Modelling in hypertension

From basic physiology to advanced epidemiology

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Chapter 4

Creatinine rise during blood pressure therapy and the risk of adverse clinical outcomes in patients with type 2 diabetes mellitus

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Abstract

Lowering blood pressure may affect renal function. Current guidelines state that reducing antihypertensive therapy should be considered in patients with a 30% serum creatinine increase after initiation of antihypertensive therapy. We examined the association between a serum creatinine increase and adverse clinical outcomes in the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure), where patients with type 2 diabetes mellitus were randomised to intensive (target systolic blood pressure <120 mmHg) and standard antihypertensive (<140 mmHg) treatment. The primary outcome was a combined end point consisting of all-cause mortality, major cardiovascular events, and renal failure. Patients were stratified into 3 groups according to serum creatinine increase between baseline and 4 months (<10%, 10%–30%, >30%). A total of 4733 patients, aged 62.2 years, 52% men with a mean estimated glomerular filtration rate 81.5 mL/ min per 1.73 m^2 were included. Follow-up was available for 4446 patients, 2231 were randomised to intensive and 2215 to standard therapy. Kaplan-Meier analysis showed no association between a serum creatinine increase and the composite end point in the intensive (p=0.20) and the standard treatment group (p=0.17). After adjusting for possible confounders, a >30% serum creatinine increase was associated with a higher risk of clinical adverse outcomes in both treatment groups, but to a similar extent. These data suggest that a >30% serum creatinine increase that coincides with lower blood pressure values should not directly lead to a reduction in antihypertensive medication in patients with type 2 diabetes mellitus.

Clinical trial registration Unique identifier: NCT00000620.
http://www.clinicaltrials.gov.

Introduction

Diabetic nephropathy is a highly frequent complication in patients with diabetes mellitus, an independent predictor of cardiovascular mortality and morbidity,[1,2] and the leading cause of renal failure in most developed countries.[3] Blood pressure (BP)-lowering treatment is effective in reducing the risk of diabetic nephropathy and for the prevention of renal function decline.[4,5] However, intensive BP-lowering treatment is also associated with a decrease in renal function. The initial rise in serum creatinine after BP-lowering treatment may be interpreted as reversal of hyperfiltration associated with uncontrolled hypertension. In this situation, the loss of renal function after initiation of therapy reflects the haemodynamic effect of a lower perfusion pressure on glomerular filtration rate, but not a loss of functional nephrons.[6] An important concern, however, is that the increase in creatinine is caused by ischemic nephropathy as a result of inadequate renal perfusion. Therefore, current guidelines recommend to monitor renal function after initiation of therapy. A serum creatinine increase up to 20% or 30% is generally accepted,[7,8,9] but it is recommended that withdrawal of therapy should be considered if creatinine levels increase by >30%.[10] This is supported by evidence from a recent cohort study in a primary care population showing that even a small creatinine increase by 10%–20% after starting an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor is associated with an increased incidence of adverse cardiorenal outcomes during 10-year follow-up.[11]

Patients with type 2 diabetes mellitus are potentially prone to the development of renal hypoperfusion because of the higher frequency of micro- and macrovascular diseases and an impaired renal autoregulation.[12,13,14] This may pose patients with diabetes mellitus and an increase in serum creatinine at increased risk for adverse clinical outcomes during intensive BP-lowering treatment. The ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) was a prospective randomised control trial of intensive, a target systolic BP (SBP) <120 mmHg, versus standard (target SBP <140 mmHg) BP-lowering therapy in patients with type 2 diabetes mellitus at high risk for cardiovascular events. Because of its design using different BP-lowering thresholds, the ACCORD study provides a unique opportunity to assess whether the rise in creatinine during BP-lowering treatment is a sign of pre-existing renal damage or points toward ischemic nephropathy caused by hypoperfusion. In the present post hoc analysis, we assessed whether the serum creatinine increase during intensive BP-lowering treatment is associated with more adverse clinical outcomes compared with standard therapy.

