RESEARCH

Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis

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Abstract

Objectives To provide a systematic and quantitative summary of the association between severe hypoglycaemia and risk of cardiovascular disease in people with type 2 diabetes and to examine the sensitivity of the association to possible uncontrolled confounding by unmeasured comorbid severe illness using a bias analysis.

Design Meta-analysis of observational studies.

Data sources Medline, Embase, the Cochrane Library, and Web of Science databases were searched to February 2013, without any language restrictions.

Eligibility criteria Two independent reviewers selected cohort studies that evaluated the association of severe hypoglycaemia with cardiovascular events in people with type 2 diabetes; we excluded studies from acute hospital settings. We extracted descriptive and quantitative data.

Results Of 3443 citations screened, six eligible studies with 903 510 participants were identified. In the conventional random effects meta-analysis, severe hypoglycaemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001). The excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycaemia (the population attributable fraction) was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001). Although moderate heterogeneity across the studies was suggested (I^2=73.1%; P=0.002 for heterogeneity), most subgroups showed similar results in stratified analyses. The bias analysis indicated that comorbid severe illness alone may not explain the association between hypoglycaemia and cardiovascular disease; to explain this association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycaemia and cardiovascular disease.

Conclusion Our findings suggest that severe hypoglycaemia is associated with a higher risk of cardiovascular disease; they also support the notion that avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

Introduction

Severe hypoglycaemia is a potential risk factor for cardiovascular disease in people with type 2 diabetes.[1][2] Meta-analyses of recent clinical trials indicated that intensive glucose control was associated with a reduced risk of non-fatal myocardial infarction in people with type 2 diabetes.[3][4] Individually, however, these recent clinical trials have failed to show a beneficial effect of intensive glucose control on overall cardiovascular disease events,[5-7] despite earlier observational studies indicating a strong positive association between diabetes or hyperglycaemia and risk of cardiovascular disease.[8-10] If severe hypoglycaemia induces cardiovascular disease events, it may also dilute the potential benefit of intensive glucose control on such events because intensive glucose control increases the risk of severe hypoglycaemia.[3] This is biologically plausible because severe hypoglycaemia has acute effects on sympathoadrenal activation,[11] inflammation,[12] and endothelial function,[13] all of which have potential adverse cardiovascular effects. In addition, cardiac ischaemia or fatal arrhythmia during hypoglycaemia may be responsible for the increased risk of cardiovascular disease among patients with severe hypoglycaemia.[14][15]

Although observational studies have reported a positive association between severe hypoglycaemia and risk of cardiovascular disease,[1][2] this association remains controversial. Some have suggested that severe hypoglycaemia may be a marker of vulnerability to cardiovascular disease events[1] because

the risk of hypoglycaemia is increased in patients with comorbid severe illnesses (for example, renal disease, liver disease, cognitive decline, and terminal cancer) that are risk factors for serious adverse health outcomes. Thus comorbid severe illnesses may confound the association between hypoglycaemia and cardiovascular disease. Randomisation of patients to hypoglycaemic and non-hypoglycaemic groups is not feasible; however, a bias analysis may help to elucidate the impact of a comorbid severe illness on the association between severe hypoglycaemia and cardiovascular disease.

We conducted a systematic review and meta-analysis to evaluate if severe hypoglycaemia is associated with risk of cardiovascular disease, and if confounding from an unmeasured comorbid severe illness accounts for the reported association between severe hypoglycaemia and cardiovascular disease, using a bias analysis.

Methods

We searched Medline, Embase, the Cochrane library, and Web of Science to February 2013, without any language restrictions (initial search on 5 September 2012; search updated 11 December 2012 and 27 February 2013); a beginning timeframe was not set. The Medline search terms were ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND ("hypoglycemia"[MeSH Terms] OR "hypoglycemia"[All Fields] OR "hypoglycaemia"[All Fields]) AND ("cardiovascular diseases"[MeSH Terms] OR "cardiovascular diseases"[All Fields] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR ("cardiovascular"[All Fields] AND "disease"[All Fields])). We adapted this search strategy for searches of Embase (using Emtree terms), the Cochrane library, and the Web of Science (see supplementary text A). We also searched the references of relevant studies. Although this meta-analysis did not have a registered review protocol, we followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[16] The researchers are experienced with systematic reviews of the literature.[17-22]

