Long-term mortality following acute myocardial infarction among those with and without diabetes: A systematic review and meta-analysis of studies in the post reperfusion era.

Short title: Diabetes and long-term mortality post myocardial infarction

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Abstract

Aims: Considerable medical advances have seen an improved survival following an acute myocardial infarction (AMI), whether these benefits extend to those with diabetes remains less clear. This systematic review and meta-analysis aim to provide robust estimates of the association between diabetes and long-term mortality (≥one year) following AMI.

Material and Methods: Medline, Embase and Web of Science databases were searched (January 1985 - July 2016) for terms related to long-term mortality, diabetes and AMI. Two authors independently abstracted the data. Hazard ratios (HR) comparing mortality in people with and without diabetes were pooled across studies using Bayesian random effects meta-analysis.

Results: Ten randomised controlled trials and 56 cohort studies, including 714,780 patients, reported an estimated total of 202,411 deaths over the median follow-up of 2.0 years (range 1 to 20). The risk of death over time was significantly higher among those with diabetes compared to those without (unadjusted Hazard Ratio (HR) 1.82; 95% Credible Interval (CrI) 1.73 to 1.91). Mortality remained higher in the analysis restricted to 23/64 cohorts which had adjusted for confounders (adjusted HR 1.48 (1.43 to 1.53)). The excess long-term mortality in diabetes was evident irrespective of the phenotype and modern treatment of AMI, and persisted in early survivors (unadjusted HR 1.82 (1.70 to 1.95)).

Conclusions: Despite medical advances, individuals with diabetes have a 50% increased long-term mortality compared to those without. Further research to understand the determinants of this excess risk are important for public health, given the predicted rise in global diabetes prevalence.

Introduction

Diabetes is a major risk factor for cardiovascular disease, conferring an approximate two-fold increase in the risk of acute myocardial infarction (AMI) [1]. Diabetes and impaired glucose tolerance are very common among people with AMI – seen in almost two thirds of patients at presentation – and are associated with two-fold increase in mortality rate compared to those with normoglycaemia [1]. Furthermore, the recent trends in improved survival following AMI, attributed to improved acute care and better use of preventative strategies, are less obvious among those with diabetes compared to those without [2].

While many studies have examined survival following AMI among individuals with diabetes, the focus has been on short-term rather than long-term mortality. Furthermore, even those studies which assessed long-term mortality post-AMI have reported inconsistent findings [3-5]. Two meta-analyses have been performed to date and, whilst informative, their findings may not provide reliable risk estimates in broader populations [6,7]. The first study included only randomised controlled trials (RCTs) and reported information on 11 trials, including 62,036 individuals from the Thrombolysis in Myocardial Infarction (TIMI) database, and therefore excluded a large number of global trials whilst assessing mortality only as far as one year post-acute coronary syndrome (ACS) [6]. The other major meta-analysis included a select group of patients with ST elevation myocardial infarction (STEMI) treated with primary percutaneous intervention (PCI) and stent insertion from 11 studies and reported on 6298 patients [7]. In order to provide more reliable evidence than hitherto possible on the impact of diabetes on long-term mortality following AMI, we conducted a systematic review and meta-analysis of all available data in the reperfusion era and compared the all-cause, long-term mortality (one year and longer) among those with and without diabetes following hospitalisation for AMI.

Materials and Methods

Data Sources and Searches

The Medline, EMBASE, and Web of Science (WOS) databases were searched for articles in English. Search strategies were tailored to the relevant databases, and, in addition, reference lists were searched for potentially eligible articles. We used keywords and medical subject headings (MeSH) related to acute myocardial infarction, acute coronary syndrome, diabetes mellitus, hyperglycaemia, blood glucose, impaired glucose regulation, mortality, morbidity, prognosis, course, outcomes and follow-up, aiming at identifying full text, published papers. For further details of search strategies refer to online Supplementary Data, Methods 1 and Table S1.

Study selection

Each title and abstract was independently scrutinised by two authors for suitability. Identified papers were independently assessed by each author to assess suitability for inclusion. In order to include AMI patients likely to have been treated by modern reperfusion or early invasive strategies, we rationalised our inclusion criteria as follows: i) articles published after January 1985 until July 2016 (Supplementary Data, Methods 2); ii) reporting studies had to have commenced recruitment after January 1985; iii) studies where recruitment commenced before 1985 but continued after 1985 would only be included if 50% of the recruitment period occurred after January 1985. We excluded studies where: i) there was < one year of follow-up; ii) there were <100 total participants; iii) the design was case control; iv) individuals were systematically screened during the index AMI admission for identifying newly diagnosed diabetes; v) individuals were diagnosed to have diabetes based solely on elevated glucose levels > 11.0 mmol/mol at index admission; vi) the report focused on mortality in relation to blood glucose levels without reporting mortality for those with and without diabetes; vii)

reporting was only on subgroups which could not be generalised e.g. reports restricted to those with left ventricular failure or cardiogenic shock. Where studies had a mixed cohort of patients with AMI and unstable angina, data related to only AMI (STEMI and non-STEMI) were extracted. Since this was analysis of hospitalised AMI, out-of-hospital deaths as a presentation of index AMI were excluded. In articles reporting more than one cohort, information on each study was extracted separately and in case of multiple reports of the same study, the data from the most informative article were used.

