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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Derivation of an Annualized Claims-Based Major Adverse Cardiovascular Event Estimator in Type 2 Diabetes

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ABSTRACT

BACKGROUND Major adverse cardiovascular events (MACE) are a leading cause of morbidity and mortality among adults with type 2 diabetes. Currently, available MACE prediction models have important limitations, including reliance on data that may not be routinely available, narrow focus on primary prevention, limited patient populations, and longtime horizons for risk prediction.

OBJECTIVES The purpose of this study was to derive and internally validate a claims-based prediction model for 1-year risk of MACE in type 2 diabetes.

METHODS Using medical and pharmacy claims for adults with type 2 diabetes enrolled in commercial, Medicare Advantage, and Medicare fee-for-service plans between 2014 and 2021, we derived and internally validated the annualized claims-based MACE estimator (ACME) model to predict the risk of MACE (nonfatal acute myocardial infarction, nonfatal stroke, and all-cause mortality). The Cox proportional hazards model was composed of 30 covariates, including patient age, sex, comorbidities, and medications.

RESULTS The study cohort comprised 6,623,526 adults with type 2 diabetes, mean age 68.1 ± 10.6 years, 49.8% women, and 73.0% Non-Hispanic White. ACME had a concordance index of 0.74 (validation index range: 0.739-0.741). The predicted 1-year risk of the study cohort ranged from 0.4% to 99.9%, with a median risk of 3.4% (IQR: 2.3%-6.5%).

CONCLUSIONS ACME was derived in a large usual care population, relies on routinely available data, and estimates short-term MACE risk. It can support population risk stratification at the health system and payer levels, participant identification for decentralized clinical trials of cardiovascular disease, and risk-stratified observational studies using real-world data. (JACC Adv 2024;3:100852) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACME = annualized claims-based MACE estimator

ASCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

MACE = major adverse cardiovascular events

MI = myocardial infarction

OLDW = OptumLabs Data Warehouse

Atherosclerotic cardiovascular disease (ASCVD), including ischemic heart disease and stroke, is a leading cause of death[1-4] and hospitalization[5] and a major driver of healthcare costs[6] among adults with diabetes. Primary and secondary prevention of ASCVD is foundational to diabetes management. Thus, quantifying ASCVD risk accurately, reliably, and in a way that is meaningful to people living with diabetes and other stakeholders is essential for evidence-based, person-centered diabetes care. As such, it is important to have ASCVD prediction models that can be implemented in a variety of settings and for different applications, both at the individual and population levels. Such models can be used to support shared decision-making conversations, population health management programs at the health system and payor levels, identification and enrollment of patients into decentralized clinical trials using claims or electronic health record tools, and the conduct of observational studies using real-world data.

Most currently available models focus on individual risk assessment and cannot be consistently implemented using routinely collected clinical or administrative data to enable population health management, conduct of decentralized trials, and observational research. The American College of Cardiology/American Heart Association ASCVD risk calculator[7] (also known as the pooled cohort equation) is the most commonly used risk tool in clinical practice and is recommended by both diabetes and cardiovascular guidelines to inform therapeutic decisions for the management of blood pressure and cholesterol.[8-10] However, it is designed to estimate the 10-year risk of a first ASCVD event, was not developed specifically for patients with diabetes, and is limited to asymptomatic individuals without prior ASCVD. Other commonly used ASCVD risk prediction, which are summarized in Supplemental Methods 1, have similar limitations. Most focus on patients without preexisting ASCVD and therefore cannot be used to risk stratify broad patient populations in clinical practice or in research. The 10-year time horizon may be less meaningful and interpretable for patients and decision-makers than a shorter time horizon. Most models include laboratory and other electronic health record data that are not available in claims data, which are increasingly used for both population health management and research. Finally, most risk scores have been developed using clinical cohorts comprised of patient volunteers, with potential for bias and lack of generalizability, particularly with respect to socioeconomic status, race, ethnicity, and rurality.

To enable ASCVD risk stratification using routinely available real-world data at both the individual (at the point of care) and population (for population health management programs) levels, we derived and internally validated a risk prediction model for major adverse cardiovascular events (MACE, defined as the composite of nonfatal myocardial infarction (MI), nonfatal stroke, and all-cause mortality) using claims data for a diverse nationwide cohort of U.S. adults with type 2 diabetes, including those with and without prior history of ASCVD. Because this annualized claims-based MACE estimator (ACME) was trained using administrative claims data, where the specific cause of death is not available, MACE includes all-cause and not cardiovascular-specific mortality but is also designed to be generalizable and relevant for diverse settings and populations. While ACME can be used to predict any level of MACE risk within any timeframe, our primary analysis focused on estimating 1-year risk, with secondary analyses examining other time horizons. We also examined the predicted MACE risk among the included patients, who, because of the size and

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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.

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diversity of the data sources, reflect a substantial segment of the U.S. adult population with diabetes, stratifying the cohort into 3 levels of 1-year MACE risk to demonstrate its use: low (<1%), moderate (≥1 to <5%), and high (≥5%).