Study selection

Two independent investigators (AG and MG) read all retrieved abstracts and titles. The inclusion criteria were: a cohort study of people with type 2 diabetes, cardiovascular disease reported as the study outcome, and provision of an association between hypoglycaemia and cardiovascular disease. We defined cohort studies as those that prospectively identified a group of people, assessed exposures of interest, and followed them for incidence of outcome events (that is, prospective cohort studies) or those that used existing data records to retrospectively identify a group of people and assess exposures of interest and incidence of outcome events (that is, retrospective cohort studies). We included randomised controlled trials as long as an observational analysis of the association between hypoglycaemia and cardiovascular disease was available. Studies in acute hospital settings were excluded. Full texts of potentially eligible studies were retrieved and screened to determine their eligibility; discrepancies between the reviewers' selections were resolved by discussion.

Data extraction

We extracted information on study characteristics (authors, design, year of publication, sample size, duration of follow-up); participants' characteristics (age, sex, duration of diabetes, cardiovascular disease history, insulin use, body mass index,

smoking status, low density cholesterol level, systolic blood pressure, glycated haemoglobin (HbA_{1c}) level, fasting plasma glucose level); exposure assessment; outcome assessment; analysis strategy; and multivariable adjusted relative risks. If the appropriate information was missing, we requested this from the investigators. Two investigators (AG and MG) extracted data independently and discrepancies were resolved by discussion.

Quality assessment

To assess study quality,[23] we evaluated each study for its design, sources of participants, follow-up time, exposure assessment, outcome assessment, and the extent of adjustment for potential confounders. We chose not to use a scoring system to formally rate study quality because such scoring submerges important information by combining disparate study characteristics into one score.[23]

Statistical analysis

We used relative risk as a measure of effect estimates. One study used logistic regression models to estimate odds ratios[24]; the others used Cox proportional hazard models to estimate hazard ratios.[1 2 25-27] Because the risk of cardiovascular disease incidence was low, we used both the hazard ratios and the odds ratios to approximate the relative risk.[23] We assessed potential publication bias using funnel plots, Begg's test,[28] and Egger's test.[29] We performed data synthesis using a conventional random effects model,[30] which ignores possible confounding by comorbid severe illness. We assessed statistical heterogeneity of relative risks across studies using the Cochrane's Q test[31] and I^2 statistics.[32] We considered low, moderate, and high degrees of heterogeneity to be I^2 values of below 25%, 25-75%, and above 75%, respectively. We also performed stratified analyses according to study design (that is, prospective studies[1 2] versus retrospective studies[24-27]), study location (United States[2 24 25] versus non-United States[1 26 27]), sex (mainly men[2 25] versus both sexes[1 24 26 27]), duration of follow-up (>1 year[1 2 25-27] versus ≤1 year[24]), insulin use (included[1 2 24 25 27] versus excluded[26]), adjustment for race and dyslipidaemia (yes[2 24-27] versus no[1]), adjustment for smoking status (yes[1 2 25] versus no[24 26 27]), and adjustment for body mass index (yes[1 25] versus no[2 24 26 27]). We computed P values for comparisons between subgroups using the χ^2 test with 1 degree of freedom.

The potential impact of uncontrolled confounding by unmeasured severe comorbid illnesses was explored. Since data have not been published regarding the distribution of comorbid severe illnesses or their effect on the risk of cardiovascular disease in people with type 2 diabetes, we assigned a wide range of plausible bias values. We then computed the adjusted relative risks and 95% confidence intervals, externally adjusted for the unmeasured comorbid severe illnesses. Specifically, we conducted a bias analysis by dividing the observed (preadjusted) relative risk of each study (i=1, 2, etc) by a bias factor, which was interpreted as the degree of bias due to failure to adjust for severe comorbid illness, using the following formula[23 33]: bias factor$_i$=$RR_{i\,preadjusted}$/$RR_{i\,adjusted}$=$(RR_{iDZ}P_{iZ1}+1-P_{iZ1})/(RR_{iDZ}P_{iZ0}+1-P_{iZ0})$ where $RR_{i\,preadjusted}$ is the observed relative risk; $RR_{i\,adjusted}$ is the relative risk adjusted for the unmeasured comorbid severe illness (Z); RR_{iDZ} is the relative risk relating the unmeasured comorbid severe illness and cardiovascular disease (D), given hypoglycaemia; P_{iZ1} is the prevalence of the unmeasured comorbid severe illness in the hypoglycaemic group; and P_{iZ0} is the prevalence of the unmeasured comorbid severe illness in the non-hypoglycaemic group in each study (i=1, 2, etc).[23] The bias adjusted relative risk ($RR_{i\,adjusted}$), which was our target, was

