Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON

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Muh Geot Wong,[1] Vlado Perkovic,[1] John Chalmers,[1] Mark Woodward,[1,2,3] Qiang Li,[1] Mark E. Cooper,[4] Pavel Hamet,[5] Stephen Harrap,[6] Simon Heller,[7] Stephen MacMahon,[1,2] Giuseppe Mancia,[8] Michel Marre,[9] David Matthews,[10] Bruce Neal,[1,11] Neil Poulter,[11] Anthony Rodgers,[1] Bryan Williams,[12] and Sophia Zoungas,[1,13] for the ADVANCE-ON Collaborative Group

OBJECTIVE

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that intensive glucose control prevents end-stage kidney disease (ESKD) in patients with type 2 diabetes, but uncertainty about the balance between risks and benefits exists. Here, we examine the long-term effects of intensive glucose control on risk of ESKD and other outcomes.

RESEARCH DESIGN AND METHODS

Survivors, previously randomized to intensive or standard glucose control, were invited to participate in post-trial follow-up. ESKD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease, was documented overall and by baseline CKD stage, along with hypoglycemic episodes, major cardiovascular events, and death from other causes.

RESULTS

A total of 8,494 ADVANCE participants were followed for a median of 5.4 additional years. In-trial HbA_{1c} differences disappeared by the first post-trial visit. The in-trial reductions in the risk of ESKD (7 vs. 20 events, hazard ratio [HR] 0.35, $P = 0.02$) persisted after 9.9 years of overall follow-up (29 vs. 53 events, HR 0.54, $P < 0.01$). These effects were greater in earlier-stage CKD ($P = 0.04$) and at lower baseline systolic blood pressure levels ($P = 0.01$). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function ($P > 0.26$).

CONCLUSIONS

Intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

Diabetes has surpassed glomerulonephritis as the commonest cause of end-stage kidney disease (ESKD) in the developed world and many developing countries (1). Although only a minority of individuals with diabetes will develop nephropathy and ESKD, the rapidly increasing number of people with type 2 diabetes is projected to result in a substantial increase in the numbers requiring renal replacement therapy, in turn leading to major growth in economic costs for health systems (2). In addition,

[1]*The George Institute for Global Health, University of Sydney, Sydney, Australia*
[2]*The George Institute for Global Health, University of Oxford, Oxford, U.K.*
[3]*Department of Epidemiology, Johns Hopkins University, Baltimore, MD*
[4]*Baker IDI Heart and Diabetes Institute, Melbourne, Australia*
[5]*Centre hospitalier de l`Universite de Montreal, Montreal, Canada*
[6]*Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia*
[7]*University of Sheffield and Sheffield Teaching Hospitals, National Health Service Foundation Trust, Sheffield, U.K.*
[8]*Policlinico di Monza and IRCCS Istituto Auxologico Italiano, University of Milano-Bicocca, Milan, Italy*
[9]*Hôpital Bichat-Claude Bernard and Université Paris 7, Paris, France*
[10]*Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, U.K.*
[11]*International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, U.K.*
[12]*Institute of Cardiovascular Science, University College, London, U.K.*
[13]*School of Public Health and Preventative Medicine, Monash University, Melbourne, Australia*

Corresponding author: Vlado Perkovic, vperkovic@georgeinstitute.org.au, or Sophia Zoungas, szoungas@georgeinstitute.org.au.

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chronic kidney disease (CKD) is recognized as one of the strongest risk factors for cardiovascular disease, particularly in the presence of diabetes, conferring a substantial increase in the risk of death and hospitalization (3).

Despite the implementation of "best practice" standards of care for lifestyle modification, blood pressure lowering, and renin-angiotensin-aldosterone system blockade, there remains a high level of progression to ESKD for those with diabetic kidney disease (4,5). Although a number of promising novel therapies are being studied in early clinical trials, none are as yet available (6). This has resulted in renewed interest in the role of intensive glucose control. Post-trial follow-up of the UK Prospective Diabetes Study (UKPDS) cohort of newly diagnosed patients with type 2 diabetes (7) and the Diabetes Control and Complications Trial (DCCT) cohort of young patients with type 1 diabetes (8) showed a sustained benefit for microvascular complications, beyond the period of intensive glucose control. In these studies, microvascular complications were composites of retinal photocoagulation, microalbuminuria, and neuropathy, with few, if any, patients developing ESKD or dying from renal disease (9).

