QUERI

Metformin Use in Patients with Contraindications or Precautions

September 2016

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Durham VA Medical Center
Durham, NC
John W. Williams, Jr., MD, MHSc, Director

Investigators:

Principal Investigators:
Matthew J. Crowley, MD
Clarissa J. Diamantidis, MD
John W. Williams, Jr, MD, MHSc

Co-Investigators:
Jennifer R. McDuffie, PhD
Blake Cameron, MD
John Stanifer, MD
Clare K. Mock, MD
Andrzej Kosinski, PhD
Xianwei Wang, MD
Shuang Tang, MD, PhD

Research Associates:
Avishek Nagi, MS
Liz Wing, MA

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

Recommended citation: Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron B, Stanifer J, Mock CK, Kosinski A, Wang X, Tang S, Williams, Jr, JW. Metformin Use in Patients with Contraindications or Precautions. VA ESP Project #09-010; 2016.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **Durham VA Medical Center, Durham, NC**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

TABLE OF CONTENTS

TABLES

FIGURES

EVIDENCE REPORT

INTRODUCTION

Metformin is a biguanide oral hypoglycemic used primarily for treating type 2 diabetes mellitus (T2D). Evidence suggests that, in addition to improving glycemic control, metformin is associated with improved all-cause and cardiovascular mortality[1] and decreased risk of some cancers (*eg*, breast cancer).[2] Despite the potential benefits, since metformin was introduced in the United States in the mid-1990s, clinicians have been advised to exercise caution in prescribing the drug to individuals with certain comorbidities due to perceived risks of serious side effects, including LA. Lactic acidosis (LA) is defined as blood lactate concentration >45mg/dl (5.0mEq/L), decreased blood pH, and electrolyte disturbances with an increased anion gap. It may result from lactate overproduction because of inadequate tissue oxygen delivery or without overt tissue hypoperfusion. The LA type classifications are explained in Table 1.

Table 1. Lactic Acidosis Type Classification[3]

Type A-LA: Clinical Evidence of Inadequate Tissue Oxygen Delivery
· Anaerobic muscular activity (*eg*, sprinting, generalized convulsions) · Tissue hypoperfusion (*eg*, shock: septic, cardiogenic, or hypovolemic; hypotension; cardiac arrest; acute heart failure; regional hypoperfusion, especially mesenteric ischemia; malaria) · Reduced tissue oxygen delivery or utilization (*eg*, hypoxemia, carbon monoxide poisoning, severe anemia)
Type B-LA: No Clinical Evidence of Inadequate Tissue Oxygen Delivery
· Type B1: Associated with underlying diseases (*eg*, ketoacidosis, leukemia, lymphoma, AIDS) · Type B2: Associated with drugs and toxins (*eg*, phenformin, cyanide, beta-agonists, methanol, nitroprusside infusion, ethanol intoxication in chronic alcoholics, antiretroviral drugs) · Type B3: Associated with inborn errors of metabolism (*eg*, congenital forms of LA with various enzyme defects such as pyruvate dehydrogenase deficiency)

Note: Table does not include all causes of LA.

Among the most serious side effects of metformin is metformin-associated LA, which is a rare (approximately 0.03 cases per 1000 person-years) but potentially highly fatal type B-LA.[4] Metformin is excreted through the kidneys, and most cases of metformin-associated LA have occurred in the setting of inappropriate dosing, significant kidney impairment, sepsis, hypovolemia, excess alcohol intake, hepatic insufficiency, age greater than 80 years, or acute/decompensated congestive heart failure (CHF).[5,6] As such, the FDA specifies chronic kidney disease (CKD) with low estimated glomerular filtration rate (eGFR) as a contraindication to metformin use, and it lists acute or unstable CHF, older age, and hepatic impairment as precautions for use.[7,8] Despite these warnings, there are efforts to expand the use of metformin, and currently more than 50% of metformin users may have an ongoing contraindication or precaution for its use.[9,10]

In 2006, the FDA relaxed its warning regarding CHF and metformin use and removed acute or unstable CHF as a contraindication. More recently, in April 2016, the definition of CKD used by the FDA in the boxed warning was modified (Appendix A).[11] Historically, metformin use was to be avoided in individuals with a serum creatinine ≥1.5mg/dL for men and ≥1.4 mg/dL for women. Serum creatinine is known to be a poor marker of kidney function.[12] Consequently, this

guideline discouraged use of metformin in many individuals with relatively normal kidney function. Therefore, the kidney function cutoff was revised to an eGFR of 45 mL/min/1.73m^2 if renal function is monitored every 3 months to 6 months, but still contraindicated if eGFR is <30 mL/min/1.73m^2, consistent with recent clinical guidelines for metformin use and best practices for estimating kidney function.[11,13,14] An estimated one million additional patients became eligible to use metformin as a result of this change.[15]

Recent literature highlights the rarity of metformin-associated LA and supports the cautious expansion of metformin use. Most notably, a 2010 Cochrane systematic review found no association between metformin use and fatal or nonfatal LA,[16] and a 2014 systematic review found the incidence of LA among metformin users to be indistinguishable from background population rates, ranging from approximately 3 per 100,000 person-years to 10 per 100,000 person-years.[5] Yet there remain uncertainties regarding metformin's appropriate use, and the benefit relative to the harm in populations with CKD, CHF, hepatic impairment *(eg,* chronic liver disease), and older age are not well understood. For this reason, we conducted a systematic review and meta-analysis in order to determine (1) the rates of LA associated with metformin use in patients with T2D and (2) the benefits and harms of metformin use in the presence of traditional contraindications or precautions.

METHODS

TOPIC DEVELOPMENT

The key questions (KQs) for this systematic review were developed after a topic refinement process that included a preliminary review of published, peer-reviewed literature; consultation with internal partners and investigators; and consultation with content experts and key VA stakeholders.

The final KQs were:

KQ 1. For patients with type 2 diabetes and an apparent contraindication/precaution to metformin use (*eg*, renal insufficiency, congestive heart failure, chronic liver disease, or older age):

a. What is the rate of lactic acidosis in patients taking metformin?

b. How does the rate of lactic acidosis in patients taking metformin compare with the rate in patients taking other hypoglycemics?

KQ 2. For patients with type 2 diabetes and an apparent contraindication/precaution to metformin use, what are the potential benefits and harms (other than lactic acidosis) of continued treatment with metformin?

We followed a standard protocol for this review, and each step was pilot-tested to train and calibrate study investigators. The PROSPERO registration number is CRD42016027708.

SEARCH STRATEGY

In consultation with an expert librarian, we conducted searches of MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (KQ 2 only), Embase, and the International Pharmaceutical Abstracts in November 2015. The exact search strategies are in Appendix B. We also searched ClinicalTrials.gov for relevant completed and ongoing studies.

We also evaluated the reference lists of systematic or nonsystematic reviews and queried Bristol-Myers Squibb, the manufacturer of Glucophage (branded formulation of metformin), for relevant studies. We used a combination of MeSH keywords and selected free-text terms to search titles and abstracts. All citations were imported into 2 electronic databases (for referencing, EndNote® Version X7, Thomson Reuters, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

STUDY SELECTION

Using prespecified inclusion/exclusion criteria (Table 2), titles and abstracts of RCTs identified through our search were reviewed by 2 reviewers for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, 2 independent reviewers were required to agree on a final inclusion/exclusion decision. Disagreements were resolved by discussion or by a third investigator. Of note, prior to excluding any potentially eligible study whose primary analysis did not address a population with a

metformin contraindication or precaution, we specifically examined the full text for analyses of relevant subgroups. Articles meeting eligibility criteria were included for data abstraction.

Table 2. Inclusion and Exclusion Criteria

Study Characteristic	Inclusion/Exclusion Criteria
Population	Adults (≥18 years of age) with T2D (using criteria valid at the time of the study) and one of the following contraindications/precautions to metformin use: CKD, CHF, CLD, or older age as defined by authors of the primary study. Exclusions: · Mixed samples where less than 80% have one or more of the specified contraindications/precautions, and results are not reported by subgroup. · Studies where less than 80% of the sample has T2D. The rationale is that relatively homogeneous samples of the population of interest are required to evaluate metformin effects. · Samples with prediabetes or metabolic syndrome, gestational diabetes mellitus, acute kidney injury in the absence of CKD, end-stage renal disease on hemodialysis, and contrast exposure (*eg*, contrast-enhanced imaging procedures). CKD may be defined as an elevated creatinine or eGFR <60 mL/min/1.73m^2; microalbuminuria alone is not considered CKD for the purposes of this review.
Interventions	Metformin use alone or in combination with other glucose-lowering treatment. Exclusion: Phenformin
Comparators	· KQ 1a: None, or any inactive control or active comparator · KQ 1b and KQ 2: Non-metformin oral or injectable hypoglycemic medication(s) in the presence of a traditional contraindication or precaution to metformin use Exclusion: Studies that did not allow evaluation of the effect of metformin (*eg,* studies that compared metformin plus a hypoglycemic medication to metformin plus a different hypoglycemic medication)
Outcomes	· KQ 1a and 1b: Incidence of fatal and nonfatal LA or metformin-associated LA[a] · KQ 2: Benefits evaluated include glycemic control (*ie*, A1c), lipid control, major adverse cardiovascular events (MACE) (*eg,* MI, CHF hospitalization), cardiovascular-related mortality, and all-cause mortality; harms included hypoglycemia and weight gain Exclusion: Studies that reported only metformin clearance, metformin levels, or lactate levels without one of the specified outcomes of interest
Timing	Studies reporting outcomes at ≥28 days (approximately 1 month) following initiation of metformin or switching to another medication
Setting	Outpatient or population-based. Studies that identified hospitalized patients with metformin-associated LA and were able to estimate a rate based on outpatient or population-based samples were eligible.

Study Characteristic	Inclusion/Exclusion Criteria
Study design	· KQ 1a: Clinical trials, prospective and retrospective cohort studies, and pharmacovigilance studies. Excluded were case reports, case-series, and cross-sectional studies because such studies cannot provide a rate of LA. · KQ 1b: Clinical trials, comparative prospective and retrospective cohort studies, case-control studies, and pharmacovigilance studies. Excluded were case reports, case-series, and cross-sectional studies. · KQ 2: RCTs, nonrandomized clinical trials, and comparative prospective and retrospective cohort studies
Publication type	Full publications in English-language, peer-reviewed journals Exclusions: Meeting abstracts, letters, editorials, and dissertations
Limits	Studies were limited to the 34 countries that are part of the Organization for Economic Cooperation and Development.[17] The rationale is to limit to countries where T2D is more prevalent and the general medical care is similar to that in United States. For KQ 1a and KQ 1b, the search was limited to 2009 through the present. For KQ 2, we searched from 1994, the year that metformin was approved by the FDA, through the present. A high-quality Cochrane review (search date October 2009[16]) included all clinical trials in patients with T2D and all observational cohort studies evaluating ≥1 month of metformin use. Outcomes were death due to LA, nonfatal LA, and blood lactate levels. Other relevant reviews[13,18] have even more recent searches.

[a] LA is defined as blood lactate concentration >45mg/dl or 5.0mEq/L, decreased blood pH, and electrolyte disturbances with an increased anion gap. Metformin-associated LA is defined as meeting the definition for LA plus either (a) elevated metformin level or (b) investigator judgment that LA is metformin-induced. We abstracted information to determine if outcomes conformed or deviated from these definitions.

Abbreviations: CHF = congestive heart failure; CKD = chronic kidney disease; CLD-chronic liver disease; eGFR = estimated glomerular filtration rate; LA = lactic acidosis; MACE = major adverse cardiovascular event; MI = myocardial infarction; RCT = randomized controlled trial; T2D = type 2 diabetes

DATA ABSTRACTION

Data from published reports were abstracted into a customized DistillerSR database by one reviewer and overread by a second reviewer. Disagreements were resolved by discussion or by a third investigator. Key characteristics abstracted were patient descriptors (including age, sex, race, and specific contraindication/precaution to metformin), setting, metformin dose, cointerventions (*eg*, other hypoglycemics), comparator, and outcomes which we selected in conjunction with our stakeholders and technical expert panel. For observational studies, we abstracted unadjusted and adjusted outcomes. Other key information included definitions related to contraindications/precautions (*eg*, definition of CKD and methods for determining CKD/estimating eGFR such as the Modification of Diet in Renal Disease formula[19] or the Cockcroft-Gault formula[20]). We treated multiple publications from a single study as a single data point, prioritizing the longest-term, most complete, and most appropriately analyzed results. When critical data were missing or unclear in published reports, we requested supplemental data from manuscript authors. Key features relevant to applicability included the match between the

sample and target populations (*eg*, metformin contraindication/precaution, age, concurrent treatments, or Veteran status).

