



Meta-analysis: Association between hypoglycaemia and serious adverse events in older patients



Katharina Mattishent, Yoon Kong Loke *

Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, UK

ARTICLE INFO

Article history:

Received 29 January 2016

Received in revised form 26 February 2016

Accepted 15 March 2016

Available online 17 March 2016

Keywords:

Hypoglycaemia

Diabetes mellitus

Falls

Fractures

Cardiovascular disease

ABSTRACT

Aims: We aimed to conduct a meta-analysis of serious adverse events (macro- and microvascular 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 1.86 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.

© 2016 Elsevier Inc. All rights reserved.

1. 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, Gadsby, Penfold, Croxson, & Bayer, 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 & Gulliford, 2015). This vulnerable group of people is also at an increased risk of falls (Schwartz et al., 2008), which result in an estimated £1.1 billion 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, Scherthaner, & Heller, 2011; Mattishent & 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, Arah, Goto, Terauchi, & Noda, 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 macrovascular disease (Bloomfield et al., 2012) and cardiovascular events remain 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, Gideon, Brockman, Fought, & Ray, 1996).

Funding Statement: We did not receive any funding or financial support for this paper.

Declaration of interests: We do not have any competing interests.

* Corresponding author at: Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK. Tel.: +44 1603 591234; fax: +44 1603 593752.

E-mail address: y.loke@uea.ac.uk (Y.K. Loke).

2. Material and methods

2.1. 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.

2.2. 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 microvascular events, fall, fractures, and death. We excluded reviews and abstracts.

2.3. Data extraction and quality assessment

Study screening and data extraction were 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.

2.4. Data synthesis and analysis

A random effects meta-analysis of odds ratios using inverse variance method (Revman 5.3, Nordic Cochrane Centre, Copenhagen) 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.

3. Results

We screened 1273 citations and included 17 studies with a total of 1,863,783 participants in the meta-analysis (Bonds et al., 2010; Chiba et al., 2015; Duckworth et al., 2011; Hsu et al., 2013; Johnston et al., 2011; Johnston, Conner, Aagren, Ruiz, & Bouchard, 2012; Kachroo et al., 2015; Khunti et al., 2015; Majumdar et al., 2013; McCoy et al., 2012; Origin Trial Investigators et al., 2013; Rajpathak, Fu, Brodovicz, Engel, & Lapane, 2015; Rathmann et al., 2013; Signorovitch et al., 2013; Zhao, Campbell, Fonseca, & Shi, 2012; Zhao et al., 2015; Zoungas et al., 2010). The flow chart of the study selection is 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 sample sizes ranging from 211 to 860,845 participants. 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.

3.1. Measurement of hypoglycemic events

Most of the studies relied on hospital or claims data records. Two studies provided participants with diaries and glucose meters (Bonds et al., 2010; Origin Trial Investigators et al., 2013) 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).

3.2. 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).

3.3. 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).

3.4. Meta-analysis

3.4.1. Association between hypoglycaemia and vascular disease (Fig. 1)

We included eight studies in the meta-analysis for macrovascular complications (Duckworth et al., 2011; Hsu et al., 2013; Johnston et al., 2011; Khunti et al., 2015; Origin Trial Investigators et al., 2013; 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 $p = 0.90$, $I^2 = 0\%$).

3.4.2. Association between hypoglycaemia and falls or fractures (Fig. 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 $p = 0.07$, $I^2 = 63\%$).

3.4.3. Association between hypoglycaemia and mortality (Fig. 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

Download English Version:

<https://daneshyari.com/en/article/2804081>

Download Persian Version:

<https://daneshyari.com/article/2804081>

[Daneshyari.com](https://daneshyari.com)