obtained by dividing the preadjusted relative risk ($RR_{i\,preadjusted}$) by the bias factor from the formula above. Although the degree of residual confounding may have differed across studies, we assigned the same bias factor to all studies for simplicity. Assuming that the standard errors of the bias adjusted relative risks were not affected by unmeasured confounding,[34 35] we estimated the standard errors of the logarithm of bias adjusted relative risks by the usual likelihood procedures. The bias adjusted relative risks were pooled using a random effects model.[30] We repeated the above adjustment process, using wide ranges of values, for the proportions of patients with comorbid severe illness and the effects of the comorbid severe illness on cardiovascular disease.

We also estimated the excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycaemia (the population attributable fraction), under the assumption that the observed association of severe hypoglycaemia with cardiovascular disease risk represented a causal effect. To estimate the population attributable fraction (PAF), we used the following formula: $PAF = p_c(RR-1)/RR$, where p_c is the proportion of exposure prevalence among patients who developed cardiovascular disease.[23] We estimated p_c using the frequency of severe hypoglycaemia seen in patients who developed cardiovascular disease in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial; only this study provided the frequency in question (35/1147=3.1%). We estimated the confidence interval for the population attributable fraction using the Monte Carlo method.[36] The analyses were performed using SAS version 9.3 and Stata version 12.1.

Results

Our initial search identified 3443 citations. Based on the titles and abstracts, 56 citations were considered potentially eligible and we evaluated the full texts of these 56 citations. A total of 50 studies were subsequently excluded; three were performed in acute hospital settings, one was a design paper, 34 did not report an association between hypoglycaemia and cardiovascular disease, and 12 were reviews or abstracts from meetings. Of the three excluded studies performed in acute hospital settings, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI-2) study showed an association between hypoglycaemia and cardiovascular disease, but its study participants were patients admitted to participating coronary care units for suspected acute myocardial infarction.[37] Thus, the DIGAMI-2 study was not included in this meta-analysis. We did not include the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[38] or the study by McCoy et al[39]; these studies provided relative risks for mortality associated with hypoglycaemia, but the relative risk for cardiovascular disease associated with severe hypoglycaemia was not available. Of the meeting abstracts identified through our search, two satisfied our eligibility criteria[40 41]; the full text articles were retrieved[25 27] and included in our meta-analysis. Therefore, six studies were eventually included in the meta-analysis (fig 1⇓).[1 2 24-27]

Study characteristics and quality assessment

Tables 1⇓ and 2⇓ show the characteristics of the studies included in the meta-analysis. Two studies (the ADVANCE[1] study and the Veterans Affairs Diabetes Trial [VADT][2]) were secondary analyses of randomised clinical trials, and the other four studies (Johnston et al,[24] Zhao et al,[25] Rathmann et al,[26] and Hsu et al[27]) were based on administrative databases. The number of participants ranged from 1522 to 860 845, with a mean age

range of 60-67 years and a mean duration of diabetes of 3.2-11.5 years; the follow-up period ranged from 1 to 5.6 years. The VADT,[2] Johnston et al,[24] and Zhao et al[25] studies were conducted in the United States; the ADVANCE study was done in Europe, Asia, Australia/New Zealand, and Canada[1]; Rathmann et al[26] in Germany; and Hsu et al[27] in Taiwan. The quality of the secondary analyses of randomised controlled trials (the ADVANCE study and VADT)[1 2] was generally high. The detailed quality assessment is described in supplementary text B and table A). All of the included studies adjusted for age, sex, history of cardiovascular disease, history of microvascular complications or its surrogate, baseline health status, and use of antihyperglycaemic agents. Other factors, such as race, dyslipidaemia, smoking status, and body mass index, were less consistently adjusted (table 2 and supplementary text). The impact of unmeasured comorbid severe illness was not assessed in these studies.

