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The quest for cardiovascular disease risk prediction models in patients with nondialysis chronic kidney disease

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Purpose of review
Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). However, traditional CVD risk prediction equations do not work well in patients with CKD, and inclusion of kidney disease metrics such as albuminuria and estimated glomerular filtration rate have a modest to no benefit in improving prediction.

Recent findings
As CKD progresses, the strength of traditional CVD risk factors in predicting clinical outcomes weakens. A pooled cohort equation used for CVD risk prediction is a useful tool for guiding clinicians on management of patients with CVD risk, but these equations do not calibrate well in patients with CKD, although a number of studies have developed modifications of the traditional equations to improve risk prediction. The reason for the poor calibration may be related to the fact that as CKD progresses, associations of traditional risk factors such as BMI, lipids and blood pressure with CVD outcomes are attenuated or reverse, and other risk factors may become more important.

Summary
Large national cohorts such as the US Veteran cohort with many patients with evolving CKD may be useful resources for the developing CVD prediction models; however, additional considerations are needed for the unique composition of patients receiving care in these healthcare systems, including those with multiple comorbidities, as well as mental health issues, homelessness, posttraumatic stress disorders, frailty, malnutrition and polypharmacy. Machine learning over conventional risk prediction models may be better suited to handle the complexity needed for these CVD prediction models.

Keywords
cardiovascular disease, chronic kidney disease, machine learning, pooled cohort equation, risk prediction

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition associated with a high risk of cardiovascular disease (CVD) morbidity and mortality, and a marked increase in healthcare expenditures [1,2]. Nonetheless, estimation of CVD risk in CKD patients is complex and not yet resolved. In the general population, dyslipidaemia as well as elevated blood pressure and obesity are established risk factors for CVD risk and mortality [3]. However, prior studies have shown that the strength of these risk factors in predicting CVD attenuates as CKD progresses [4,5▪▪,6,7] and that traditional CVD risk prediction equations are not useful in CKD patients [8]. Although risk factors such as diabetes and hypertension can lead to the development of CKD and CVD simultaneously, CKD patients have increased inflammation, increased arterial calcification, endothelial dysfunction and arterial stiffness, which may

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KEY POINTS

- Although cardiovascular disease burden is exceptionally high in patients with chronic kidney disease (CKD), traditional cardiovascular risk prediction equations that are based on dyslipidaemia, hypertension, diabetes, smoking and/or obesity do not work well in this population.
- As CKD progresses, associations of traditional risk factors such as BMI, lipids and blood pressure with cardiovascular disease outcomes are attenuated or even reverse.
- Additional CKD-associated risk factors for cardiovascular disease risk include albuminuria, estimated glomerular filtration rate, acute kidney injury events, inflammation and oxidative stress.
- Large national cohorts of persons with CKD such as the US Veteran cohort may provide excellent platforms for the developing cardiovascular disease risk prediction models, and sophisticated machine learning using computerized programs may be a tool to that end.
- Putative nontraditional risk factors for cardiovascular disease risk in US Veterans with and without CKD include posttraumatic stress disorders, depression, other mental health issues, homelessness, malnutrition or protein-energy wasting, frailty, race and ethnicity, socioeconomic status, service connection, alcoholism or other substance use, comorbid conditions, limb amputation and polypharmacy, among others.

explain the exacerbated risk of CVD outcome in patients with CKD [9]. A recent commentary [10] argued that CKD needs more attention and more campaigns should push for patient clinician awareness to screen for CKD as a CVD risk factor due to the known associations between lower estimated glomerular filtration rate (eGFR) and elevated albuminuria with higher CVD risk outcomes.