METHODS

STUDY DESIGN. We retrospectively analyzed medical and pharmacy claims data from OptumLabs Data Warehouse (OLDW) linked to a 100% sample of Medicare fee-for-service ("traditional Medicare") beneficiaries. OLDW includes deidentified claims data for enrollees in commercial and Medicare Advantage plans representing a diverse mixture of ages, racial and ethnic groups, income levels, and geographic regions across the United States.[11,12] The 2 datasets (OLDW and Medicare fee-for-service) were linked to personal identifiers by OptumLabs and then deidentified prior to being made available to researchers. This linkage allows for an unprecedented ability to examine health outcomes in a diverse population spanning all U.S. states, multiple health systems, and different health plans (including as patients transition between health plans). The study was exempt from Mayo Clinic Institutional Review Board review and is reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guideline.[13] Risk of bias and applicability are examined using the Prediction Model Risk of Bias Assessment Tool.[14]

STUDY COHORT. We identified adults with type 2 diabetes (established using validated Healthcare Effectiveness Data and Information Set criteria)[15] included in OLDW and Medicare fee-for-service data between 1/1/2014 and 12/31/2021 who had 12 months of uninterrupted medical and pharmacy coverage before their index date (Supplemental Figure 1). We then excluded: patients who were <21 years old on the index date; patients with diagnosis codes for type 1 diabetes during the baseline period (in the absence of diagnosis codes, insulin fills were used to adjudicate diabetes type as described in Supplemental Methods 2); and patients who were pregnant or had metastatic cancer during the baseline period.

PRIMARY OUTCOME. The first MACE is defined as the composite of hospitalization for nonfatal acute MI or nonfatal stroke and all-cause mortality after the index date. These were captured using ICD-9 and ICD-10 codes in positions 1 and 2 of a hospital claim, as detailed in Supplemental Table 1.

INDEPENDENT VARIABLES. Thirty variables used for the ACME prediction model were ascertained from the baseline period and included patient demographic characteristics that influence ASCVD risk (age, in 5-year groups; sex), known ASCVD risk factors, established ASCVD events, and medication prescriptions. These variables were chosen by the study team and a multidisciplinary Patient and Stakeholder Advisory Group, who convened to inform the design and conduct of this study based on their known association with ASCVD risk. ASCVD risk factors and disease episodes included prior history of coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, chronic kidney disease (CKD) (staged as stage 3-4 or stage 5/end-stage kidney disease), current smoking, hypertension, obesity, and atrial fibrillation or flutter; all were ascertained using ICD-9 and ICD-10 codes in any position in any Evaluation & Management claim during the baseline year as detailed in Supplemental Table 1. Because recent cardiovascular disease (CVD) episodes may confer greater risk of short-term recurrence, MI, stroke, revascularization procedure (coronary artery bypass surgery and stenting), and heart failure hospitalization events were further classified as occurring during months 10 to 12 of the baseline period (ie, within 3 months prior to the index date) or during months 1 to 9 of the baseline period. Nondiabetes medications that modify ASCVD risk were also included in the model (Supplemental Table 2); specifically, anticoagulants, antiplatelets, lipid-lowering drugs (statins, ezetimibe, PCSK-9 inhibitors), renin angiotensin system inhibitors, diuretics, beta-blockers, calcium-channel blockers, mineralocorticoid receptor antagonists, sacubitril/valsartan, and other antihypertensives. Diabetes medications were not included because they may modify CVD risk extemporaneous to baseline CVD risk. Social determinants of health and socioeconomic data were not available in the linked dataset and therefore could not be included (these variables are also not uniformly available in the data sources where ACME is likely to be implemented).

STATISTICAL ANALYSIS. Baseline patient characteristics were summarized as mean ± SD, median (IQR), and counts (percentage), as appropriate. Missing data was reported as a separate "missing/unknown" category. The outcome was modeled as the time from index date to the MACE event, with right-censoring at discontinuation of coverage or end of study follow-up, whichever came first. A Cox proportional hazards model was used, including all independent

variables. To account for the different reasons for enrollment in Medicare for patients <65 years old compared to those ≥65 years old (ie, disability, end-stage kidney disease) and their expected differences in age trends on risk of MACE, an interaction term between having Medicare fee-for-service as the health plan at the index date and age categories up to age 64 was included in the model. The performance of the prediction model was evaluated using Harrell's Concordance Index.[16] To evaluate the impact of follow-up time on the concordance index estimate, observations were sequentially right-censored from 7 years to 1 year, and the concordance index was evaluated. Sensitivity analyses evaluated the change in predictions when 2-way interactions between the comorbidities and their indicated medications (Supplemental Table 3) were added to the model, and in a separate analysis, the impact of stratifying by established ASCVD vs not. The parameter estimates from the Cox proportional hazards model were combined with an estimate of the baseline hazard using the Nelson-Aalen estimator to allow conditional survival predictions, including the predicted risk at years 1 through 5 post-index date.[17] Calibration of the prognosis predictions was assessed using the model-based framework from Crowson et al[18] for the overall cohort and for subgroups of race and ethnicity. The latter were performed to assess for algorithmic bias, as race and ethnicity were not included in the ACME model. For any evidence of miscalibration, Platt scaling[19] was used to improve the calibration of the final predictor. Reverse censoring[20] with the Kaplan-Meier estimator was used for follow-up time estimation.

The model was internally validated using a Monte Carlo subsampling cross-validation procedure.[21] A random sample of one-third of the total sample size was drawn, and the entire model development was replicated on the subsample and then evaluated on the held-out samples not used to estimate the risk model. This process was repeated 50 times, and the average and range of performance estimates on the held-out samples were calculated. The cross-validation estimates of the concordance index, calibration, and model parameter stability were assessed.[22]

We then estimated the final model using the full cohort and assessed the concordance index and calibration. To examine the characteristics of patients with different levels of predicted MACE risk, we used ACME to identify patients with lower (<1%), moderate (≥1% to <5%), and higher (≥5%) 1-year risk of experiencing a MACE event. These risk level thresholds were informed by the definition of "high" CVD risk in the major type 2 diabetes treat-to-target and cardiovascular outcomes trials, where participants in the placebo arms experienced nonfatal MI, nonfatal stroke, or all-cause mortality at an approximate annualized rate between 3% and 6%.[23-35] Patient demographic and clinical characteristics of each MACE risk level category were summarized, as was the distribution of MACE risk levels across each demographic and clinical characteristic.