Conventional random effects meta-analysis

The six studies included 903 510 participants, with 1 to 5.6 years of follow-up. During the follow-up period, 0.6% to 5.8% experienced severe hypoglycaemia. The conventional random effects meta-analysis, which ignores unmeasured confounding, indicated that severe hypoglycaemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001) (table 3⇓ and fig 2⇓). Moderate heterogeneity among these studies was indicated (I^2=73.1%; P=0.002 for heterogeneity). There was little evidence of publication bias. The funnel plot did not indicate asymmetry; Begg's P value was 0.71 and Egger's bias coefficient was 1.49 (95% confidence interval −1.50 to 4.47; P=0.24) (see supplementary figure A). We also estimated the population attributable fraction for cardiovascular disease associated with severe hypoglycaemia, assuming that the observed association between severe hypoglycaemia and cardiovascular disease reflected a causal effect of severe hypoglycaemia on risk of cardiovascular disease in people with type 2 diabetes. The excess fraction of cardiovascular disease incidence attributable to severe hypoglycaemia was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001).

Stratified analysis

To examine possible sources of heterogeneity across studies, we carried out stratified analyses according to study design, study location, sex, duration of follow-up, insulin use, adjustment for race and dyslipidaemia, adjustment for smoking status, and adjustment for body mass index (table 3). Stratified analysis according to study design did not indicate apparent heterogeneity. Subgroups by duration of follow-up and by adjustment for race and dyslipidaemia seemed to differ in the magnitude of relative risk estimates. In a stratified analysis according to duration of follow-up, the pooled relative risk from studies with a duration of follow-up of more than one year[1 2 25-27] (that is, the pooled relative risk excluding the study by Johnston et al) was larger than the relative risk from the study by Johnston et al[24] (2.16, 95% confidence interval 1.77 to 2.64 *v* 1.79, 1.69 to 1.89; P=0.07 for interaction). In addition, the ADVANCE[1] study did not adjust for race and dyslipidaemia, and it had larger a relative risk than the pooled relative risk from the other studies[2 24-27] (3.45, 2.34 to 5.08 *v* 1.93, 1.70 to 2.18; P=0.005 for interaction). However, stratification by these factors did not explain much of the heterogeneity in results, with I^2 statistics moderate to high within each stratum.

Random effects meta-analysis with bias analysis

All studies showed a strong positive association between hypoglycaemia and cardiovascular disease (with point estimates of the relative risk ranging from 1.60 to 3.45). We performed a bias analysis to provide quantitative estimates, externally adjusted for comorbid severe illness (fig 3⇓ and supplementary table B). The bias analysis indicated that comorbid severe illness, alone, may not explain the observed association between severe hypoglycaemia and cardiovascular disease. To explain the association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycaemia and cardiovascular disease. For example, to account for the association, comorbid severe illness would have needed to be 10 times more prevalent in patients with severe hypoglycaemia than in those without severe hypoglycaemia, and would have to have had a relative risk of 10.

Discussion

In this meta-analysis of 903 510 people with type 2 diabetes, we observed a higher risk of cardiovascular disease among those with severe hypoglycaemia. The bias analysis indicated that the observed association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by severe comorbid illness. Although moderate heterogeneity across the studies was indicated, most subgroups showed similar results in stratified analyses. The strength of association observed in the ADVANCE[1] study seemed to be greater than that in the other studies, possibly owing to differences in adjustment for potential confounding factors, study design, or study population; the strength of association in Johnston et al was lesser than that of the other studies, possibly because of its short duration of follow-up (one year). Given the concern that severe hypoglycaemia might be a risk factor for cardiovascular disease, avoiding severe hypoglycaemia may be important to prevent cardiovascular disease, and less stringent glycaemic targets may be considered for people with type 2 diabetes who are at high risk for hypoglycaemia. The findings provide additional support for the patient centred approach of the intervention for type 2 diabetes and glycaemic goal setting that aims to minimise the risk of hypoglycaemia, as recommended by the American Diabetes Association and the European Association for the Study of Diabetes.[42]

The association of severe hypoglycaemia with a higher risk of cardiovascular disease is biologically plausible. The sympathetic nervous response to severe hypoglycaemia increases catecholamine levels, resulting in acute adverse effects on the myocardium and the vascular system.[11] The increase in catecholamine also leads to platelet activation, leucocyte mobilisation, and coagulation,[12] which may trigger cardiovascular disease events. Inflammation and endothelial dysfunction are also induced by acute hypoglycaemia,[13] and both play roles in the development of atherosclerosis. Furthermore, cardiac ischaemia or fatal arrhythmia during hypoglycaemia may lead to cardiovascular disease.[14 15]