We previously reported, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, that intensive glucose control in patients with type 2 diabetes significantly reduced the risk of a range of renal outcomes including new or worsening nephropathy and ESKD (10). However, the small number of ESKD events observed during the trial limited the strength of the conclusions. In addition, the safety of intensive glucose control in the presence of CKD has been questioned, with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (11) recently reporting that its intensive glucose-lowering strategy increased the risk of cardiovascular and all-cause death among participants with CKD but not in those with normal kidney function.

The outcomes of the 6-year post-trial follow-up of the ADVANCE trial cohort, also known as the ADVANCE-ObservatioNal (ADVANCE-ON) study, were recently published (12). Here, we report on further analyses that examine the long-term effects of the intensive glucose control strategy on ESKD, cardiovascular events, and death, including analyses across different levels of kidney function, in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

ADVANCE Trial

The original trial design and methods have previously been published (13,14). Briefly, 11,140 individuals with type 2 diabetes aged 55 years or older, with at least one additional risk factor for cardiovascular disease, were enrolled from 215 centers in 20 countries between 2001 and 2003. Patients were randomly assigned in a 2 × 2 factorial design to *1*) a gliclazide modified-release (MR)–based intensive glucose control regimen, aiming for an HbA_{1c} level of 6.5% or lower, or to standard glucose control based on local guidelines of participating countries, and *2*) a single pill (fixed dose) combination of perindopril and indapamide (4 mg and 1.25 mg, respectively) or matching placebo, after a 6-week active run-in period. The last trial visits for the glucose control comparison were completed in January 2008, after a median follow-up period of 5.0 years, and the results for the blood pressure (13) and glucose (14) interventions were reported then. All patients then ceased the randomized interventions and returned to usual care through their treating physician.

ADVANCE-ON Study

ADVANCE-ON was a post-trial follow-up study of surviving ADVANCE trial patients.

All local ADVANCE trial sites were invited to participate in ADVANCE-ON, and 172 of 215 sites (80%) agreed. After approval by the local ethics review boards of each participating site, all surviving trial patients at those sites were invited to enter post-trial follow-up. In January 2010, annual post-trial visits commenced. At the first post-trial visit, informed consent was obtained and a standardized questionnaire completed on the occurrence of all study outcomes of interest and all medications taken. A random subset of 2,000 patients, balanced across regions and across the prior randomized treatment arms, was also invited to undergo assessment of HbA_{1c}, fasting blood glucose, blood pressure, weight, serum creatinine, and urinary albumin-to-creatinine ratio at the first post-trial visit to determine whether in-trial differences persisted. For patients known to have died after the final in-trial visit, the cause and date of death were recorded. For patients unwilling or unable to attend study visits in person, follow-up was conducted by telephone or home visit, or information was provided by the primary care physician, other health care providers, or next of kin. At annual visits, patients completed a questionnaire on medication taken and the occurrence of study outcomes. In addition, at the final visits, that occurred between 1 January 2013 and 28 February 2014, patients attending visits in person (whether or not they had completed assessment at the first visit) were invited to undergo reassessment of HbA_{1c}, fasting blood glucose, weight, blood pressure, serum creatinine, and urinary albumin-to-creatinine ratio.

Study Outcomes

The prespecified renal outcomes for ADVANCE-ON were ESKD (requirement for dialysis or renal transplantation) and death due to renal disease. Other outcomes included death due to any cause, major cardiovascular events (myocardial infarction, stroke, or cardiovascular death, examined jointly and separately), and major hypoglycemia. It was not possible to replicate the outcome "new or worsening nephropathy" as defined in the original trial (development of macroalbuminuria [urinary albumin-to-creatinine ratio >300 μg/mg or 33.9 mg/mmol/L], doubling of serum creatinine to a level of 200 μmol/L [2.26 mg/dL], ESKD, and death due to renal disease) because levels of serum creatinine and urinary albumin were only measured in a subgroup of patients during post-trial follow-up. Outcomes occurring during post-trial follow-up were as reported by the study centers using the standardized definitions used during the trial, without central adjudication.

