Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kausik K Ray, Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya*, Rupa Sivakumaran*, Sarah Nethercott*, David Preiss, Sebhat Erqou, Naveed Sattar*

Summary

Background Whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus is unclear. We undertook a meta-analysis of randomised controlled trials to determine whether intensive treatment is beneficial.

Methods We selected five prospective randomised controlled trials of 33 040 participants to assess the effect of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen. We gathered information about events of non-fatal myocardial infarction, coronary heart disease (fatal and non-fatal myocardial infarction), stroke, and all-cause mortality, and did a random-effects meta-analysis to obtain summary effect estimates for the clinical outcomes with use of odds ratios calculated from the raw data of every trial. Statistical heterogeneity across trials was assessed with the χ^2 and I^2 statistics.

Findings The five trials provided information on 1497 events of non-fatal myocardial infarction, 2318 of coronary heart disease, 1127 of stroke, and 2892 of all-cause mortality during about 163 000 person-years of follow-up. The mean haemoglobin A_{1c} concentration (HbA_{1c}) was 0·9% lower for participants given intensive treatment than for those given standard treatment. Intensive glycaemic control resulted in a 17% reduction in events of non-fatal myocardial infarction (odds ratio 0·83, 95% CI 0·75–0·93), and a 15% reduction in events of coronary heart disease (0·85, 0·77–0·93). Intensive glycaemic control had no significant effect on events of stroke (0·93, 0·81–1·06) or all-cause mortality (1·02, 0·87–1·19).

Interpretation Overall, intensive compared with standard glycaemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of HbA_{1c} reduction might be different in differing populations.

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See **Editorial** page 1735

See **Comment** page 1737

*These authors contributed equally

Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (K K Ray MD, S R Kondapally Seshasai MD, S Wijesuriya BA, R Sivakumaran BA, S Nethercott BA, S Erqou MD); **Department of Cardiology, Addenbrooke's Hospital, Cambridge, UK** (K K Ray); **and Department of Medicine, University of Glasgow, Glasgow, UK** (D Preiss MRCP, Prof N Sattar FRCPath)

Correspondence to:
Dr Kausik K Ray, Department of Public Health and Primary Care, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK
kkr25@medschl.cam.ac.uk

Introduction

Type 2 diabetes mellitus is a well established risk factor for cardiovascular disease. Several observational studies have shown a positive correlation between measures of glycaemic control and both cardiovascular outcomes and microvascular disease, independent of risk factors known to cluster with diabetes.[1–3] Consequently, randomised controlled trials have aimed to assess whether more intensive control of glucose reduces long-term clinical events and lengthens lifetime compared with standard treatment. By contrast with the substantial benefits to microvascular outcomes,[4,5] individually these trials have failed to show consistent beneficial effects on cardiovascular events.[5–8]

Such inconsistent evidence has resulted in the American Heart Association, the American College of Cardiology, and the American Diabetes Association providing a conservative class IIb recommendation with level of evidence A[9] for the benefit of glycaemic control on cardiovascular disease. However, individually these trials might have been underpowered to show clinical benefit—especially if event rates were lower than were expected because of improved control of risk factors; duration of treatment was shorter than was needed to show a clinical benefit;[10] or differences in glycaemic control between patient groups were too small to show any benefit. To address such uncertainties, we quantitatively assessed whether intensive glucose-lowering treatment in individuals with type 2 diabetes mellitus resulted in a reduction of cardiovascular events and all-cause mortality. We present data from a meta-analysis of randomised controlled clinical trials, which aimed to assess the effect of differential glycaemic control on cardiovascular outcomes.

Methods

Data sources

We searched Medline, Cochrane Central, and EmBase for articles published in English from January, 1970, to January, 2009, with terms related to diabetes and vascular outcomes (eg, "cardiovascular diseases", "diabetes mellitus", "glucose", and "HbA_{1c}"). We restricted the search to randomised controlled trials. This search provided 2439 articles, which were further screened for inclusion

	UKPDS[4,7]	PROactive[18-20]	ADVANCE[5]	VADT[21,22]	ACCORD[8]	Overall*
Number of patients	4620	5238	11140	1791	10251	33040
Location	23 centres in England	321 centres in 19 countries†	215 centres in 20 countries‡	20 centres in USA	77 centres in USA and Canada	..
Year of publication	1998	2005	2008	2008	2008	..
Baseline demographic characteristics						
Age (years)	53 (9)	62 (8)	66 (6)	60 (9)	62 (7)	62 (7)
Time since diagnosis of type 2 diabetes mellitus (years)	<1 (NS)	8 (6)§	8 (6)	12 (8)	10 (NS)	8 (6)
Men	2709 (59%)	3463 (66%)	6407 (58%)	1739 (97%)	6299 (61%)	20617 (62%)
Current smokers	1388 (30%)	721 (14%)	1550 (14%)	299 (17%)	1435 (14%)	5393 (16%)
Cardiovascular disease¶	NS||	5238 (100%)	3590 (32%)	723 (40%)	3608 (35%)	..
Systolic blood pressure (mm Hg)	136 (20)	143 (18)	145 (22)	132 (17)	136 (17)	140 (19)
LDL concentration (mmol/L)	3·53 (1·02)	2·90 (0·75)§	3·12 (1·03)	2·78 (0·83)	2·71 (0·88)	3·00 (0·93)
BMI (kg/m²)	28 (5)	31 (5)	28 (5)	31 (4)	32 (6)	30 (5)
HbA_{1c} concentration	7·1% (1·5)	7·9% (1·1)§	7·5% (1·6)	9·4% (2·0)	8·3% (1·1)	7·8% (1·4)
Study design	Randomised, open-label	Randomised, placebo-controlled	Factorial randomised trial	Randomised, open-label	Randomised, 2×2 factorial design	..
Randomisation ratio (intensive:standard)	3071:1549	2605:2633	5571:5569	892:899	5128:5123	..
Method of random allocation	Computer-generated	Randomised permuted blocks within centre; study medication assigned via central interactive voice response system	Computer-generated	Permuted block randomisation; randomisation codes generated by biostatistician at coordinating centre	NS	..
Method of blinding	NA (open label)	Double blind	NA	NA (open label)	NA (unblinded)	..
Primary endpoint	Aggregate of any diabetes-related clinical endpoint, diabetes-related death, and all-cause mortality	Composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or lower limb arteries, and above-ankle amputation	Composites of major macrovascular and major microvascular events	Major cardiovascular event	Composite of non-fatal MI, non-fatal stroke, or death from cardiovascular causes	..
Treatment protocol						..
Intensive	Sulphonylurea, insulin, or metformin. Target FPG <6 mmol/L	15–45 mg oral pioglitazone plus current medication	30–120 mg oral gliclazide modified release, with or without metformin, thiazolidinedione, glinide, acarbose, or insulin. Target HbA_{1c} concentration ≤6·5%	Maximum dose of metformin, with either rosiglitazone (BMI >27) or glimepiride and rosiglitazone (BMI <27)	Treatment with metformin, sulphonylurea, glinide , thiazolidinedione, acarbose, insulin, or a combination of these. Target HbA_{1c} concentration <6%	..
Standard	Standard diet. Target FPG <15 mmol/L	Current medication	Standard treatment as per local guideline	Half-dose of intensive treatments	Standard treatment. Target HbA_{1c} concentration 7–7·9%	..
Average follow-up (years)	10·1 (7·7–12·4)	2·9 (NS)	5·0 (NS)	5·6 (NS)	3·5 (NS)	4·95
Total follow-up (person-years)	46237	15059	55700	10030	35879	162905
HbA_{1c} concentration at follow-up						
Standard treatment	7·9% (NS)	7·6% (NS)**	7·3% (1·3)	8·4% (1·1)§	7·5% (0·7)§	7·5%(1·1)
Intensive treatment	7·0% (NS)	7·0% (NS)**	6·8% (0·9)	6·9% (0·6)§	6·4% (0·6)§	6·6% (0·8)