All analyses were conducted using R version 4.1.

RESULTS

The study cohort was comprised of 6,623,526 adults with type 2 diabetes, of whom 2,634,889 had commercial or Medicare Advantage insurance coverage and 3,988,637 had Medicare fee-for-service coverage. Mean age of the study cohort was 68.1 ± 10.6 years, 49.8% were women, and 73.0% were Non-Hispanic White (**Table 1**). **Table 1** also summarizes patients' baseline rates of ASCVD events, risk factors, and relevant medication use. Patients were observed in the data for a median of 3.84 (IQR: 1.59-6.84) years and experienced 1,487,694 MACE events (366,586 events in the OLDW cohort and 1,121,108 events in the Medicare fee-for-service cohort). The 2 cohorts were linked and examined together to maximize the generalizability of study findings.

The overall approach for ACME development and implementation is shown in the **Central Illustration**. Model coefficients are summarized in **Table 2**; the concordance index was 0.74 (se = 0.0002). The estimate of predictive performance aligned with the concordance index from the Monte Carlo cross-validation, mean (range) of 0.740 (0.739-0.741) indicating no evidence of overfitting (Supplemental Figure 2). The concordance index increased as we progressively shortened the follow-up time from 0.7402 (observed follow-up time) to 0.7713 (1-year follow-up) indicating predictions were stronger for near-term events compared to longer-term events (Supplemental Table 4). As expected, risk increased progressively with age and was higher among men than women (HR: 1.16, 95% CI: 1.15-1.16). History of a MI, stroke, or heart failure hospitalization was associated within highest risk of MACE, particularly when these events occurred closer to the index date (ie, months 10-12 of the baseline year more than months 1-9). Undergoing a revascularization procedure was associated with lower risk of MACE. Peripheral vascular disease, CKD, smoking, hypertension, and atrial fibrillation/flutter were all associated with

TABLE 1 Baseline Characteristics of the Study Cohort

	OLDW (n = 2,634,889)	M-FFS (n = 3,988,637)	Combined (N = 6,623,526)
Age, y	63.3 ± 12.6	71.2 ± 7.6	68.1 ± 10.6
Age category, y			
21-44	221,998 (8.43%)	26,441 (0.66%)	248,439 (3.75%)
45-64	1,034,027 (39.24%)	352,430 (8.84%)	1,386,457 (20.93%)
65-74	867,885 (32.94%)	2,260,073 (56.66%)	3,127,958 (47.22%)
≥75	510,979 (19.39%)	1,349,693 (33.84%)	1,860,672 (28.09%)
Sex			
Female	1,297,191 (49.2%)	1,998,398 (50.1%)	3,295,589 (49.8%)
Male	1,337,698 (50.8%)	1,990,239 (49.9%)	3,327,937 (50.2%)
Race/ethnicity[a]			
White	1,545,356 (58.65%)	3,291,772 (82.53%)	4,837,128 (73.03%)
Black	481,168 (18.26%)	317,835 (7.97%)	799,003 (12.06%)
Hispanic	383,184 (14.54%)	190,395 (4.77%)	573,579 (8.66%)
Asian	114,049 (4.33%)	89,617 (2.25%)	203,666 (3.07%)
Other/unknown	111,132 (4.22%)	99,018 (2.48%)	210,150 (3.17%)
Region			
Midwest	619,364 (23.51%)	1,051,928 (26.37%)	1,671,292 (25.23%)
Northeast	351,064 (13.32%)	648,584 (16.26%)	999,648 (15.09%)
South	1,363,806 (51.76%)	1,694,966 (42.49%)	3,058,772 (46.18%)
West	298,296 (11.32%)	581,549 (14.58%)	879,845 (13.28%)
Unknown	2,359 (0.09%)	11,610 (0.29%)	13,969 (0.21%)
ASCVD risk factors			
Heart failure hospitalization			
Months 10-12 of baseline	34,110 (1.3%)	66,667 (1.7%)	100,777 (1.5%)
Months 1-9 of baseline	53,716 (2.0%)	106,486 (2.7%)	160,202 (2.4%)
Other heart failure	200,482 (7.6%)	413,281 (10.4%)	613,763 (9.3%)
Chronic kidney disease			
Stages 3-4	243,484 (9.2%)	424,889 (10.7%)	668,373 (10.1%)
Stage 5 or ESKD	36,628 (1.4%)	104,851 (2.6%)	141,479 (2.1%)
Current smoking	292,510 (11.1%)	417,121 (10.5%)	709,631 (10.7%)
Hypertension	2,132,339 (80.9%)	3,561,492 (89.3%)	5,693,831 (86.0%)
Obesity	836,078 (31.7%)	1,030,434 (25.8%)	1,866,512 (28.2%)
Atrial fibrillation/flutter	217,247 (8.2%)	573,673 (14.4%)	790,920 (11.9%)
At least 1 ASCVD risk factor	2,305,124 (87.5%)	3,700,836 (92.8%)	6,005,960 (90.7%)
Established ASCVD			
Acute MI			
Months 10-12 of baseline	14,265 (0.5%)	21,983 (0.6%)	36,248 (0.5%)
Months 1-9 of baseline	20,957 (0.8%)	38,048 (1.0%)	59,005 (0.9%)
Other coronary artery disease	536,815 (20.4%)	1,245,027 (31.2%)	1,781,842 (26.9%)
Revascularization procedure			
Months 10-12 of baseline	26,381 (1.0%)	52,459 (1.3%)	78,840 (1.2%)
Months 1-9 of baseline	49,800 (1.9%)	111,758 (2.8%)	161,558 (2.4%)
Other peripheral vascular disease	377,759 (14.3%)	719,652 (18.0%)	1,097,411 (16.6%)
Acute stroke			
Months 10-12 of baseline	13,884 (0.5%)	21,867 (0.5%)	35,751 (0.5%)
Months 1-9 of baseline	19,828 (0.8%)	35,520 (0.9%)	55,348 (0.8%)
Other cerebrovascular disease	274,095 (10.4%)	642,241 (16.1%)	916,336 (13.8%)

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higher MACE risk, while obesity was associated with lower risk. Lipid-lowering and renin-angiotensin-aldosterone system inhibitor medication use was associated with significantly lower risk of MACE, while other medications were associated with higher risk. The Nelson-Aalen estimate for the cumulative hazard of the baseline group at 1 year was 0.007, reflecting the estimate for the cumulative event rate if all covariates were equal to 0 (the reference group).