Statistical Methods

Analyses were conducted according to the initial treatment assignment. Treatment effects were examined using cumulative incidence survival curves and Cox proportional hazards models. Patients were censored at the first relevant end point: the date of death, date of last visit (for those still alive), or date last known to be alive for those whose

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vital status was unknown at the end of the study (28 February 2014). Hazard ratios (HRs) were estimated for the in-trial period and over the entire period of follow-up. An additional post hoc observational analysis was performed for the post-trial period alone. Serial HRs with 95% CIs were estimated at the end of each calendar year of post-trial follow-up. The homogeneity of treatment effects for prespecified subgroups was tested by adding an interaction term to the relevant Cox models.

The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR). For analyses by baseline CKD status, participants were divided into those with CKD stage 1 (eGFR $\geq$90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio $\geq$30 μg/mg), CKD stage 2 (eGFR between 60 and 89 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio $\geq$30 μg/mg), and CKD stage $\geq$3 (eGFR $<$60 mL/min/1.73 m^2 with or without albuminuria and those without CKD (eGFR $\geq$60 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio $<$30 μg/mg) (15).

The analyses were performed with SAS (version 9.2). All tests were two-sided, and P values $<$0.05 were considered to indicate statistical significance. The protocol prespecified that no adjustments would be made for the multiple statistical testing (12). In light of this, the findings were interpreted with the appropriate degree of caution.

RESULTS

Of 10,082 patients originally assigned to the randomized treatments and alive at the end of the trial, 8,494 (4,283 vs. 4,211 for intensive vs. standard glucose control, respectively) entered post-trial follow-up and 5,131 (2,638 vs. 2,493) of those still alive completed a visit during the final year of the study (12). The median in-trial, post-trial, and total follow-up periods were 5.0 years, 5.4 years, and 9.9 years, respectively (Supplementary Fig. 1). As previously reported, the prerandomization characteristics of the original glucose control trial population and of the follow-up study cohort were similar (16).

Use of Glucose-Lowering and Other Therapies

During post-trial follow-up, there was less use of sulfonylureas (including gliclazide modified release), metformin, glitazones, and α-glucosidase inhibitors but more use of insulin and other glucose-lowering therapies (including gliptins and glucagon-like peptide 1 analogs) in both the intensive and standard glucose control groups, irrespective of CKD stage (Supplementary Tables 1–3). The use of blood pressure–lowering agents, statins, and antiplatelet agents was also comparable across the groups, irrespective of the CKD stage (Supplementary Tables 1–3).

Glycemic Control

The mean difference in HbA_{1c} (0.67% [95% CI 0.64, 0.70], $P < 0.001$) observed at the end of randomized therapy was lost when measured on average 2.9 years later at the first post-trial visit (0.08% [95% CI −0.07, 0.22], P = 0.29). There was a rise in HbA_{1c} in the intensive control group approaching that observed in the standard control group. The HbA_{1c} levels of the two groups converged at the first post-trial visit (7.3% vs. 7.3%, P = 0.29) and remained similar at the last post-trial visit (12).

ESKD or Renal Death

During the in-trial period, 27 patients recorded ESKD events and 37 patients died due to renal causes. During the post-trial period, an additional 55 patients recorded ESKD events and 64 patients died due to renal causes (Table 1).

The significant reduction in the risk of ESKD observed with intensive glucose control during the in-trial period (7 vs. 20 events, HR 0.35 [95% CI 0.15, 0.83], P = 0.02) persisted after a total of 9.9 years of follow-up (29 vs. 53, HR 0.54 [95% CI 0.34, 0.85], $P < 0.01$) (Fig. 1).

Subgroup analyses examining the effects of intensive glucose control by patient characteristics at trial baseline suggested no heterogeneity with similar risk reductions for males and females, those aged above and below 65 years, and those with HbA_{1c} levels above and below the median (7.2%) (Fig. 2).

