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

EXECUTIVE SUMMARY

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 and decreased risk of some cancers. However, clinicians have been advised by the U.S. Food and Drug Administration (FDA) to exercise caution in prescribing metformin to individuals with chronic kidney disease (CKD), unstable congestive heart failure (CHF), chronic liver disease (CLD), and older age due to perceived risk of side effects, including lactic acidosis (LA).

Recent literature highlights the rarity of metformin-associated LA and supports the cautious expansion of metformin use. In addition, in April 2016 the FDA modified its position on CKD to extend use of metformin to some patients with moderate CKD. Yet there remain uncertainties regarding the risks and benefits of metformin use in populations with CKD, CHF, CLD, and older age. For this reason, we conducted a systematic review and meta-analysis in order to determine the answers to the following key questions:

KQ 1. For patients with type 2 diabetes and an apparent contraindication or 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 or precaution to metformin use, what are the potential benefits and harms (other than lactic acidosis) of continued treatment with metformin?

METHODS

Data Sources and Searches

We searched MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (KQ 2 only), Embase, the International Pharmaceutical Abstracts, and ClinicalTrials.gov. 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.

Study Selection

Using prespecified inclusion/exclusion criteria, the abstracts of RCTs identified through our search were reviewed by 2 reviewers and those deemed relevant underwent full-text review. Articles meeting eligibility criteria were included for data abstraction.

Data Abstraction and Quality Assessment

Key characteristics abstracted by one reviewer and overread by another were patient descriptors, setting, definitions of contraindications or precautions of interest, metformin dose, cointerventions, comparator, and outcomes. Quality was assessed independently by 2 reviewers using the Cochrane Risk of Bias tool for RCTs 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*, adapted to this specific topic and customized to observational studies.

Data Synthesis and Analysis

We summarized the primary literature using relevant data abstracted from the eligible studies and determined the feasibility of completing a quantitative synthesis (*ie*, meta-analysis) to estimate summary effects. For all analyses, we focused on studies at low or moderate risk of bias and analyzed RCTs and observational studies as well as patients with different contraindications or precautions to metformin separately. Quantitative synthesis was feasible only for mortality and major adverse cardiovascular event (MACE) outcomes using a random-effects model to generate hazard ratios. When quantitative synthesis was not feasible, we analyzed the data qualitatively. Strength of evidence (SOE) was assessed using the approach described in the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide.*

RESULTS

Results of Literature Search

We reviewed a total of 4,849 abstracts and 523 full-text articles. Of these, 37 (29 observational studies and 8 RCTs) were retained for data abstraction. 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).

Summary of Results for Key Questions

Since a 2010 Cochrane review, there are limited new data examining the rate of LA with metformin use; however, we found 9 contemporary observational studies reporting on this outcome in individuals with an identified precaution or contraindication to metformin use.

KQ 1a: Limited data (2 studies) suggest the incidence of LA in metformin users who have CKD is slightly higher than the upper bounds (4.3/100,000) reported in the Cochrane review. The limited data (2 studies) on incidence rates of LA among older adults are inconclusive. The risk of bias for these studies was judged to be high. No studies reported incidence rates for individuals with CHF or CLD.

KQ 1b: Five studies 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. The risk of bias for these studies was judged to be low (n = 2) or moderate (n = 3). No study reported this outcome for older adults without one of these comorbid conditions.

Based on our synthesis of observational evidence, the risk of LA with metformin use among individuals with a contraindication or precaution appears to be low (*ie*, not higher than the risk of LA with other hypoglycemic medications).

KQ 2: Among patients with T2D and CKD, metformin use is associated with a significantly lower risk of all-cause mortality (n = 5); limited evidence was identified for major adverse cardiovascular events (MACE, n = 2). Among patients with T2D and CHF, metformin use is also associated with a significantly lower risk of all-cause mortality (n = 11) and heart failure readmission (n = 4), but risk of cardiovascular mortality did not differ (n = 3). Among patients with T2D and CLD, limited evidence suggests a lower risk of all-cause mortality (n = 3) may be associated with metformin use. There was no evidence identified for MACE in relation to CLD. Among patients with T2D and older age (generally age ³ 65 years), limited evidence suggests that metformin is not associated with a higher risk of all-cause mortality (n = 4), MACE (n = 1), or hypoglycemia (n = 6). These results are all in comparison to non-metformin treatment.

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. 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.

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 or CHF. 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, but does not indicate increased harm from the use of metformin compared to nonuse.

DISCUSSION

Key Findings and Strength of Evidence

Consistent with prior reviews, we found that metformin use is associated with an overall low risk of LA among individuals with traditional contraindications or precautions, with the exception that identified studies did suggest that patients with CKD may experience a slightly higher rate of LA while using metformin compared to general diabetes populations; this risk appears highest in individuals with eGFR <30. 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.

When used to treat T2D among patients with CKD or CHF, metformin is associated with a lower risk of all-cause mortality and CHF readmission compared to non-metformin therapies. Based on limited evidence, we found no associations between use of metformin and other outcomes of interest (MACE, glycemic control, lipid control, weight, hypoglycemia, or vitamin B12 deficiency) in T2D populations with historical contraindications or precautions.

Using data from 209 RCTs, a prior Cochrane review identified no cases of LA; however, these trials did not seek out individuals with the contraindications or precautions of interest. We identified 5 observational studies reporting LA in patients 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. For patients with a contraindication or precaution to metformin, we judged the SOE insufficient to determine the rate of LA for metformin users versus non-users. In relation to all-cause mortality, in CKD, CHF, and older adults, there are uniformly fewer deaths among patients taking metformin (low SOE).

Applicability

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. In the wake of these recent changes in FDA labeling, prescribing of metformin will undoubtedly increase. 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 precautions. Our findings will directly inform clinicians' prescribing practices for T2D patients with traditional restrictions to receiving this medication. In addition to informing clinician practice, this review may help inform the revision of prescribing guidelines within VA and professional societies.

Research Gaps/Future Research

The primary gap in the current evidence regarding metformin use in populations with traditional contraindications or precautions is the lack of randomized trials in this domain; large simple pragmatic trials could fill this gap. 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 or precautions (especially CKD). Additional, observational studies will also be useful in comparing metformin to newer diabetes agents in these populations. Additional studies focusing specifically on cohorts with eGFR 30-45 mL/min/1.73m^2 or even <30 mL/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. The possibility of tailoring prescribing recommendations based on the severity of historical contraindications or precautions would also benefit from further research. Finally, future research is warranted to explore CLD and outcomes of interest beyond mortality. It will also be crucial to evaluate whether the mortality benefit associated with metformin use persists as prescribing in populations with historical contraindications or 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. 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 inform clinical practice, and point toward important areas for future research.

ABBREVIATIONS TABLE

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
CHF	Congestive heart failure
CKD	Chronic kidney disease
CLD	Chronic liver disease
eGFR	Estimated glomerular filtration rate
ESP	Evidence-based Synthesis Program
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HSR&D	Health Services Research & Development
KQ	Key question
LA	Lactic acidosis
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MD	Mean difference
MeSH	Medical subject heading
PICOTS	Population, intervention, comparator, outcome, timing, and setting
QUERI	Quality Enhancement Research Initiative
RCT	Randomized controlled trial
SMD	Standardized mean difference
SOE	Strength of evidence
T2D	Type 2 diabetes
VA	Veterans Affairs
VHA	Veterans Health Administration

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.

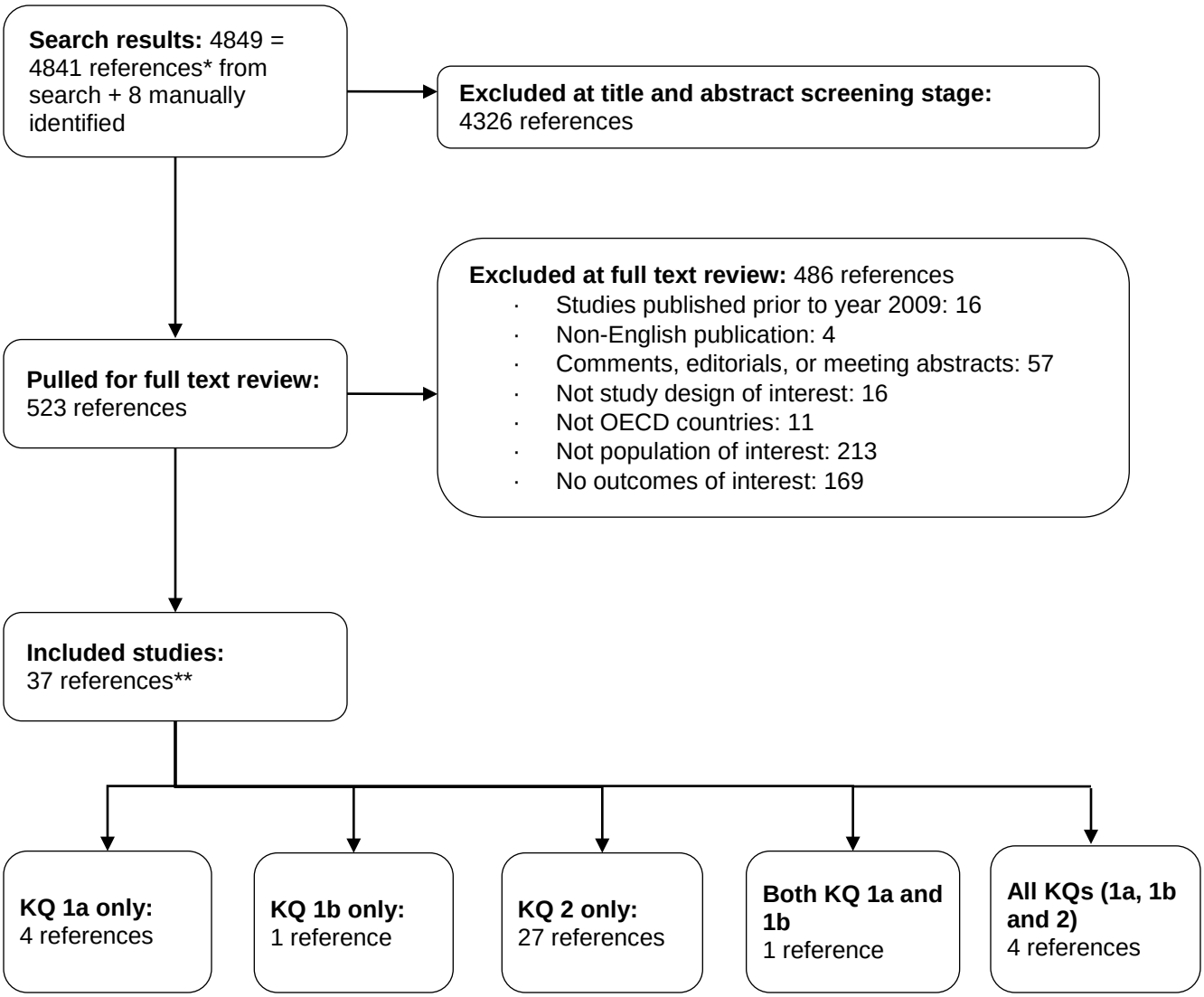
RESULTS

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]

