Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure

Systematic Review of Observational Studies Involving 34,000 Patients

Dean T. Eurich, PhD; Daniala L. Weir, BSc; Sumit R. Majumdar, MD, MPH; Ross T. Tsuyuki, PharmD, MSc; Jeffrey A. Johnson, PhD; Lisa Tjosvold, MLIS; Saskia E. Vanderloo, MSc; Finlay A. McAlister, MD, MSc

Background—There is an ongoing controversy regarding the safety and effectiveness of metformin in the setting of heart failure (HF). Therefore, we undertook a systematic review of the trial and nontrial evidence for metformin in patients with diabetes mellitus and HF.

Methods and Results—We conducted a comprehensive search for controlled studies, evaluating the association between metformin and morbidity and mortality in people with diabetes mellitus and HF. Two reviewers independently identified citations, extracted data, and evaluated quality. Risk estimates were abstracted and pooled where appropriate. As measures of overall safety, we examined all-cause mortality and all-cause hospitalizations. Nine cohort studies were included; no randomized controlled trials were identified. Most (5 of 9) studies were published in 2010 and were of good quality. Metformin was associated with reduced mortality compared with controls (mostly sulfonylurea therapy): 23% versus 37% (pooled adjusted risk estimates: 0.80; 0.74–0.87; P<0.001). No increased risk was observed for metformin in those with reduced left ventricular ejection fraction (mortality pooled adjusted risk estimate: 0.91; 0.72–1.14; P=0%; P=0.34), nor in those with HF and chronic kidney disease (pooled adjusted risk estimate: 0.81; 0.64–1.02; P=0.08). Metformin was associated with a small reduction in all-cause hospitalizations (pooled adjusted risk estimate: 0.93; 0.89–0.98; P=0%; P=0.01). Metformin was not associated with increased risk of lactic acidosis.

Conclusions—The totality of evidence indicates that metformin is at least as safe as other glucose-lowering treatments in patients with diabetes mellitus and HF and even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease. Until trial data become available, metformin should be considered the treatment of choice for patients with diabetes mellitus and HF. (Circ Heart Fail. 2013;6:395-402.)

Key Words: diabetes mellitus ■ heart failure ■ metformin ■ mortality

Heart failure (HF) is a serious and common comorbidity in patients with type 2 diabetes mellitus. It is the fastest growing of all the cardiovascular diagnoses, and patients with diabetes mellitus are at high risk, with incidence rates 2 to 5 times greater than those in the general population. Morbidity and mortality rates remain particularly high (20%–30% within 1 year) and are substantially higher in patients with diabetes mellitus and HF compared with either condition alone.9,10

Clinical Perspective on p 402

There is increasing attention to the potential role of hyperglycemia, and its management, in HF. Although the risk of HF substantially increases with elevations in A1c, the impact of hyperglycemia in those with diabetes mellitus and established HF is less clear. There is still a large degree of uncertainty in the best management approach for glycemic control in those with comorbid diabetes mellitus and HF. This is likely due to the fact that patients with HF have been generally excluded from the trials of glucose lowering therapies; thus, reliance on clinical experience and observational evidence is required to judge the safety and effectiveness of antihyperglycemia drugs in patients with concomitant HF.

Historically, metformin had been considered absolutely contraindicated in patients with HF attributable to concerns about lactic acidosis. However, both the US Food and Drug Administration (2006) and Health Canada (2010) have removed the absolute HF contraindication from metformin (although strong warnings persist) in response to observational studies and clinical experience, suggesting that the risk of metformin-associated lactic acidosis is minimal and similar to

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From the Department of Public Health Sciences, School of Public Health (D.T.E., D.L.W., R.T.T., J.A.J.), Department of Medicine, Faculty of Medicine and Dentistry (S.R.M., R.T.T., F.A.M.), ACHORD, Li Ka Shing Center, University of Alberta, Edmonton, Alberta, Canada (L.T.); and Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada (S.E.V.).

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Correspondence to Dean T. Eurich, PhD, 2–040 Li Ka Shing Center for Health Research Innovation, University of Alberta, Edmonton, Alberta, Canada, T6G 2E1. E-mail deurich@ualberta.ca

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that of other diabetes mellitus drugs.\textsuperscript{11,12} Despite a continued warning for its use in patients with HF, some clinical practice guidelines recommend metformin as first-line therapy in patients with diabetes mellitus and HF, including Canadian and American Diabetes Association Clinical Practice guidelines and the recent European Society of Cardiology guidelines for the treatment of HF.\textsuperscript{13–15} To our knowledge, it has been at least 5 years since the data with respect to metformin has been systematically reviewed. Therefore, we undertook a systematic review and meta-analysis of the use of metformin in patients with diabetes mellitus and HF. We examined randomized and nonrandomized data, and considered comparative safety and effectiveness with other antidiabetic agents. Furthermore, we examined 2 important subpopulations: those with reduced left ventricular ejection fraction (LVEF) and those with concomitant chronic kidney disease.

**Methods**

**Objectives**

We evaluated the relationship between metformin treatment and morbidity and mortality in people with HF and diabetes mellitus. Our main outcome was all-cause mortality and secondary outcomes were all-cause hospitalization and HF-specific morbidity and mortality. In addition, because chronic kidney disease is a common comorbidity in patients with diabetes mellitus and HF,\textsuperscript{16} we further explored the potential role of metformin in patients with diabetes mellitus and HF with compromised kidney function. Although it was not registered, the protocol for this study was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\textsuperscript{17}

**Search Strategy**

We used a comprehensive search strategy, based on earlier work,\textsuperscript{7} until April 2012 of various electronic databases (HealthStar [1966–2011], EMBASE [1980–2012], AMED [Allied and Complementary Medicine Database] [1985–2011], CINAHL [Cumulative Index to Nursing and Allied Health Literature] [1982–2012], IPA [International Pharmaceutical Abstracts] [1970–2012], Medline [1996–2012], Web of Science [1900–2012], and Cochrane Central Registry of Controlled Trials [1991–2012]), manually searched reference lists, and contacted experts to identify all controlled studies of metformin in patients with diabetes mellitus and HF.\textsuperscript{7} The searches were not restricted by study design but were restricted to English language.