In contrast, heterogeneity was observed for patients according to CKD stage, as well as patients with systolic blood pressure (SBP) levels below or above 140 mmHg (Fig. 2, both $P <$ 0.05). A graded reduction in the strength of the effect of intensive glucose control on ESKD was seen as CKD stage increased (Fig. 2) ($P_{heterogeneity}$ = 0.04). In patients at trial baseline with SBP levels $<$140 mmHg, the risk reduction in ESKD was greater than in those with SBP levels $>$140 mmHg (HR 0.19 [95% CI 0.06, 0.55] vs. HR 0.77 [95% CI 0.46, 1.30], respectively, $P_{heterogeneity}$ = 0.01) (Fig. 2).

The nonsignificant effect on the risk of death due to renal disease observed during the in-trial period (HR 0.85 [95% CI 0.45, 1.62]) remained similar after a total of 9.9 years of follow-up (HR 0.89 [95% CI 0.60, 1.31]) (Fig. 1).

Absolute Renal Effects

Across the entire population over 9.9 years, 194 participants would need to be treated with intensive glucose control to prevent one ESKD event (Table 1). Further, the number that would need to be treated (NNT) by CKD stage was 109 for CKD stages 1 and 2 and 393 for CKD stage 3 or greater. The NNT by SBP was 120 for baseline SBP $<$140 mmHg and 368 for baseline SBP $\geq$140 mmHg (Table 1).

Other Outcomes

The rate of major hypoglycemia was low overall, and the increase in risk for the intensive versus the standard glucose control group observed during the trial was no longer evident after post-trial follow-up (Supplementary Fig. 2). The absolute risk of hypoglycemia tended to be slightly higher for the group with CKD stage 3 or greater compared with no CKD or CKD stage 1 and 2 irrespective of the original randomized groups. However, the increase in risk for the intensive versus standard glucose control groups was similarly no longer evident for subgroups of patients defined by CKD stage after post-trial follow-up (overall study period $P_{heterogeneity}$ = 0.92).

Intensive glucose control had no clear effects on overall all-cause mortality, cardiovascular death, major cardiovascular events, myocardial infarction, or stroke. In addition, there was no evidence that baseline CKD status had any impact on the effect of intensive glucose control on these outcomes (Fig. 3) (all $P_{heterogeneity} > 0.2$) during the in-trial period or during extended follow-up.

CONCLUSIONS

After following the ADVANCE trial cohort for a total of 9.9 years, we show that a prior period of intensive glucose

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Table 1—Comparison of NNT over 5 years and 9.9 years to prevent one ESKD event overall

	5-Year follow-up period				9.9-Year follow-up period			
		Annual event rate				Annual event rate		
Population and subgroup	Participants, *N* (%)	Standard, %	Intensive, %	NNT to prevent one ESKD event over 5 years	Participants, *N* (%)	Standard, %	Intensive, %	NNT to prevent one ESKD over 9.9 years
Overall	11,140 (100)	0.075	0.026	410	11,140 (100)	0.112	0.061	194
No CKD	5,935 (53.3)	0.014	0.007	2,839	5,935 (53.3)	0.046	0.008	259
CKD stages 1 and 2	2,404 (21.6)	0.106	0.035	283	2,404 (21.6)	0.14	0.048	109
CKD stage ≥3	2,256 (20.3)	0.129	0.039	220	2,256 (20.3)	0.232	0.207	393
SBP <140 mmHg	4,704 (42.2)	0.053	0.009	453	4,704 (42.2)	0.103	0.019	120
SBP ≥140 mmHg	6,435 (57.8)	0.091	0.039	384	6,435 (57.8)	0.12	0.092	368

NNT over 5 years = 1/(annual event rate in standard × 5 − annual event rate in intensive × 5). NNT over 10 years = 1/(annual event rate in standard × 10 − annual event rate in intensive × 10). Stage 1 CKD was defined as eGFR ≥90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio ≥30 μg/mg; stage 2 CKD was defined as eGFR between 60 and 89 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio ≥30 μg/mg; stage ≥3 was defined as eGFR <60 mL/min/1.73 m^2 with or without albuminuria. Mild CKD included patients with stages 1 and 2 and moderate CKD included patients with stage 3 CKD. eGFR is calculated using the EPI-CKD formula.

