Association between medication adherence and risk of cardiovascular disease, all-cause mortality and hospitalisation in people with type 2 diabetes: systematic review and meta-analysis

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ABSTRACT

Objectives
To assess the association between cardiovascular medication adherence and risk of cardiovascular disease, all-cause mortality and hospitalisation in people with type 2 diabetes.

Design
Systematic review and meta-analysis of randomised and observational studies.

Data sources
Medline, Embase, Allied and Complementary Medicine, Cumulative Index to Nursing and Allied Health Literature, Educational Research Information Center, HealthSTAR, PsycINFO, Web of Science from inception to 27 April 2016.

Eligibility criteria
Randomised controlled trials, case-control and cohort studies that compared good and poor medication adherence in adults with type 2 diabetes, and explicitly reported the outcome of cardiovascular disease, all-cause mortality or hospitalisation.

Data collection and analysis
Two reviewers independently screened for eligible studies, assessed risk of bias, and extracted data. Pooled relative risks were calculated using a random-effects meta-analysis; risk of bias in each of the included studies was assessed using the GRADE approach.

Results
Eight observational studies were included (n=318125). The mean rate of poor adherence among included studies was 37.8% (95% CI 37.6-38.0). The relative risks of good (≥ 80%) versus poor adherence to medication were 0.72 (95% confidence interval 0.62-0.82, I²=0%, 3 studies) for all-cause mortality and 0.90 (0.87-0.94, I²=63%, 7 studies) for hospitalisation. No evidence of small study bias was observed.

Conclusions
Pooled estimates from available observational studies suggest that good medication adherence reduces the risk of all-cause mortality and hospitalisation in people with type 2 diabetes.
What is already known on this topic
Poor adherence to medication has been associated with increased mortality and health care costs across a range of chronic conditions. Adherence is considered a critical barrier to effective treatment of chronic conditions; however, the relationship between adherence and outcome in populations with type 2 diabetes is not clear.

What this study adds
Poor medication adherence in people with type 2 diabetes is associated with increased all-cause mortality and hospitalisation. Efforts to improve health outcomes in type 2 diabetes should address adherence to medication.
INTRODUCTION

Adherence refers to the extent to which patients take their medication regime as prescribed by their healthcare provider.\(^1\) Pooled data suggest around a quarter of patients are nonadherent, and rates of adherence are higher among patients with acute conditions when compared to chronic conditions.\(^2\) Even in the resource-intensive setting of clinical trials, the average adherence rates for trial drugs in chronic disease are between 43% and 78%.\(^3-5\) A systematic review of 11 studies in patients with type 2 diabetes remaining on treatment with oral hypoglycaemic agents (OHAs) for 6 to 24 months reported adherence rates of between 36 to 93%.\(^6\) Evidence from individual studies suggests that adherence is poorer among patients with depression,\(^7\) multimorbidity,\(^8,9\) and those on polytherapy or twice-daily regimens compared with monotherapy and once-daily regimens, respectively.\(^7,10,11\)

The increasing global prevalence of type 2 diabetes, driven by rising rates of obesity and population ageing,\(^12\) accounts for considerable cardiovascular morbidity and mortality. The inevitable rise in disease-specific complications including blindness, kidney failure and amputations, is placing further strain on resources in developed and developing healthcare systems alike. Despite evidence from randomised controlled trials demonstrating reductions in microvascular and macrovascular complications with improved control of glycaemia,\(^13-15\) achievement of HbA1c goals has been elusive on a population level. It is known that less than a quarter of patients with diabetes in the UK are meeting guideline targets for HbA1c, blood pressure and low density lipoprotein (LDL) cholesterol.\(^16\) The Guideline Adherence to Enhance Care (GUIDANCE) study on 7597 participants with type 2 diabetes from eight European countries reported within target HbA1c measurements in around half of the sample and only 6.5% meeting all three targets for HbA1c, blood pressure and LDL cholesterol.\(^17\) Progress in US diabetes care is not dissimilar; between 30 and 50% of people with diabetes still do not meet individualized goals for glycaemic control, blood pressure or lipid control, and only 14.3% meet targets for all three in the absence of tobacco use.\(^18\)

