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RESEARCH LETTER

Use of Guideline-Recommended Risk Reduction Strategies Among Patients With Diabetes and Atherosclerotic Cardiovascular Disease

Insights From Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD)

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Patients with atherosclerotic cardiovascular disease (ASCVD) and concomitant diabetes mellitus are at particularly high risk for new and recurrent ischemic events and heart failure, and therefore derive greater absolute benefit from secondary prevention therapies than patients without concomitant diabetes mellitus.[1] Previous analyses reported suboptimal use of evidence-based therapies in this vulnerable group,[1,2] but did not include data on newer lipid and glucose-lowering therapies. Given the emergence of nonstatin low-density lipoprotein–lowering agents and glucose-lowering medications with cardiovascular benefits, the number of evidence-based therapies for secondary prevention has expanded. Thus, we examined contemporary use of medications to reduce cardiovascular risk in a large cohort of US patients with diabetes mellitus and ASCVD.

GOULD (Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management) is an ongoing US-based registry designed to describe longitudinal cholesterol treatment patterns among patients with ASCVD. Eligible patients had (1) ASCVD (coronary artery, cerebrovascular, or peripheral artery disease) and (2) low-density lipoprotein ≥70 mg/dL or on a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor. Patient demographics, comorbidities, medications, and laboratory data were obtained at the enrollment visit. Only baseline data were used for this analysis. The prespecified criterion for guideline-recommended optimal medical therapy among patients with diabetes and ASCVD was high-intensity statin, antiplatelet agent (or anticoagulant, excluding triple therapy), ACE-I/ARB ([angiotensin-converting enzyme-inhibitors/angiotension II receptor blockers] excluding glomerular filtration rate [GFR] <30 mL/min per 1.73m^2), and (for patients with type 2 diabetes; excluding GFR <30 mL/min per 1.73m^2) either SGLT2i (sodium-glucose cotransporter 2 inhibitors) or GLP-1 RA (glucagon-like peptide-1 receptor agonists).[3] Each site obtained Institutional Review Board approval; all patients provided informed consent.

Among 5006 patients enrolled between 2016 to 2018 from 119 sites and 118 providers (46% cardiology), 1735 (34.7%) had diabetes mellitus (95.6% type 2). Mean age among patients with diabetes mellitus was 67.5±9.6 years, 59.9% were men, 33.3% had a previous myocardial infarction, and 17.2% had heart failure. Median (IQR) low-density lipoprotein was 92 mg/dL (78–114), median triglycerides were 141 mg/dL (102–196), and mean creatinine was 1.2±0.8 mg/dL (n=1154). Overall statin use was 87.8%, 45.4% were on high-intensity statins, and 9.7% were on ezetimibe (Figure). ACE-I/ARBs were used in 72.0%, and 87.3% were on an antiplatelet agent or anticoagulant (0.9% on triple therapy). SGLT2i and GLP-1 RA were used in 9.0% and 7.9%, respectively, whereas sulfonylureas were used in >20%. Only 6.9% received therapy that met the definition of optimal medical management for secondary prevention. Rates were slightly lower among patients treated by cardiologists versus noncardiologists (5.6% versus 8.0%; *P*=0.057).

Key Words: coronary artery disease ■ diabetes mellitus ■ quality of care

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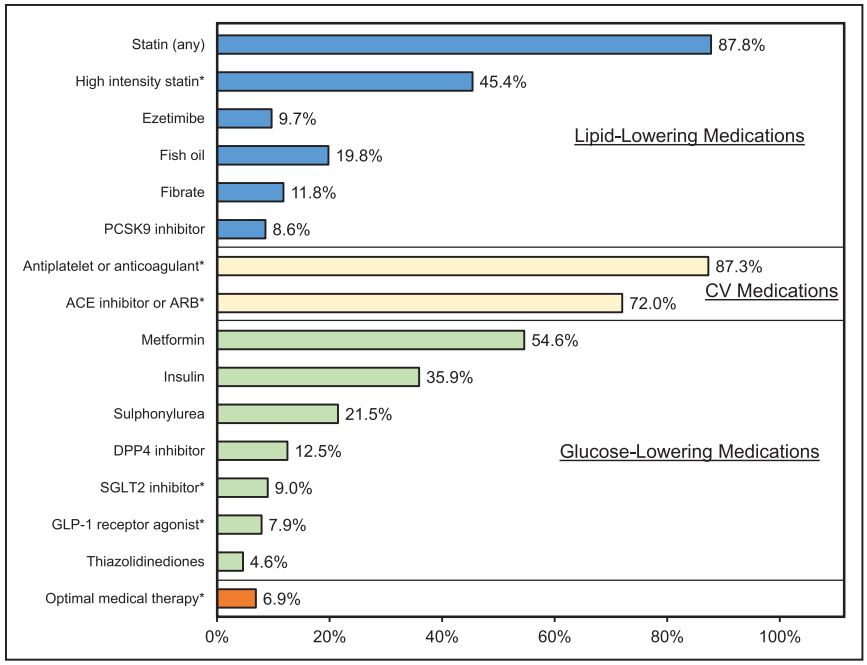

