Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials

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Summary

Background **Guidelines, including the 2017 American College of Cardiology and American Heart Association blood pressure guideline, recommend tighter control of systolic blood pressure in people with type 2 diabetes. However, it is unclear whether intensive lowering of systolic blood pressure increases the incidence of chronic kidney disease in this population. We aimed to compare the effects of intensive systolic blood pressure control on incident chronic kidney disease in people with and without type 2 diabetes.**

Methods **The Systolic Blood Pressure Intervention Trial (SPRINT) tested the effects of a systolic blood pressure goal of less than 120 mm Hg (intensive intervention) versus a goal of less than 140 mm Hg (standard intervention) in people without diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial tested a similar systolic blood pressure intervention in people with type 2 diabetes. Our study is a secondary analysis of limited access datasets from SPRINT and the ACCORD trial obtained from the National Institutes of Health. In participants without chronic kidney disease at baseline (n=4311 in the ACCORD trial; n=6715 in SPRINT), we related systolic blood pressure interventions (intensive *vs* standard) to incident chronic kidney disease (defined as >30% decrease in estimated glomerular filtration rate [eGFR] to <60 mL/min per 1·73 m²). These trials are registered with ClinicalTrials.gov, numbers NCT01206062 (SPRINT) and NCT00000620 (ACCORD trial).**

Findings **The average difference in systolic blood pressure between intensive and standard interventions was 13·9 mm Hg (95% CI 13·4–14·4) in the ACCORD trial and 15·2 mm Hg (14·8–15·6) in SPRINT. At 3 years, the cumulative incidence of chronic kidney disease in the ACCORD trial was 10·0% (95% CI 8·8–11·4) with the intensive intervention and 4·1% (3·3–5·1) with the standard intervention (absolute risk difference 5·9%, 95% CI 4·3–7·5). Corresponding values in SPRINT were 3·5% (95% CI 2·9–4·2) and 1·0% (0·7–1·4; absolute risk difference 2·5%, 95% CI 1·8–3·2). The absolute risk difference was significantly higher in the ACCORD trial than in SPRINT (p=0·0001 for interaction).**

Interpretation **Intensive lowering of systolic blood pressure increased the risk of incident chronic kidney disease in people with and without type 2 diabetes. However, the absolute risk of incident chronic kidney disease was higher in people with type 2 diabetes. Our findings suggest the need for vigilance in monitoring kidney function during intensive antihypertensive drug treatment, particularly in adults with diabetes. Long-term studies are needed to understand the clinical implications of antihypertensive treatment-related reductions in eGFR.**

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Introduction

Hypertension is strongly associated with stroke, heart failure, sudden death, end-stage renal disease, and death from all causes.[1–5] Findings of the Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive lowering of systolic blood pressure (target <120 mm Hg, *vs* standard lowering to <140 mm Hg) reduced the risk of death and major cardiovascular events in people without diabetes, but at high cardiovascular risk.[6,7] However, the SPRINT Research Group also reported that people undergoing intensive lowering had a 3·5-fold higher risk of incident chronic kidney disease,[6,8] defined a priori in the protocol as a reduction in estimated glomerular filtration rate (eGFR) of 30% or higher with a second confirmed eGFR below 60 mL/min per 1·73 m².

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial in people with type 2 diabetes tested the same systolic blood pressure intervention as in SPRINT (intensive *vs* standard lowering) in addition to intensive versus standard glycaemic control (HbA_{1c} <6% [42 mmol/mol] *vs* 7·0–7·9% [53–64 mmol/mol]) in a 2×2 factorial design.[9] Compared with the standard systolic blood pressure intervention, participants who underwent intensive lowering of systolic blood pressure had lower mean eGFR at the final study

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Research in context

Evidence before this study

The 2017 American College of Cardiology and American Heart Association blood pressure guidelines based on systematic review and meta-analysis, recommended a systolic blood pressure goal of less than 130 mm Hg in people with and without diabetes. Findings of the Systolic Blood Pressure Intervention Trial (SPRINT) in individuals without diabetes showed a lower risk of cardiovascular disease events and all-cause mortality but a higher risk of incident chronic kidney disease with intensive lowering of systolic blood pressure (goal <120 mm Hg) compared with standard systolic blood pressure control (goal <140 mm Hg). Whether the magnitude of increased incidence of chronic kidney disease with intensive lowering of systolic blood pressure is higher in people with type 2 diabetes compared with those without diabetes is not known.

Added value of this study

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial in people with type 2 diabetes, a systolic blood pressure intervention was tested similar to that assessed in SPRINT. Despite a clinically similar reduction in systolic blood pressure in both the ACCORD trial and SPRINT, at 3 years, the absolute risk difference between the intensive and standard interventions for incident chronic kidney disease was 5·9% (95% CI 4·3–7·5) in the ACCORD trial and 2·5% (1·8–3·2) in SPRINT (p=0·0001 for interaction).

