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Intensive glucose lowering and the risk of vascular events and premature death in patients with decreased kidney function: the ADVANCE trial

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Abstract

To assess effects of intensive glucose-control on the risk of major clinical outcomes according to estimated glomerular filtration rate (eGFR) levels in type 2 diabetes. Among 11,140 ADVANCE trial participants, 11,096 participants with baseline eGFR measurements were included, classified into three groups: eGFR ≥90, 60-89, and <60 ml/min/1.73m^2. Relative risk reduction of randomised intensive glucose-control on the composite of major macro- and microvascular events, all-cause death, and cardiovascular death did not significantly vary by eGFR levels (p for heterogeneity ≥0.49). The risk of severe hypoglycaemia increased with intensive glucose-control; however, this risk did not vary across eGFR groups (p for heterogeneity=0.83). The risk-benefit profile of intensive glucose-control in patients with type 2 diabetes and impaired kidney function appears comparable to that observed in those with preserved kidney function.

Clinical trial registration number: NCT00145925, ClinicalTrials.gov

Introduction

Glycaemic control reduces the risk of long-term diabetic complications and thus has a central role in diabetes care.[1] However, there is ongoing uncertainty as to the risk-benefit balance of intensive glucose lowering, particularly with respect to premature death in patients with chronic kidney disease (CKD).[2,3] Although, dose adjustment of glucose lowering therapies occurs in the setting of decline in kidney function, the effects of intensive glucose lowering on clinical outcomes across different levels of kidney function remain unclear.

The aim of this study was to examine whether the effects of intensive glucose lowering differ across different level of kidney function defined by eGFR in type 2 diabetes.

Methods

Study design and population

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a factorial randomised controlled trial to evaluate the effects of intensive blood glucose lowering treatment and blood pressure lowering on vascular outcomes in patients with type 2 diabetes (ClinicalTrials.gov number, NCT00145925).[4-6] Briefly, 11,140 individuals with type 2 diabetes at high risk of cardiovascular events were enrolled from 215 centres in 20 countries, and were randomised to either a gliclazide (modified release)-based intensive glucose-control (target HbA1c ≤6.5%) or standard glucose-control based on local guideline of participating countries and to either a fixed-dose combination of perindopril (2 mg) and indapamide (0.625 mg) or matching placebo after a 6-week run-in period, during which they continued their usual methods of glucose-control and received perindopril and indapamide in a fixed combination. Dosing and titration of glucose-control therapy during the trial was at the discretion of the responsible physician. Participants were followed up for a median of 5.0 years. Ethics approval for the trial was

obtained from each centre's institutional review board. All participants provided written informed consent.

eGFR evaluations

eGFR was calculated by the CKD-EPI equation.[7] Only participants with baseline eGFR measurements were included (n=11,096), and were classified into 3 groups: eGFR ≥90, 60-<90, <60 ml/min/1.73m^2), guided by international staging along of CKD,[8] whilst keeping analysis groups reasonably large.

Outcomes

The outcomes assessed in this analysis were 1) the composite of major macrovascular (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular (new or worsening nephropathy or retinopathy) events, 2) all-cause death, 3) cardiovascular death, 4) major coronary events, 5) major cerebrovascular events, 6) new or worsening nephropathy, 7) new or worsening retinopathy, and 8) severe hypoglycaemia, as previously defined.[6]

Statistical analysis

Linear trends of baseline characteristics across categories were tested by linear regression analysis and logistic regression analysis, as appropriate. Mean HbA_{1c} levels during the follow-up period were calculated by linear mixed models, according to randomised treatment and baseline eGFR levels. The effects of randomised treatment on outcomes were assessed by unadjusted Cox regression models according to subgroups defined by baseline eGFR, based on the intension-to-treat principle. Heterogeneity in treatment effects across subgroups was tested by adding interaction terms to the relevant models. Sensitivity analyses

were conducted, in which subgroups were defined as eGFR of ≥90, 60-<90, 45-<60, and <45 ml/min/1.73m^2. We also performed additional analyses, in which participants were grouped according to urine albumin-to-creatinine ratio (UACR, <30, 30-150, ≥150 μg/mg) or The Kidney Disease: Improving Global Outcomes (KDIGO) risk categories[8] based on both eGFR and UACR (low, moderate, high/very high). Statistical analyses were performed with SAS 7.11 (SAS Institute, Cary NC, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Of 11,096 participants, 22% had an eGFR ≥90 ml/min/1.73m^2, 56% had an eGFR 60-<90 ml/min/1.73m^2, and 22% had an eGFR <60 ml/min/1.73m^2 at baseline (Supplementary Table 1). Participants with lower eGFR were more likely to be older, have longer duration of diabetes, have a history of macro- and microvascular disease, have lower baseline HbA_{1c}, higher BMI, and UACR levels, and less likely to be treated with metformin (all p for trend <0.001). The proportion of patients treated with gliclazide, other sulfonylureas or insulin did not differ across subgroups (p for trend ≥0.08).

