Effects of intensive interventions compared to standard care in people with type 2 diabetes and microalbuminuria on risk factors control and cardiovascular outcomes: a systematic review and meta-analysis of randomised controlled trials

Muhammad Usman¹, MSc

Dr. Clare L Gillies¹, PhD

Professor Kamlesh Khunti^{1,2}, FMedSci

Professor Melanie J Davies^{1,3}, FRCP

¹Diabetes Research Centre, University of Leicester, Leicester, UK

²NIHR Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM), Leicester, UK

³NIHR Leicester Biomedical Research Centre, UK

Corresponding Author:

Muhammad Usman

Leicester Diabetes Centre, Leicester General Hospital, LE5 4PW Leicester, UK

Email: mu47@leicester.ac.uk

Phone: +44 0116 258 4384

Abstract

Aims The effect of intensive glycaemic control, blood pressure control and lipid levels control alone or as part of a multifactorial intervention has not been fully evaluated. We aimed to estimate the effects of more intensive interventions, compared with standard care, on risk factor control and cardiovascular outcomes in people with type 2 diabetes and microalbuminuria.

Methods We searched MEDLINE, Embase and the Cochrane library without language restrictions from inception to August 10, 2018. We included randomised controlled trials that evaluated intensive interventions in adults with type 2 diabetes and microalbuminuria. The review was registered on PROSPERO (registration number 42017055208). We used random effects meta-analysis to calculate overall pooled effect estimates across studies.

Results A total of seven ($n = 1210$) randomised controlled trials were included, four studies ($n = 758$) reported HbA1c, six studies ($n = 950$) reported blood pressure measurements, and three studies ($n = 896$) examined non-fatal MI, non-fatal stroke, cardiovascular mortality, and all-cause mortality. Intensive interventions indicated statistically significant reductions in both systolic and diastolic blood pressure, and a nonsignificant trend for reduction in HbA1c, total cholesterol, LDL, triglycerides and urinary albumin excretion rate. There was no evidence to suggest that compared with standard care, intensive interventions reduced the risk of non-fatal MI [risk ratio (RR) 0.50 ; 95% CI 0.20, 1.22; $P = 0.127$], non-fatal stroke (RR 0.44; 95% CI 0.10, 1.91; $P = 0.275$), CV mortality (RR 0.95; 95% CI 0.48, 1.86; $P = 0.874$) or all-cause mortality (RR 0.80; 95% CI 0.51, 1.25; $P = 0.324$).

Conclusions Apart from blood pressure outcomes, there was no evidence that intensive interventions improve or worsen HbA1c, total cholesterol, LDL, triglycerides, urinary albumin excretion rate, risk of cardiovascular or mortality outcomes in people with type 2

diabetes and microalbuminuria. Results of this review are mainly influenced by one small trial, hence uncertainty surrounding the effect of intensive interventions in people with type 2 diabetes and microalbuminuria still exists. Large studies are urgently required in this high risk cardiovascular group of patients.

Keywords Intensive interventions, Meta-analysis, Microalbuminuria, Risk factor, Type 2 diabetes

1. Introduction

Diabetes is associated with an increased risk of developing a number of serious health complications that reduce life expectancy. These complications include nephropathy, retinopathy, amputation, and cardiovascular disease. The estimated diabetes prevalence for adults between the ages of 20 to 70 worldwide for 2015 was 415 million, and it is projected to increase to 642 million by 2040, affecting an estimated one person in every ten [1]. Cardiovascular disease is the main cause of higher mortality rates in type 2 diabetes patients [2]. Microalbuminuria is an independent risk factor for macrovascular complications and mortality in people with type 2 diabetes, and screening for microalbuminuria is recommended by the majority of clinical guidelines for the management of diabetes [3]. Microalbuminuria is defined as levels of albumin between 30 to 300 mg per day (equivalent to 20 to 200 mcg/minute in a timed overnight urine collection, or 20 to 200 mg/L on spot urine specimen, or albumin-to-creatinine ratio 2.5 to 30 mg/mmol in males or 3.5 to 30 mg/mmol in females) [4]. The prevalence of microalbuminuria in individual with diabetes has been addressed by many studies. The United Kingdom Prospective Diabetes Study (UKPDS) reported at baseline, nearly seven percent of the patients with type 2 diabetes had microalbuminuria and after five, ten and fifteen years; the prevalence was 17%, 25%, and 28% respectively [5]. An individualised, target base approach for management of type 2 diabetes is advised by all major clinical bodies for diabetes [6]. The management strategy should be tailored to the needs and conditions of patients with type 2 diabetes, taking into account patients personal preferences, risks, and comorbidities [7]. All major clinical guidelines for the management of individuals with type 2 diabetes state that all patients with type 2 diabetes and microalbuminuria or macroalbuminuria should be prescribed an Angiotensin-converting-enzyme inhibitor or Angiotensin II receptor blockers to mitigate nephropathy [3, 8]. Without

specific interventions, 20% to 40% of type 2 diabetes patients with microalbuminuria progress to overt nephropathy [9].