Implications of all the available evidence

The risk of incident chronic kidney disease was higher in people with type 2 diabetes than in those without this disease with intensive systolic blood pressure lowering. Chronic kidney disease is known to be a risk factor for future cardiovascular events. However, it is unclear whether incident chronic kidney disease due to intensive lowering of systolic blood pressure increases the risk of future cardiovascular events. Further studies are warranted to ascertain whether the higher risk of incident chronic kidney disease with intensive lowering of systolic blood pressure is outweighed by the expected reductions in cardiovascular disease and all-cause mortality in type 2 diabetes in the long term.

visit (74·8 mL/min per 1·73 m² [SD 25·0] *vs* 80·6 mL/min per 1·73 m² [24·8]), with a similar prevalence of a prespecified primary microvascular outcome composite of renal failure and retinopathy (11·4% *vs* 10·9%) and end-stage renal disease (2·5% *vs* 2·4%).[9,10]

To our knowledge, a detailed analysis of the effects of intensive systolic blood pressure lowering in people with type 2 diabetes on incident chronic kidney disease has not been published. Examination of the magnitude of the effect of systolic blood pressure lowering on kidney outcomes in individuals with type 2 diabetes and without chronic kidney disease is highly relevant, because most people with type 2 diabetes do not have chronic kidney disease, particularly in the early years of their condition. Therefore, we aimed to investigate the effects of intensive systolic blood pressure control on incident chronic kidney disease in the ACCORD trial and compared the magnitude of these effects with those noted in SPRINT.

Methods

Participants

For the **ACCORD trial dataset** see https://biolincc.nhlbi.nih.gov/studies/accord/

For the **SPRINT dataset** see https://biolincc.nhlbi.nih.gov/studies/sprint_pop/

See Online for appendix

We did a secondary analysis of limited-access ACCORD trial and SPRINT datasets obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Details of study population, interventions, and study procedures for the ACCORD trial[9,11] and SPRINT[6,12] are published elsewhere.[13,14] In brief, 4733 participants with type 2 diabetes were randomly assigned in the ACCORD trial (2×2 factorial design) to either intensive glycaemic control (HbA_{1c} target <6·0% [42 mmol/mol]) or standard control (HbA_{1c} target 7·0–7·9% [53–64 mmol/mol]) and to either intensive systolic blood pressure treatment (goal <120 mm Hg) or standard treatment (goal <140 mm Hg). In SPRINT, 9361 participants without type 2 diabetes were randomly allocated to a similar systolic blood pressure intervention. Both studies used a similar protocol to achieve the systolic blood pressure intervention.[13,14]

Procedures

The SPRINT protocol prespecified incident chronic kidney disease (based on the four-variable Modification of Diet in Renal Disease [MDRD] study equation to estimate GFR) in participants without chronic kidney disease at their baseline visit (MDRD eGFR ≥60 mL/min per 1·73 m²) as a greater than 30% decrease in MDRD eGFR from baseline value, with an end value of less than 60 mL/min per 1·73 m², confirmed at the next available SPRINT blood draw. In an earlier report,[8] we noted that the effects of intensive systolic blood pressure lowering on incident chronic kidney disease defined either with the MDRD equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation were similar. In our analysis, we used the SPRINT protocol definition of incident chronic kidney disease in both SPRINT and ACCORD trial datasets.

Statistical analysis

Additional details of statistical methods are provided in the appendix. We used intention-to-treat analyses for all randomised comparisons between intensive and standard systolic blood pressure interventions in both SPRINT and the ACCORD trial. We censored follow-up for incident chronic kidney disease at the time of final serum creatinine measurement. We used separate Cox regression analyses in the two studies to provide estimates of hazard ratios (HRs) for the intensive versus standard systolic blood

pressure interventions for incident chronic kidney disease. We compared the effects of the intensive systolic blood pressure interventions, expressed as the relative reduction in hazards between the intensive and standard systolic blood pressure groups between the ACCORD trial and SPRINT, by comparing the difference between the estimated log-transformed HRs in the two studies to the SE of this difference. We tested Schoenfeld residuals and no evidence of non-proportionality was seen.

Kaplan-Meier curves depicted the absolute cumulative risk of incident chronic kidney disease, by intervention, for each study. We estimated absolute risk reductions in these outcomes at 3 years between the intensive and standard interventions with a generalised linear model using an identity link with a robust variance estimate, and pseudo-survival probabilities as the outcome.[15,16] We compared the absolute risk reductions between the ACCORD trial and SPRINT by comparing the difference in the estimated risk reductions in the two studies with the SE of this difference. We repeated the above analyses in subgroups with normal albuminuria (urinary albumin:creatinine ratio [ACR] <3·4 mg/mmol) or elevated albuminuria (ACR ≥3·4 mg/mmol) to examine effect modification by baseline albuminuria.

We examined whether the effects of intensive systolic blood pressure lowering on incident chronic kidney disease were modified by the glycaemia intervention in the ACCORD trial by repeating the above analyses for the two glycaemia interventions in the ACCORD trial. We also investigated the incidence of end-stage renal disease events (as defined in the respective protocols) with intensive systolic blood pressure lowering in SPRINT and ACCORD trial participants without chronic kidney disease.

