Prognostic Variation Among Very High-Risk and High-Risk Individuals With Atherosclerotic Cardiovascular Disease

Given the availability of an effective but expensive lipid-lowering medication, proprotein convertase subtilisin/kexin type 9 inhibitors, the American Heart Association and the American College of Cardiology 2018 cholesterol guideline introduced a new classification of "very high-risk" (i.e., multiple major atherosclerotic cardiovascular diseases [ASCVDs] or a major ASCVD + multiple high-risk conditions) versus "high-risk" for patients with prior ASCVD (1). A few recent studies reported risk variation within very high-risk ASCVD, with multiple ASCVDs conferring higher risk than 1 ASCVD + ≥2 high-risk conditions (2,3). However, these studies did not evaluate whether the constellation of high-risk conditions in 1 ASCVD may equate to the risk of multiple ASCVDs or whether the new classification has implications for heart failure.

We studied 877 participants from the ARIC (Atherosclerosis Risk In Communities) study with prevalent major ASCVD (recent myocardial infarction [≤1 year], history of myocardial infarction [>1 year], ischemic stroke, or symptomatic peripheral artery disease) at study baseline (1996 to 1998, visit 4). The outcomes of interest were composite and individual outcomes of all-cause mortality, cardiovascular mortality, myocardial infarction, ischemic stroke, and heart failure. We quantified the risk of adverse outcomes between very high-risk and high-risk ASCVD, with a special interest in risk gradient within the very high-risk group (i.e., 1 ASCVD + 2 to 3 high-risk conditions [n = 459, 52%], 1 ASCVD + ≥4 high-risk conditions [n = 133, 15%], and ≥2 ASCVDs [n = 82, 9%]). The institutional review board at each participating institution (Johns Hopkins University, University of North Carolina, University of Minnesota, and University of Mississippi) approved the study.

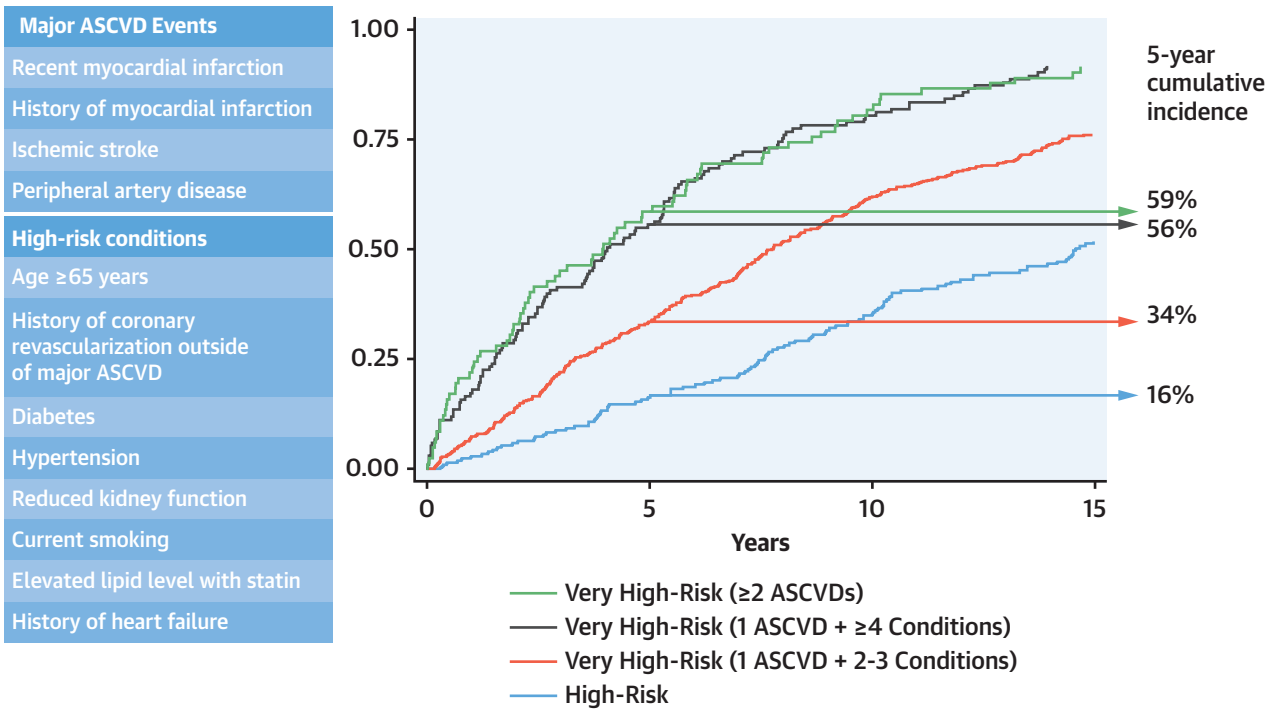
During a median follow-up of 7.6 years, 760 participants (87%) developed composite outcomes. Five-year cumulative incidence of composite outcome was lowest in high-risk participants (16%) and varied within very high-risk participants from 34% in 1 major ASCVD + 2 to 3 high-risk conditions to 56% to 59% in 1 major ASCVD + ≥4 high-risk conditions and ≥2 ASCVDs (**Figure 1**). This pattern remained consistent after accounting for sex and race-ARIC field centers (4), with hazard ratios (HRs) of 3.79 (95% confidence interval [CI]: 2.86 to 5.02) in ≥2 ASCVDs, 3.86 (95% CI: 3.02 to 4.92) in 1 ASCVD + ≥4 high-risk conditions, and 2.02 (95% CI: 1.66 to 2.45) in 1 ASCVD + 2 to 3 high-risk conditions versus "high-risk." Among individual outcomes, the risk gradient across these groups was especially evident in cardiovascular mortality (corresponding HRs of 6.14 [95% CI: 4.02 to 9.39], 6.01 [95% CI: 4.04 to 8.93], and 1.94 [95% CI: 1.37 to 2.74], respectively) and heart failure (corresponding HRs of 5.71 [95% CI: 3.91 to 8.34], 6.64 [95% CI: 4.74 to 9.31], and 2.44 [95% CI: 1.82 to 3.27], respectively). Compared with the dichotomy of very high-risk versus high-risk, this finer categorization resulted in higher C-statistics (0.593 [95% CI: 0.571 to 0.615] vs. 0.633 [95% CI: 0.612 to 0.654]).

