VOL. 78, NO. 1, 2021
ISSN 0735-1097/$36.00

Albuminuria and Prognosis Among Individuals With Atherosclerotic Cardiovascular Disease

The ARIC Study

The American College of Cardiology and the American Heart Association 2018 Cholesterol Guideline proposed the new classification of "very high-risk" atherosclerotic cardiovascular disease (ASCVD) (multiple ASCVDs or 1 ASCVD plus ≥2 high-risk conditions) to guide intensive secondary prevention (1). This guideline takes into account reduced glomerular filtration rate (GFR) as a high-risk condition, but not albuminuria, a measure of kidney damage (2), that is more strongly associated with cardiovascular outcomes than reduced GFR (3). Importantly, the assessment of albuminuria is already recommended in patients with diabetes and hypertension, and thus, data of albuminuria are readily available in many patients with ASCVD (3). We explored whether urine albumin-to-creatinine ratio (ACR) is independently associated with adverse outcomes and can improve risk prediction in persons with ASCVD beyond the high-risk conditions in the guideline.

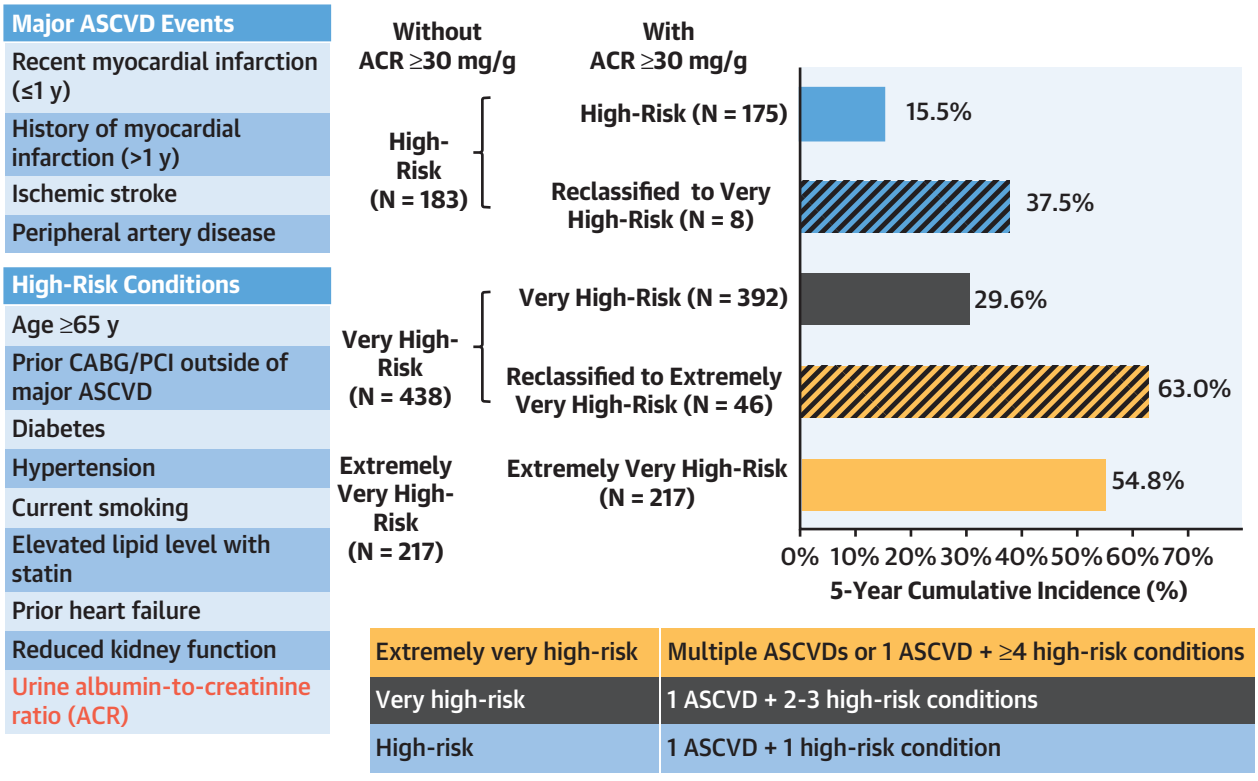
We included 838 participants from the ARIC (Atherosclerosis Risk In Communities) study with ASCVD (history of myocardial infarction, ischemic stroke, or symptomatic peripheral artery disease) at baseline (1996-1998). We quantified the independent association of ACR with adverse outcomes (a composite of mortality, myocardial infarction, ischemic stroke, and heart failure) beyond 8 high-risk conditions (eg, older age and diabetes) (**Figure 1**) (1). We evaluated c-statistic by adding ACR to the high-risk conditions. We also used high sensitivity C-reactive protein (hs-CRP) as a comparator. Last, we assessed the risk classification (extremely very high-risk [multiple ASCVDs or 1 ASCVD plus ≥4 high-risk conditions], very high-risk [1 ASCVD plus 2-3 high-risk conditions], and high-risk [remainder]) (4), when taking into account ACR ≥30 mg/g. The study was approved by the institutional review board at each participating institution (Johns Hopkins University, University of North Carolina, University of Minnesota, and University of Mississippi).