QUALITY ASSESSMENT

Quality assessment was done independently by 2 investigators. Disagreements were resolved by consensus between the 2 investigators or, when needed, by arbitration by a third investigator.

We used the Cochrane Risk of Bias tool for RCTs[21] and the key quality criteria described in the Agency for Healthcare Research and Quality's (AHRQ's) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[22] adapted to this specific topic and customized to observational studies.[23] For RCTs, these criteria are adequacy of randomization and allocation concealment; blinding of participants, personnel, and outcomes assessment; whether incomplete data were addressed appropriately; selective reporting, and other bias. We assigned a summary risk of bias score (low, unclear, or high) to individual studies (Appendix C). For observational studies, we used a tool customized to this project that addresses risk of bias from selection, performance, attrition, detection, and selective outcome reporting (Appendix D).[24]

DATA SYNTHESIS

We summarized the primary literature using relevant data abstracted from the eligible studies. Summary tables describe the key study characteristics of the included studies: metformin contraindication/precaution (including severity such as CKD stage), patient demographics (including age), and details of the intervention and comparator. When necessary,[25,26,25,26] relevant hazard ratios (HRs) with the same reference group were pooled in a weighted fashion based on the subject counts in each category, incorporating an approximation of the correlation resulting from the shared reference. In the absence of a reported HR,[27] we estimated the HR and variance from the reported frequencies and odds ratio (OR) using an established approach.[28] We then determined the feasibility of completing a quantitative synthesis (*ie*, meta-analysis) to estimate summary effects. For all analyses, we analyzed RCTs separately from observational studies.[29] We aggregated outcomes when there were at least 3 studies with the same outcome, based on the rationale that one or 2 studies do not provide adequate evidence for summary effects. Analyses were conducted separately for patients with different contraindications or precautions to metformin (*eg*, CKD vs CHF), using rates adjusted for potential confounders. We planned to conduct subgroup analyses by severity of contraindication/precaution (*eg*, CKD stage), by single (metformin monotherapy) versus combined treatment (*eg*, metformin plus other hypoglycemics with or without metformin), and by comparator (lifestyle or placebo vs other hypoglycemics). However, there were too few studies to support the planned subgroup analyses.

Studies reported dichotomous outcomes (*eg*, LA, mortality, hypoglycemic events) and continuous outcomes (*eg*, A1c, weight, lipid values). Quantitative synthesis was feasible only for mortality and major adverse cardiovascular event (MACE) outcomes. These outcomes were combined using a random-effects model to generate summary hazard ratios. For analyses with few ($n<20$) studies, we used the Knapp-Hartung approach to adjust the standard errors of the estimated coefficients.[30,31] Sensitivity analyses omitted studies with severe disease (*eg*, eGFR < 30ml/min/1.73m^2. We evaluated statistical heterogeneity using visual inspection and Cochran's Q and I^2 statistics. Publication bias was assessed using funnel plots (when there were >10 studies in an analysis).

When quantitative synthesis was not feasible, we analyzed the data qualitatively. We gave more weight to the evidence from higher-quality studies with more precise estimates of effect. A qualitative synthesis focuses on documenting and identifying patterns in efficacy and safety of the interventions across conditions and outcome categories. We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

RATING THE BODY OF EVIDENCE

Strength of evidence (SOE) was assessed using the approach described in the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide*.[22] We limited Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings[32] to those outcomes identified by the stakeholders and technical expert panel as critical to decision making. These included nonfatal and fatal LA and mortality. In brief, this approach assesses 4 domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate and included coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating was assigned after discussion by 2 investigators as high, moderate, or low strength of evidence. In some cases, high, moderate, or low ratings were impossible or imprudent to make. In these situations, a grade of insufficient was assigned. This 4-level rating scale consists of the following definitions:

- High—We are confident that the true effect lies close to the estimate of effect.
- Moderate—We are moderately confident of the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Insufficient—We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

PEER REVIEW

A draft of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is provided in Appendix E.

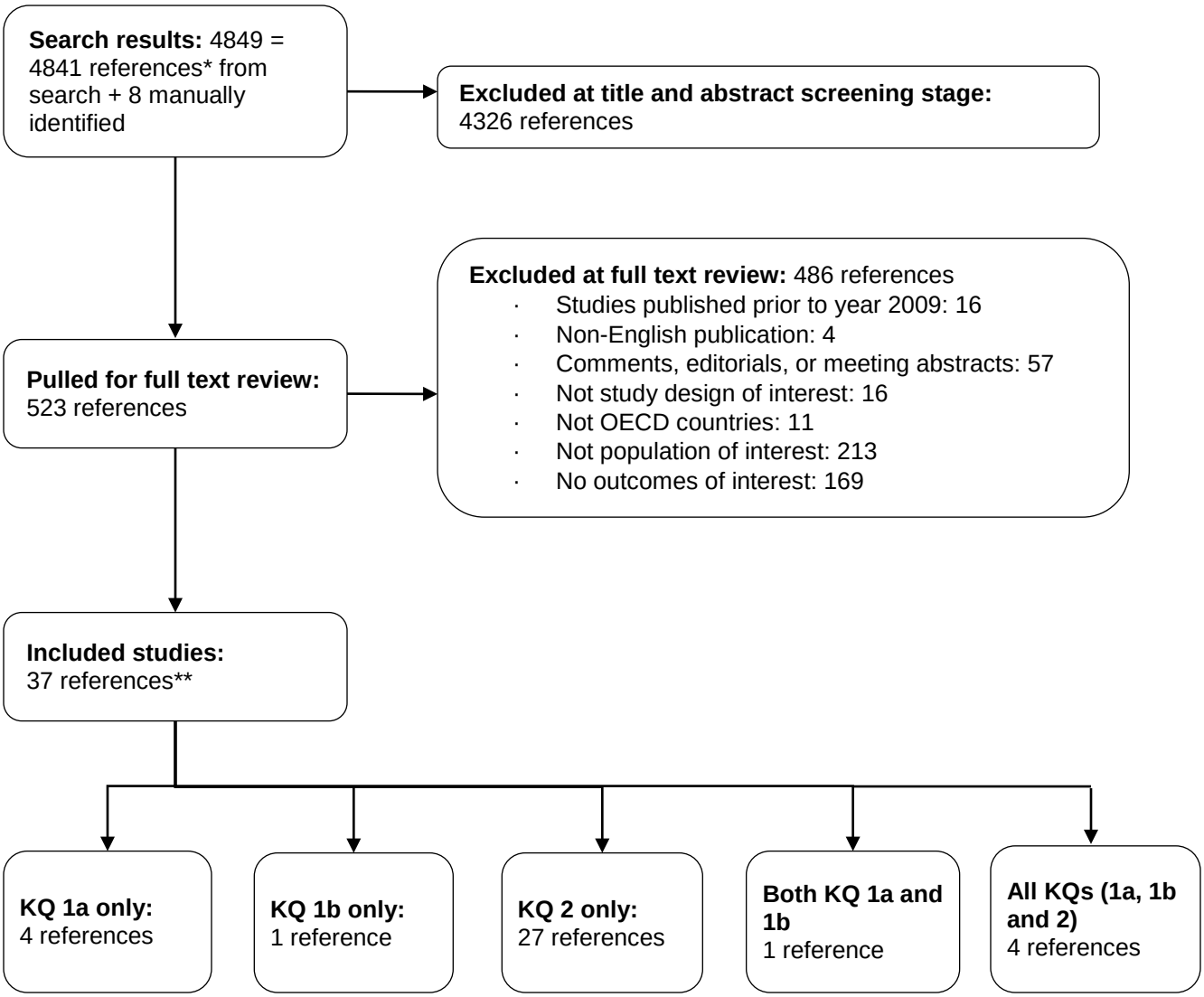
RESULTS

LITERATURE FLOW

Figure 1 shows the flow of articles through the literature search and screening process. The literature search identified 4,841 unique citations from a combined search of MEDLINE® (via PubMed®), the Cochrane Registry of Controlled Trials, Embase®, and International Pharmaceutical Abstracts. An additional 8 articles were identified from manual searches of bibliographies and current literature published after the search date for a total of 4,849 unique citations. After applying inclusion and exclusion criteria at the title-and-abstract screening level, 523 full texts were retrieved for further review. Of these, 37 were retained for data abstraction. We attempted to contact 13 authors for additional study information; however, 7 could not be reached, and the remaining 6 all replied that the data were not available.

Among the 37 included studies, 29 were observational studies and 8 were randomized controlled trials (RCTs), of which one was a companion paper. Some studies reported results applicable to more than one key question (KQ) or one precaution or contraindication. By KQ, 9 studies addressed KQ 1 and 32 studies addressed KQ 2. By precaution, studies reported data relevant to older adults (n = 16), patients with CHF (n = 11), patients with CKD (n = 9), and patients with CLD (n = 3). Most studies were conducted in samples from Europe and used a retrospective cohort design; 4 studies were conducted in Veteran samples. Of note, we identified no ongoing studies meeting our inclusion criteria in ClinicalTrials.gov.

Figure 1. Literature Flow Chart



* Search results are from Embase (2512), PubMed (2312), Cochrane (17).
** The report's reference list includes all the studies (CHF/cardiovascular studies, n = 18; the remaining studies are elderly). One of the included studies is a companion paper.

KEY QUESTION 1: For patients with type 2 diabetes and an apparent contraindication/precaution to metformin use (*eg*, renal insufficiency, congestive heart failure, chronic liver disease, or older age):

a. What is the rate of lactic acidosis in patients taking metformin?

b. How does the rate of lactic acidosis in patients taking metformin compare with the rate in patients taking other hypoglycemics?

Key Findings

- There are limited new data examining the rate of lactic acidosis (LA) with metformin use since the 2010 Cochrane review; however, a small number of contemporary studies have reported on this outcome in individuals with an identified precaution or contraindication to metformin use.
- KQ 1a: Limited data suggest that the incidence of LA in metformin users who have chronic kidney disease (CKD) is slightly higher than the upper bounds (4.3/100,000) reported in the Cochrane review. The limited data on incidence rates of LA among older adults are inconclusive. No studies reported incidence rates for individuals with CHF or chronic liver disease (CLD).
- KQ 1b: The data comparing rates of LA with metformin use versus non-metformin diabetes treatment do not suggest a higher rate of LA with metformin use among individuals with CKD, CHF, or CLD. No study reported this outcome for older adults without one of these comorbid conditions.

Recommendations regarding the use of metformin in the treatment of type 2 diabetes (T2D) are limited by concerns of the development of fatal or nonfatal LA among individuals with a contraindication to metformin therapy. In 2010, Salpeter et al published a scientifically rigorous Cochrane review of studies through 2009 describing the rate of fatal and nonfatal LA with metformin use in patients with T2D.[16] The authors found no cases of LA in 70,490 patient-years of metformin use using pooled data from 347 comparative trials and cohort studies. Using Poisson statistics, the upper 95% confidence interval (CI) for the rate of LA was estimated at 4.3 per 100,000 person-years in metformin users and 5.4 per 100,000 person-years in nonusers. However, there was insufficient information to estimate the number of participants studied with renal insufficiency, cardiovascular diseases, or liver disease. As an update to those findings, our review describes results in patients with a precaution/contraindication to metformin from publications in years 2009 through 2015.

Since 2009, 9 observational studies have evaluated the rate of LA in individuals with T2D taking metformin and a contraindication/precaution to its use.[25,33-40] We did not identify any RCTs enrolling patients with a precaution/contraindication or reporting relevant subgroup analyses for this outcome. Seven of the 9 studies were conducted in Europe,[25,33-35,37,39,40] one in North America,[38] and one in Japan.[36] All 9 studies evaluated the rate of LA in individuals taking metformin; 5 studies compared the rate of LA in metformin users with the rate in individuals taking other hypoglycemics.[25,34,35,38,40] Due to significant heterogeneity across studies and metformin precautions, a meta-analysis was not performed and studies were synthesized qualitatively.

