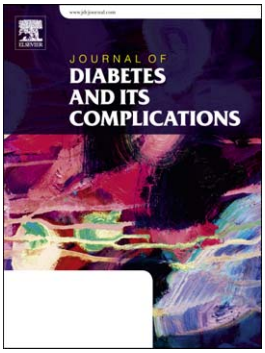

Meta-Analysis: Association between Hypoglycaemia and Serious Adverse Events in Older Patients

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Running title: Hypoglycaemia and Serious Adverse Events

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Aims: We aimed to conduct a meta-analysis of serious adverse events (macro- and micro-vascular events, falls and fractures, death) associated with hypoglycaemia in older patients.

Methods: We searched MEDLINE and EMBASE spanning a ten-year period up to March 2015 (with automated PubMed updates to October 2015). We selected observational studies reporting on hypoglycaemia and associated serious adverse events, and conducted a meta-analysis. We assessed study validity based on ascertainment of hypoglycaemia, adverse events and adjustment for confounders.

Results: We included 17 studies involving 1.5 million participants. Meta-analysis of eight studies demonstrated that hypoglycemic episodes were associated with macrovascular complications, odds ratio (OR) 1.83 (95% Confidence Interval [CI] 1.64, 2.05), and microvascular complications in two studies OR 1.77 (95% CI 1.49, 2.10). Meta-analysis of four studies demonstrated an association between hypoglycaemia and falls or fractures, OR 1.89 (95% CI 1.54, 2.32) and 1.92 (95% CI 1.56, 2.38) respectively. Hypoglycaemia was associated with increased likelihood of death in a meta-analysis of eight studies, OR 2.04 (95% Confidence Interval 1.68, 2.47).

Conclusion*:* Our meta-analysis raises major concerns about a range of serious adverse events associated with hypoglycaemia. Clinicians should prioritize individualized therapy and closer monitoring strategies to avoid hypoglycaemia in susceptible older patients.

Keywords: Hypoglycaemia, Diabetes Mellitus, Falls, Fractures, Cardiovascular Disease

Introduction

Diabetes is major chronic disease, affecting millions of people worldwide. In the UK, it is seen in 10-25% of older people and is often associated with other co-morbidities, such as cardiovascular disease and cognitive impairment (Sinclair et al., 2001). Hamada et al found that 28% of over 80-year olds in the UK had co-morbid diabetes and cardiovascular disease and 5% had co-morbid diabetes and cognitive impairment/dementia (Hamada and Gulliford, 2015). This vulnerable group of people is also at an increased risk of falls (Schwartz et al., 2008), which result in an estimated £1.1billion in hospital costs annually from hip fractures in the UK (Leal et al., 2015).

Hypoglycaemia is a well-recognised side effect of diabetes treatment and concerns have been raised about potentially serious consequences of hypoglycaemia on the cardiovascular system and cognition in older people (Frier et al., 2011) (Mattishent and Loke, 2015). Bloomfield et al found evidence for an association between severe hypoglycaemia and all-cause mortality, neurological events, hospital and emergency department utilization and decreased quality of life, but there was insufficient data on cardiovascular disease, falls and traumatic injuries (Bloomfield et al., 2012). More recent evidence has since emerged from an observational study reporting an association between hypoglycaemia and falls, whilst a meta-analysis of six studies revealed a significantly increased likelihood of cardiovascular disease associated with severe hypoglycaemia (Chiba et al., 2015) (Goto et al., 2013).

In light of these recent developments, we aimed to systematically review and analyze contemporary evidence on the relationship between hypoglycaemia and adverse events (vascular events, falls and fractures, death) in older patients treated with glucose lowering drugs. We focused on vascular adverse events because patients with diabetes have an increased risk of micro- and macro- vascular disease (Bloomfield et al., 2012) and cardiovascular events remains the primary cause of death among insulin-treated people with diabetes (Khunti et al., 2015). We also aimed to evaluate falls and fractures because injuries are a leading cause of death in older people and can result in significant physical, psychological and social consequences (Thapa et al., 1996).

Material and Methods

Data sources and searches

Our database search covered MEDLINE and EMBASE for 10 years up to March 2015 (details of the search are provided in the supplementary **eMethods**), restricted to English language articles. The search was focused on the last 10 years, as we wanted more recent studies based on contemporary practice and populations. In addition, we received PubMed automated updates (most recent October 2015) regarding newly published articles on hypoglycaemia in older patients. We reviewed the reference lists of included studies for any potentially relevant studies.