The STENO-2 (2003) [10] study in Denmark, and the MEMO (2011) [11] study in the UK, have shown that intensive interventions result in greater improvements in metabolic control and cardiovascular risk profiles, however the collective evidence across available studies for the superiority of intensive interventions compared to standard care for reducing renal disease, cardiovascular disease, and mortality in people with type 2 diabetes and microalbuminuria is uncertain, and needs to be evaluated. A previous systematic review of cohort studies has shown microalbuminuria as a strong predictor of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality in people with type 2 diabetes [12]. It is therefore relevant to clarify whether intensive intervention regimens, targeted to reduce one or more of blood glucose, blood pressure and lipids, actually improve important patient outcomes such as renal disease, cardiovascular disease, and mortality in this population group. However, to our knowledge a systematic review of randomised controlled trials of intensive interventions compared to standard care, in people with type 2 diabetes and microalbuminuria, has not been explored.

In brief, there are still uncertainties concerning the optimal therapy for people with type 2 diabetes and microalbuminuria. The balance of benefits and harms of intensive multifactorial glycaemic, blood pressure and lipid levels control are still unknown and need to be explored. This systematic review therefore aims to assess the clinical effectiveness of intensive interventions targeting intensive glycaemic control, blood pressure control, and lipid levels control, either singularly or in combination as a multifactorial intervention, in people with type 2 diabetes and microalbuminuria.

2. Materials and methods

2.1 Search strategy and selection criteria

This study is reported according to a pre-specified protocol available in the supplementary appendix (pp 2–6), and registered on PROSPERO (registration number 42017055208). The review was undertaken following standard guidelines for the conduct and reporting of systematic reviews and meta-analyses [13, 14]. The electronic sources, MEDLINE (1946 to August 2018), Embase (1974 to August 2018), and the Cochrane library (2018, Issue 8) were searched. The overall search strategy combined terms for type 2 diabetes and microalbuminuria with a search filter for randomised controlled trials. The keyword combinations and search terms which have been used for the search strategy are “Diabetes mellitus type 2”, “type II diabetes”, “non-insulin dependent”, “noninsulin dependent”, “niddm”, “adult onset diabetes”, “late onset diabetes”, “mature onset diabetes”, “slow onset diabetes”, “Albuminuria”, “microalbuminuria”, “micro-albuminuria”, “kidney failure”, “renal insufficiency”, “chronic kidney disease”, “urine specimen collection”, “albumin creatinine ratio”, “urine albumin excretion”. The full MEDLINE search is available in the supplementary appendix (pp 6–7).

The references of any articles that met the inclusion criteria, as well as published reviews that considered intensive interventions in people with type 2 diabetes and microalbuminuria, were also checked. Study selection was restricted to randomised controlled trials of any design comparing intensive control of blood glucose, blood pressure, and lipid levels, either singularly or in combination as intensive multifactorial interventions. No language restriction was applied; however the search was restricted to humans and from year “1980 to current”. Randomised controlled trials of adults (≥ 18 years), where at least a subgroup of participants with diagnoses for both type 2 diabetes, and microalbuminuria were included. The diagnosis

of type 2 diabetes and microalbuminuria should have been established at randomisation into the trial using standard criteria [4].

2.2 Data extraction and quality assessment

Two authors independently performed the literature search and extracted study information by using standardised predefined forms. Extracted data included study characteristics (inclusion and exclusion criteria of the study, study methodology, description of the study interventions) and outcome measured (randomised group specific number of participants, mean difference and standard deviation (SD) for continuous outcomes; total number of participants and participants with events for dichotomous outcomes in each treatment arm). Data were extracted on an intention to treat basis; that is, every participant who underwent randomisation contributed to data according to their randomised treatment assignment.