In order to establish a comprehensive equation to estimate CVD risk, a large cohort of patients is needed that includes a substantial number of patients with CKD and with the ability to account for a number of comorbid and laboratory factors. Data from the US Veteran cohort have demonstrated potency in examining associations and have shown to be an excellent dataset to test equations for prediction of CVD risk. Epidemiologic data show that US Veterans are disproportionately affected by CKD, wherein the prevalence of CKD ranges from 16.4 to 36.3% [11▪] in Veterans depending on definition versus 7% in the general population [2]. Approximately 13 000 US Veterans transition to end-stage renal disease (ESRD) each year [2]. These US Veterans with CKD therefore have a high risk of CVD outcomes as well as a high risk of CKD progression. However, US Veterans also have a higher prevalence of certain comorbid conditions than the US general population, such as homelessness, mental health issues, including posttraumatic stress syndrome, nutritional derangements and frailty that increase their CVD and mortality risk (Table 1). These risk factors as well as those related to CKD (such as albuminuria, estimated glomerular filtration rate, acute kidney injury events, inflammation and oxidative stress) should be considered when designing a CVD risk model in special populations such as US Veterans with CKD. Individualization of

Table 1. Putative conventional and nontraditional cardiovascular disease risk factors in US Veterans with and without chronic kidney disease

Conventional risk factors	Additional (Transitional) risk factors	Nontraditional risk factors in Veterans
Hypertension	Albuminuria	Posttraumatic stress disorders
Dyslipidaemia	eGFR	Depression
Diabetes mellitus	Acute kidney injury events	Other mental health issues
Smoking	Inflammation	Homelessness
Obesity	Oxidative stress	Malnutrition (protein-energy wasting)
		Frailty
		Race/ethnicity
		Socioeconomic status
		Service connection
		Alcoholism and other substance use
		Comorbid conditions, for example COPD, hepatitis, HIV infection
		Limb amputation
		Polypharmacy

Additional or transitional CVD risk factors may also play a role in those with CKD as CKD progresses towards more sever stages.
COPD, chronic obstructive pulmonary disease.

CVD prevention therapy while mitigating risk of CKD progression may markedly improve the health and quality of life of patients with CKD.

The CVD risk prediction equations for the general population have been developed mainly for the purpose of deciding to prescribe a cholesterol lowering intervention, as trials studying this intervention had the highest relative risk reduction and the most predictable results. The association of CKD and ASCVD has been traditionally ignored in older guidelines. The 2016 American College of Cardiology and the American Heart Association (ACC/AHA) guideline [12] and then the 2018 ACC/AHA guideline [3] addressed this omission by attributing CKD the role of risk enhancer without attempting to calculate the magnitude of risk. The reason is that an equation for risk prediction is at best generalizable to a subgroup depending on the percentage of the subgroup in the population from which it was derived. A more correct estimate of CVD risk in CKD can only be obtained by addressing the problem in a cohort enriched in CKD patients. In this article, we will describe the efforts to address CVD disease prediction in patients with different levels of renal function.

CARDIOVASCULAR DISEASE RISK PREDICTION IN THE GENERAL POPULATION

In 2013, the ACC/AHA combined data from several US community-based cohorts of adults that had at least 12 years of follow up in order to develop a pooled cohort equation (PCE) risk calculator for prediction of 10-year risk of atherosclerotic cardiovascular disease (ASCVD) events, including coronary heart disease (CHD) death, nonfatal myocardial infarction (MI) and fatal or nonfatal stroke [13]. White and African–American adults age 40–79 years were included in the calculator, which created four separate equations according to sex and race. Variables included in the equations were age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP) (treated or untreated status), diabetes mellitus (diabetes) and current smoking status. These equations are still recommended by subsequent guidelines [3].

Although eGFR and albuminuria were among a list of candidate predictors, the work group determined that these predictors had an uncertain value and expressed concerns regarding measurement quality. They therefore advised that kidney markers such as these should only be used to assist clinicians in creating sound clinical judgement regarding treatment decisions and are referred to as ASCVD risk enhancers.

The calibration (or agreement between observed and predicted outcomes) of this calculator in other US community populations has also been found to be acceptable [14]. Conversely, the calibration was poor when applied to cohorts, including selected groups such as healthy women [15], hypertensive patients [16], Korean patients [17], patients aged over 75 years [18▪▪] and the calibration varied with the social-economic status [19].

Poor calibration is not only attributable to population selection bias but also to intervention after the baseline evaluation, which reduces the initial risk. Consequently, The Million Hearts Initiative [20] devised the ASCVD Risk Assessment Tool that accounted for changes in ASCVD risk that would be expected with initiation of risk management recommended based on results of clinical trials. Incorporating individual patient responses to these therapies over time allows for dynamic, longitudinal ASCVD risk prediction.