Strengths and limitations of this review

The strengths of this study include the large sample size and the use of bias analysis. This type of analysis has the advantage of quantitatively accounting for possible sources of bias.[43] Most published meta-analyses of observational studies do not explicitly and quantifiably evaluate those sources; instead, they are usually discussed in a more qualitative and abbreviated manner. However, when there are concerns that biases may be large, or when the observed associations seem precise, bias analyses can play an important role in drawing conclusions from these results.[43] We encourage the use of bias analysis in meta-analyses of observational studies, especially when performing risk assessments or determining policy implications. This meta-analysis also has several limitations. Firstly, the analysis was confined to published studies, and individual patient data were not available. Although the funnel plot, Begg's test, or Egger's test did not indicate publication bias, the possibility of bias remains. For example, the ACCORD trial was not included in our meta-analysis because the relative risk for cardiovascular disease associated with severe hypoglycaemia was not available. If the findings from the ACCORD trial become available, the pooled estimates need to be updated. Secondly, several additional biases are likely to exist. Selection bias may exist, especially in studies using data extracted from electronic medical records,[25] claims based databases,[24 27] or primary care databases.[26] Biases due to measurement error are also likely to be present, and may vary, in the included studies. The ICD-9-CM (international classification of diseases, ninth revision, clinical modification) or ICD-10 (international classification of diseases, 10th revision) coding may have led to outcome misclassification, biasing the results. Thirdly, there may also be other confounders, in addition to comorbid severe illness. A confounder, however, is required to have an effect substantially larger than the observed association and have a strong association with exposure,[23] and comorbid severe illness is the only such factor currently suggested. Fourthly, the outcomes included heterogeneous manifestations of cardiovascular disease. Severe hypoglycaemia may have affected the risk of one or more, but not of all, of the subcategories of cardiovascular disease; this may have diluted the effect of severe hypoglycaemia on cardiovascular disease, as a single category, in this meta-analysis. Fifthly, all of the included studies examined the association between hypoglycaemia and cardiovascular disease in secondary analyses. Thus future work should include well designed, prospective cohort studies with the primary intention of evaluating the association between hypoglycaemia and risk of cardiovascular disease. Until then we believe that our results provide the best available evidence. Finally, our study was restricted to people with type 2 diabetes, which may limit the ability to generalise our findings to people with type 1 diabetes. Indeed, a recent study of relatively young people with type 1 diabetes found no association between severe hypoglycaemia and cardiovascular disease.[44] Although severe hypoglycaemia occurs more commonly in people with type 1 diabetes than those with type 2 diabetes, cardiovascular disease events are relatively rare among young people with type 1 diabetes.[44] Therefore, severe hypoglycaemia may have little impact on the risk of cardiovascular disease in these people.

Implications

Comorbid severe illness has been proposed to explain the positive association between severe hypoglycaemia and cardiovascular disease.[1] However, our bias analysis indicated that confounding due to comorbid severe illness is unlikely to explain the association. To explain this association, the prevalence of comorbid severe illness would have needed to be unrealistically high among patients who experienced severe hypoglycaemia, and the strength of the association between severe illness and cardiovascular disease would have needed to be extremely strong. Given that the observed association was already adjusted for a wide range of covariates, uncontrolled, residual severe illness in the individual studies was unlikely to be unequally distributed in this extreme fashion. Therefore, the

present findings suggest that the association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by comorbid severe illness.

New recommendations for antihyperglycaemic therapy in non-pregnant adults with type 2 diabetes have recently been proposed by the American Diabetes Association and the European Association for the Study of Diabetes[42]; these recommendations emphasise individualisation of glycaemic goals. Because intensive glucose control increases the risk of severe hypoglycaemia,[3] the findings of this study add to the evidence supporting individualised glycaemic targets in people with type 2 diabetes.[42 45] Intensive therapy in the ACCORD trial was associated with a 22% increase in total mortality and a threefold increase in severe hypoglycaemia.[5] Furthermore, a subgroup analysis of the ACCORD trial indicated that the increased mortality associated with intensive therapy was limited to those with a glycated haemoglobin (HbA_{1c}) level of >8.0%,[5] suggesting that intensive glycaemic control may not be appropriate for those with poor glycaemic control. Our findings also support the notion that glucose lowering agents with a low propensity to induce hypoglycaemia (for example, metformin[46]) should be considered to avoid hypoglycaemia. Importantly, many severe hypoglycaemic episodes are preceded by a change in food intake,[47] suggesting that such episodes could be prevented by behavioural changes. In addition, particularly for patients treated with insulin, self monitoring of blood glucose can be useful in preventing hypoglycaemia.[48]