For KQ 1, we present the detailed results by condition, starting with incidence (KQ 1a) and then comparison (KQ 1b). Details on study characteristics are in Appendix F.

Rate of Lactic Acidosis with Metformin Use

Four studies examined the rate of LA among individuals taking metformin alone or in combination with another diabetic medication.[33,36,37,39] There were no studies evaluating the individual effect of metformin on the occurrence of LA among individuals with CHF or CLD.

Chronic Kidney Disease

Two studies focused on the rate of LA in individuals with CKD.[33,39] Of these, one prospective study with high risk of bias (ROB) included 588 French patients older than age 65 and evaluated the appropriateness of metformin dosing based on baseline estimated glomerular filtration rate (eGFR), which was derived using Cockcroft-Gault corrected for body surface area, or CKD-EPI estimating equations.[39] Over an average follow-up of 3 years, there were no reported deaths due to LA irrespective of the appropriateness of metformin dosing. The study does not comment on the occurrence of nonfatal LA and does not present a time-adjusted analysis.

The other study used records from a large UK database to examine the rate of LA in individuals on metformin with normal, mildly impaired, moderately impaired, or severely impaired renal function.[33] CKD categories were based on diagnosis code of CKD stage or eGFR. This retrospective, high ROB study included 77,601 patients and 337,590 patient-years, during which there were 35 LA events (captured by ICD-9 code) over an average follow-up of 4.35 years. The overall rate of LA in individuals receiving metformin was 10.37 per 100,000 patient years (95% CI 7.22 to 14.42), higher than the estimate reported in the Cochrane review. The rate of LA by eGFR category was 7.61, 4.64, 17.18, and 39.0 per 100,000 patient-years among eGFR >90 (normal), >60 to ≤90 (mildly impaired), >30 to ≤60 (moderately impaired), and ≤30 ml/min/1.73m^2 (severely impaired), respectively. There were no statistically significant differences in the incidence rate ratio (IRR) of LA across mildly, moderately, and severely impaired renal function compared with normal renal function (IRR 0.61 [95% CI 0.12 to 5.26], 2.27 [0.56 to 20.0], 5.26 [0.37 to 71.43], respectively), but confidence intervals were wide and did not exclude a clinically significant difference.

Older Adults

Two studies examined the rate of LA among older metformin users. One small pharmacovigilance study with high ROB evaluated the rates of elevated lactate or LA among 180 Japanese adults ≥65 years of age retrospectively studied for one year.[36] The most commonly used metformin dose was 750mg per day. There was no significant difference in elevated lactate level between elderly and nonelderly individuals, and no cases of LA were identified. A second study used a central Swedish registry to retrospectively identify the occurrence of LA (lactate levels >5mmol/L and serum pH <7.35).[37] Median age was 67 (Table 3). Over 2 years, there were 3 cases of LA (ages 65, 73, 75), among 5,408 individuals (equivalent to 27.7 per 100,000 person years), one of which was found to have metastatic pancreatic cancer and died the subsequent day. This is substantially higher than the rate of LA reported in the Cochrane review.

Table 3. Rate of LA with Metformin Use

Study Country	Precaution Analysis Sample	Outcome
Becquemont, 2015[39] France	CKD: eGFR category based on metformin adaptation n = 588	Fatal LA: none over a mean follow-up of 3 years
Richy, 2014[33] UK	CKD: eGFR >90, >60-90, >30-60, <30 n = 77,601	LA based on ICD-9: 10.3 per 100,000 patient years over a mean follow-up of 4.35 years. Rates did not differ by category of renal impairment
Ito, 2014[36] Japan	Older adults ≥65 n = 180	LA based on laboratory data: none over 1 year follow-up No difference in lactate levels
Sterner, 2012[37] Sweden	Older adults n = 5,408	LA based on lactate >5mmol/L and pH <7.35: 3 cases over 2 year follow-up

Abbreviations: CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICD = International Classification of Diseases; LA = lactic acidosis; ROB = risk of bias

Lactic Acidosis with Metformin Use Compared with Other Hypoglycemic Medications

Five studies evaluated the rate of LA with metformin use compared with other hypoglycemic medications.[25,34,35,38,40] There were no studies comparing the rate of LA with metformin use versus other hypoglycemic medications in older adults.

Chronic Kidney Disease

Two studies with moderate ROB compared the rate of LA with metformin use versus other hypoglycemic medications among individuals with CKD.[34,40] The first study, performed in a Swedish pharmaceutical database, was a retrospective cohort study using a composite definition of acidosis/serious infection, categorized as fatal or any.[40] Compared with metformin monotherapy, the risk of the any acidosis/serious infection was increased with insulin monotherapy (HR 1.37, 95% CI 1.26 to 1.50) or other oral hypoglycemic agent (OHA) monotherapy (HR 1.16, 95% CI 1.04 to 1.28). The relative rates of LA or serious infection were also reported by renal function, using other OHAs as the referent. Metformin compared with other OHAs showed lower rates of LA or serious infection in patients with eGFR ≥60ml/min/1.73m^2 (HR 0.91, 95% CI 0.84 to 0.98) and eGFR 45 to <60 (HR 0.85, 95% CI 0.74 to 0.97) and no increased risk in patients with eGFR 30 to 45 (HR 0.98, 95% CI 0.79 to 1.21).

The second study, also with moderate ROB, compared risk of LA among metformin users with never users of a noninsulin antidiabetic drug (NIAD).[34] Over a mean follow-up of 4.3 years, the overall incidence rate of LA or elevated lactate concentrations (>5mmol/L) was 7.4 events per 100,000 person-years among metformin users compared with 2.2 events per 100,000 person-years among NIAD users. Current metformin users had an increased, albeit not statistically significant, risk of LA or elevated lactate compared with NIAD users who had never used metformin, HR 4.03 (0.97 to 16.8). Subgroup analysis by renal function category (eGFR ≥ 60, 45 to 59, 30 to 44, <30ml/min/1.73m^2) revealed an adjusted HR of composite LA outcome in metformin users compared with never users of 2.87 (95% CI 0.67 to 12.3), 6.06 (1.37 to 27.1),

5.47 (1.05 to 28.5), 25.7 (3.57 to 185), respectively. The different comparative rates of LA reported in these 2 studies may be related to outcome assessment, with the former study using diagnosis codes for acidosis, serious infection, shock or acute renal failure as proxies for LA, while the latter study used both diagnosis codes for LA and serum lactate levels to define the outcome of interest.

Congestive Heart Failure

A study with moderate ROB evaluated the safety of metformin use among 10,920 heart failure patients (diagnosed by ICD 9 code) with T2D.[25] Danish individuals taking various permutations of metformin, sulfonylurea, and or insulin therapy were followed for a median of 844 days, during which there were no documented reports of LA across all therapies. A prospective study with low ROB from Spain evaluated the effect of newly initiated metformin therapy in individuals with new-onset heart failure (based on Framingham criteria) and previously unknown T2D.[35] The authors matched 592 heart failure patients with T2D not treated with metformin to 592 patients who began metformin therapy. Over a median follow-up of 56.7 months, there were no cases of LA in either group.

Chronic Liver Disease

A single study with low ROB from the United States evaluated the risk of metformin use in individuals with cirrhosis and T2D.[38] Individuals on metformin at the time of cirrhosis diagnosis were categorized into those who continued on metformin therapy and those who discontinued metformin use. The majority (172, 68.8%) of individuals continued metformin therapy whereas 78 (31.2%) discontinued use following a cirrhosis diagnosis. The median duration of metformin use in those who continued therapy was 26.8 months. Over a median survival of 11.8 years in those who continued metformin and 5.6 years in those who discontinued metformin, there were no reported cases of LA in either group (Table 4). Characteristics of studies evaluating the rate of LA with metformin use compared with other hypoglycemic medications.

Table 4. Rate of LA with Metformin Use Compared with Other Hypoglycemic Medications

Study Country	Precaution Analysis Sample	Comparison	Outcome
Ekstrom, 2012[40] Sweden	CKD: eGFR category (30 to <45, 45 to <60, ≥60ml/min/1.73m^2) n = 51,675	Metformin versus use of other oral antidiabetic agent (dose NR)	LA or serious infection: lower in eGFR ³ 60ml/min and 45 to <60; no increase in eGFR 30 to 45 over a mean follow-up of 3.9 years.
Eppenga, 2014[34] Great Britain	CKD: eGFR category >60, 45-59, 30-44, <30 n = 258,539	Metformin versus never use of metformin but current use of other NIAD	LA: 7.4/100,000 vs 2.2/100,00 persons-years, p = NS, over mean follow-up of 4.3 years
Andersson, 2010[25] Denmark	CHF: First CHF hospitalization based on diagnostic codes n = 10,920	Multiple comparator arms	LA : none in any group over a median follow-up of 844 days
Romero, 2013[35] Spain	CHF: Framingham criteria n = 1,184	Metformin versus no metformin use	LA: none reported over a median 56.9 months follow-up

Study Country	Precaution Analysis Sample	Comparison	Outcome
Zhang, 2014[38] US	CLD: Biopsy-proven cirrhosis with additional clinical evaluation N = 250	Continued metformin versus discontinued metformin use	LA: none in either group over 5-10 years follow-up

Abbreviations: CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICD = International Classification of Diseases; LA = lactic acidosis; ROB = risk of bias

Quality of Evidence for Key Question 1

Studies examining the rate of LA among metformin users with a precaution used observational designs and were judged high ROB. Frequent quality issues were incomplete adjustment for difference in baseline characteristics, unequal follow-up, and outcomes assessed with knowledge of the intervention or with measures that included events other than LA. With the exception of unequal baseline characteristics, similar issues were observed for studies comparing rates of LA in metformin users versus nonusers. Due to significant heterogeneity across studies and contraindications, meta-analysis was not performed.

Summary of Findings

Based on our qualitative synthesis of observational evidence, the risk of LA with metformin use among individuals with a precaution appears to be low. Risk of LA with metformin use does not appear to be higher than the risk of LA with other hypoglycemic medications. In patients with CKD, the risk of LA with metformin use appears to be highest in individuals with eGFR <30ml/min/1.73m^2. In limited studies of patients with CHF, there were no cases of LA with metformin use. A single study evaluating the rate of LA with metformin use in cirrhosis reported no cases of LA. Reports on the risk of LA among older adults are conflicting.

KEY QUESTION 2: For patients with type 2 diabetes and an apparent contraindication/precaution to metformin use, what are the potential benefits and harms (other than lactic acidosis) of continued treatment with metformin?

Key Findings

- Among patients with medically treated T2D and CKD, metformin use is associated with a significantly lower risk of all-cause mortality when compared with non-metformin treatment (high heterogeneity present on meta-analysis); limited evidence was identified for major adverse cardiovascular events (MACE).
- Among patients with medically treated T2D and CHF, metformin use is associated with a significantly lower risk of all-cause mortality and heart failure readmission when compared with non-metformin treatment, but risk of cardiovascular mortality did not differ (moderate-to-high heterogeneity present on meta-analyses).
- Among patients with medically treated T2D and CLD with cirrhosis, limited evidence suggests that a lower risk of all-cause mortality may be associated with metformin use when compared with non-metformin treatment.
- Among patients with medically treated T2D and older age (generally age ³ 65 years), limited evidence suggests that, compared with non-metformin treatment, metformin may be associated with a lower risk of all-cause mortality and some MACE outcomes.
- No evidence was identified regarding the effects of metformin on glycemic control, lipid control, weight, hypoglycemia, or vitamin B12 deficiency among patients with medically treated T2D and CKD, CHF, or CLD; additionally, no evidence was identified for MACE in CLD.
- While limited evidence suggests that progressively lower estimated glomerular filtration rate (eGFR) may diminish the mortality benefit associated with metformin use, the impact of CHF severity, CLD severity, and increasing older age on the effects of metformin is unclear.