Study selection

We specified inclusion criteria for cohort studies (prospective and retrospective), that examined the association between hypoglycaemia and serious adverse events.

We included studies that enrolled participants aged >55 years who had pre-diabetes or diabetes mellitus. The outcomes of interest were macro- and micro-vascular events, fall, fractures, and death. We excluded reviews and abstracts.

Data extraction and quality assessment

Study screening and data extraction was performed by the authors, by independently scanning all titles and abstracts for relevant articles, before obtaining full text versions for further checking. YKL and KM resolved uncertainties and discrepancies through discussion.

Data collection was completed by using a standardized form, which included details of the study design, date of the study and country of origin, setting, selection criteria, participants' characteristics and outcome measures. Odds or hazard ratios were extracted as a measure of the association between hypoglycaemia and adverse events.

In order to assess study validity, YKL and KM independently checked the methods used for recording hypoglycaemia and determining serious adverse events, as well as adjustment for potential confounding factors.

Data synthesis and analysis

A random effects meta-analysis of odds ratios using inverse variance method (Revman 5.3, Nordic Cochrane Centre, Kobenhavn) was performed. Heterogeneity was assessed by using the chi-squared test, I^2 statistic and visual inspection of the

forest plots. We aimed to construct a Funnel plot if we had more than 10 studies in the meta-analysis (without evidence of statistical heterogeneity). We did not have a pre-registered protocol on web registry.

Results

We screened 1273 citations and included 17 studies with a total of 1498358 participants in the meta-analysis (Bonds et al., 2010, Chiba et al., 2015, Duckworth et al., 2011, Hsu et al., 2013, Origin Trial Investigators et al., 2013, Johnston et al., 2012, Johnston et al., 2011, Kachroo et al., 2015, Khunti et al., 2015, Majumdar et al., 2013, McCoy et al., 2012, Rajpathak et al., 2015, Rathmann et al., 2013, Signorovitch et al., 2013, Zhao et al., 2012, Zhao et al., 2015, Zoungas et al., 2010). The flow chart of the study selection in shown in the supplementary **eFigure**. Characteristics of the included studies and participants are shown in the supplementary **eTable**.

The included studies consisted of twelve retrospective, one prospective and four post-hoc analyses of randomized controlled trials (RCTs). The studies had a total of participants (sample size from 211 to 860,845). Geographical locations were diverse and included North America, Japan, Taiwan and Europe. All the included studies were conducted in older patients (mean age >60 years, or participants selected on basis of being 60 years of age or older).

Thirteen studies focused on patients with Type 2 diabetes, whereas the remaining four had a mix of Type 1, Type 2 and impaired glucose tolerance/impaired fasting glucose. Four of the studies looked only at oral agents. The remaining studies included insulin users as well as patients on oral antidiabetic drugs (or a mix of insulin and tablets).

We report details of study validity (ascertainment of adverse outcomes, and confounding factors) in Table 1, and summarize the key features below.

Measurement of hypoglycemic events

Most of the studies relied on hospital or claims data records. Two studies provided participants with diaries and glucose meters (Origin Trial Investigators et al., 2013) (Bonds et al., 2010) and two studies relied on questionnaires (Chiba et al., 2015) (McCoy et al., 2012). Two of the studies relied on routine trial monitoring (Duckworth et al., 2011) (Zoungas et al., 2010).

Measurement of adverse events

Four of the included studies used pre-specified outcomes from RCTs with independent adjudication by a blinded committee. Twelve studies measured adverse events through database or medical records codes and one study relied on a professional interviewer with questionnaire (Chiba et al., 2015).

Confounding factors

All studies attempted to address confounding through the use of multiple logistic regression models, and in addition three studies used Propensity Scores (Hsu et al., 2013) (Origin Trial Investigators et al., 2013, Zhao et al., 2012) .

Meta-analysis

Association between hypoglycaemia and vascular disease (Figure 1)

We included eight studies in the meta-analysis for macrovascular complications(Duckworth et al., 2011, Hsu et al., 2013, Origin Trial Investigators et

al., 2013, Johnston et al., 2011, Khunti et al., 2015, Rathmann et al., 2013, Zhao et al., 2012, Zoungas et al., 2010) . The pooled odds ratio was 1.83 (95% Confidence Interval 1.64, 2.05). There was moderate heterogeneity (chi-squared p= 0.07, I^2=46%). Hypoglycaemia was significantly associated with macrovascular complications.

There are two studies in the meta-analysis which reported on the association between hypoglycaemia and microvascular complications (Zhao et al., 2012, Zoungas et al., 2010). The pooled odds ratio was 1.77 (95% Confidence Interval 1.49, 2.10) with no evidence of heterogeneity (chi-squared p= 0.90, I^2=0%).