Randomised treatment effects of intensive glucose-control according to baseline eGFR

The mean HbA_{1c} levels during the follow-up period in intensive glucose-control were 6.70%, 6.66%, and 6.71% in participants with eGFR ≥90, 60-<90, <60 ml/min/1.73m^2 (Figure 1). The corresponding values were higher in standard glucose control, with 7.42%, 7.29%, and 7.32% in each eGFR subgroup. Proportion of participants who were initiated insulin treatment during follow-up among those without insulin at baseline was lower in those with lower eGFR at baseline (Supplementary Table 2). When restricting to participants who have never treated

with insulin throughout the trial period, similar reductions in HbA_{1c} levels were observed (Supplementary Figure 1).

Overall, intensive glucose-lowering significantly reduced the risk of the composite of major macrovascular and microvascular events (hazard ratio [HR] 0.89, 95% CI 0.82-0.97, Figure 2) and there was no evidence of heterogeneity in the randomised effects across baseline eGFR levels (p for heterogeneity=0.51). The corresponding HRs (95% CIs) for all-cause death, cardiovascular death, major coronary events, major cerebrovascular events, new or worsening nephropathy, and new or worsening retinopathy were 0.93 (0.82-1.05), 0.87 (0.73-1.03), 0.91 (0.78-1.06), 0.96 (0.81-1.15), 0.78 (0.66, 0.93), and 0.95 (0.82, 1.10), with consistent risk reductions across eGFR subgroups (all p for heterogeneity ≥0.21), with the exception of new or worsening nephropathy (p for heterogeneity=0.03). However, this heterogeneity was not evident when trend in the effects across subgroups was examined (p for trend=0.79). The risk of severe hypoglycaemia increased with intensive glucose-control (HR 1.86, 95% CI 1.42-2.44) and this increased risk did not vary by baseline eGFR levels (p for heterogeneity=0.83). Results were broadly the same when participants with eGFR <60 ml/min/1.73m^2 were split into those with <45 and 45-<60 ml/min/1.73m^2 (p for heterogeneity ≥0.13, Supplementary Figure 2). Additional analyses, in which participants were classified by baseline UACR or KDIGO risk categories, also showed no significant heterogeneity in the effects of intensive glucose lowering across subgroups (Supplementary Figure 3 and 4).

Conclusions

In this analysis, intensive glucose lowering resulted in consistent treatment effects on vascular events and death among patients with type 2 diabetes across different levels of eGFR. Although the occurrence of severe hypoglycaemia was more common at lower eGFR levels, the risk associated with intensive glucose lowering was similar across eGFR subgroups. Our

results suggest that the risk-benefit balance of intensive glucose-control in patients with type 2 diabetes with impaired kidney function may be comparable to that observed in patients with preserved kidney function.

The ACCORD trial previously reported that intensive glycaemic control in patients with type 2 diabetes with CKD significantly increased the risk of all-cause and cardiovascular mortality, compared with standard glycaemic control.[2] One explanation for this may be an increased risk of severe hypoglycaemia in CKD. Severe hypoglycaemia is associated with an increased risk of death[9,10] and cardiovascular events.[9] Taken together, intensive glucose lowering in patients with CKD has been suggested to be detrimental and inappropriate.[2] However, in the ACCORD trial, CKD subgroups were defined by both urinary albumin-to-creatinine ratio and eGFR[2] and not solely by measures of kidney function which are directly associated with renal clearance and dosage adjustments of therapies in CKD. To our knowledge, the present study is the first to report on the consistency of the randomised treatment effects of intensive glucose lowering according to eGFR levels. Overall, intensive glucose-control reduced the risk of all-cause and cardiovascular death, as well as other vascular events, to a similar extent, regardless of baseline eGFR level. The relative risk of severe hypoglycaemia associated with intensive glucose lowering was also similar across eGFR subgroups. Similar tendencies were observed when participants were subgrouped based on baseline UACR or KDIGO risk categories (using both baseline eGFR and UACR), whereas the ACCORD trial showed evidence of harm associated with intensive glucose-lowering in CKD,[2] as mentioned above. The reason for the inconsistency is unclear, but it may be partly due to the difference in characteristics of study population and approaches to glucose-lowering.[11,12] For example, participants in ACCORD have longer duration of diabetes (ACCORD: 10.9 years,[2] ADVANCE: 7.9 years) and experienced severe hypoglycemia more frequently under intensive

