Very High-Risk ASCVD and Eligibility for Nonstatin Therapies Based on the 2018 AHA/ACC Cholesterol Guidelines

The 2018 American Heart Association/American College of Cardiology Multisociety Cholesterol Guidelines (1) recommend risk stratification among patients with atherosclerotic cardiovascular disease (ASCVD) to identify "very high-risk ASCVD patients." These patients have characteristics associated with a higher risk of recurrent ASCVD events; consequently, they derive a higher net absolute benefit from addition of ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) to statin therapy. From a clinical and payer's perspective, we assessed the proportion of patients with ASCVD who will qualify as very high-risk based on the guideline criteria, their current lipid management, and how this will change with maximizing statin therapy and stepwise use of ezetimibe before consideration for a PCSK9i, as recommended by the 2018 cholesterol guideline (1).

We identified patients with ASCVD (ischemic heart disease, peripheral arterial disease, or ischemic cerebrovascular disease) who sought care in the entire Veterans Affairs health care system (141 facilities) between October 1, 2014 and September 30, 2015 using International Classification of Diseases-Clinical Modification-9th Revision and current procedural terminology codes. Positive predictive value for identification of ASCVD was 95% compared with chart review of 200 random patients.

Our final analytical cohort included 1,038,903 patients with ASCVD. Of these, approximately 43% met the criteria for very high-risk ASCVD (>2 major ASCVD events or at least 1 major event plus >2 high-risk conditions) (**Figure 1**). Among these very high-risk patients, 82% were on statins (35% on high-intensity) and 2% were on ezetimibe. Sixty-seven percent of these very high risk patients had low-density lipoprotein cholesterol (LDL-C) of ≥70 mg/dl, and 72% had either LDL-C ≥70 mg/dl or non–high-density lipoprotein cholesterol (HDL-C) ≥100 mg/dl, making them potentially eligible for ezetimibe and/or PCSK9i.

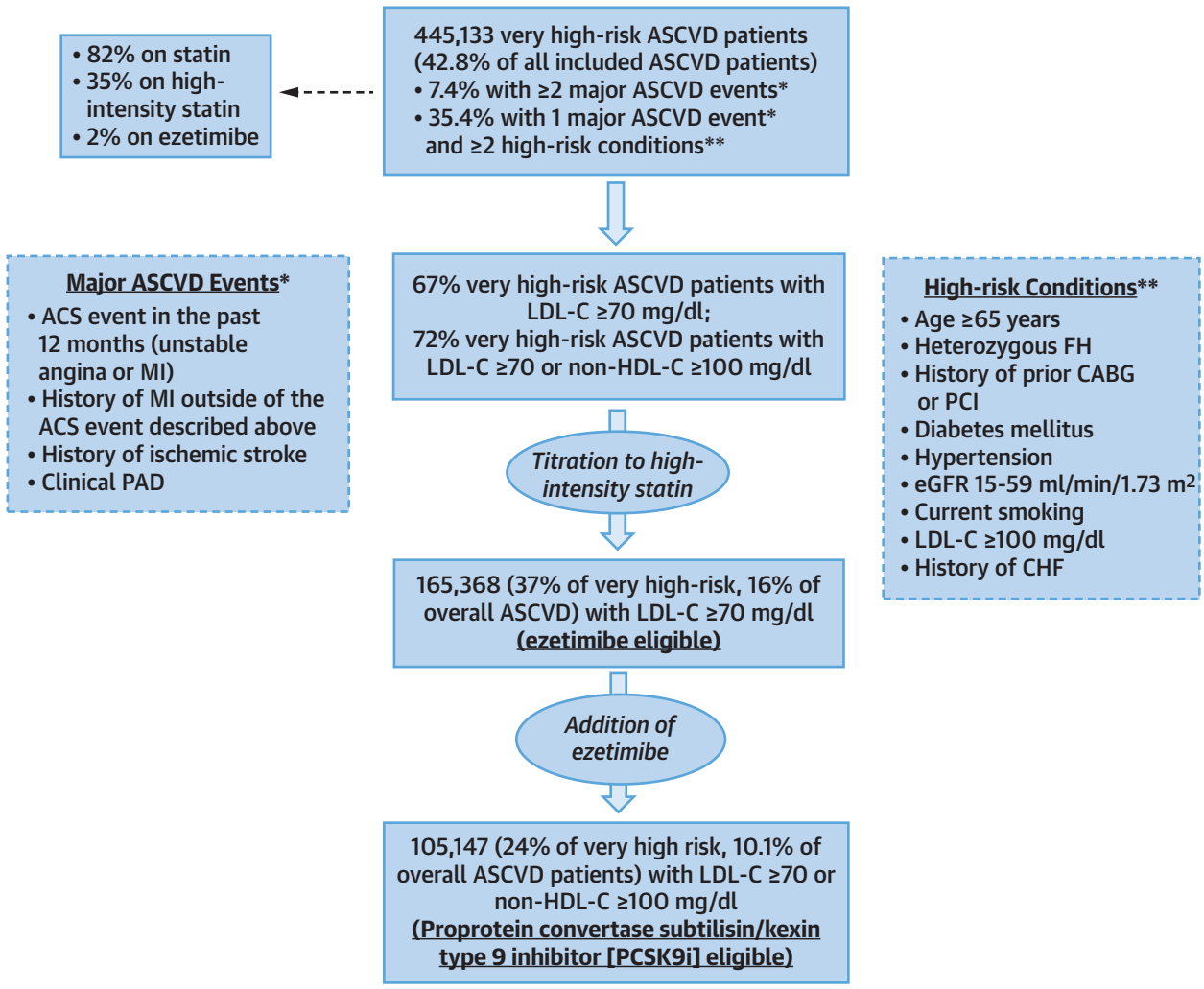
The guidelines (1) recommend maximizing statins before considering nonstatin therapy use in these patients. Assuming a 6% LDL-C reduction with every doubling of statin dose, we estimated that approximately 37% of the very high-risk patients will continue to have LDL-C levels ≥70 mg/dl after titration to high-intensity statins. As per the guideline, ezetimibe therapy can be considered in these patients.