Methods

Study design and patient eligibility

All data used for this study has been made publicly available at the Biolincc repository and can be requested at https://biolincc.nhlbi.nih.gov/studies/accord/. The ACCORD trial was a randomised control trial conducted from January 2001 to June 2009 at 77 clinical sites in the United States and Canada, which enrolled 10 251 high-risk patients with type 2 diabetes mellitus, who were randomised to either intensive or standard glycaemia control. Inclusion ended in 2005. Using a 2 by 2 factorial design a subgroup of 4733 participants was assigned to intensive or standard BP-lowering treatment in the ACCORD-BP trial. ACCORD-BP was designed to have 94% power to detect a 20% reduction in the rate of cardiovascular events in the intensive treatment group. The design, rationale, main results, and safety outcomes of this study have been published elsewhere.[15,16] Participants were eligible if they had a diagnosis of type 2 diabetes mellitus, had glycated haemoglobin level of 7.5% or more, and were older than 40 years with cardiovascular disease or older than 55 years with anatomic evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for cardiovascular disease (dyslipidaemia, hypertension, smoking, or obesity). Patients with a serum creatinine level of > 132.6 μmol/L were excluded. For inclusion in the BP trial, participants were required to have an SBP between 130 and 180 mmHg with 3 or fewer antihypertensive medications, and a 24-hour protein excretion rate of <1.0 g. This trial was sponsored by the National Heart, Lung and Blood Institute, and the protocol was approved by the institutional review board of each participating centre and by an independent review committee of the National Heart, Lung and Blood Institute. The use of the data set for the present analysis was approved by the institutional review board of Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands, and the data were obtained via the National Heart, Lung and Blood Institute.

Trial intervention

Participants were randomly assigned to an SBP target of <120 mmHg (intensive treatment group) and an SBP of <140 mmHg (standard treatment group). The allocation was performed centrally using permuted blocks through the study's website. Participants and physicians were not blinded to treatment strategy. In the intensive treatment group, visits were scheduled once a month for the first 4 months and every 2 months thereafter. In the standard treatment group, visits were in month 1, month 4, and every 4 months thereafter. At each visit, BP mediation could be titrated or switched to reach the target SBP according to the protocol. No specific medication was required and treatment strategies of normal

clinical practice could be applied. At each 4-month visit information about study outcome and adverse events were obtained. During the first year, at 4 months intervals, serum creatinine was determined, after this information was obtained on yearly basis. The planned average follow-up was 5.6 years.

Outcomes

For the present analysis, we used the occurrence of adverse clinical outcomes, defined as the composite of the first major cardiovascular event, renal failure, or death because of any cause as primary outcome measure. After the definitions used in ACCORD, a major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke or cardiovascular death. Renal failure was defined as renal transplantation, initiation of dialysis, or a rise in serum creatinine 291.7 μmol/L in the absence of an acute reversible cause. Secondary outcomes were the individual components of the primary outcome and the original primary outcome, a major cardiovascular event. All clinical end points were adjudicated by a committee blinded to the treatment assignment.

Statistical analysis

After previous publications,[17,18] we chose to stratify patients into 3 groups according to their initial increase in serum creatinine (<10%, 10%–30%, >30%). As initial increase, we used the difference between serum creatinine at baseline and 4 months after randomisation. Kaplan-Meier analysis was used to investigate the relation between serum creatinine increase and the primary end point. For the primary and secondary outcomes, Cox-regression analysis was performed. In the crude model, correction was performed for age and sex. An additional term for baseline renal function and baseline SBP was added to the model. Renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, taking ethnicity into account.[19] Use of medication was determined from the ACCORD-BP trial medication logbook. For the medication and the difference in SBP between baseline and 4 months, the value at 3 or 6 months was used if the value at 4 months was missing. Baseline characteristics were compared between the different strata and treatments groups using the appropriate tests (χ^2, ANOVA, Kruskal-Wallis). All statistical analyses were conducted with R version 3.4.3 using the Survival version 2.41–3 and Tableone version 0.9.2 packages (Vienna, Austria). The figures were created using Graphpad Prism, version 7 (California).