We did several sensitivity analyses for incident chronic kidney disease. First, for the ACCORD trial, we defined incident chronic kidney disease as a 40% decline in eGFR to less than 60 mL/min per 1·73 m², with confirmation. Second, for the ACCORD trial, because serum creatinine was measured only annually after month 12, we assumed participants with a 30% decrease in eGFR to a value less than 60 mL/min per 1·73 m²—but missing a confirmatory value because of death or censoring before the next creatinine measurement—had incident chronic kidney disease. Third, for the ACCORD trial, we defined incident chronic kidney disease as a 30% decline in eGFR estimated with the CKD-EPI equation to less than 60 mL/min per 1·73 m², with confirmation. Fourth, for SPRINT, we did additional Cox regressions excluding participants with a baseline fasting glucose greater than 6·9 mmol/L. Fifth, for both the ACCORD trial and SPRINT, we examined the cumulative incidence of incident chronic kidney disease (defined as a 30% decline in eGFR to <60 mL/min per 1·73 m², with confirmation) in a competing risk framework, with death treated as a competing risk.[17] Finally, for both the ACCORD trial and SPRINT, we examined the absolute risk differences in the incidence of chronic kidney disease with intensive systolic blood pressure lowering stratified by the level of baseline eGFR (≥90 mL/min per 1·73 m², 80–89 mL/min per 1·73 m², 70–79 mL/min per 1·73 m², and 60–69 mL/min per 1·73 m²).

	ACCORD trial		SPRINT	
	Standard (n=2162)	Intensive (n=2149)	Standard (n=3367)	Intensive (n=3348)
Age (years)	61·7 (57·4–66·7)	61·4 (57·4–66·4)	65 (60–73)	65 (59–73)
Female sex	1007 (47%)	992 (46%)	1127 (33%)	1147 (34%)
White ethnic origin	1224 (57%)	1280 (60%)	1808 (54%)	1813 (54%)
Never smoked	938 (43%)	925 (43%)	1471 (44%)	1444 (43%)
Clinical atherosclerotic disease*	707 (33%)	716 (33%)	503 (15%)	503 (15%)
Antihypertensive agents (n per patient)	1·6 (1·1)	1·7 (1·1)	1·7 (1·0)	1·7 (1·0)
Systolic blood pressure (mm Hg)	139 (15)	139 (16)	140 (15)	140 (16)
Diastolic blood pressure (mm Hg)	76 (10)	76 (10)	79 (12)	79 (12)
Duration of diabetes (years)	11 (8)	11 (8)	N/A	N/A
HbA_{1c} (%)	8·3 (1·0)	8·4 (1·0)	N/R	N/R
HbA_{1c} (mmol/mol)	67 (11)	68 (11)	N/R	N/R
Fasting plasma glucose (mmol/L)	9·6 (3·0)	9·8 (3·0)	5·5 (0·8)†	5·5 (0·8)†
Body-mass index (kg/m²)	32·1 (5·3)	32·1 (5·6)	30·0 (5·7)	30·1 (5·8)
eGFR‡ (mL/min per 1·73 m²)	94·0 (20·8)	94·2 (20·7)	81·1 (15·5)	81·3 (15·5)
Urinary ACR (mg/mmol)	1·6 (0·8–5·1)	1·7 (0·8–5·0)	1·0 (0·6–1·9)	1·0 (0·6–1·9)

Data are number of patients (%), mean (SD), or median (IQR). ACCORD=Action to Control Cardiovascular Risk in Diabetes. ACR=albumin:creatinine ratio. eGFR=estimated glomerular filtration rate. MDRD=Modification of Diet in Renal Disease. N/A=not applicable. N/R=not reported. SPRINT=Systolic Blood Pressure Intervention Trial. *Defined in the ACCORD trial as one or more of myocardial infarction, stroke, angina, coronary-artery bypass graft, percutaneous transluminal coronary intervention, or other revascularisation procedure. Defined in SPRINT as one or more of myocardial infarction, acute coronary syndrome, coronary revascularisation, carotid revascularisation, peripheral arterial disease with revascularisation, greater than 50% stenosis of coronary, carotid, or lower extremity artery, or abdominal aortic aneurysm 5 mm or larger. †113 participants assigned the standard intervention and 112 allocated the intensive intervention had a fasting plasma glucose greater than 6·9 mmol/L at baseline. ‡Estimated by four-variable MDRD equation.

Table: **Baseline characteristics by study and blood pressure intervention in participants with baseline eGFR 60 mL/min per 1·73 m² or higher**