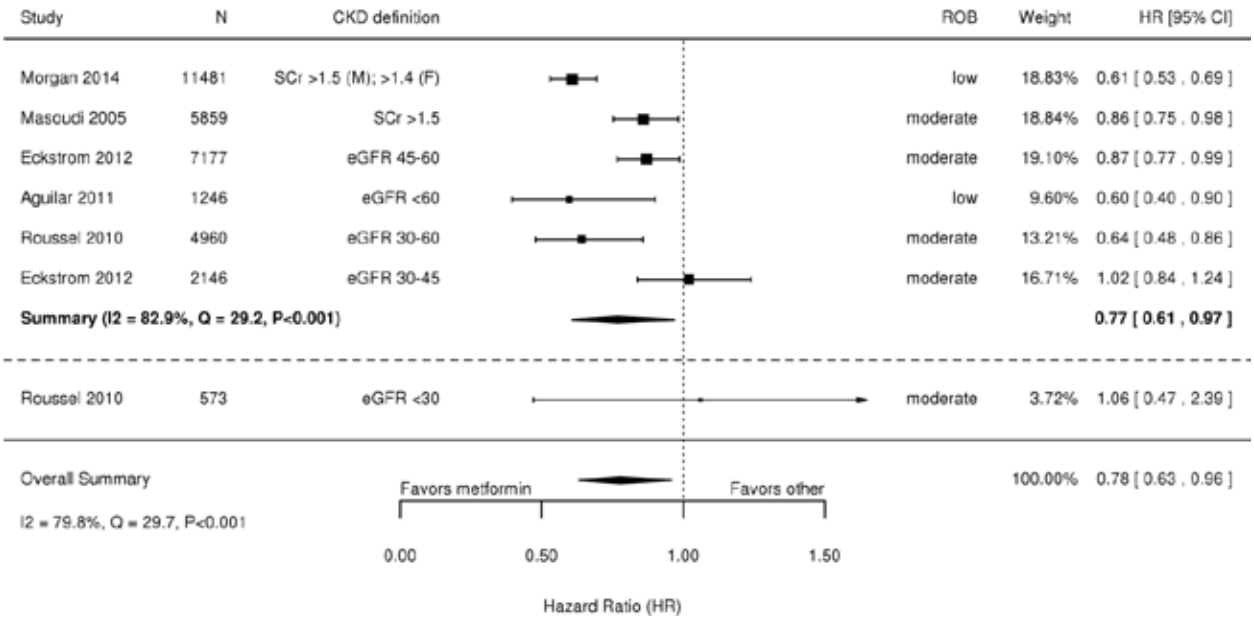
All-cause Mortality

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]

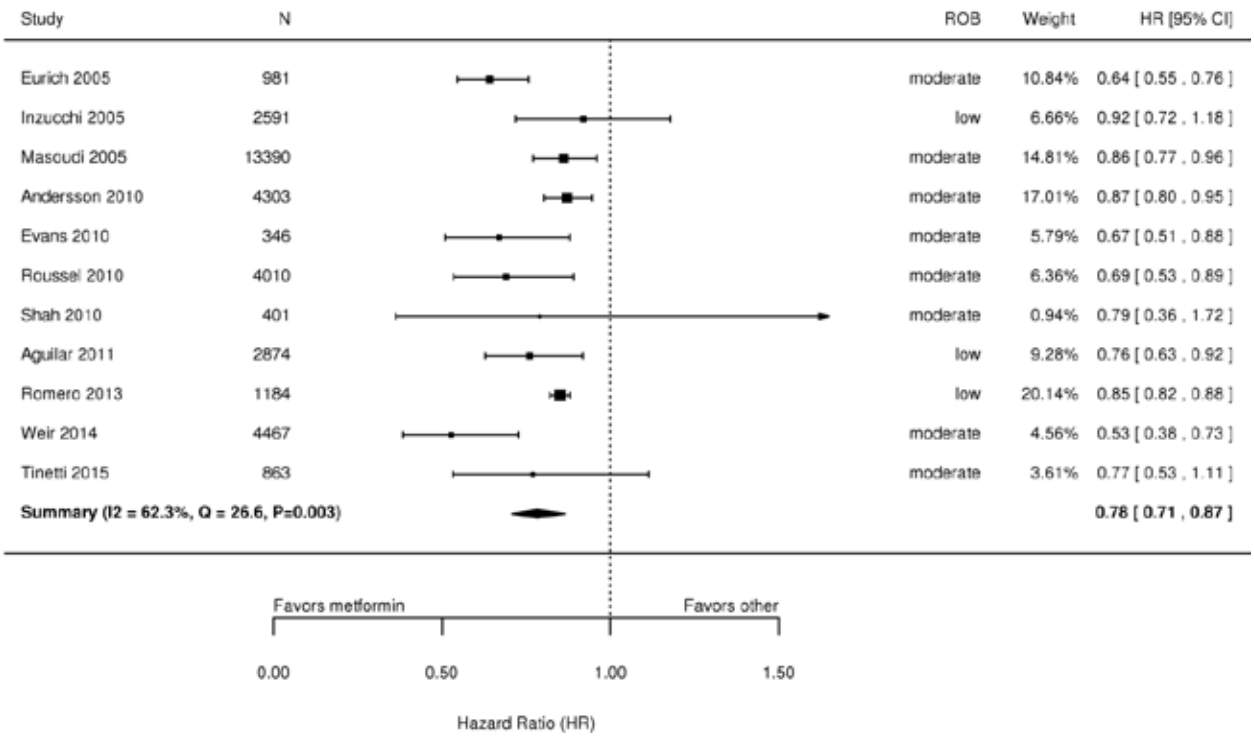
All-cause Mortality

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.

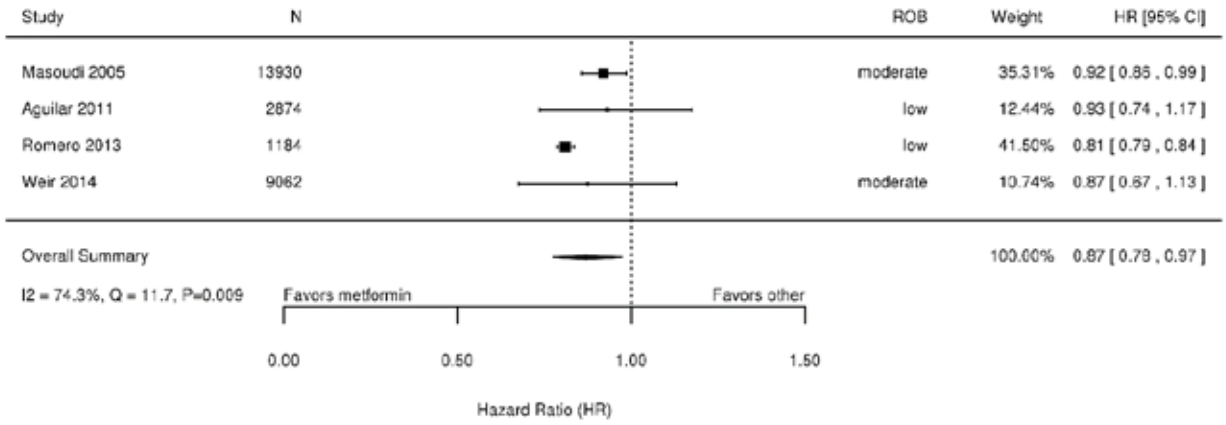
Major Adverse Cardiovascular Events

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]

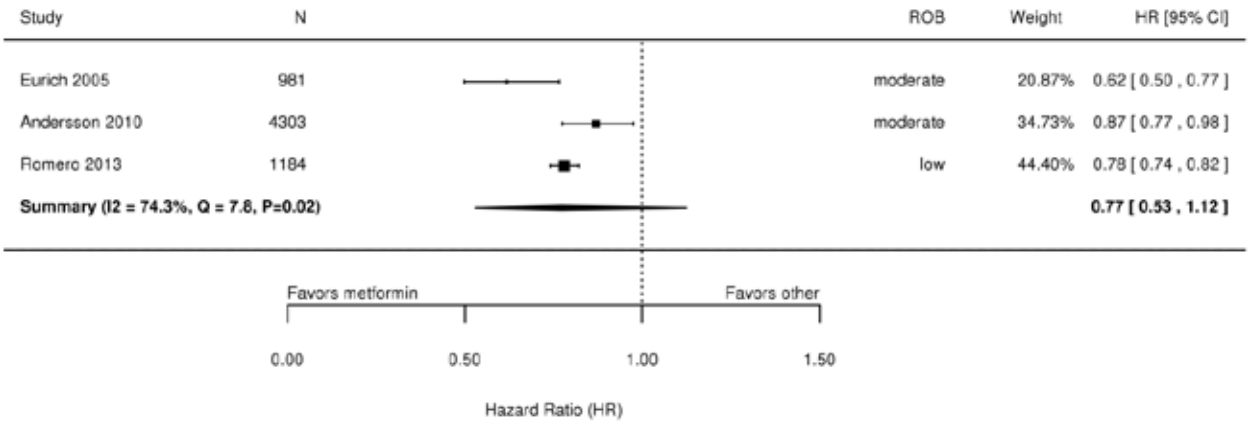
These studies were deemed to have sufficient conceptual homogeneity to perform quantitative synthesis; we performed separate meta-analyses for each MACE outcome. Based on meta-analysis of available patients, there was a small but statistically significant summary HR for CHF readmission favoring metformin (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.