**Inclusion Criteria and Data Abstraction**

Two reviewers (D.L.W. and S.E.V.) independently identified citations and included them if they described original research, included subjects with both diabetes mellitus and HF, evaluated the effect of metformin on hospital admission (all-cause or HF-specific) or mortality, and included a contemporaneous control group for comparison. Any discrepancies were resolved by consensus after review by a third investigator (D.T.E.). All data were extracted independently by 2 reviewers (D.L.W. and D.T.E.) and independently assessed for methodological quality using the validated Downs and Black checklist (D.T.E. and D.L.W.). A score of ≥12 was considered as acceptable quality as we, and others, have done previously.\textsuperscript{7,10,19}

**Statistical Analysis**

To summarize the effects of metformin on mortality or hospitalizations, we abstracted the crude data and the adjusted risk estimates and 95% confidence intervals from each study. For studies with insufficient information, we contacted the primary study authors to acquire and verify data where possible.\textsuperscript{20} Because we expected heterogeneity between the studies, we pooled adjusted risk estimates across studies using random effects models with inverse variance weighting as recommended in the Cochrane handbook;\textsuperscript{21} heterogeneity was assessed using the $F$ statistic, with an $F$ statistic >50% being considered as moderate heterogeneity. There was not an a priori degree of heterogeneity that precluded pooling. Only 2 studies evaluated metformin as a monotherapy;\textsuperscript{12,22} the remainder evaluated metformin as monotherapy or metformin in combination with other oral antidiabetic agents.\textsuperscript{11,20,21,22} For studies evaluating end points at multiple time points, short-term mortality (1 or 2 years) was used when possible for the pooling of the results because the majority of studies evaluated short-term outcomes, although additional sensitivity analyses were also conducted to evaluate the effect of metformin on longer-term outcomes (>2 years).

In addition to the overall effect of metformin, we a priori evaluated the safety and effectiveness of metformin in 2 high-risk subgroups: those patients with diabetes mellitus and reduced LVEF and in those with chronic kidney disease, where possible. We used the definitions that were used by the primary authors to categorize patients according to LVEF and renal function. Additional analyses were conducted where studies with comparator groups, that included thiazolidinediones, were removed because they are associated with poor outcomes in HF.\textsuperscript{20,24,26} Two separate subgroup analyses were also conducted according to insulin use. First, studies with comparator groups that included insulin were removed;\textsuperscript{11,20,23,24,26} because insulin may be viewed as a marker of an advanced disease state. Second, we specifically restricted our analyses to only those studies that included insulin in the metformin or control groups;\textsuperscript{1,20,23–24,26,27} to evaluate effects of metformin in those with presumably more severe diabetes mellitus. In addition, studies evaluating metformin monotherapy groups were analyzed separately from studies specifically evaluating metformin combination therapy groups.\textsuperscript{1,23–25} Finally, we specifically evaluated the rates of lactic acidosis reported among patients using metformin compared with those who do not use metformin in the studies. All analyses were conducted using Cochrane Review Manager 5.0.\textsuperscript{21}

**Results**

Among 12 994 citations, 9 observational studies were included in the review (Figure 1). No randomized controlled trials of the use of metformin in patients with diabetes mellitus and HF were identified, although 1 trial protocol for an abandoned (attributable to futility) trial was found (Patients With Heart Failure and Type-2 Diabetes Treated With Placebo or Metformin Study [PHANTOM]) and 2 ongoing pilot trials were identified. Interobserver agreement for study inclusion was high with $k=0.90$.

Among the 9 studies, 34 504 patients with diabetes mellitus and HF were included, with 6624 patients (19%) using metformin. The majority of studies evaluated the use of metformin in combination with other oral agents or insulin (Table).\textsuperscript{11,20,22–26} Two studies specifically evaluated the use of metformin as monotherapy.\textsuperscript{12,27} In 3 of the studies, the active comparator was sulfonylurea monotherapy (n=4605); 1 study used a comparison group that received no active diabetes mellitus medications (diabetes mellitus was managed with diet and lifestyle, n=1306); 2 studies used a comparison group consisting of sulfonylureas, nonsulfonylurea secretagogues, $\alpha$-glucosidase inhibitors, and insulin (n=14 253); and the remaining 3 studies had comparator groups composed of all available therapies, including thiazolidinediones and insulin (n=7716). Overall, sulfonylurea therapy was the most common agent used in the comparator group in the 9 studies. No study included newer incretin-based therapies in the comparator group. Overall study quality was acceptable with methodological scores ranging from 14 (44%) to 19 (59%); median score was 17 (53%) (see the online-only Data Supplement).
 Patients included in the cohorts were selected from a wide range of settings, including clinical registries, hospital discharges, and community and primary care settings. There were no sex limitations in any of the studies; the average age of cohort patients ranged from 56 to 78 years of age, and patients with preserved or reduced LVEF were included. All of the studies included demographics, comorbidities, and other related drug therapies. The majority of studies (7 of 9) also included additional laboratory or clinical information related to diabetes mellitus, including blood glucose levels, body mass index, and estimated renal function. Four studies also contained additional HF-specific information (ie, New York Heart Association Functional Class or LVEF). Two studies were typical administrative analyses with no additional laboratory or clinical information.

Mortality

All studies evaluated the effect of metformin on all-cause mortality; 3 evaluated the effect of metformin on mortality at multiple time points. Five studies evaluated 1-year mortality, 3 evaluated 2-year mortality, and 4 studies evaluated longer-term mortality that is >4 years of follow-up (Table).

