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Incremental risk of cardiovascular disease and/or chronic kidney disease for future ASCVD and mortality in patients with type 2 diabetes mellitus: ACCORD trial

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ABSTRACT

Background: Cardiovascular disease (CVD) and chronic kidney disease (CKD) are complications of type 2 diabetes mellitus (DM). Current cholesterol guidelines recommend the same prevention strategy for patients with DM alone as patients with DM + CKD. However, the incremental risk of these common complications for incident cardiovascular disease and mortality has not been well studied.

Methods: We compared the incremental risk of having DM + CKD, DM + CVD and DM + CVD + CKD in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial participants for incident CVD as the primary outcome and all-cause mortality.

Results: After a mean (SD) follow up of 4.7(1.4) years, 1,046(10%) participants developed CVD. DM +vCKD, DM + CVD, and DM + CKD + CVD had a significantly increased risk of the primary outcome compared to DM alone [adjusted hazard ratio(95%CI): 1.41 (1.06-1.89), $p = 0.02$; 2.20 (1.92-2.53), $p < 0.001$); 2.35 (1.81-3.04), $p < 0.001$), respectively]. All-cause mortality had a graded increased risk compared to the reference group [adjusted hazard ratio(95%CI): 1.39 (1.01-1.90), $p = 0.04$; 1.29 (1.51-2.12), $p < 0.0001$; 2.36 (1.75-3.13), $p < 0.0001$), respectively].

Conclusion: Our post hoc analysis shows an incremental graded risk for CVD outcomes and all-cause mortality with the development of CKD and/or CVD in individuals with DM.

1. Introduction

Type 2 DM represents the 7th leading cause of death in the U.S.; much of which can be attributed to CVD, the leading cause of death.[1,2] The existence of DM is identified as being a risk factor for atherosclerotic cardiovascular disease (ASCVD)[2–5] and even an equivalent.[6] The idea that DM is a CVD equivalent with similar event rates as those with prior CVD is based on antiquated data.[7] Individuals with DM are also at an increased risk of CKD along with microalbuminuria, conditions that have been associated with an increased cardiovascular risk.[4,8] The management goals of diabetes mellitus are, therefore, to minimize the occurrence of complications which includes CKD and CVD.[2,4]

Current DM, hypertension and cholesterol guidelines have acknowledged the very common coexistence of these diseases (CKD and CVD) with DM and have recommended much more aggressive CVD risk factor modifications when these comorbidities are present in diabetic patients.[2,9–11] However, the additional risk the presence of CKD and/or CVD adds to the already heightened CVD risk in patients with DM has not been demonstrated in the literature.

In this report, we use the public data of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to assess the incremental risk associated with the presence of CKD and/or CVD in people with DM for future atherosclerotic cardiovascular disease (ASCVD) and mortality.

2. Methods

2.1. Study population and design

We conducted a post hoc analysis of the data from the ACCORD trial. This trial was a multicenter factorial randomized controlled trial that compared intensive blood pressure, glycemic and lipid treatments with standard care in patients with diabetes mellitus. The trial included 10,251 participants in 77 North American centers between 2001 and 2005. A detailed description of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial including participants' demographics, characteristics, study design and analysis has been published.[12] The inclusion criteria for the ACCORD trial was type 2 diabetes mellitus, hemoglobin A1C (HbA1c) ≥7.5%, age 40 to 79 with coronary artery disease

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(CAD) or 55 to 79 years with: anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy or ≥2 cardiovascular risk factors (dyslipidemia, hypertension, current smoking, and obesity). The exclusion criteria from the ACCORD trial were frequent or recent serious hypoglycemic events, unwillingness to perform home glucose monitoring or insulin injections, BMI >45 kg/m^2, serum creatinine >1.5 mg/dL and serious illness. The ACCORD trial was stopped after the safety committee recommended discontinuation of intensive therapy.[13] Funding for medications, equipment, and supplies were provided by NIH grants from the NHLBI, other NIH departments, the CDC, General Clinical Research Centers, Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough. The ACCORD study was approved by the Institutional Review Board (IRB) for each study site, and written informed consent was obtained from all participants.