Association between hypoglycaemia and falls or fractures (Figure 2)

There are four studies reporting on falls (Chiba et al., 2015) (Kachroo et al., 2015) (Signorovitch et al., 2013) (Zhao et al., 2015) with a pooled odds ratio of 1.89 (95% Confidence Interval 1.54, 2.32) and moderate heterogeneity (chi-squared p= 0.16, I^2=43%).

We included three studies for fractures (Johnston et al., 2012) (Kachroo et al., 2015) (Rajpathak et al., 2015) with a pooled odds ratio of 1.92 (95% Confidence Interval 1.56, 2.38) and substantial heterogeneity (chi-squared p= 0.07, I^2=63%).

Association between hypoglycaemia and mortality (Figure 3)

There are eight studies reporting on overall mortality with a pooled odds ratio of 2.04 (95% Confidence Interval 1.68, 2.47) with substantial heterogeneity (chi-squared p< 0.001, I^2=82%)(Bonds et al., 2010, Hsu et al., 2013, Origin Trial

Investigators et al., 2013, Khunti et al., 2015, Majumdar et al., 2013, McCoy et al., 2012, Zhao et al., 2012, Zoungas et al., 2010). Despite the heterogeneity, we note that direction of association was consistent across all the studies in the Forest plot.

We explored the contribution of the specific studies to the heterogeneity, by removing single studies, one at a time, and we found that the only occasion where heterogeneity was markedly reduced (from 82% to 63%) was when Zhao's study was excluded. (Zhao et al., 2012) This is the only study that did not find a statistically significant association between hypoglycaemia and mortality (Hazard Ratio 1.29 with a 95% Confidence Interval 0.94, 1.77), which the authors attributed to small sample size (number of patients evaluated in the matched cohort was 1522).

We identified two studies that reported on the association between hypoglycaemia and a death due to a cardiovascular cause (Origin Trial Investigators et al., 2013) (Zoungas et al., 2010). The pooled OR was 2.07 (95% Confidence Interval 1.34, 3.21) for this association.

Sensitivity Analysis

We aimed to clarify the temporal relationship between cardiovascular events and hypoglycaemia through a sensitivity analysis restricted to studies that excluded participants who had a history of recent macrovascular events. Pooled analysis of three studies showed that hypoglycaemia was significantly associated with new-onset macrovascular events, OR 1.76 (1.42, 2.18).

Publication bias and selective outcome reporting

We did not construct a funnel plot, because we did not have more than ten studies for any specific outcome.

Discussion

Our meta-analysis of 17 observational studies (involving a total of almost 1.5 million participants) raises major concerns about a range of serious adverse events associated with hypoglycaemia in older patients treated with glucose-lowering drugs. We found consistent evidence of an 80% relative increase in the likelihood of vascular events (both macro- and microvascular complications, as well as cardiovascular death) with hypoglycemic episodes. Our meta-analysis also addresses previous uncertainties by revealing a significant relationship between hypoglycaemia and risk of falls and fractures, as well as a doubling in the likelihood of death**.** The abundance and consistency of evidence regarding serious harm leads us to believe that treatment strategies aimed at minimizing hypoglycaemia should be prioritized in older patients who are already prone to suffer from cardiovascular events, falls, and fractures.

There are a number of proposed biological mechanisms behind the adverse impact of hypoglycaemia on the cardiovascular system. Hypoglycaemia can lead to activation of the sympatho-adrenal system resulting in end-organ stimulation and release of adrenaline. This in turn provokes autonomic and hemodynamic changes resulting in an increased heart rate and peripheral systolic blood pressure, a fall in central blood pressure, reduced peripheral arterial resistance, increased myocardial

contractility, stroke volume and cardiac output (Frier et al., 2011) (Wright and Frier, 2008). The effect of all of these physiological changes is cardiac stress, which can have potentially serious consequences (eg myocardial ischaemia) in older people with diabetes and likely underlying coronary artery disease. In addition, the first hypoglycemic episode can lead to further episodes that are asymptomatic and associated with cardiovascular and proarrhythmic changes (Zhao et al., 2012). Evidence has also shown that hypoglycaemia can result in abnormal electrical activity in the heart, strengthening the theory that hypoglycaemia can provoke sudden death (Frier et al., 2011). Episodes of hypoglycaemia also result in impaired cardiac autonomic function which is associated with increased mortality among with patients at high cardiovascular risk, including those with diabetes (Zoungas et al., 2010).