Table 1: Baseline characteristics

Characteristics	Intensive			Standard			*p*
	<10%	10–30%	>30%	<10%	10–30%	>30%	
Number of subjects	1231	741	259	1478	615	122	
Age, y	62.6 (6.6)	62.8 (6.5)	62.8 (6.5)	62.7 (6.7)	63.0 (6.8)	61.7 (7.0)	0.41
Female	588 (47.8)	328 (44.3)	138 (53.3)	680 (46.0)	294 (47.8)	66 (54.1)	0.08
Race or ethnic group							0.36
Black	298 (24.2)	166 (22.4)	56 (21.6)	331 (22.4)	159 (25.9)	30 (24.6)	
Hispanic	79 (6.4)	43 (5.8)	11 (4.2)	101 (6.8)	46 (7.5)	6 (4.9)	
Other	120 (9.7)	78 (10.5)	26 (10.0)	175 (11.8)	49 (8.0)	15 (12.3)	
White	734 (59.6)	454 (61.3)	166 (64.1)	871 (58.9)	361 (58.7)	71 (58.2)	
SBP, mmHg	137.0 (15.4)	140.5 (15.9)	143.8 (18.0)	137.8 (15.0)	141.4 (15.4)	146.2 (16.9)	<0.001
DBP, mmHg	75.2 (10.2)	76.7 (11.0)	77.5 (10.4)	75.6 (10.2)	76.4 (10.0)	77.8 (11.4)	0.001
History of CV disease	399 (32.4)	257 (34.7)	89 (34.4)	479 (32.4)	207 (33.7)	51 (41.8)	0.33
Framingham 10–y risk of CV death	30.8 [20.8, 43.2]	33.2 [23.1, 46.8]	34.2 [24.9, 46.9]	29.8 [20.9, 42.4]	32.0 [21.7, 45.6]	33.7 [22.8, 44.6]	0.001
Smoker	163 (13.2)	105 (14.2)	27 (10.4)	194 (13.1)	80 (13)	17 (13.9)	0.79
Body mass index, kg/m^2	32.2 (5.6)	32.3 (5.6)	32.6 (5.5)	32.0 (5.4)	32.2 (5.2)	33.1 (5.5)	0.24
Serum creatinine, mmol/L	84.0 (21.2)	74.3 (17.7)	71.6 (22.1)	83.1 (21.2)	73.4 (16.8)	69.8 (21.2)	<0.001
eGFR, mL/ min per 1.73 m^2	77.8 (18.0)	86.0 (15.4)	86.9 (18.9)	78.7 (17.5)	86.4 (15.0)	88.9 (18.1)	<0.001
Ratio of urinary albumin (mg) to creat (mmol)	1.47 [0.79, 4.18]	1.81 [0.85, 5.54]	2.37 [1.13, 9.49]	1.58 [0.79, 4.92]	1.81 [0.79, 5.71]	2.26 [1.05, 9.46]	<0.001
Total cholesterol, mmol/L	5.01 (1.13)†	4.98 (1.17)	5.23 (1.33)	4.93 (1.07)†	4.91 (1.16)	5.24 (1.53)	<0.001
Total HDL, mmol/L, mean (SD)	1.20 (0.34)†	1.20 (0.34)	1.16 (0.35)	1.22 (0.37)†	1.18 (0.35)	1.12 (0.33)	0.01
Aspirin use	674 (55.0)	395 (53.4)	136 (52.7)	780 (53.0)	308 (50.7)	58 (47.5)	0.45
Statin use	763 (62.2)†	496 (67.0)	168 (65.1)	983 (66.8)†	395 (65.0)	80 (65.6)	0.19
ACEi/ARB use at 4 months	1132 (92.0)†	699 (94.3)†	245 (94.6)	1159 (78.5)†	494 (80.5)†	109 (90.1)	<0.001
ΔSBP baseline and 4 months, mmHg	-12.7 (17.1)†	-18.0 (17.8)†	-25.4 (18.8)†	-4.1 (16.8)†	-8.6 (16.5)†	-16.3 (20.9)†	<0.001

Data are presented as mean (SD), median [IQR] or n (%). ACE angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV cardiovascular; DBP, diastolic BP, eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; y, years; mo, months; SBP, systolic BP, y, years. *P*-values indicate comparison between strata based on treatment arm and creatinine increase. †Significantly ($p<0.05$) different between intensive and standard treatment arm for a specific creatinine increase stratum.