Overall, 1497 of 6624 metformin users (23%) died compared with 10221 of 27880 (37%) in the control group (pooled unadjusted risk estimate: 0.69; 0.61–0.79; F=87%; P<0.001; Figure 2). All studies suggested reduced risk of all-cause mortality with metformin-based regimens, although 2 did not reach statistical significance (Figure 3).

After pooling of the adjusted risk estimates, metformin-based regimens were associated with a statistically significant 20% relative reduction in all-cause mortality compared with other treatments (pooled adjusted risk estimate: 0.80; 0.74–0.87; F=15%; P<0.001; Figure 3). Removal of the 2 administrative database studies (that could not adjust for additional clinical factors, such as HbA1C and body mass index) from the pooled analysis did not materially alter the results (22% versus 34% mortality; pooled adjusted risk estimate 0.79; 0.71–0.87; F=24%; P<0.001). Further subgroup analysis in the 7 studies that evaluated only 1- and 2-year mortality resulted in similar results (20% versus 33%; pooled adjusted risk estimate: 0.80; 0.73–0.88; F=12%; P<0.001), as did analyses among the 4 studies that evaluated the effect of metformin on longer-term (>4 years) mortality (38% versus 59%; pooled risk estimate: 0.74; 0.64–0.86; F=39%; P<0.001). Only 1 study evaluated cardiovascular-related mortality with results similar to that observed for all-cause mortality (10% versus 15%; adjusted risk estimate: 0.80; 0.61–1.04).

In additional subgroup analyses for all-cause mortality, removal of studies that included thiazolidinediones in the
Andersson et al,27 Roussel et al,26 2010 Metformin (n=1220) vs no-insulin
Aguilar et al,20 2011 Metformin monotherapy and

were pooled11,20,22–24,26,27 (our proxy for more severe diabetes
including insulin in either the metformin or the control group
P
<0.001). Moreover, when adjusted risk estimates from studies
adjusted risk estimates from studies
P
<0.001). Metformin was also associated
with advanced systolic HF (defined as having a LVEF <40%,
advanced systolic HF (defined as having a LVEF <40%,
interaction between metformin treatment and left ventricular
systolic function on mortality). Similarly, in a study of patients
with advanced systolic HF (defined as having a LVEF <40%,
87% of the cohort were in New York Heart Association classes III or IV), metformin-based regimens were associated
with a nonsignificant trend for improved survival compared
with nonmetformin treatment (adjusted risk estimate: 0.83; 95% CI
32% versus 45%; pooled adjusted risk estimate: 0.6; F=0%; P<0.001) and in studies where metformin was specifically evaluated as combination therapy11,23–25 (28% versus 37%; pooled adjusted risk estimate: 0.86; 0.78–0.96; F=0%; P<0.001).

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**Table. Results of Studies Assessing Metformin in the Treatment of Diabetes Mellitus in Patients With Heart Failure**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent vs Comparator</th>
<th>Outcome</th>
<th>Crude Events (Treatment/Control)</th>
<th>Unadjusted Risk Estimate (95% CI)</th>
<th>Adjusted Risk Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inzucchi et al23 2005</td>
<td>Metformin monotherapy and combotherapy (n=406) vs no-insulin sensitizer* (n=2184)†</td>
<td>1-year A/C mortality</td>
<td>93/768</td>
<td>0.55 (0.43–0.70)</td>
<td>0.92 (0.72–1.18)</td>
</tr>
<tr>
<td>Masoudi et al11 2005</td>
<td>Metformin monotherapy and combotherapy (n=1861) vs no-insulin sensitizer* (n=12,069)</td>
<td>1-year A/C mortality</td>
<td>460/4345</td>
<td>0.58 (0.52–0.65)</td>
<td>0.86 (0.78–0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year A/C hospitalization</td>
<td>1265/8702</td>
<td>0.82 (0.74–0.91)</td>
<td>0.94 (0.89–1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year HF hospitalization</td>
<td>1091/7821</td>
<td>0.52 (0.57–0.48)</td>
<td>0.92 (0.86–0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year A/C mortality renal impairment subgroup</td>
<td>N/A</td>
<td>N/A</td>
<td>0.89 (0.74–1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year A/C mortality advanced HF subgroup</td>
<td>N/A</td>
<td>N/A</td>
<td>0.91 (0.72–1.14)</td>
</tr>
<tr>
<td>Shah et al24 2010</td>
<td>Metformin monotherapy and combotherapy (n=99) vs no metformin (n=302)†</td>
<td>2-year A/C mortality</td>
<td>22/112</td>
<td>0.51 (0.30–0.87)</td>
<td>0.79 (0.36–1.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year A/C mortality</td>
<td>9/72</td>
<td>0.37 (0.18–0.76)</td>
<td>0.63 (0.21–1.89)</td>
</tr>
<tr>
<td>Evans et al25 2010</td>
<td>Metformin monotherapy and combotherapy (n=205) vs SU monotherapy (n=217)</td>
<td>1-year A/C mortality</td>
<td>137/183</td>
<td>0.56 (0.38–0.84)</td>
<td>0.6 (0.37–0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term A/C mortality</td>
<td>N/A</td>
<td>0.53 (0.33–0.67)</td>
<td>0.67 (0.51–0.88)</td>
</tr>
<tr>
<td>Eurich et al26 2005</td>
<td>Metformin monotherapy (n=208) vs SU monotherapy (n=773)</td>
<td>1-year A/C mortality</td>
<td>29/200</td>
<td>0.46 (0.30–0.71)</td>
<td>0.66 (0.44–0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year A/C hospitalization</td>
<td>102/406</td>
<td>0.87 (0.64–1.18)</td>
<td>0.84 (0.67–1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term A/C mortality</td>
<td>69/404</td>
<td>0.4 (0.29–0.56)</td>
<td>0.7 (0.54–0.91)</td>
</tr>
<tr>
<td>Roussel et al28 2010</td>
<td>Metformin (n=1220) vs no-insulin sensitizer,* TZDs (n=2790)</td>
<td>2-year A/C mortality</td>
<td>221/488</td>
<td>1.04 (0.88–1.24)</td>
<td>0.69 (0.54–0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-year CV mortality</td>
<td>116/419</td>
<td>0.59 (0.48–0.74)</td>
<td>0.8 (0.61–1.04)</td>
</tr>
<tr>
<td>MacDonald et al29 2010</td>
<td>Metformin monotherapy (n=376) vs no antidiabetic agent (n=1306)</td>
<td>Long-term A/C mortality</td>
<td>155/733</td>
<td>0.54 (0.42–0.68)</td>
<td>0.65 (0.48–0.87)</td>
</tr>
<tr>
<td>Aguilar et al30 2011</td>
<td>Metformin monotherapy and combotherapy (n=1561) vs no metformin (n=4624)†</td>
<td>2-year A/C mortality</td>
<td>246/1117</td>
<td>0.58 (0.57–0.67)</td>
<td>0.76 (0.63–0.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-year A/C hospitalization</td>
<td>638/2215</td>
<td>0.75 (0.67–0.85)</td>
<td>0.94 (0.83–1.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-year HF hospitalization</td>
<td>171/180</td>
<td>0.66 (0.55–0.79)</td>
<td>0.93 (0.74–1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-year A/C mortality renal impairment subgroup</td>
<td>N/A</td>
<td>N/A</td>
<td>0.7 (0.52–0.94)</td>
</tr>
<tr>
<td>Andersson et al31 2010</td>
<td>Metformin monotherapy and combotherapy (n=688) vs SU monotherapy (n=3615)</td>
<td>Long-term A/C mortality</td>
<td>239/2344</td>
<td>0.29 (0.34–0.24)</td>
<td>0.85 (0.75–0.98)</td>
</tr>
</tbody>
</table>