The calibration plots for the risk model before and after recalibration are shown in **Figures 1A and 1B**. The coefficients from the Platt recalibration were 0.30

TABLE 1 Continued

	OLDW (n = 2,634,889)	M-FFS (n = 3,988,637)	Combined (N = 6,623,526)
At least 1 established ASCVD	896,955 (34.0%)	1,869,557 (46.9%)	2,766,512 (41.8%)
ASCVD risk modifying drugs			
Anticoagulants	186,148 (7.1%)	439,651 (11.0%)	625,799 (9.4%)
Antiplatelets	222,234 (8.4%)	440,248 (11.0%)	662,482 (10.0%)
Lipid-lowering medications	1,657,370 (62.9%)	2,651,698 (66.5%)	4,309,068 (65.1%)
RAAS inhibitors	1,662,950 (63.1%)	2,682,019 (67.2%)	4,344,969 (65.6%)
Sacubitril/valsartan	7,281 (0.3%)	4,964 (0.1%)	12,245 (0.2%)
Diuretics	1,038,618 (39.4%)	1,870,533 (46.9%)	2,909,151 (43.9%)
MRA	93,963 (3.6%)	175,372 (4.4%)	269,335 (4.1%)
Beta-blockers	921,869 (35.0%)	1,814,879 (45.5%)	2,736,748 (41.3%)
Calcium-channel blockers	711,584 (27.0%)	1,253,882 (31.4%)	1,965,466 (29.7%)
Other antihypertensives	188,716 (7.2%)	348,221 (8.7%)	536,937 (8.1%)
Duration of follow-up (d), median (OQR)	781 (365-1,582)	1,950 (916-2,684)	1,403 (582-2,495)
Median (IQR)			
Number of MACE events			
MACE	366,586 (13.9%)	1,121,108 (28.1%)	1,487,694 (22.5%)
Nonfatal MI	57,519 (2.2%)	134,876 (3.4%)	192,395 (2.9%)
Nonfatal stroke	51,753 (2.0%)	122,293 (3.1%)	174,046 (2.6%)
Death	258,187 (9.8%)	865,988 (21.7%)	1,124,175 (17.0%)

Values are mean ± SD or n (%). [a]Race is classified in the OLDW as Non-Hispanic Asian (Asian), Hispanic, Non-Hispanic Black (Black), Non-Hispanic White (White), or other/unknown based on self-report or derived rule sets based on name and ZIP code.

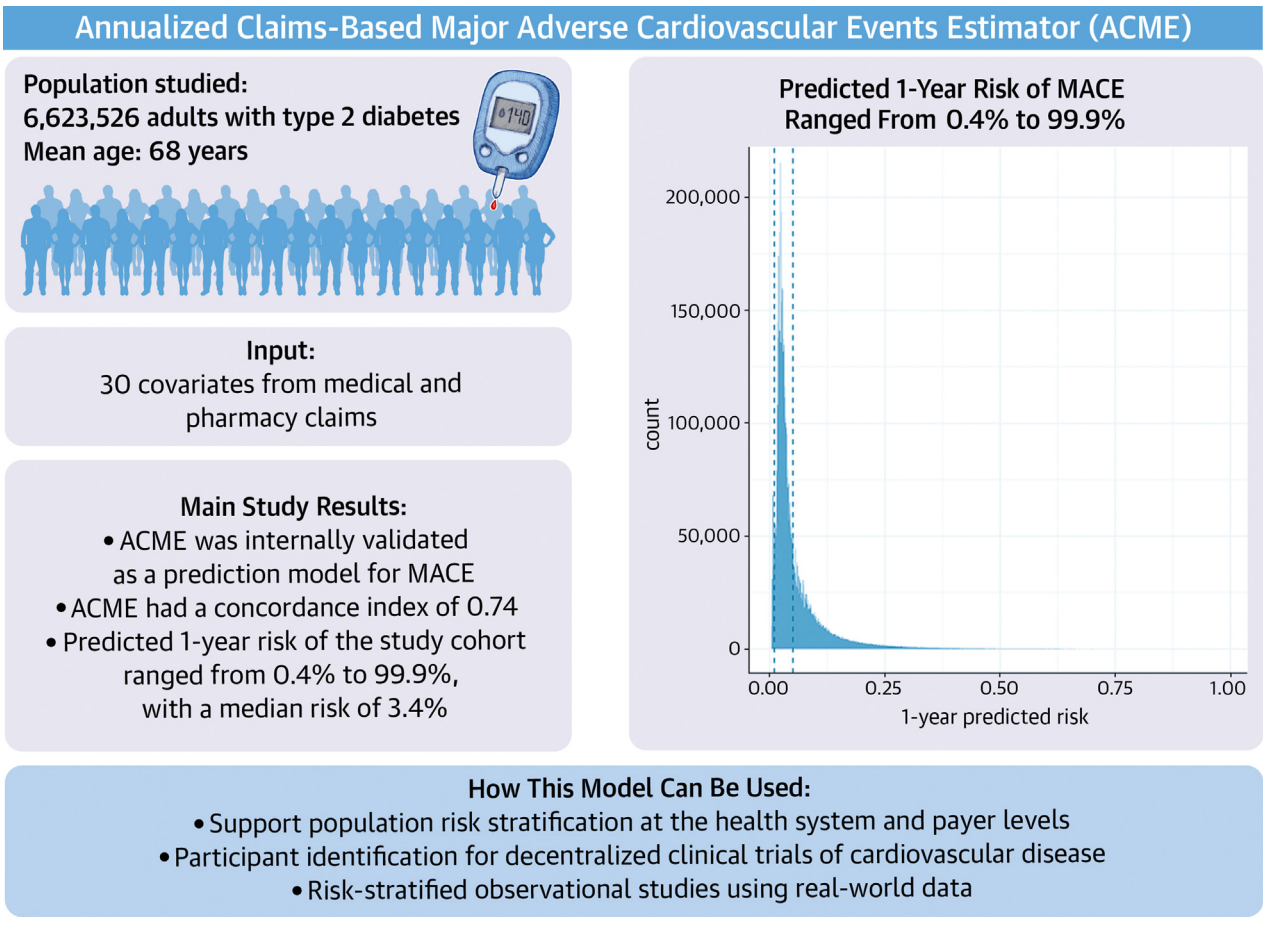
ASCVD = atherosclerotic cardiovascular disease; ESKD = end-stage kidney disease; M-FFS = Medicare fee-for-service; MRA = mineralocorticoid receptor antagonist; OLDW = OptumLabs DataWarehouse; RAAS = renin-angiotensin-aldosterone system.