control continues to protect against the development of ESKD in patients with type 2 diabetes. The patients who appear to benefit the most are those with preserved kidney function, with intermediate effects in the group with CKD stage 1 or 2 and lesser effects in participants with CKD stage 3 or greater at baseline. Greater reductions in ESKD were also observed in participants with better blood pressure control at baseline (SBP <140 mmHg). Importantly, the impact of intensive glucose control on mortality or major cardiovascular events was not adversely affected by CKD at baseline during either the trial or overall study follow-up.

Our data provide the strongest evidence to date regarding the renal benefits of intensive glucose lowering and are consistent with data on intermediate outcomes from other studies. These include the Epidemiology of Diabetes Interventions and Complications (EDIC) study in a population of younger individuals with type 1 diabetes, which reported that a prior period of intensive glucose control reduced the long-term risk of developing renal impairment (eGFR <60 mL/min/1.73 m^2) by 50% after a median follow-up of 22 years (17). However, in that study a clear benefit for ESKD was not demonstrated, most likely because

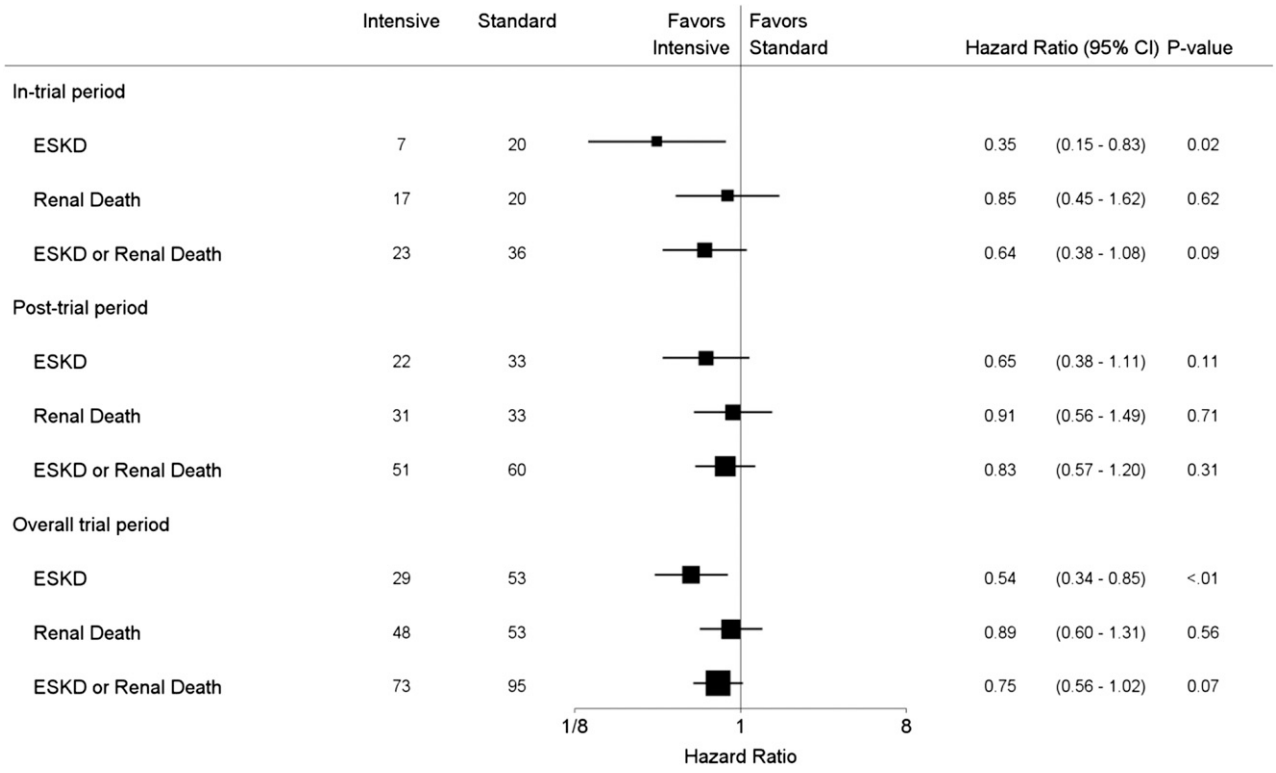

Figure 1—Summary plot showing the effects of intensive glucose lowering compared with standard glucose lowering on ESKD and/or death due to renal cause during the in-trial, post-trial, and overall study periods of follow-up. Renal death, death due to renal causes.