glucose-lowering[11] (HR [95% CIs], ACCORD: 3.07 [2.59, 3.63], ADVANCE: 1.86 [1.42, 2.44]), in comparison with those in ADVANCE. These findings suggest the long-term benefits of intensive glucose lowering may be observed even in patients with decreased kidney function, although careful attention to the occurrence of hypoglycaemia is required. Furthermore, more intensive glucose-control decreased HbA_{1c} levels even without insulin administration, thus demonstrating the potentially efficacy of glycaemic intensification without initiation of insulin in patients with decreased kidney function. This may have important clinical implications for preventing vascular events and premature death in these patients.

The strengths of this study include the large sample recruited internationally, long-term follow-up, and rigorous central adjudication of the outcomes, which enabled precise assessment of the randomised treatment effects at different eGFR levels. However, study participants consisted of those enrolled in a randomised trial, which may limit the applicability of the results to broader general populations with diabetes.

In conclusion, our results suggest that an intensive glycaemic control strategy may be recommended for patients with type 2 diabetes with impaired kidney function as well as those with preserved kidney function. Attention to prevention of hypoglycaemia is warranted across all levels of kidney function.

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Conflict of Interest

TO and LL report no conflicts of interest. SZ reports participation in advisory boards, expert committees or educational meetings outside the submitted work on behalf of Monash University for Boehringer-Ingelheim, Sanofi, AstraZeneca, Novo Nordisk, and MSD Australia (payment to institution). MJ reports receiving grant support from the National Health and Medical Research Council of Australia (Project Grant: 1148060) and unrestricted grant support from VentureWise (a wholly owned commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. GM reports personal fees from Servier Laboratories, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini Group, Recordati, and Takeda Pharmaceutical Company. MM received personal fees from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme, Abbott, Novartis, Servier, and AstraZeneca and grant support from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme and Novartis. AR receives salary in part from George Health Enterprises, the social enterprise arm of The George Institute. George Health Enterprises has received investment to develop fixed-dose combinations containing aspirin, statin, and blood pressure lowering drugs. BW reports speaker fees for Servier, Novartis, Daiichi Sankyo, Pfizer and Boehringer Ingelheim and serves on trial steering committees for Novartis, Relypsa and Vascular Dynamics. MW

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Author Contributions

TO, SZ, MJ, MW and JC contributed to the concept and rationale for the study and interpretation of the results, and drafted the manuscript. TO conducted statistical analysis with advice from MW. All authors contributed to discussion and reviewed and edited the manuscript. JC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1. Mean HbA_{1c} levels at baseline and during follow-up according to glucose-control strategy and baseline eGFR.

Mean values during follow-up were presented as mean (SE).

Figure 2. Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline eGFR.

White diamonds indicate the HRs for subgroups defined by baseline eGFR.

Black diamonds indicate the HRs of overall for the current study.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