A/C indicates all-cause; CI, confidence interval; CV, cardiovascular; HF, heart failure; N/A, not available; SU monotherapy, sulfonylurea monotherapy; and TZD, thiazolidinedione.
*No-insulin sensitizer includes SU, non-SU secretagogues, α-glucosidase inhibitors, and insulin.
†No metformin can include any other oral antidiabetic agent (SU, non-SU secretagogues, α-glucosidase inhibitors, TZDs) ± insulin.

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Reduced LVEF

Only 2 studies specifically evaluated metformin in patients with reduced LVEF. In a subgroup of patients with LVEF of <30%, Masoudi et al31 did not observe any increased mortality associated with metformin compared with nonmetformin-based therapies (adjusted risk estimate: 0.91; 0.72–1.14; P=0.8 for interaction between metformin treatment and left ventricular systolic function on mortality). Similarly, in a study of patients with advanced systolic HF (defined as having a LVEF <40%, 87% of the cohort were in New York Heart Association classes III or IV), metformin-based regimens were associated with a nonsignificant trend for improved survival compared with nonmetformin treatment (adjusted risk estimate: 0.63; 0.21–1.89; P=0.40).24 Using the primary author-defined groups for reduced LVEF, pooled analysis indicates that metformin was not associated with benefit or increased risk in patients with reduced LVEF and diabetes mellitus (pooled adjusted risk estimate: 0.90; 0.72–1.12; P=0.34; F=0%).
With the exception of the 2 administrative database studies,12,27 all studies adjusted for the potential confounding effects of renal impairment (eg, estimated glomerular filtration rate, stage of kidney disease, or creatinine levels). Among the studies, metformin-based regimens were used in patients with all levels of renal impairment, although the majority of patients had normal renal function. However, only 2 studies undertook specific subgroup analyses in patients with renal impairment. In a retrospective cohort study of Medicare beneficiaries, Masoudi et al11 evaluated the use of metformin in subgroups of patients with serum creatinine <133 μmol/L and ≥133 μmol/L. No difference in all-cause mortality was observed for those below (adjusted risk estimate: 0.89; 0.74–1.06) and above this threshold (0.86; 0.75–0.98; P=0.3 for interaction). Similar results were also observed for all-cause hospitalization; however, a trend toward a reduction in HF-specific hospitalization was observed for metformin use in those with serum creatinine <133 μmol/L (P=0.07 for interaction). In a second study of patients treated in ambulatory clinics at Veteran Affairs medical centers, Aguilar et al20 observed a trend toward improvement in those with estimated glomerular filtration rate <60 mL/min treated with metformin (adjusted risk estimate: 0.70; 0.52–0.94) compared with those with estimated glomerular filtration rate >60 mL/min (adjusted risk estimate: 1.00; 0.75–1.35; P=0.09 for interaction). Using the primary author-defined groups for impaired renal function, pooled analysis indicates that metformin is not associated with any increased risk of mortality. Indeed, the reduction in all-cause mortality in the subgroup with renal impairment is nearly identical to the overall effect of metformin, although it did not reach statistical significance (pooled adjusted risk estimate: 0.81; 0.64–1.02; P=0.08).

Hospitalization

Only 3 studies11,12,20 evaluated the effect of metformin on all-cause hospitalization and 211,20 evaluated HF-specific hospitalizations. Treatment with metformin-based regimens was associated with a statistically significant relative reduction in all-cause hospitalization compared with other treatments (35% versus 64%; pooled adjusted risk estimate: 0.93; 0.89–0.98; P=0.01). Nearly identical results were also observed in the 2 studies evaluating HF-specific hospital admission (34% versus 51%; pooled adjusted risk estimate: 0.92; 0.86–0.98; P=0.01). Individually, no study observed statistically significant reductions in all-cause hospitalization, and only 1 study observed reductions in HF-specific hospitalizations.