We followed the recommended approach for assessing risk of bias in studies reported in the Cochrane risk of bias tool [15]. This tool addresses specific bias domains including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data and selective outcome reporting. Each item is adjudicated within each study; the adjudication of the risk of bias is achieved by answering pre-specified questions about the methods reported by each study in relation to the risk domain, such that the conclusion is either low risk of bias, unclear risk of bias or high risk of bias. It was not feasible in all trials to blind the healthcare provider, and the participants in the treatment groups (intensive multifactorial interventions), blinding was therefore considered adequate if the outcome assessors were blinded. If the two independent reviewers disagreed on the eligibility of an article, extracted information, or quality assessment, consensus was reached by re-evaluation of the article and consultation with a third reviewer.

2.3 Data analysis

All outcomes were pre-specified in the study protocol is available in the supplementary appendix (pp 2–6). The outcomes were glycated hemoglobin (HbA1c), blood pressure, urinary albumin excretion rate (UAER), lipids measurements, non-fatal myocardial infarction (MI), non-fatal stroke, cardiovascular (CV) mortality, and all-cause mortality.

Stata, version 14.1 (Stata Corporation, College Station, Texas, USA), was used for all meta-analyses, and results are reported with 95% confidence intervals (CIs). We performed pairwise random effects meta-analyses by using the Knapp-Hartung method with the metareg command [16]. We used arm-specific mean differences (MD) from baseline, for the HbA1c, blood pressure and lipids outcomes for each study, and the standardised mean difference for UAER to take into account the fact that different studies had reported this outcome in different units. We used the number randomised and the reported number of events in the intensive intervention and standard care groups of each study to calculate separate risk ratios (RRs) for non-fatal MI, non-fatal stroke, CV mortality, and all-cause mortality. We added 0.5 when studies reported no events in a randomised group [17]. Heterogeneity of outcomes between studies was assessed and quantified using the I-squared statistic and the between study variance parameter tau-squared. Publication bias was assessed by visual inspection of funnel plots for evidence of asymmetry, and the Egger's test [18]. One of the studies (ADDITION-Europe) [19] included in the analysis is a cluster randomised control trial and the individual patient data of the subgroup of participants with microalbuminuria at baseline was obtained from the study investigators and analysed using SAS version 9.4 (SAS Institute, Cary NC, USA) to get the baseline, and follow-up summary statistics for each treatment arm. We accounted for the effect of clustering in this trial by estimating the design effect ($=1.256$) based on the average cluster size ($=9$) and intra-cluster correlation coefficient ($=0.032$) [20]. We used effective sample size approach to adjust this study data [14]. For dichotomous

outcomes, both the number of participants and the number of events in each treatment group, and for continuous outcomes only the number of participants in each intervention group, were divided by the design effect [21]. We also investigated the association between the pooled treatment effect (i.e. the effect of intensive interventions on clinical, CV, and mortality outcomes) and study level mean age, and mean baseline eGFR, using meta-regression analyses.

3. Results

7097 articles were identified by the MEDLINE, Embase and Cochrane searches. The selection process is outlined in the flow chart in figure 1. After duplicates articles were removed, 4894 articles were screened. The full text of 140 articles was reviewed. Overall, seven randomised controlled trials were included in this systematic review and meta-analysis; the remaining were excluded due to reasons including interventions not related to this review; non-randomised studies, including type 1 diabetes or non-diabetes participants, meta-analysis articles, cost-effectiveness studies, quality of life studies; post-hoc/AD-Hoc/extension analysis articles; protocol, design and rationale studies; patient population with type 2 diabetes and other conditions but not microalbuminuria.

Seven trials (1210 participants) met the inclusion criteria for this systematic review ADDITION-Europe (2011) [19], Ahmad et al. (1997) [22], Estacio et al. (2006) [23], Levin et al. (2000) [24], MEMO (2011) [11], STENO-2 (2003) [10], and Zandbergen et al. (2003) [25]. In four trials, Ahmad et al. (1997) [22], MEMO (2011) [11], STENO-2 (2003) [10], and Zandbergen et al. (2003) [25], all participants had both type 2 diabetes and microalbuminuria, totalling 599 participants. In two trials Estacio et al. (2006) [23] and Levin et al. (2000) [24], 64 participants had both type 2 diabetes and microalbuminuria at baseline, and outcomes were presented for this subgroup. In the remaining one trial ADDITION-Europe (2011) [19],

the individual patient data of 547 participants of the subgroup of patients having microalbuminuria at baseline was obtained from the study investigators.