APPENDIX A. FDA SAFETY ANNOUNCEMENTS FOR METFORMIN

This appendix explains both the original and updated US Food and Drug Administration's safety warnings in relation to the use of metformin.

Original ALERT: U.S. Boxed Warning for Lactic Acidosis

Lactic acidosis is a rare but serious metabolic complication that can occur because of metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (5 mmol/L or more), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of 5 mcg/mL or more are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient-years, with approximately 0.015 fatal cases per 1,000 patient-years). In more than 20,000 patient-years' exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal function impairment, including intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure (CHF) requiring pharmacologic management, in particular those with unstable or acute CHF who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Therefore, the risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, accompany treatment of elderly patients with careful monitoring of renal function. Do not initiate metformin treatment in patients 80 years of age and older unless measurement of creatinine clearance (CrCl) demonstrates that renal function is not reduced because these patients are more susceptible to developing lactic acidosis. In addition, promptly withhold metformin in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because hepatic function impairment may significantly limit the ability to clear lactate, generally avoid using metformin in patients with clinical or laboratory evidence of hepatic disease. Caution patients against excessive alcohol intake, either acute or chronic, when taking metformin because alcohol potentiates the effects of metformin on lactate metabolism. In addition, temporarily discontinue metformin prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's health care provider must be aware of the possible importance of such symptoms. Instruct patients to notify their health care provider immediately if these symptoms occur. Withdraw metformin until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood

metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, GI symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of GI symptoms could be caused by lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal (ULN) but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explained by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Suspect lactic acidosis in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, immediately discontinue the drug and promptly institute general supportive measures. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Updated Safety Announcement, April 8, 2016

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes toexpand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneysdo not work normally. We were asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. We have concluded our review, and are requiring changes to the labeling of all metformin-containing medicines to reflect this new information.

Health care professionals should follow the latest recommendations when prescribingmetformin-containing medicines to patients with impaired kidney function. Patients should talk to their health care professionals if they have any questions or concerns about taking metformin.

Metformin-containing medicines are available by prescription only and are used alongwith diet and exercise to lower blood sugar levels in patients with type 2 diabetes (T2D). When untreated, T2D can lead to serious problems, including blindness, nerve andkidney damage, and heart disease. Metformin-containing medicines are available assingle-ingredient products and also in combination with other drugs used to treat diabetes (see FDA Approved metformin-containing Medicines). The current drug labeling strongly recommends against metformin use in some patients whose kidneys do not work normally because use of metformin in these patients can increase the risk of developing a serious and potentially deadly condition called lactic acidosis, in which too much lacticacid builds up in the blood.

We have concluded from the review of studies published in the medical literature that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. We are requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment.

We are also recommending that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of kidney function in patients with kidney disease (i.e., glomerular filtration rate estimating equation [eGFR]).

Health care professionals and patients should report side effects involving metformin or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

FDA-approved metformin-containing medicines*

Brand name	Active ingredients
Actoplus Met	metformin and pioglitazone
Actoplus Met XR	metformin and pioglitazone, extended release
Avandamet	metformin and rosiglitazone
Fortamet	metformin extended release
Glucophage	metformin
Glucophage XR	metformin extended release
Glucovance	metformin and glyburide
Glumetza	metformin extended release
Invokamet	metformin and canagliflozin
Janumet	metformin and sitagliptin
Janumet XR	metformin and sitagliptin, extended release
Jentadueto	metformin and linagliptin
Kazano	metformin and alogliptin
Kombiglyze XR	metformin and saxagliptin, extended release
Prandimet	metformin and repaglinide
Riomet	metformin
Synjardy	metformin and empagliflozin
Xigduo XR	metformin and dapagliflozin, extended release

*These medicines are also available in multiple generic versions.

Facts about metformin

- Metformin-containing medicines are available by prescription only and are used along with diet and exercise to treat type 2 diabetes.
- Metformin helps control blood sugar in a number of ways. These include helping the body respond better to the insulin it makes naturally, decreasing the amount of sugar the liver makes, and decreasing the amount of sugar the intestines absorb from food.

- Metformin is available as a single-ingredient product and also in combination with other medicines used to treat diabetes. See FDA Approved metformin-containing Medicines.
- Common side effects of metformin include diarrhea, nausea, and upset stomach.

Additional information is available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm **(Accessed July 1, 2016)**

APPENDIX B. SEARCH STRATEGY

Key Question 1—PubMed: November 20, 2015

Set	Query	Results
1	"Acidosis, Lactic"[Mesh] OR "Lactic Acid/blood"[Mesh] OR "lactic acidosis"[tiab] OR hyperlactatemia[tiab] OR hyperlactataemia[tiab]	13168
2	"Diabetes Mellitus"[Mesh] OR diabetes[tiab] OR diabetic[tiab]	513282
3	"Renal Insufficiency, Chronic"[Mesh] OR "Heart Failure"[Mesh] OR "Hepatic Insufficiency"[Mesh] OR "Liver Cirrhosis"[Mesh] OR "Diabetic Nephropathies"[Mesh] OR "Aged"[Mesh] OR "Age Factors"[Mesh] OR "Geriatrics"[Mesh] OR CKD[tiab] OR CRD[tiab] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "heart failure"[tiab] OR CHF[tiab] OR "chronic liver disease"[tiab] OR "liver insufficiency"[tiab] OR "hepatic insufficiency"[tiab] OR "liver cirrhosis"[tiab] OR "diabetic nephropathies"[tiab] OR "diabetic nephropathy"[tiab] OR aged[tiab] OR elderly[tiab] OR older[tiab] OR geriatric[tiab]	3427067
4	"Metformin"[Mesh] OR metformin[tiab]	13077
5	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR "case-control studies"[MeSH] OR "cohort studies"[MeSH] OR "Drug Information Services"[Mesh] OR "case-control"[tiab] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "follow up"[tiab] OR "Case Reports" [Publication Type] OR "case series"[tiab] OR pharmacovigilance[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	6464701
6	#1 AND (#2 OR #3) AND #4 AND #5	298

Key Question 2—PubMed: November 20, 2015

Set	Query	Results
1	"Diabetes Mellitus"[Mesh] OR diabetes[tiab] OR diabetic[tiab]	513282
2	"Renal Insufficiency, Chronic"[Mesh] OR "Heart Failure"[Mesh] OR "Hepatic Insufficiency"[Mesh] OR "Liver Cirrhosis"[Mesh] OR "Diabetic Nephropathies"[Mesh] OR "Aged"[Mesh] OR "Age Factors"[Mesh] OR "Geriatrics"[Mesh] OR CKD[tiab] OR CRD[tiab] OR "chronic kidney"[tiab] OR "chronic renal"[tiab] OR "heart failure"[tiab] OR CHF[tiab] OR "chronic liver disease"[tiab] OR "liver insufficiency"[tiab] OR "hepatic insufficiency"[tiab] OR "liver cirrhosis"[tiab] OR "diabetic nephropathies"[tiab] OR "diabetic nephropathy"[tiab] OR aged[tiab] OR elderly[tiab] OR older[tiab] OR geriatric[tiab] OR "Acidosis, Lactic"[Mesh] OR "Lactic Acid/blood"[Mesh] OR "lactic acidosis"[tiab] OR hyperlactatemia[tiab] OR hyperlactataemia[tiab] OR "Metformin/adverse effects"[Mesh]	3438398
3	"Metformin"[Mesh] OR metformin[tiab]	13077

Set	Query	Results
4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "follow up"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR "Case Reports" [Publication Type]) NOT (animals[mh] NOT humans[mh])	**4823517**
5	#1 AND #2 AND #3 AND #4	**2218**

Key Question 1—Embase: November 20, 2015

Set	Query	Results
1	'lactic acidosis'/exp OR 'lactic acid'/exp OR "lactic acidosis":ab,ti OR hyperlactatemia:ab,ti OR hyperlactataemia:ab,ti	**67408**
2	'diabetes mellitus'/exp OR diabetes:ab,ti OR diabetic:ab,ti	**825055**
3	'chronic kidney failure'/exp OR 'heart failure'/exp OR 'liver failure'/exp OR 'liver cirrhosis'/exp OR 'diabetic nephropathy'/exp OR 'aged'/exp OR 'age'/exp OR 'geriatrics'/exp OR CKD:ab,ti OR CRD:ab,ti OR "chronic kidney":ab,ti OR "chronic renal":ab,ti OR "heart failure":ab,ti OR CHF:ab,ti OR "chronic liver disease":ab,ti OR "liver insufficiency":ab,ti OR "hepatic insufficiency":ab,ti OR "liver cirrhosis":ab,ti OR "diabetic nephropathies":ab,ti OR "diabetic nephropathy":ab,ti OR aged:ab,ti OR elderly:ab,ti OR older:ab,ti OR geriatric:ab,ti	**4045218**
4	'metformin'/exp OR metformin:ab,ti	**41795**
5	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab OR ‘clinical trials’:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR ‘evaluation study’:ab,ti OR ‘evaluation studies’:ab,ti OR ‘intervention study’:ab,ti OR ‘intervention studies’:ab,ti OR ‘case control’:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR ‘follow up’:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR ‘comparative study’:ab,ti OR ‘comparative studies’:ab,ti OR 'drug surveillance program'/exp OR pharmacovigilance:ab,ti OR 'case report'/exp OR 'case study'/exp OR 'case series":ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR 'note'/exp)	**11802586**
6	#1 AND (#2 OR #3) AND #4 AND #5	**1205**
7	#6 AND [embase]/lim NOT [medline]/lim	**387**