Conclusions

In summary, results from this meta-analysis suggest that severe hypoglycaemia is associated with approximately twice the risk of cardiovascular disease. Furthermore, a bias analysis indicates that the observed association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by comorbid severe illness. The findings support the notion that avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

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What is already known on this topic

Earlier studies suggested a higher risk of cardiovascular disease in people with type 2 diabetes who experienced severe hypoglycaemia

The association is, however, controversial and some researchers have proposed that severe hypoglycaemia is merely a marker of comorbid severe illness

Moreover, a systematic and quantitative summary of published studies is not available

What this study adds

Conventional meta-analysis suggests that severe hypoglycaemia is associated with a higher risk of cardiovascular disease

Furthermore, a bias analysis indicates that comorbid severe illness alone may not entirely explain the positive association between severe hypoglycaemia and risk of cardiovascular disease

Avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes

infarction in patients with type 2 diabetes: a report from the DIGAMI 2 trial. *Heart* 2009;95:721-7.

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Tables

Table 1| Characteristics of studies included in meta-analysis

Study (year of publication), location	Male (%)	Mean age (years)	Follow-up (years)	No of participants	Duration of diabetes (years)
ADVANCE (2010), Europe, Asia, Australia/New Zealand, Canada[1]	58	66	5.0 (median)	11 140	8 (mean)
VADT (2011), USA[2]	97	60	5.6 (median)	1791	11.5 (mean)
Johnston et al (2011), USA[24]	51	61	1.0 (mean)	860 845	NA
Zhao et al (2012), USA[25]	96	63	3.9 (median)	1522	NA
Rathmann et al (2012), Germany[26]	53	67	2.0 (mean)	25 712	3.2 (mean)
Hsu et al (2012), Taiwan[27]	47	65	2.8 (mean)	2500	3.8 (mean)

NA=not available.

Table 2| Exposures, outcomes, and adjustment for potential confounders of studies included in meta-analysis

Study	Exposure assessment	Outcome assessment	Adjustment for potential confounders
ADVANCE[1]	Hypoglycaemic episode that caused transient dysfunction of central nervous system and prevented patients from treating themselves (requiring help from someone else). 231 patients (2.1%) experienced severe hypoglycaemic episode	Death from cardiovascular cause, non-fatal myocardial infarction, or non-fatal stroke, which were validated by independent adjudication committee. Outcome occurred in 35 patients with hypoglycaemic episode (16.8%) and 1112 without hypoglycaemic episode (10.2%)	Age, sex, treatment assignment, duration of diabetes, history of macrovascular or microvascular complications, smoking status at baseline, and time dependent covariates during follow-up (age, glycated haemoglobin (HbA$_{1c}$), body mass index, creatinine levels, ratio of urinary albumin to creatinine, systolic blood pressure, and use of antihyperglycaemic agents or antihypertensive agents)
VADT[2]	Hypoglycaemic episode within previous three months that was life threatening or fatal, caused disability or incapacity, or required admission to hospital or medical intervention. 104 patients (5.8%) experienced severe hypoglycaemic episode	Myocardial infarction, cardiovascular death, cardiovascular accident, amputation due to ischaemia, surgical intervention for vascular disease, new or worsening congestive heart failure, stroke, and inoperable coronary artery disease that were adjudicated by an endpoints committee. Outcome occurred in 499 patients (27.9%)	Age, treatment assignment, duration of diabetes, previous cardiovascular event, insulin use, race, smoking status, and glycated haemoglobin (HbA$_{1c}$) at baseline. Time dependent covariates during follow-up included total cholesterol, high density lipoprotein cholesterol, and creatinine levels
Johnston et al[24]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.0, 251.1, 251.2, and 250.8) using healthcare claims. 27 065 patients (3.1%) experienced hypoglycaemic episode	ICD-9-CM coded coronary artery bypass graft, revascularisation, percutaneous coronary intervention, acute myocardial infarction, or incidence of unstable angina, identified by healthcare claims. Outcome occurred in 5.3% of patients with hypoglycaemic episode and 2.2% without hypoglycaemic episode	Age, sex, location of residence, insurance type, Charlson comorbidity index, Agency for Healthcare and Research Quality comorbidity index, hypercholesterolaemia, hypertension, peripheral vascular disease, chronic kidney disease, baseline microvascular complications, baseline medical expenditures, number of medical encounters with diagnosis of diabetes, previous cardiovascular disease, and use of antihyperglycaemic, antiplatelet, antihypertensive, or anticoagulant agents
Zhao et al[25]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.0, 251.1, 251.2, and 250.8) using data from electronic medical records. 761 patients (1.7%) experienced hypoglycaemic episode	ICD-9-CM coded myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease identified by data from electronic medical records. Outcome occurred in 30.65% patients with hypoglycaemic episode and 17.48% without hypoglycaemic episode	Age, sex, race, marital status, body mass index, insurance, renal disease, mental disorder, substance misuse, tobacco use, Charlson comorbidity index, and use of antihyperglycaemic agents, antihypertensive agents, or statins
Rathmann et al[26]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-10 codes E16.0, E16.1 and E16.2) using primary care databases. Hypoglycaemic episode documented in 0.7% of patients	ICD-10 coded coronary heart disease, myocardial infarction, stroke, and peripheral vascular disease, identified by data from primary care databases. Outcome occurred in 12.5% of patients	Age, sex, location of residence, insurance type, practice (diabetologist), Charlson comorbidity index, hyperlipidaemia, hypertension, baseline microvascular complications, and use of antihyperglycaemic, antihypertensive, lipid lowering, or antithrombotic agents
Hsu et al[27]	Hypoglycaemic episode identified by diagnosis of hypoglycaemia (ICD-9-CM codes 251.2×) using inpatient claims. Hypoglycaemic episode documented in 0.6% of patients	ICD-9-CM coded cardiovascular diseases (ICD-9-CM codes 390 to 459) from hospital claim dataset. Outcome occurred in 106/1000 person years in patients without hypoglycaemic episode and 324/1000 person years in patients with hypoglycaemic episode	Age, sex, duration of diabetes, dyslipidaemia, hypertension, atrial fibrillation, liver cirrhosis, renal disease, mental disease, previous cancer, previous stroke, previous heart disease, high social economic status, good compliance, and use of antihyperglycaemic agents