Data are mean (SD), number (%), or median (IQR). BMI=body-mass index. FPG=fasting plasma glucose. HbA_{1c}=haemoglobin A_{1c}. LDL=low-density lipoprotein. MI=myocardial infarction. NA=not applicable. NS=not stated. *Pooled across studies and weighted by study size. †Austria, Belgium, Denmark, Estonia, Finland, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Slovakia, Sweden, Switzerland, and UK. ‡Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, and UK. §These SD values were estimated from IQR assuming an approximately normal distribution of the variable. ¶Includes myocardial infarction, revascularisation procedure, stroke, and peripheral arterial disease. Definition differs between studies. ||Study excluded individuals with angina or heart failure at baseline, and those who had more than one major vascular event in their lifetime or a myocardial infarction in the previous year. **Taken from median HbA_{1c} concentration at end of follow-up.

Table 1: **Baseline characteristics of participants and study design of clinical trials to compare intensive glucose-lowering versus standard treatment**

	Non-fatal myocardial infarction		Coronary heart disease		Stroke		All-cause mortality	
	Intensive treatment	Standard treatment	Intensive treatment	Standard treatment	Intensive treatment	Standard treatment	Intensive treatment	Standard treatment
UKPDS[4,7]	7·2	9·1	12·8	16·7	4·5	5·0	16·2	19·5
PROactive[18-20]*†	15·9	19·0	21·9	26·7	11·5	14·1	23·6	24·6
ADVANCE[5]	5·5	5·6	11·1	12·1	8·5	8·8	17·9	19·1
VADT[21,22]	12·8	15·5	15·4	17·9	5·6	7·2	20·4	18·9
ACCORD[8]	10·4	13·1	11·4	13·8	4·2	4·0	14·3	11·3
Overall‡	10·0	12·3	14·3	17·2	6·8	7·7	18·3	18·6

Data are rates per 1000 person-years. *Non-fatal strokes only. †Coronary heart disease includes cardiac mortality. ‡Calculated by pooling study specific rates with a random-effects model meta-analysis. §Event rates were calculated with the total person-years in each study group, which was estimated from the average follow-up in each study.

Table 2: **Event rates for cardiovascular outcomes of intensive glucose-lowering versus standard treatment§**

from titles, abstracts, or full texts, or a combination of these. We supplemented the electronic search from reference lists of relevant articles including meta-analyses and reviews, and by discussion with experts.

Study selection

Our predefined inclusion criteria required clinical trials to: (1) randomly assign individuals with type 2 diabetes mellitus either to an intensive lowering of glucose versus a standard regimen (placebo, standard care, or glycaemic control of reduced intensity), with significantly different glycaemic control (measured by haemoglobin A_{1c} [HbA_{1c}]) between patient groups during follow-up; (2) measure outcome with a primary endpoint based on cardiovascular events, and report complete information about effect estimates or provision of information to allow calculation of effect estimates for non-fatal myocardial infarction, coronary heart disease (fatal or non-fatal myocardial infarction), stroke, and all-cause mortality; and (3) be done in stable individuals only, which excluded studies in an acute hospital setting. 16 articles from 11 trials that met the above inclusion criteria were identified with information about cardiovascular outcomes and glycaemic control sourced from the title or abstract, or both, of primary and secondary published articles, and study websites.

Six trials that were initially screened were excluded: ADOPT[11] and RECORD[12] did not assess cardiovascular outcomes in the primary endpoint,[11,12] and RECORD had only interim data for some of the outcomes of interest without provision of the change in HbA_{1c} concentration during follow-up; DREAM[13] was done in individuals with impaired glucose tolerance; UGDP[14,15] included patients with diabetes and impaired glucose tolerance, and did not provide either separate information about those with diabetes or effect estimates for the outcomes of interest in each treatment group; STENO 2[16] tested several interventions and therefore did not assess intensive glucose control compared with standard treatment; and Kumamato[17] reported a composite endpoint of cardiovascular events, including peripheral vascular disease and angina, rather than the individual endpoints of interest (additionally, events included in the primary endpoint of this study were neither definitive nor clearly adjudicated).

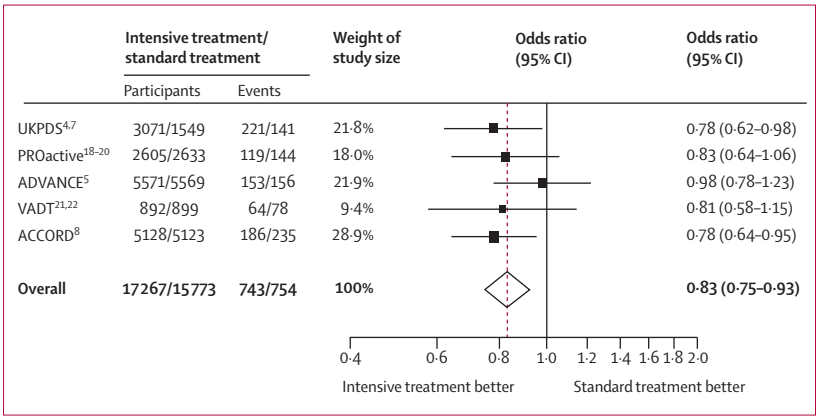

Figure 1: **Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment**

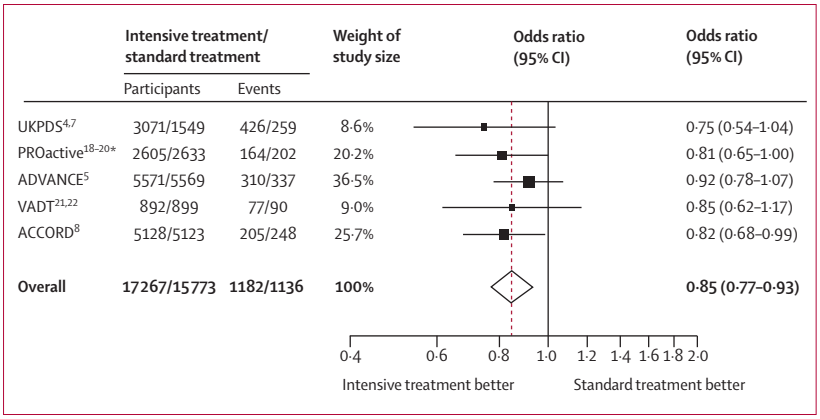

Figure 2: **Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment**

*Included non-fatal myocardial infarction and death from all-cardiac mortality.