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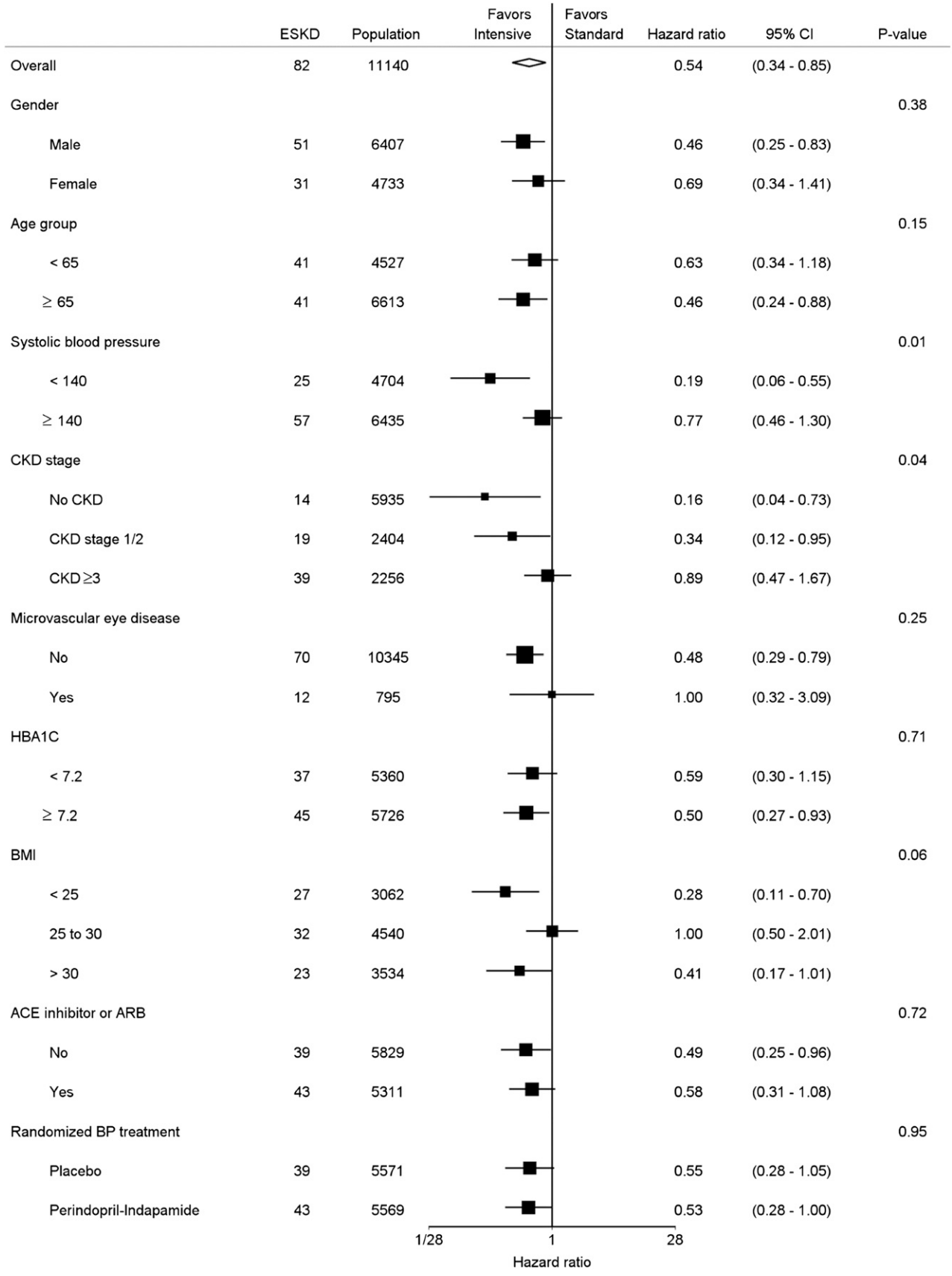

Figure 2—Subgroup analyses by baseline characteristics for the outcome of ESKD. The *P* value provided represents test for heterogeneity between subgroups. ARB, angiotensin receptor blocker; BP, blood pressure.