Data extraction and Quality Assessment

Data were independently obtained from each selected article by the two authors. We included both cohort studies and RCTs. Important prognostic variables stratified by diabetes status were extracted, including: age, sex, prior medical history, prior medications, phenotype, presentation and severity of AMI, acute treatments and medications at discharge. Information on duration of follow-up, the absolute number of deaths over the whole follow-up period and measures of risk (hazard ratio, relative risk, odds ratio) together with confidence intervals were extracted. In addition, information on variables used in the adjusted analysis was obtained. Furthermore, when reported, we obtained data on long-term mortality in early survivors – those who survived to discharge or the first 30 days following the index AMI. For the studies not reporting actual death numbers, authors were contacted. When such information wasn't available from the authors, the death numbers were derived from survival graphs [10], and percentage. The quality of the study was assessed by two independent reviewers using the US Preventive Service Task Force (USPSTF) Quality Rating Criteria for the RCTs and cohort studies, and studies were categorised into good, fair and poor quality groups (Supplementary Data, Box S1) [11]. Disagreements related to any aspects of the review, selection, data extraction or quality assessment were resolved through discussion.

Data Synthesis and Analyses

We performed analysis in two different ways, producing two sets of outcome data. First, for all selected studies, risk ratios were derived from the reported number of patients and the number of deaths in diabetes and non-diabetes groups. It was assumed that the number of deaths in the two groups follows binomial distribution and that the probability of death is dependent on the mean (or median) length of follow-up, under the assumption that the risk of death remains constant over the entire follow-up period [12]. The time-dependent risk ratios were then log-transformed and pooled across all the studies using Bayesian random effects meta-analysis to produce a summary hazard ratio and 95% Credible Intervals (CrI, Bayesian equivalent of confidence intervals). The second analysis involved only those studies in which adjusted hazard or odd ratios and 95% confidence intervals were reported. For these studies, additional information on covariates included in the maximally adjusted multivariable models was obtained. The subsequent maximally adjusted hazard/odds ratios and standard error (derived from the corresponding confidence intervals) were log-transformed and pooled across theses studies using Bayesian random effects meta-analysis to produce a summary hazard ratio and 95% Credible Intervals.

The model accounts for the heterogeneity in the hazard ratios across different study populations by assuming that the association between long-term mortality and diabetes varies from study to study. The full extent of heterogeneity in hazard ratio was quantified using a between-study variance parameter τ *(tau)*. Note that the pooled mean effect in a random effects meta-analysis only represents the average of effect sizes across individual studies and may not accurately represent the effect sizes across the different study populations. Therefore, to comply with best practice [13], we also obtained the estimate of *predictive mean effect and interval,* which incorporates the full extent of heterogeneity in meta-analysis.

The predictive interval typically widens the uncertainty around the mean effect and thus provides a conservative but robust estimate of the true effect. Such a predictive effect and its interval can be seen as the equivalent of expected mean effect size and its variance in the outcomes, if new studies are undertaken in the future [13]. The sources of heterogeneity were assessed through subgroups analysis. To eliminate any bias related to difference in early case fatalities between the diabetes subgroups, we conducted a separate meta-analysis of selective studies reporting long-term mortality in early survivors – those who survived to discharge or the first 30 days post AMI. For this analysis, we pooled data on mortality after 30 days (or after hospital discharge) until the end of follow-up from the studies reporting such event data, and conducted Bayesian random effects meta-analysis.

Publication bias was assessed by visual inspection of funnel plots and Egger's test [14]. Where significant publication bias was found, the Duval and Tweedie [15] nonparametric trim-and-fill method was used to provide an estimate of the number of unpublished studies and an estimate of predicted effect if all studies were available. The meta-analyses were carried out using WinBUGS [16]. The WinBUGS codes used to fit the analysis are given in online Supplementary Data, Methods 3. Publication bias assessment was carried out using Stata. Statistical significance relates to $p<0.05$ and 95% Credibility Intervals are quoted throughout.

Results

A total of 65 articles, reporting data on 66 cohorts (10 RCTs and 56 non-RCT) [2-5, 7, 17-76] were eligible for the meta-analysis (Figure 1). Data on estimated 202,411 deaths in 714,780 individuals, over the median follow-up of 2.0 years (range 1 to 20) were reported [2-5, 7, 17-76].

Studies included and patient characteristics

Detail characteristics of the selected studies including: type and sampling structure of each study, recruitment period, number of participants, mean age, gender, acute intervention for AMI (RCT), absolute number of deaths, measures of risk (hazard ratio, relative risk, odds ratio), and information on variables used in the adjusted analysis, are presented in Supplementary Table S2. The studies covered the globe with 14.0% multinational studies (mostly from Western and developed countries), 13.5% from North America, 48.5% from Western Europe, 10.6% multinational and the remainder from other regions. All studies were incepted between 1985 and 2011 except two, which commenced recruitment prior to 1985 (1979 and 1981) and continued after 1985 [26, 38]. In 26/66 studies the recruitment commenced in the year 2000 onwards. In 15/66 studies [3,7,17,18,27,30,40,41,45,49,52,55,58,68,76], outcome data were not reported in a suitable format and were derived from survival graphs or other sources as described in Supplementary Results 1. Adjusted analysis for the outcome of long-term mortality was reported in 23/66 studies [4,5,7,25,26,27,29,32,40,41,43,48,51,52,54,56,58,59,61,66,67,76]. Ascertainment of diagnosis of diabetes varied across the studies, and was based on: self-reporting/admission records/physician-ascertainment (52/66) plus new diagnosis during the admission established using routine glucose measurement (13/66); and information in the discharge records (1/66). The definition of AMI in the 66 cohorts varied. In general, prior to the year 2000, the diagnosis of AMI was based on symptoms, raised cardiac enzymes and characteristic electrographic (ECG) changes [77,78], while after the year 2000, studies used the European Society of Cardiology/American College of Cardiology criteria of changes in troponin levels plus typical symptoms and/or ECG changes [79,80]. In 10/66 studies no such method was explicitly provided.