2.2. Independent variables

The independent variables included in this study were history of DM, CKD, and prior CVD. CKD was defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m2. CVD was defined as nonfatal myocardial infarction (MI) or nonfatal stroke. These were adjudicated at baseline via self-report; the full description of ascertainment has been described in the literature.[12] The following baseline covariates were ascertained: age, race/ethnicity, gender, and body mass index (BMI). Body mass index was calculated per the standard equation: weight (kg) divided by height (m)^2.[14] The participants of the ACCORD trial were divided into 4 groups based on the presence or absence of CKD and CVD at baseline.

2.3. Outcomes

The outcomes of this study were the primary outcomes of the ACCORD trial described as non-fatal myocardial infarction, non-fatal stroke or CVD death. In addition, all-cause mortality was assessed. The adjudication process of incident cardiovascular and mortality events from the ACCORD trial was conducted by a central committee blinded by the study-group assignments. The details regarding variable adjudication have been published.[12]

2.4. Study analysis

Baseline characteristics including demographics of the four risk strata groups were compared. Kaplan Meier analysis was used to assess the ASCVD-free survival of the four groups during the trial. Cox proportional hazard analysis was used to assess the incremental risk of DM + CKD, DM + CVD and DM + CKD + CVD for future ASCVD and mortality adjusting for known confounders. The models generated included a univariate analysis with risk factors only and multivariable analysis which included possible confounding variables. These variables were considered possible confounders based on their association with incident cardiovascular events. Considering this was a clinical trial and participants were assigned to different treatment arms, we adjusted for the mean HbA1c and lipids throughout the ACCORD trial. Our full models were adjusted for age, race/ethnicity, gender, BMI, arm of the study, mean HbA1c, mean HDL, mean LDL, baseline diabetes medication use (insulin vs. non-insulin), blood pressure medication use, statin medication use, aspirin use, mean systolic and diastolic blood pressure and smoking status. A two-tailed value of $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC).