Because the guidelines recommend a stepwise approach of maximizing statins plus ezetimibe before considering a PCSK9i, we evaluated what proportion would continue to have LDL-C ≥70 mg/dl or non–HDL-C ≥100 mg/dl after intensifying statin therapy (6% LDL-C and 4% non–HDL-C lowering with each doubling of dose) and adding ezetimibe (18% LDL-C and 16% non–HDL-C reduction on top of statin therapy) (2). Our analyses showed that 24% of very high-risk patients (10.1% of overall ASCVD population) would be candidates for a PCSK9i after maximizing statins and adding ezetimibe.

We also found large facility-level variation in the number of patients with ASCVD who could potentially be eligible for a PCSK9i (median: 695 patients/facility; interquartile range: 469 to 945). Because the total number of patients with ASCVD receiving care per-facility might also vary, we also calculated the proportion of patients with ASCVD per-facility who would qualify as very high risk and be eligible for a PCSK9i after titration to a high-intensity statin plus ezetimibe. Our analyses showed that a median of 10.2% of total patients with ASCVD per-facility (interquartile range: 8.6% to 11.6%) would be eligible for a PCSK9i.

Our analyses evaluated the potential impact of the 2018 cholesterol management guidelines (1) for secondary ASCVD management in a large health care system. We found that a large proportion (43%) would meet criteria for very high-risk ASCVD, with approximately two-thirds not currently on evidence-based statin therapy and with a LDL-C ≥70 mg/dl or non–HDL-C ≥100 mg/dl. Titration to high-intensity statins would further reduce this proportion to

FIGURE 1 Very High-Risk ASCVD Patients Eligible for Various Nonstatin Therapies



A total of 42.8% of all patients with atherosclerotic cardiovascular disease (ASCVD) will meet criteria for very high risk per the 2018 American Heart Association/American College of Cardiology cholesterol guideline. A total of 67% of these very high-risk ASCVD patients had low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dl, and 72% had either LDL-C ≥70 mg/dl or non–high-density lipoprotein cholesterol (HDL-C) ≥100mg/dL. Titration to high-intensity statin therapy will lead to 37% of very high-risk (16% of overall ASCVD) patients being potentially eligible for ezetimibe. Titration to high-intensity statin therapy and the addition of ezetimibe will lead to 24% of very high-risk (10.1% of overall) patients with ASCVD being potentially eligible for a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i). ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

37% of the very high-risk patients. Stepwise use of ezetimibe after maximizing statin therapy would further reduce the need for guideline-concordant discussion regarding a PCSK9i for 24% of these very high-risk patients or 10.1% of the total ASCVD population. Our limitations included the veteran ASCVD population (which could be higher risk than other ASCVD populations) and assumption of an average response to statins and ezetimibe (some could have higher or lower than average response). Our analyses assumed 100% tolerability (some patients might not be able to tolerate high-intensity statins) and 100% adherence, and therefore, the overall number of patients who were candidates for PCSK9i could be higher.

Our results from the Veterans Affairs health care system highlight room for improvement by health care systems to maximize statin therapy and statin adherence before considering nonstatin therapies. In addition, the need for a PCSK9i could be reduced

substantially with the addition of ezetimibe. Very high-risk ASCVD patients who could benefit from a PCSK9i were not evenly distributed across facilities. This might lead to large facility-level variation in the budgetary impact of implementing the guidelines for very high-risk patients with ASCVD because of the cost associated with PCSK9i.

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