During a median follow-up of 7.7 years, 734 (87.6%) participants developed the composite outcome. ACR ≥30 mg/g and hs-CRP ≥3 mg/L were associated with the risk of composite outcome (adjusted HR: 1.43 [95% CI: 1.19-1.72] and 1.24 [95% CI: 1.06-1.44], respectively) beyond the 8 high-risk conditions. ACR, but not hs-CRP, significantly improved the c-statistic (Δ0.011 [95% CI: 0.003-0.019] for ACR vs Δ0.004 [−0.002 to 0.009] for hs-CRP from c-statistic of 0.660 for 8 high-risk conditions). ACR ≥30 mg/g reclassified 4.4% of high-risk to very high-risk and 10.5% of very high-risk to extremely very high-risk (**Figure 1**). The 5-year cumulative incidence of composite outcome was numerically higher in those who were reclassified to a higher risk category by elevated ACR than those who were not (eg, 37.5% in those who were reclassified to very high-risk vs 15.5% in those who stayed in high-risk regardless of ACR). Also, participants who were reclassified to a higher risk category by elevated ACR had a similar 5-year cumulative incidence to those who stayed at the same risk category (eg, 37.5% in participants reclassified to very high-risk vs 29.6% in very high-risk regardless of ACR).

The importance of long-term risk prediction in ASCVD patients is greater than ever, because a few effective but expensive preventive mediations like proprotein convertase subtilisin/kexin type 9 inhibitors and sodium-glucose cotransporter-2 inhibitors are currently available. Our findings support the inclusion of elevated ACR as a high-risk condition to classify the future risk in ASCVD patients. Notably, the new UK guideline for chronic kidney disease has extended the recommendation of assessing ACR to patients with cardiovascular disease (5).

Our study has a few limitations: lacking full information on the high-risk conditions in the guideline (ie, familial hypercholesterolemia and drug doses of statin), heart failure based on discharge codes, and only including Black and White races from 4 US communities. Also, the variability of ACR is

FIGURE 1 Cumulative Incidence of Composite Outcome in Risk Categories With and Without Incorporating Elevated Urine ACR ≥30 mg/g



Striped bars represent participants who were reclassified to a higher risk category by elevated ACR. ACR = urine albumin-to-creatinine ratio; ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

well-known, and thus our results are likely to underestimate true associations.

In conclusion, albuminuria was an independent predictor of adverse outcomes among patients with ASCVD and improved risk prediction beyond the established high-risk conditions. Although confirmatory studies in other racial/geographic populations are needed, our findings suggest the potential usefulness of ACR to guide the secondary prevention for patients with ASCVD.

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https://doi.org/10.1016/j.jacc.2021.04.089

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, under contract nos. HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN268201700004I. The authors have reported that they have no relationships relevant to the contents of this 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 Author Center.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American

Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285–350.

2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013; Suppl 3:1–150.

3. Mok Y, Ballew SH, Sang Y, et al. Albuminuria as a predictor of cardiovascular outcomes in patients with acute myocardial infarction. J Am Heart Assoc 2019; 8(8):e010546.

4. Mok Y, Ballew SH, Stacey RB, et al. Prognostic variation among very high-risk and high-risk individuals with atherosclerotic cardiovascular disease. J Am Coll Cardiol 2020;76(3):346–8.

5. National Institute for Health and Care Excellence Guideline for Chronic kidney disease; 2021. Available at: https://www.nice.org.uk/guidance/GID-NG10118/documents/draft-guideline. Accessed May 18, 2021.