Interestingly, Yun et al have recently published the findings of a prospective cohort study demonstrating that a history of cardiovascular disease was an independent risk factor for the development of severe hypoglycaemia (Yun et al., 2015). In order to assess the possibility of cardiovascular disease causing hypoglycaemia rather than the other way round, we conducted a sensitivity analysis based on studies that excluded patients with recent cardiovascular events. Our findings indicate that hypoglycaemia was associated with incident cardiovascular events, even in those patients with no cardiovascular history. Khunti et al. assessed the association between hypoglycaemia and cardiovascular events in subgroups of patients with, or without cardiovascular history, and found that the risk was similarly elevated in both subgroups, (Khunti et al., 2015) thus refuting Yun's hypothesis.

Alternatively, hypoglycaemia may simply be a surrogate marker/indicator for greater disease burden or frailty in older patients, and there may actually be no direct mechanistic pathway linking hypoglycaemia to cardiovascular events or death(Bonds et al., 2010, Origin Trial Investigators et al., 2013) . However, Goto's review included a bias analysis which reported that comorbid severe illness alone would not be sufficient to explain the reported association between hypoglycaemia and cardiovascular disease. (Goto et al., 2013) Given the multi-factorial nature of adverse events in the elderly, it seems prudent to consider that hypoglycaemia may be one factor amongst a host of others that can contribute to serious harm, and that all efforts should be made to reduce this risk. It is also tempting to speculate whether hypoglycaemia episodes that trigger acute cardiovascular events may be the unifying factor in explaining the associated falls and increased mortality (particularly as our meta-analysis identified an increased likelihood of death from cardiovascular cause in patients with hypoglycaemia).

Strengths

Our systematic review and meta-analysis provides a comprehensive synthesis of the most up to date evidence covering a range of adverse events that are a major burden in older patients with diabetes. We have overcome the uncertainties regarding cardiovascular events and fall/fractures that were limitations within Bloomfield's wide-ranging systematic review (Bloomfield et al., 2012). We have further built upon Goto's cardiovascular-focused systematic review,(Goto et al., 2013) by including additional studies to distinguish between macrovascular and

microvascular events, and conducting a specific analysis of cardiovascular deaths and overall mortality, rather than just composite cardiovascular events.

Limitations

We are aware of limitations in our meta-analyses, in particular the inability to prove causality due to the observational nature of the studies. However, we do not consider it ethical or feasible to conduct a randomized trial in older patients to expose them to hypoglycaemia. We chose to restrict our search to articles published in the past 10 years in order to focus on contemporary management of diabetes mellitus rather than more historical approaches, and our synthesis was restricted to English-language articles only.

There is some heterogeneity, especially regarding the association between hypoglycaemia and mortality. This may stem from differences amongst the included study designs, which included post-hoc analyses of randomized controlled trials, in contrast to observational studies involving healthcare databases. We also noted considerable variation in the severity of disease and use of hypoglycaemic agents in the patients, and this may account for heterogeneity in subsequent risk of adverse events. Moreover, the included studies employed a very wide definition of adverse events, particularly when constructing a composite endpoint for vascular disease. This stems from the variation in the use of administrative codes for the definition of cardiovascular events, as well as hypoglycaemia.

Our systematic review and meta-analysis highlights the importance of avoiding hypoglycaemia. This is especially true in older patients with diabetes mellitus and other co-morbidities, as they are at risk of serious adverse events associated with hypoglycemic episodes. Individualized treatment rather than achieving rigid targets should be a priority. This approach has recently also been highlighted by Caverley et al and coincides with the Department of Veterans' Affairs' launch of a hypoglycaemia safety initiative to decrease overtreatment among veterans with diabetes mellitus (Caverly et al., 2015) (Office of Public and Intergovernmental Affairs, 2014). Older patients and their physicians should aim to strike a pragmatic individualized balance between tight blood sugar control against the avoidance of adverse drug reactions, in particular hypoglycaemia and its associated serious harm.