A summary of study characteristics is presented in table 1. In the ADDITION-Europe (2011) [19], MEMO (2011) [11] and STENO-2 (2003) [10] trials, the intensive multifactorial interventions aimed to achieve target driven control for blood glucose, blood pressure, and lipid levels through a combination of behaviour modifications, lifestyle changes, and pharmacological therapies. Three trials Ahmad et al. (1997) [22], Estacio et al. (2006) [23], and Zandbergen et al. (2003) [25] were looking at the effect of intensive control for blood pressure against standard care or placebo. One trial Levin et al. (2000) [24] was assessing the effect of tight blood glucose levels set by targets for HbA1c to be achieved in the treatment arm compared with standard care.

All seven studies included in the meta-analyses were randomised controlled trials of intensive interventions (intensive control of blood glucose, blood pressure, and lipid levels either singularly or in combination as a multifactorial interventions) compared against standard care or placebo and ranged from year 1997 to 2011. The average age range was 50 to 63 years in the included studies, and average range for known duration of diabetes where reported was 2 to 10 years (except for ADDITION-Europe (2011) [19], where participants were recruited without known diabetes, from general practices through screening).

The risk of bias assessment of the included trials was performed using Cochrane risk of bias tool [15]. The generation of the allocation sequence, incomplete data and selective reporting were addressed adequately in all included studies and low risk of bias classification was assigned to all studies in these bias domains. As it was not possible to blind the healthcare providers and the patients in the treatment groups (intensive interventions), blinding was considered satisfactory if the outcome assessors were blinded. The method of blinding of

outcome assessment was adequately described in the ADDITION-Europe (2011) [19], MEMO (2011) [11], STENO-2 (2003) [10] and Zandbergen et al. (2003) [25], in the remaining trials method of blinding of outcome assessment was classified as unclear.

The meta-analyses results of HbA1c, blood pressure, UAER and lipids measurements are presented in the Table 2 and the Forest plots are in the supplementary appendix (figs. 1–3, pp 9–11). Statistically significant reduction was found in systolic blood pressure (SBP) (MD -5.88; 95% CI -10.48, -1.27; $P = 0.012$), and diastolic blood pressure (DBP) (MD -2.57; 95% CI -4.60, -0.54; $P = 0.013$). HDL (MD -0.03; 95% CI -0.04, -0.01; $P = 0.000$) was significant, favouring the standard care arm. Meta-analysis of HbA1c (MD -0.33; 95% CI -0.78, 0.12; $P = 0.150$), total cholesterol (MD -0.51; 95% CI -1.37, 0.36; $P = 0.255$), LDL (MD -0.45; 95% CI -1.03, -0.14; $P = 0.132$), triglycerides (MD -0.22; 95% CI -0.71, 0.27; $P = 0.382$), and UAER (SMD -0.21; 95% CI -0.45, 0.04; $P = 0.098$) indicated a nonsignificant trend of reduction. Data was available on non-fatal myocardial infarction, non-fatal stroke, cardiovascular disease mortality, and all-cause mortality in three studies (intensive multifactorial interventions studies) ADDITION-Europe (2011) [19], MEMO (2011) [11], and STENO-2 (2003) [10]. The meta-analyses (fig. 2 and table 2) indicated that compared with standard care, intensive multifactorial intervention did not reduce the risk of non-fatal MI (RR 0.50; 95% CI 0.20, 1.22; $P = 0.127$), non-fatal stroke (RR 0.44; 95% CI 0.10, 1.91; $P = 0.275$), CV mortality (RR 0.95; 95% CI 0.48, 1.86; $P = 0.874$) and all-cause mortality (RR 0.80; 95% CI 0.51, 1.25; $P = 0.324$).