Table 3| **Stratified analysis of severe hypoglycaemia and risk of cardiovascular disease**

Group	No of studies	Relative risk* (95% CI)	P for heterogeneity†	I² (%)	P for interaction‡
Total	6	2.05 (1.74 to 2.42)	0.002	73.1	
Design:					
Prospective	2	2.67 (1.48 to 4.80)	0.10	63.8	0.29
Retrospective	4	1.93 (1.68 to 2.21)	0.03	65.4	
Study location:					
USA	3	1.81 (1.71 to 1.90)	0.58	0.0	0.18
Non-USA	3	2.29 (1.62 to 3.24)	0.02	76.2	
Sex:					
Men (>95%)	2	1.99 (1.64 to 2.41)	0.85	0	0.71
Both	4	2.10 (1.67 to 2.65)	<0.001	83.4	
Follow-up (years):					
>1	5	2.16 (1.77 to 2.64)	0.048	58.2	0.07
≤1	1	1.79 (1.69 to 1.89)	—	—	
Insulin users:					
Included	5	2.13 (1.77 to 2.57)	0.001	77.6	0.15
Excluded	1	1.60 (1.13 to 2.26)	—	—	
Adjustment for race and dyslipidaemia:					
Yes	5	1.93 (1.70 to 2.18)	0.07	53.9	0.005
No	1	3.45 (2.34 to 5.08)	—	—	
Adjustment for smoking status:					
Yes	3	2.37 (1.61 to 3.47)	0.043	68.2	0.32
No	3	1.91 (1.59 to 2.29)	0.02	75.0	
Adjustment for body mass index:					
Yes	2	2.56 (1.50 to 4.36)	0.01	83.3	0.30
No	4	1.91 (1.62 to 2.34)	0.046	62.5	

*Relative risk estimates obtained using conventional random effects model.

†P values for heterogeneity across studies computed using Cochrane's Q test.