CARDIOVASCULAR DISEASE RISK IN SPECIAL POPULATIONS

A 2017 article by Sussman *et al.* [21] sought to recalibrate an ASCVD risk score in the Veterans Affairs (VA) population, known as US Veterans, that is persons who have provided uniform services including in war zones. Using the same variables as the ASCVD risk model [namely age, smoking status, non-HDL cholesterol, race (Black/non-Black), diabetes and SBP], they developed new equations based on the electronic health records of the VA population. Patients included Veterans age 45–80 years with no documented history of CVD or heart failure not excluding patients on statins. The VA Risk Score for Cardiovascular Disease (VARS-CVD) model was compared with other models including the ACC/AHA ASCVD risk score. They found the standard ASCVD score substantially overestimated CVD events, particularly for those with a higher observed risk with an average predicted event rate of 0.091 events (C-statistic: 0.657) versus 0.056 observed events (C-statistic 0.664) in the VARS-CVD model per 5 years in male Veterans. The authors advocated that using a calculator developed on the basis of the electronic health records from its own population rather than external cohorts has substantial advantages and that locally created risk scores can be updated and account for changing demographics and trends.

Recently, Vassy *et al.* [22▪▪] improved the risk predicting equations in Veterans and published an online calculator at: *bosmav.github.io/ACVD_Risk_Calculator/*. The calculator is not only specific for VA patients but also addresses the prediction modification induced by statin therapy.

CARDIOVASCULAR DISEASE RISK PREDICTION IN CHRONIC KIDNEY DISEASE PATIENTS

Patients with CKD have a high risk of CVD outcomes; however, risk calculators perform poorly in this population and none of the risk predictor systems presented above is addressing specifically this issue. In 2007, Weiner *et al.* [23] tested the ability of a CVD prediction score to predict incident MI or CHD mortality among stage 3 or 4 CKD patients with CVD comorbidity using data from ARIC and CHS cohorts. In this study, the Framingham Risk Score poorly discriminated men who developed and did not develop the CVD outcome in participants with CKD. They saw improvements in model discrimination when they used a 'best Cox' model, which used the same variables as the Framingham Risk Score, but different weights for each variable. The study attributed the poor ability of the score to competing risk of death in CKD, since patients who were more likely to die were also those more likely to have a CVD event. In the study, the 10-year mortality rate for CKD patients was nearly four times higher than the cohort of patients used to develop the Framingham Risk Score.

In 2011, Chang and Kramer [8] summarized the data on reports evaluating addition of CKD predictors to the Framingham risk score. CKD factors evaluated to improve CVD risk prediction include GFR, cystatin C, serum creatinine and urine albumin creatinine ratio (UACR). The review demonstrated that the addition of the CKD factors to the equation did not improve prediction in populations not enriched with CKD patients.

Subsequently, Matsushita *et al.* [24] meta-analysed data on 637 315 patients with no CVD from 24 cohorts and tested the addition (or removal) of eGFR and albuminuria to traditional risk factors for CVD risk prediction. There was modest but significantly improved CVD risk prediction for the outcomes of CVD mortality, heart failure, coronary disease and stroke with the addition of these two CKD factors. When both eGFR and albumin to creatinine ratio (ACR) were removed from a model including those factors as well as traditional predictors, the C-statistic for CVD mortality fell by 0.0227, while it only fell by 0.007 max with the removal of any of traditional cardiovascular risk factors (race or ethnic origin, age, sex, SBP, antihypertensive drug use, total and HDL cholesterol, smoking, diabetes and hypertension). The recommendation from both manuscripts [8,24] is to create better risk calculators for this population and they proposed that for prediction of CVD events in adults with CKD future studies should explore risk equations including traditional CVD risk factors and the unique comorbidities associated with CKD. In 2019, Matsushita *et al.* [25▪▪] reported on creation of a 'predictor patch' for adding CKD-related predictors to traditional calculators. The authors proposed to estimate the risk in the cohort using the traditional risk factors and correct the data with a patch estimated from another study. The patch is based on an estimate of the hazard ratio for the new predictor (eGFR or ACR) from the traditional risk factors. When the 'CKD patch' was added to each participant in the base dataset, the model predicted CVD mortality well in each cohort (c-statistic 0.78–0.91), and addition of kidney measures using a patch improved discrimination to a similar degree as refitting the actual kidney measures in each base dataset.