Key Question 2—Embase: November 20, 2015

Set	Query	Results
1	'diabetes mellitus'/exp OR diabetes:ab,ti OR diabetic:ab,ti	825055
2	'chronic kidney failure'/exp OR 'heart failure'/exp OR 'liver failure'/exp OR 'liver cirrhosis'/exp OR 'diabetic nephropathy'/exp OR 'aged'/exp OR 'age'/exp OR 'geriatrics'/exp OR CKD:ab,ti OR CRD:ab,ti OR "chronic kidney":ab,ti OR "chronic renal":ab,ti OR "heart failure":ab,ti OR CHF:ab,ti OR "chronic liver disease":ab,ti OR "liver insufficiency":ab,ti OR "hepatic insufficiency":ab,ti OR "liver cirrhosis":ab,ti OR "diabetic nephropathies":ab,ti OR "diabetic nephropathy":ab,ti OR aged:ab,ti OR elderly:ab,ti OR older:ab,ti OR geriatric:ab,ti OR 'lactic acidosis'/exp OR 'lactic acid'/exp OR "lactic acidosis":ab,ti OR hyperlactatemia:ab,ti OR hyperlactataemia:ab,ti OR 'metformin'/exp/dd_ae	4104859
3	'metformin'/exp OR metformin:ab,ti	41795
4	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab OR ‘clinical trials’:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR ‘evaluation study’:ab,ti OR ‘evaluation studies’:ab,ti OR ‘intervention study’:ab,ti OR ‘intervention studies’:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR ‘follow up’:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR ‘comparative study’:ab,ti OR ‘comparative studies’:ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'case series":ab,ti OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)	9867450
5	#1 AND #2 AND #3 AND #4	8122
6	#5 AND [embase]/lim NOT [medline]/lim	2610

Key Question 2—Cochrane Central Register of Controlled Trials: November 20, 2015

Set	Terms	Results
1	[mh "Diabetes Mellitus"]	17098
2	diabetes:ab,ti OR diabetic:ab,ti	36056
3	#1 OR #2	37538
4	[mh "chronic Renal Insufficiency"] OR [mh "Heart Failure"] OR [mh "Hepatic Insufficiency"] OR [mh "Liver Cirrhosis"] OR [mh "Diabetic Nephropathies"] OR [mh Aged] OR [mh "Age Factors"] OR [mh Geriatrics] OR [mh "lactic Acidosis"] OR [mh "Lactic Acid"] OR [mh Metformin/AE]	24846
5	"lactic acidosis":ab,ti OR hyperlactatemia:ab,ti OR hyperlactataemia:ab,ti OR CKD:ab,ti OR CRD:ab,ti OR "chronic kidney":ab,ti OR "chronic renal":ab,ti OR "heart failure":ab,ti OR CHF:ab,ti OR "chronic liver disease":ab,ti OR "liver insufficiency":ab,ti OR "hepatic insufficiency":ab,ti OR "liver cirrhosis":ab,ti OR "diabetic nephropathies":ab,ti OR "diabetic nephropathy":ab,ti OR aged:ab,ti OR elderly:ab,ti OR older:ab,ti OR geriatric:ab,ti	85344
6	#4 OR #5	98264
7	[mh Metformin]	1651
8	Metformin:ab,ti	3292
9	#7 OR #8	3417
10	#9 AND #6 AND #3	471
11	Limit: Cochrane Central Register of Controlled Trials	454

APPENDIX C. QUALITY ASSESSMENT FOR RANDOMIZED CONTROLLED TRIALS

QUALITY CRITERIA

General instructions: Rate each risk of bias item listed below as “Low,” “High,” or “Unclear.”

Rating of individual items for study #_____ :

1. Selection bias
a. Domain: Random sequence generation

(Support for judgement: *Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.)*

Was the allocation sequence adequately generated?

○ Low risk ○ High risk ○ Unclear risk

b. Domain: Allocation concealment?

(Support for judgement*: Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment)*

Was allocation adequately concealed?

○ Low risk ○ High risk ○ Unclear risk

2. Performance bias
Domain: Blinding of participants and "treating" personnel - i.e. the person(s) delivering the intervention.

(Support for judgement: *Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.)*

Was knowledge of the allocated intervention adequately prevented during the study?

○ Low risk ○ High risk ○ Unclear risk ○ Outcome NR

3a. Detection bias (outcome 1 =)
Domain: Blinding of outcome assessment

(Support for judgement: *Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the*

intended blinding was effective.)

Was knowledge of the allocated intervention adequately prevented from outcome assessors?

○ Low risk ○ High risk ○ Unclear risk [ ] ○ Outcome NR

3b. Detection bias (outcome 2 = [ ])
Domain: Blinding of outcome assessment

***(Support for judgement:** Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.)*

Was knowledge of the allocated intervention adequately prevented from outcome assessors?

○ Low risk ○ High risk ○ Unclear risk [ ] ○ Outcome NR

3c. Detection bias (outcome 3 = [ ])
Domain: Blinding of outcome assessment

***(Support for judgement:** Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.)*

Was knowledge of the allocated intervention adequately prevented from outcome assessors?

○ Low risk ○ High risk ○ Unclear risk [ ] ○ Outcome NR

3d. Detection bias (outcome 4 = [ ])
Domain: Blinding of outcome assessment

***(Support for judgement:** Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.)*

Was knowledge of the allocated intervention adequately prevented from outcome assessors?

○ Low risk ○ High risk ○ Unclear risk [ ] ○ Outcome NR

4. Attrition bias
Domain: Incomplete outcome data

***(Support for judgement:** Describe the completeness of outcome data for each main outcome, including*

attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.)

Were incomplete outcome data adequately addressed?

○ Low risk ○ High risk ○ Unclear risk

5. Reporting bias
Domain: Selective outcomes reporting

***(Support for judgement:** State how the possibility of selective outcome reporting was examined by the review authors, and what was found.)*

Are reports of the study free of suggestion of selective outcome reporting? (i.e., the author states they will measure an outcome but do not report it)

○ Low risk ○ High risk ○ Unclear risk

6. Other
Domain: Other sources of bias

***(Support for judgement:** State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.)*

Are reports of the study free from other bias due to problems not covered above?

☐ Low risk ☐ High risk ☐ Unclear risk ☐ Describe:

Overall risk of bias rating

○ Low risk

○ Unclear risk

○ High risk

* Items contained in the Cochrane Risk of Bias Tool

QUALITY ASSESSMENT RESPONSE TABLE—RCTS

For full study citations, please refer to the report's main reference list.

Study[a]	1a	1b	2	3a	3b	3c	3d	4	5	6	Overall Risk of Bias Rating
Blonde, 2002[51]	Unclear	Unclear	Low	Low	Low	NA	NA	Unclear	Low	Unclear	Unclear
Cryer, 2005[52]	Unclear	Unclear	High	NA[b]	Low	Unclear	NA	Low	Low	Low	Low
Garber, 2002[53]	Unclear	Unclear	Low	Low	Low	NA	NA	Unclear	Low	Unclear	Unclear
Gregorio, 1999[54]	Low	Unclear	Unclear	Unclear	NR	Low	NR	Low	Low	Low	High
Hanefeld, 2004[55]	Low	Unclear	Unclear	Low	NA	Unclear	Low	Low	NA	Low	Low
Marre, 2002[56]	Unclear	Unclear	Low	Low	Low	NA	NA	Unclear	Low	Unclear	Unclear
Schweizer, 2009[57]	Unclear	Unclear	Low	Low	Low	Low	NA	Low	Low	Low	Low

[a] The companion paper does not appear in this table.
[b] For mortality, blinding does not apply.

APPENDIX D. QUALITY ASSESSMENT FOR OBSERVATIONAL STUDIES

QUALITY CRITERIA

This tool is intended to evaluate the quality of observational studies examining the outcomes of metformin use in patients with contraindications/precautions. Use this risk of bias tool for the following study designs: nonrandomized controlled trial, cohort studies, and case-control studies. Each item that is marked "C" applies to nonrandomized trials and cohort studies, "CC" to case-control studies, and "CS" to case-series.

Instructions for use:
1. Items are organized by risk of bias domains (selection, performance, attrition, detection and reporting bias). Rate each question using the response categories listed. Focus on study design and conduct, not quality of reporting.

2. Two questions: basic study design, sample size/power are not used in the overall ratings but are collected for descriptive purposes.

3. After answering each item, rate the study overall as "low risk of bias," "moderate risk of bias," or "high risk of bias" based on the following definitions. This overall rating is specific to the basic study design used. For example, if the basic study design was a cohort study, then the risk of bias rating would be interpreted as "For a cohort study, the risk of bias is _____."

- "**Low Risk of Bias**" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.

- "**Moderate Risk of bias**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.

