, median (IQR), y                 | 67 (59-73)        | 62 (55-71)            | 67 (60-73)             | <.001   |
| Male                                 | 1055 (67.5)       | 174 (67.2)            | 881 (67.5)             | .92     |
| Latinoethnicity                      | 139 (8.9)         | 21 (8.1)              | 118 (9.0)              | .80     |
| Body mass index, median (IQR)        | 29.9 (26.9-33.9)  | 29.2 (25.6-33.0)      | 30.0 (27.0-34.1)       | .01     |
| Waist circumference, median (IQR), cm| 100.3 (91.4-110.7)| 96.9 (90.2-109.2)     | 101.6 (91.4-111.8)     | .20     |
| Systolic blood pressure, median (IQR), mmHg | 128 (118-139) | 124 (116-136)        | 128 (118-140)          | .003    |
| Diastolic blood pressure, median (IQR), mmHg | 74 (68-82)       | 72 (66-80)            | 74 (68-82)             | .03     |
| Hypertension                         | 1377 (88.0)       | 212 (81.9)            | 1165 (89.3)            | <.001   |
| Current smoking                      | 216 (13.8)        | 43 (16.6)             | 173 (13.3)             | .15     |
| Diabetes                             | 589 (37.7)        | 89 (34.4)             | 500 (38.3)             | .23     |
| Heart failure                        | 259 (16.6)        | 36 (13.9)             | 223 (17.1)             | .21     |
| Prior percutaneous coronary intervention | 163 (10.4)    | 48 (18.5)             | 115 (8.8)              | <.001   |
| Prior coronary bypass graft surgery  | 86 (5.5)          | 19 (7.3)              | 67 (5.1)               | .16     |
| Prior stroke                          | 123 (7.9)         | 23 (8.9)              | 100 (7.7)              | .51     |
| Peripheral arterial disease          | 173 (11.1)        | 25 (9.7)              | 148 (11.3)             | .43     |
| Atrial fibrillation                  | 193 (12.3)        | 32 (12.4)             | 161 (12.3)             | .99     |
| Total cholesterol, median (IQR), mg/dL | 165 (147-192)   | 172 (152-197)         | 164 (146-190)          | <.001   |
| Triglycerides, median (IQR), mg/dL   | 128 (90-176)      | 127 (92-171)          | 129 (90-178)           | .94     |
| High-density lipoprotein cholesterol, median (IQR), mg/dL | 44 (37-53) | 42 (35-50)         | 44 (37-54)             | .001    |
| Low-density lipoprotein cholesterol, median (IQR), mg/dL | 90 (78-113) | 101 (83-126)        | 89 (77-111)            | <.001   |

Abbreviations: IQR, interquartile range; MI, myocardial infarction.

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

* Body mass index is calculated as weight in kilograms divided by height in meters squared.

Table 2. Secondary Prevention Medication Use in Patients With a Prior MI

| Medication                           | Patients, No. (%) | MI <1 y ago (n = 259) | MI ≥1 y ago (n = 1305) | P value |
|--------------------------------------|-------------------|-----------------------|------------------------|---------|
| Total (N = 1564)                      |                   |                       |                        |         |
| MI<1yago (n = 259)                   |                   |                       |                        |         |
| MI≥1yago (n = 1305)                  |                   |                       |                        |         |
| Antplatelet or anticoagulant         | 1475 (94.3)       | 253 (97.7)            | 1222 (93.6)            | .01     |
| P2Y<sub>12</sub> plus aspirin or anticoagulant | 605 (38.7) | 177 (68.3)        | 428 (32.8)             | <.001   |
| β-blocker                            | 1219 (77.9)       | 211 (81.5)            | 1008 (77.2)            | .13     |
| Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker | 1024 (65.5) | 164 (63.3)        | 860 (65.9)             | .42     |
| Any statin                           | 1361 (87.0)       | 235 (90.7)            | 1126 (86.3)            | .05     |
| Statin intolerance                   | 174 (11.1)        | 19 (7.3)              | 155 (11.9)             | .03     |
| High-intensity statin                | 758 (48.5)        | 160 (61.8)            | 598 (45.8)             | <.001   |
| Ezetimibe                            | 151 (9.7)         | 22 (8.5)              | 129 (9.9)              | .49     |
| Proprotein convertase subtilisin/kexin type 9 inhibitor | 148 (9.5) | 8 (3.1)            | 140 (10.7)             | <.001   |
| Fish oil                             | 299 (19.1)        | 29 (11.2)             | 270 (20.7)             | <.001   |
| Among patients with type 2 diabetes  |                   |                       |                        |         |
| No.                                  | 564               | 83                    | 481                    |         |
| Glucagon-like peptide-1 receptor agonists | 45 (8.0) | 5 (6.0)             | 40 (8.3)               | .41     |
| Sodium-glucose cotransporter-2 inhibitors | 60 (10.6) | 6 (7.2)             | 54 (11.2)              | .28     |
| Optimal medical therapy<sup>a</sup>  | 571 (36.5)        | 95 (36.7)             | 476 (36.5)             | .95     |

Abbreviation: MI, myocardial infarction.