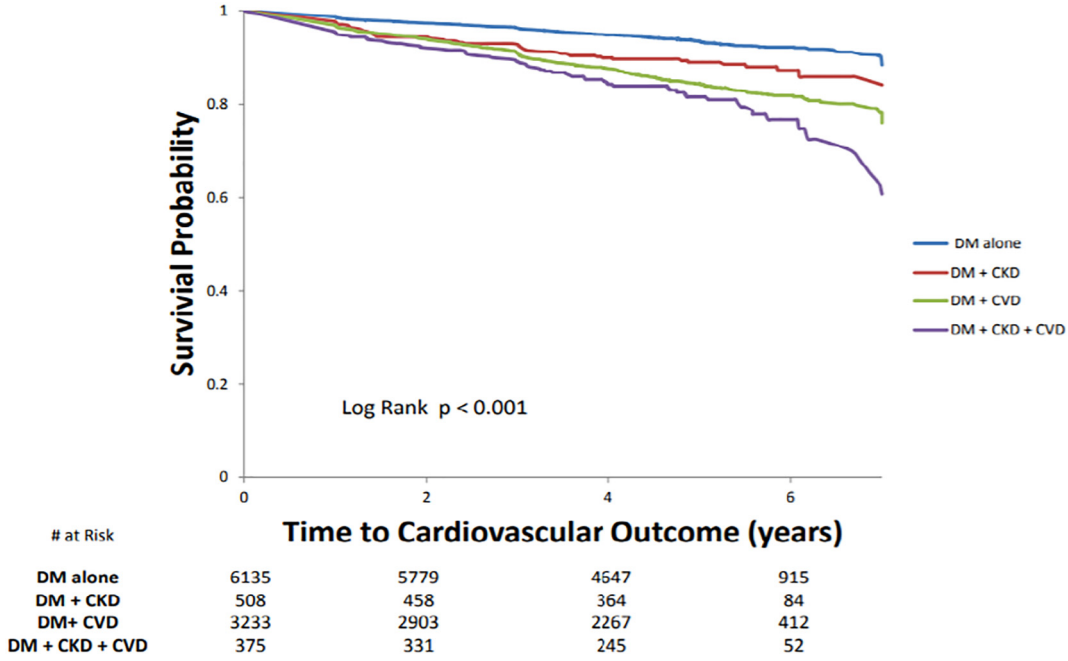
3. Results

Out of the 10,251 ACCORD trial participants, 6135 (60%) had only DM alone, 508 (5%) had DM + CKD, 3233 (31.5%) had DM + CVD, and 375 (3.5%) had DM + CKD + CVD. Table 1 shows the demographics and clinical characteristics of the ACCORD trial participants included in this analysis. The cohort was predominately White male, but almost half were female in each group except DM + CVD. Approximately one-third of participants were non-White in each group. After a mean (SD) follow up of 4.7 (1.4) years, a total of 1046 (10%) study subjects (10.2%) had an adjudicated composite outcome (6.7% in DM only, 11.5% in DM + CKD, 15.5% in DM + CVD and 20% in DM + CKD + CVD) and 715 (7%) died. As shown in Fig. 1, there was significant graded CVD risk with the least

Table 1
Demographic and clinical characteristics of ACCORD trial participants.

Variable	DM alone $N = 6135$	DM + CKD $N = 498$	DM + CVD $N = 3233$	DM + CKD + CVD $N = 375$
Age	62.6 ± 5.8	66.2 ± 6.1	62.1 ± 7.8	66.9 ± 7.2
Female (%)	2627 (42.8)	296 (59.4)	852 (26.4)	170 (45.3)
Race/ethnicity				
White	3683 (60.0)	336 (67.5)	2101 (65.0)	266 (70.9)
Non-White	2452 (40.0)	162 (32.5)	1132 (35.0)	109 (29.1)
BMI (kg/m^2)	32.3 ± 5.5	33.0 ± 5.7	32.1 ± 5.2	31.7 ± 5.4
Smokers (%)	832 (13.6)	43 (8.6)	514 (15.9)	40 (10.7)
Years of DM	10.1 ± 7.2	12.4 ± 8.1	11.4 ± 7.9	14.7 ± 8.9
Cholesterol (mg/dl)				
Total	172.8 ± 32.1	178.2 ± 34.6	168.6 ± 33.4	168.7 ± 33.3
LDL	96.4 ± 25.5	98.6 ± 26.6	93.5 ± 26.1	92.5 ± 26.7
HDL	44.2 ± 11.0	43.6 ± 10.8	40.5 ± 9.8	39.5 ± 9.2
Triglycerides	163.1 ± 89.0	180.8 ± 91.1	177.3 ± 97.8	185.5 ± 97.9
Blood pressure (mmHg)				
Systolic	129.0 ± 11.2	131.0 ± 13.1	128.5 ± 12.0	131.3 ± 12.7
Diastolic	70.2 ± 11.2	68.1 ± 7.9	68.4 ± 8.4	65.9 ± 8.2
HBA1C	8.3 ± 1.0	8.2 ± 1.0	8.3 ± 1.0	8.3 ± 1.0
GFR (ml/min/1.73 m^2)	94.0 ± 20.3	52.6 ± 6.4	92.5 ± 20.3	51.8 ± 6.5
Statin use (%)	3428 (56.2)	300 (60.5)	2466 (76.5)	299 (79.7)
BP Med use (%)	4708 (76.7)	435 (87.4)	2872 (88.8)	348 (92.8)
P. CVD outcome	412 (6.7)	57 (11.5)	502 (15.5)	75 (20.0)

Footnote: DM Alone: diabetes mellitus (DM) Without chronic kidney disease (CKD) or prior cardiovascular disease (CVD); DM + CKD: diabetes mellitus with CKD but no CVD; DM + CVD: diabetes mellitus with CVD but no CKD; DM + CKD + CVD: diabetes mellitus with CKD and CVD. GFR: Glomerular filtration rate. BMI: body mass index. LDL: low density lipoprotein. HDL: high density lipoprotein. HBA1C: glycated hemoglobin. BP: blood pressure. P. CVD: Primary cardiovascular disease.