- "**High Risk of Bias**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

1. Basic Design

Is the study design prospective, retrospective, or mixed? *[Abstractor: Prospective design requires that the investigator plans a study before any data are collected. Mixed design includes case-control, nested case-control, or cohort studies in which one group is studied prospectively and the other retrospectively.]*

Prospective Mixed Retrospective Cannot determine

2. Selection Bias

2.1 Inclusion/exclusion criteria [C, CC, CS]

a. Are the inclusion/exclusion criteria clearly stated (does not require the reader to infer)? *[Key eligibility criteria are: age, diabetes type/level of control, use of metformin and/or other hypoglycemic medication, presence of metformin contraindication/precaution, certain comorbidities. Abstractor: use "Partial" if only some criteria are stated or if some criteria are not clearly stated.]*

Yes Partial No

b. Did the study apply valid and reliable measures to determine inclusion/exclusion criteria that were applied criteria uniformly to all comparison groups i.e., the group on metformin and the group not on metformin? *[C, CC] Pay particular attention to determination of DM2 and precaution. Measures accepted:*

T2D: ICD codes or medical record diagnosis; ≥ 2 HbA1c measures with values ≥ 6.5, **FBS values > 126 mg/dl**

Use of metformin: prescription, pharmacy database, medical record. If reported, please note whether it is incident use of metformin or prevalence of metformin use or NR in the text box.

Precautions: Age – take whatever is given; Liver disease – biopsy, imaging (fibrscan or CT), ICD codes, medical record diagnosis; CHF – echo or other cardiac imaging, ICD codes, medical record IF structured criteria (*eg*, BNP, list of symptoms, PE findings); CKD – eGFR <60, 90 days apart, ICD codes or medical record diagnosis

Yes Partial No Not applicable (no comparator)

***2.2*. Recruitment (prospective studies only)**: [Prospective Cohort]

Did the strategy for recruiting/entering participants into the study differ across study groups?

Yes No Cannot determine NA (retrospective)

2.3 Baseline characteristics similar or appropriate adjusted analysis [C]

Are key characteristics of study participants *[age, race, gender, diabetes severity, metformin contraindications/precautions, etc.]* similar between intervention and comparator groups? If not similar, did the analyses appropriately adjust for important differences *[Design: stratification, matching; Analysis: multiple regression, propensity score adjustment, etc.]*? Pay particular attention to whether the metformin precautions are

similar between groups, i.e., rates of CHF, levels of kidney function, and prevalence of liver disease.

Yes PartialNo NA (no comparison group)

2.4 Comparison Group (KQ1b/2 only) [C, CC]

Is the selection of the comparison group appropriate? *[Comparison group must include DM2 patients with a precaution of interest – then, less importantly, other DM treatment, eg, exposed to one or more non-metformin hypoglycemic medications.]*

Yes No Cannot determine NA (KQ1a)

Box given on form for comments on Selection bias:

3. Performance Bias [C, CC, CS]

Were metformin and comparison group patients treated **similarly?** Or was there a difference that might affect outcomes? If so, in selecting the population or analyzing the data, did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? For example:

a. for MALA, are there other likely causes of LA?
b. for hypoglycemia, consider use of other hypoglycemics, especially insulin, when metformin use is not the only difference between groups,
c. for A1c, are there differences in treatment other than metformin, especially insulin or very intense lifestyle intervention program?
d. for mortality or CV mortality, was overall management of other disease states comparable – HTN treatment, use of statins, etc.,
e. For MACE (major adverse cardiovascular events, *eg*, MI, hospitalization, CHF) consider that same concern about equitable treatment for other disease states between groups.

Yes Partial No Unclear NA

Box given on form for comments on Performance bias:

4. Attrition Bias

4.1 Equality of length of follow-up for participants [C, CC]

In cohort studies, is the length of follow-up similar between the groups, or appropriately accounted for using statistical techniques? For case-control studies, is the time period between the intervention/exposure and outcome the same for cases and controls?*[Abstractor: Where follow-up was the same for all study patients the answer is yes. If different lengths of follow-up were adjusted by statistical techniques, for example,*

survival analysis, the answer is yes. Studies where meaningful differences in follow-up are ignored should be answered no. A meaningful difference is more than 3 months.]

Yes **No** **Unclear** **NA**

4.2 Completeness of follow-up [C, CC]

Was there **a low rate** of differential or overall attrition? *[Attrition is measured in relation to the time between baseline (allocation in some instances) and outcome measurement. Standard for overall attrition is <20 percent for <1 year f/u and <30 percent for longer term ≥ 1 year). Standard for differential attrition is ≥ 10% absolute difference.* ***Pay particular attention it this is a KQ1 study on LA or MALA as differential drop-out is more problematic in these studies****.]*

Yes **No** **Unclear** **NA**

4.3 Attrition affecting Participant Composition [C]

Was attrition small enough that it did not result in a difference in group characteristics between baseline and follow-up?

Yes **No** **Unclear** **NA**

Box given on form for comments on Attrition bias:

5. Detection Bias

5.1 Blind outcomes assessment [C, CC, CS; doesn't apply to MALA or mortality]

Were the outcome assessors blinded to the intervention or exposure status of participants? [If outcomes based on clinical codes, then "No" unless additional review because they are determined clinically]

Yes **No** **NA (not an intervention study)**

5.2 Source of information: Outcomes

Are primary outcomes (*eg*, LA, MACE, mortality) assessed using valid and reliable measures and implemented consistently across all study participants**?**

[*LA is defined typically as blood lactate concentration >45mg/dl or 5.0mEq/L, decreased blood pH, and electrolyte disturbances with an increased anion gap**.***

***MALA is defined** as meeting the definition for LA plus either (a) elevated metformin level or (b) investigator judgment that LA is metformin-induced.*]

Yes **No** **Cannot determine (measurement not reported)**

5.3 . Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? *[Major potential confounders include: age, race, gender, diabetes severity (i.e. glycemic control and complications), comorbidities, metformin contraindications/precautions, etc.]*

Yes **Partial** **No** **Cannot determine**

Box given on form for comments on Detection bias:

6. Reporting Bias

Are findings for all primary outcomes reported? [Abstractor needs to identify all pre-specified, primary outcomes that should be reported in the study.]

Yes **Partially (some outcomes NR)** **No (Primary outcomes not pre-specified)**

Box given on form for comments on Detection bias:

7. Other Risk of Bias Issues [C, CC, CS]

No (no other concerns present) **Yes (other concerns present)**

QUALITY ASSESSMENT RESPONSES—OBSERVATIONAL STUDIES

For full study citations, please refer to the report's main reference list.

Study	1	2.1a	2.1b	2.2	2.3	2.4	3	4.1	4.2	4.3	5.1	5.2	5.3	6	7	Overall Risk of Bias Rating
Aguilar, 2011[41]	Ret	Yes	Yes	NA	Yes	Yes	Par	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ampuero, 2012[49]	Ret	Par	Par	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Par	Yes	No	Mod
Andersson, 2010[25]	Ret	Yes	Par	NA	Yes	Yes	Yes	Unc	Unc	Unc	No	Yes	Yes	Yes	No	Mod
Bannister, 2014[58]	Ret	Yes	Par	NA	Par	Yes	Unc	Yes	Yes	Yes	NA	Yes	Unc	Yes	No	Mod
Becquemont, 2015[39]	Pro	Yes	NA	No	NA	NA	Yes	NA	Unc	Unc	NA	Unc	Unc	Yes	Yes	High
Bodmer, 2008[59]	Mix	Yes	Yes	NA	Yes	Yes	Unc	Yes	Unc	NA	NA	Yes	Yes	Yes	No	Low
Ekstrom, 2012[40]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	None	Mod
Eppenga, 2014[34]	Ret	Par	No	NA	Yes	No	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	No	Mod
Eurich, 2005[26]	Ret	Par	Par	NA	Yes	Yes	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	No	Mod
Evans, 2010[45]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Unc	Unc	Unc	NA	Yes	Yes	Yes	No	Mod
Huizinga, 2010[60]	Ret	Yes	Par	NA	Par	Yes	Yes	Yes	No	Unc	Yes	Yes	Yes	Yes	Yes	Mod
Inzucchi, 2005[46]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Ito, 2011[36]	Ret	Yes	Yes	NA	No	Yes	Unc	Unc	Unc	Unc	No	Unc	No	Yes	No	High
Leung, 2010[61]	Pro	Par	Par	Unc	No	Unc	Unc	Unc	Unc	Unc	No	Yes	No	Yes	No	High
Masoudi, 2005[42]	Ret	Yes	Yes	NA	Par	Yes	Yes	Yes	Yes	Yes	No	Yes	Par	Par	Yes	Mod
Morgan, 2014[43]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unc	Yes	NA	Yes	Yes	Yes	No	Low
Nkontchou, 2011[50]	Pro	Yes	Yes	No	No	Unc	Yes	Yes	Yes	Yes	NA	Unc	Unc	Yes	Yes	High
Richy, 2014[33]	Ret	Yes	Yes	NA	No	NA	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	High
Romero, 2013[35]	Pro	Yes	Yes	No	Yes	Yes	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Low
Roumie, 2012[62]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Unc	Yes	Yes	NA	Yes	Yes	Yes	No	Low
Roussel, 2010[44]	Pro	Yes	Par	No	Par	Yes	Par	Yes	No	Unc	NA	Yes	Yes	Yes	No	Mod
Shah, 2010[47]	Ret	Yes	Yes	NA	Par	Yes	Par	Unc	Unc	Unc	NA	Yes	Yes	Yes	No	Mod
Sterner, 2012[37]	Ret	Par	Par	NA	NA	NA	Yes	Unc	Unc	Unc	No	Yes	Unc	Yes		High