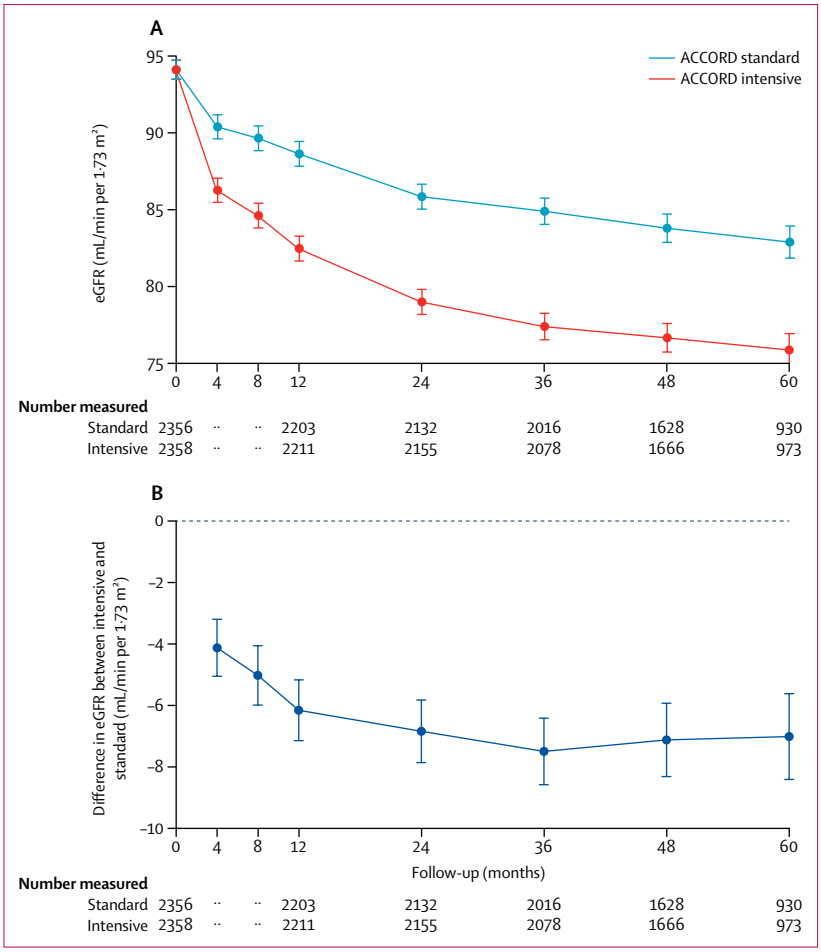

Figure 1: **(A) Follow-up eGFR in ACCORD trial participants with baseline eGFR of 60 mL/min per 1·73 m² or higher and (B) difference in eGFR between intensive and standard interventions**
Datapoints represent the mean and errors bars denote the 95% CI. Data were obtained using maximum likelihood estimation under a longitudinal model with an unstructured covariance matrix and common baseline means in each treatment group. eGFR calculated by the four-variable MDRD equation. ACCORD=Action to Control Cardiovascular Risk in Diabetes. eGFR=estimated glomerular filtration rate. MDRD=Modification of Diet in Renal Disease.

The ACCORD trial and SPRINT are registered with ClinicalTrials.gov, numbers NCT00000620 and NCT01206062, respectively.

Role of the funding source

SPRINT and ACCORD trial data were obtained from BioLINCC via the funder. The funder had no role in study design, data analysis, data interpretation, or writing of the report. SB, TG, RB, GW, and GS had access to data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The current analysis included 4311 individuals from the ACCORD trial and 6715 people from SPRINT; all participants had a baseline eGFR of 60 mL/min per 1·73 m² or higher (ie, they did not have chronic kidney disease; appendix). Baseline demographic, clinical, and laboratory characteristics were similar for people allocated the intensive and standard systolic blood pressure interventions within the ACCORD trial and SPRINT (table). However, compared with the SPRINT population who did not have diabetes, the ACCORD trial population was younger, more likely to be female, and had higher BMI, eGFR, and albuminuria (appendix). Baseline blood pressure and the number of antihypertensive drugs taken per person were similar in both studies.

The intensive intervention lowered systolic blood pressure effectively in both studies (appendix), but the average difference between the intensive and standard treatments was lower in the ACCORD trial than in SPRINT (mean 13·9 mm Hg, 95% CI 13·4–14·4 *vs* 15·2 mm Hg, 14·8–15·6; p=0·0001; appendix). The mean number of drugs used for the intensive systolic blood pressure intervention in the ACCORD trial was 2·8 (SD 1·5), compared with 1·9 (1·2) drugs with the standard treatment (p<0·0001); in SPRINT, these numbers were 2·8 (1·1) and 1·8 (1·1), respectively (p<0·0001). The proportions of participants who either were lost to follow-up or withdrew consent were similar in the intensive and standard intervention groups in the ACCORD trial (5·2% *vs* 4·9%; p=0·57) and in SPRINT (5·7% *vs* 5·5%; p=0·64; appendix).

An early steep decline in eGFR was noted during the first 12 months with both the standard and intensive interventions in the ACCORD trial (figure 1), but the decline was more pronounced with the intensive intervention (first 12 months, mean change –11·6 mL/min per 1·73 m², 95% CI –12·4 to –10·9, *vs* –5·5 mL/min per 1·73 m², –6·5 to –4·7; p<0·0001). Over the 2-year interval between months 12 and 36, the mean change in eGFR was –5·1 mL/min per 1·73 m² (95% CI –5·8 to –4·4) with the intensive intervention versus –3·7 mL/min per 1·73 m² (–4·4 to –3·0) with the standard intervention (p=0·009). After 36 months, the mean change in eGFR over the subsequent 2-year interval to month 60 did not differ between intensive and standard treatments (–1·5 mL/min per 1·73 m², 95% CI –2·4 to –0·7, *vs* –2·0 mL/min per 1·73 m², –2·8 to –1·2; p=0·43). Similar data for eGFR were not available in the SPRINT limited-access public dataset obtained from BioLINCC.

Incident chronic kidney disease events were lower in both intervention groups in SPRINT than in the ACCORD trial. In the ACCORD trial, 333 (15%) of 2149 participants assigned the intensive systolic blood pressure intervention and 160 (7%) of 2162 participants allocated standard treatment had an incident chronic kidney disease event over the duration of the study (mean follow-up 4·6 years [SD 1·4]). In SPRINT, 127 (4%) of 3348 participants assigned the intensive intervention and 37 (1%) of 3367 allocated standard treatment had an incident chronic kidney disease event (mean follow-up 3·1 years [SD 0·9]).