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Contributors: KM and YKL conceived the study, conducted study selection and data extraction, and analysed the data. Both authors drafted the manuscript and approved the final version. YKL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Table 1: Study outcomes, results and risk of bias

Study ID	Method of diagnosing each type of adverse event	Method of diagnosing or determining that patients had hypoglycemia	Statistical adjustments for confounding factors (if any)	Results with 95% CI
Bonds 2010 (Bonds et al., 2010)	Pre-specified primary outcome: non-fatal MI or non-fatal stroke and cardiovascular death Pre-specified secondary outcome: all cause mortality Blinded independent adjudication of outcomes	Investigators asked patients (who were given home glucose monitors) about hypoglycemic events at each visit. -symptomatic severe hypoglycemic event requiring medical assistance (HMA); blood glucose <2.8mmol/L or symptoms resolved with treatment -symptomatic severe hypoglycemic event requiring any assistance (HA)	Cox regression models (stepwise procedure) Confounders: baseline covariates, age, gender, ethnicity, education, BMI, alcohol, smoking, cardiovascular disease, diabetes duration, diabetic complications, cardiovascular risk factors, medication, trial treatment assignment	Association between any hypoglycemic event and mortality intensive arm aHR 1.41 (1.03, 1.93) standard care arm aHR 2.30 (1.46, 3.65)
Chiba 2015 (Chiba et al., 2015)	Professional interviewer with questionnaire about frequency and type of falls (defined as unexpected event in which the person came to rest on the ground, floor, lower level. Complicated with a head injury or fractures).	Professional interviewer with validated questionnaire regarding hypoglycemic symptoms. Severe: coma, convulsion, inability of self-management and recovery from symptoms. Mild: hypoglycemic symptoms with recovery within 10 minutes by self-administered sugar or glucose.	Multiple regression analysis: age, sex, cognitive impairment (MMSE <26), TUG score, GDS-15 scores, Falls Risk Index, presence of hypoglycemia.	Presence of hypoglycemia OR 3.62 (1.24, 10.53), associated with presence of multiple falls, and any fall OR 2.05 (0.93-4.535). Prevalence of falls increased as the frequency of hypoglycemia increased.
Duckworth 2011 (Duckworth et al., 2011)	Cardiovascular event is pre-specified composite: MI, stroke, CV death, cardiac failure, vascular surgery, inoperable coronary artery disease, amputation for gangrene Blinded independent adjudication of outcomes	Routine trial monitoring for adverse events	Multivariate regression analysis Confounders: prior cardiovascular event, age, baseline insulin, ethnicity, smoking status, HbA1c, lipids, creatinine, diabetes treatment and duration	HR for composite cardiovascular event 1.88 (1.029, 3.432)
Hsu 2013 (Hsu	Cancer, stroke, coronary heart disease	Hospital claims dataset for severe	Propensity score, Cox proportional	HR 2.09 (1.63, 2.67) for

et al., 2013)	and cardiovascular disease identified from hospital claims dataset, ICD-9-CM codes Death status ascertained according to discharge reasons with death or critically ill at discharge, or if insurance cover stopped due to death.	hypoglycemia Outpatient claims dataset for mild hypoglycemia ICD-9-CM codes	hazard model, Kaplan-Meier Variables in propensity score matching: age, sex, diabetes duration, hypertension, heart disease, renal and liver disease, cancer, mental disease, socio-economic status, treatment adherence.	cardiovascular diseases, HR 2.51 (2.00, 3.16) for all-cause hospitalisation, HR 2.48 (1.41, 4.38) for total mortality
Johnston 2011 (Johnston et al., 2011)	Acute cardiovascular events: coronary artery bypass graft, revascularisation, percutaneous coronary intervention – ≥one inpatient or outpatient claim ICD-9-CM code Acute MI, incident unstable angina – ≥1 inpatient claim with an ICD-9-CM code	≥1 outpatient claim with ICD-9-CM diagnosis code for hypoglycemia (hypoglycemic events were allowed to occur at any time during the evaluation period, including after acute cardiovascular events)	Multiple logistic regression and backwards stepwise selection Adjusted for age, sex, geography, insurance type, comorbidity scores, cardiovascular risk and prior events, diabetes complications, total baseline medical expenditures.	OR 1.79 (1.69, 1.89) for acute cardiovascular events Patients >age 65 years OR1.78 (1.65, 1.92)
Johnston 2012 (Johnston et al., 2012)	Emergency department claim with ICD-9-CM diagnosis code, for fractures of the spine, hip, pelvis, femur, leg, ankle, upper arm, forearm and hand Broad algorithm: fall-related fracture without evidence of associated code for non-fall causes. Narrow algorithm: fall-related fracture with associated code for falls.	≥1 outpatient claim with ICD-9-CM diagnosis code for hypoglycemia (hypoglycemic events allowed to occur at any time during evaluation period, including after fracture)	Multiple logistic regression Confounders: patient demographics, baseline co-morbid conditions, baseline medications, CCI, medical encounters for diabetes, total baseline medical expenditures, number of medical codes	aOR for fall-related fractures 1.70 (1.58, 1.83). Findings were similar for both the broad and narrow algorithm.
Kacharoo 2015 (Kachroo et al., 2015)	Admin claim data for fall-related events (ICD-9-CM codes for fractures and head injury, with fall being the external cause based on ICD-9-CM E-codes E880-E888 recorded within +/-2 days of each other in any order.	Admin claim data ICD-9-CM codes 250.8, 251.0, 251.1 and 251.2	Logistic regression analysis Patients matched on age and gender; statistical adjustment on CCI	Risk of fall-related events aOR 1.95 (1.70, 2.2) Fracture – aOR 2.16 (1.74 -2.67)
Khunti 2015 (Khunti et al.,	Cardiovascular event defined as a composite of MI, stroke or	Data on hypoglycemic episodes were obtained from HES via ICD-10 codes	Mutivariate Cox regression models Covariates: age, sex, smoking status,	All-cause mortality for T2DM: HR 1.94 (1.52,