Study	1	2.1a	2.1b	2.2	2.3	2.4	3	4.1	4.2	4.3	5.1	5.2	5.3	6	7	Overall Risk of Bias Rating
Tinetti, 2015[48]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unc	Unc	NA	Yes	Unc	Yes	No	Mod
Tzoulaki, 2009[64]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Low
Wang, 2014[63]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Unc	Unc	Unc	NA	Yes	Yes	Yes	Yes	Mod
Weir, 2011[74]	Ret	Yes	Par	NA	Yes	Yes	Yes	Unc	Unc	Unc	No	Yes	Yes	Yes	No	Mod
Weir, 2014[27]	Ret	Par	Par	NA	Yes	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	No	Mod
Zhang, 2008[38]	Ret	Yes	Yes	NA	Yes	Yes	Yes	Unc	Yes	Yes	NA	Yes	Yes	Yes	No	Low

Abbreviations: Mix = Mixed; Mod = Moderate; Par = Partial; Pro = Prospective; Ret = Retrospective; Unc = Unclear

APPENDIX E. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Reviewer	Comment	Response
Question 1. Are the objectives, scope, and methods for this review clearly described?		
1	Yes	Acknowledged
3	Yes	Acknowledged
4	Yes	Acknowledged
Question 2. Are there any published or unpublished studies that we may have overlooked?		
1	No	Acknowledged
3	No	Acknowledged
4	Yes - A recent meta-analysis examined comparative effectiveness of glucose-lowering agents with respect to CV mortality, as well as several other outcomes: all-cause mortality, serious adverse events, myocardial infarction, stroke, HbA1c level, treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and weight (Palmer et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes JAMA July 19, 2016). In that meta-analysis, there were no significant differences in associations between any drug class as monotherapy, dual therapy, or triple therapy with odds of cardiovascular or all-cause mortality (including metformin). The meta-analysis came out after the authors submitted their review, but I recommend that they include this in their discussion and specifically address why their findings were different from the findings of the meta-analysis with respect to CV and all-cause mortality outcomes.	Thank you for identifying this recent review by Palmer et al. We added a discussion of the review's findings and how they relate to our results.
Question 3. Is there any indication of bias in our synthesis of the evidence?		
1	No	Acknowledged
3	No	Acknowledged
4	No	Acknowledged

Reviewer	Comment	Response
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	Very useful ESP document, and as usual, very well done. Despite the fact that FDA released new guidance after this was commissioned, the review remains very relevant- and in fact may be even more important as this document states, it is likely that metformin will be used more often in "higher risk" populations. Just a couple of minor thoughts: 1) "Black Box" on page 6, line 56-57: The correct term would be "boxed warning". FDA does not recognize the Black Box terminology. Not a big deal if left in. 2) Limitations: You might add that most of the studies compared metformin to sulfonylureas and to a lesser extent, TZDs. Both of these drug classes have their issues- and so it might be reasonable to acknowledge that the comparisons do not include the newer anti-diabetic agents. 3) Likewise- research should make these same comparisons with newer agents. THANKS AGAIN to ESP for doing this review.	Thank you. 1) Thank you for this correction. The wording has been changed as recommended. 2) A statement about the majority of comparisons being to sulfonylureas and thiazolidinediones has been added to limitations. 3) A statement about the need for these comparisons has been added to future research.
3	The review was comprehensive, and appropriately noted that limitations of the observational data literature.	Thank you.
4	The authors reviewed the use of metformin among patients with relative contraindications or precautions to its use, compared the risk of lactic acidosis among users of metformin versus users of other glucose-lowering agents, and compared other outcomes association with the use of metformin versus other glucose-lowering agents. The review focuses on an important clinical question and is well executed and well written. Specific concerns:	Thank you.

Reviewer	Comment	Response
4 continued	KQ2: Limited data exist with respect to comparative benefits and harms of glucose-lowering agents. Authors have selected several outcomes for evaluation: glycemic control, lipid control, MACE, CV mortality, all-cause mortality, hypoglycemia, and weight gain. I recommend discussing rationale for the selection of these outcomes. What about other outcomes of importance to patients, such as microvascular complication rates, health-related quality of life? I understand there are limited data with respect to these outcomes, but this should not preclude them being included as a key question (which perhaps can't be answered at this time).	Outcomes selected for evaluation were prioritized with input from our stakeholders and Technical Expert Panel. We have added this detail to the Methods section.
	Inclusion and exclusion criteria: I agree with the authors' decision to include studies with the outcome of lactic acidosis (high lactate, low pH, and high anion gap). This definition of lactic acidosis should be stated in the text (currently as footnote to Table 2). This is an important point since there are some studies, which examined lactate levels alone; lactate levels are poor surrogates for lactic acidosis.	Acknowledged and thank you. We have added the definition of lactic acidosis to the introduction.
	Page 15, lines 40-52: Recommend including information on what percentage of studies included in Salpeter's review had stated contraindications to metformin use.	Because of limitations in the reporting of trial eligibility criteria, the Salpeter review concluded "There was insufficient information to estimate the number of participants studied with hypoxemic co-conditions such as renal insufficiency, cardiovascular diseases, liver diseases, or pulmonary disease." A statement to this effect has been added to the results section of KQ 1.

Reviewer	Comment	Response
4 continued	CV mortality and all-cause mortality: A recent meta-analysis examined comparative effectiveness of glucose-lowering agents with respect to CV mortality, as well as several other outcomes: all-cause mortality, serious adverse events, myocardial infarction, stroke, HbA1c level, treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and weight (Palmer et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes JAMA July 19, 2016). In that meta-analysis, there were no significant differences in associations between any drug class as monotherapy, dual therapy, or triple therapy with odds of cardiovascular or all-cause mortality (including metformin). The meta-analysis came out after the authors submitted their review, but I recommend that they include this in their discussion and specifically address why their findings were different from the findings of the meta-analysis with respect to CV and all-cause mortality outcomes.	Thank you for identifying this recent review by Palmer et al. We have added a discussion of the review's findings and how they relate to our results.
	Page 32, lines 45-50: Lack of evidence with respect to harm does not necessarily mean that the harm does not exist. Overall, the studies included in the systematic review had moderate risk of bias, with no existing randomized clinical trials designed to assess the safety of the use of metformin in patients with CKD with respect to lactic acidosis. Therefore, I recommend that some of the conclusions are restated to reflect ongoing uncertainty.	We incorporated findings from the Palmer review (as noted previously) and describe the uncertainty this introduces and the need for large pragmatic comparative effectiveness trials. We also describe how the change in FDA guidance is likely to make future observational studies more useful.
	Tables 9 and 10 are very clear and nicely represent the SOE summary. Strengths and limitations section is well balanced. Discussion of the recent FDA recommendations for new labeling changes for metformin is important and well executed.	Thank you.

APPENDIX F. STUDY CHARACTERISTICS TABLES

Table 1. KQ 1 Study Characteristics by Condition

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator[a]	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Chronic kidney disease (CKD)						
Becquemont, 2015[39] Prospective cohort France NR *KQ 1a only*	T2D: diagnosis, Rx CKD: eGFR category (based on whether metformin was adapted to eGFR)	Metformin use assessed prospectively Median dose 2000mg daily (IQR 1700-2550) Comparator: NA	LA: not specified Event rate	Mean 3 years No time-adjusted analysis	Age, eGFR	High
Ekstrom 2012[40] Retrospective cohort, population-based Sweden Government *KQ 1a and 1b*	T2D: diagnosis, Rx CKD: eGFR category (45-60, 30-45)	12 months use of metformin Median dose 1100-1900mg Comparator: 12 months use of other oral antidiabetic agent (dose NR)	LA or serious infection: defined by diagnostic code Event rate, hazard ratio	Mean 3.9 years No time-adjusted analysis	Age, sex, HbA1c, smoking, BMI, eGFR, comorbidities, medications	Mod
Eppenga, 2014[34] Retrospective cohort, population-based Great Britain Government, Industry *KQ 1a and 1b*	T2D: Rx CKD: eGFR category >60, 45-59, 30-44, <30	Current metformin use Stratified by yearly or daily dose Comparator: never use of metformin but current use of other NIAD	LA: defined by Read code or lactate >5 mmol/L Event rate, hazard ratio	Mean 4.3 years Time-adjusted analysis using intervals	Age, sex, BMI, CHF, medications	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator[a]	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Richy, 2014[33] Retrospective cohort, population-based Great Britain Industry *KQ 1a only*	T2D: diagnosis, Rx CKD: eGFR category >90, >60-90, >30-60, <30	Any metformin Rx Dose NR Comparator: NA	LA: defined by ICD-9, fatal LA if death within 14 days Incidence rate	Mean 4.35 years Time-adjusted analysis using person-years	None	High
Congestive heart failure (CHF)						
Andersson, 2010[25] Retrospective cohort, population-based Denmark Government *KQ 1a and 1b*	T2D: Rx CHF: First CHF hospitalization based on diagnostic codes	Metformin use based on Rx records Dose NR Comparator: multiple comparator arms	LA: defined by ICD-9 Event rate	Median 844 days Secondary time-adjusted analysis based on individual drug coverage	Year, age, sex, Charlson, diabetes complications, medications (but NA here)	Mod
Romero, 2013[35] Prospective cohort, community-based Spain Government *KQ 1a and 1b*	T2D: diagnosis, Rx, laboratory values CHF: Framingham criteria	Metformin use based on Rx records Dose NR Comparator: no metformin use (dose NR)	LA: NR Event rate	Median 56.9 months Time-adjusted analysis using person-years	Multivariate analysis (but NA here)	Low