<sup>a</sup> Defined as antiplatelet or anticoagulant (P2Y<sub>12</sub> or aspirin or anticoagulant) if MI occurred <1 year ago, high-intensity statin or β-blocker (if MI occurred <3 years ago), and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (if patient has diabetes).
259 patients with an MI within the past year, 177 (68.3%) were taking dual-antiplatelet therapy (or a P2Y12 inhibitor plus an anticoagulant), 160 (61.8%) were taking a high-intensity statin, 211 (81.5%) were taking a β-blocker, and 164 (63.3%) were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Overall, 571 of 1564 patients (36.5%) were receiving optimal medical therapy for secondary prevention, which did not differ by latency of MI (Table 2).

**Discussion**

In a large contemporary cohort of US patients with a prior MI and elevated LDL cholesterol levels, we identified a number of concerning gaps in secondary prevention. Patients with a prior MI and elevated LDL cholesterol levels are at particularly high risk for recurrent ischemic events and need to be targeted with aggressive medical therapy over time to maximize survival and quality of life. Prior analyses\(^2,3,5\) have shown secondary prevention medication prescription rates to be high at discharge, but the intensity of preventative therapies tends to wane over time because of a combination of clinical decisions along with patient nonpersistence.\(^3,6\) Persistence with each of these classes of medications substantially reduces recurrent ischemic events, heart failure, and cardiovascular mortality. As such, ensuring that patients with a prior MI and elevated LDL cholesterol levels, who represent some of the highest risk patients, are receiving consistent and aggressive secondary prevention therapy over time (and not just at hospital discharge) must be a priority.

This study has some limitations. It is important to note that we were unable to account for contraindications to medications, patient preferences, or nonadherence, and our findings should, therefore, be interpreted as highlighting the opportunities for improvement, as opposed to an indictment of current care. Furthermore, because elevated LDL cholesterol level was 1 of the inclusion criteria, this cohort was likely enhanced with patients who may not tolerate high-intensity statins, which was part of our definition of optimal care. In addition, because our cohort included uniquely high-risk patients (which could affect prescribing decisions), it is unknown whether our results could be generalized to patients with prior MI and controlled LDL cholesterol levels.
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Additional Information: The data that support the findings of this study and research materials, as well as as experimental procedures and protocols, are available from the corresponding author upon reasonable request.

REFERENCES
1. Mathews R, Wang W, Kaltenbach LA, et al. Hospital variation in adherence rates to secondary prevention medications and the implications on quality. Circulation. 2018;137(20):2128-2138. doi:10.1161/CIRCULATIONAHA.117.029160
2. Arnold SV, Spertus JA, Masoudi FA, et al. Beyond medication prescription as performance measures: optimal secondary prevention medication dosing after acute myocardial infarction. J Am Coll Cardiol. 2013;62(19):1791-1801. doi:10.1016/j.jacc.2013.04.102
3. Shore S, Jones PG, Maddox TM, et al. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. Heart. 2015;101(10):800-807. doi:10.1136/heartjnl-2014-306754
4. Mathews R, Wang TY, Honeycutt E, et al; TRANSLATE-ACS Study Investigators. Persistence with secondary prevention medications after acute myocardial infarction: Insights from the TRANSLATE-ACS study. Am Heart J. 2015;170(1):62-69. doi:10.1016/j.ahj.2015.03.019
5. Motivallaa AA, Cannon CP, Srinivas VS, et al. Changes in myocardial infarction guideline adherence as a function of patient risk: an end to paradoxical care? J Am Coll Cardiol. 2011;58(17):1760-1765. doi:10.1016/j.jacc.2011.06.050
6. Huber CA, Meyer MR, Steffel J, Blozik E, Reich O, Rosemann T. Post-myocardial infarction (MI) care: medication adherence for secondary prevention after MI in a large real-world population. Clin Ther. 2019;41(1):107-117. doi:10.1016/j.clinthera.2018.11.012