The cohort size varied from 198 to 141,680 (median 2250, interquartile range (IQR) 5401) with the diabetes prevalence ranging from 7.2% to 43.6 % (median 18.0%, IQR 10.0%). The follow-up varied, ranging from 1 year to 20 years (median 2.0 years, IQR 4.0 years). The majority of the studies assessed longer term mortality – up to five years after index AMI – while in eight studies long-term mortality – up to 20 years – was assessed. In most of the 23/66 cohorts reporting adjusted data, the adjusted analysis included important confounders including age, gender, co-morbidities, severity of AMI and acute reperfusion therapies (Supplementary Table S2). There were 57,034 deaths in 155,526 participants with diabetes (36.7%) compared with 145,377 deaths in 559,254 patients (26.0%) without diabetes, $p<0.00001$.

Most studies did not differentiate between types of diabetes, and therefore 'diabetes' was considered as one diagnosis with no differentiation between type 1 and type 2 diabetes. Compared to people without diabetes, those with diabetes were older (median age, 65.0 years (IQR 4.0) vs 63.0 years (IQR 5.0)) and less frequently male (median proportion, 64.0% (IQR 7.8) vs 73.1% (IQR 8.6)) (Supplementary Table S2). Reporting of cardiovascular risk factors varied widely across the studies. Those with diabetes had higher prevalence of hypertension (median prevalence, 54.0% (IQR 16.5) vs 36.5% (IQR 14.6)), and prior myocardial infarction (median prevalence, 22.5% (IQR 16.3) vs 17.0% (IQR 11.0)) and lower prevalence of smoking (median prevalence, 32% (IQR 22) vs 47.0% (IQR 18.5)).

Quality Assessment

Based on the USPSTF Quality Rating Criteria (Box S1) [11], 43/66 studies not reporting any adjusted data for mortality risk among patients with compared to without diabetes were rated as 'poor'(Table S2). In a majority of these studies, people with diabetes were older and had

higher prevalence of cardiovascular risk factors at baseline which could have contributed to their higher mortality rates. Among the 23/66 studies reporting adjusted data, three studies adjusting analyses for key confounders (baseline difference in clinical characteristics and risk factors, acute therapies for AMI and secondary prevention therapies post AMI) and also achieving >80% follow-up as per the requirement of the USPSTF criteria were graded as 'good' (Table S2). The rest 20/23 adjusted studies were graded as 'fair' (Table S2).

Outcomes

Diabetes and long-term mortality

From the meta-analysis of all 66 cohorts, there was evidence that long-term mortality was significantly higher among those with diabetes compared to without (unadjusted HR 1.82; 95% CrI 1.73, 1.91) (Figure 2). In the meta-analysis of 23/66 cohorts reporting adjusted analysis, the adverse association between diabetes and excess long-term mortality was still seen after adjusting for various confounders (adjusted HR 1.48 (95% CrI 1.43,1.53)) (Figure 3). The Bayesian predictive effect was HR 1.81 (95% CrI 1.31, 2.49) for analysis based on the actual event data (66/66 cohorts) and HR 1.48 (95% CrI 1.31, 1.68) for the analysis using the reported adjusted HRs/ORs (23/66 cohorts).

In the subgroup analysis, diabetes remained associated with excess mortality with no evidence of interaction across phenotypes of AMI, first or recurrent AMI, recruitment period before or after year 2000, cohort studies or RCTs, and different length of follow-up (Figure 4). Statistically an interaction was found (p=0.032) when the cohorts of patients with STEMI treated with PCI were compared with rest of the cohorts of AMI, although diabetes was associated with a significant excess mortality in both. To account for the advances in acute management of AMI over recent years, we did a subgroup analysis of studies with the

recruitment taking place before and after year 2000. For this analysis we excluded studies in which the recruitment commenced before and continued after the year 2000 with the total recruitment period exceeding five years (35,42,50,51,54,55,57,60,64,68,69,72). The adverse impact of diabetes on mortality was not significantly higher in studies with recruitment taking place before (HR 1.88 (95% CrI 1.75, 2.02) compared to after year 2000 (HR 1.74 (95% CrI 1.74 (1.60, 1.91), p=0.178. Additionally, on analysing mortality as per time since index AMI, adverse impact of diabetes was not significantly different in subgroups of studies with different length of follow-up (up to 1 year, >1 to 5 years, >5 to 10 years and >10 years) (Figure 4).

To assess for any differential effect of age or gender on mortality among those with and without diabetes, we conducted analyses using the between-group difference in mean age and mean percentage of men reported in each study as a covariate in the meta-regression. While the risk of excess long-term mortality in the diabetes group was significantly higher in studies with older patients (interaction term 1.054 per year; 95% CrI 1.016, 1.092; p = 0.007) no such effect was seen in the studies with a higher proportion of men (interaction term 1.002 per percentage point; 95% CI 0.996, 1.008; p = 0.487).

Assessment of publication bias and heterogeneity

There was evidence of funnel plot asymmetry (indicating possible publication bias) on visual inspection of the funnel plot for long-term mortality outcome (Figure 5), which was confirmed on formal testing (Egger's test t=11.67, p ≤0.000) (14), and suggested a tendency for negative findings from small studies to remain unpublished. Adjusting for publication bias using the trim and fill method [15] reduced the HR to 1.38 (95% CI 1.32, 1.46) for the unadjusted analysis (66/66 cohorts), however the HR remained the same at 1.46 (1.37 to

1.55) for the analysis based on the adjusted data (23/66 cohorts). Estimates of the between-study standard deviation parameter, τ on the log hazard-ratio scale was 0.16 (95% CI 0.13, 0.21) for cohorts with unadjusted data, and 0.17 (95% CI 0.12, 0.24) for cohorts with adjusted analyses, indicating a minimal to moderate degree of variance in the HRs across the two analyses.