2015)	cardiovascular death (cause of death obtained through linkage to Office for National Statistics).	9E16.0, E16.2)	geographical region, history of cardiovascular events before index date, use of oral antidiabetic medications, Charlson comorbidity index, BMI, HbA1c	2.47) and 2.39 (2.13, 2.67) for those with and without a history of CVD Cardiovascular events for T2DM: HR 1.70 (1.09, 2.64) and 1.50 (1.19, 1.88) for those with and without a history of CVD
Majumdar 2013 (Majumdar et al., 2013)	Primary outcome: all-cause mortality Secondary end points included all-cause hospitalisations and hypoglycemia-associated hospitalisations. Mortality and dates of hospitalisation determined by linkage to provincial health ministry databases.	Defined severe hypoglycemia by the presence of any inpatient discharge diagnosis of hypoglycemia (ICD-10 code E15 or E16)	Multivariable Cox proportional hazard methods Adjusted for age, sex, socioeconomic status (based on individual health insurance premium level and median neighbourhood income), index eGFR, prevalent hypoglycemia, co-morbidities, use of diabetes medications	Mortality associated with any hospitalisation with hypoglycemia in patients with diabetes: aHR 2.46 (2.17, 2.80)
McCoy 2012 (McCoy et al., 2012)	Ascertainment of mortality from medical records and social security death index	Investigator asked patients about hypoglycemic events -mild hypoglycemia: symptoms consistent with hypoglycemia not requiring any assistance -severe hypoglycemia: similar symptoms requiring external assistance	Logistic regression Confounders: age, gender, type of diabetes and duration, CCI, HbA1c	OR 3.38 (1.55, 7.39) Association between severe hypoglycemia and 5 year mortality
Mellbin 2013 (Origin Trial Investigators et al., 2013)	Composite of cardiovascular death (any death for which no non-cardiovascular cause could be identified), non-fatal MI (based on clinical presentation, elevated cardiac markers, and /or new electrocardiographic changes), or stroke (based on clinical presentation and imaging) -Mortality	Participants recorded hypoglycemic events with glucose meters and diaries. Investigators asked about hypoglycemia at each study visit. Non-severe hypoglycemia: relevant symptoms confirmed by glucose reading <3mmol/L. -severe hypoglycemia: symptomatic	Propensity score matching, as well as Cox regression models addressing potential confounders: age, gender, ethnicity, education, prior cardiovascular events, hypertension, depression, current smoking, alcohol intake, albumin/creatinine ratio >30 mg/g, diabetes and cardiovascular drugs, BMI, waist-hip ratio, HbA1c, fasting plasma	In those with severe hypoglycemia HR 1.58 (1.24, 2.02) for composite event. HR 1.71 (1.27, 2.30) for cardiovascular death. HR 1.74 (1.39, 2.19) for