Five randomised controlled trials fulfilled our selection criteria and were included in the meta-analysis (table 1). We combined data from the two United Kingdom Prospective Diabetes Study (UKPDS) reports—UKPDS 33[4] (intensive glucose control with sulphonylureas or

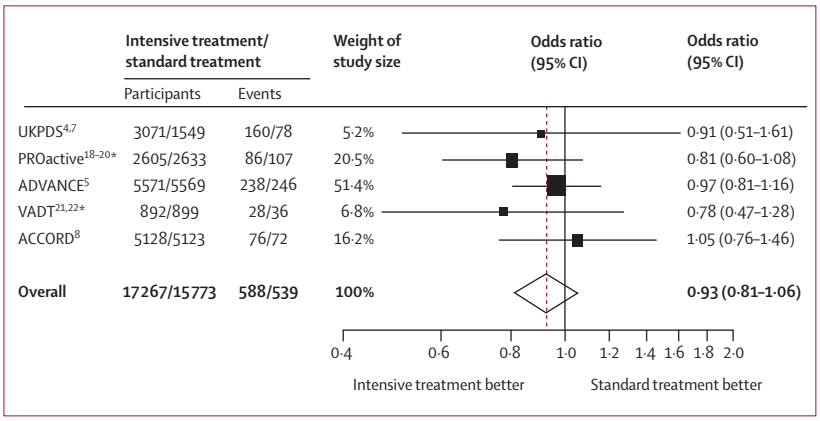

Figure 3: **Probability of events of stroke with intensive glucose-lowering versus standard treatment**
*Included only non-fatal strokes.

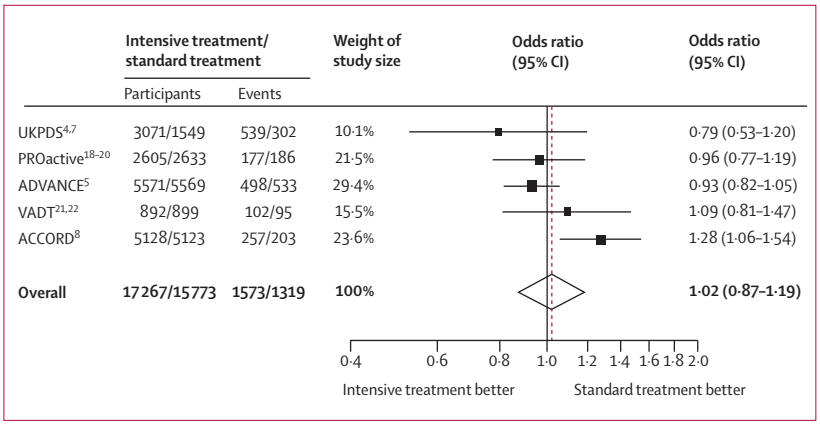

Figure 4: **Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment**

insulin compared with usual care) and UKPDS 34[7] (intensive glucose control with metformin compared with diet therapy in overweight patients)—into one study (UKPDS). The other four studies were the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive),[18–20] the Action in Diabetes and Vascular Disease:Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[5] the Veterans Affairs Diabetes Trial (VADT),[21,22] and the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD).[8]

Data extraction

We (SW, RS, SN, and DP) gathered information in duplicate using a standardised format from all relevant studies and, where necessary, another investigator (KKR) adjudicated any discrepancies. Information was obtained for several baseline characteristics of the participants (eg, age, HbA_{1c} concentration, blood pressure, body-mass index), the absolute number of events (non-fatal myocardial infarction, coronary heart disease, stroke, and all-cause mortality), and the event rates for both treatment groups. Additional information was obtained about heart failure, type of death, HbA_{1c} during follow-up, and adverse events including hypoglycaemia and weight gain. Event rates were calculated from published information about average duration of follow-up and the number of participants in each randomisation group. Follow-up duration was reported as mean (SD) in PROactive[18–20] and ACCORD,[8] and median (IQR) in UKPDS,[4,7] ADVANCE,[5] and VADT.[21,22] To estimate the total number of person-years of follow-up in UKPDS,[4,7] ADVANCE,[5] and VADT,[21,22] the median was assumed to approximate to the arithmetic mean.

See Online for webappendix

Statistical analysis

Three studies (UKPDS, PROactive, and ADVANCE) provided hazard ratios and 95% CIs for the four main outcomes of interest, whereas two studies (VADT and ACCORD) provided absolute numbers of events. To standardise reporting of our results, odds ratios (ORs) and 95% CIs were calculated from raw data of every trial. We assessed the effect of intensive glucose-lowering versus standard treatment on the outcomes of interest with a random-effects-model meta-analysis, which assumes that the true underlying effect varies between studies. Statistical heterogeneity across trials was assessed with χ^2 ($p<0·1$) and I^2 statistics. The I^2 statistic is derived from Cochran's Q—ie, χ^2 statistic $[(Q-df/Q)\times100]$—and measures the proportion of overall variation that is attributable to between-study heterogeneity. Additionally we assessed the probability of publication bias with funnel plots and the Egger test.

To calculate the absolute rates of every endpoint of interest in the intensive versus standard treatment groups, we divided the absolute number of events by the number of person-years of follow-up. We obtained summary data for every endpoint by combination of rates across studies. Other summary characteristics are presented as mean values weighted by study size. UKPDS 33[4] and 34[7] are combined and reported as UKPDS, with use of the random-effects model or calculation of weighted means as appropriate for each analysis. As a sensitivity analysis, odds ratios from the main analysis were compared with corresponding rate ratios in a random-effects-model meta-analysis. All p values are two-sided ($p<0·05$). Analyses were done with Stata (version 10.1).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

Table 1 shows the study design, baseline demographic characteristics of participants, duration of follow-up, and mean HbA_{1c} concentration in the five randomised controlled trials. The criteria for diagnosis of type 2 diabetes and eligibility for the studies are shown on webappendix p 2. 33 040 participants were enrolled from predominantly western populations (table 1).

UKPDS[4,7] enrolled individuals within 1 year after diagnosis, whereas the remaining four studies enrolled participants with longstanding diabetes, diagnosed at least 8 years earlier (table 1). Four studies reported a history of macrovascular disease in 32–100% of participants; in PROactive,[18–20] macrovascular disease was a criterion for eligibility. Participants were aged 53–66 years, and more than half were men (table 1). Baseline LDL concentration, systolic blood pressure, and HbA_{1c} concentration are also shown. At follow-up, participants given intensive treatment had a mean HbA_{1c} concentration of 0·9% (95% CI 0·88–0·92) lower than had those given usual treatment (table 1).

We looked at four cardiovascular endpoints from the five trials (definitions webappendix p 2). During about 163 000 person-years of follow-up, we recorded 1497 events of non-fatal myocardial infarction, 2318 of coronary heart disease, 1127 of fatal and non-fatal stroke, and 2892 of deaths from any cause. Table 2 reports the event rates per 1000 person-years of follow-up in the more versus less intensively treated populations in every trial. 2·3 fewer events of myocardial infarction or 2·9 fewer events of coronary heart disease took place for every 200 patients on intensive treatment for 5 years. However, the event rates for stroke and all-cause mortality were not statistically different between the treatment groups.