Figure 1

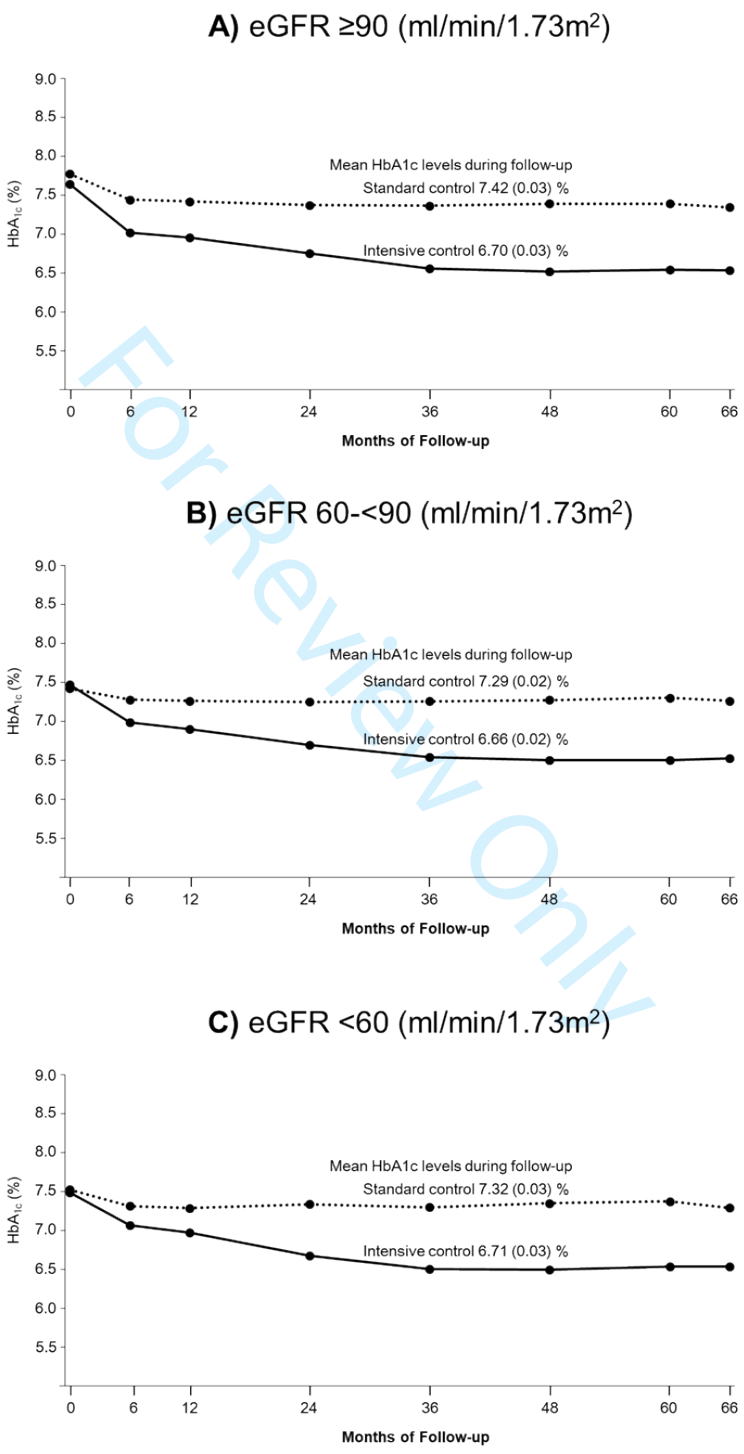
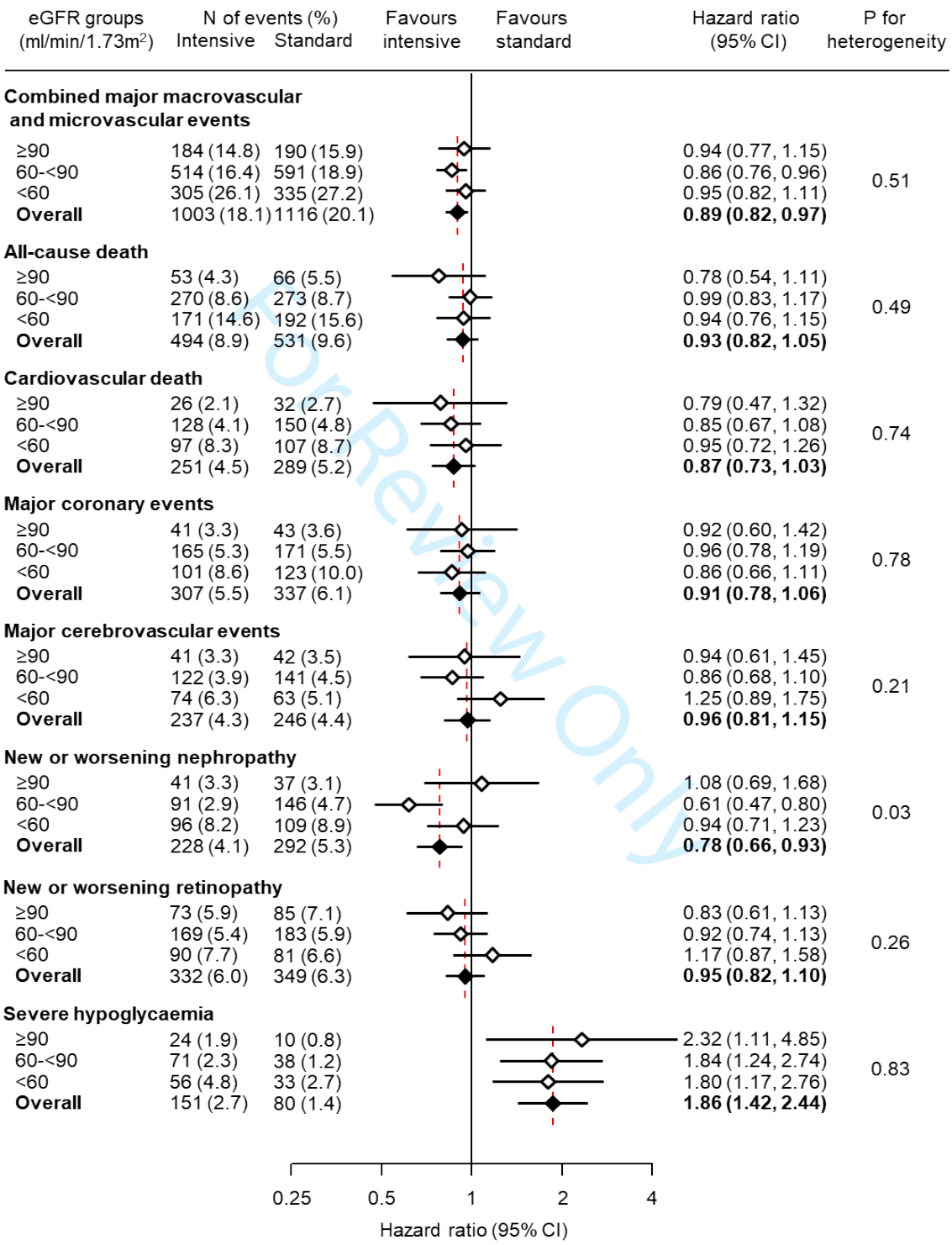