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator[a]	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Liver disease						
Zhang, 2014[38] Retrospective cohort, population-based USA Government *KQ 1a and 1b*	T2D: diagnosis by clinician, Rx, self-report, or laboratory values Liver disease: biopsy-proven cirrhosis with additional clinical evaluation	Continuation or discontinuation of metformin after cirrhosis (defined as cessation of metformin within 3 months after diagnosis) Dose NR Comparator: discontinued metformin use	LA: categorical Mortality: 10-year survival; categorical	5-10 years	Age, sex, albumin, MELD score, AFP level, etiology of cirrhosis	Low
Older adults						
Ito, 2011[36] Pharmacovigilance Japan NR *KQ 1a only*	Rx, laboratory Exclusion: receiving unknown combination drugs, poor drug compliance, unclear initiation date of metformin, surgery	Metformin: 250mg, 500mg, 750mg, 1000mg (majority 750mg) Comparator: NA	LA: categorical; LA level above upper limit of reference values (2.28 mmol/L)	1 year after initiation of metformin	NR	High
Sterner, 2012[37] Retrospective Sweden Not funded *KQ 1a only*	Diagnosis: ICD code or NR eGFR using CKD-EPI formula Age categories in years: 60-69, 70-79, 80-89, ≥90 Median age 67 years	Metformin: dose NR No metformin: dose NR	Lactic acidosis measured by lactate levels >5mmol/L and serum pH <7.35	2 years	NR	High

[a] Comparator applies only to KQ 1b.
Abbreviations: AFP = alpha-fetoprotein; BMI = body mass index; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; ICD-9 = International Classification of Diseases-9; IQR = interquartile range; KQ = key question; LA = lactic acidosis; MACE = major adverse cardiac event; MELD = model for end-stage liver disease; Mod = moderate; NA = not applicable; NIAD = noninsulin antidiabetic drug; NR = not reported; Rx = prescription; T2D = type 2 diabetes

Table 2. KQ 2 Study Characteristics by Condition

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Chronic kidney disease (CKD)						
Aguilar, 2011[41] Retrospective cohort, outpatient-based USA Government	T2D: diagnosis, Rx CKD: eGFR based on most recent serum creatinine	Metformin Rx 90 days pre-index to 30 days post-index date Dose NR Comparator: no metformin Rx	All-cause mortality: time to death over 2 year follow-up after index visit Hazard ratio	2 years complete follow-up No time-adjusted analysis	Propensity score matching	Low
Ekstrom, 2012[40] Retrospective cohort, population-based Sweden Government	T2D: diagnosis, Rx CKD: eGFR category (45-60, 30-45)	12 months use of metformin Median dose 1100-1900mg Comparator: 12 months continuous use or use of other oral antidiabetic agent	All-cause mortality: by death registry MACE: diagnosis of included conditions Event rate, hazard ratio	Mean 3.9 years No time-adjusted analysis	Age, sex, HbA1c, smoking, BMI, eGFR, comorbidities, medications	Mod
Masoudi, 2005[42] Retrospective cohort, population-based USA Government	T2D: diagnosis by medical record, Rx CKD: serum creatinine >1.5 mg/dL	Metformin use after index hospitalization Dose NR Comp: no metformin or pioglitazone	All-cause mortality: time from index hospitalization to death or readmission for heart failure MACE Hazard ratio	Described as 1 year No time-adjusted analysis	Year, provider, hospital, baseline medical factors with $p<0.05$	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Morgan, 2014[43] Retrospective cohort, population-based UK Industry	T2D: incident diagnosis based on codes and/or Rx Hypoglycemia: NR CKD: clinical diagnosis or baseline serum creatinine >132 or 123 µmol/l (male, female)	New metformin Rx from medical records Dose NR Comparator: new sulfonylurea Rx	All-cause mortality: determined by date of death in medical record Hazard ratio	Metformin: 2.9 years Sulfonylurea: 3.1 years No time-adjusted analysis	All baseline factors with difference, p<0.2	Low
Roussel, 2010[44] Prospective cohort, outpatient-based Multiple countries Foundation, Industry	T2D: Rx CKD: eGFR based on baseline serum creatinine	Metformin use at baseline assessment Dose NR Comparator: no metformin use	All-cause mortality: per 2-year follow-up assessment Event rate, hazard ratio	Mean 20.8 and 20.9 months for metformin users, nonusers No time-adjusted analysis	All baseline factors with difference, p<0.2 and propensity score	Mod
Weir, 2011[74] Nested case-control Canada Government	T2D: ICD code and medical records CKD: impaired eGFR based on serum creatinine values	Metformin: given at all eGFR levels; dose NR Comparator: Insulin, Glyburide: Dose NR	Hypoglycemia: by ICD-9 codes Odds ratio	120-day interval immediately preceding index date to identify DM prescriptions	Hypoglycemic events, comorbidities, recent hospitalization, medications, internist visits	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Congestive heart failure (CHF)						
Aguilar, 2011[41] Retrospective cohort, outpatient-based USA Government	T2D: diagnosis and/or Rx for diabetes medication CHF: diagnosis by ICD-9 codes	Metformin Rx 90 days pre-index to 30 days post-index date Dose NR Comparator: no metformin	All-cause mortality: time to death over 2 years after index visit MACE Event rate, hazard ratio	2 years complete follow-up No time-adjusted analysis	Propensity score matching	Low
Andersson, 2010[25] Retrospective cohort, population-based Denmark Government	T2D: Rx CHF: first CHF hospitalization based on diagnostic codes	Metformin use based on Rx records Dose NR Comparator: multiple comparator arms	All-cause mortality: determined from death registry MACE Event rate, hazard ratio	Median 844 days Secondary time-adjusted analysis based on individual drug coverage	Year, age, sex, comorbidities, diabetes complications, medications	Mod
Eurich, 2005[26] Retrospective cohort, population-based Canada Government, Foundation	T2D: Rx for oral diabetes medication CHF: First CHF hospitalization by ICD-9 codes	Metformin alone or in combination Dose NR Comp: sulfonylurea alone	All-cause mortality: method of determination NR at 1 year and follow-up MACE Event rate, hazard ratio	Mean 2.5 years Time adjustment not needed per design	CDS, number visits, medications, propensity score analysis	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Evans, 2010[45] Retrospective cohort, population-based Scotland Foundation and private business	T2D: diagnosis or Rx medication 1994-2003 CHF: first hospitalization with ICD codes	Rx for metformin or metformin + sulfonylurea Dose NR Comparator: sulfonylurea alone	All-cause mortality: by death certificate records Odds ratio	Range: 1-9 years (mean NR) No time-adjusted analysis	All factors with univariate p<0.05	Mod
Inzucchi, 2005[46] Retrospective cohort USA Government	T2D: Clinician diagnosis, medication records CHF: first CHF hospitalization based on diagnostic codes	Metformin alone or Metformin and Thiazolidinedione Dose: NR Comparator: No insulin sensitizer	Mortality: all-cause mortality with impaired LVEF, 1 year mortality, readmission for heart failure, MI. MACE Hazard ratio	Reported at 1 year	Age, sex, race; cardiac and noncardiac comorbidities, clinical characteristics at admission (*eg*, SBP), sample frame for index hospitalization	Low
Masoudi, 2005[42] Retrospective cohort, population-based USA Government	T2D: diagnosis by medical record, Rx CHF: ICD-9 codes at index hospitalization	Metformin use after index hospitalization Dose NR Comparator: no metformin	All-cause mortality: Medicare data (time from index date to death) MACE Hazard ratio	Reported as 1 year, no mean No time-adjusted analysis	Year, provider, hospital, baseline medical factors with difference, p<0.05	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Romero, 2013[35] Prospective cohort, community-based Spain Government	T2D: diagnosis, Rx, laboratory values CHF: Framingham criteria	Metformin use based on Rx records Dose NR Comparator: no metformin use (dose NR)	All-cause mortality: determined by medical records MACE Event rate, hazard ratio	Median 56.9 months Time-adjusted analysis using person-years	Multivariate analysis	Low
Roussel, 2010[44] Prospective cohort, outpatient-based Multiple countries Foundation, Industry	T2D: Rx CHF: means of diagnosis unclear, likely clinical	Metformin use at baseline assessment Dose NR Comparator: no metformin use	All-cause mortality: per 2 year follow-up assessment Event rate, hazard ratio	Mean 20.8 and 20.9 months for metformin users, nonusers No time-adjusted analysis	All baseline factors with difference, p<0.2 and propensity score	Mod
Shah, 2010[47] Retrospective cohort, outpatient-based USA Government, Foundation	T2D: diagnosis by clinician, medical record, self-report CHF: diagnosis by LVEF ≤40%	Metformin use at first visit Dose NR Comparator: no metformin use	All-cause mortality: determined clinically (not including urgent heart transplant)	Follow-up at 1 year and 2 years No time-adjusted analysis	Age, sex, LVEF, renal function, BMI, diabetes duration, medications	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Tinetti, 2015[48] Retrospective cohort, population-based USA Government	T2D: diagnosis by medical records CHF: diagnosis by ICD-9 codes or claims data	Metformin Rx Dose NR Comparator: no metformin	All-cause mortality: determined by Medicare vital status file Hazard ratio	Median 24 months Time adjustment analysis	Age, sex, race, income, smoking, medication, insurance, physical and mental function	Mod
Weir, 2014[27] Retrospective cohort, population-based USA NR	T2D: Rx for oral diabetes medication Hypoglycemia: NR CHF: First CHF hospitalization by ICD-9 codes	Exposure to metformin based on pharmacy claims within 90 days of index event Mean dose NR Comparator: no exposure to metformin	All-cause mortality: U.S. national death index files Event rate, odds ratio	Median 1.4 years Partial time adjustment	Propensity score analysis	Mod
Liver disease						
Ampuero, 2012[49] Retrospective cohort Spain Government	T2D: by clinician Liver biopsy-proven cirrhosis with additional clinical evaluation	Metformin treatment Dose: 0, 20, 50, 100 and 200 mmol/L Comparator: no metformin	All-cause mortality: overall survival rate trend; categorical	Metformin: 39.6 ± 28.3 months Comparator: 45.5 ± 26.5 months	Yes	Mod