We assessed the effect of intensive control of glucose versus standard treatment on non-fatal myocardial infarction (figure 1), coronary heart disease (figure 2), stroke (figure 3), and all-cause mortality (figure 4). Intensive glucose-lowering treatment significantly reduced events of non-fatal myocardial infarction by 17% (OR 0·83, 95% CI 0·75–0·93; figure 1) and events of coronary heart disease by 15% (OR 0·85, 0·77–0·93; figure 2); the effect estimate was not heterogeneous between studies for either of these outcomes (non-fatal myocardial infarction I^2=0·0%, 95% CI 0·0–69·3, p=0·61; coronary heart disease I^2=0·0%, 0·0–52·7, p=0·78). However, intensive treatment did not significantly affect stroke (figure 3) or all-cause mortality (figure 4); the effect estimate was not heterogeneous for stroke (I^2=0·0%, 0·0–62·0, p=0·70), but heterogeneity was high for all-cause mortality (I^2=58·0%, 0·0–84·4, p=0·049). Rate ratios also showed that compared with standard treatment, intensive treatment significantly reduced non-fatal myocardial infarction and events of coronary heart disease, but not stroke or all-cause mortality (webappendix p 4). Funnel plots did not show a publication bias (webappendix p 5).

Intensive glucose-lowering treatment did not significantly affect heart failure (OR 1·08, 95% CI 0·90–1·31). However pronounced heterogeneity was recorded between studies (I^2=62·9%, 95% CI 1·74–85·96, p=0·029), and between subgroups of studies separated by differential glitazone use (PROactive[18–20] and ACCORD[8] *vs* UKPDS,[4,7] ADVANCE,[5] and VADT[21,22]), suggesting that glitazone use was associated with an excess risk of heart failure (I^2=89·9%, 95% CI 63·05–97·26, p=0·002) (webappendix p 6).

Data for cardiovascular mortality and non-cardiovascular mortality were restricted to four studies of 28 420 participants because UKPDS[4,7] did not record data for these endpoints. Intensive glucose-lowering treatment did not significantly affect the type of death (webappendix p 7). The effect of intensive glucose-lowering treatment on myocardial infarction, coronary heart disease, stroke, and heart failure in this restricted cohort was consistent with the main results (webappendix p 7).

Additionally, we recorded the effect of intensive glucose-lowering on hypoglycaemia and weight gain (webappendix p 3). As expected, a higher proportion of participants on intensive treatment than standard treatment had a hypoglycaemic episode (weighted averages 38·1% *vs* 28·6%). Overall, severe hypoglycaemia was much less common than was hypoglycaemia, but almost twice as many participants on intensive treatment compared with those on standard treatment had a severe hypoglycaemic event (weighted averages 2·3% *vs* 1·2%). Participants receiving intensive treatment were a mean of 2·5 kg (SD 1·2) heavier than those on standard treatment by the end of the study.

Discussion

This meta-analysis of five relevant randomised controlled trials has shown consistently that intensive glucose-lowering treatment has cardiovascular benefit compared with standard treatment for individuals with type 2 diabetes. During about 5 years of treatment, reduction of HbA_{1c} concentration by 0·9% resulted in a significant 17% reduction in events of non-fatal myocardial infarction, a significant 15% reduction in events of coronary heart disease, and a non-significant 7% reduction in events of stroke, with no significant heterogeneity recorded across studies that varied with respect to participant characteristics, baseline HbA_{1c} concentration, or, more importantly, the hypoglycaemic regimens used. However, intensive treatment did not significantly affect all-cause mortality, and we recorded obvious heterogeneity across studies.

In the early 1970s, the UGDP study[23] of intensive glycaemic control with sulphonylureas versus usual care suggested an excess mortality with intensive treatment, but with potential benefits of insulin-based regimens. This study was small—about 200 participants per group—and compared patients in several groups receiving different intensive treatments. By contrast, the much larger UKPDS study[4] compared intensive and standard glycaemic control, but failed to show benefit to cardiovascular outcomes. However, a small subgroup of 753 overweight individuals randomly assigned to metformin versus usual care showed a clinical benefit of intensive glucose control.[7] Post-hoc observational data from UKPDS[3] suggested that for every 1% reduction in HbA_{1c} concentration, risk of myocardial infarction

was reduced by 14%. More recently, extension of the initial randomised groups in the UKPDS study[10] has shown a reduction in myocardial infarction and all-cause mortality with both metformin and sulphonylurea-insulin regimens. This result was achieved despite the fact that HbA_{1c} concentrations were similar during the extension phase,[10] suggesting that these initial studies were underpowered to assess the effect of intensive treatment on cardiovascular outcomes.

Two large studies have suggested that significant differences in HbA_{1c} concentration might not confer substantial benefits to macrovascular events.[5,8] Furthermore, the ACCORD trial[8] suggested that lowered HbA_{1c} concentration might cause an excess risk of all-cause mortality. By contrast, an earlier meta-analysis[24] of data from UKPDS[4,7] and two small studies[17,25] of 60 cardiovascular events suggested that lowered HbA_{1c} concentration caused a 19% reduction in the combined endpoint of acute and non-acute cardiovascular events that included revascularisation. The absence of convincing data and concerns about possible harm has led consensus groups to provide a conservative endorsement (class IIb recommendation, level of evidence A) for the cardiovascular benefits of intensive glycaemic control: "usefulness and efficacy are less well established by evidence or opinion, with data derived from multiple randomized clinical trials or meta-analyses".[9]

Our quantitative analysis of randomised controlled trials provides reliable large-scale evidence of a consistent beneficial effect of intensive treatment on non-fatal myocardial infarction and coronary heart disease, without increased risk of all-cause mortality. The reduction of myocardial infarction from a decrease in HbA_{1c} concentration of 0·9% is broadly consistent with observational data from the UKPDS study.[3] We recorded a non-significant benefit for stroke, but 370 fewer events of stroke than myocardial infarction were reported, which conferred less power to ascertain whether a significant benefit exists.

The implications and context of these findings with respect to public health policy merit careful consideration in view of the established benefits of intensive glucose control for microvascular disease. Evidence is well established that in individuals with diabetes, statin treatment and intensive blood pressure control reduce both macrovascular events and, by contrast with our findings, all-cause mortality (9% and 27%, respectively).[26–29] Despite the benefits of statin treatment and blood pressure control, individuals with diabetes have a heightened risk of cardiovascular events, and the rate of events is even higher for those with diabetes and existing cardiovascular disease.

Our analysis shows that the mean (weighted) mortality rate of participants on standard treatment is 18·6 per 1000 person-years of follow-up, and those who achieve a 0·9% reduction in mean HbA_{1c} concentration over 5 years (from a mean HbA_{1c} concentration of 7·8% at baseline) have about two events of non-fatal myocardial infarction or three of coronary heart disease fewer for about every 200 individuals treated for 5 years. These estimates correspond to a number needed to treat over 5 years of 87 and 69, respectively. This benefit is much more modest than is that from a per mmol/L reduction in LDL cholesterol or from a 4 mm Hg lower blood pressure (8·2 and 12·5 events of cardiovascular disease prevented, respectively).[26,29] In view of the burden of cardiovascular risk in individuals with type 2 diabetes, a general approach to cardiovascular risk that uses several interventions, including stricter glycaemic control, is warranted.[16]

Intensive glucose control was associated with adverse effects of 2·5 kg difference in weight gain and nearly double severe hypoglycaemic episodes compared with standard treatment. Two studies—ACCORD[8] and VADT[21,22]—with increased mortality in the intensive treatment group also had patients with the longest duration since diabetes diagnosis at baseline (≥10 years); the highest HbA_{1c} concentration at baseline; and a greater risk of hypoglycaemia. Additionally, the ACCORD study[8] had a significantly increased risk of cardiovascular death and non-coronary cardiovascular death.