Sensitivity analysis

In the sensitivity analysis – excluding the studies (15/66) that did not report outcome data in the suitable format – no difference to the findings of association between diabetes and long-term mortality was seen (Supplementary Table S3). Furthermore when the entire analyses were restricted to the subgroup of early survivors (42/64 studies), association between diabetes and excess mortality was still evident (unadjusted HR1.82, 95% CrI 1.70, 1.95; Bayesian predictive effect HR 1.82, 95% CrI 1.28, 2.59) (Figure S1). Further details on analyses of early survivors are provided in the Supplementary Data: Results 2, Figures S1, S2 and Table S4.

Discussion

We examined the association between diabetes and long-term mortality following AMI using a meta-analysis of all data in the post-reperfusion era. Our results based on the findings of 66 studies conducted over the last three decades and including information on estimated 202,411 deaths in 714,780 individuals over the median follow-up of 2.0 years (range 1 to 20) clearly show an adverse association between diabetes and long-term mortality post-AMI. Compared to people without diabetes, those with diabetes had about 80% excess risk of long-term mortality on univariate analysis, and about 50% on multivariate analysis adjusted for important confounders including demographic characteristics, co-morbidities, severity of

AMI, and management at index admission. Furthermore, this association between diabetes and risk of mortality remained consistent (40 to 50% excess risk) after adjusting for publication bias. These findings robustly show that diabetes is strongly and independently associated with poor long-term survival following AMI.

The findings were consistent across major subgroups, including cohorts of STEMI or first AMI. The findings persisted in early survivors - those who survived to discharge or the first 30 days after index AMI, and remained relevant in the long-term up to 20 years after index AMI (Figure 4). Furthermore, the excess risk of mortality associated with diabetes was similar in cohorts with different proportions of men and was greater in cohorts whose patients were older. Importantly, in contrast to some of the reports [5,25,51,54,72], increased mortality in diabetes was persistent despite modern background management of diabetes and AMI, as reflected in subgroup analysis of studies with the recruitment taking place before and after the year 2000 and additionally of patients with STEMI treated with primary PCI.

Our findings are consistent with previous meta-analyses. In the meta-analysis of 11 trials from the TIMI group involving 62,036 patients with ACS (STEMI 46577, non-STEMI/unstable angina 15459), all-cause mortality at 1 year was two-folds higher in patients with diabetes than those without [6]. Another meta-analysis of 11 trials involving 6298 patients with STEMI treated with stents showed all-cause mortality at mean 3.3 years being 76% higher in patients with diabetes compared to those without [7]. In a more recent meta-analysis of 61 studies, assessing mortality at 6 to 12 months after index AMI or ACS, people with diabetes had 86% higher mortality on univariate analysis compared to those without [81]. Unlike these previous meta-analyses, our findings are based on much larger sample size and event numbers, and involve both unselected patients managed in real-world practice from

the cohort studies, as well as selected patients managed in the highly controlled environment of RCTs. Our report confirms the findings of these previous meta-analyses and extends it to a broader group of patients with AMI followed up for much longer period of up to 20 years.

In the contemporary practice, compared to STEMI, presentation of non-STEMI is more common, especially in those with co-morbidities such as diabetes and is associated with a similar or higher mortality rate in the longer term [82]. In the meta-analysis of TIMI trials [6], the risk of diabetes-associated mortality at 1 year was stronger amongst those with unstable angina or non-STEMI (adjusted RR 1.65; (95% CI 1.30, 2.10) compared to those with STEMI (adjusted RR 1.22 (95% CI 1.08, 1.38). In our subgroup analysis no such difference in the adverse impact of diabetes across STEMI, non-STEMI/non-Q wave AMI and mixed phenotypes of AMI was observed. Conversely, we found the adverse impact of diabetes on mortality being greater in cohorts with older patients. While this finding could indicate risk of excess mortality increasing with age in diabetes, we could not explore this finding in detail due to the limitation of using summary data of mean age in each cohort for this analysis. It is possible that in older patients factors related to both longer duration and severity of diabetes independently contribute to increased risk of cardiovascular events and consequent long-term mortality [83]. In line with previous reports, our findings of subgroup analyses support the notion that the gap in survival after AMI between patients with and without diabetes still persists in the modern treatment era [2,6,81]. That we found no difference in the adverse impact of diabetes among cohorts with different proportion of men perhaps supports the growing body of evidence that diabetes attenuates any gender-related survival benefits in women [84].

There could be several factors specific to diabetes operational both at presentation of AMI and over a longer period thereafter, affecting survival post-AMI [85]. These include: diffuse multi-vessel coronary disease; distinct pathophysiology of coronary atherothrombosis with associated increased risk of recurrent ischaemic events; a characteristic patient profile of older age and multiple co-morbidities; and as yet unknown novel pathological risk factors. Additional contributory factors could be those known to compromise long-term management of chronic conditions including suboptimal care in the community setting, clinical inertia in utilization of evidence-based interventions, and patient compliance [85].

Diabetes is a major driver behind incident CHD, especially AMI; almost two thirds of those presenting with CHD now have either diabetes or impaired glucose regulation [1]. Our findings highlight the challenges faced by healthcare professionals and policy makers from the rising prevalence and fatal impact of diabetes among people with CHD. Our study provides both patients and healthcare professionals with a robust estimate of excess mortality risk associated with diabetes, which they should consider while making treatment decisions. We believe that to improve long–term survival after AMI in people with diabetes, a broader approach to care after the event is needed, incorporating intensification of care at various levels, aggressive management of multiple cardiovascular risk factors, and importantly, patient education and support [1,85-92]. Recent guidelines from professional societies incorporate several new recommendations for effective management of CHD in diabetes, including coronary bypass grafting surgery instead of PCI for multi-vessel or complex coronary lesions and the use of newer, more potent antiplatelet agents [1,86,87]. The latest reports on cardioprotective benefits of glucose lowering agents Empagliflozin and Liraglutide bring new hopes in improving outcomes in people with type 2 diabetes at high risk for cardiovascular events [88,89]. Structured education programmes improve heath behaviour