(intercept) and 1.081 (slope). Calibration plots for Asian, Black, Hispanic, and White patients separately are shown in Supplemental Figure 3. Calibration was comparable among Black, Hispanic, and White patients, but risk was overestimated in Asian patients. While race and ethnicity were not variables in the risk model, we evaluated the concordance index within each subgroup. The concordance index was highest for Asian (0.768) and Hispanic (0.762) patients, followed by Black (0.745) and White (0.734) patients.

The distribution of 1-year predicted MACE risks for the study cohort of adults with diabetes is shown in **Figure 2** The predicted 1-year risk of the study cohort ranged from 0.4% to 99.9%, with a median 1-year risk of 3.4% (IQR: 2.3%-6.5%). Overall, 4.3% of patients were predicted to have <1% 1-year risk of MACE ("low risk"), 62.8% were predicted to have ≥1 to <5% 1-year risk ("moderate risk"), and 32.9% were predicted to have ≥5% 1-year risk ("high risk"). Characteristics of patients in each 1-year MACE risk category are presented in **Table 3**. As expected, patients in the low-risk group were younger than those in higher-risk groups, with mean age of low-risk patients 40.6 ± 6.7 years, moderate-risk patients 65.8 ± 7.7 years, and high-risk patients 76.0 ± 7.2 years. The prevalence of all comorbidities and medications were lower in lower-risk patients, with almost no low-risk patients having had baseline acute MI (<0.01%), acute stroke (<0.01%), heart failure hospitalization (<0.01%), peripheral vascular disease (1.5%), CKD (0.4%), or atrial fibrillation/flutter (0.3%). At least 1 risk factor for ASCVD was present in 72.7% of patients in the low-risk group compared to 88.5% and 97.2% in the moderate- and high-risk groups, respectively. Established ASCVD was in 3.8% of patients in the low-risk group, 27.0% in the moderate-risk group, and 74.7% in the high-risk group. We similarly calculated 2-, 3-, 4-, and 5-year predicted probabilities of MACE, as shown in Supplemental Figure 4, demonstrating the feasibility of this approach for calculating MACE risk for any time horizon of interest.

We also examined the distribution of predicted 1-year MACE risk within each patient demographic and clinical characteristic (Supplemental Table 5). Among patients 21 to 44 years old, 82.2% were low risk and 1.1% were high risk, while among patients ≥75 years old, <0.1% were low risk, 20.9% were moderate risk, and 79.1% were high risk. Among White patients, 3.0% had low predicted MACE risk, compared to 6.1% of Black patients, 10.3% of Hispanic patients, and 9.8% of Asian patients. Conversely, 35.2% of White patients were high-risk, as were 30.5%

CENTRAL ILLUSTRATION Overview and Implementation of ACME



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ACME = annualized claims-based major adverse cardiovascular events estimator.

of Black patients, 24.4% of Hispanic patients, and 21.9% of Asian patients.

SENSITIVITY ANALYSES. Adding 2-way interactions between comorbidities and their indicated medications only increased the concordance index to 0.742 (se = 0.0002) from 0.740 in the original model. Most interaction terms were statistically significant (Supplemental Table 6), given the large sample size, but the larger model had little impact on the predicted risk. Additionally, models were estimated within patients with and without established ASCVD independently. This led to a small decrease in the concordance index. Most individual hazard ratios were similar in these subgroup models, except for age, where individuals with established ASCVD had a smaller impact of age compared to individuals without established ASCVD (Supplemental Table 7).