The cumulative incidence of chronic kidney disease was consistently higher in ACCORD trial participants throughout the follow-up period with both systolic blood pressure interventions compared with individuals in SPRINT (figure 2). At 3 years, the cumulative incidence of chronic kidney disease in ACCORD trial participants assigned the intensive and standard systolic blood pressure interventions was 10·0% (95% CI 8·8–11·4) and 4·1% (3·3–5·1), respectively (figure 3A), with an absolute risk difference of 5·9% (95% CI 4·3–7·5; figure 3B). In SPRINT participants, the 3-year incidence of chronic kidney disease was 3·5% (95% CI 2·9–4·2) with the intensive strategy and 1·0% (0·7–1·4) with standard systolic blood pressure lowering (figure 3A), with an absolute risk difference of 2·5% (95% CI 1·8–3·2; figure 3B). The difference between the ACCORD trial and SPRINT in absolute risk difference was significant (interaction p=0·0001).

The incidence of chronic kidney disease for the entire duration of the ACCORD blood pressure trial was 3·69 (95% CI 3·31–4·11) per 100 person-years of follow-up for the intensive systolic blood pressure intervention and 1·62 (1·39–1·90) per 100 person-years of follow-up for the standard strategy; respective values in SPRINT were 1·21 (1·02–1·44) per 100 person-years of follow-up and 0·35 (0·25–0·48) per 100 person-years of follow-up (figure 3C). Although the incidence of chronic kidney disease was much higher in the ACCORD trial than in SPRINT, the risk for incident chronic kidney disease was more pronounced in SPRINT (HR 3·49, 95% CI 2·42–5·03) than in the ACCORD trial (2·29, 1·89–2·76; p=0·037 for interaction; figure 3D).

The above patterns were even stronger in participants with a baseline urinary ACR of 3·4 mg/mmol or higher. The incidence of chronic kidney disease in SPRINT participants with urinary ACR of less than 3·4 mg/mmol was 2·9% (95% CI 2·3–3·6) in those assigned the intensive systolic blood pressure intervention and 0·8% (0·5–1·2) in those allocated the standard lowering strategy (figure 4A), with an absolute risk difference of 2·1 (95% CI 1·4–2·9; figure 4B). By contrast, the incidence of chronic kidney disease was much higher in individuals in the ACCORD trial with urinary ACR of 3·4 mg/mmol or higher (13·6% [95% CI 11·1–16·6] and 6·6% [4·9–8·9], respectively; absolute risk difference 7·0, 95% CI 3·7–10·4; p=0·005 for interaction). In SPRINT participants with urinary ACR less than 3·4 mg/mmol, the risk of chronic kidney disease for the entire duration of the trial (figure 4C) when comparing the intensive systolic blood pressure intervention with the standard treatment was much higher (HR 3·65, 95% CI 2·34–5·68) compared with the risk in ACCORD trial participants with urinary ACR of 3·4 mg/mmol or higher (1·90, 1·44–2·51; interaction p=0·015; figure 4D).

In ACCORD trial participants who did not have chronic kidney disease at baseline, the intensive systolic blood pressure intervention resulted in similar increases in the risk of incident chronic kidney disease with intensive and standard glycaemic control (appendix). No incident end-stage renal disease events were reported in participants in SPRINT who did not have chronic kidney disease. In ACCORD trial participants without chronic kidney disease, 49 (2%) of 2162 assigned the standard treatment and 53 (2%) of 2149 allocated intensive systolic blood pressure control developed an ACCORD protocol-defined renal failure outcome (end-stage renal disease or serum creatinine ≥290 μmol/L).

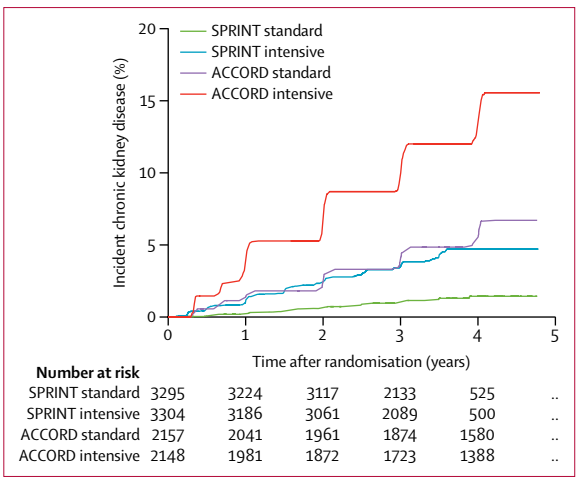

Figure 2: **Cumulative incidence of chronic kidney disease with intensive and standard systolic blood pressure interventions in SPRINT and the ACCORD trial**
Data obtained from participants with baseline eGFR of 60 mL/min per 1·73 m² or higher. ACCORD=Action to Control Cardiovascular Risk in Diabetes. eGFR=estimated glomerular filtration rate. SPRINT=Systolic Blood Pressure Intervention Trial.