Lactic Acidosis

The occurrence of lactic acidosis was low in the 3 studies that specifically evaluated this end point, and no difference between metformin-based regimens and other treatments were observed. Andersson et al27 and Eurich et al12 did not observe
any cases of lactic or metabolic acidosis, and Masoudi et al\(^{11}\) observed similar rates of readmission for metabolic acidosis for patients receiving metformin (2.3%) and other treatments (2.6%; \(P=0.40\)).

**Discussion**

Diabetes mellitus and HF places a tremendous burden on patients and the healthcare system. Indeed, our systematic review indicates that 27% of patients with both conditions died within 2 years and 37% died over longer-term follow-up with rates of hospitalization 2-fold higher. Patients included in the studies were from diverse settings with a wide range of disease severity; however, all the 9 identified studies were observational because of a paucity of randomized controlled trials evaluating metformin versus other glucose lowering agents in these patients. Overall, metformin was associated with improved clinical outcomes compared with other agents in the setting of diabetes mellitus and HF. Our review provides the best available evidence to suggest that metformin is at least as safe as other glucose lowering therapies in patients with diabetes mellitus and HF.

Although concerns have been raised about the safety and effectiveness of metformin in patients with HF,\(^{24}\) it is used commonly in clinical practice. Overall, metformin-based regimens accounted for 20% of all therapies used for glycemic control in patients with HF in these studies. From a safety perspective, our data support the recent actions by regulatory bodies in the United States and Canada who have removed the black box contraindication for the use of the metformin in patients with diabetes mellitus and HF. We did not find any safety signals with respect to either all-cause hospitalization or mortality. On the contrary, small reductions in all-cause or heart failure-specific hospitalizations were observed, as well as a statistically significant and clinically important 20% reduction in all-cause mortality in pooled analyses of risk adjusted data. In addition, no risk of lactic acidosis was observed with metformin therapy, consistent with a previous meta-analysis, where metformin therapy was not associated with increased risk of lactic acidosis compared with other antihyperglycemic treatments.\(^{28}\)

Our review also provides some insight into the management of patients with diabetes mellitus, HF, and kidney disease. Similar to HF, there have been historical concerns with using metformin in patients with reduced renal function, despite almost no supporting evidence.\(^{27}\) Within the studies we examined, metformin users, on average, had slightly higher estimated renal function compared with those using nonmetformin-based regimens. However, \(\leq 10\%\) of metformin users had moderate to severe renal impairment in the studies. The 2 studies that specifically evaluated metformin in subgroups with renal impairment\(^{11,28}\) reported associations with reduced all-cause mortality that were similar to the overall metformin results. Indeed, in pooled analyses, metformin was associated with a nearly identical 19% proportional reduction in mortality in patients with moderate to severe renal dysfunction, although this failed to reach statistical significance likely due to the reduced sample size for these analyses. Nevertheless, metformin was not associated with increased harm in this perceived higher-risk subgroup.

It is important to consider that all the available evidence for the use of metformin in patients with HF comes from observational data. Although observational data are often preferred to randomized controlled trials when evaluating safety, particularly when events rates are low, randomized trials are still the highest level of evidence for efficacy. Although the observed associations may represent a true beneficial effect of metformin in this population, unmeasured confounding may also partially or fully explain our study findings. The large reduction in mortality without proportional reductions in hospitalizations may be related to unmeasured confounding within the studies included in our review. Moreover, even though our results are consistent with the overall findings of the United Kingdom Prospective Diabetes Study (UKPDS), where metformin was associated with a reduction in macrovascular events in overweight patients,\(^{20}\) 2 recent meta-analyses of randomized controlled trials did not show significant benefits of metformin in the broader population of patients with diabetes mellitus.\(^{31,32}\) Importantly, patients with HF were excluded in these randomized controlled trials, and the populations evaluated were at low risk of mortality compared with our review. That being said, several studies in animal models with HF suggest multiple potential benefits of metformin. Metformin has been shown to improve cardiac function through attenuation of oxidative stress–induced cardiomyocyte apoptosis, improved insulin resistance, and left ventricular end diastolic pressure, and prevent the progression of HF in canine models.\(^{33}\) Metformin also seems to enhance cardiac structure, function, and improve survival in murine models with ischemic heart disease through activation of adenosine monophosphate-activated protein kinase.\(^{34}\) In addition, metformin has been shown to attenuate left ventricular remodeling, as well as improve cardiac mechanical efficiency and systolic and diastolic indices in insulin resistant rats.\(^{39}\) Again, whether any of these observed mechanisms occur in humans is less clear.

Although we conducted an exhaustive search for literature and conducted our systematic review in accordance to the highest reporting standards, our review is not without limitations. First, studies showing limited or negative associations between metformin use and mortality may not have been identified because of publication bias. Moreover, studies that only evaluated metformin in sensitivity or subgroup analyses in patients with HF may not have been easily identified. However, a funnel plot of the included studies did not suggest publication bias (plot available on request), and we manually searched reference lists and contacted experts in the field as to the possibility of additional literature with none being identified. Second, although many of these studies conducted rigorous risk adjustment, unmeasured confounding may still explain our study findings because none of the included studies were randomized controlled trials. Third, our approach yielded the comparative safety of metformin in this population related to other antidiabetic agents; it could be that metformin is safe and mortality neutral, and it is the active comparators that are associated with increased mortality. However, in the study to evaluate metformin compared with lifestyle therapy alone, metformin was associated with mortality reductions similar to our pooled results.\(^{22}\)
Conclusions
The prevalence of diabetes mellitus in patients with HF is high and continues to rise. However, large-scale randomized trial evidence is unlikely to be forthcoming. Patients with HF have generally been excluded from the randomized controlled trials evaluating metformin against other agents, and we are aware of only 3 small pilot randomized trials evaluating the impact of metformin on clinical outcomes in patients with HF (1 of which was terminated because of lack of feasibility). The total-ity of available evidence indicates that, compared with other treatments, metformin is a safe option for glycemic control in patients with HF. This supports current Canadian and American Diabetes Association Clinical Practice guidelines, as well as those of the European Cardiology Society, which list metformin as a viable option in patients with diabetes mellitus and HF.