The results of the meta-regression analyses are reported in the supplementary appendix (table 1, pp 8 & fig. 5, pp 14–19), where the size of the circle represents the standard error (SE) of the log risk ratio for non-fatal MI, non-fatal stroke, CV mortality and all-cause mortality or SE of the mean difference for HbA1c, SBP, DBP, total cholesterol, LDL, HDL and triglycerides or SE of the standardised mean difference for UAER, and the weight given to

each study estimate. There was no evidence to suggest that the effect of intensive intervention on CV and mortality outcomes was associated with study level values of mean age, and baseline mean eGFR. Likewise no evidence to suggest the association between the effect of intensive intervention on HbA1c, SBP, DBP, total cholesterol, LDL, HDL, triglycerides, and UAER was associated with mean age, and baseline mean eGFR. Heterogeneity in the intervention effect was assessed to be no heterogeneity for CV mortality and all-cause mortality, low heterogeneity for the non-fatal MI, but moderately high heterogeneity for non-fatal stroke outcomes (see heterogeneity statistics for each outcome on fig. 2). Visual inspection of the funnel plots displayed in the supplementary appendix (fig. 4, pp 12–13) does not appear to show marked evidence of asymmetry for all outcomes, however due to the small number of studies included in the meta-analyses interpretation of funnel plots is limited. The Egger's test for publication bias was not statistically significant (for non-fatal MI, Egger's test $t = -0.03$, $P = 0.979$; for non-fatal stroke, Egger's test $t = 4.17$, $P = 0.150$; for CV mortality, Egger's test $t = -1.90$, $P = 0.309$ and for all-cause mortality, Egger's test $t = -5.27$, $P = 0.119$). The Egger's test results of remaining outcomes are presented in the supplementary appendix (table 2, pp 8). Publication bias was not identified for the HbA1c, SBP, DBP, total cholesterol, LDL, HDL, and UAER Egger's test p-value (> 0.05). For the triglycerides meta-analysis the Egger's test was statistically significant $P = 0.002$, which may indicate publication bias was an issue for this outcome.

Two studies MEMO (2011) [11] and STENO-2 (2003) [10] have reported data on hypoglycemia. Overall the incidence of at least one minor episode of hypoglycaemia at the end of the studies was 81 in the intensive group and 70 in the standard care group. Five patients in the intensive group and 18 in the standard care group had at least one major hypoglycemic event. The majority of the major hypoglycemic events were coming from STENO-2 (2003) [10] study where 12 patients in the conventional-therapy group and five in

the intensive-therapy group had at least one major hypoglycemic event. Whilst the MEMO (2011) [11] study reported the incidence of severe hypoglycemic events between intensive and control patients at the end of the study was zero versus six.

4. Discussion

In this systematic review and meta-analysis of well-conducted randomised controlled trials, we have been able to compare the effect of intensive interventions (single and multifactorial) compared to standard care on HbA1c, blood pressure, UAER, lipids measurements, major CV, and mortality outcomes in individuals with type 2 diabetes and microalbuminuria. We also investigated the association between the treatment effect and study-level characteristics (mean age, and baseline mean eGFR). The most pronounced reduction was seen in blood pressure outcomes across studies, and the subgroup analysis of intensive multifactorial intervention studies alone, which showed a statistically significant reduction. There was a nonsignificant trend of reduction in HbA1c (and borderline statistically significant reduction for the subgroup analysis of intensive multifactorial intervention), total cholesterol, LDL, triglyceride, and UAER for intensive interventions. HDL estimate was significant, however was more favourable in the standard care arm. There were no overall statistically significant benefits in terms of reductions in non-fatal MI, non-fatal stroke, cardiovascular disease mortality, or all-cause mortality for intensive multifactorial interventions, however there were trends towards a reduction for all event rates favouring the intensive multifactorial intervention group.

The result of the meta-regression analysis suggest no evidence of association between the effect of intensive interventions on CV, mortality and clinical outcomes and study level mean age, and baseline mean eGFR. Overall the heterogeneity in the intervention effect between the studies was assessed to be low. We found no evidence of publication bias in the meta-

analysis of CV, mortality and clinical outcomes excluding triglyceride assessed by visual inspection of the funnel plots and Egger's test.

Our meta-analysis utilise data from all published randomised controlled trials comparing the effect of the intensive interventions (i.e. intensive control of blood glucose, blood pressure, and lipid levels either singularly or in combination as multifactorial interventions), against standard care in individuals with both type 2 diabetes, and microalbuminuria, making this review of intensive interventions unique in term of its patient's population. Our search strategy has found several trials of intensive interventions for patients with type 2 diabetes, where a percentage of microalbuminuria patients were present ranging from (19% to 31%) at baseline [26-31]. Although these studies lack the reporting of cardiovascular and other outcomes for this patient's group both at baseline and at the end of follow-up period.