For KQ 2, we present the detailed results ordered by precaution (CKD, CHF, CLD, and older age) and, within precaution, by major outcomes. Details on study characteristics are in Appendix F. Further details on results for older adults by study design are in Appendix G.

Chronic Kidney Disease

Five studies – all of which used observational cohort designs (4 retrospective,[40-43] one prospective[44]) – evaluated the effect of metformin on KQ2 outcomes in patients with T2D and CKD. Two studies were conducted in the United States,[41,42] 2 in Europe (Sweden and UK),[40,43] and one across multiple continents.[44] One study was conducted specifically among Veterans using VA data.[41] Three studies reported government funding only,[40-42] one reported industry funding only,[43] and one reported both industry and foundation funding.[44]

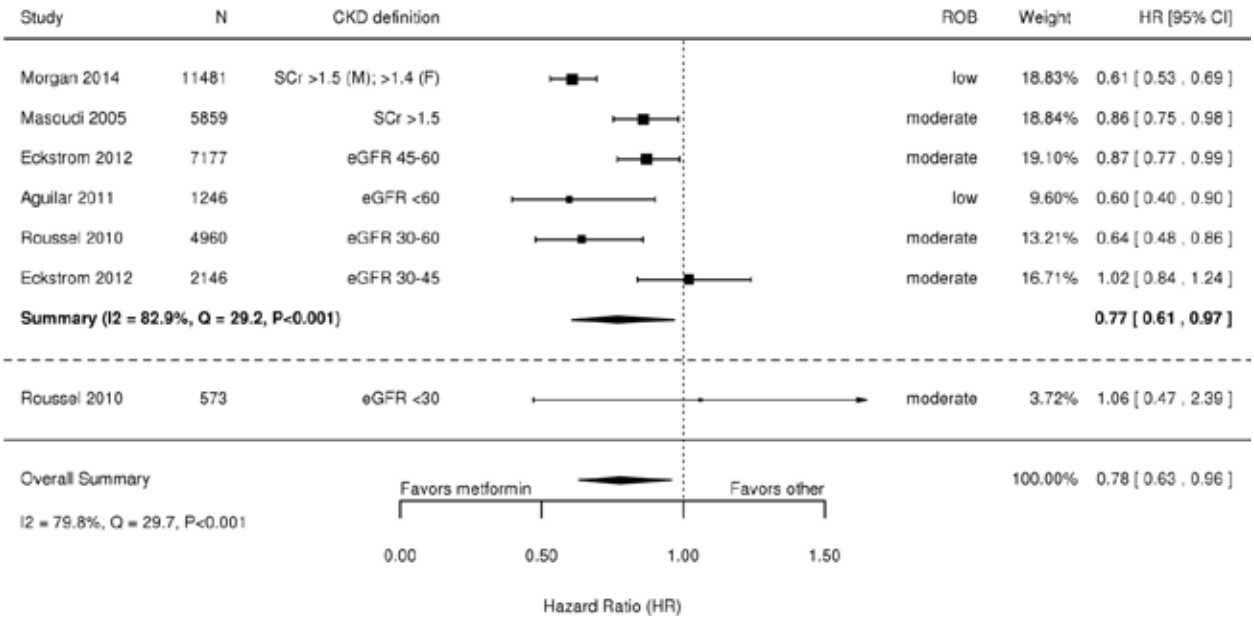
All-cause Mortality

All 5 studies evaluated the effect of metformin on all-cause mortality compared with non-metformin treatments in adults with T2D and CKD. Two studies had low risk of bias (ROB)[41,43] and 3 had moderate ROB.[40,42,44] In all, these studies involved 33,442 patients with CKD; while the entire population had CKD in 3 studies,[40-42] we examined a CKD subgroup in the remaining 2.[43,44] Individual study sample sizes ranged from 1,246 to 11,481 patients with CKD. Mean follow-up periods ranged from one to 3.9 years.

The mean/median age of study participants ranged from approximately 65 to 76 years. CKD definitions varied between studies, with 3 reporting eGFR-based definitions[40,41,44] and 2 using serum creatinine-based definitions.[42,43] Two studies provided outcomes by CKD severity subcategory,[40,44] while the other studies did not provide data on CKD severity. Only one study reported the population's median metformin dose (1100mg to 1900mg daily in different subgroups).[40] Mortality was defined using medical record or administrative data for the 4 retrospective studies, while the single prospective study determined mortality on 2-year follow-up assessment.[44] All studies performed statistical adjustment based on multiple baseline population differences between metformin users and nonusers; 2 studies utilized propensity score matching.[41,44]

Individually, most studies indicated that metformin use was associated with lower mortality when compared with non-metformin treatment. These studies were deemed to have sufficient conceptual homogeneity to perform quantitative synthesis. Based on meta-analysis of all patients (Figure 2), there was a statistically significant summary hazard ratio (HR) for mortality favoring metformin (HR 0.78, 95% CI 0.63 to 0.96). Significant statistical heterogeneity was present. Two studies reported mortality by CKD severity subcategory and suggested that patients with eGFR <45 mL/min/1.73m^2 experienced less benefit with metformin (Figure 2).[40] A sensitivity analysis that excluded a subgroup of 573 patients specifically identified by one study as having eGFR <30 mL/min/1.73m^2 produced similar findings to the overall meta-analysis.[44]

Figure 2. Meta-analysis of All-cause Mortality with Use of Metformin Versus Non-metformin Treatment Among Patients with CKD[a,b]



[a] Studies on the forest plot are ordered by increasing CKD severity.
[b] Eckstrom, 2012, and Roussel, 2010, stratified their respective populations by eGFR; these eGFR categories are presented separately for these studies.

Major Adverse Cardiovascular Events

Two studies evaluated the effect of metformin on MACE versus non-metformin treatments in adults with T2D and CKD, both of which had moderate ROB.[40,42] In all, these studies reported MACE outcomes in 14,408 patients with CKD. One study included a subgroup of 8,549 patients with CKD (mean age approximately 65 years) followed for a mean of 3.9 years,[40] while the other included a subgroup of 5,859 patients with CKD (mean age approximately 76 years) followed for a mean of one year.[42]

One study used an eGFR-based definition of CKD (with reporting of CKD subcategories),[40] while the other used a serum creatinine-based definition.[42] Only one study reported the population's median metformin dose (1100mg to 1900mg daily in different subgroups).[40] Both studies utilized different MACE outcomes; one used administrative data to identify MACE-associated diagnosis codes,[40] and the other used administrative data to identify readmission for heart failure.[42] Both studies performed statistical adjustment based on multiple baseline population differences between metformin users and nonusers.

Given the low number of studies and differences in MACE outcomes presented, quantitative synthesis was not attempted. One study found no statistically significant difference in MACE-associated diagnoses between metformin users and nonusers with eGFR 45 to <60 (n = 6655, HR 0.94, 95% CI 0.84 to 1.05) or 30 to <45 (n = 1894, HR 1.00, 95% CI 0.83 to 1.19).[40] The other study found that metformin use was significantly associated with slightly lower CHF readmission (n = 5859, HR 0.91, 95% CI 0.84-0.99).

Other Outcomes

No studies were identified that evaluated the effect of metformin on other outcomes of interest (glycemic control, lipid control, hypoglycemia, weight gain, B12 deficiency) in adults with T2D and CKD.

Congestive Heart Failure

Eleven studies—all of which used observational designs (8 retrospective cohort,[25,26,41,42,45-48] 2 prospective cohort,[35,44] and one nested case-control[27])—evaluated the effect of metformin on KQ 2 outcomes in patients with T2D and CHF. Six studies were conducted in the United States,[27,41,42,46-48] 3 in Europe,[25,35,45] one in Canada,[26] and one across multiple continents.[44] One study was conducted specifically among Veterans using VHA data.[41] Six studies reported government funding only,[25,35,41,42,46,48] one reported foundation funding only,[45] 2 reported both government and foundation funding,[26,47] one reported both industry and foundation funding,[44] and one did not report funding.[27]

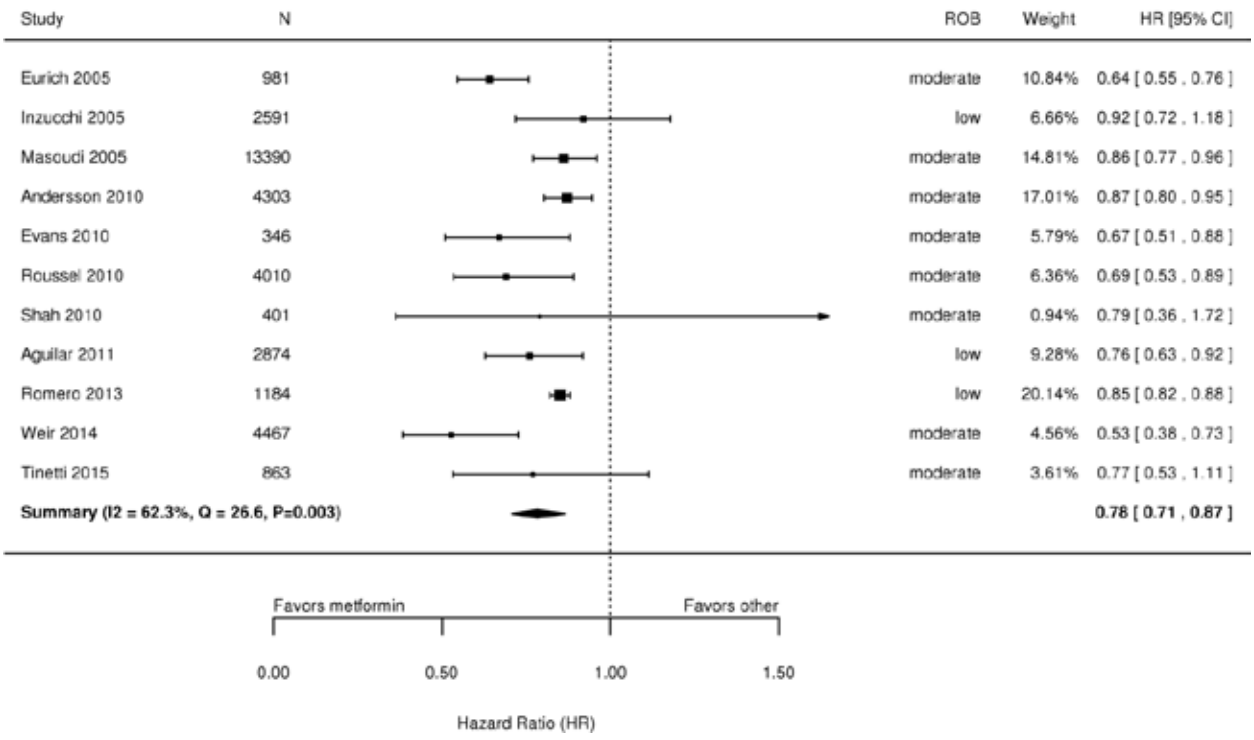
All-cause Mortality

All 11 studies evaluated the effect of metformin on all-cause mortality versus non-metformin treatment in adults with T2D and CHF. Two studies had low ROB[35,41] and the others had moderate ROB. In all, these studies involved 35,410 patients with CHF; while the entire population had CHF in 9 studies,[25-27,35,41,42,45-47] we examined a CHF subgroup in the remaining 2.[44,48] Individual study sample sizes ranged from 346 to 13,930 patients with CHF. Mean follow-up periods ranged from one to 4.7 years.