Sources of Funding
Dr Eurich is a Population Health Investigator with Alberta Innovates Health Solutions and a New Investigator with the Canadian Institute for Health Research. Drs Majumdar, Johnson, and McAlister are Health Scholars with Alberta Innovates Health Solutions. Dr Majumdar holds the Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences Endowed Chair in Patient Health Management. Dr Johnson holds a Centennial Professor with the University of Alberta. Dr McAlister holds the University of Alberta/Canada Health Chair in Cardiovascular Outcomes Research.

Disclosures
None.

References
Heart failure (HF) is a serious and common comorbidity in patients with diabetes mellitus associated with major morbidity and mortality. There is still a large degree of uncertainty related to the most appropriate method for glycemic control in patients with comorbid diabetes mellitus and HF. Historically, metformin has been considered inappropriate in this patient population attributable to concerns over lactic acidosis. Increasing evidence suggests, however, that metformin may be a safe option in patients with HF. In our systematic review evaluating the association between metformin and morbidity and mortality in patients with diabetes mellitus and HF, 9 observational studies were identified. Compared with controls (who were predominantly managed with sulfonylurea therapy), pooled adjusted risk estimates indicated that metformin use was associated with a 20% lower mortality rate. Moreover, no increased risk of mortality was observed in those with reduced left ventricular ejection fraction or chronic kidney disease in those treated with metformin. With respect to overall safety, no increased risk of hospitalization or lactic acidosis was observed in metformin-treated subjects. It is important to consider that all available evidence for the use of metformin in patients with HF comes from observational data. Thus, unmeasured confounding may partially or fully explain our study findings. Until randomized controlled trial evidence is generated, our review supports the current recommendations set by major diabetes mellitus and cardiology clinical practice guidelines, endorsing the use of metformin in patients with diabetes mellitus and HF.
Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure: Systematic Review of Observational Studies Involving 34,000 Patients

Dean T. Eurich, Daniela L. Weir, Sumit R. Majumdar, Ross T. Tsuyuki, Jeffrey A. Johnson, Lisa Tjosvold, Saskia E. Vanderloo and Finlay A. McAlister

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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2013/03/18/CIRCHEARTFAILURE.112.000162.DC1
### Supplemental Table 1. Methods, Design, Quality, Limitations of Studies for Metformin in the Treatment of Diabetes with Heart Failure

**Inzucchi et al. 2005**

<table>
<thead>
<tr>
<th>Design, dataset (n), and duration</th>
<th>Retrospective cohort study of Medicare beneficiaries (n=2,875) with up to 1 year of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major inclusion and exclusion criteria</td>
<td>Patients with diabetes receiving antidiabetic agents upon discharge from hospital for MI between April 1998 and March 1999 or July 2000 and June 2001 were included. Patients with unconfirmed MI, long term hemodialysis, &lt;65 years of age, died during hospitalization, unknown date of death, unknown readmission data, discharge to a hospice, transferred to another hospital, left against medical advice, no pharmacological treatment for diabetes at discharge were excluded.</td>
</tr>
<tr>
<td>Agents Evaluated</td>
<td>Metformin, No insulin sensitizer (sulfonylureas, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, and/or insulin)</td>
</tr>
<tr>
<td>Covariates Included in Analysis</td>
<td>Demographics (age, sex, race); cardiac history (history of HF, MI, hypertension, revascularization; non-CV history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia) clinical characteristics at admission (systolic blood pressure, respiratory rate, HF, Na+, glucose, BUN, Cr, WBC count, hematocrit); hospital course (AF, HF/pulmonary edema on admission, cardiac catheterization, PTCA, CABG, diabetes complications); discharge prescriptions; diabetes severity; sampling time frame; patient clustering by hospital</td>
</tr>
<tr>
<td>Methodologic quality checklist score</td>
<td>47%</td>
</tr>
<tr>
<td>Study limitations</td>
<td>Selection bias (&gt;65 years post MI only); Small sample size (few subjects in LV dysfunction subgroup); Uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain); Short duration of follow-up (1 yr outcomes)</td>
</tr>
</tbody>
</table>

**Masoudi et al. 2005**

<table>
<thead>
<tr>
<th>Design, dataset (n), and duration</th>
<th>Retrospective cohort study of Medicare beneficiaries (n=16,417) with up to 1 year of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major inclusion and exclusion criteria</td>
<td>Patients receiving antidiabetic agents upon discharge with a principle discharge diagnosis of HF from April 1998 to March 1999 or July 2000 to June 2001 were included. Patients &lt;65 years of age, died during hospitalization, unknown date of death, unknown readmission data, discharge to a hospice, no pharmacological treatment for diabetes at discharge were excluded.</td>
</tr>
<tr>
<td>Agents Evaluated</td>
<td>Metformin, No insulin sensitizer (sulfonylureas, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, and/or insulin)</td>
</tr>
<tr>
<td>Covariates Included in Analysis</td>
<td>Demographics (age, sex, race); cardiac history (history of MI, hypertension, CAD, PTCA; non-CV history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia) clinical characteristics at admission (systolic blood pressure, respiratory rate, HF, Na+, glucose,</td>
</tr>
</tbody>
</table>
Eurich et al. 2005³
Design, dataset (n), and duration Retrospective cohort study of the Saskatchewan Health databases (n=1,833) with mean follow-up time of 2.5 years
Major inclusion and exclusion criteria New users of oral antidiabetic agents from 1991 to 1996 with incident onset HF were included. Patients using insulin, with prevalent HF (diagnosis of HF prior before starting oral antidiabetic agents) were excluded.
Agents Evaluated Metformin, sulfonylurea
Covariates Included in Analysis Age, sex, modified chronic disease score, prescription medications affecting outcomes in people with diabetes and/or HF, total physician visits prior to HF diagnosis, propensity score (not included in final models)
Methodologic quality checklist score 50%
Study limitations Uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain); Short duration of follow-up (1 yr outcomes); Results limited to a select population of patients (>65 years of age)