The intensive multifactorial interventions trials included in this review are STENO-2 (2003), MEMO (2011) and ADDITION-Europe (2011). The STENO-2 (2003) study comprised of nearly eight years of intervention, resulting in significant benefits for composite microvascular and macrovascular events including cardiovascular mortality [Hazard ratio (HR) 0.47; 95% CI 0.24, 0.73; $P = 0.008$] [10]. The MEMO (2011) study had an average 1.5 years intervention duration, and reported improvements in HbA1c, blood pressure, and total cholesterol, as well as a non-significant difference between the randomised groups for cardiovascular events and all-cause mortality [11]. The ADDITION-Europe (2011) study, conducted in people without known diabetes through screening from general practices, had a treatment follow up of 5.3 years, and reported a reduction in the incidence of composite cardiovascular events (HR 0.83; 95% CI 0.65, 1.05; $P = 0.12$) and all-cause mortality (HR 0.91; 95% CI 0.69, 1.21) [19]. The results of our review is mostly influenced by the STENO-2 (2003) study, which had the longest average intervention period among the included studies, and was carried out in a single specialist centre setting. We acknowledge that the

number of trials of intensive interventions (single and multifactorial) compared to standard care in this population group (type 2 diabetes and microalbuminuria) is relatively small and heterogeneous in terms of the both patient population and trial duration. However we found overall the heterogeneity in the intervention effect between the studies was assessed to be low, as measured by the I-squared statistics from random effect meta-analyses, and the interventions delivered across the three trials were broadly similar. Therefore, the study results were combined using meta-analyses models, whilst acknowledging the study differences and heterogeneity. Evidence on the effects of intensive multifactorial interventions across available studies in this population group is currently lacking, and this study helps inform this current gap in evidence. This study highlights some important issues and summarises the findings from individual studies in people with type 2 diabetes and microalbuminuria.

As far as we are aware this is the first systematic review and meta-analysis of randomised controlled trials assessing the effects of intensive interventions (single and multifactorial) compared to standard care in individuals with both type 2 diabetes, and microalbuminuria. Our findings are not dissimilar to the conclusions of the review of the effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in patients with type 2 diabetes by Boussageon et al., (2011) [32], who concluded that compared with standard treatment, intensive glucose lowering did not significantly affect all-cause mortality and deaths from cardiovascular causes. Our results extend these conclusions by providing a quantified estimation of the impact of intensive interventions in both individuals with type 2 diabetes, and microalbuminuria. Moreover the results of our review are also consistent with the systematic review of intensive glucose lowering and multifactorial intervention on cardiovascular and mortality outcomes in patients with type 2 diabetes by Seidu et al., (2016) [33], who concluded that intensive glucose control and

multifactorial interventions significantly reduced the risk of non-fatal MI, but found no benefits in terms of reductions in non-fatal stroke, cardiovascular disease mortality, and all-cause mortality. Our review supports and extends these conclusions for the subgroup of individuals with both type 2 diabetes and microalbuminuria, although for this review no statistically significant benefit for non-fatal MI was found.

This review found no evidence to suggest that intensive multifactorial intervention reduced the risk of non-fatal MI, non-fatal stroke, cardiovascular disease mortality and all-cause mortality. Intensive single and multifactorial risk factors control intervention showed statistically significant reduction in blood pressure outcomes, and a nonsignificant trend of reduction in HbA1c, total cholesterol, LDL, triglyceride, and UAER. Results of this review are mainly derived from one small single centre trial, therefore uncertainty surrounding the effect of intensive interventions in people with type 2 diabetes, and microalbuminuria still exist. Further large RCTs are required, along with an updated evidence review once more data becomes available, in this high risk cardiovascular group of patients.

Contributors

KK conceived and designed the study. MU led on the literature search, data extraction, data analysis, and produced the first draft of the paper. KK, MD and CG were involved in study selection and data extraction, drafting the article or revising it critically for important intellectual content, and approved the final version to be published. MU and CG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

Mr. Muhammad Usman and Dr. Clare L Gillies have no conflict of interests to declare.

Professor Melanie J Davies has been a consultant, speaker and advisory board member for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, an advisory board member for Servier and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim and Janssen. Professor Kamlesh Khunti has been a consultant, speaker, and advisory board member for Amgen, AstraZeneca, Novartis, Novo Nordisk, SanofiAventis, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim. He has also received grants in support of investigator and investigator initiated trials from Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche.

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Figure legends

Figure 1: Flow diagram of literature search

Figure 2: Meta-analyses results of cardiovascular and mortality outcomes

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