The mean/median age of study participants ranged from approximately 55 to 77 years. CHF definitions varied widely between studies, with most using diagnosis codes. CHF severity was likewise reported variably, with 4 studies reporting left ventricular ejection fraction-based definitions,[35,41,42,47] 2 reporting New York Heart Association-based definitions (both of which also reported left ventricular ejection fraction data),[35,47] and 2 reporting other clinical definitions (*eg*, "decompensated heart failure" or "moderate-to-severe heart failure").[25,46] The remaining 5 studies did not report CHF severity.[26,27,44,45,48] No studies reported mortality for specific CHF severity subgroups. No studies reported their population's median metformin dose. Mortality was defined using medical record or administrative data for 9 studies.[25,27,35,41,42,45-48] One prospective study determined mortality on 2-year follow-up assessment[44] and one study did not report how mortality was defined.[26] All studies performed statistical adjustment based on multiple baseline population differences between metformin users and nonusers; 4 studies utilized propensity score matching.[26,27,41,44]

These studies were deemed to have sufficient conceptual homogeneity to perform quantitative synthesis. Based on meta-analysis of all patients, there was a statistically significant summary HR for mortality favoring metformin (Figure 3). Moderate heterogeneity was present. Two studies reported mortality by CHF subcategory. One reported mortality by LVEF category and found no difference with metformin use in subgroups with moderate CHF (LVEF 30% to 39%; HR 0.87; 95% CI 0.67 to 1.13) or severe CHF (LVEF <30%; HR 0.87; 95% CI 0.69 to 1.08).[42] The other included only patients with LVEF <40% and found no mortality difference with metformin use (HR 0.79; 95% CI 0.36 to 1.71).[47]

Figure 3. Meta-analysis of All-cause Mortality with Use of Metformin Versus Non-metformin Treatment Among Patients with CHF[a]



[a] Studies on the forest plot are ordered chronologically.

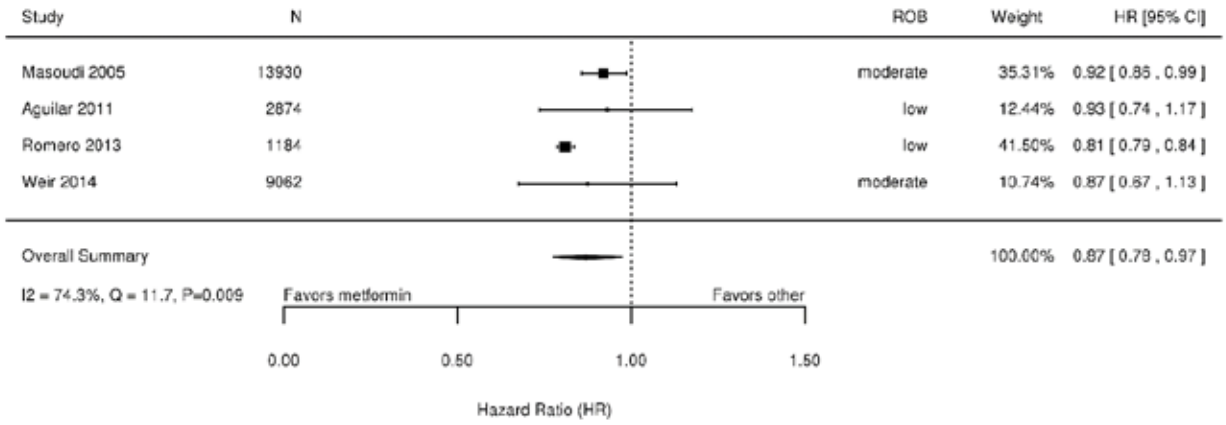
Major Adverse Cardiovascular Events

Six studies evaluated the effect of metformin on MACE outcomes versus non-metformin treatments in adults with T2D and CHF.[25-27,35,41,42] Two studies had low ROB[35,41] and the others had moderate ROB. In all, these studies involved 26,510 CHF patients with CHF readmission as an outcome and 6,468 with cardiovascular mortality as an outcome; also, in all 6 studies, the entire population had CHF. Individual study sample sizes ranged from 981 to 13,390 patients with CHF. Mean follow-up periods ranged from one to 4.7 years.

The mean/median age of study participants ranged from approximately 55 to 77 years. Most studies used diagnosis codes to define CHF. CHF severity was reported variably, with 3 studies reporting left ventricular ejection fraction-based definitions,[35,41,42] one reporting a New York Heart Association-based definition (also reported left ventricular ejection fraction data),[35] and one reporting a clinical definitions ("decompensated heart failure").[25] The remaining 2 studies did not report CHF severity.[26,27] No studies reported MACE outcomes for specific CHF severity subgroups. No studies reported their population's median metformin dose. Two MACE outcomes were reported by these studies: CHF readmission and cardiovascular mortality. CHF readmission was reported by 4 studies,[27,35,41,42] all of which defined this outcome using medical record or administrative data. Cardiovascular mortality was reported by 3 studies, 2 of which defined this outcome using medical record or administrative data,[25,35] and one of which did not report how the outcome was defined.[26] All studies performed statistical adjustment based on multiple baseline population differences between metformin users and nonusers; 3 studies utilized propensity score matching.[26,27,41]

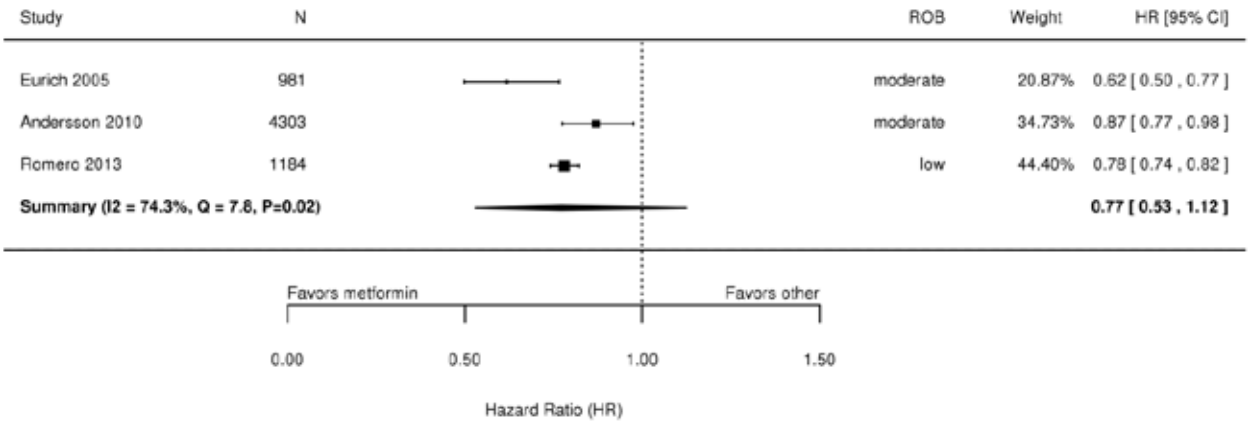
These studies were deemed to have sufficient conceptual homogeneity to perform quantitative synthesis; we performed separate meta-analyses for each MACE outcome. Based on meta-analysis of available patients, there was a small but statistically significant summary HR for CHF readmission favoring metformin (Figure 4) though high heterogeneity was present. The summary HR for cardiovascular mortality also favored metformin (Figure 5) but was not statistically significant; high heterogeneity was present.

Figure 4. Meta-analysis of CHF Readmission with Use of Metformin Versus Non-metformin Treatment Among Patients with CHF[a]



Abbreviations: CI=confidence interval; CHF=congestive heart failure; HR=hazard ratio; ROB=risk of bias
[a] Studies on the forest plot are ordered chronologically.

Figure 5. Meta-analysis of Cardiovascular Mortality with Use of Metformin Versus Non-metformin Treatment Among Patients with CHF[a]



[a] Studies on the forest plot are ordered chronologically.

Other Outcomes

No studies were identified that evaluated the effect of metformin on other outcomes of interest (glycemic control, lipid control, hypoglycemia, weight gain, B12 deficiency) in adults with T2D and CHF.

Chronic Liver Disease

Three studies, 2 of which used retrospective cohort designs[38,49] and one of which used a prospective cohort design,[50] evaluated the effect of metformin on KQ 2 outcomes in patients with T2D and CLD (Table 5). Two studies were conducted in Europe[49,50] and one in the United States.[38] No studies specifically addressed Veterans. One study reported government funding only,[49] one reported both government and foundation funding,[38] and one did not report funding.[50]

All-cause Mortality

All 3 studies evaluated the effect of metformin on all-cause mortality versus non-metformin treatment in adults with T2D and CLD. One study had low ROB[38] and one had moderate ROB.[49] The other study[50] was well-designed in general but was considered to have high ROB with regard to the outcome of all-cause mortality because only unadjusted event rates could be derived from the information presented in the article. In all, these studies involved 432 patients with CLD; in all 3 studies, the entire population had CLD. Individual study sample sizes ranged from 82 to 250 patients. Median follow-up time ranged from about 4.5 to 5.7 years.

All studies focused on patients with CLD with known cirrhosis, as defined by histologic criteria with other adjunctive clinical criteria (ultrasound, biochemical parameters). No studies reported the population's median metformin dose. Mortality was defined based on medical record or administrative data in the 2 retrospective studies,[38,49] and by every-6-month assessment in the prospective study.[50] All studies performed statistical adjustment based on baseline population differences between metformin users and nonusers for their primary analyses; however, as above, only all-cause mortality event rates were provided in 2 studies, so incidence was unadjusted.[49,50]

Given the low number of studies and differences in study quality with regard to the outcome of all-cause mortality, quantitative synthesis was not attempted. The study with low ROB found a significantly longer survival associated with metformin therapy (n = 250, HR 0.43, 95% CI 0.24 to 0.78), which was observed regardless of cirrhosis severity (Child-Pugh class A: HR 0.47, 95% CI 0.27 to 0.82; class B/C: HR 0.46, 95% CI 0.21 to 0.98).[38] Of note, on additional post-hoc subgroup analysis, the beneficial effect of metformin on survival was seen only among patients with cirrhosis secondary to nonalcoholic steatohepatitis (n = 142, HR 0.33, 95% CI 0.17 to 0.63); no statistically significant differences were seen among the relatively small groups of patients with cirrhosis related to alcohol, hepatitis C virus, or hepatitis B virus.

The study with moderate ROB found a trend toward a lower all-cause mortality rate among cirrhotic patients taking metformin compared with nonusers of metformin (n = 82, 7.3% [3/41] versus 17.1% [7/41], p = NR).[49] In the study with high ROB, there was likewise an apparently lower all-cause mortality rate among patients taking metformin compared with nonusers (n = 100, 7.7% [2/26] versus 48.6% [36/74], p = NR); however, as above, baseline population differences were present without adjustment.[50]

Table 5. Effects of Metformin on Mortality in Patients with CLD

Study	Design	Comparison	Outcome (Adjusted analysis)
Ampuero, 2012[49]	Retrospective cohort	Metformin versus no	Rate of all-cause mortality: 7.3% vs 17.1%, p = NR

	n = 82	metformin	
Nkontchou, 2011[50]	Prospective cohort n = 100	Metformin versus no metformin	Rate of all-cause mortality: 7.7% vs 48.6%, p = NR
Zhang, 2014[38]	Retrospective cohort n = 250	Metformin continuation versus discontinuation	Survival: 11.8 versus 5.6 years (p<0.0001), HR 0.43 (95% CI 0.27 to 0.82, p = 0.005) Survival subgroup analysis: Child-Pugh class A: HR 0.47 (95% CI 0.27 to 0.82) class B/C: HR 0.46 (95% CI 0.21 to 0.98)

Other Outcomes

No studies were identified that evaluated the effect of metformin on other outcomes of interest (MACE, glycemic control, lipid control, hypoglycemia, weight gain, B12 deficiency) in adults with T2D and CLD.

Older Adults

Fourteen studies evaluated the effect of metformin in older adults (7 RCTs,[51-57] 7 observational[58-64]). Most studies were conducted in North America, with the remaining conducted in Europe or across multiple continents. Three large observational studies were conducted using VA data.[58,62,63] Results are organized by major outcomes, and within outcomes, by RCT then observational studies.

All-cause Mortality and Major Adverse Cardiovascular Events

A single large RCT evaluated the effects of metformin compared to other usual care treatments in adults with T2D who were suboptimally controlled on diet or sulfonylurea.[52] This 1-year trial with moderate ROB randomized 7,200 adults to metformin and 1,200 to non-metformin treatment as directed by their physician. Outcomes were reported in the subgroups <65 years of age and ³ 65 years of age. In the older subgroup (n = 3,084), all-cause mortality did not differ between metformin and usual care (2.4% vs 2.1%, p = 0.878). The rate of emergent cardiac disorders was identical between groups (5.6%).