Figure 2



Supporting information

Supplementary Table 1. Baseline characteristics of study participants according to baseline eGFR

Variable	eGFR levels (ml/min/1.73m^2)			P for trend
	≥90	60-<90	<60	
Number of participants	2433	6263	2400	
Demographic factors				
Age (years)	62 (5)	66 (6)	69 (6)	<0.001
Female (%)	41	39	52	<0.001
Residence in Asia (%)	53	33	33	<0.001
Medical and Lifestyle history				
Duration of diabetes mellitus (years)	7.6 (5.9)	7.8 (6.4)	8.5 (6.6)	<0.001
History of macrovascular disease at baseline (%)	29	31	37	<0.001
History of microvascular disease at baseline (%)	10	9	15	<0.001
Current smoking (%)	20	15	10	<0.001
Risk factors				
Systolic BP (mmHg)	142 (21)	145 (21)	147 (23)	<0.001
Diastolic BP (mmHg)	81 (11)	81 (11)	80 (11)	<0.001
Hemoglobin A_{1c} (%)	7.7 (1.7)	7.4 (1.5)	7.5 (1.6)	<0.001
(mmol/mol)	60.7 (18.4)	57.9 (16.3)	58.5 (17.1)	
LDL cholesterol (mmol/l)	3.2 (1.0)	3.1 (1.0)	3.1 (1.1)	0.32
HDL cholesterol (mmol/l)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)	<0.001
Triglycerides (mmol/l)	1.6 (1.2-2.4)	1.6 (1.2-2.3)	1.7 (1.2-2.4)	0.007
Body mass index (kg/m^2)	27.9 (5.2)	28.4 (5.1)	28.6 (5.2)	<0.001
eGFR (ml/min/1.73m^2)	97.3 (6.5)	74.9 (8.6)	50.2 (8.4)	<0.001
UACR (μg/mg)	15.0 (7.5-39.8)	13.8 (6.5-33.6)	18.6 (8.0-61.9)	<0.001
Blood glucose-lowering treatments				
Gliclazide (modified release)† (%)	8	8	7	0.69
Other sulfonylurea (%)	65	62	65	0.77
Metformin (%)	64	60	57	<0.001
Thiazolidinedione (%)	3	4	4	0.24
α-glucosidase inhibitor (%)	10	8	8	0.04

Glinide (%)	2	2	2	0.70
Any oral hypoglycemic agents† (%)	93	90	90	<0.001
Insulin (%)	1	1	2	0.08

Values shown are means (SDs) for continuous variables, except for triglycerides and UACR, where medians (interquartile intervals) are given, and percentages for categorical variables.