Figure. Use of cardiovascular and glucose-lowering medications among patients with diabetes mellitus and atherosclerotic cardiovascular disease.
*Components of optimal medical therapy: high-intensity statin, antiplatelet agent or anticoagulant (excluding triple therapy), ACE inhibitor or ARB (excluding glomerular filtration rate <30 mL/[min·1.73 m^2]), and SGLT2 inhibitor or GLP1 receptor agonist (for type 2 diabetes mellitus; excluding glomerular filtration rate <30 mL/[min·1.73 m^2]). ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; PCSK9, proprotein convertase subtilisin/kexin type 9; and SGLT2, sodium-glucose cotransporter-2.

In summary, in a large contemporary US cohort of patients with diabetes mellitus and ASCVD, few patients received comprehensive guideline–recommended medical therapies for cardiovascular risk reduction. Although most patients were on a statin, antiplatelet agent or anticoagulant, and ACE-I/ARB, we found suboptimal use of many effective secondary prevention strategies. For example, fewer than half of patients were on a high-intensity statin, <10% were receiving ezetimibe despite low-density lipoprotein ≥70 mg/dL, <20% were prescribed glucose-lowering therapies with cardiovascular benefit, and a strikingly low proportion received a combination of all guideline-recommended risk reduction treatments.

Our data confirm the slow uptake of SGLT2i and GLP-1 RAs in patients with type 2 diabetes mellitus and ASCVD, with only slightly higher use than was previously shown in a large US cohort from 2013 to 2016.[4] Notably, use was markedly higher for sulfonylureas and dipeptidyl peptidase-4 inhibitors, agents with (at best) neutral cardiovascular impact. Although key cardiovascular outcomes trials were published in 2015 to 2017,[3] changes to guidelines and medication indications lagged somewhat, which could explain some of the delay in uptake of these effective medications. Furthermore, despite trial evidence demonstrating efficacy of ezetimibe for event reduction in patients after acute coronary syndromes, particularly those with diabetes mellitus,[5] ezetimibe was used less frequently than fibrates and fish oil—agents with weak evidence of benefit (except in the case of markedly elevated triglycerides; at least at the time of this study).

Importantly, because we were unable to account for intolerance, contraindications, or other barriers to optimal medical therapy, these findings should not automatically be considered inappropriate care. For example, costs can be an important barrier to the use of SGLT2i, GLP-1 RAs, and PCSK9i. However, we also found that inexpensive medications such as aspirin, high-intensity statins, ezetimibe, and metformin were also suboptimally prescribed. In addition to multiple trials showing substantial reductions in ischemic events, heart failure, and cardiovascular mortality with the individual classes of agents that contributed to our composite definition of optimal secondary prevention, observational analyses have also estimated an ≈50% lower relative risk of mortality with combinations of these therapies in patients with ASCVD.[1,2] Thus, our findings highlight a critical opportunity to improve care and outcomes in these high-risk patients.

In conclusion, in a large contemporary multicenter cohort, we found suboptimal rates of use of secondary prevention therapies in high-risk patients with diabetes mellitus and ASCVD, particularly with high-intensity statins and glucose-lowering therapies with proven cardiovascular benefit. Given the high cardiovascular event rates in this patient population, improving use of these guideline-recommended therapies is an important potential opportunity to improve care and, in turn, reduce the risk of recurrent ASCVD events, heart failure hospitalizations, and cardiovascular mortality.

ARTICLE INFORMATION

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Data sharing: The data that support the findings of this study and research materials, as well as experimental procedures and protocols, are available from the corresponding author upon reasonable request.

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REFERENCES

1. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, Redmon JB, Sperling L, Rutter MK; BARI 2D Study Group. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D Trial. *J Am Coll Cardiol.* 2015;66:765–773. doi: 10.1016/j.jacc.2015.06.019
2. Chen SJ, Liu W, Huang BT, Tsauo JY, Pu XB, Peng Y, Chen M, Huang DJ. The impact of optimal medical therapy at discharge on mortality in patients with coronary artery disease. *J Geriatr Cardiol.* 2017;14:100–107. doi: 10.11909/j.issn.1671-5411.2017.02.004
3. American Diabetes A. 10. Cardiovascular disease and risk management: Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S103–S123.
4. Arnold SV, Inzucchi SE, Tang F, McGuire DK, Mehta SN, Maddox TM, Goyal A, Sperling LS, Einhorn D, Wong ND, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR® Research to Practice project. *Eur J Prev Cardiol.* 2017;24:1637–1645. doi: 10.1177/2047487317729252
5. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, Park JG, White JA, Bohula EA, Braunwald E; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation.* 2018;137:1571–1582. doi: 10.1161/CIRCULATIONAHA.117.030950