and self-management in patients with diabetes [1, 90] and need to be offered more widely, perhaps as an integral part of the patient's cardiac rehabilitation programme. Integration of specialist and community care is a novel way to optimise care of chronic conditions, and would help provide comprehensive assessment and management of both CHD and diabetes in the long-term after AMI [91,92]. It is equally important that attention is paid to the primary prevention of CHD in people with diabetes by intensive management of multiple risk factors to reduce their risk of developing AMI [93]. Finally, research is essential for greater understanding and explanation of novel risk factors and drivers of excess CHD risk in diabetes. Future research programmes need to drive the development of novel interventions addressing both pathophysiological and care process-related factors behind poor survival in diabetes.

Limitations

The type duration and therapies (insulin versus non-insulin) for diabetes, adequacy of long-term glycaemic control, and prevalence and management of acute hyperglycaemia at admission with AMI were not universally reported and therefore not considered in the analysis. The outcome in diabetes may differ in the subgroups defined by these characteristics. We excluded studies reporting long-term mortality in patients with screen-detected diabetes. Such patients newly diagnosed with diabetes during index admission are likely to have differential and possibly worse prognoses compared to those known to have diabetes and who were treated adequately prior to the index AMI. Management of diabetes has revolutionised in recent years, with cardiovascular risk of contemporary cohorts being better than those in the past. On the other hand, the definition of AMI changed after the year 2000 and widespread use of the more sensitive cardiac biomarker of troponin since then has lowered the diagnostic threshold. As a result, the contemporary cohort of AMI has a higher

proportion of people with non-STEMI who often have a higher burden of co-morbidities and are over-represented in the diabetes cohort. Confounders related to lower diagnostic thresholds and modern management of both diabetes and CHD affecting our findings cannot be excluded. Our analysis is based on summary data rather than patient-level data and does not include cause-specific mortality. Despite these limitations, the key strength of our analysis is the inclusion of a very large number of participants from across the globe from cohort studies and RCTs who were followed up for up to 20 years, providing enough power for robust assessment of association between diabetes and long-term mortality post-AMI.

Conclusions:

We found that diabetes is associated with at least a 50% increase in long-term mortality following AMI, even after adjusting for confounders including demographic characteristics, co-morbidities, severity of AMI and management at index admission. Furthermore, the excess mortality in diabetes was consistent irrespective of presentation and modern treatment of AMI, persisted in the long-term post AMI and was evident in those who survived to discharge or first 30 days after index AMI. More research to understand mechanisms behind this excess risk and develop novel intervention is needed.

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Conflicts of interest

N.N.G, F.A. and L.G. have no conflicts of interests to declare. M.J.D has acted as consultant, advisory board member and speaker 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. K.R has received honoraria for lectures or advisory boards from Takeda, Novo Nordisk, Astra Zeneca and Boehringer Ingelheim and Jannsen. K.K. is an advisor to the United Kingdom, Department of Health's National Screening Committee on Vascular Risk, and a clinical advisor for the Diabetes National Institute For Clinical Excellence (NICE)-led Quality and Outcome Framework (QOF) Panel.

Author Contributions

N.N.G., K.K. and M.J.D. conceived and planned the study. N.N.G. and F.A. acquired and analysed the data, with statistical analysis conducted by F.A., N.N.G. and L.G. All authors contributed to the interpretation of the data. N.N.G. prepared the first draft of the manuscript and all other authors contributed to the critical revision and intellectual content of the manuscript. N.N.G. and F.A. had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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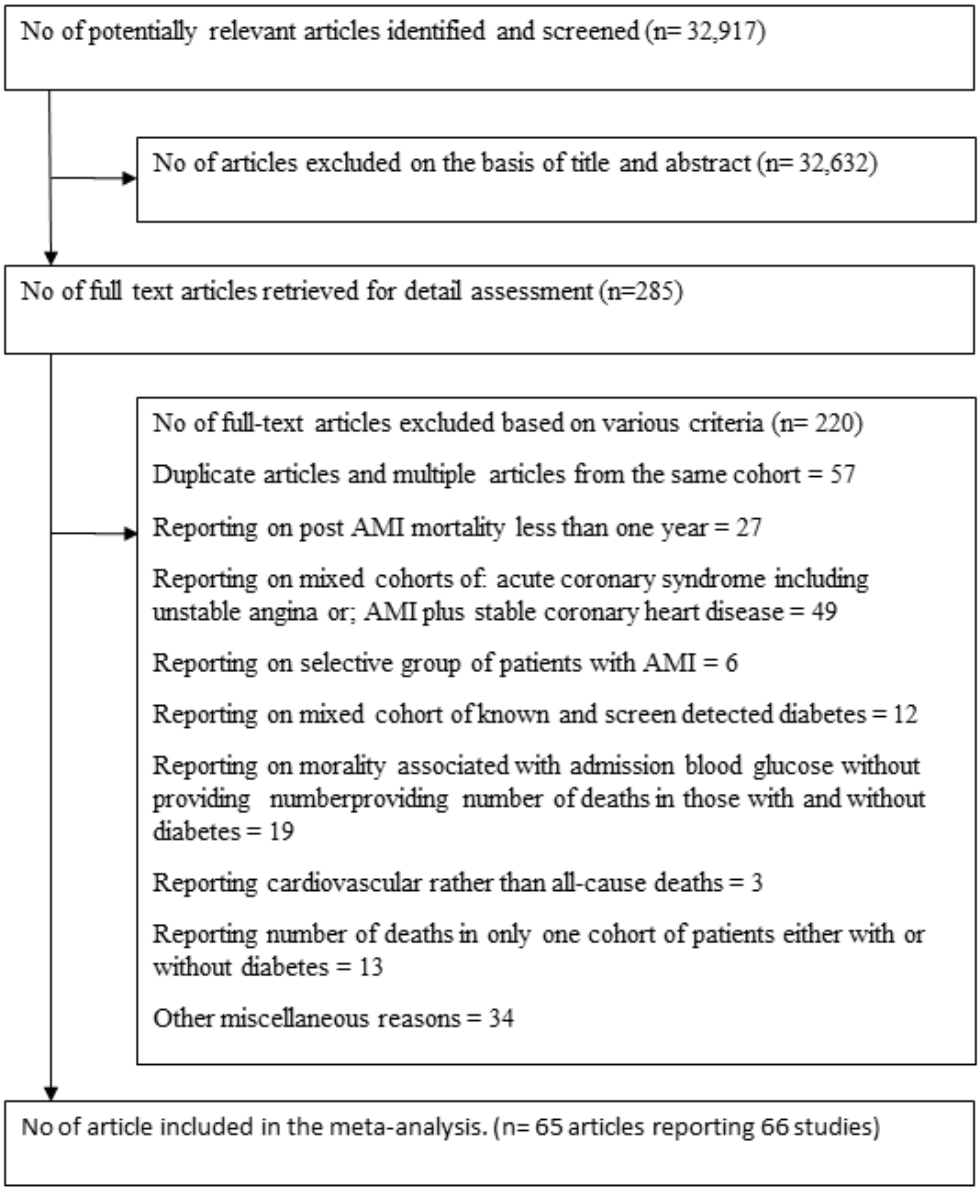