In a contemporary cohort of 27 615 US Veterans with incident transition to end-stage renal disease (ESRD), our group implemented a machine learning model on 49 variables obtained at or prior to transition and developed prediction models for all-cause mortality at 30, 90, 180 and 365 days after transition [26▪▪]. In variable importance analysis, eGFR, SBP and age were consistently the three most important predictors for death over the four periods. Other variables that were important include DBP, blood urea nitrogen (BUN), BMI, serum alkaline phosphatase, serum albumin, race, heart failure and chronic obstructive pulmonary disease. The equation included 15 predictive variables for the four death risk periods.

In another study in a cohort of 35 878 US veterans with incident ESRD who transitioned to dialysis, we developed a mortality risk prediction model at month 3, 6, 9 and 12 for all-cause mortality [27]. We used data from 4284 Kaiser Permanente Southern California (KPSC) patients who transitioned to dialysis to externally validate the developed model. The best fit model according to C-statistics created separate models according to whether a patient's last eGFR prior to transition was less than 15 or at least 15 ml/min per 1.73 m^2 during transition. Variables included in the model were age, race, ethnicity, cause of ESRD, comorbidities, BMI, last eGFR and labs: White blood cell count, albumin, BUN, sodium, alkaline phosphatase. The calculator had similar C statistics in the KPSC external validation cohort, and is published online at www.dialysisscore.com. Figure 1 shows that schematic representation of the interaction between conventional and nontraditional CVD risk factors over the course of CKD progression.

NON-ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND MORTALITY RISK IN CHRONIC KIDNEY DISEASE PATIENTS

The aforementioned models predict ASCVD risk, but as a patient progresses through worsening CKD, risk

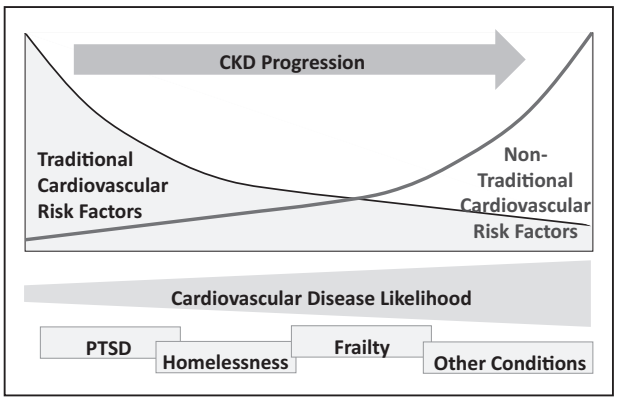

FIGURE 1. Schematic representation of conventional and nontraditional cardiovascular disease risk factor in chronic kidney disease and the effect modification of CKD progression. PTSD, posttraumatic stress disorder.

of non-ASCVD events and mortality may be of larger concern and serve as a competing risk for the ASCVD event, wherein contributions of ASCVD events plateau and non-ASCVD events increase as CKD progresses contributing to an overall increase in the rate of CVD events, and risk of fatality after the CVD event. Data from the Medicare 5% sample's fee-for-service patients age 66 and older, which included 1 262 072 patients, of whom 175 840 had CKD also demonstrated this point [2]. It showed that although heart failure is common in both CKD and non-CKD patients, the ratio of heart failure events to acute MI events is much larger in CKD than without CKD. Additional summarized data from a review as part of the AHA/ACC statement on CKD as a risk factor for CVD by Sarnak *et al.* [28] demonstrate the prevalence of left ventricular hypertrophy related to non-ASCVD outcomes far exceeds ischemic heart disease in CKD. As non-ASCVD events and mortality are of great concern as the patient progresses through CKD stages, it would be of interest to create risk prediction models for these outcomes and in consideration of these outcomes as competing risk as well, as they are very relevant in CKD and might require different management intervention than ASCVD.