Andersson et al. 2010⁴
Design, dataset (n), and duration Retrospective cohort study of the Danish National Patient Register (n=10 920) with mean follow-up time of 2.3 years
Major inclusion and exclusion criteria Patients aged ≥30 years and hospitalized for HF in the period between 1997 and 2006 who were alive 30 days after discharge and were receiving treatment with metformin, sulfonylureas and/or insulin within 90 days preceding HF hospitalization were included. Patients with previous hospitalizations for HF during the period from 1978 until 1996 or patients with concomitant use of alpha-glucosides or thiazolidinediones were excluded.
Agents Evaluated Metformin, sulfonylurea
Covariates Included in Analysis Age, sex, concomitant pharmacotherapy (lipid lowering drugs, RASi, beta blockers, calcium channel blockers, thiazides, spironolactone, digitoxin, aspirin, clopidogrel, vitamin k agonists) loop diuretic dosage, heart failure type, diabetic complications, diabetes duration ≥2 years, year of hospitalization, history of cancer, history of ischemic heart disease, myocardial infarction and cerebrovascular disease
Methodologic quality checklist score 46%
Study limitations Sensitivity of the HF diagnosis in the registers is 29% and therefore
the present analysis is based only on a subgroup of all HF patients in Denmark and the
positive predictive value of the heart failure diagnosis is 81% in the registries, and it can
not be excluded that the 19% who do not have heart failure may blur the picture.
Unmeasured confounders such as body mass index, blood pressure, HbA1c levels,
diabetes duration, smoking habits, lipid profiles, brain natriuretic peptide concentrations,
creatine clearance and echocardiography variables were lacking, therefore, some degree
of residual and hidden confounding by indication with those receiving metformin
potentially being healthier than those not receiving metformin can not be excluded. Also
unable to discern between type 1 and type 2 diabetes

Shah et al. 2010

Design, dataset (n), and duration Retrospective cohort study of patients referred to the
Ahmanson-UCLA cardiomyopathy Centre (n=401) with up to 2 years of follow-up
Major inclusion and exclusion criteria Patients with prior diagnosis of type II diabetes
and advanced systolic heart failure referred for heart failure management or heart failure
evaluation between 1994 and 2008 were included. Patients with LVEF > 40%, without
detailed information on diabetes medication or are treated by diet alone were excluded.
Agents Evaluated Metformin, No insulin sensitizer (sulfonylureas, non-sulfonylurea
secretagogues, alpha-glucosidase inhibitors, and/or insulin)
Covariates Included in Analysis Age, sex, LVEF, renal function, BMI, hemoglobin,
DM duration, ACE inhibitor/ ARB use and β-blocker use
Methodologic quality checklist score 56%
Study limitations Cohort is a select population of patients with advanced systolic heart
failure and diabetes mellitus referred to a single university center, glycemic outcomes and
hospitalizations not tracked, significant baseline differences between the two patient
groups (notably in creatine and blood urea nitrogen levels, NYHA class and duration of
diabetes), data not available on all laboratory, echo and medication at the time of follow
up

Evans et al. 2010

Design, dataset (n), and duration Retrospective cohort study using the Diabetes Audit
and Research (DARTS) in Tayside Scotland (n=422) with over 4 years of follow-up
Major inclusion and exclusion criteria Patients with a diagnosis of diabetes from
December 1993 to 2003 and incident HF (fulfilling one of three criteria) were included.
Patients that received an oral hypoglycemic agent prescription before 1994 or received
insulin at any point during the study period, plasma creatine concentrations >200µmol/l
before prescription of a loop diuretic, received first prescription of metformin or SU
within 1 year of CHF and the date of CHD diagnosis had to occur after the date of
diabetes diagnosis.
Agents Evaluated Metformin, sulfonylurea
Covariates Included in Analysis Gender, age at index, duration of diabetes at index
date, Hb A1C, creatine, previous hospital admission for major CV event, ACE inhibitor,
aspirin, diuretic, or β-blocker usage
Methodologic quality checklist score 53%
<table>
<thead>
<tr>
<th>Study limitations</th>
<th>Study is observational, therefore impossible to account for all possible confounding influences that may have biased to observed differences between the groups considered</th>
</tr>
</thead>
</table>
| MacDonald et al. 2010<sup>7</sup> | **Design, dataset (n), and duration** Nested case-control study using the U.K. General Practice Research Database (n= 3,266) with mean follow-up time of 2.8 years  
**Major inclusion and exclusion criteria** Patients <35 years of age, with newly diagnosed type II diabetes and heart failure between January 1988 and October 2007 were included. Patients with prevalent diagnosis of diabetes or heart failure before 1988 and those with type I, gestational or drug induced diabetes were excluded.  
**Agents Evaluated** Metformin  
**Covariates Included in Analysis** Age, Systolic BP, diastolic BP, BMI, Hemoglobin, Hemoglobin A1C, GFR, hypertension, prior myocardial infarct or coronary revascularization, valvular heart disease, angina, atrial fibrillation, dyslipidemia, chronic obstructive lung disease, cerebrovascular disease, smoking status, peripheral vascular disease, cancer, dementia, peptic ulcer disease, medication use within 90 days of index date (ACE inhibitor/ARB, aspirin, Digitoxin, β-blocker, statin, spironolactone)  
**Methodologic quality checklist score** 59%  
**Study limitations** No independent conformation of LVEF other than physician diagnoses, potential selection bias in the choice of antidiabetic agents (‘lower risk’ patients being selected for metformin treatment), duration of diabetes may be associated with current antidiabetic therapy (metformin used in patients earlier in their course of diabetes), analysis focused on current drug treatment at patient’s index date so does not inform about the long term effects of these therapies or the impact of switching between drug classes |
| Roussel et al. 2010<sup>8</sup> | **Design, dataset (n), and duration** Subgroup analysis of prospective cohort study using the Reduction of Atherothrombosis for Continued Health (REACH) registry (n=4,010) with up to 2 years of follow-up  
**Major inclusion and exclusion criteria** Patients with diabetes undergoing a secondary prevention strategy in the International Reduction of Atherothrombosis for continued Health (REACH) Registry enrolled by a physician between December 1, 2003 and December 31, 2004, <45 years of age with established coronary artery disease, cerebrovascular disease or peripheral arterial disease (or patients with at least three atherothrombotic risk factors) were included. Patients with only baseline data were excluded.  
**Agents Evaluated** Metformin, No insulin sensitizer (sulfonylureas, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, and/or insulin), TZDs  
**Covariates Included in Analysis** Sex, age, history of CHF, estimated glomerular filtration rate, No. vascular beds, Insulin, TZD, SU or other antidiabetic agent use  
**Methodologic quality checklist score** 44%  
**Study limitations** Duration of diabetes and metformin usage not recorded, lack of information on glycylated hemoglobin, potential allocation bias due to major differences |
in clinical characteristics between metformin users and non-users, limited extrapolation to other populations