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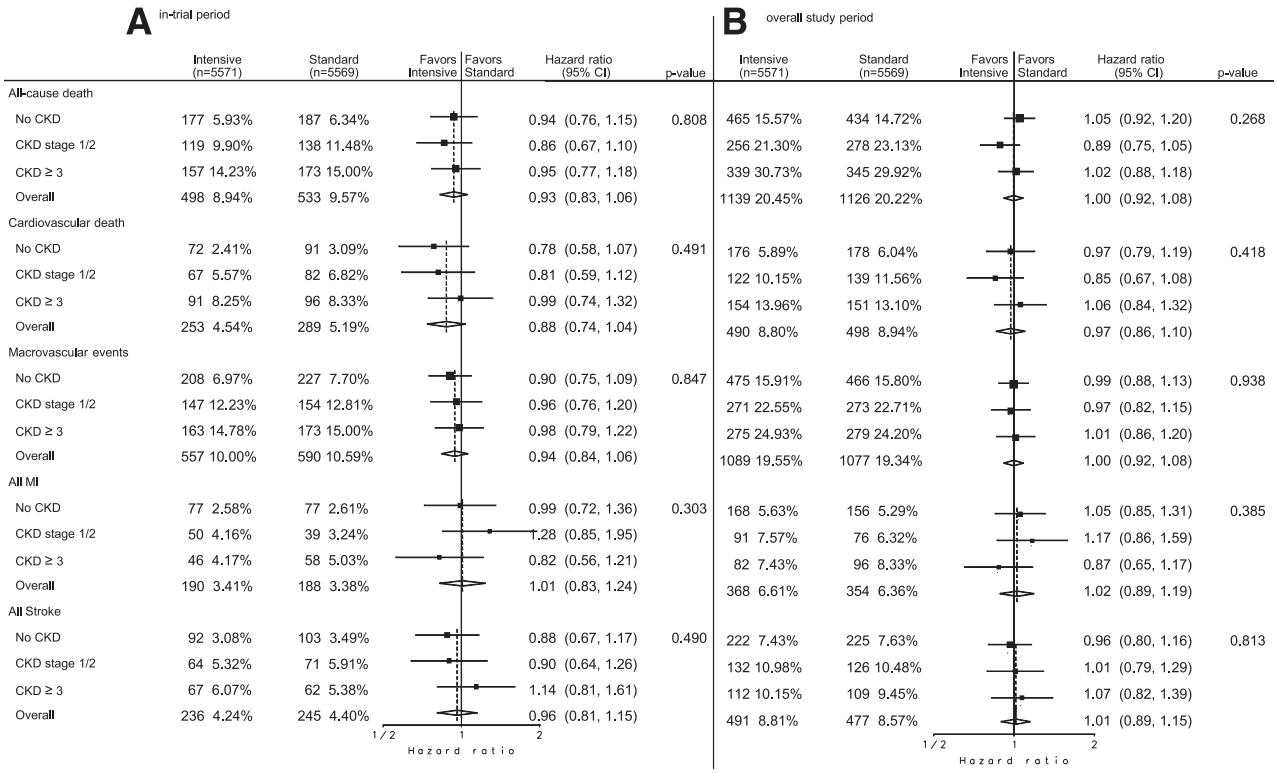

Figure 3—Forest plots of all-cause mortality and major cardiovascular events by randomized subgroups for the in-trial period (*A*) and overall study period (*B*). The *P* value provided represents a test for heterogeneity between subgroups. MI, myocardial infarction.

few ESKD events were recorded. Similarly the long-term follow-up of the UKPDS cohort of patients newly diagnosed with type 2 diabetes reported persistent microvascular (eye and renal events) and emerging macrovascular benefits in those previously assigned to intensive glucose lowering, with benefits for kidney failure defined by lower risk of increases in serum creatinine to >250 μmol/L. The ACCORD study reported a numerically lower risk of renal failure with intensive glucose lowering; however, this did not achieve statistical significance (18). The results regarding the effects on ESKD in the long-term follow-up of the ACCORD trial are awaited with interest.