Poor adherence has been linked to adverse outcomes and higher healthcare costs.\(^1\) In a meta-analysis of 21 studies including participants across a range of conditions, good adherence was associated with an almost halving of all-cause mortality compared with poor adherence.\(^19\) Whether these associations hold true in patients with type 2 diabetes remains unclear. Reports linking suboptimal adherence rates with poor control of modifiable risk factors in previous studies\(^20,21\) suggest that failure to meet targets may be due, in part, to poor adherence. In this context, we conducted a systematic review and meta-analysis of relevant studies to quantify the relationship between cardiovascular medication adherence in type 2 diabetes and incident cardiovascular disease, all-cause mortality and all-cause hospitalisation.

METHODS
Study selection
We sought randomised controlled trials, case-control and cohort studies that determined adherence at baseline and then recorded cardiovascular disease (defined as fatal CVD, non-fatal myocardial infarction or ischaemic stroke) during follow-up. Data from studies recording cases of all-cause mortality and hospitalization (secondary outcomes) were also extracted. Pre-specified inclusion criteria required studies that reported an objective measure of adherence with separate reporting of the primary or secondary outcome(s) among groups with good and poor adherence to cardiovascular drug therapy. In the absence of a gold-standard method for estimation of adherence, acceptable methods to quantify adherence included pharmacy refill data, pill count, electronic drug monitoring systems and self reported measures in questionnaire or patient diaries. A threshold of 80% was used to define good adherence, the level at which patients have generally been categorised as adherent in the literature and trials outside those treating patients with the human immunodeficiency virus.1, 24

We searched electronic databases without language restrictions (Allied and Complementary Medicine, Cumulative Index to Nursing and Allied Health Literature, Embase, Educational Research Information Center, HealthSTAR, Medline, PsycINFO, Web of Science) from inception date to 27 April 2016. Both medical subject heading (MeSH) and keywords were used to search for terms related to type 2 diabetes, adherence, cardiovascular disease, mortality and hospitalisation (S1 in Appendix). We supplemented the search by examining reference lists of included studies, reviews1, 24 and meta-analyses.6, 19

Information on the following variables was independently obtained by two contributors: study design; study location; study size; measure of adherence; patient characteristics and absolute event rates. Any conflicts were resolved by the lead author. Where studies reported duplicate data, the most recent report from the same cohort was used to reflect contemporary practice and increase power. This meta-analysis was conducted according to the protocol registered with PROSPERO (Registration number CRD42016041380) and in accordance with PRISMA and MOOSE guidelines (S2 and S3 in Appendix).25, 26

Statistical analysis
Where available, summary characteristics of subjects with good and poor adherence are presented as mean values weighted by study size. The relative risks (RRs) and 95% confidence intervals (CIs) for good versus poor adherence to medication were calculated for cardiovascular disease, all-cause mortality and all-cause hospitalisation based on observed data for individual studies. Study-specific estimates were pooled using a random effects meta-analysis with the DerSimonian and Laird method.27 A random effects approach was taken in response to between-study heterogeneity anticipated in the effect size. Statistical heterogeneity of RR estimates was quantified using the $I^2$ statistic.[PMID: 12958120] The $I^2$ statistic is a measure of the proportion
of total variation in effect size that is due to heterogeneity. Where not directly reported, crude event rates were calculated by dividing the absolute number of events by the total person-years of follow-up. Publication bias was assessed using Begg’s funnel plots and Egger’s regression symmetry tests where five or more studies were available for pooled analyses. Study quality was assessed using the Newcastle-Ottowa scale for cohort studies, which awards a maximum of 9 points based on categories of selection (4), comparability (2) and outcome (3). Statistical analyses were two-sided with a significance level of 0.05; calculations were performed with Stata release 11 (Stata corp, College Station, TX, USA).