Results of sensitivity analyses using alternative definitions for incident chronic kidney disease in the ACCORD trial, and excluding participants with baseline fasting blood sugar greater than 6·9 mmol/L in SPRINT (appendix), were similar to those of the main analyses. When all-cause death was considered as a competing risk for incident chronic kidney disease, the incidence of chronic kidney disease remained highest in ACCORD trial participants assigned the intensive systolic blood pressure intervention and lowest in SPRINT participants allocated standard treatment (appendix). In analyses stratified by baseline eGFR, compared with standard systolic blood pressure control, participants assigned the intensive intervention had a greater incidence of chronic kidney disease in both SPRINT and the ACCORD trial, and absolute risk differences were higher in the ACCORD trial (appendix).

Discussion

Our analyses show that intensive systolic blood pressure lowering increased the risk of incident chronic kidney disease in people both with and without type 2 diabetes. Furthermore, for a clinically similar level of systolic

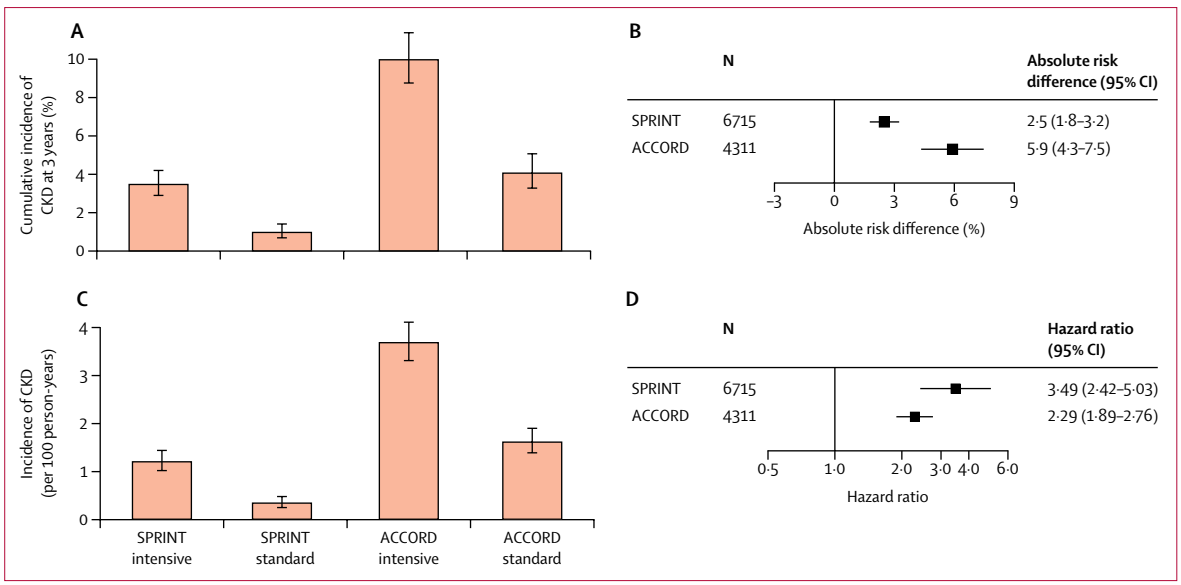

Figure 3: **Incidence of CKD with intensive and standard systolic blood pressure interventions in SPRINT and the ACCORD trial**
(A) Cumulative incidence of CKD at 3 years with intensive and standard systolic blood pressure interventions in SPRINT and the ACCORD trial. Bars represent mean and error bars 95% CI. (B) Absolute risk difference in cumulative incidence at 3 years between intensive and standard interventions in SPRINT and the ACCORD trial. (C) Incidence of CKD per 100 person-years of follow-up with intensive and standard systolic blood pressure interventions for the entire duration of SPRINT and the ACCORD trial. Bars represent mean and error bars 95% CI. (D) Risk of incident CKD between intensive and standard interventions for the entire duration of SPRINT and the ACCORD trial. ACCORD=Action to Control Cardiovascular Risk in Diabetes. CKD=chronic kidney disease. SPRINT=Systolic Blood Pressure Intervention Trial.

