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.