Figure 1. Flow Diagram – Study Identification, Selection and Exclusion

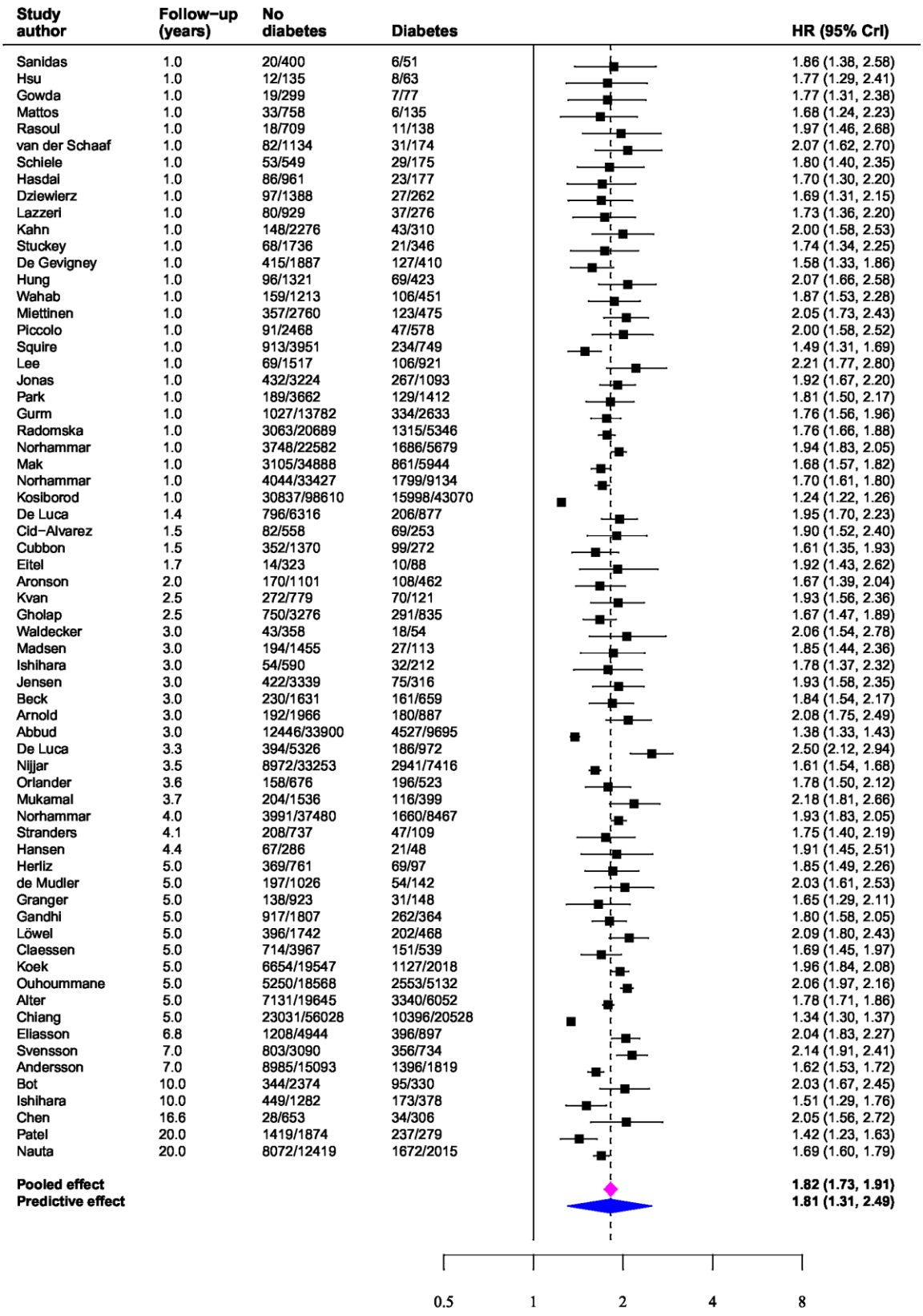

Figure 2. Unadjusted hazard ratio (HR) for long-term mortality in people with diabetes compared to those without. HR greater than 1 indicates increased risk of death in people with diabetes compared to those without. Follow-up time refers to mean, median or maximum duration of follow-up. The figures on the left hand side of the forest plot under the 'No diabetes' and 'Diabetes' columns refer to number of deaths (numerator) and the total number of participants (denominator) respectively in each study.