† Randomised treatment with gliclazide was not included.

Abbreviations: BP, blood pressure, eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urine albumin to creatinine ratio.

Supplementary Table 2. Proportion of participants who were introduced insulin during follow-up, among those who were not treated with insulin at baseline (n = 10,937)

Baseline eGFR (ml/min/1.73m^2)	Glucose-control strategy		
	Intensive control	Standard control	Overall participants
≥90	56%	34%	45%
60-<90	47%	30%	39%
<60	46%	29%	38%
Overall participants	49%	31%	

Figure legends

Supplementary Figure 1. Mean HbA_{1c} levels at baseline and during follow-up according to glucose-control strategy and baseline eGFR, in participants who have never treated with insulin throughout the trial period.

Mean values during follow-up were presented as mean (SE).

Supplementary Figure 2. Sensitivity analysis: Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline eGFR.

White diamonds indicate the HRs for subgroups defined by baseline eGFR.

Black diamonds indicate the HRs of overall for the current study.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

Supplementary Figure 3. Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline UACR.

White diamonds indicate the HRs for subgroups defined by baseline UACR.

Participants with baseline UACR measurement were included in the subgroups analyses (n=10,638).

Black diamonds indicate the HRs of overall for the current study.

Abbreviations: CI, confidence interval; UACR, urine albumin-to-creatinine ratio.

Supplementary Figure 4. Randomised effects of intensive glucose control on the risk of major clinical outcomes according to baseline KDIGO risk categories.

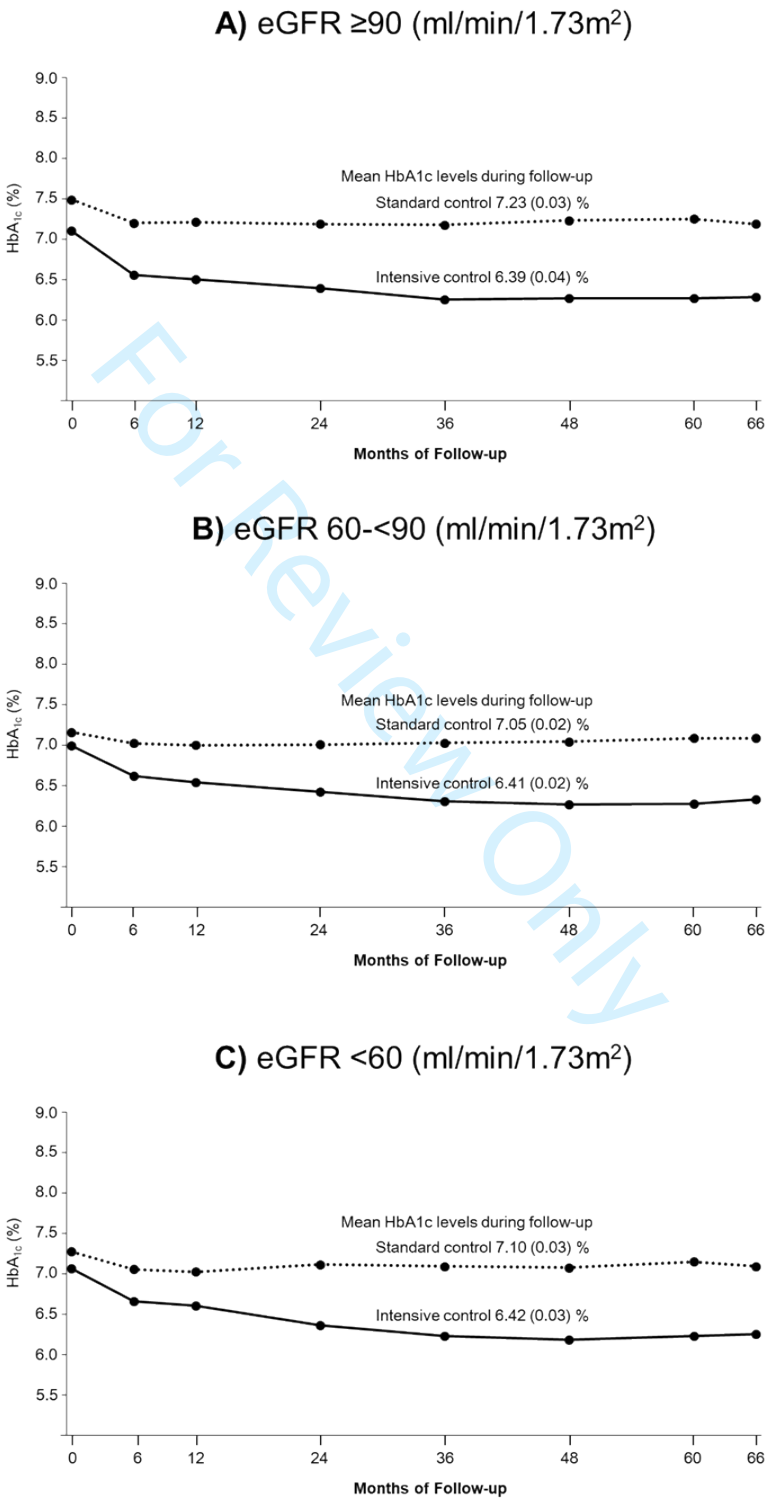
White diamonds indicate the HRs for subgroups defined by baseline KDIGO risk categories.