In ACCORD,[8] HbA_{1c} fell by around 1·5% within 6 months and the average HbA_{1c} was less than 6·0% by 1 year in intensively treated individuals through early and aggressive use of insulin with the use of bolus doses when necessary. Additionally, a greater proportion of intensively treated participants received rosiglitazone at the end of follow-up (92% [n=4677]) compared with those receiving standard treatment (58% [n=2946]).[30] By contrast, in ADVANCE[5] HbA_{1c} fell by only 0·5% within 6 months and the target HbA_{1c} concentration of 6·5% or less was achieved much more slowly (about 36 months), with much lower use of insulin and with preparations that were long acting. Participants were also encouraged to adopt a favourable lifestyle and were closely monitored for outcomes and adverse events. Although the data presented in our meta-analysis cannot substantiate or refute such mechanistic associations, a practical clinical approach might be to reduce HbA_{1c} concentration steadily with care taken to avoid severe hypoglycaemia. Furthermore, less stringent targets might be appropriate for patients with more advanced disease of longer duration and higher baseline HbA_{1c} concentration.[31]

Our study has several potential limitations. First, meta-analysis is retrospective research that is affected by the methodological rigour of the studies included, comprehensiveness of search strategies, and possibility of publication bias. We tried to keep the probability of bias to a minimum by developing a detailed protocol a priori, doing a thorough search for published and unpublished data, and using explicit criteria for study selection, data collection, and data analysis. Therefore,

some notable studies were not eligible for our meta-analysis for legitimate reasons. We believe that we have been robust in our approach and that the results and conclusions can therefore provide reliable recommendations for clinical practice.

Second, as in other meta-analyses, these results should be interpreted with caution because individual studies varied greatly with respect to the demographic characteristics of participants, duration of follow-up, and drugs used for intensive glucose control. Therefore, our report can provide information only about whether intensive glucose-lowering treatment is safe and effective for reduction of macrovascular events compared with standard treatment. The study cannot provide evidence of superiority or harm of a specific glucose-lowering regimen, but we did not record any significant heterogeneity across studies with respect to the effects of different glucose-lowering regimens on non-fatal myocardial infarction, coronary heart disease, or stroke. Combination of such data with the vastly different ancillary metabolic effects of the range of glucose-lowering regimens (eg, metformin, sulphonylureas, insulin, and glitazones) used in the five trials, suggests that the common action to lower glucose is to at least partly bring about the reported benefits in the reduction of the risk of cardiovascular events. Although we did not see an effect on all-cause mortality, significant heterogeneity was recorded across studies, which could not be further clarified without access to individual participant data.

Third, sufficient data were not available to analyse the effects of intensive glycaemic control within various patient subgroups (eg, by age, men *vs* women, duration of diabetes, baseline HbA_{1c}, prevalence of cardiovasular disease at baseline, comorbitity). Such analyses are most informative when done with individual participant data, to which we did not have access, and similar approaches (adjusted for the same confounders in each study) to establish whether the magnitude of reduction of HbA_{1c} concentration is correlated with cardiovascular events and all-cause mortality. Therefore, our findings will help to encourage pooling of individual participant data into a database, analogous to that of blood pressure and cholesterol, which have proved highly informative.

Fourth, we used odds ratios rather than hazard ratios (which were available in only a proportion of studies), to enable data for all endpoints from all five trials to be incorporated, thus maximising the available data. In sensitivity analyses we did a random-effects-model meta-analysis with rate ratios to calculate effect estimates, which were of similar magnitude to the odds ratio. However, in three studies, we had to assume that the median number of person-years of follow-up was approximate to the arithmetic mean. In variables with a skewed continuous distribution such as follow-up duration, the median is usually not a good approximation of the mean.

Our findings provide reassurance about the effectiveness of glycaemic control for cardiovascular risk reduction, but we have not proven a clear benefit to all-cause mortality. By contrast, strong evidence suggests that lipid-lowering treatment and blood pressure reduction does benefit all-cause mortality reduction, which reinforces the crucial importance of these treatments to reduce cardiovascular events and all-cause mortality in individuals with type 2 diabetes. The optimum methods to achieve glycaemic control need to be established, and guidelines drawn up with specific recommendations for reduction of HbA_{1c} concentration in a range of patient populations.

Contributors

KKR designed the study. SW, RS, SN, and DP participated in the review of published work and data extraction, with guidance from KKR, NS, and SRKS. SRKS, SE, and DP did the statistical analysis with guidance from KKR. All authors participated in data interpretation. KKR wrote the first draft of the report, and all other authors commented on the draft and approved the final version.

Conflicts of interest

SRKS, SW, RS, SN, DP, and SE declare that they have no conflicts of interest. For giving lectures and acting as members of advisory boards, KKR has received honoraria from Novartis, and NS has received honoraria from Merck, GSK, MSD, and Novo Nordisk.

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THE LANCET

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ray K K, Seshasai S R K, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; **373:** 1765–72.

Supplementary material

Supplementary tables

Supplementary Table 1: Definitions of diabetes and clinical end-points used in clinical trials
(Footnote: * UKPDS 33 and 34 used the same criteria for defining endpoints)

Supplementary Table 2. Adverse events in five clinical trials included in a meta-analysis of more vs less intensive glucose control
(Footnotes:
The numbers shown reflect numbers of subjects with the proportion of subjects in parenthesis
*these values indicate number of events (instead of number of individuals) and values given in parentheses are event rates per 100 person-years; these values were not included in the calculation of the combined proportion
Δ Any hypoglycaemic episodes refer to those with symptoms compatible with hypoglycaemia. Serious episodes are those that required hospital admission
Ω Hypoglycaemia defined as blood glucose<2.8 mmol/l or the presence of typical signs and symptoms of hypoglycaemia without another apparent cause. Patients with transient dysfunction of the central nervous system, who were unable to treat themselves, requiring help from another person, were said to have serious hypoglycaemia. Also note that both treatment groups lost weight, expressed as negative weight gain
δ Any episodes are those hypoglycaemic episodes with symptoms, and serious episodes are life threatening, or those that cause hospitalization, disability, death or incapacity
^ Any hypoglycaemic event refers to events requiring any form of assistance. Serious events are those that required medical assistance.
For weight gain, numbers are mean weight gain for each group at 3 yrs of follow up)

Supplementary figures

Supplementary figure 1. Rate ratios showing effect of differential blood glucose control on various clinical outcomes
(Footnote: * Rates given per 1000 patient years
† Combined rates were calculated by pooling study specific rates using random-effects model meta-analysis)
Supplementary figure 2. Funnel plots of effect estimates for various clinical outcomes
Supplementary figure 3. Odds ratios showing effect of differential blood glucose control on heart failure
Supplementary figure 4. Composite forest plot of clinical outcomes in studies with available information on these outcomes*
(Footnote:
* List of contributing studies include: PROactive, ADVANCE, VADT & ACCORD)

Supplementary Table 1: Definitions of diabetes and clinical end-points used in clinical trials

