QUERI

Metformin Use in Patients with Contraindications or Precautions

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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.

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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