	Blinded independent adjudication of outcomes	hypoglycemia requiring assistance of another person with (i) prompt recovery after oral carbohydrate and/or (ii) documented plasma glucose level <2mmol/L	glucose, lipids, serum creatinine, mini-mental status, prior diabetes mellitus	total mortality.
Rajpathak 2015 (Rajpathak et al., 2015)	Hip fracture defined as an ICD-9 code 820.xx recorded at any clinical encounter.	ICD-9 codes based on validated algorithm	Multivariable logistic regression based on propensity score as well as adjustment for confounders:: age, sex, Medicare cover, region, coronary heart disease, stroke, osteoporosis, dementia, CKD	aOR 2.42 (1.35, 4.34) for hip fractures in those with documented hypoglycemia
Rathmann 2013 (Rathmann et al., 2013)	Macrovascular complications were determined based on primary care diagnoses (ICD-10 codes) for coronary heart disease (I20, I24 and I25), MI (I21, I22, I23 and I25.2), stroke (I63, I64, G45) and peripheral vascular disease (E10.5, E11.5, E14.5 and I73.9)	ICD-10 codings (E16.0, E16.1, E16.2) Frequency of patients with >1 hypoglycemic event assessed 30, 90, 183, 365 and 730 days after index date	Adjusted for age, sex, type of practise (diabetologist), practise region, health insurance status (private), antidiabetic co-medication, episodes of hypoglycemia, microvascular complications, hypertension, hyperlipidaemia, antihypertensive, lipid-lowering and antithrombotic drugs and Charlson co-morbidity index	HR 1.6 (1.1, 2.2) for incident macrovascular complications
Signorovitch 2013 (Signorovitch et al., 2013)	Inpatient and emergency department claims based on ICD9-CM codes, grouped into three codes: accidental falls, motor vehicle accidents and other accidents	ICD-9-CM codes for hypoglycemia at any place of service	Multivariable Cox-proportional hazard models adjusted for age, gender, demographics, co-morbidities of diabetes, accident risk factors, CCI, inpatient admissions, use of oral hypoglycemics.	Hypoglycemia associated with accidental falls aHR 1.36 (1.13, 1.65) For age >65: aHR 1.52 (1.18, 195)
Zhao 2012 (Zhao et al., 2012)	ICD-9-CM codes. Macrovascular: MI, stroke, congestive heart failure, peripheral vascular disease. Microvascular: renal, ophthalmic or neurologic manifestations with diabetes.	ICD-9-CM codes	Propensity score matching (greedy 5 to 1 method) for noncomparable baseline characteristics Cox proportional hazard regression models controlling for covariates, including baseline demographic and illness characteristics, vital signs, prior	HR 2.00 (1.63-2.44) for cardiovascular events, HR 1.76 (1.46, 2.11) for microvascular complications HR 1.29 (0.94, 1.77) for mortality.

			medication, and index drug	
Zhao 2015 (Zhao et al., 2015)	Fall-related events (fractures, head injuries) defined using ICD-9-CM codes between 800.x-995.x, with a fall being the external cause (based on ICD-9-CM E-codes E880- E888 within two-day window).	ICD-9-CM codes	McNemar tests, Generalised estimating equation (GEE) Matching on age, gender, ethnicity and medical service Adjustments for social demographic and illness characteristics, vital signs and medication use	aOR 2.70 (1.64, 4.47) for fall-related events in the hypoglycemia group
Zoungas 2010 (Zoungas et al., 2010)	First major macrovascular event=death from cardiovascular cause, non-fatal MI, non-fatal stroke First major microvascular event=new or worsening nephropathy or retinopathy Secondary outcomes=death from any cause and death from a cardiovascular event Independent adjudication by blinded committee	Blood glucose level <2.8 mmol/L or typical symptoms/signs without other apparent cause. Those with transient neurological dysfunction who required help from 3rd party were considered to have severe hypoglycemia. Minor hypoglycemia if transient dysfunction of CNS and able to treat themselves.	Cox proportional-hazard models adjusted for covariates. Baseline: sex, duration of diabetes, treatment allocation, history of macrovascular or microvascular disease, ever smoker. Time dependent covariates during follow-up: age, HbA1c, body mass index, creatinine, urine albumin to creatinine ratio, systolic blood pressure, diabetes and blood pressure drugs.	HR 2.88 (2.01, 4.12) major macrovascular events, HR 1.81 (1.19, 2.74) major microvascular events, HR 2.68 (1.72, 4.19) death from cardiovascular cause, HR 2.69 (1.97, 3.67) death from any cause

OR= Odds ratio, HR=Hazard ratio, 95% CI= 95% Confidence Interval, T2DM=Type 2 diabetes mellitus, HbA1C=glycated haemoglobin, CKD=chronic kidney disease, DPP-4=dipetidyl-peptidase-4, SU=Sulfonylureas, MI=myocardial infarction, AF=atrial fibrillation, CVD= cardiovascular disease, HES=Hospital Episode Statistic, CPRD= Clinical Practice Research Datalink database, TUG=Timed Up and Go Test, GDS-15=Geriatric Depression Scale, CCI= Charlson comorbidity index, IFG=impaired fasting glucose, IGT= impaired glucose tolerance