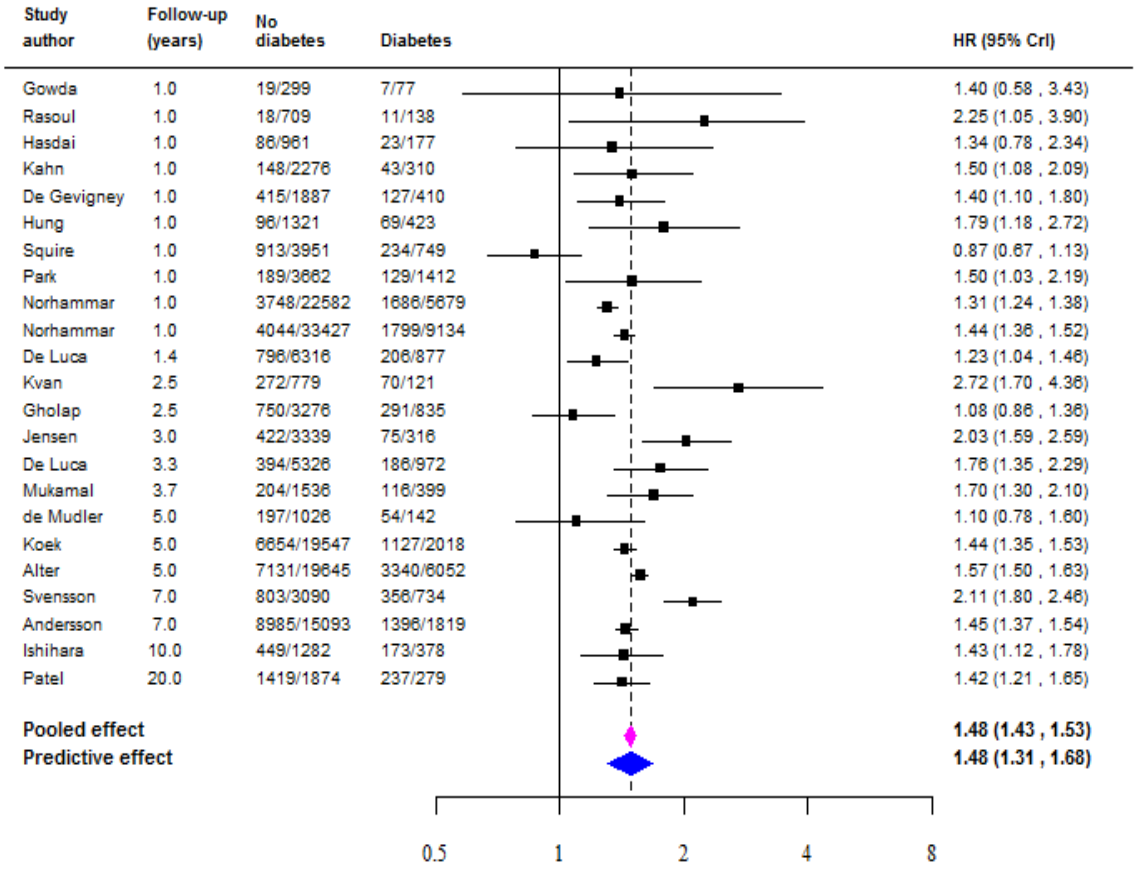

Figure 3. Adjusted hazard ratio (HR) for long-term mortality in people with diabetes compared to those without. Follow-up time refers to mean, median or maximum duration of follow-up. The figures on the left hand side of the forest plot under the 'No diabetes' and 'Diabetes' columns refer to number of deaths (numerator) and the total number of participants (denominator) respectively in each study.