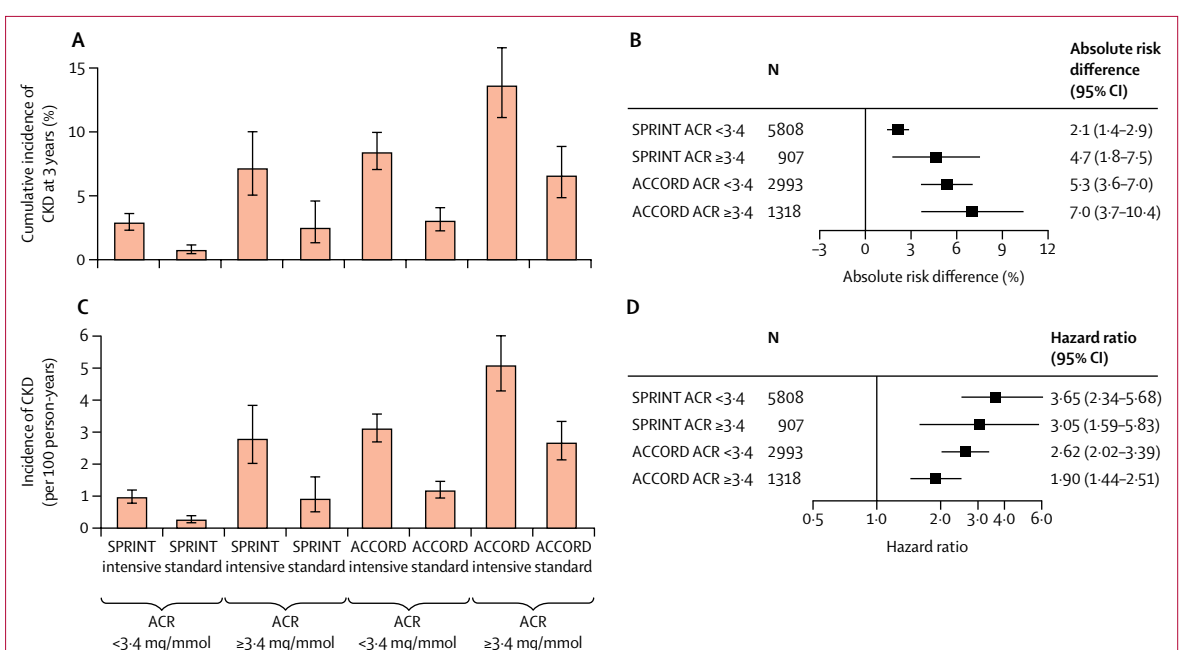

Figure 4: **Incidence of CKD with intensive and standard systolic blood pressure interventions in SPRINT and the ACCORD trial, according to ACR less than 3·4 mg/mmol or 3·4 mg/mmol or higher**
(A) Cumulative incidence of CKD at 3 years with intensive and standard systolic blood pressure interventions in SPRINT and ACCORD trial participants with urinary ACR less than 3·4 mg/mmol or 3·4 mg/mmol or higher. (B) Absolute risk difference in cumulative incidence at 3 years between intensive and standard interventions in SPRINT and ACCORD trial participants with urinary ACR less than 3·4 mg/mmol or 3·4 mg/mmol or higher. (C) Incidence of CKD per 100 person-years of follow-up with intensive and standard systolic blood pressure interventions for the entire duration of SPRINT and the ACCORD trial in participants with urinary ACR less than 3·4 mg/mmol or 3·4 mg/mmol or higher. (D) Risk of incident CKD between intensive and standard interventions for the entire duration of SPRINT and the ACCORD trial in participants with urinary ACR less than 3·4 mg/mmol or 3·4 mg/mmol or higher. ACCORD=Action to Control Cardiovascular Risk in Diabetes. ACR=albumin:creatinine ratio. CKD=chronic kidney disease. SPRINT=Systolic Blood Pressure Intervention Trial.

blood pressure lowering, the absolute risk increase for incident chronic kidney disease was higher in ACCORD trial participants with type 2 diabetes than in SPRINT participants without type 2 diabetes.

Incident chronic kidney disease was one of the prespecified secondary outcomes in SPRINT, but not in the ACCORD trial. However in people with type 2 diabetes, chronic kidney disease—as defined by lower eGFR—is a very strong risk factor for cardiovascular disease events and death.[18] Furthermore, chronic kidney disease accounts predominantly for the excess mortality seen in people with type 2 diabetes.[19] Hence, it is of public health importance to understand the effect of lowering systolic blood pressure on incident chronic kidney disease in individuals with type 2 diabetes.

The intensive systolic blood pressure intervention in both studies also led to a larger early decline in eGFR over the first 12 months compared with the standard intervention (mean difference –6·1 mL/min per 1·73 m² in the ACCORD trial; reported difference –4·4 mL/min per 1·73 m² in SPRINT).[8] This finding suggests that the effect of a given change in systolic blood pressure on eGFR decline was about 50% greater in ACCORD trial participants with type 2 diabetes than in SPRINT participants without diabetes.

In addition to differences in early eGFR decline between intensive and standard systolic blood pressure interventions, the early decline in eGFR was notably steeper in the ACCORD trial compared with SPRINT, with both the intensive systolic blood pressure intervention (mean change –11·6 mL/min per 1·73 m² *vs* –4·8 mL/min per 1·73 m²) and the standard treatment (–5·5 mL/min per 1·73 m² *vs* –0·4 mL/min per 1·73 m²). The cause of the faster early decline in the ACCORD trial compared with SPRINT is unclear.

Nonetheless, results from our current analysis of two randomised systolic blood pressure goals in two large studies suggest caution is warranted in extrapolating SPRINT findings to people with type 2 diabetes. Although the cardiovascular disease and all-cause mortality benefits in SPRINT seemed to outweigh the potential effects of the intervention on incident chronic kidney disease,[8] the ACCORD trial intervention substantially increased the risk of incident chronic kidney disease.