RESULTS

Of 8175 citations, we identified 105 studies for full-text review. Eight studies published between 2004 and 2015, reporting on 318,125 patients and 461,747 person-years of follow-up, were included in the final analyses (Figure 1). All eligible studies reported on retrospective cohorts, sourced from a combination of administrative claims data (n=6), diabetes registry data (n=1), or primary care datasets (n=1). Observer agreement on which studies were eligible for inclusion was good (Cohen’s unweighted κ =0.79). Only one study reported on the primary outcome (CVD) by adherence, whereas three and seven studies reported on all-cause mortality and all-cause hospitalisation respectively. Table 1 lists the characteristics of the included studies. All studies monitored adherence of antihyperglycaemic medications as the exposure variable, with the exception of one study that measured combined adherence of OHAs, antihypertensives and statins. Sample sizes ranged from 900 to 96,734, and the mean length of follow-up ranged from 12 to 24 months. The proportion of study participants with poor adherence varied from 25% to 91%, with a weighted mean of 37.8% (120,209/318,125). Mean quality scores (Newcastle-Ottowa Scale) were 8.0 and 7.1 for studies reporting on all-cause mortality and hospitalisation, respectively (table S4 in appendix).

The only study to report cardiovascular outcomes by adherence, showed a significant reduction in CVD events with good adherence (RR 0.68, 95% CI 0.66-0.71, p<0.001).[ref 28] During a total of 193,468 person-years of follow-up, there were 10,396 incident cardiovascular events (crude event rate 53.7 per 1000 person-years). Male sex, increasing age, greater comorbidity burden (Charlson comorbidity index), and high income were all associated with improved levels of adherence.

The association between medication adherence and all-cause mortality was reported in three studies involving 75,681 participants, 119,568 person-years of follow-up and 1189 deaths (1.6%). The pooled RR from these studies was 0.72 (95% CI 0.62-0.82, p<0.001)) for all-cause mortality when comparing good with poor adherence (Figure 2). No heterogeneity was observed in the effect size between studies analysed (I²=0.0%, Q statistic p=0.65).
Data on all-cause hospitalisation were recorded across seven studies involving 221,391 individuals, 265,279 person-years of follow-up and 46,535 hospitalisation events. Good adherence was associated with benefits in reduced hospitalisation rates (RR 0.90, 95% CI 0.87-0.94, p<0.001). Each individual study considered in this analysis reported lower hospitalisation rates among a group with good adherence (Figure 3). Moderate heterogeneity was observed between studies; the $I^2$ was 63.4% and Q statistic p=0.012. There was no evidence of small study bias such as publication bias with Egger’s test for hospitalisation (P=0.61) (Fig S5 in appendix).

**DISCUSSION**

This meta-analysis is the first to examine the relationship between medication adherence and clinical outcomes specifically in people with type 2 diabetes. We found that individuals with good adherence had a 10% significant reduction in hospitalization events and a 28% significant reduction in all-cause mortality when compared to a group with poor adherence. Our analyses support and extend those of a report examining the association between adherence to drug therapy and mortality across a range of conditions including HIV, myocardial infarction, heart failure and hyperlipidaemia. In that study, good adherence corresponded with an approximately 50% reduction in the risk of mortality when compared to individuals with poor drug compliance.

Despite consistent improvements in the quality of care for diabetes in recent decades, it remains a harbinger of substantial premature mortality. A meta-analysis of 97 prospective studies by the Emerging Risk Factors Collaboration suggests the presence of diabetes is associated with a 1.8 fold increase in the risk of death, and more than half of recorded deaths in that study were attributable to cardiovascular disease. There are more recent data from the Swedish National Diabetes Register that suggest mortality in type 2 diabetes may be falling; it reported hazard ratios of 1.15 (1.14-1.16) and 1.14 (1.13-1.15) for all-cause and cardiovascular mortality, respectively. The relatively low mortality compared to previous reports may be attributed to more aggressive treatment with statins and blood pressure medications, in addition to improvements in glycaemic control over time. The earlier use of diabetes drug classes with the ability to modify cardiovascular risk beyond glycaemia may have a role in further reducing overall mortality; however, their full benefit will only be realised if patients can adhere to the prescribed regimens.