Results

Baseline characteristics

A flowchart of participants included in the present analysis is presented in Figure 1. Of the 2362 participants randomised to intensive therapy, 2231 (94.5%) were included in the present analysis. Of the 2371 participants randomised to standard therapy, 2215 (93.4%) were included. Exclusion of participants was because of missing creatinine data. Baseline characteristics stratified according to treatment group and creatinine increase are given in Table 1. The >30% stratum (n=259; 11.6%) in the intensive treatment group was more than twice as high compared with the standard treatment group (n=122; 5.5%). Systolic BP decreased by 15.9 mmHg in the intensive treatment group and by 6.0 mmHg in the standard treatment group between baseline and 4 months. Compared with subjects without a significant increase in serum creatinine, subjects with a >30% increase had a more profound decrease in systolic BP.

In patients with a <10% increase in serum creatinine, SBP decreased by 12.7 mmHg in the intensive and 4.1 mmHg in the standard treatment group, whereas in those with a >30% increase in creatinine SBP decreased by 25.4 and 16.3 mmHg, respectively. Subjects with a >30% increase had a higher SBP and diastolic BP at baseline, had a higher estimated glomerular filtration rate (eGFR), a higher Framingham-risk score and higher urinary-to-albumin ratio. In the intensive treatment group, more patients received an ACE inhibitor or ARB after 4 months than in the standard treatment group, except for the >30% stratum, where the use of ACE inhibitors or ARBs was 94.6% in the intensive and 90.1% in the standard treatment group. At the last study visit, delta SBP with baseline and the use of ACE inhibitors or ARBs remained similar, with a difference of −22.1 and −12.3 mmHg between the intensive and standard treatment group in the >30% stratum and an 89.6% and 83.6% use of ACE inhibitors or ARBs.

Primary and secondary outcomes

After a mean follow-up of 4.9 years, 306 of the subjects developed an event in the intensive treatment group compared with 333 in the standard treatment group. Kaplan-Meier analysis is shown in Figure 2. When stratified to creatinine increase, 161 subjects in the <10% stratum, 105 subjects in the 10%–30% stratum, and 40 subjects in the >30% stratum developed an adverse clinical event in the intensive treatment group, whereas in the standard treatment group, 228 subjects in the <10% stratum, 82 subjects in 10%–30% stratum, and 23 subjects in the >30% stratum had an event. In both the intensive and standard treatment group no significant association was found between an increase in serum creatinine and the primary outcome (p=0.20 for intensive and p=0.17 for standard treatment).