	ACCORD	ADVANCE	PROactive	UKPDS*	VADT
Diabetes	Diagnosis of Type 2 DM defined according to the 1997 ADA criteria for 3 months or longer AND an HbA1c level ≥7.5%.	Eligibility relied on a diagnosis of Type 2 DM at age 30 years or older & pt is 55 years or older at entry, with the diagnosis made 10 or more years before entry. Specifically there were no entry criteria for HbA1c concentration or fasting blood glucose.	All pts diagnosed with type 2 DM. HbA1c above upper limit of normal i.e. local equivalent of 6.5% for a DCCT (Diabetes control & complications trial) traceable assay, despite existing treatments with diet alone or oral glucose lowering agents, with or without insulin.	Pts with new diagnosis referred within 2 weeks of first diagnosis of type 2 DM. Eligible pts had a fasting plasma glucose of <6.00mmol/L on two mornings 1-3 weeks apart.	All pts diagnosed with type 2 DM. Centrally measured HbA1c level >4sd above normal mean i.e. ≥7.5%. Or local HbA1c ≥8.3%.
Non-fatal MI	Prolonged ischaemic symptoms lasting >20 minutes and raised cardiac enzymes and/or serum CK-MB. Included Q-wave MIs, non Q-wave MIs, silent MIs, probable non Q-wave MIs, MI after cardiovascular invasive interventions, MI after coronary bypass graft surgery and MI after non-cardiovascular surgery.	ICD 9 code 410	Survived more than 24h after onset of symptoms, and in absence of PCI or CABG, had at least two of: symptoms suggestive of MI, ECG evidence of MI, raised serum cardiac markers; or after PCI or CABG patient had ECG evidence of MI. Included Silent MI (defined as new Q-waves on 2 contiguous leads or R-wave reduction in praecordial leads without a change in access deviation). Data refers to first event of that type.	WHO clinical criteria with ECG/enzyme changes or a new pathological Q-wave. ICD9 code 410.	First events of non-fatal MIs. Not further specified.
Stroke	Definite ischaemic stroke: CT or MRI within 14 days of onset of focal neurological deficit lasting more than 2 hours with evidence of brain infarction; no intraparenchymal haemorrhage, no significant blood in the subarachnoid space. Also included definite primary intracerebral haemorrhage, subarachnoid haemorrhage, stroke of unknown aetiology, non-fatal stroke after cardiovascular invasive interventions and non-fatal stroke post non-cardiovascular surgery.	Death due to cerebrovascular events and non-fatal stroke.	Acute focal neurological deficit lasting for longer than 24 hours or resulting in death within first 24 hours of symptoms. Data refers to a first event of that type.	Major strokes defined as signs or symptoms for 1 month or longer. Non-fatal strokes - ICD9 codes 430-434.9 and 436 and fatal strokes ICD9 codes 430-438.9	First events of strokes.
Total Coronary Heart Disease	Non-fatal MI and fatal MI.	Death due to coronary heart disease (incl. Sudden death) and non-fatal MI.	Non-fatal MI excluding silent MI plus cardiac mortality (fatal MIs plus death from other cardiac disease) Data refers to first event of that type.	Nonfatal MI (ICD9 code 10) + Fatal MI (ICD9 codes 410-414.9, 428-428.9)	First non-fatal MIs and fatal MIs.
Heart Failure	Congestive Heart Failure Death or hospitalisaion for Congestive Heart Failure (with documented clinical and radiological evidence)	Death due to heart failure, hospitalization for heart failure, or worsening New York Heart Association class	Those requiring hospital admissions	Not associated by MI, with clinical symptoms confirmed by Kerley B lines, rales, raised JVP or 3rd heart sound ICD9 codes 411-428.1	New or worsening heart failure
Cardiovascular Mortality	Death from MI, heart failure, arrhythmia, invasive CV interventions, CV causes after non-CV surgery, stroke, unexpected death presumed to be from ischaemilc CV disease occuring within 24 hours after the onset of symptoms and death from other vascular diseases		Includes all cardiovascular deaths that occurred as a first event	ICD codes 430-438.9	Includes first events of Deaths from MI, Congestive heart failure, Coronary Revascularization, Stroke, Cerebrorevascularization, Complications of occlusions, peripheral revascularization, sudden death and pulmonary embolus

* UKPDS 33 and 34 used the same criteria for defining endpoints

Supplementary Table 2. Adverse events in five clinical trials included in a meta-analysis of more vs less intensive glucose control

Study	Any hypoglycaemic event [N patients (%)]		Serious hypoglycaemic event [N patients (%)]		Mean Weight gain (kg)		
	More Intensive	Less Intensive	More Intensive	Less Intensive	More intensive	Less Intensive	Difference
UKPDS	606 (19.8)	146 (9.4)	39 (1.3)	11 (0.7)	-	-	2.4
PROactive Δ	726(27.9)	528(20.1)	19 (0.7)	11 (0.4)	3.6	-0.4	4
ADVANCE Ω	2952(53.0)	2116(38.0)	150 (2.7)	81 (1.5)	-0.1	-1	0.9
VADT δ	1333 events (26.7)*	383 events (7.6)*	76 (8.5)	28 (3.1)	8.2	4.1	4.1
ACCORD^	830 events (4.6)*	261 events (1.5)*	538 events (3.0)*	179 events (1.0)*	3.5	0.4	3.1
Combined Ψ	**38.1**	**28.6**	**2.3**	**1.2**	**2.4**	**-0.1**	**2.5**

The numbers shown reflect numbers of subjects with the proportion of subjects in parenthesis

*these values indicate number of events (instead of number of individuals) and values given in parentheses are event rates per 100 person-years; these values were not included in the calculation of the combined proportion

Δ Any hypoglycaemic episodes refer to those with symptoms compatible with hypoglycaemia. Serious episodes are those that required hospital admission