The rise of performance indicators in the assessment of quality of care underscores the importance of long-term adherence, given that greater attainment of treatment targets for HbA1c, blood pressure, and LDL cholesterol have all been linked to medication adherence. It is therefore vital that healthcare professionals can recognize and treat poor adherence. This is particularly relevant in type 2 diabetes where patients require increasingly complex treatment regimens that result from deterioration in
glycaemia with disease progression and the development of multiple comorbidities. Unfortunately, interventions to improve adherence have met with mixed results, and those that have achieved success have done so at significant cost and by complex means.\cite{43} In a recent update of a Cochrane review on the subject across many conditions, even the most effective interventions did not lead to large improvements in adherence.\cite{43} Adherence has been called the “next frontier in quality improvement”,\cite{44} and without effective strategies to improve it on a population level, progress in clinical outcomes in type 2 diabetes achieved over recent decades may plateau, in spite of improvements in conventional quality of care indicators and the range of therapies available.

Although population strategies have achieved some success in preventing or delaying complications of type 2 diabetes in high-income countries, the rapid escalation in numbers of those affected in developing countries is of great concern. Global strategies to address the diabetes epidemic should rightly focus on, and direct funds towards, preventing type 2 diabetes; however, the cost of treating complications alone has the potential to absorb a large proportion of existing healthcare budgets. In developed countries, the burden of diabetes is thought to account for around 5-14% of healthcare spending,\cite{45,46} yet less than a quarter of this cost is related to the management of diabetes itself; the treatment of complications of the disease accounts for the remaining budget.\cite{45} In developing countries, where prevalence is rising most quickly and 80% of diabetes cases live,\cite{47} expenditure on diabetes as a proportion of total health budget is currently low.\cite{46} This is alarming as the proportion of young to middle-aged individuals with type 2 diabetes is higher in developing countries and an accelerated course of diabetes-related complications is observed in this group.

The estimates presented in this study suggest that efforts to improve adherence may help to reduce both mortality rates and the frequency of hospitalisation in type 2 diabetes, with possible implications for cost savings on a population level. Our findings add to calls for high quality studies on interventions to improve adherence in type 2 diabetes in clinical practice settings. Further investigation with access to individual participant data is required to establish the mechanisms behind the protective effect of adherence and to guide strategies for improving adherence. Unresolved questions relate to whether improvement in clinical outcomes observed in people with good adherence are due to improved control of modifiable risk, a healthy adherer effect or other as yet unmeasured factors. Whether good adherence is associated with benefits for the prevention of diabetes-specific complications also merits further consideration, as they carry significant morbidity and mortality, and account for a disproportionate share of overall healthcare expenditure.

A key strength of the present study is the size of included studies. The pooled cohorts for all-cause mortality and hospitalization outcomes involved 119,569 and 265,279 person-years of follow-up, respectively. There are certain limitations with this study. Firstly, and common to all meta-analysis that lack individual participant data, the risk ratios presented are not adjusted for potential confounding variables. The cohorts
studied also differed between, and within, studies in their baseline characteristics. Given the limited number of studies, we were unable to assess the associations by relevant subgroups. Despite conducting a detailed literature search, we found only a single study meeting our eligibility requirements that reported on cardiovascular events separately among groups with good and poor adherence. We were therefore unable to assess the association with adherence beyond its findings. There are a wide range of measures of adherence, the most commonly encountered methods were medication possession ratios and percentage of days covered. In the absence of a gold-standard measure and threshold for good adherence, we took a pragmatic approach to define good adherence as 80% that is common in the literature. Again, individual participant data linking numerical values for adherence with outcome may have yielded greater precision in our estimates. The limited number of studies precluded the ability to investigate the possibility of publication bias in greater detail. Lastly, with the exception of one study that considered adherence across three classes of medications, all studies reported adherence rates to antihyperglycaemic therapy only. In a real-world setting, patients with type 2 diabetes are frequently prescribed a range of medication classes to modify cardiovascular risk including blood pressure treatments and statins. We were unable to differentiate the impact of adherence to other medications apart from antihyperglycaemic agents.