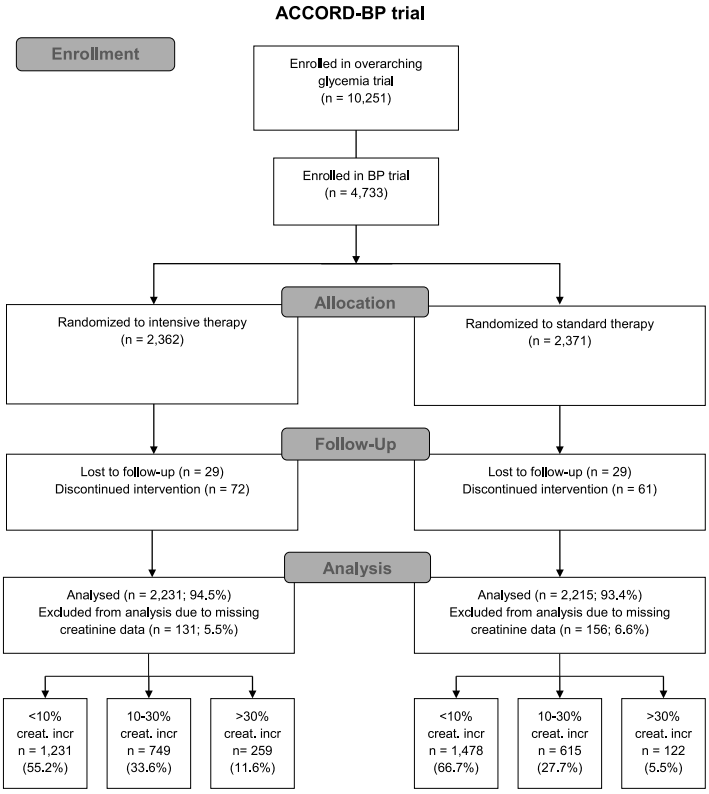

Figure 1: Flowchart of the post-hoc analysis of the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure). Creat. incr. indicates the creatinine increase between baseline and 4 months.

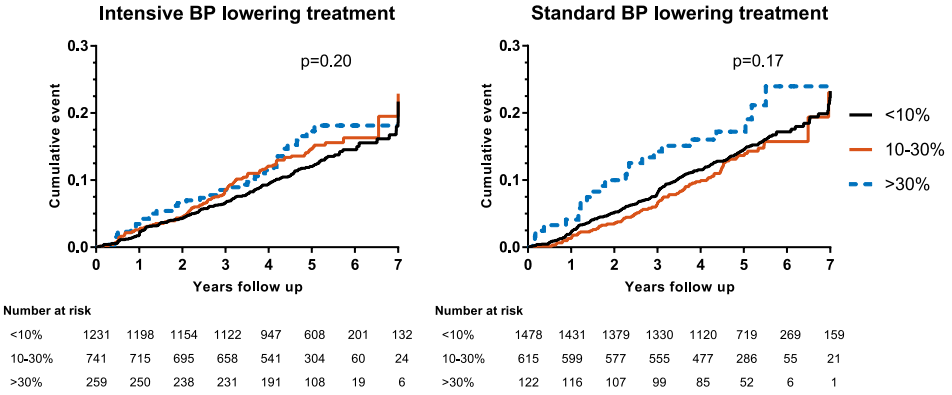

Figure 2: Kaplan-Meier analysis of initial serum creatinine increase versus adverse clinical outcomes, intensive (left) versus standard (right) BP lowering treatment.

Table 2: Results of Cox-regression analysis for primary and secondary outcomes

Endpoint	Intensive (event rate)	HR	L95	U95	*p*	Standard (event rate)	HR	L95	U95	*p*
Primary outcome										
<10%	13.1%	**1.00**				15.4%	**1.00**			
10–30%	14.2%	**1.16**	0.90	1.48	0.25	13.3%	**0.91**	0.70	1.17	0.45
>30%	15.4%	**1.32**	0.94	1.88	0.11	18.9%	**1.47**	0.96	2.27	0.08
All-cause mortality										
<10%	4.9%	**1.00**				5.6%	**1.00**			
10–30%	5.8%	**1.34**	0.90	1.99	0.14	5.7%	**1.11**	0.75	1.66	0.60
>30%	9.7%	**2.37**	1.48	3.80	<0.001	5.7%	**1.29**	0.59	2.79	0.52
Nonfatal myocardial infarction										
<10%	5.5%	**1.00**				6.6%	**1.00**			
10–30%	5.4%	**1.02**	0.69	1.52	0.91	5.0%	**0.81**	0.54	1.21	0.30
>30%	3.5%	**0.70**	0.35	1.40	0.31	9.0%	**1.64**	0.87	3.06	0.12
Nonfatal stroke										
<10%	1.4%	**1.00**				2.6%	**1.00**			
10–30%	1.5%	**1.13**	0.53	2.42	0.76	2.1%	**0.83**	0.44	1.57	0.57
>30%	0.8%	**0.62**	0.14	2.70	0.53	0.8%	**0.35**	0.05	2.58	0.31
Renal failure										
<10%	2.7%	**1.00**				2.8%	**1.00**			
10–30 %	2.2%	**0.83**	0.46	1.52	0.55	1.8%	**0.68**	0.35	1.32	0.26
>30%	3.5%	**1.47**	0.70	3.08	0.31	6.6%	**2.62**	1.23	5.61	0.013
Cardiovascular mortality										
<10%	1.5%	**1.00**				2.2%	**1.00**			
10–30%	3.0%	**2.36**	1.26	4.43	0.008	1.6%	**0.82**	0.40	1.67	0.59
>30%	3.9%	**3.16**	1.45	6.91	0.004	4.1%	**2.46**	0.95	6.35	0.06
Major cardiovascular events										
<10%	7.9%	**1.00**				10.4%	**1.00**			
10–30%	9.6%	**1.30**	0.96	1.77	0.09	8.0%	**0.80**	0.58	1.10	0.17
>30%	7.7%	**1.09**	0.67	1.77	0.73	13.1%	**1.51**	0.90	2.53	0.12