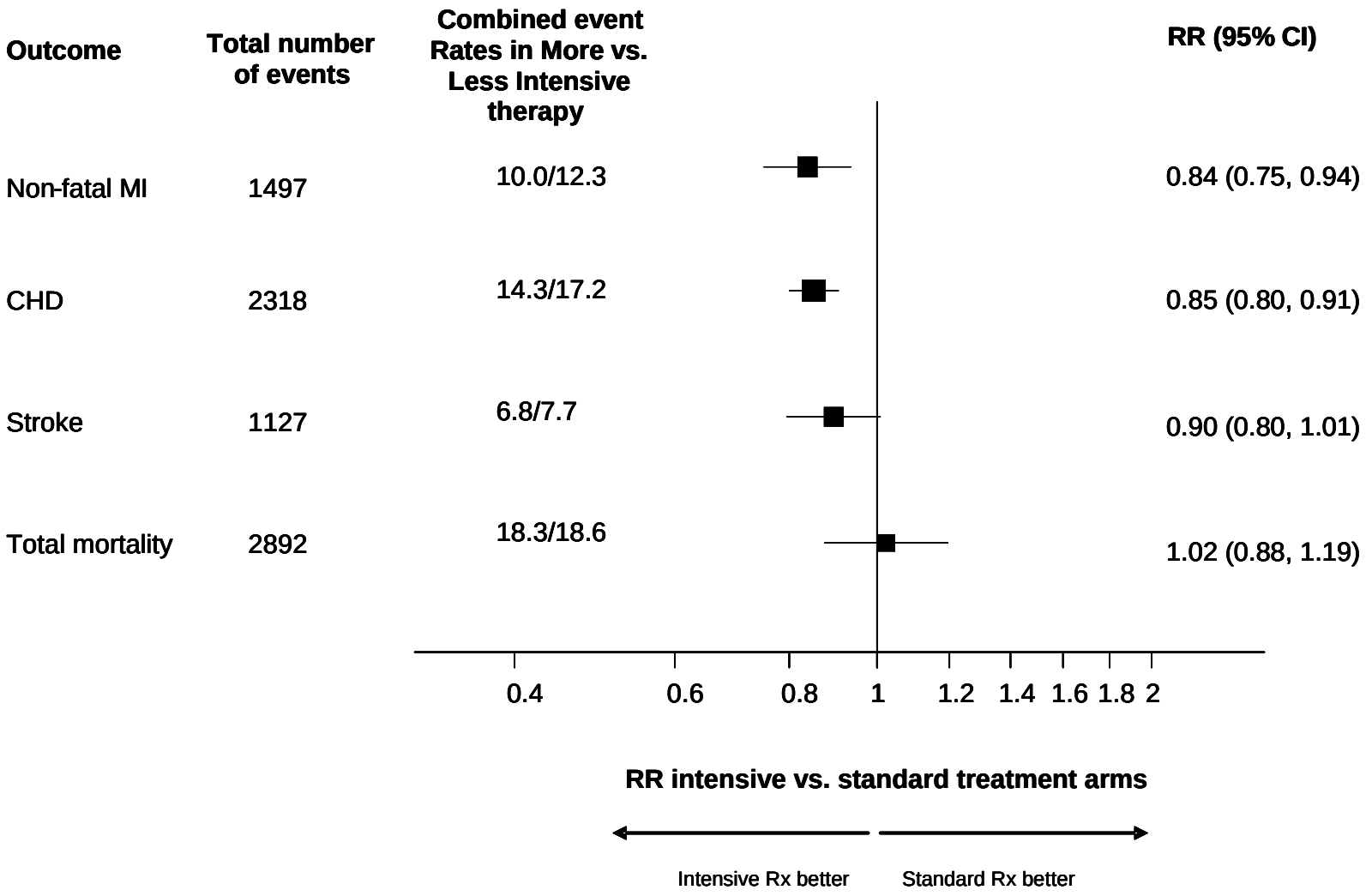
Ω Hypoglycaemia defined as blood glucose<2.8 mmol/l or the presence of typical signs and symptoms of hypoglycaemia without another apparent cause. Patients with transient dysfunction of the central nervous system, who were unable to treat themselves, requiring help from another person, were said to have serious hypoglycaemia. Also note that both treatment groups lost weight, expressed as negative weight gain

δ Any episodes are those hypoglycaemic episodes with symptoms, and serious episodes are life threatening, or those that cause hospitalization, disability, death or incapacity

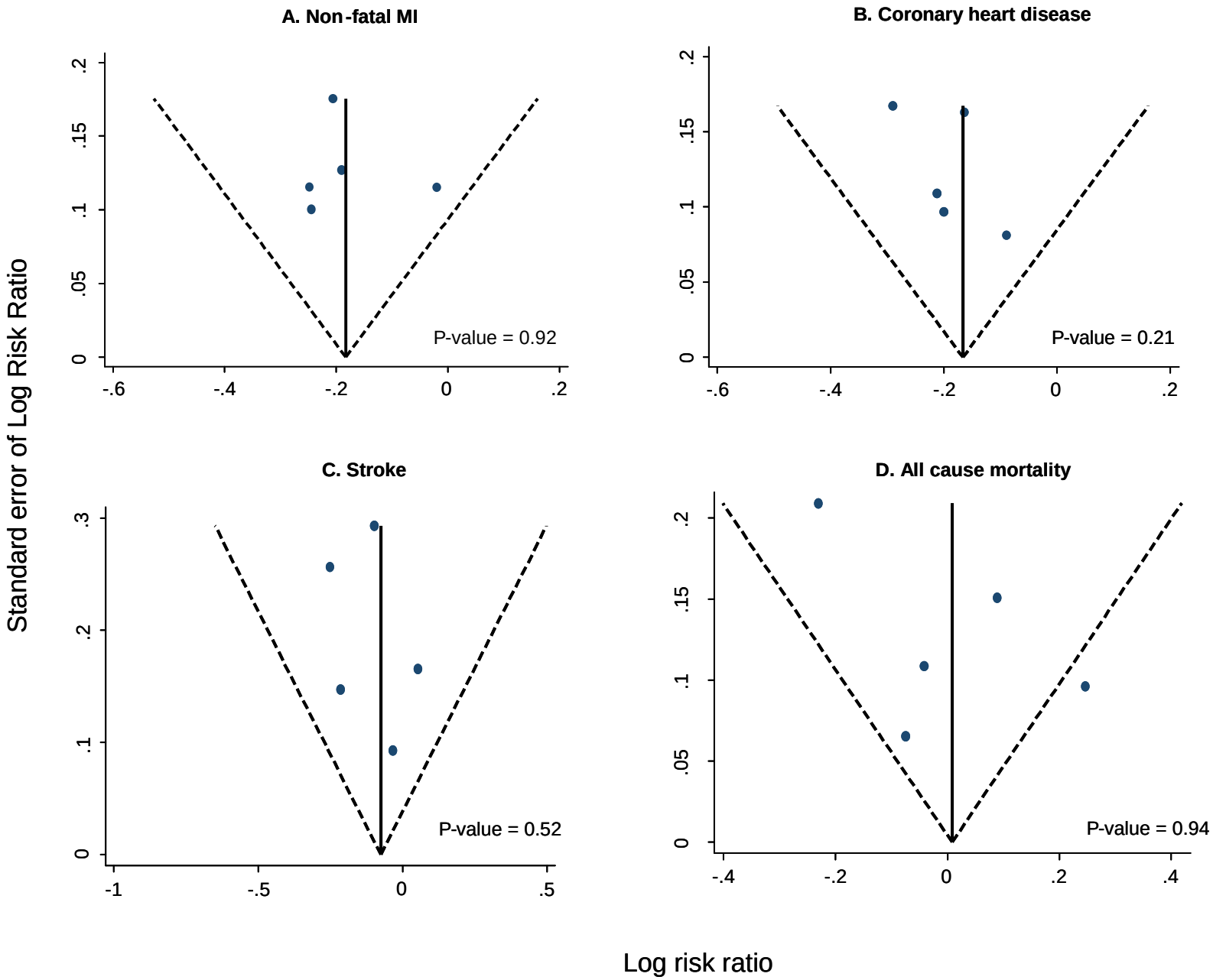
^ Any hypoglycaemic event refers to events requiring any form of assistance. Serious events are those that required medical assistance.