Three retrospective cohort studies evaluated the effects of metformin on all-cause mortality[58,63,64] and one reported effects on a composite measure of acute MI, stroke, or death.[62] All 4 studies showed lower mortality or a composite of major cardiovascular event and mortality in older adults treated with metformin compared with a sulfonylurea. However, the study conducted in a cohort of older Veterans[63] found no effect in those who were frail as defined by an ICD-9 code for anemia, fluid electrolyte imbalance, fall, fracture, head injury coagulopathy, or weight loss (Table 6). Rosiglitazone monotherapy (but not combination therapy) was associated with increased CHF (HR 1.32; 95% CI 1.07, 1.63).

Table 6. Effects of Metformin on Mortality or MACE in Older Adults

Study	Design	Comparison	Outcome (Adjusted Analysis)
Bannister, 2014[58]	Retrospective cohort n = 90,463	Sulfonylurea versus metformin	Survival Age 64-71: Survival time ratio 0.55 (95% CI 0.47 to 0.65)

			Age >88: Survival time ratio 0.58 (95% CI 0.54 to 0.63)
Cryer, 2005[52]	RCT n = 7,200	Usual care versus metformin	Mortality in subgroup age ³ 65 years: 2.1% vs 2.4%, p = 0.88
Roumie, 2012[62]	Retrospective cohort n = 253,690	Sulfonylurea versus metformin	MACE or mortality HR 1.18 (95% CI 1.09, 1.28) MACE: HR 1.13 (95% CI 1.03, 1.24)
Tzoulaki, 2009[64]	Retrospective cohort n = 91,521	Second- generation sulfonylurea versus metformin Rosiglitazone versus metformin	Subgroup age ³ 65 years: Mortality: HR 1.35 (95% CI 1.28, 1.42) Myocardial infarction: HR 1.22 (95% CI 1.10, 1.35) CHF: HR 1.18 (95% CI 1.10, 1.26) No difference in mortality or myocardial infarction. Increased CHF (HR 1.32, 95%CI 1.07, 1.63) with monotherapy but not in combination with other hypoglycemic drugs
Wang, 2014[63]	Retrospective cohort n = 2,415	Metformin versus sulfonylurea	Mortality With frailty: HR 0.92 (95% CI 0.90, 1.31) Without frailty: HR 0.69 (95% CI 0.60, 0.79)

Glycemic Control

Six RCTs (1144 patients) evaluated the effects of metformin on glycemic control.[51,53-57] One trial enrolled patients >70 years of age;[54] all other trials enrolled or analyzed subgroups of patients ≥65 years of age. In 4 trials, eligible patients had suboptimal glycemic control on a sulfonylurea or metformin monotherapy.[51,54-56] All but one trial specifically excluded patients with renal disease, and the majority excluded patients with CLD or CHF.[55] In 4 trials, metformin monotherapy was compared with a sulfonylurea[51,53,56] or DPP-4 inhibitor monotherapy.[57] One 2-arm trial[54] and 3 multi-arm trials[51,53,56] included a comparison of metformin plus sulfonylurea with sulfonylurea alone. One trial compared a combination of metformin plus a sulfonylurea with pioglitazone plus a sulfonylurea.[55] Outcomes were assessed at a median of 22 weeks (range: 16 weeks to 18 months). ROB was assessed as low in 5 trials and high in 1 trial, but in 4 studies, results were based on post-hoc subgroup analyses. Appendix F has details on the study characteristics.

Effects of treatment were analyzed differently across trials, and statistical tests were not always reported for between group comparisons (Table 7). However, the differences between metformin and sulfonylurea or DDP-4 inhibitor monotherapy were uniformly small (HbA1c difference £0.3% between metformin and comparator groups). Metformin plus a sulfonylurea compared with metformin plus pioglitazone yielded similar reductions in A1c. When metformin was combined with a sulfonylurea and compared to treatment with a sulfonylurea alone,[51,53,54,56] the combination was associated with greater reductions in A1c in 2 of the 4 trials (range: -0.7 to -1.8 combination versus +0.2 to -1.2 for sulfonylurea monotherapy).

One study used a retrospective cohort design to evaluate the effects of metformin on glycemic control in 2,107 Veterans.[60] Outcomes were adjusted for multiple demographic and clinical covariates. Twelve-month A1c was similar in metformin and sulfonylurea users overall; no interaction effects were found by age group (<65, 65-75, and >75 years of age).

Table 7. Effects of Metformin on A1c in Older Adults—RCTs

Study	Precaution Analysis Sample	Intervention (average dose): Effect on A1c[a] Comparator (average dose): Effect on A1c
Blonde, 2002[51]	Age ≥65 n = 65, subgroup	· Metformin (1840mg): A1c change +0.2% · Glibenclamide (20mg): A1c change -0.1% · Metformin (1759mg) + Glibenclamide (8.8mg): A1c change -1.5% · Metformin (1744mg) + Glibenclamide (17.4mg): A1c change -1.8%
Garber, 2002[53]	Age ≥65 n = 74, subgroup	· Metformin (1324mg): A1c change -0.9% · Glibenclamide (5.4mg): A1c change -1.2% · Metformin (568mg) + Glibenclamide (2.8mg): A1c change -1.5% · Metformin (840mg) + Glibenclamide (4.2mg): A1c change -1.3%
Gregorio, 1999[54]	Age >70 n = 174, whole sample	· Metformin (1518mg) + Sulfonylurea: A1c mean 8.54 (SE 0.12) · Glibenclamide (13.2mg) or Glycoside (214.7mg): A1c mean 8.58 (SE 0.12)
Hanefeld, 2004[55]	Age ≥65 n = 169, subgroup	· Metformin + Sulfonylurea (NR): A1c change -1.46 (SE 0.08) · Pioglitazone + Sulfonylurea (NR): A1c change -1.41 (SE 0.09)

Study	Precaution Analysis Sample	Intervention (average dose): Effect on A1c[a] Comparator (average dose): Effect on A1c
Marre, 2002[56]	Age ≥65 n = 59, subgroup	· Metformin (1660mg): A1c change -0.1% · Glibenclamide (13.4mg): A1c change +0.2% · Metformin (1225mg) + Glibenclamide (6.1mg): A1c change -1.3% · Metformin (170mg)+ Glibenclamide (11.7mg): A1c change -0.7%
Schweizer, 2009[57]	Age >65 n = 335, whole sample	· Metformin (1500mg): A1c change -0.75% · Vildagliptin (100mg): A1c change -0.64%

[a] Average dose is reported for the sample overall; dose for older adult subgroup is not known.

Cholesterol and Weight

Two trials (386 patients) reported the effects of metformin on cholesterol and weight in older adults.[54,55] A study with low ROB conducted a post-hoc analysis of 212 adults >65 years of age with inadequate control on a sulfonylurea who were randomized to pioglitazone or metformin.[55] At 52 weeks, the change in LDL cholesterol did not differ significantly between groups, but HDL increased more in the pioglitazone group (pioglitazone 16.77 vs metformin 7.85, $p<0.05$). More patients in the pioglitazone group gained weight than in the metformin group (4.8% vs 1%, p = NR). One trial with high ROB that enrolled 174 patients >70 years of age compared the addition of metformin to increased doses of a sulfonylurea in patients with A1c ³ 95 on sulfonylurea monotherapy.[54] At 18-month follow-up, LDL decreased significantly and HDL increased significantly for the metformin group. However, treatment differences between groups were not reported. Change in weight differed by less than 1kg between the 2 groups.

Adverse Effects: Hypoglycemia, B12

Five RCTs (742 patients)[51,53,55-57] and a nested case-control study[59] reported rates of hypoglycemia (Table 8). Definitions of hypoglycemia varied, with some studies requiring fasting plasma glucose below 50mg/dl to 60mg/dl and other studies relying on symptoms. Hypoglycemic events in the RCTs were low except in one study that did not report the definition used for hypoglycemic episodes.[55] Hypoglycemic events were lower for metformin compared with a sulfonylurea in one of 3 studies,[53] and did not differ in the single trial comparing metformin with vildagliptin.[55] In a trial comparing metformin used in combination with a sulfonylurea versus in combination with pioglitazone, hypoglycemic events did not differ between metformin and comparators, but 95% confidence intervals are extremely broad because of the small number of trials and patients enrolled.[57]

Table 8. Effects of Metformin on Hypoglycemic Events in Older Adults

Study	Design	Comparison	Hypoglycemic Outcomes[a]
Blonde, 2002[51]	RCT n = 65	Metformin vs sulfonylurea	OR = 2.82 (95% CI, 0.11 to 71.84)*
Bodmer, 2009[59]	Nested case control n = 7,753	Sulfonylurea vs metformin	OR for age ³ 65 years = 3.30 (95% CI 2.18 to 5.00)
Garber, 2002[53]	RCT n = 74	Metformin vs sulfonylurea	OR 0.08 (95% CI 0.01 to 0.68)*
Hanefeld, 2004[55]	RCT n = 212	Metformin vs vildagliptin	OR 1.24 (95% CI, 0.57 to 2.73)*
Marre, 2002[56]	RCT n = 59	Metformin vs sulfonylurea	OR 0.24 (95% CI, 0.01 to 5.17)*
Schweizer, 2009[57]	RCT n = 322	Metformin + sulfonylurea versus metformin + pioglitazone	OR 5.12 (95% CI 0.24 to 107.51)*

[a] OR and 95% CI calculated from data reported.

The nested case-control study with low ROB used data from the UK-based General Practice Research Database to compare rates of hypoglycemia in current sulfonylurea users with current metformin users.[59] Overall, 2,025 case subjects with hypoglycemia were compared with 7,728 matched-control subjects; stratified analyses for patients <70 and ³ 70 years of age were presented. The risk of hypoglycemia was elevated for sulfonylurea users in those <70 (OR 2.71; 95% CI 2.04 to 3.61) and those ³ 70 (OR 3.30; 95% CI 2.18 to 5.00).

A single small, nonrandomized trial compared vitamin B12 (cobalamin) levels in 10 older adults assigned to metformin and 10 controls.[59] Outcomes were assessed at 3 months' follow-up. Patients assigned to metformin compared with the control group had a significant decrease in total cobalamin levels (-110pM vs -26pM).

Quality of Evidence for Key Question 2

Studies included for KQ 2 were mostly rated as moderate ROB, with some rated low ROB (Appendix F). Few studies were rated high ROB. Common quality concerns included (1) incomplete accounting for differences in baseline characteristics and confounding by indication, though some studies did use propensity score matching; (2) limited assessment of metformin use throughout the study period (*eg*, assessment at baseline only without accounting for subsequent metformin discontinuation in the exposed group or initiation in the unexposed group), though some studies did analyze metformin exposure status in 'intervals' to account for this concern; (3) incomplete assessment and description of attrition within the study populations; and (4) unblinded outcome assessment. These factors may have contributed to the heterogeneity in our qualitative and quantitative syntheses.

Summary of Findings

Based on our quantitative syntheses of observational evidence, metformin use is associated with a lower risk of all-cause mortality when compared with non-metformin treatment among patients with medically treated T2D and CKD. High heterogeneity was present on meta-analysis, but appeared to be related to variance in the magnitude of effects that consistently favored

metformin. The impact of CKD severity on the apparently beneficial effect of metformin on all-cause mortality is not completely clear based on available data, but limited evidence may indicate less benefit with progressively lower eGFR. Qualitative synthesis of limited observational evidence shows that metformin use may be associated with a lower risk of CHF readmission when compared with nonuse among patients with medically treated T2D and CKD, and with a similar risk of MACE-associated diagnoses.

Based on our quantitative syntheses of observational evidence, metformin use is associated with a lower risk of all-cause mortality when compared with non-metformin treatment among patients with medically treated T2D and CHF. Moderate heterogeneity was present on meta-analysis, but appeared to be related to variance in the magnitude of effects that consistently favored metformin. The impact of CHF severity on the apparently beneficial effect of metformin on all-cause mortality is unclear. Based on our quantitative syntheses of observational evidence, metformin use is associated with a lower risk of CHF readmission when compared with nonuse among patients with medically treated T2D and CHF, though high heterogeneity was present. A quantitative synthesis of available data showed no difference in the risk of cardiovascular mortality with metformin use versus non-metformin treatment.

Limited evidence is available regarding all-cause mortality in CLD, but qualitative synthesis of available evidence suggests that metformin may be beneficial in this population.