HR is adjusted for age and sex. L95 and U95 indicate the 95%CI. Less than 10%, 10%–30%, >30% indicate the different creatinine increase strata. HR indicates hazard ratio.

Cox-regression analysis performed to estimate the hazard ratio using the crude model, taking only age and sex into account, yielded the same results and showed no significant association between serum creatinine increase and the primary outcome in both treatment groups (Table 2). In the secondary outcome analysis, a serum creatinine increase was associated with an increased hazard ratio for all-cause mortality and cardiovascular mortality in the intensive treatment group, while in the standard treatment group, no such association was found. However, in the standard treatment group, a >30% serum creatinine

increase was associated with an increased hazard ratio for adverse renal events, while in the intensive treatment group, a serum creatinine rise was not associated with adverse renal outcomes. Additional correction for SBP and eGFR at baseline, resulted in a significant association between a >30% serum creatinine increase and adverse clinical outcomes with an adjusted hazard ratio of 1.47 (95%CI 1.03–2.11) and 1.57 (95%CI 1.01–2.43) in the intensive and the standard treatment group, while no significant association was present for the 10% to 30% strata. Further analysis showed that the difference between the crude and the fully adjusted model was mainly driven by baseline eGFR: a lower eGFR was associated with an increased hazard ratio for adverse clinical outcomes. The results of the Cox-regression using the fully adjusted model for the primary and secondary outcomes are shown in Supplemental table 1. Additional adjustment for allocation to glycaemic treatment arm did not materially change the association between the increase in serum creatinine and adverse clinical events.

Discussion

Our results show that, when stratified to initial serum creatinine increase, intensive BP treatment does not lead to an increased risk of adverse clinical outcomes compared with standard therapy in patients with type 2 diabetes mellitus. However, in both treatment groups, patients with a >30% serum creatinine increase had a significantly higher risk for adverse outcomes compared with the other strata when adjusted for potential confounders. This suggests that a serum creatinine rise after initiation of antihypertensive therapy is a marker to identify high-risk patients, but that intensive therapy itself does not lead to a further increase in the risk for adverse outcomes. Our results suggest that in patients with diabetes mellitus treatment decisions about the benefits of intensive BP-lowering therapy should not be influenced by an initial serum creatinine increase and that a >30% rise in serum creatinine should alert the clinician to an increased risk for adverse outcomes, but may not necessarily mean that BP-lowering medication needs to be reduced.

Meta-analyses have shown that intensive BP-lowering treatment reduces cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients with and without diabetes mellitus.[20,21] Therefore, current guidelines emphasise the importance to achieve lower BP goals, but this carries an increased concern of iatrogenic ischaemic kidney damage as a result of hypoperfusion.[8] Evidence that a >30% rise in creatinine may be harmful is derived from an earlier meta-analysis of randomised trials showing that in patients with pre-existing renal insufficiency a serum creatinine increase by >30% is rare and may point toward hypoperfusion.[10] In the present post hoc analysis, we found no association between a serum creatinine increase and adverse renal events in the intensive treatment group. In the standard treatment group, however, a >30% creatinine increase was associated with an

increased risk of renal failure. This difference may be explained by the fact that in the standard treatment group other causes for a decrease of renal function than the initiation of antihypertensive therapy were more likely leading to a serum creatinine elevation at higher SBP targets.