‡P values for comparisons between subgroups computed using χ^2 test with 1 degree of freedom.
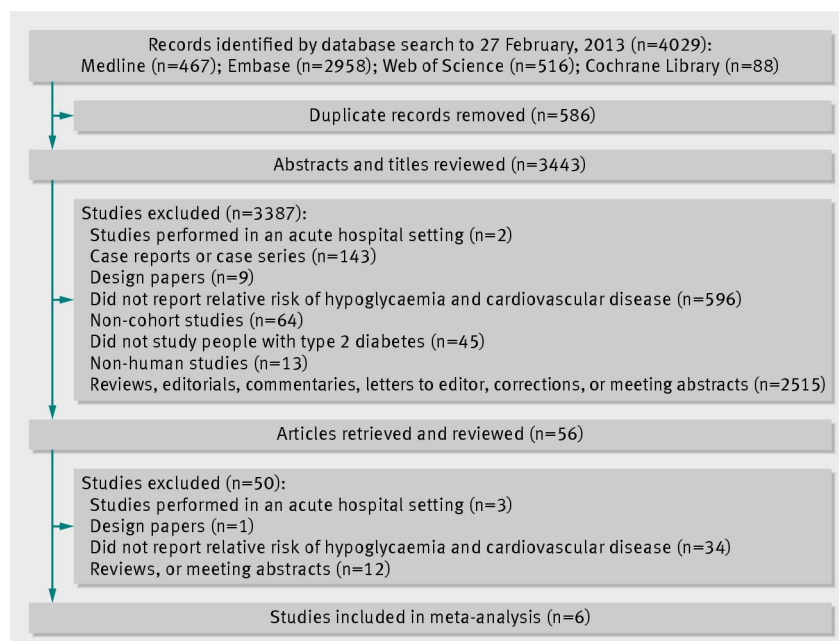
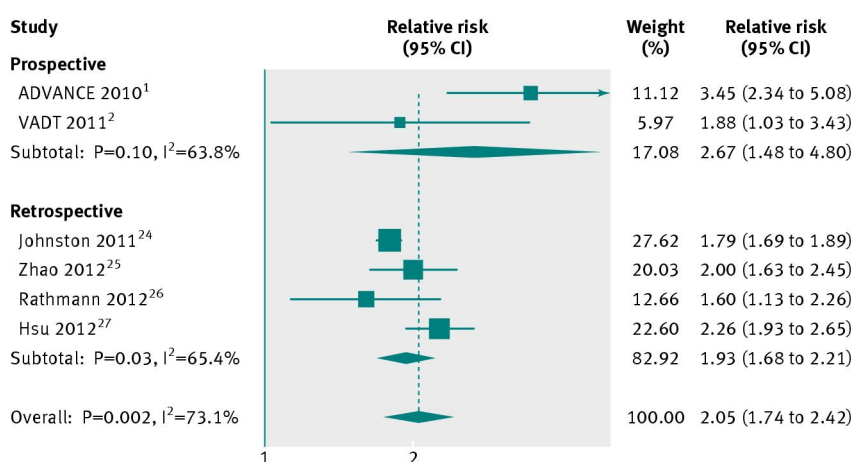# Figures

Fig 1 Flow of studies through review

Fig 2 Conventional random effects meta-analysis according to study design. ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT=Veterans Affairs Diabetes Trial. Dots indicate relative risks for severe hypoglycaemia and cardiovascular events in people with type 2 diabetes. Horizontal lines indicate 95% confidence intervals for relative risks. Diamonds represent pooled relative risk estimates with 95% confidence intervals
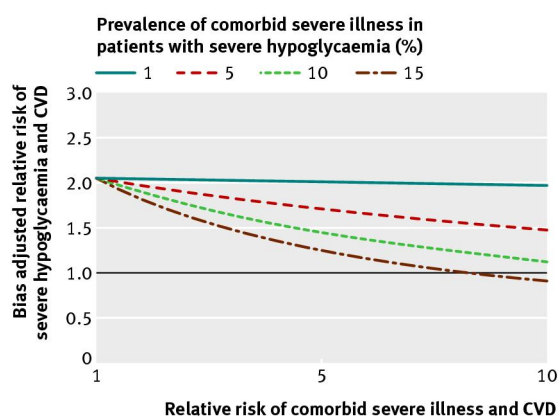
Fig 3 Random effects meta-analysis with bias analysis. Bias adjusted relative risks of severe hypoglycaemia and cardiovascular disease were computed to examine the sensitivity of the association to possible confounding by comorbid severe illness. The prevalence of comorbid severe illness in patients without severe hypoglycaemia was assumed to be 0.5%. CVD=cardiovascular disease