# at Risk				
DM alone	6135	5779	4547	915
DM + CKD	508	458	364	84
DM+ CVD	3233	2903	2267	412
DM + CKD + CVD	375	331	245	52

Fig. 1. Survival analysis demonstrating time to cardiovascular outcome for DM, DM + CKD, DM + CVD, DM + CKD + CVD.

CVD risk in DM alone and the highest risk in DM + CKD + CVD sample. With the DM alone subgroup as the reference, DM + CKD, DM + CVD and DM + CKD + CVD had significantly higher risk for incidence of the primary outcome [adjusted hazard ratio (95% CI): 1.41 (1.06–1.89), $p = 0.02$; 2.20 (1.92–2.53), $p < 0.001$; 2.35 (1.81–3.04), $p < 0.001$, respectively] (Table 2). Similar estimates were obtained when the cohort was stratified by race (White and non-White) except for DM + CKD in non-White participants [adjusted hazard ratio (95% CI): 0.98 (0.51–1.86), $p = 0.94$] which was not significant (Table 2). In terms of all-cause mortality, compared to the DM alone subgroup as the reference, there was a graded increased risk of all-cause mortality with highest risk in DM + CKD + CVD and lowest risk in DM patients alone [adjusted hazard ratio (95% CI): 1.39 (1.01–1.90), $p = 0.04$; 1.29 (1.51–2.12), $p < 0.0001$; 2.36 (1.75–3.13), $p < 0.0001$, respectively] with similar estimates obtained when the cohort was stratified by race (White and non-White), except DM + CKD which was not significant after stratification in either race groups (Table 3).

4. Discussion

The goal of this analysis was to provide data for the incremental risk for our primary outcome, future ASCVD, and all-cause mortality associated with the presence of CKD and/or CVD in type 2 diabetes mellitus. Our study demonstrated this statistically significant risk for these primary and secondary outcomes. We observed a 40% and 30% increased risk with the primary outcome for patients with DM + CKD respectively; which doubles with DM + CKD + CVD. The presence of CKD or CVD with DM is associated with an almost 30% increased risk of all-cause mortality in all participants, which doubles for DM + CKD + CVD. Notably, DM + CKD in non-White participants did not show an increased risk of ASCVD compared to DM alone. As well, DM + CKD did not show an increased risk for all-cause mortality compared to DM alone after stratification by race. This may be explained by the heterogeneity of risk for the different stages of CKD and differences in GFR amongst African-Americans and Hispanic/Latino Americans compared to Caucasians.[15] Patients with Crt >1.5 mg/dL were excluded from this study preventing any conclusions to be made about patients meeting this criterion including end-stage renal disease. This study is the first of its kind to demonstrate this graded risk of CVD and mortality with DM and the addition of the mentioned comorbidities.

It is known that CKD, CVD, and DM have independent increased risks of CVD and mortality. It makes sense that a patient with all three comorbidities would have an even greater risk of CVD or death. Papademetriou et al. conducted a study with the ACCORD trial

Table 2
Association between diabetes mellitus groups and primary outcome of the ACCORD Trial.