A previous analysis of the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) and TRANSCEND trial (Telmisartan Randomised Assessment Study in ACE Intolerant Participants With Cardiovascular Disease) showed an increased risk of adverse renal and cardiovascular outcomes in patients with a >12.7% decrease in renal function after treatment with an ACE inhibitor or ARB.[22] A similar finding was also observed in a recent study, which showed that a serum creatinine increase larger than 10% after initiation of an ACE inhibitor or ARB was associated with increased cardiorenal and mortality risk in a UK primary care population.[11] The results from the present study confirm these findings by showing that a serum creatinine increase of >30% is associated with a higher risk of cardiorenal events and death. However, they also illustrate that the increased risk of cardiovascular and renal complications is independent of the attained BP level. This supports the hypothesis that a decline in renal function as a result of antihypertensive therapy should not be interpreted as harmful.

Our findings are in line with an earlier post hoc analysis from the AASK (African American Study of Kidney Disease and Hypertension) and MDRD trial (Modification of Diet in Renal Disease) that examined the effects of intensive BP-lowering treatment in CKD patients without diabetes mellitus. Here, a >20% decline in renal function during intensive BP therapy was associated with an increased risk for renal failure, while in the standard treatment arm a >5% decline was already predictive for renal failure.[17] A post-analysis of the RENAAL trial (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) found that the initial fall in eGFR after initiation of an ARB in diabetic patients attenuated the decrease in eGFR on the long term, but that the initial change in eGFR was associated with more renal events, the risk being higher in the placebo than the ARB treatment group.[18] As the target SBP in the RENAAL trial was <140 mmHg, this finding is in line with the findings of our analysis and those by Ku et al[17] supporting that an increased risk of adverse renal outcomes is present in patients with a creatinine increase during BP-lowering therapy, but may be protective in the long run.

Our data are in apparent contrast with an earlier analysis of the SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD trials that reported an increased risk of CKD in patients receiving intensive BP-lowering treatment with and without diabetes mellitus.[23] However, both in the original and our post hoc analysis of the ACCORD trial, no evidence for an increased risk for renal failure was found in the intensive group compared with the standard group. Because Beddhu et al[23] defined incident CKD as an eGFR decrease of ≥30%, it is conceivable that the increase in renal events was merely a reflection of the re-

versal of hyperfiltration during antihypertensive treatment. Similar, an analysis of acute kidney injury in the SPRINT trial by Rocco et al[24] showed an increased risk for acute kidney injury in the intensive compared with the standard treatment group. However, acute kidney injury was already defined as a rise >0.3 mg/dL (26.5 mmol/L) or increase >1.5–fold from baseline. The notion that hyperfiltration is implicated in the serum creatinine rise after antihypertensive treatment is supported by a subgroup analysis in patients with CKD in SPRINT that showed no difference between eGFR reduction after 6 months between the standard and intensive BP targets.[25]

The strength of our study is that ACCORD-BP was a large randomised control trial of high-risk patients with type 2 diabetes mellitus who were prone to develop adverse events. This allowed us to determine the contribution of the BP-lowering therapy to the increased risk in patients with an initial serum creatinine increase. The limitation is that this is a post hoc analysis, and the study was not originally powered to answer this question. Most patients received an ACE inhibitor or ARB as part of their BP-lowering treatment, but the choice of medication was left at the discretion of the physician. We, therefore, cannot conclude from our data if the effect observed is primarily the result of lower BP or a result of the use of specific antihypertensive medication. Finally, the ACCORD-BP study only included patients with type 2 diabetes mellitus and although the association between an increase in serum creatinine and increased risk of adverse clinical outcomes is also observed in other populations, effects of intensive BP-lowering treatment may be different.