CARDIOVASCULAR DISEASE RISK FACTORS IN CHRONIC KIDNEY DISEASE PATIENTS (OTHER THAN ESTIMATED GLOMERULAR FILTRATION RATE AND URINE ALBUMIN CREATININE RATIO)

As discussed above, CVD risk prediction equations do not predict outcomes well in patients with CKD. Furthermore, studies demonstrate that the relationship of these CVD risk factors with CVD risk attenuates or changes with progressing CKD. Possible reasons for this attenuation may be due competing risk of non-ASCVD and mortality or high risk of malnutrition and inflammation in CKD wherein a seemingly healthier CVD risk profile, including lower lipid, BMI and SBP may actually represent malnutrition, inflammation and unhealthy status.

In a study by Soohoo *et al.* [5▪▪], using a cohort of 2 086 904 U.S. Veterans with a triglyceride measurement obtained at baseline and a median follow up of 9.2 years, we examined associations of baseline triglyceride level with all-cause and CVD mortality across CKD stages using Cox proportional hazard models (Fig. 2). In this study, low levels of TGs were associated with a higher risk of mortality across all stages, whereas triglyceride levels at least 240 mg/dl were only associated with a higher risk of all-cause and CVD mortality in non-CKD and CKD stages 3A, 3B and 4 (reference: triglyceride 120–160 mg/dl). The relationship of higher triglycerides with mortality incrementally attenuated across worsening

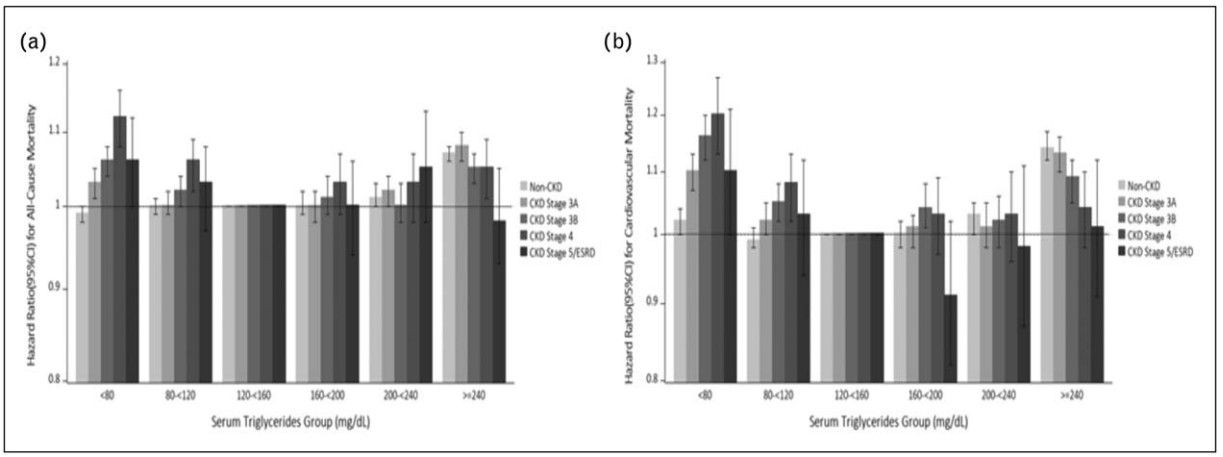

FIGURE 2. Association of serum triglycerides with all-cause (a) and cardiovascular (b) mortality in 2 086 904 US Veterans across strata of CKD stage according to estimated glomerular filtration rate. Adapted from [5▪▪].

stages of CKD and attenuated to the null among patients with CKD stage 5/ESRD.

Lu *et al.* [6] in 2014 examined the relationship of BMI categories with mortality in 453 946 US Veterans with nondialysis-dependent CKD and found a consistent U-shaped association. BMI levels less than 25 kg/m^2 were associated with worse outcomes in all patients, independent of severity of CKD. BMI levels at least 35 kg/m^2 were associated with worse outcomes in patients with earlier stages of CKD, but this association was attenuated in those patients with eGFR less than 30 ml/min per 1.73 m^2. It has been suggested that this 'obesity paradox' in CKD might be partially due to inflammation not controlled for or accounted for in the model, as inflammation increases with advancing CKD severity. However, in a 2019 study, we examined the relationship of BMI with mortality across CKD stages with bias-adjustment for plausible uncontrolled confounding due to inflammation [29]. In the results, we found a reverse J-shape relationship consistent with each eGFR strata of CKD, and the lowest mortality risk was observed for moderately high BMI. Moreover, we found consistent results with and without application of bias analysis conditioning for inflammation.