Figure 1. Meta-analysis of association between hypoglycemia and vascular events

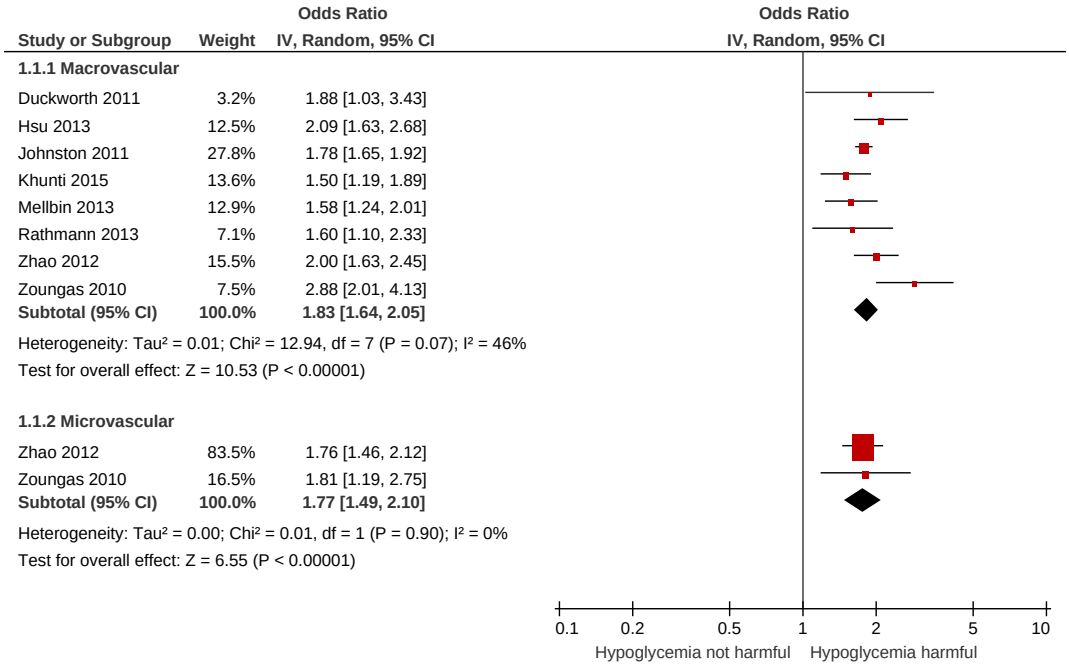

Figure 2. Meta-analysis of association between hypoglycemia and falls and fractures

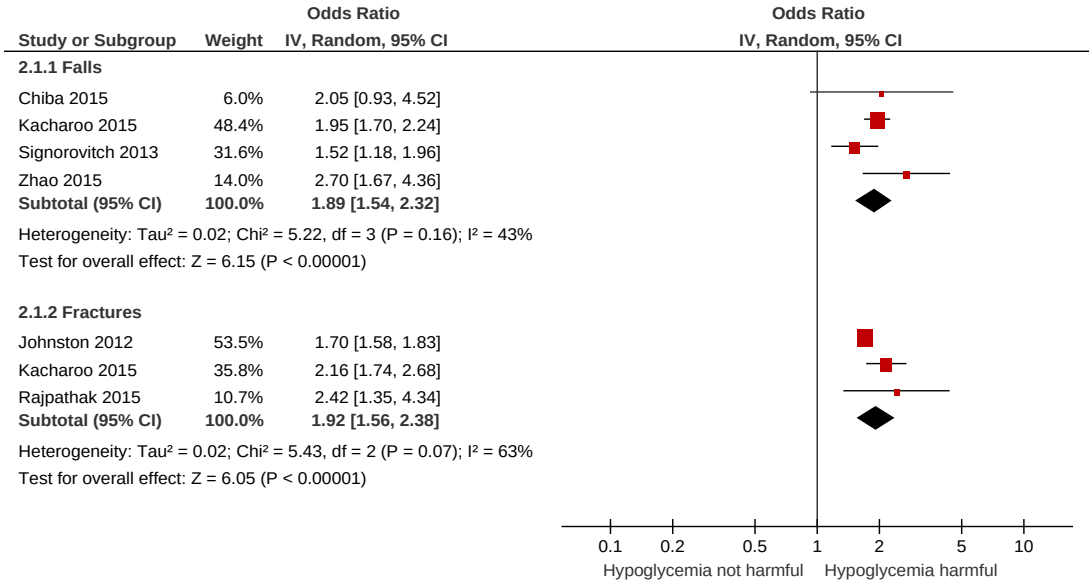

Figure 3. Meta-analysis of association between hypoglycemia and mortality