For weight gain, numbers are mean weight gain for each group at 3 yrs of follow up

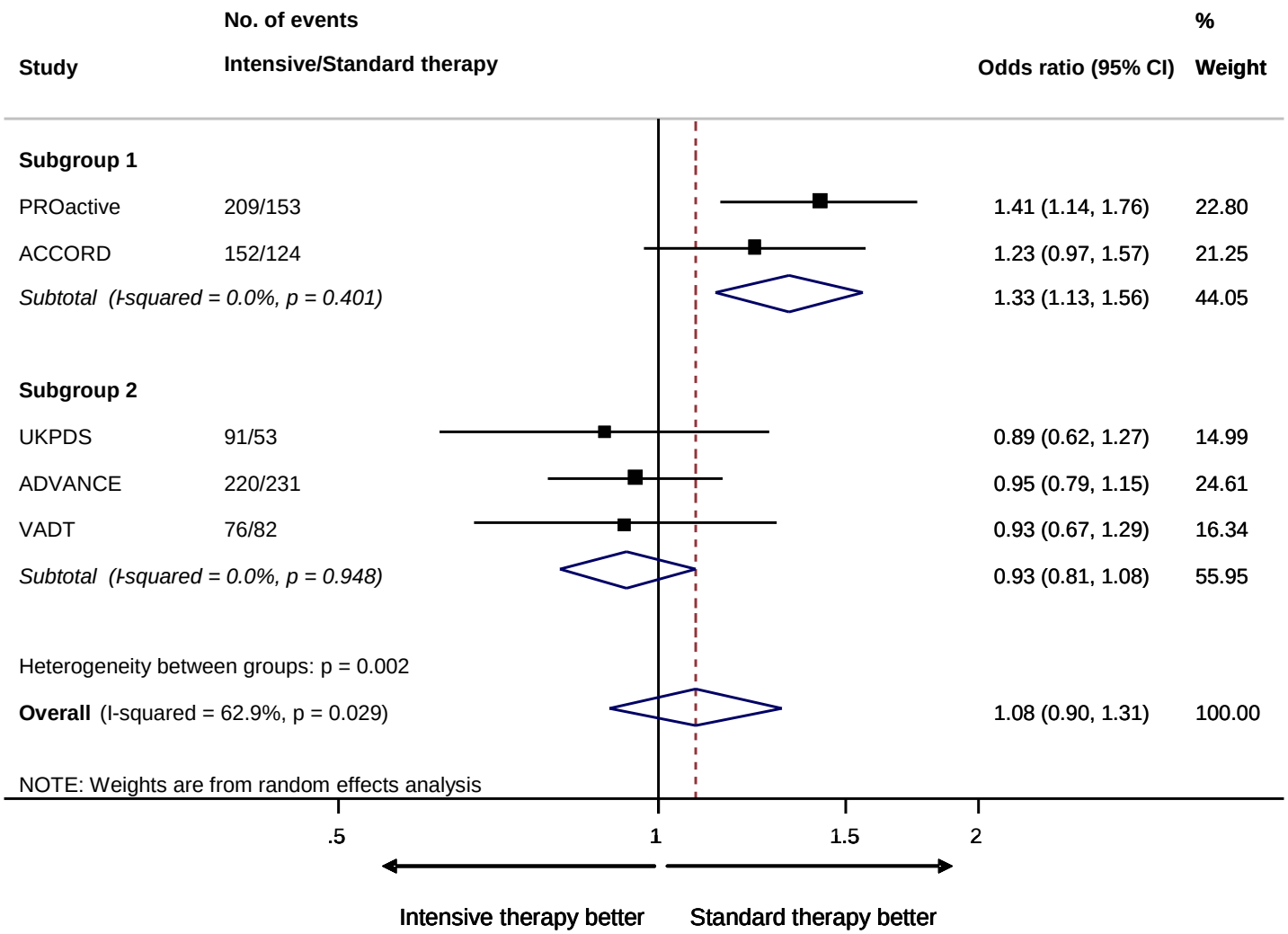
Supplementary figure 1. Rate ratios showing effect of differential blood glucose control on various clinical outcomes



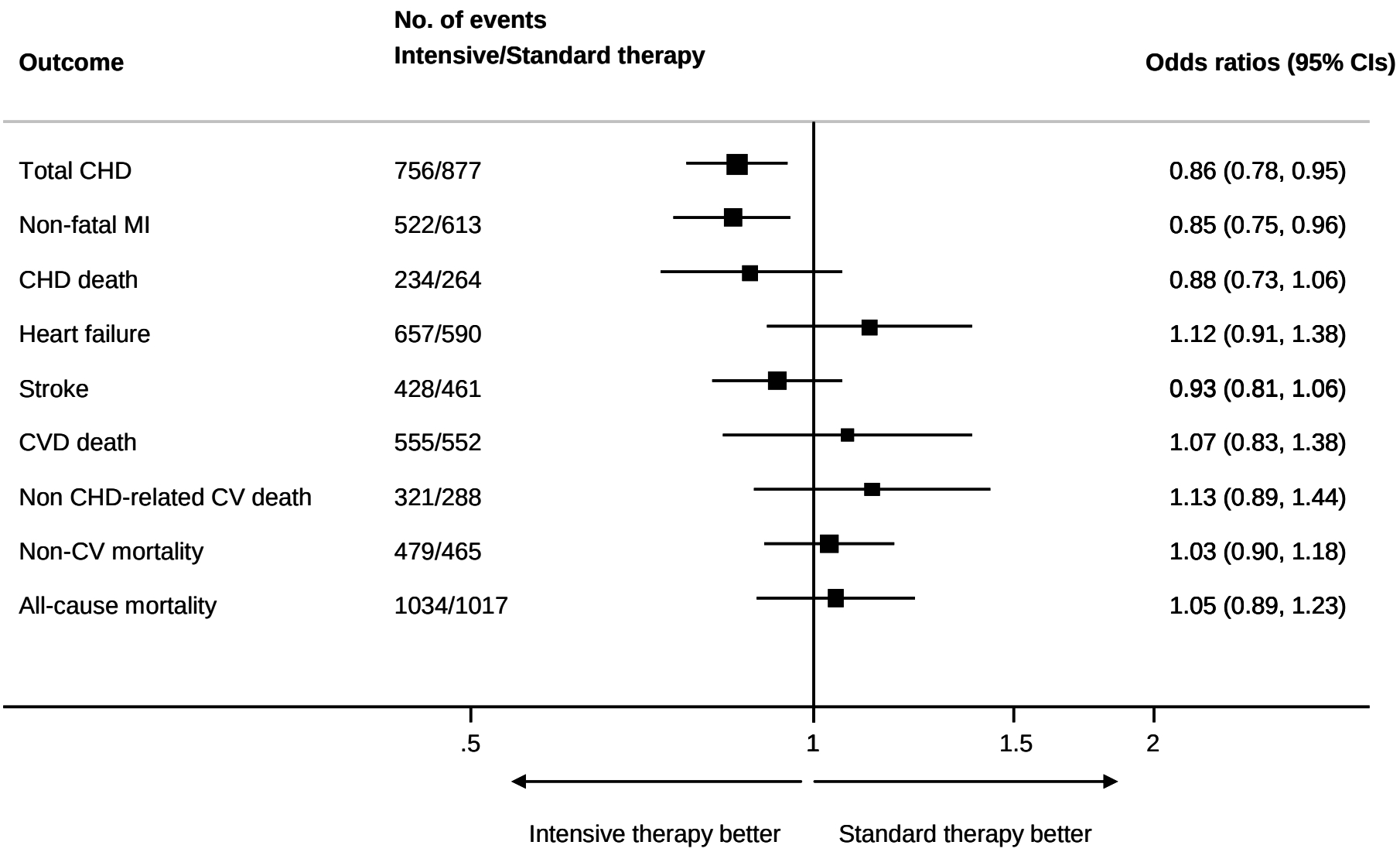
Supplementary figure 2. Funnel plots of effect estimates for various clinical outcomes



Supplementary figure 3.Odds ratios showing effect of differential blood glucose controon heart failure



Supplementary figure 4. Composite forest plot of clinical outcomes in studies with available information on these outcomes*



*List of contributing studies include: PROactive, ADVANCE, VADT & ACCORD