DISCUSSION

Leveraging claims data for over 6.6 million adults with diabetes included in commercial, Medicare Advantage, and Medicare fee-for-service plans across the United States, we derived and internally validated a prediction model for MACE that can be used to risk-stratify patients across a wide range of risk levels and time horizons. In contrast to other

TABLE 2 Annualized Claims-Based MACE Estimator Model Coefficients

Age category, y	
<45	ref
45-49	1.59 (1.53-1.66)
50-54	2.05 (1.97-2.12)
55-59	2.65 (2.56-2.74)
60-64	3.52 (3.41-3.64)
65-69	3.37 (3.26-3.47)
70-74	4.27 (4.14-4.41)
75-79	5.62 (5.44-5.80)
80-84	9.81 (9.51-10.12)
≥85	14.40 (13.93-14.89)
Sex	
Female	ref
Male	1.16 (1.15-1.16)
ASCVD risk factors	
Heart failure hospitalization	
Months 1-9 of baseline	1.74 (1.73-1.75)
Months 10-12 of baseline	1.87 (1.86-1.89)
Other heart failure	1.57 (1.57-1.58)
Chronic kidney disease	
Stages 3-4	1.31 (1.30-1.31)
Stage 5 or ESKD	2.07 (2.05-2.08)
Current smoking	1.37 (1.37-1.38)
Hypertension	1.07 (1.06-1.08)
Obesity	0.92 (0.92-0.92)
Atrial fibrillation/flutter	1.22 (1.21-1.23)
Established ASCVD	
Acute MI	
Months 1-9 of baseline	1.35 (1.34-1.37)
Months 10-12 of baseline	2.50 (2.46-2.53)
Revascularization procedure	
Months 1-9 of baseline	0.88 (0.87-0.89)
Months 10-12 of baseline	0.95 (0.93-0.96)
Other cerebrovascular disease	1.29 (1.29-1.30)
Acute stroke	
Months 1-9 of baseline	1.58 (1.56-1.60)
Months 10-12 of baseline	3.15 (3.11-3.19)
Other peripheral vascular disease	1.34 (1.33-1.34)
Other coronary artery disease	1.22 (1.22-1.23)
ASCVD risk modifying drugs	
Anticoagulants	1.00 (1.00-1.01)
Antiplatelets	1.18 (1.18-1.19)
Lipid-lowering medications	0.77 (0.77-0.77)
RAAS inhibitors	0.87 (0.87-0.88)
Calcium-channel blockers	1.07 (1.07-1.07)
Beta-blockers	1.10 (1.09-1.10)
Diuretics	1.10 (1.09-1.10)
Other antihypertensives	1.11 (1.10-1.11)
MRA	1.16 (1.15-1.17)
Sacubitril/valsartan	0.99 (0.95-1.03)
Insurance plan interaction terms	
M-FFS and <65 y	2.36 (2.24-2.48)
M-FFS and 45-49 y	0.77 (0.72-0.82)
M-FFS and 50-54 y	0.69 (0.65-0.73)
M-FFS and 55-59 y	0.62 (0.59-0.65)
M-FFS and 60-64 y	0.52 (0.50-0.55)

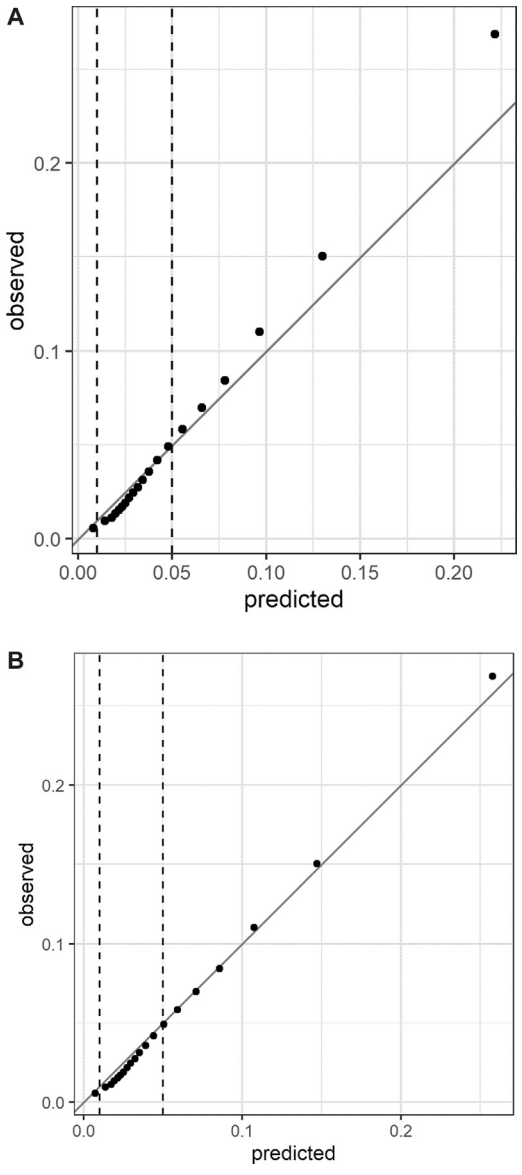
Values are HR (95% CI).

ASCVD = atherosclerotic cardiovascular disease; ESKD = end-stage kidney disease; MACE = major adverse cardiovascular event; M-FFS = Medicare fee-for-service; MRA = mineralocorticoid receptor antagonist; RAAS = renin-angiotensin-aldosterone system.

currently available and commonly used ASCVD risk prediction models, ACME can be used to risk-stratify patients using administrative claims and electronic health record data, which can support population health management efforts, identification or enrollment of patients into decentralized and point-of-care pragmatic trials, and conducting observational studies using real-world data that require assessment of MACE risk. ACME is additionally strengthened by its focus and calibration on patients with type 2 diabetes, on predicting short-term event risk, and development and validation in a heterogeneous and diverse patient cohort that is reflective of usual care conditions.