	# events (%)	Univariate model HR (95% CI)	*p* value	Multivariable model[a] HR (95% CI)	*p* value
DM alone	412 (6.7)	Reference	–	Reference	–
DM + CKD (ALL)	57 (11.5)	1.75 (1.32–2.30)	<0.0001	1.41 (1.06–1.89)	0.02
White		1.97 (1.45–2.69)		1.56 (1.12–2.16)	0.008
Non-White		1.07 (0.56–2.03)	0.84	0.98 (0.51–1.86)	0.94
DM + CVD (ALL)	502 (15.5)	2.45 (2.15–2.80)	<0.001	2.20 (1.92–2.53)	<0.001
White		2.44 (2.08–2.86)		2.17 (1.83–2.56)	
Non-White		2.41 (1.92–3.02)		2.26 (1.79–2.86)	
DM + CKD + CVD (ALL)	75 (20.0)	3.22 (2.52–4.12)	<0.001	2.35 (1.81–3.04)	<0.001
White		2.96 (2.20–3.99)		2.14 (1.57–2.92)	
Non-White		3.72 (2.40–5.78)		2.92 (1.83–4.67)	

Footnote: ALL: indicates call races. DM: diabetes mellitus Without chronic kidney disease (CKD) or prior cardiovascular disease (CVD); DM + CKD: diabetes mellitus with CKD but no CVD; DM + CVD: diabetes mellitus with CVD but no CKD; DM + CKD + CVD: diabetes mellitus with CKD and CVD.

[a] Adjusted for age, race/ethnicity, gender, BMI, arm of the study, mean HbA1c, mean HDL, mean LDL, baseline diabetes medication use (insulin vs. non-insulin), blood pressure medication use, statin medication use, aspirin use, mean systolic and diastolic blood pressure and smoking status.

Table 3
Risk of mortality stratified by diabetes alone v. diabetes with co-morbidities.

	# events	Univariate model HR (95% CI)	*p* value	Multivariable model[a] HR (95% CI)	*p* value
DM alone	308	Reference	–	Reference	–
DM + CKD (ALL)	49	1.92 (1.42–2.60)	<0.0001	1.39 (1.01–1.90)	0.04
White		1.26 (0.99–3.14)		1.38 (0.74–2.54)	0.31
Non-White		1.94 (1.36–2.77)	0.0002	1.33 (0.92–1.93)	0.13
DM + CVD (ALL)	302	1.92 (1.64–2.20)	<0.001	1.29 (1.51–2.12)	<0.0001
White		1.76 (1.33–2.32)		1.29 (1.34–2.40)	<0.0001
Non-White		1.97 (1.62–2.38)		1.76 (1.43–2.16)	<0.0001
DM + CKD + CVD (ALL)	59	3.28 (2.48–4.32)	<0.0001	2.36 (1.75–3.13)	<0.0001
White		2.82 (1.62–4.52)	0.0003	2.19 (1.20–4.00)	0.01
Non-White		3.35 (2.42–4.63)	<0.0001	2.34 (1.66–3.31)	<0.0001

Footnote: ALL: indicates call races. DM: diabetes mellitus Without chronic kidney disease (CKD) or prior cardiovascular disease (CVD); DM + CKD: diabetes mellitus with CKD but no CVD; DM + CVD: diabetes mellitus with CVD but no CKD; DM + CKD + CVD: diabetes mellitus with CKD and CVD.
[a] Adjusted for age, race/ethnicity, gender, BMI, arm of the study, mean HbA1c, mean HDL, mean LDL, baseline diabetes medication use (insulin vs. non-insulin), blood pressure medication use, statin medication use, aspirin use, mean systolic and diastolic blood pressure and smoking status.

participants evaluating the contribution of mild-to-moderate CKD on CVD risk in DM patients.[16] Similar to this study, they found that DM patients with CKD had an increased risk of CVD compared to DM patients without CKD (hazard ratio of 1.866; 95% CI: 1.65–2.110). Our study is distinct for a few reasons. Their study did not adjust for statin and aspirin use, which are important possible confounders associated with CVD risk. Also, race and ethnicity were not adjusted or considered for stratification. Our study was stratified by race which is important considering the differences in shared variants that confer risk of CKD and CVD in African Americans compared to Caucasians.[15,17,18] Gore et al. discussed the heterogeneity in risk of CVD in DM patients, but only speculated that DM and CKD would increase risk of CVD in DM patients.[19] This study demonstrated the increased incremental risk of cardiovascular disease and mortality with the addition of existing CKD and/or CVD history. One study did demonstrate an incremental risk of CVD associated with DM and the addition of a comorbidity.[20] Saely et al. demonstrated that DM along with a diagnosis of peripheral artery disease (PAD) increases risk for CVD events and mortality. This study found that with DM and PAD the cardiovascular disease event rate was significantly higher than DM alone, PAD alone, or neither disease. Although this study demonstrated that DM and another comorbidity can add increased risk of CVD outcomes, they only included PAD. Our study included a more comprehensive risk model including more risk factors.