In conclusion, a >30% serum creatinine increase during BP-lowering treatment in patients with type 2 diabetes mellitus is associated with a higher risk of adverse clinical outcomes, irrespective of whether standard or intensive BP-lowering therapy is used. However, when stratified to initial serum creatinine increase, intensive BP-lowering treatment does not lead to a higher risk of adverse clinical outcomes compared with standard therapy. Furthermore, there was no association between incidence of renal failure and initial serum creatinine increase in the intensive treatment group. Only during standard therapy, a >30% creatinine increase was associated with an increased hazard ratio for renal failure.

Perspectives

Current guidelines state that reducing antihypertensive therapy should be considered in patients with a >30% serum creatinine increase. This is based on studies showing that an initial serum creatinine increase during antihypertensive therapy is associated with an increased risk for all-cause mortality, cardiovascular events, and renal failure. This post hoc analysis of the ACCORD-BP trial shows that an initial >30% serum creatinine increase is associated with adverse clinical outcomes, but does not lead to a higher risk of cardiovascular and renal outcomes in patients receiving intensive treatment compared with standard

antihypertensive therapy. These data suggest that a serum creatinine increase that coincides with a lower BP should not be interpreted as harmful and lead to a reduction in BP-lowering medication. Further research should focus on whether there is an optimal cut-off value for serum creatinine increase after BP-lowering treatment related to the difference in blood pressure.

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Supplemental material

Supplemental table 1: Results of Cox-regression analysis for primary and secondary outcomes with additional correction

Endpoint	Intensive (event rate)	HR	L95	U95	*p*	Standard (event rate)	HR	L95	U95	*p*
Primary outcome										
<10%	13.1%	**1.00**				15.4%	**1.00**			
10–30%	14.2%	**1.28**	0.99	1.66	0.06	13.3%	**0.97**	0.74	1.26	0.81
>30%	15.4%	**1.47**	1.03	2.11	0.03	18.90%	**1.57**	1.01	2.43	0.04
All-cause mortality										
<10%	4.9%	**1.00**				5.6%	**1.00**			
10–30%	5.8%	**1.48**	0.98	2.23	0.06	5.7%	**1.22**	0.81	1.85	0.34
>30%	9.7%	**2.64**	1.62	4.32	<0.001	5.7%	**1.47**	0.67	3.23	0.34
Nonfatal myocardial infarction										
<10%	5.5%	**1.00**				6.6%	**1.00**			
10–30%	5.4%	**1.10**	0.73	1.66	0.64	5.0%	**0.80**	0.53	1.22	0.31
>30%	3.5%	**0.76**	0.37	1.55	0.46	9.0%	**1.61**	0.85	3.06	0.14
Nonfatal stroke										
<10%	1.4%	**1.00**				2.6%	**1.00**			
10–30%	1.5%	**1.26**	0.57	2.81	0.57	2.1%	**0.86**	0.45	1.65	0.65
>30%	0.8%	**0.64**	0.14	2.87	0.56	0.8%	**0.34**	0.05	2.5	0.29
Renal failure										
<10%	2.7%	**1.00**				2.8%	**1.00**			
10–30%	2.2%	**0.90**	0.48	1.67	0.73	1.8%	**0.83**	0.42	1.64	0.59
>30%	3.5%	**1.58**	0.74	3.40	0.24	6.6%	**3.10**	1.41	6.81	0.005
Cardiovascular mortality										
<10%	1.5%	**1.00**				2.2%	**1.00**			
10–30%	3.0%	**3.07**	1.58	5.95	<0.001	1.6%	**1.02**	0.49	2.14	0.95
>30 %	3.9%	**4.24**	1.88	9.56	<0.001	4.1%	**3.34**	1.26	8.83	0.02
Major cardiovascular events										
<10%	7.9%	**1.00**				10.4%	**1.00**			
10–30%	9.6%	**1.50**	1.09	2.07	0.014	8.0%	**0.84**	0.6	1.18	0.31
>30%	7.7%	**1.27**	0.77	2.08	0.35	13.1%	**1.58**	0.93	2.68	0.09

Hazard ratio is adjusted for age, sex, baseline SBP and baseline eGFR. L95 and U95 indicate the 95%CI. Less than 10%, 10%–30%, >30% indicate the different creatinine increase strata. HR indicates hazard ratio.