Participants with both baseline eGFR and UACR measurement were included in the subgroups analyses (n=10,595).

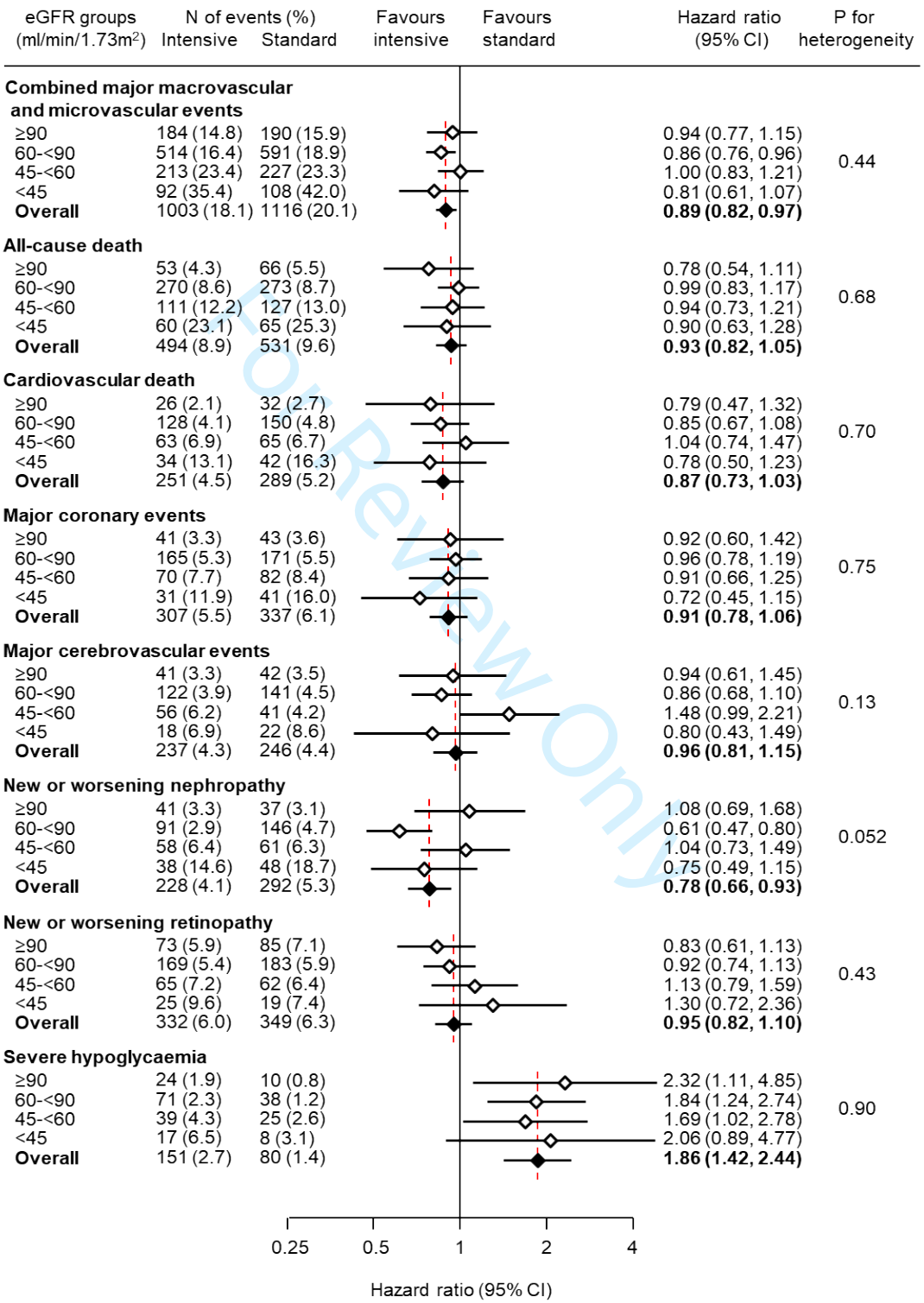
Black diamonds indicate the HRs of overall for the current study.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; KDIGO, The Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio.