Our study presents the idea that DM patients should be considered at increased risk of CVD and mortality in the guidelines, if these patients also have CKD and/or CVD. Historically, one study from a Finnish population concluded that DM was a CVD equivalent,[6] yet the 2018 ACC/AHA cholesterol guidelines recommend starting patients with DM on moderate- intensity statin for primary prevention instead of high-intensity which is recommended for patients with CVD.[9] This previous study was not very generalizable and is considered outdated; the equivalency of DM and CVD is considered questionable.[7] In addition, the added risk of DM and these additional comorbidities is not considered clinically using the pooled cohort equation, when assessing the risk of CVD in DM patients.[3]

This study supports the consideration of DM + CKD/CVD to be treated as high risk for CVD and, therefore, treated with high risk intervention strategies. The 2018 cholesterol guidelines already acknowledges the increased risk of DM and prior CVD by labeling these patients as high risk requiring the initiation of a high-intensity statin[9] with the addition of additional lipid lowering medications including PCSK9 inhibitors if needed. This study would add the addition of DM and CKD be considered for high intensity lipid lowering therapy despite the pooled cohort equation risk estimate.[3] The 2017 hypertension guidelines have different systolic blood pressure (SBP) treatment targets for patients with DM and CKD. For patients with DM assuming ASCVD ≥10%, the SBP goal <130 mm Hg and diastolic blood pressure <80 mm Hg which is designated for the highest risk groups.[10] For patients with CKD, the guidelines also recommend SBP goal <130/80 mm Hg. Secondary prevention of ASCVD in patients with CVD includes this blood pressure goal as well. This study further validates these blood pressure goals. In addition, this study also validates the use of additional ASCVD risk lowering strategies including HgbA1c management with diabetes medications, smoking cessation, and lifestyle modifications in diabetic patients with CKD and/or CVD for primary and secondary prevention. Based on this data, it is appropriate to treat patients with DM alone based on the PCE.

Our study demonstrates important strengths and some limitations as well. This study was conducted utilizing the ACCORD trial data from a well-established and vetted cohort. The ACCORD trial enrolled a large sample size from multiple sites which provided great power and geographic diversity. An additional strength was the assessment of graded risk of CVD outcomes, which included analyses adjusted for confounders such as HgbA1c, lipid levels, different treatment arms, and use of CVD reducing medications. Although we aimed to adjust for many confounders, these results may still be due to residual confounding. This includes not adjusting for diabetic medications associated with attenuation of CVD risk including metformin,[21] as well as not adjusting for statin intensity. Considering ACCORD was a factorial trial, the actual medication administration adherence and changes in use throughout the trial were not included for adjustment. As well, ACCORD is subject to a selection bias considering the cohort was chosen via a recruitment process. The trial was mainly White males, and complete extrapolation to other groups for generalizability should include further consideration. As well, these results do not extend to patients who met the exclusion criteria of the ACCORD trial such as patients with end-stage renal disease.

In conclusion, our ACCORD trial post hoc analysis shows an incremental graded risk for incident cardiovascular disease and all-cause mortality with the development of chronic kidney disease and/or cardiovascular disease in individuals with type 2 diabetes mellitus. Considering this increased risk, patients with type 2 diabetes mellitus and CKD and/or CVD should be treated as high risk and recommended for aggressive risk factor modification strategies.

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