Study Design Country Funding	Condition Definitions	Metformin Use Dose Comparator	Outcome Definition Reporting	Exposure Duration	Statistical Adjustment	ROB
Nkontchou, 2011[50] Prospective cohort France NR	T2D: Rx, laboratory values Liver disease: 1. Biopsy-proven cirrhosis with additional clinical evaluation 2. Presence of anti-HCV antibodies 3. Presence of serum HCV RNA	Metformin treatment Dose NR Comparator: no metformin	All-cause mortality: liver-related death; categorical	Median follow-up of 5.7 years (range 3.8-9.5)	Age, platelet count, BMI, alcohol abuse, diabetes duration	High
Zhang, 2014[38] Retrospective cohort, population-based USA Government, Foundation	T2D: by clinician, Rx, self-report, or laboratory values Liver biopsy-proven cirrhosis with additional clinical evaluation)	Continuation or discontinuation of metformin after cirrhosis (defined as cessation of metformin within 3 months after diagnosis) Dose NR Comparator: discontinued metformin use	LA: categorical All-cause mortality: 10-year survival; categorical	5-10 years	Age, sex, albumin, MELD score, AFP level, etiology of cirrhosis	Low

Abbreviations: AFP = alpha-fetoprotein; BMI = body mass index; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LA = lactic acidosis; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac event; MELD = model for end-stage liver disease; NA = not applicable; NR = not reported; RNA = ribonucleic acid; Rx = prescription; T2D = type 2 diabetes

APPENDIX G. RESULTS FOR OLDER ADULTS BY STUDY DESIGN

KQ 2 Older Adults—Study Characteristics of RCTs

Study Country Funding	T2D Condition Age in Years (N)	Other Precautions Excluded	Metformin Dose Comparator Dose	Outcome Definition Reporting	Exposure Duration	ROB
Blonde, 2002[51] USA Industry	Diagnosis by clinician, laboratory value (A1c remains ≥7.4% with diet, exercise, sulfonylurea) ≥65 subgroup (134)	Liver disease, renal disease, heart failure	Metformin: 500-2000mg Glibenclamide: 2.5mg or 5.0mg	A1c: laboratory value Hypoglycemia: blood sugar <60 mg/dl	16 weeks	Low
Cryer, 2005[52] USA Industry	Diagnosis by clinician ("suboptimal control" on diet or sulfonylurea) ≥65	Abnormal renal or liver function	Metformin: 500-2500mg Usual care: any nonmetformin medication	LA: medical record MACE: medical record Mortality: medical record	1 year	Mod
Garber, 2002[53] USA Industry	Diagnosis by clinician, laboratory value (A1c remains >7% with diet, exercise) ≥65 subgroup (159)	Abnormal renal, liver function	Metformin: 500-2000mg Glibenclamide: 2.5mg or 5.0 mg	A1c: laboratory value Hypoglycemia: glucose <50 mg/dl or <100 if on metformin	20 weeks	Low
Gregorio,1999[54] Italy NR	Diagnosis by clinician (A1c remains ≥9% with sulfonylurea) >70 (174)	Abnormal liver function, respiratory or heart failure, Creatinine >1 or CrCl<100 ml/min/m2	Metformin: NR Sulfonylurea: increased dose (exact dose NR)	Weight: clinical scale A1c, LDL, HDL, total cholesterol: laboratory values	18 months	High

Study Country Funding	T2D Condition Age in Years (N)	Other Precautions Excluded	Metformin Dose Comparator Dose	Outcome Definition Reporting	Exposure Duration	ROB
Hanefeld, 2004[55] Europe, Canada Foundation, Industry	Diagnosis by clinician, laboratory value (A1c remains 7.55-11% on sulfonylurea) >65 subgroup (212)	History of MI, TIA, or stroke in prior 6 months; symptomatic CHF	Metformin + sulfonylurea: 500-2500mg/dl Pioglitazone + sulfonylurea: NR	Weight: clinical scale A1c, LDL, hypoglycemia: laboratory value	52 weeks	Low
Marre, 2002[56] Europe Industry	Diagnosis by laboratory value (FPG ≥126 on metformin, diet & exercise) ≥65 subgroup (130)	Renal disease, hepatic dysfunction, severe respiratory disease, acute heart failure, MI	Metformin: 500-2000mg Glibenclamide: 2.5mg or 5.0 mg	A1c: laboratory value Hypoglycemia: glucose <50 mg/dl or <100 if on metformin	16 weeks	Low
Schweizer, 2009[57] Americas, Asia, Europe Industry	Diagnosis by clinician plus laboratory value (A1c 7%-9% off hypoglycemic) ≥65 (335)	CHF requiring medication; liver disease, renal disease	Metformin: 500-1500mg Vildagliptin: 100mg	A1c: laboratory value Hypoglycemia: glucose <60 mg/dL	24 weeks	Low

Abbreviations: A1c = glycated hemoglobin; CHF = congestive heart failure; FPG = fasting plasma glucose; HDL = high-density lipoprotein; LA = lactic acidosis; LDL = low-density lipoprotein; MACE = major adverse cardiac event; MI = myocardial infarction; NR = not reported; Rx = prescription; T2D = type 2 diabetes; TIA = transient ischemic attack

KQ 2 Older Adults—Study Characteristics of Observational Studies

Study Design Country Funding	T2D Condition Exclusions Age in Years (N)	Metformin Dose Comparator Dose	Outcome	Exposure Duration	Statistical Adjustment	ROB
Bodmer, 2008[59] Nested case control UK Industry	Oral Rx Exclusions: T1D ≥70 (50,048)	Metformin: NR Sulfonylurea: NR	LA, hypoglycemia leading to emergency department visit or death	NR	Use of sulfonylureas, other oral antidiabetic medications, insulin, BMI, smoking, comorbidities, other medications	Low
Bannister, 2014[58] Retrospective cohort UK Industry	Diagnosis by clinician Exclusions: None >70 (90,463)	Metformin: NR Sulfonylurea: NR	All-cause mortality	Mean 2.8 years	Age, comorbidity index, sex, smoking status, medications	Mod
Huizinga, 2010[60] Retrospective cohort USA Government	Oral Rx Exclusions: CHF, CKD, liver disease 65-75, >75 years (2096-2484)	Metformin: NR Sulfonylurea: NR	A1c, BMI	1 year	Age, sex, race, BMI, medications, outpatient visits, hospitalizations, psychiatric comorbidities	Mod
Leung, 2010[61] Prospective cohort Canada NR	Diagnosis by clinician Exclusions: NR 67-91 (20)	Metformin: NR No metformin	Vitamin B12	3 months	None	High

Study Design Country Funding	T2D Condition Exclusions Age in Years (N)	Metformin Dose Comparator Dose	Outcome	Exposure Duration	Statistical Adjustment	ROB
Roumie, 2012[62] Retrospective cohort USA Government	Diagnosis by ICD code, Rx, laboratory values Exclusions: None ≥65 (253,690)	Metformin: NR Sulfonylurea: NR	Acute MI, stroke or death Acute MI or stroke	Metformin: median 0.78 years Sulfonylurea: median 0.61 years	Age, sex, race, HbA1c/other clinical variables, health care utilization, smoking, medications, comorbidities	Low
Tzoulaki, 2009[64] Retrospective cohort UK Not funded	T2DM: diagnosis by ICD code Exclusion: patients not taking oral antidiabetic drugs, or patients taking insulin >65 (91,521)	Metformin: NR Sulfonylurea: NR Thiazolidinedione: NR	MACE; mortality	Metformin: median: 5.59 years Sulfonylurea: median 8.5 years (first generation), 6.6 years (second generation) Thiazolidinedione: median 6.7 years	Sex, BMI, smoking SBP, other laboratory variables (*eg,* HbA1c), duration of diabetes, stratified by year and age quartiles at treatment; comorbidities, other medications, complications from diabetes	Low
Wang, 2014[63] USA Government Retrospective cohort	Diagnosis by ICD code for T2D and oral Rx Exclusions: CKD, liver disease 65-90 (2415)	Metformin: NR Sulfonylurea: NR	All-cause mortality	≥24 weeks	Age, race/ethnicity, diabetes duration, comorbidity score, statin use, smoking, BMI, LDL, A1c	Mod

Abbreviations: BMI = body mass index; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; ICD-9 = International Classification of Diseases-9; LA = lactic acidosis; LDL = low-density lipoprotein; MACE = major adverse cardiac event; Mod = moderate; NR = not reported; Rx = prescription; SBP = systolic blood pressure; T1D- type 1 diabetes; T2D = type 2 diabetes

ERRATA AND CORRECTIONS

Page 1, paragraph titled "Data Sources and Searches"

***Formerly*:** "We searched MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (KQ 2 only), Embase, and the International Pharmaceutical Abstracts."

***Now*:** "We searched MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (KQ 2 only), Embase, the International Pharmaceutical Abstracts, and ClinicalTrials.gov."

Page 9, paragraph titled "Search Strategy"

***Added*:** "We also searched ClinicalTrials.gov for relevant completed and ongoing studies."

Page 12, final paragraph

***Changed*:** Guideline for Knapp-Hartung correction from n<10 to n<20. Guideline was applied to all analyses; no results changed.

Page 14, final paragraph

***Added*:** "Of note, we identified no ongoing studies meeting our inclusion criteria in ClinicalTrials.gov."

Page 23, final paragraph

***Formerly*:** "The other study did find a significantly lower likelihood of congestive heart failure readmission among metformin users versus nonusers (n = 5859, HR 0.91, 95% CI 0.84-0.99)."

***Now*:** "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)."

Page 24, paragraph titled "All-cause Mortality"

***Correction*:** "[…] 13,390 patients with CHF" to "[…] 13, 930 patients with CHF."

Page 26, figure 4

Updated forest plot to reflect number correction from Masoudi 2005 (see page 24 correction, above). MA results did not change when data was corrected.