To our knowledge, this is the first study showing an equivalent risk between 1 ASCVD + ≥4 high-risk conditions and multiple major ASCVDs. Given the limited utilization of proprotein convertase subtilisin/kexin type 9 inhibitors despite the American Heart Association and the American College of Cardiology guideline recommendation (1), our results suggest that, within the very high-risk ASCVD classification, 1 major ASCVD + ≥4 high-risk conditions and ≥2 major ASCVDs should be prioritized for extensive secondary prevention. Importantly, the validity of this concept can be checked in proprotein convertase subtilisin/kexin type 9 inhibitor trials as secondary data analysis.

Also, our findings indicate the importance of therapeutic approaches reducing heart failure risk in patients with ASCVD. In this context, sodium-glucose cotransporter-2 inhibitors have been shown to considerably reduce heart failure in diabetes and nondiabetes (5).

Our study's findings are limited by the lack of some information on high-risk conditions such as familial

FIGURE 1 Cumulative Incidence of Composite Outcome in High-Risk Versus Very High-Risk ASCVD



Cumulative incidence of composite outcome in high-risk atherosclerotic cardiovascular disease (ASCVD) versus subgroups of very high-risk ASCVD. Five-year cumulative incidence was highest in ≥2 ASCVDs and 1 ASCVD + ≥4 high-risk conditions (56% to 59%) followed by 1 ASCVD + 2 to 3 high-risk conditions and high-risk ASCVD.

hypercholesterolemia and drug dosage of statins, heart failure based on discharge codes, and racial groups being limited to whites and blacks.

We observed a notable risk gradient within the very high-risk category, with an especially elevated risk in ≥2 ASCVDs and 1 ASCVD + ≥4 high-risk conditions. The risk gradient was particularly evident for heart failure. These findings will have implications on secondary prevention approaches in ASCVD.

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https://doi.org/10.1016/j.jacc.2020.04.077

Please note: This work was supported by the National Heart, Lung, and Blood Institute. The ARIC study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (grants HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Dr. Coresh has received grants from the National Institutes of Health and the National Kidney Foundation. All other authors have reported that they have no relationships relevant to the contents of the paper to disclose. The authors thank the staff and participants of the ARIC study for their important contributions. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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