In this meta-analysis, improved adherence to medication in adults with type 2 diabetes corresponded with reduced rates of all-cause mortality and hospitalisation. These findings have several implications. In conjunction with previous studies, these data should encourage healthcare professionals to routinely assess adherence in clinical practice and make efforts to improve it where it falls below 80%. In addition, our findings should serve to reinforce to patients the importance of taking medications as prescribed, in order to avoid premature death and preventable admissions to hospital. Finally, high quality studies examining the effectiveness of interventions to improve adherence in chronic disease are needed to guide international efforts to curb the effects of the diabetes epidemic.

**Contributors:** KK, SS, KS and MD conceived the study. KK designed the study. JB and RH performed the literature search and extracted the data. KK resolved any conflicts in study identification. JB carried out the statistical analysis. JB and KK drafted the manuscript, which was critically appraised by SS, KS and MD. All authors have read and approved the final manuscript.

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KK has received funds for research, honoraria for speaking at meetings and or served on Advisory Boards for Astra Zeneca, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk.

SS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly and BI.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly.

**Ethical approval:** Not required.

**Transparency:** The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been disclosed.

**Data sharing:** No additional data available.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type (administrative claims data)</th>
<th>Treatment group (no participants)</th>
<th>Adherence measures</th>
<th>Threshold for good adherence</th>
<th>Prevalence of poor adherence</th>
<th>Follow-up</th>
<th>Location</th>
<th>Cardiovascular disease, Events / Participants, n (%)</th>
<th>All-cause mortality, Events / Participants, n (%)</th>
<th>All-cause hospitalisation, Events / Participants, n (%)</th>
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<tr>
<td>Gibson et al 2010</td>
<td>Retrospective cohort study</td>
<td>T2DM on at least one OHA (96734)</td>
<td>Percentage of days covered</td>
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<td>25.5%</td>
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<td>6918/72067 (9.6)*</td>
<td>3478/24667 (14.1)*</td>
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<td>Zhu et al 2015</td>
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<td>T2DM on at least one OHA (24067)</td>
<td>Percentage of days covered</td>
<td>PDC ≥80%; PDC &lt;80%</td>
<td>90.6%</td>
<td>12 months</td>
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<td>25/2269 (1.1)</td>
<td>294/21798 (1.3)</td>
<td>377/2269 (16.6)</td>
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<td>MPR ≥80%; MPR &lt;80%</td>
<td>70.6%</td>
<td>24 months</td>
<td>South Korea</td>
<td>86/11800 (0.7)</td>
<td>276/28282 (1.0)</td>
<td>1456/11800 (13.1)</td>
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<td>Ho et al 2006</td>
<td>Retrospective cohort study (Kaiser Permanente diabetes register)</td>
<td>DM including diet controlled, those on OHAs and insulin (11532)</td>
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<td>PDC ≥80%; PDC &lt;80%</td>
<td>21.3%</td>
<td>16 months</td>
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<td>145/2456 (5.9)</td>
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<td>PDC ≥100%; PDC &lt;50%</td>
<td>47.5%</td>
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<td>6663/34244 (19.5)</td>
<td>3680/16713 (22.0)</td>
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T2DM indicates type 2 diabetes, OHA, oral hypoglycaemic agent, PDC, percentage of days covered, MPR, medication possession ratio. * Cerebrovascular disease and acute myocardial infarction; ** Ischaemic heart disease and stroke
Figure 1. Study selection
DM, diabetes mellitus, RR, relative risk

<table>
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<tr>
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<th>Events (poor)</th>
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<th>Weight, %</th>
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\( I^2 = 0.0\%, p = 0.648 \)

Figure 2. Association between medication adherence and all-cause mortality in type 2 diabetes
Figure 3. Association between medication adherence and all-cause hospitalisation in type 2 diabetes
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