With regards to BP, in a cohort 0f 651 749 US Veterans, Kovesdy *et al.* [7] examined the relationship between SBP and DBP with mortality risk among nondialysis-dependent CKD patients. The study found a J-curve relationship for both SBP and DBP, showing observational evidence that a BP target less than 140/90 mmHg in patients with CKD could lead to negative outcomes. This association was consistent across strata of eGFR, although risk estimates for high BP compared to the reference were incrementally weaker in eGFR strata representing more advanced CKD.

In a meta-analysis and systematic review, Major *et al.* in 2018 [30] evaluated the association of 29 routinely collected risk factors with fatal and nonfatal CVD events in nondialysis-dependent CKD. The results found that, within the traditional risk factors, male sex, increasing age, smoking, established CVD disease, diabetes mellitus and total cholesterol, but not SBP and DBPs, were all associated with a statistically significant increased risk of a CVD event. The study also identified that serum albumin, phosphate, urate and haemoglobin were all found to be statistically significant in their association with future CVD events among CKD patients.

VETERAN-SPECIFIC CARDIOVASCULAR DISEASE RISK FACTORS

The VA population represents a unique set of patients with a constellation of risk factors not frequently observed in the general population that confers high mortality and CVD risk. The factors best studied are posttraumatic stress disorder (PTSD) [31–33] with an estimated prevalence in the VA population of approximately 10% [34], depression [35–37], homelessness [38,39], which is 30% to three-fold higher in US Veterans than the general populations [40] and frailty [41] impacting approximately 30% of US Veterans. In addition, traditional risk factors are more likely to be poorly controlled [38] (see Table 1).

Other conditions with a higher prevalence among Veterans that may be important for CVD outcomes include socioeconomic status, service connection, brain injury, smoking, alcoholism and drug use, comorbid conditions such chronic obstructive pulmonary disease and hepatitis or HIV infection. Amputation is also prevalent among Veterans and may impact estimation of eGFR [42] and therefore should be an important consideration in models for CKD patients.

RACE AND CARDIOVASCULAR RISK

In the United States, Black Americans have higher rates of CVD mortality as compared to non-Hispanic Whites [43]. Black Americans have higher rates of heart failure, peripheral vascular disease [44], cerebrovascular disease, left ventricular hypertrophy and sudden cardiac death as well as coronary artery disease despite a lower burden of atherosclerosis as compared to whites [45], but lower rates of atrial fibrillation [46]. Factors such as higher prevalence and worse control of hypertension [47] and diabetes [48], and high rates of smoking [49] and obesity [50] all contribute to these racial disparities in CVD event rates. In addition, there are racial differences in a number of important CVD biomarkers such as lipoprotein(a) and high sensitivity C-reactive protein [51▪] and adjustment for these biomarkers attenuated CVD risk in both Black men and women. US data have shown that non-Hispanic blacks have a lower prevalence of eGFR less than 60, but a higher prevalence of urine albumin creatinine ratio (UACR) at least 30[2].

In ESRD, Black Americans comprise almost 35% of the dialysis population despite the proportion of Black Americans in the US being only 14% [52]. Nonetheless, studies from our research group as well as others have shown that in Black Americans with ESRD, a racial paradox exists where Black Americans have better survival than whites, possibly owed to a different nutritional profile [53,54]. Kovesdy *et al.* [55] also found that Black Americans had better survival than whites in the nondialysis-dependent CKD population that the hazard ratios were lower as

with each stage of worsening CKD. Data from their study showed that younger age, lower prevalence of CVD disease and lower white blood cell count of Black American patients may contribute to the better survival despite having higher prevalence of diabetes and Charlson comorbidity scores. Kovesdy *et al.* [56] conducted a parallel analysis of a large cohort of non-CKD US Veterans patients and a cohort of non-CKD patients from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004. In Veterans, Black race was associated with 24% lower all-cause mortality, 37% lower incidence of CHD but a similar incidence of ischemic stroke. However, in the NHANES data, Black race was associated with a 42% higher adjusted mortality. They speculated that the racial discrepancies in outcomes in the NHANES population may be explained by challenges in open access to healthcare that are not prevalent among the VA population or that genetic differences may in part lead to differences in cardiovascular pathophysiology and outcomes. In a follow-up study, Norris *et al.* [57] found that age is an effect modifier in the race-cardiovascular outcome relationship among Veterans whereby the lower risk for CVD outcomes were stronger for younger Black Americans and attenuated with patient age.