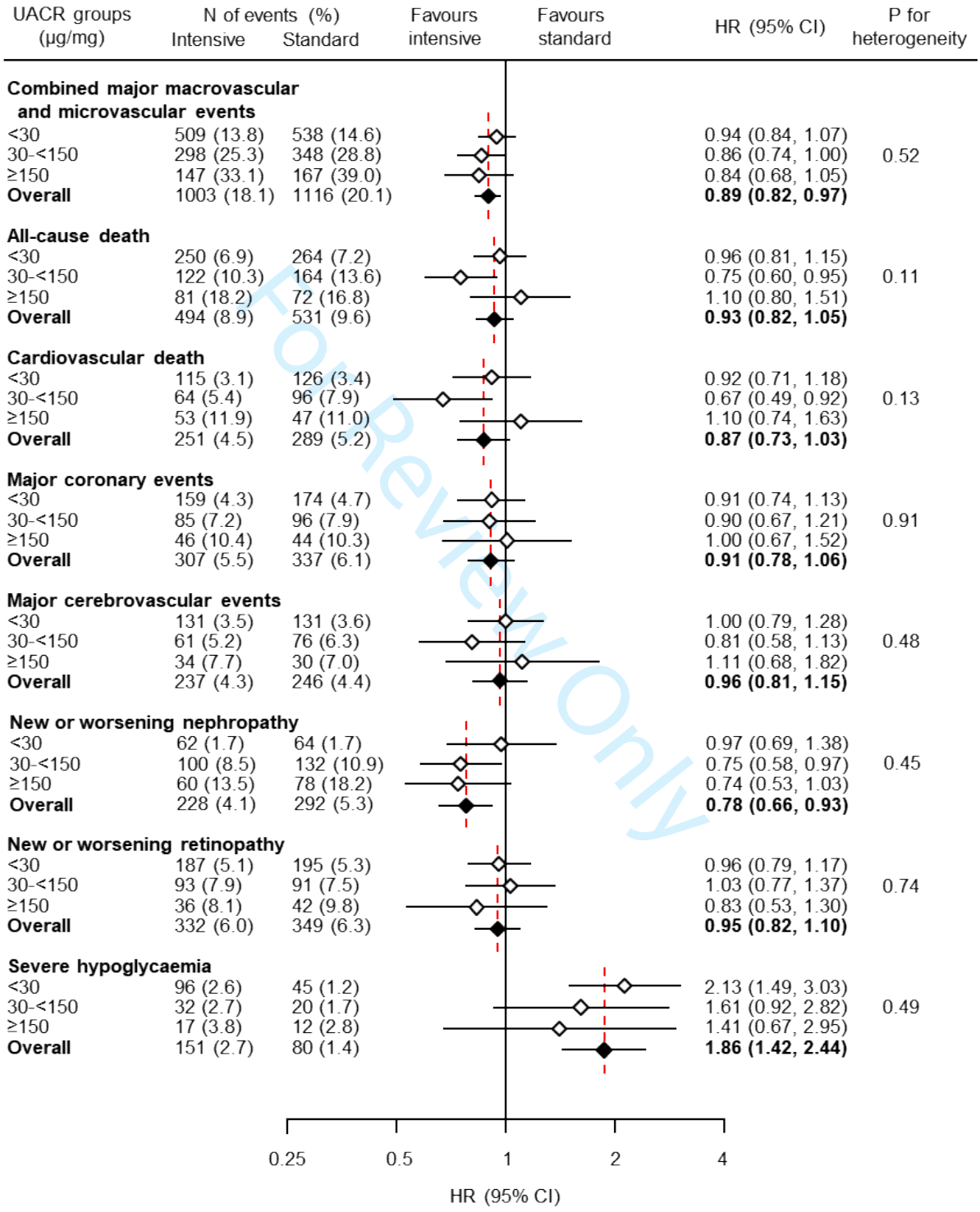
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4