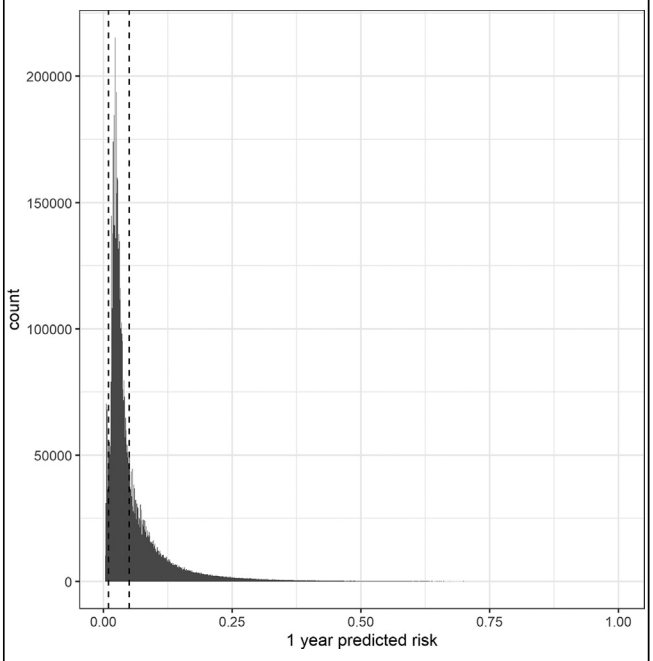
To examine the implementation of ACME in claims, we chose cutoffs for moderate (1%) and high (5%) CVD risk based on the frequency at which patients traditionally considered as "high risk" in the placebo arms of large type 2 diabetes treat-to-target and cardiovascular outcomes trial experienced nonfatal MI, nonfatal stroke, or all-cause mortality.[23-35] However, these thresholds are also somewhat arbitrary, as different clinical scenarios and decisional dilemmas may warrant different definitions of what constitutes low or high level of risk. Indeed, the lack of standardized definitions of "high," "moderate," and "low" CVD risk has precluded direct comparisons across clinical trials, as there is marked variation in how CVD risk is assessed and quantified. We hope that by proposing a data-driven, generalizable, and easy-to-implement model, our work will pave the way toward more individualized approaches to risk stratification. This can also enable trials that focus on specific CVD risk levels, building on most currently available trials that are either conducted in patients with established CVD or at high CVD risk or in patients with no CVD risk factors and hence very low CVD risk.

FIGURE 1 ACME Calibration and Recalibration Plots for 1-Year MACE Risk



Plots compare observed vs predicted 1-year MACE risk (A) before and (B) after recalibration. Each point is 1/20th of the data, with the x-axis the median within group prediction and the y-axis the Kaplan-Meier estimate at 1-year after index date. ACME = Annualized Claims-Based MACE Estimator; MACE = major adverse cardiovascular event.

FIGURE 2 Distribution of Predicted 1-Year Risk of a Major Adverse Cardiovascular Event in the Study Cohort



Vertical lines reflect the proposed thresholds for low (<1%), moderate (1-5%), and high (>5%) 1-year MACE risk.

Using this risk stratification approach, we found that only 4.3% of patients in our cohort were at low risk (<1%) for experiencing a MACE outcome in the next year, while 62.8% were at moderate risk (≥1 to <5%) and 32.9% were at high risk (≥5% 1-year risk). This was not unexpected given the older age of our cohort and the presence of diabetes, but it is important because most trials of CVD risk reduction, particularly in patients with type 2 diabetes, focus on those at high risk for CVD. There is almost no data on CVD management in patients at moderate risk for CVD, despite them comprising the majority of the population with type 2 diabetes. Health plans and health systems with high proportions of high-risk individuals may want to invest in proactive program efforts to engage highest-risk patients, make sure they receive education and guideline-directed medical therapy to reduce their risk of ASCVD, consider nonmedical programs to lower ASCVD risk (such as gym memberships, health meal delivery, and home health services), and support healthcare providers who care for highest-risk patients. The subgroup with >90% of patients having ≥5% risk of experiencing a MACE in the coming year included patients with recent (within the past 3 months) acute MI, recent acute stroke, heart failure hospitalization in the past year, and stage 5 or end-stage kidney disease. Such patients may benefit from longer-term care transitions, cardiac rehabilitation, and intensive disease management programs to optimize their health and reduce the likelihood of recurrent ASCVD events,

TABLE 3 Patient Characteristics as a Function of Predicted 1-Year Risk of Major Adverse Cardiovascular Events

	Low Risk (<1%) (n = 282,676)	Moderate Risk (≥1% to <5%) (n = 4,157,656)	High Risk (≥5%) (n = 2,183,194)
Number of MACE events[b]	3,723	497,633	986,338
Myocardial infarction	1,476 (0.5%)	101,228 (2.4%)	89,691 (4.1%)
Stroke	1,014 (0.4%)	310,206 (7.5%)	812,727 (37.2%)
Death	1,242 (0.4%)	87,600 (2.1%)	85,432 (3.9%)
Health plan			
Commercial or Medicare advantage	99.9%	41.8%	28.1%
Medicare fee-for-service	0.1%	58.2%	71.9%
Age, y	40.6 ± 6.7	65.8 ± 7.7	76.0 ± 7.2
Age category, y			
21-44	72.2%	1.0%	0.1%
45-64	27.7%	27.4%	7.7%
65-74	<0.1%	62.2%	24.8%
≥75	<0.1%	9.4%	67.4%
Sex			
Female	51.2%	51.0%	47.2%
Male	48.8%	49.0%	52.8%
Race/ethnicity[a]			
White	50.6%	71.9%	78.1%
Black	17.1%	12.2%	11.1%
Hispanic	20.8%	9.0%	6.4%
Asian	7.0%	3.3%	2.0%
Other/unknown	4.5%	3.5%	2.3%
ASCVD risk factors			
Heart failure hospitalization			
Months 1-9 of baseline	<0.1%	0.1%	7.1%
Months 10-12 of baseline	<0.1%	0.1%	4.5%
Other heart failure	0.1%	2.0%	24.2%
Chronic kidney disease			
Stages 3-4	0.4%	5.0%	21.0%
Stage 5 or ESKD	<0.1%	0.2%	6.1%
Current smoking	6.6%	8.9%	14.7%
Hypertension	53.1%	83.6%	94.7%
Obesity	45.0%	30.1%	22.4%
Atrial fibrillation/flutter	0.3%	4.3%	28.0%
At least 1 risk factor	72.7%	88.5%	97.2%
Established ASCVD			
Acute myocardial infarction			
Months 1-9 of baseline	<0.1%	0.3%	2.2%
Months 10-12 of baseline	<0.1%	<0.1%	1.6%
Other coronary artery disease	1.5%	16.2%	50.6%
Revascularization procedure			
Months 1-9 of baseline	0.1%	1.3%	4.9%
Months 10-12 of baseline	<0.1%	0.5%	2.6%
Other peripheral vascular disease	1.5%	8.0%	34.9%
Acute stroke			
Months 1-9 of baseline	<0.1%	0.2%	2.2%
Months 10-12 of baseline	<0.1%	<0.1%	1.6%
Other cerebrovascular disease	0.8%	6.6%	29.2%
At least 1 established ASCVD	3.8%	27.0%	74.7%

