

# Review: Evidence for major benefits and harms of antidiabetic agents for diabetes with heart failure is limited

Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ*. 2007;335:58-9.

**Clinical impact ratings:** GIM/FP/GP ★★★★★★ Cardiology ★★★★★☆☆ Endocrinology ★★★★★☆☆

## QUESTION

In patients with heart failure (HF) and diabetes, what is the relation between antidiabetic therapy and morbidity and mortality?

## METHODS

**Data sources:** MEDLINE (1966 to 2007), EMBASE/Excerpta Medica (1980 to 2007), Cochrane Central Register of Controlled Trials (1991 to 2007), 5 other databases, reference lists, and experts.

**Study selection and assessment:** Randomized controlled trials (RCTs) or cohort studies evaluating the association between antidiabetic drugs (insulin, metformin [MET], sulfonylurea [SFU], and thiazolidinedione [TZD]) and hospitalization or all-cause mortality in patients with HF and diabetes. Quality assessment of individual studies was based on a validated checklist (maximum score 32; scores ≥ 12 indicate acceptable quality). 8 studies met the selection criteria: 1 RCT, 2 post hoc analyses from RCTs, 4 retrospective cohort studies, and 1 prospective cohort study; quality scores ranged from 13 to 22. Meta-analysis was not done because of significant statistical heterogeneity (except for studies on TZDs and hospitalization for HF).

**Outcomes:** All-cause hospitalization, hospitalization for HF (cardiovascular morbidity), and all-cause mortality.

## MAIN RESULTS

In 2 of 3 studies, MET was associated with lower risk for mortality than other drugs, and in 1 study, MET plus SFU was associated with lower risk for mortality than SFU alone (Table); groups did not differ for all-cause hospitalization. In 3 of 4 studies, insulin was associated with higher risk for mortality than other drugs (Table). In 4 studies, TZD was associated with lower risk for mortality but higher risk for hospitalization for HF than other drugs (Table). In 1 study, SFU and non-SFU drugs did not differ for mortality.

## CONCLUSION

Metformin and thiazolidinediones are associated with reduced risk but insulin is associated with increased risk for all-cause mortality in patients with heart failure and diabetes.

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### Comparisons of various antidiabetic drugs in patients with heart failure (HF) and diabetes at 1 year or until end of study\*

Outcomes	Number of studies (n)	Comparisons	WERs	RRR (95% CI)	NNT (CI)
All-cause mortality	1 (13 930)	MET vs other drugs	25% vs 36%	12% (2 to 18)	25 (16 to 116)
	1 (981)	MET vs SFU	33% vs 52%	23% (6 to 37)	9 (6 to 31)
	1 (1625)	MET + SFU vs SFU	31% vs 52%	31% (21 to 39)	7 (5 to 10)
	4 (22 476)	TZD vs other drugs†	29% vs 33%	12% (2 to 21)	26 (15 to 150)
			RRI (CI)	NNH (CI)	
CV morbidity and mortality	1 (496)	INS vs diet, SFU, and MET	41% vs 26%	51% (17 to 92)	8 (5 to 23)
	1 (2160)	INS vs diet, SFU, MET, TZD†	35% vs 30%	16% (2 to 31)	21 (11 to 161)
	1 (132)	INS vs diet, SFU, MET, TZD†	30% vs 11%	169% (34 to 358)	6 (3 to 27)
Hospitalization for HF	1 (496)	INS vs diet, SFU, and MET	58% vs 46%	25% (4 to 46)	9 (5 to 52)
	1 (2160)	INS vs diet, SFU, MET, TZD†	52% vs 41%	26% (15 to 37)	10 (7 to 16)
Hospitalization for HF	4 (22 476)	TZD vs other drugs†	54% vs 51%	6.0% (1.9 to 9.8)	33 (21 to 103)

\*CV = cardiovascular; INS = insulin; MET = metformin; SFU = sulfonylurea; TZD = thiazolidinedione; WERs = weighted event rates; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from control event rates and adjusted hazard ratios using a random-effects model. †RRR, RRI, NNT, NNH, and CI calculated from control event rates and unadjusted odds ratios.

## COMMENTARY

Type 2 diabetes mellitus is a progressive disease that requires escalating treatment, and most patients eventually require insulin (1). Many patients and physicians are apprehensive about starting insulin therapy (IT) until all other therapeutic options fail (2). Because IT is often initiated as the final line of therapy, those who receive insulin have had diabetes and have been exposed to the ill effects of hyperglycemia for a longer period than those taking other drugs.

In the review by Eurich and colleagues, most included studies were retrospective; only 1 RCT that allocated individuals with diabetes and a history of HF to different glycemic control strategies was identified (3). This presents a potential selection bias in different treatment groups, especially the insulin group. The data on TZDs also appear quite limited. Although the review showed that TZDs reduced mortality, this finding was based on retrospective studies rather than RCTs and must be interpreted with caution. Similarly, studies comparing MET with SFUs were also retrospective and had potential selection bias.

All of the above issues can only be well-addressed in an RCT. As the number of individuals with diabetes and history of HF progressively

risks, the need for well-designed RCTs evaluating the effect of different glycemic control strategies on cardiovascular endpoints in this group will become ever greater.

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