Data on the effects of metformin in older adults are limited, with most coming from subgroup analyses of randomized trials and in samples without coexisting CHF, CKD, or CLD. Qualitative synthesis of available data indicates that metformin use does not increase all-cause mortality or MACE relative to nonuse. Qualitative synthesis of available data suggests that metformin monotherapy provides similar reductions in HbA1c as sulfonylurea or vildagliptin monotherapy does. Qualitative synthesis of available data indicates that metformin use is not associated with higher rates of hypoglycemia than non-metformin treatment.

No evidence was identified regarding the effects of metformin on glycemic control, lipid control, weight, hypoglycemia, or vitamin B12 deficiency among patients with medically treated T2D and CKD, CHF, or CLD; additionally, no evidence was identified for MACE in CLD. Likewise, the impact of CHF severity, CLD severity, and increasing older age on the effects of metformin use is unclear based on available evidence.

SUMMARY AND DISCUSSION

This systematic review examined outcomes associated with metformin use in T2D populations with traditional contraindications or precautions to receiving metformin. In KQ 1 we assessed the incidence of LA with metformin use among patients with CKD, CHF, CLD, or older age (KQ 1a); we also evaluated the comparative incidence of LA in these populations with use of metformin compared with other antidiabetic agents (KQ 1b). We focused on data published since 2009, when Salpeter et al last updated their Cochrane review of LA with metformin use.[16] Consistent with prior reviews,[5] we found that metformin use is associated with an overall low risk of LA among individuals with traditional contraindications or precautions. Identified studies did suggest that patients with CKD may experience a slightly higher rate of LA while using metformin when compared with general diabetes populations; this risk appears highest in individuals with eGFR <30 mL/min/1.73m^2. We identified no new cases of metformin-associated LA for patients with CHF or CLD and found no data to suggest higher rates of LA with metformin use among older adults. Based on limited available evidence, the comparative risk of LA associated with metformin use among patients with CKD, CHF, or CLD does not appear higher than the risk with use of other hypoglycemic medications. We found no comparative studies examining LA in older adults.

In KQ 2 we examined the incidence of other key outcomes with use of metformin compared with other diabetes medications among patients with T2D and CKD, CHF, CLD, or older age. In patients with T2D and CKD—including some with eGFR down to 30 mL/min—we found that metformin is associated with a lower risk of all-cause mortality compared with non-metformin therapies. In CHF, use of metformin is also associated with a lower risk of all-cause mortality compared with non-metformin therapies. Although data regarding all-cause mortality in CLD and older age were limited, we found no evidence for an association between metformin use and increased all-cause mortality among patients with these precautions. While relatively few studies addressed MACE, metformin appears to be associated with lower rates of CHF readmission among patients with CHF; associations between metformin use and other MACE outcomes are unclear in other populations of interest. Also based on limited evidence, we found no clear association between metformin use and other outcomes of interest (glycemic control, lipid control, weight, hypoglycemia, or vitamin B12 deficiency) in T2D populations with historical contraindications or precautions to receiving metformin.

Overall, data from general diabetes populations has established metformin as effective, unlikely to cause hypoglycemia or weight gain, and possibly associated with reduced cardiovascular events and reduced mortality[1,65,66]; although we found limited data in some areas, there is no evidence to suggest that metformin's positive associations do not hold true in most populations with historical restrictions to metformin use.

STRENGTH OF EVIDENCE

In Table 9, we summarize the strength of evidence (SOE) for the effects of metformin use on the risk of LA. Using data from 209 RCTs, a prior Cochrane review identified no cases of LA; however, these trials did not recruit individuals with the precautions of interest. We identified 5 observational studies reporting LA in patient using metformin compared to non-metformin users. For cases of CKD, findings were inconsistent, but suggest that rates of LA in patients with CKD may be higher than metformin users overall. For CHF and CLD, there were no cases of LA.

Table 9. Strength of Evidence for Effects of Metformin Use Versus Non-Metformin Use on Risk of LA (KQ 1b)

Study Type	# Studies (Patients)	Findings	SOE Rationale by Domain
LA in patients with CKD, CHF, or CLD			
RCTs[a]	209 (NR)	No cases, but trials did not recruit patients with contraindications or precautions	Low SOE Moderate ROB, Consistent, Precise, Indirect
Observational	3 (12,354)	No cases in 2 cohort studies of patients with CHF and 1 study in patients with CLD.	Insufficient SOE Moderate ROB, Consistent, Imprecise, Direct
	2 (310,214)	Inconsistent findings in 2 studies of patients with CKD	Insufficient SOE Moderate ROB, Inconsistent, Imprecise, Indirect

[a] Data are from the Cochrane review.[16]

In Table 10, we summarize the SOE for effects of metformin use on mortality and MACE. Because of the observational nature of the vast majority of studies examining this question, no firm conclusions may be drawn. However, in relation to all-cause mortality, in CKD, CHF and older adults, there is uniformly low SOE for fewer deaths among patients taking metformin. Further, in patients with CHF, there is also low SOE that metformin use may lower CHF readmission. There is insufficient evidence to determine whether this benefit may extend to cardiovascular mortality in patients with CHF. Specifically among older adults, there is low SOE that risk of myocardial infarction or stroke may be lower in patients taking metformin.

Table 10. Strength of Evidence for Effects of Metformin Use Versus Non-Metformin Use on Mortality and MACE (KQ 2)

Outcome	# Studies (Patients)	Findings	SOE Rationale by Domain
Patients with CKD			
All-cause mortality	5 observational (33,442)	HR 0.77 (95% CI 0.61, 0.97) 48 fewer deaths/1,000 (81 to 6 fewer)	Low SOE Moderate ROB, Inconsistent, Precise, Direct
Patients with CHF			
All-cause mortality	11 observational (35,410)	HR 0.78 (95% CI 0.71, 0.87) 48 fewer deaths per 1,000 (64 to 29 fewer)	Low SOE Moderate ROB, Consistent, Precise, Direct
Cardiovascular mortality	3 observational (6,468)	HR 0.77 (0.53, 1.12) 66 fewer deaths/1,000 (136 fewer to 35 more)	Insufficient SOE Moderate ROB, Consistent, Imprecise, Direct
CHF readmission	4 observational (26510)	HR 0.87 (95% CI 0.78, 0.97) 12 fewer readmissions per 1,000 (20 to 3 fewer)	Low SOE Low ROB, Consistent, Precise, Direct
Older Adults			
All-cause mortality	1 RCT (3,084) 3 observational (184,399)	Risk difference 0.3%, p = 0.88 Lower mortality except in frail older adults	Low SOE Moderate ROB, Inconsistent, Precise, Direct

Outcome	# Studies (Patients)	Findings	SOE Rationale by Domain
MACE	2 observational (345,211)	Lower composite myocardial infarction or stroke, lower MI, lower CHF versus sulfonylurea	Low SOE Low ROB, Consistent, Precise, Direct

CLINICAL AND POLICY IMPLICATIONS

As the consensus first-line therapy for patients with T2D, metformin is the most widely prescribed diabetes drug in the world.[67] Beyond its blood sugar–lowering effects, metformin is an appealing diabetes treatment option because it is safe, does not cause weight gain, and may be associated with improved long-term outcomes in general diabetes populations. [1,65,66] However, due to concerns about metformin-associated LA,[5] FDA labeling has traditionally specified renal impairment as a contraindication to metformin use, and acute or unstable CHF, hepatic impairment, and older age as precautions with metformin use. Recently, though, the FDA has relaxed restrictions on metformin prescribing. In April 2016, the FDA issued a statement supporting metformin initiation in patients with an eGFR >45 mL/min/1.73m^2 and continuation with appropriate monitoring in patients with an eGFR >30-45 mL/min/1.73m^2.[11]

In the wake of these recent changes in FDA labeling, prescribing of metformin will undoubtedly increase. It has previously been estimated that one million additional patients would become eligible to use metformin in the United States alone if an eGFR cutoff of 30 mL/min/1.73m^2 were implemented.[68] It is therefore critically important that clinicians understand the full spectrum of risks and benefits associated with metformin use in populations with historical contraindications and precautions. This systematic review provides a comprehensive, up-to-date evaluation of existing literature regarding multiple key outcomes associated with metformin use in T2D populations with traditional contraindications or precautions. Our findings support FDA's recent actions and will directly inform clinicians' prescribing practices for T2D patients with traditional restrictions to receiving this medication.

This analysis adds to existing knowledge about long-term outcomes of metformin use. Lamanna et al conducted a meta-analysis of randomized trials that suggested an association between metformin monotherapy and improved survival in general diabetes populations.[1] In contrast, Palmer et al conducted a subsequent network meta-analysis that found no differences in mortality with different antihyperglycemic agents, including metformin.[69] Our review differs fundamentally from these analyses in that we focused exclusively on diabetes populations with traditional metformin contraindications or precautions. Consequently, we included observational studies with longer follow-up periods, which are better suited to examining associations that require longer exposure to observe (*eg*, mortality). Our findings regarding CHF are consistent with those of Eurich et al,[18] who found that metformin is associated with reduced mortality in CHF; our analysis included 3 additional studies (n = 6,514),[27,35,48] and excluded another that did not employ an active comparator.[70]

In addition to informing clinician practice, this review may help inform the revision of prescribing guidelines within VA and professional societies. The 2016 American Diabetes Association guidelines already note that "accumulating observational data suggest that metformin may be safely continued down to glomerular filtration rate (GFR) of 45

mL/min/1.73m^2 or even 30 mL/min/1.73 m^2."[65] Our review, together with other reviews and the recent FDA labeling changes, may support strengthening this endorsement.

STRENGTHS AND LIMITATIONS

This review's strengths include a rigorous methodology, a thorough review of existing literature (which included a search for relevant RCT subgroup analyses), a comprehensive consideration of multiple traditional contraindications and precautions to metformin use, and an evaluation of multiple critical outcomes of interest. However, our approach has some limitations. First, because a Cochrane review described the risk of LA with metformin use based on literature published through 2009, we limited our KQ 1 literature search to articles published after this time. We limited our literature search for KQ 2 to articles published after 1994—the year FDA approved use of metformin in the United States. While it is possible we may not have captured relevant articles published before these dates, we searched the reference lists of prior published reviews and consulted content experts to ensure that no critical data were overlooked.

Second, in order to assure relevance for our VA stakeholders, we limited our search to studies conducted in OECD countries. Although this approach may have excluded some potentially relevant articles from non-OECD countries, we feel that this decision enhances the applicability of our findings to our target population. Third, although we examined numerous relevant outcomes as informed by our VA stakeholders and technical expert panel, we did not examine all outcomes of potential interest. Because our primary interest was providing data to inform the safe prescribing of metformin in populations with traditional contraindications and precautions, we focused on outcomes we feel would be the most clinically relevant for prescribers.

Beyond these limitations, the existing evidence base calls for additional caution in interpreting our findings. The studies we identified were primarily observational and, as such, come with potential limitations. First, although most included studies attempted to account for baseline differences between metformin and non-metformin populations through statistical adjustment (and in some cases, propensity score matching), confounding by indication remained a potential source for measured and unmeasured population differences. For example, most studies did not closely examine precaution severity; multiple studies included all patients whose eGFR fell below a certain cutoff or all patients with CHF diagnosis codes without accounting for ejection fraction. Unaccounted-for between-group differences in precaution severity could therefore have influenced our findings. Second, while some studies analyzed outcomes based on specific time intervals during which patients were or were not exposed to metformin, most studies defined metformin use at baseline only. As a result, some patients categorized as metformin-exposed could have discontinued metformin, and some unexposed patients could potentially have initiated treatment after baseline. Third, it is likely that different comparator therapies were utilized in different study populations. Most studies (including nearly all meta-analyzed studies) sought to compare T2D patients whose treatment regimens included metformin to those whose did not. As such, intervention and comparator patients alike may have used sulfonylureas, insulin, and other common diabetes medications, preventing assessment of outcomes with metformin versus specific comparators. We found few explicit comparisons to newer anti-diabetic agents like DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT-2 inhibitors. Fourth, studies used different strategies for assessing outcomes of interest; this issue was particularly relevant for LA, where varying outcome assessment definitions contributed to markedly different incidence estimates. Fifth, the timing of outcome assessment varied between studies, and little

information was typically provided on attrition in study populations. All of these factors may have contributed to the heterogeneity on our qualitative and quantitative syntheses. However, because most meta-analyzed studies showed metformin use to be associated with improved outcomes of interest, the heterogeneity identified in our analyses appears related to variance in the precise magnitude of an overall consistent effect favoring metformin.