Values are % or mean ± SD unless otherwise indicated. All percentages are calculated down columns for all categories within a given covariate. [a]Race is classified in the OLDW as nonHispanic Asian (Asian), Hispanic, nonHispanic Black (Black), nonHispanic White (White), or other/unknown based on self-report or derived rule sets based on name and zip code. [b]N = 2,922 individuals had both a stroke and MI on the same day, but was only counted as a single MACE event.

ASCVD = atherosclerotic cardiovascular disease; ESKD = end-stage kidney disease; MACE = major adverse cardiovascular event.

though the effectiveness of ACME-informed risk stratification and intervention will have to be prospectively evaluated in future research.

Our model performed as well as, or better than commonly used MACE prediction models. However, direct comparisons among models are not possible because they were all developed in different patient populations, included a wide and heterogeneous range of predictor variables, and used disparate data sources. Recent evaluation of 22 most commonly used ASCVD risk models, including 9 derived specifically among adults with type 2 diabetes and 13 in the general population, found that all had Harell's concordance index below 0.70,[36] compared to concordance of the ACME model in this cohort of 0.74 (se = 0.0002).

STRENGTHS AND LIMITATIONS. Our study is strengthened by size, heterogeneity, and diversity of the study cohort treated under routine care conditions used to derive and internally validate this risk prediction model. The cohort was comprised of people across the entire United States receiving care in diverse clinical settings and insured by a wide range of health plans (commercial, Medicare Advantage, and Medicare fee-for-service), and is 27% nonWhite and 49.8% female. Using claims data is a major strength, as it will allow ACME to be implemented in different settings, including where electronic health record data are not sufficiently robust to enable point-of-care risk prediction, ensure that included patients are representative of the general population, and avoid the biases inevitable with studies that rely on cohort enrollment and prospective participation. As such, it is representative of the general population of adults with diabetes, and we expect the results to generalize to other patient populations across the United States.

Our study also has important limitations. External validation in other settings, cohorts, and data types will be needed, as our findings may not generalize to patients without health insurance, in other countries, or with different age and clinical complexity compositions. By relying exclusively on data available in claims data, our model can be widely used and scaled, but it also misses informative patient information such as blood pressure, lipid and glycemic control, central adiposity, and other metabolic derangements that have been included in prior models. Family history and genomic data were similarly not available. We did not include information on social determinants of health in the model—both because it was not available and because we focused on biological and not social constructs—but we also could not assess model fairness as a function of socioeconomic status. The duration of diabetes, as well as the duration of other CVD risk factors, could not be included in the model because these data are not available in administrative claims. We were not able to specifically examine cardiovascular mortality and focused on all-cause mortality, as causes of death are not available in our data. However, this is common in other studies in this field,[37] enabling cross-study comparisons and broader ACME applications. Since some patients in our cohort were treated to reduce their risk of cardiovascular events, the current model does not reflect a natural history risk prediction but a contemporary reflection of MACE risk among patients with type 2 diabetes in the United States. Concordance indices with time-to-event predictions are also sensitive to the follow-up time.

CONCLUSIONS

We have shown that administrative claims data can be used to risk-stratify adults with type 2 diabetes based on their 1-year, or any other time horizon, risk of MACE. This model will need to be externally validated in different settings and cohorts but has the potential to support population health programs at the health system or health plan levels, decentralized and point-of-care trials that seek to enroll patients using electronic health record or claims-based data, and observational research using real-world data that wants to include measures of CVD risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Routinely available healthcare data in administrative claims and electronic health records can be used to predict major adverse cardiovascular event risk at variable time horizons and in heterogeneous patient populations.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: The ability to calculate and discuss with patients their predicted short-term cardiovascular disease risk can support shared decision-making conversations.

COMPETENCY IN SYSTEMS-BASED PRACTICE: The ability to identify patients at specific ranges of predicted cardiovascular disease risk can support proactive patient engagement and care delivery at the health system and payor levels.

TRANSLATIONAL OUTLOOK: The annualized claims-based major adverse cardiovascular event estimator can support population risk stratification at the health system and payer levels, participant identification for decentralized clinical trials of cardiovascular disease, and risk-stratified observational studies using real-world data.

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KEY WORDS **cardiovascular disease, claims analysis, major adverse cardiovascular event, prediction model, real-world data, risk prediction, risk stratification, type 2 diabetes**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**