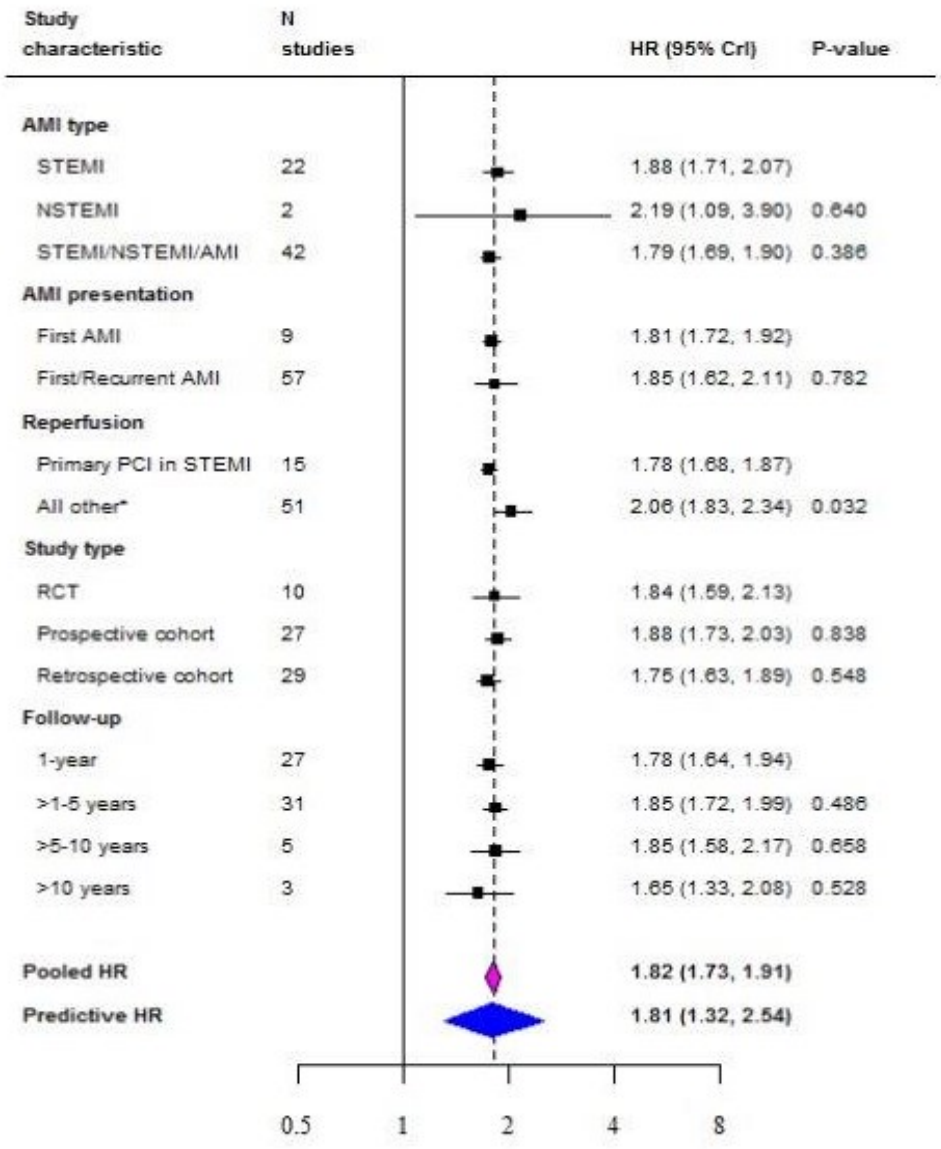

Figure 4. The risk of long-term mortality in people with diabetes compared to those without across various subgroups. Hazard ratios greater than 1 indicate increased risk of death in people with diabetes compared to those without.
*studies with mixed population of patients with STEMI/NSTEMI/AMI.

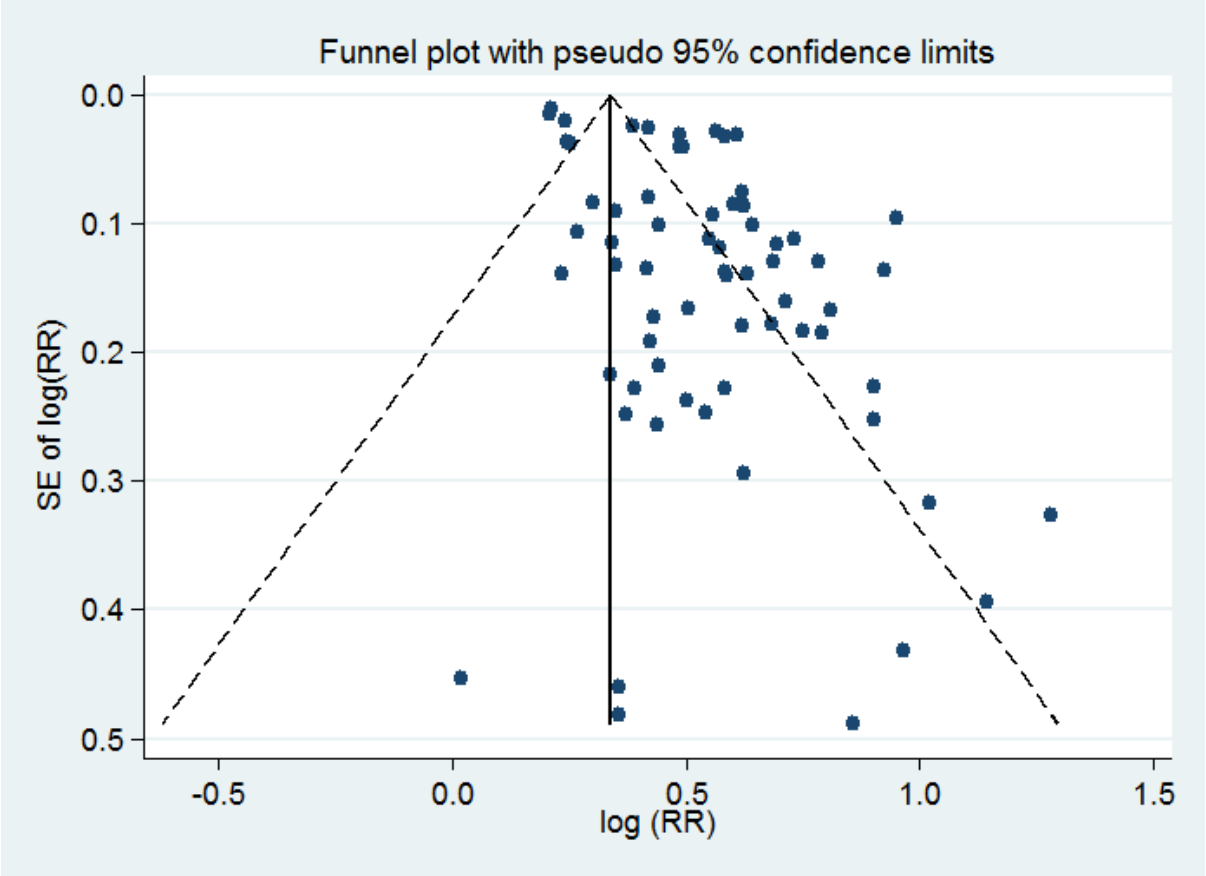

Figure 5. Funnel plot of the standard error of risk ratio versus risk ratio on logarithmic scale assessing publication bias in the evidence on risk of long-term mortality in people with diabetes compared to those without.