Of note, because our syntheses relied on observational data, we were limited in our ability to assess publication bias as part of our review. Existing study registries (*eg,* ClinicalTtrials.gov) do not apply to observational studies, which precluded a statistical analysis of publication bias.

FUTURE RESEARCH

To date, many diabetes pharmacotherapy RCTs have excluded patients with CKD, advanced CHF, and other historical contraindications or precautions to metformin use. As such, the primary gap in the current evidence regarding metformin use in populations with traditional contraindications and precautions is the lack of randomized trials in this domain. Currently, various factors reduce the feasibility of conducting RCTs addressing the use of metformin in populations with traditional contraindications and precautions, including the fact that metformin is a generic medication widely considered to be the consensus first-line treatment for T2D. The length of time required for appropriate assessment of relevant outcomes may also be prohibitive. A large pragmatic trial akin to the Diuretic Comparison Project, an ongoing VA Cooperative Study comparing hydrochlorothiazide and chlorthalidone for cardiovascular risk reduction in hypertension,[71] may be a feasible strategy for assessing the comparative effectiveness of metformin and other agents among patients with historical contraindications and precautions. Even without RCTs, new observational studies will remain important to ensure that rates of metformin-associated LA do not rise as metformin prescribing increases among populations with traditional contraindications (especially CKD). As the use of newer diabetes classes becomes more prevalent within VA, observational studies will remain a viable approach for comparing metformin with newer agents in these populations.

The impact of contraindication or precaution severity on the apparently beneficial effects of metformin remains unclear based on available data. For example, while our primary CKD meta-analysis did include patients with eGFR down to 30 mL/min/1.73m^2, additional studies focusing specifically on cohorts with eGFR 30-45 mL/min/1.73m^2 or even <30mL/min/1.73m^2 would further inform prescribing of metformin in these groups, and refinement of clinical guidelines. Data regarding the impact of precaution severity in CHF, CLD, and older age are sparse, and further observational research could address these gaps.

Building on the issue of severity, the possibility of tailoring prescribing recommendations based on the severity of historical contraindications or precautions would benefit from further research. For example, metformin dose reduction based on eGFR has long been recommended in Canadian prescribing guidelines,[72] and US thought leaders have recently suggested a maximum metformin dose of 2550 mg for patients with eGFR >60, 2000 mg daily for eGFR 45-<60 mL/min/1.73m^2 and 1000 mg/day for eGFR 30-<45 mL/min/1.73m^2.[5] Given that the kidneys excrete metformin unchanged in the urine,[73] the idea of such dose adjustment has a clear rationale, but at this time there are no experimental data and limited observational data to support such an approach.

Finally, data were particularly limited for certain conditions (*eg*, CLD) and outcomes of interest beyond mortality (*eg*, MACE, hypoglycemia); future observational research is warranted to explore these areas in greater detail. It will also be crucial to evaluate whether the mortality benefit associated with metformin use persists as prescribing in populations with historical contraindications and precautions expands.

CONCLUSIONS

Based on limited evidence, the rate of LA associated with metformin use among patients with historical contraindications or precautions does not appear higher than that of other diabetes medications. Metformin appears to be associated with reduced all-cause mortality in patients with CKD and patients with CHF, and appears to be associated with reduced CHF readmission in patients with CHF. Though data are otherwise limited, other risks of metformin use do not appear higher than those associated with other diabetes medications among patients with historical contraindications or precautions. Despite this review's limitations, our findings support recent FDA labeling changes, may help inform clinical practice and revision of clinical guidelines, and point toward important areas for future research.

REFERENCES

1. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 2011;13(3):221-228.

2. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS One.* 2013;8(8):e71583.

3. Cohen RD, Woods HF. *Clinical and biochemical aspects of lactic acidosis*. Philadelphia: Blackwell Scientific Publications; 1976.

4. Metformin hydrochoride. Boxed warning. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid = b8004451-7b26-425b-b5ea-cbb1b08e30e3&type = display. Accessed October 6, 2015.

5. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA.* 2014;312(24):2668-2675.

6. Gan SC, Barr J, Arieff AI, Pearl RG. Biguanide-associated lactic acidosis. Case report and review of the literature. *Arch Intern Med.* 1992;152(11):2333-2336.

7. Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology.* 2010;254(1):261-269.

8. Kajbaf F, Arnouts P, de Broe M, Lalau JD. Metformin therapy and kidney disease: a review of guidelines and proposals for metformin withdrawal around the world. *Pharmacoepidemiol Drug Saf.* 2013;22(10):1027-1035.

9. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med.* 2002;162(4):434-437.

10. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with Type 2 diabetes--a population-based study of adherence to prescribing guidelines. *Diabet Med.* 2001;18(6):483-488.

11. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed June 16, 2016.

12. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354(23):2473-2483.

13. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabtologia.* 2015;58(3):429-442.

14. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis.* 2012;60(5):850-886.

15. Flory JH, Hennessy S. Metformin use reduction in mild to moderate renal impairment: possible inappropriate curbing of use based on food and drug administration contraindications. *JAMA Intern Med.* 2015;175(3):458-459.

16. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2010(4):CD002967.

17. Organization for Economic Cooperation and Development. Available at: http://www.oecd.org/about/membersandpartners/list-oecd-member-countries.htm. Accessed October 20, 2015.

18. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail.* 2013;6(3):395-402.

19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130(6):461-470.

20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

21. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.

22. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction = displayproduct&productid = 318. Accessed October 6, 2015.

23. Santaguida PL, Raina P, Ismaila P. The Development of the McHarm Quality Assessment Scale for adverse events. 2012.

24. Viswanathan M, Ansari M, Berkman N. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. 2012 Mar 8. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK91433/. Accessed October 6, 2015.

25. Andersson C, Olesen JB, Hansen PR, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. *Diabetologia.* 2010;53(12):2546-2553.

26. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care.* 2005;28(10):2345-2351.

27. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin use in patients with diabetes and heart failure: a population-based retrospective cohort study. *JACC Heart Fail.* 2014;2(6):573-582.

28. Wang Z. Converting odds ratio to relative risk in cohort studies with partial data information. *Journal of Statistical Software.* 2013;55(5):1-11.

29. Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. *JAMA.* 2014;312(6):623-630.

30. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-188.

31. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med.* 2003;22(17):2693-2710.

32. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406.

33. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care.* 2014;37(8):2291-2295.

34. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care.* 2014;37(8):2218-2224.

35. Romero SP, Andrey JL, Garcia-Egido A, et al. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community. *Int J Cardiol.* 2013;166(2):404-412.

36. Ito H, Ohno Y, Yamauchi T, Kawabata Y, Ikegami H. Efficacy and safety of metformin for treatment of type 2 diabetes in elderly Japanese patients. *Geriatr Gerontol Int.* 2011;11(1):55-62.

37. Sterner G, Elmståhl S, Frid A, et al. Renal function in a large cohort of metformin treated patients with type 2 diabetes mellitus. *British Journal of Diabetes and Vascular Disease.* 2012;12(5):227-231.

38. Zhang X, Harmsen WS, Mettler TA, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology.* 2014;60(6):2008-2016.

39. Becquemont L, Bauduceau B, Benattar-Zibi L, et al. Cardiovascular Drugs and Metformin Drug Dosage According to Renal Function in Non-Institutionalized Elderly Patients. *Basic Clin Pharmacol Toxicol.* 2015.

40. Ekström N, Schiöler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish National Diabetes Register. *BMJ Open.* 2012;2:4 Article Number: e001076.

41. Aguilar D, Chan W, Bozkurt B, Ramasubbu K, Deswal A. Metformin use and mortality in ambulatory patients with diabetes and heart failure. *Circulation: Heart Failure.* 2011;4(1):53-58.

42. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation.* 2005;111(5):583-590.

43. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. *Diabetes Obes Metab.* 2014;16(10):957-962.

44. Roussel R, Travert F, Pasquet B, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med.* 2010;170(21):1892-1899.

45. Evans JM, Doney AS, AlZadjali MA, et al. Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. *Am J Cardiol.* 2010;106(7):1006-1010.

46. Inzucchi SE, Masoudi FA, Wang Y, et al. Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. *Diabetes Care.* 2005;28(7):1680-1689.

47. Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. *J Card Fail.* 2010;16(3):200-206.

48. Tinetti ME, McAvay G, Trentalange M, Cohen AB, Allore HG. Association between guideline recommended drugs and death in older adults with multiple chronic conditions: population based cohort study. *BMJ.* 2015;351:h4984.

49. Ampuero J, Ranchal I, Nunez D, et al. Metformin inhibits glutaminase activity and protects against hepatic encephalopathy. *PloS One.* 2012;7(11):e49279.

50. Nkontchou G, Cosson E, Aout M, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab.* 2011;96(8):2601-2608.

51. Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. *Diabetes Obes Metab.* 2002;4(6):368-375.

52. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. *Diabetes Care.* 2005;28(3):539-543.

53. Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab.* 2002;4(3):201-208.

54. Gregorio F, Ambrosi F, Manfrini S, et al. Poorly controlled elderly Type 2 diabetic patients: the effects of increasing sulphonylurea dosages or adding metformin. *Diabet Med.* 1999;16(12):1016-1024.

55. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care.* 2004;27(1):141-147.

56. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin. *Diabet Med.* 2002;19(8):673-680.

57. Schweizer A, Dejager S, Bosi E. Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Obes Metab.* 2009;11(8):804-812.

58. Bannister CA, Holden SE, Jenkins-Jones S, et al. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes Obes Metab.* 2014;16(11):1165-1173.

59. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care.* 2008;31(11):2086-2091.

60. Huizinga MM, Roumie CL, Greevy RA, et al. Glycemic and weight changes after persistent use of incident oral diabetes therapy: a Veterans Administration retrospective cohort study. *Pharmacoepidemiol Drug Saf.* 2010;19(11):1108-1112.

61. Leung S, Mattman A, Snyder F, Kassam R, Meneilly G, Nexo E. Metformin induces reductions in plasma cobalamin and haptocorrin bound cobalamin levels in elderly diabetic patients. *Clin Biochem.* 2010;43(9):759-760.

62. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med.* 2012;157(9):601-610.

63. Wang CP, Lorenzo C, Espinoza SE. Frailty Attenuates the Impact of Metformin on Reducing Mortality in Older Adults with Type 2 Diabetes. *J Endocrinol Diabetes Obes.* 2014;2(2).

64. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ.* 2009;339:b4731.

65. American Diabetes Association. Standards of Medical Care in Diabetes--2016. Available at: http://care.diabetesjournals.org/content/39/Supplement_1. Accessed June 30, 2016.

66. Bolen S, Tseng E, Hutfless S, et al. AHRQ Comparative Effectiveness Reviews. *Diabetes Medications for Adults With Type 2 Diabetes: An Update*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.

67. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149.

68. Tuot DS, Lin F, Shlipak MG, et al. Potential impact of prescribing metformin according to eGFR rather than serum creatinine. *Diabetes Care.* 2015;38(11):2059-2067.

69. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *Jama.* 2016;316(3):313-324.

70. MacDonald MR, Eurich DT, Majumdar SR, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care.* 2010;33(6):1213-1218.

71. U.S. Department of Veterans Affairs. Office of Research & Development. VA CSP Study No. 597: Diuretic Comparison Project. Available at: http://www.research.va.gov/programs/csp/597/. accessed August 29, 2016.

72. Canadian Diabetes Association. Clinical Practice Guidelines: Pharmacotherapy for Type 2 Diabetes. Available at: http://guidelines.diabetes.ca/bloodglucoselowering/pharmacologyt2-(1). Accessed June 30, 2016.

73. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics.* 2012;22(11):820-827.

74. Weir MA, Gomes T, Mamdani M, et al. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. *Nephrol Dial Transplant.* 2011;26(6):1888-1894.