In ADVANCE, the difference in the rate of ESKD events between the intensive and the standard glucose control groups took >2 years to emerge but then persisted (with a further numerically lower number of events) to the end of the overall study period, even after the HbA_{1c} converged. The risk reduction for ESKD events observed in ADVANCE-ON likely goes beyond a simple carry forward of the effects observed during the original trial period. As the development of ESKD often takes decades to appear after the onset of diabetes, it might well be anticipated that slowing of this process would take years to become evident, especially if it requires abrogation of diabetes-induced structural changes in the glomerulus (19,20). In contrast, the effects of renin-angiotensin-aldosterone system blockade and blood pressure lowering are likely to have a more rapid onset and offset in response to treatment.

Our results highlight the importance of commencing intensive glucose control before diabetic kidney disease develops, as lesser renal benefit was observed in participants with an established reduction in kidney function, suggesting that the relative contribution of glucose-dependent and glucose-independent pathways may vary at different levels of kidney function. The lesser benefit in those with moderately reduced kidney function (CKD stage 3 or greater) may indicate that glucose-independent mechanisms of renal progression are predominant in the later stages of the disease (21). In the subgroup of patients without baseline CKD, the benefits for ESKD were maintained in the long term, suggesting the earlier period of intensive glucose control may have prevented structural changes in both the glomeruli and tubulointerstitium, when renal function was relatively intact.

Similar differences were found in subgroups defined by baseline blood pressure, with a much greater reduction in ESKD by the end of overall follow-up in participants with SBP at baseline below the hypertensive range (<140 mmHg). These findings also support the premise that greater benefits will be obtained through intensive glucose control earlier in the life course of the patient with type 2 diabetes. While a recent report has raised concerns regarding a possible increase in the risk of adverse outcomes in the presence of CKD with intensive glucose control, particularly risk of death (11), we found no evidence for this. Collectively, these data support early intensive glucose control and optimal blood pressure levels for the prevention of long-term renal complications in individuals with type 2 diabetes.

An interesting finding was the lack of consistency in the results for ESKD and renal death. A low number of events is one reason. Death purely attributed to

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renal causes is less common than death due to cardiovascular or cerebrovascular causes. However, establishing cause of death during any clinical trial may be challenging. During the ADVANCE trial, renal death was adjudicated, whereas during the ADVANCE-ON post-trial follow-up renal death could not be adjudicated. In addition, it may be difficult to ascertain whether a death is due to progressive kidney failure, intercurrent cardiovascular event, or some combination of the two. This could result in greater uncertainty as to the effects on this outcome compared with that of ESKD, which is simpler to define as requirement for dialysis or renal transplantation. Indeed, other clinical trials such as Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) have similarly not been able to identify beneficial effects regarding renal death (4,5). It was also not possible to report progression or regression of albuminuria or doubling of serum creatinine as occurred in the original trial because serum creatinine levels and urinary albumin-to-creatinine ratios at the first post-trial visit were only available and able to be collected for a subset of participants (13).

A clear strength of this study is the long-term follow-up of a large and diverse patient population with type 2 diabetes. The limitations include nonadjudicated renal end points and the lack of complete biochemical data for all participants during the post-trial follow-up. Additionally, although the number of ESKD events tripled during the post-trial period, the number of events remained small. This limitation is especially important to bear in mind when interpreting differences between subgroups and between stages of CKD.

Our data build on a growing body of evidence indicating an important role for intensive glucose control in limiting the progression of kidney disease and in curbing the growing number of patients around the world with type 2 diabetes requiring dialysis or transplantation as a result of diabetic kidney disease.

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