Aguilar et al. 2011

**Design, dataset (n), and duration** Retrospective cohort study of a national cohort of patients treated in ambulatory clinics at Veteran Affairs medical centers (n=6185) with up to 2 years of follow-up

**Major inclusion and exclusion criteria** Patients who were prescribed hypoglycemic medications and treated in ambulatory clinics at Veteran affairs (VA) medical centers using the VA External Peer Review Program (EPRP) data between October 2000 and September 30, 2002 were included. Patients with missing creatinine values were excluded.

**Agents Evaluated** Metformin, No insulin sensitizer (sulfonylureas, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, and/or insulin), TZDs

**Covariates Included in Analysis** Age, sex, ethnicity, BMI, SBP, LVEF, history of diabetic complication, peripheral vascular disease, hypertension, atrial fibrillation, past myocardial infarction, prior HF hospitalization within 2 years, COPD, Cancer, HBA1C, GFR, BUN, hemoglobin, cholesterol, sodium, medication use (insulin, SU, TZD, ACE/ARB, spironolactone, beta-blocker, statin)

**Methodologic quality checklist score** 53%

**Study limitations** The incidence of lactic acidosis was not obtained, NYHA classification not available, medication use was assessed only at baseline and changes in medications over the time of follow up are not available
Figure Legends

Supplemental Figure 1.

Pooled adjusted risk ratios for metformin compared with other treatments for all cause hospital admission.

Supplemental Figure 2.

Pooled adjusted risk ratio for metformin compared with other treatments for all cause mortality in those with reduced renal function.

Supplemental Figure 3.

Pooled adjusted risk ratio for metformin compared with other treatments for HF admission

Supplemental Figure 4.

Pooled adjusted risk ratio for metformin compared with other treatments for all cause mortality in those with advanced HF.

Supplemental Figure 5.

Pooled adjusted risk ratios for metformin compared with other treatments for long term all cause mortality.

**Supplemental Figure 1.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurich</td>
<td>5.6%</td>
<td>0.84 [0.68, 1.05]</td>
<td>2005</td>
</tr>
<tr>
<td>Masoudi</td>
<td>75.5%</td>
<td>0.94 [0.89, 1.00]</td>
<td>2005</td>
</tr>
<tr>
<td>Aguilar</td>
<td>18.9%</td>
<td>0.94 [0.84, 1.06]</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

100.0% 0.93 [0.89, 0.98]

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%

Test for overall effect: Z = 2.59 (P = 0.010)
Supplemental Figure 2.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masoudi</td>
<td>62.3%</td>
<td>0.89 [0.74, 1.07] 2005</td>
<td></td>
</tr>
<tr>
<td>Aguilar</td>
<td>37.7%</td>
<td>0.70 [0.52, 0.94] 2011</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.81 [0.64, 1.02]
Heterogeneity: Tau² = 0.01; Chi² = 1.89, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 1.77 (P = 0.08)

Supplemental Figure 3.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masoudi</td>
<td>92.2%</td>
<td>0.92 [0.86, 0.99] 2005</td>
<td></td>
</tr>
<tr>
<td>Aguilar</td>
<td>7.8%</td>
<td>0.93 [0.74, 1.18] 2011</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.92 [0.86, 0.98]
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)

Supplemental Figure 4.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masoudi</td>
<td>95.8%</td>
<td>0.91 [0.72, 1.14] 2005</td>
<td></td>
</tr>
<tr>
<td>Shah</td>
<td>4.2%</td>
<td>0.63 [0.21, 1.89] 2010</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.90 [0.72, 1.12]
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)

Supplemental Figure 5.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euirich</td>
<td>21.1%</td>
<td>0.70 [0.54, 0.91] 2005</td>
<td></td>
</tr>
<tr>
<td>Evans</td>
<td>19.6%</td>
<td>0.67 [0.51, 0.88] 2005</td>
<td></td>
</tr>
<tr>
<td>Andersson</td>
<td>41.6%</td>
<td>0.85 [0.74, 0.97] 2010</td>
<td></td>
</tr>
<tr>
<td>MacDonald</td>
<td>17.7%</td>
<td>0.65 [0.48, 0.87] 2010</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.74 [0.64, 0.86]
Heterogeneity: Tau² = 0.01; Chi² = 4.89, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 4.02 (P < 0.0001)
Supplementary References