In a previous ACCORD trial analysis,[9] intensive systolic blood pressure lowering resulted in a non-significant decrease of cardiovascular disease events and a non-significant increase in all-cause mortality. Perkovic and Rodgers[20] suggested that the ACCORD trial was underpowered to detect true differences in cardiovascular disease outcomes. In a participant-level pooled meta-analysis of SPRINT and ACCORD trial participants, intensive systolic blood pressure lowering decreased the risk of cardiovascular disease events in the combined cohort.[21] In another post-hoc analysis of the ACCORD trial,[22] SPRINT selection criteria were applied to the standard glycaemia arm of the ACCORD trial, and intensive systolic blood pressure lowering was associated with lower risk of cardiovascular disease outcomes. These study findings might support the 2017 practice guideline recommendation of a systolic blood pressure goal of less than 130 mm Hg in all people with type 2 diabetes[23] or in individuals with type 2 diabetes at high risk for cardiovascular disease.[24]

Apart from the inclusion or not of people with type 2 diabetes, the ACCORD blood pressure trial and SPRINT have other different inclusion and exclusion criteria. The higher baseline eGFR, higher BMI, and higher ACR in the ACCORD trial compared with SPRINT reflect conditions associated with type 2 diabetes, with higher than normal eGFR probably due to hyperfiltration in some ACCORD trial participants.[25] Relative to SPRINT, the higher baseline eGFR in the ACCORD trial obligated a larger absolute decline to meet the eGFR of less than 60 mL/min per 1·73 m² threshold, which might have led to underestimation of incident chronic kidney disease with intensive systolic blood pressure lowering in the ACCORD trial.

A methodological observation in our study is that although intensive systolic blood pressure lowering resulted in a much higher absolute risk of incident chronic kidney disease in individuals with type 2 diabetes (ACCORD trial) than in those without this disorder (SPRINT), the relative risk (HR) was significantly higher in people without diabetes. This finding is even more pronounced when comparing the effects of intensive systolic blood pressure lowering on incident chronic kidney disease in people without diabetes and with low urinary ACR versus individuals with type 2 diabetes and urinary ACR of 3·4 mg/mmol or higher. Relative risks are much more pronounced in populations at lower risk of events than in populations at higher risk of events.[26] Thus, the lower HR for incident chronic kidney disease with intensive systolic blood pressure lowering in individuals with type 2 diabetes and albuminuria compared with people without diabetes and albuminuria should not be interpreted as meaning intensive systolic blood pressure lowering confers a lower risk of incident chronic kidney disease in people with type 2 diabetes and albuminuria, rather as a reflection of the higher baseline hazard of incident chronic kidney disease in this population.

The strengths of our analysis include use of data from two large randomised controlled trials that investigated the effect of targeting the same intensive systolic blood pressure goal in people with and without type 2 diabetes. Although randomisation was not stratified by the presence of chronic kidney disease at baseline in either study, the subgroup without chronic kidney disease represents more than 70% of the SPRINT cohort and more than 90% of the ACCORD trial cohort. In view of the large size of the subgroup without chronic kidney disease, and since baseline characteristics between individuals assigned the intensive and standard systolic blood pressure interventions within the ACCORD trial

and SPRINT are similar, comparisons between the intensive and standard interventions can be inferred to represent the randomised controlled trial designs of each study.

The limitations of our analysis include the relatively short duration of follow-up in each study. The long-term implications of increased risk of incident chronic kidney disease with intensive systolic blood pressure control in people with and without diabetes are unclear. Longer term follow-up is needed to ascertain whether chronic kidney disease induced by intensive systolic blood pressure lowering has the same downstream risk of chronic kidney disease induced by, or associated with, other conditions.

In conclusion, intensive systolic blood pressure lowering resulted in a high risk of incident chronic kidney disease in people with and without type 2 diabetes. However, for a clinically similar level of intensive systolic blood pressure lowering, the risk of incident chronic kidney disease seems much higher in individuals with type 2 diabetes. The early and steeper decline in eGFR with intensive systolic blood pressure lowering suggests a greater susceptibility to haemodynamic effects in type 2 diabetes. Further studies are warranted to ascertain the long-term effects of incident chronic kidney disease with intensive systolic blood pressure lowering in people with and without type 2 diabetes.

Contributors

SB, TG, WCC, AKC, PKW, and GMC contributed to the idea for and design of the study. TG, RB, GW, and GS contributed to data analysis. SB, TG, RB, GW, PKW, PLK, and GMC contributed to writing of the report. SB, WCC, JHI, MC, HK, AKC, and GMC contributed to patients' recruitment or provided study materials. TG, RB, GW, and GS contributed to the statistical analysis. All authors contributed to data interpretation. critical revision of the report, and final approval. SB, TG, WCC, JHI, MC, HK, AKC, and GMC obtained funding. SB and TG provided administrative, technical, or logistical support. SB, TG, and GMC take responsibility for all aspects of the report and all authors take responsibility for their contributions.

Declaration of interests

GMC reports grants from Amgen; personal fees for trial steering committee membership from Akebia, AMAG, Amgen, Ardelyx, AstraZeneca, Gilead, and Keryx; has stock options with Durect, Ardelyx, Outset Medical, Physiowave, and Puracath; and reports personal fees for data safety monitoring board membership from Bayer, ReCor, Otsuka, and Bristol-Myers Squibb, outside the submitted work. AKC reports grants from the National Institutes of Health (as a SPRINT investigator), during the conduct of the study. SB reports grants from Bayer and AbbVie; and consultation fees from Raeta, outside the submitted work. TG reports personal fees from Pfizer and Janssen, outside the submitted work. WCC reports grants from the National Heart, Lung, and Blood Institute, during the conduct of the study; and uncompensated consulting for Novartis and Takeda related to treatment of hypertension and diabetes. All other authors declare no competing interests.

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