Studies from our group have shown that race can impact the association of clinical markers with outcomes in CKD patients [58,59,60▪,61]. In addition, there have also been reports in racial-ethnic differences in drug response [62] particularly in antihypertensive drug groups. These differences in risk contributed to the inclusion of a race adjustor in CVD risk prediction. However, a recent editorial [63▪▪] has summarized concerns regarding the use of race adjustment in risk prediction or clinical algorithms. The article states, 'By embedding race into the basic data and decisions of healthcare, these algorithms propagate race-based medicine. Many of these race-adjusted algorithms guide decisions in ways that may direct more attention or resources to White patients than to members of racial and ethnic minorities'. We propose to examine the use of the race-adjusted algorithms in the context of CVD risk prediction in CKD and determine if race adjustment is necessary, if risk factors for CVD outcomes in CKD are different according to race. Moreover, a further understanding is needed of what race may be representing, ancestral gene polymorphisms, the impact of structural racism on social determinants of health (e.g. education, socioeconomic status, employment, access to care) or other. Second, if a race adjustor is needed, the proposed underlying mechanism (e.g. differential prevalence of specific gene polymorphisms, the unlikely to be modified soon impact of structural racism related impact on nutritional status and so on that may affect medication effectiveness/side effects or other differences) should be examined. By deepening the understanding, it will promote a rethinking of how to create better predictive models that incorporates tangible and reproducible elements to improve outcomes and determine best treatment practices. Third, a discussion is needed if the inclusion of race in our models would direct attention or resources to patients with the greatest need.

CARDIOVASCULAR DISEASE RISK PREDICTION IN THE GENERAL POPULATION-MACHINE LEARNING

Development in data collection, manipulation and analysis has led to developments in risk prediction, and the modern era has tapped into artificial intelligence by way of a method called machine learning with the goal of developing algorithms improving risk prediction. Machine learning offers an opportunity to improve accuracy by exploiting complex interactions between risk factors. It can also address issues of multiple and correlated predictors, and nonlinear relationships. Thereby, machine learning techniques can exploit more data and build complex models that consider more features.

Several studies have developed machine learning models of CVD risk and compared results with traditional models. One study from Greece [64] found similar accuracy between a traditional devised risk score and different models of machine learning. However, another cohort study using routine clinical data from UK family practices found machine learning methods, which added an additional 22 variables to the core risk variables, were superior to the established risk score with a discrimination estimate area under the curve (AUC) that was +1.7 to +3.6% higher than the ACC risk calculator. [65]. Using data from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, models were tested to predict all-cause death, stroke, all CVD disease, CHD, atrial fibrillation and heart failure events. Machine learning techniques improved prediction accuracy by 10–25% compared with established risk scores [66]. Another study also used patients from the MESA cohort to create a machine learning model and externally validated it in the Flemish Study of Environment, Genes and Health Outcomes cohort. Results showed that machine learning greatly outperformed the ACC/AHA model [67]. Because of its ability to create predictions from complex data, machine learning technology may replace the traditional calculators in the future.

CONCLUSION

Specific equations need to be derived for prediction of ASCVD and non-ASCVD events in patients with nondialysis-dependent CKD. This global risk estimate is expected to result in individualization of level and type of intervention recommended. The global risk equation should be derived from cohorts including large numbers of patients with CKD, acceptable racial and ethnic diversity and enriched in patients with socioeconomic risk factors. The US Veterans are a suitable cohort with the limitations that access to healthcare is nondiscriminatory and women are under-represented.

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Conflicts of interest

Dr K. Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, AstraZeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, ZS-Pharma. ES has received honoraria from Edwards.

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