

Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review

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ABSTRACT

Objective To review the literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes.

Design Systematic review and meta-analysis of controlled studies (randomised trials or cohort studies) evaluating antidiabetic agents and outcomes (death and admission to hospital) in patients with heart failure and diabetes.

Data sources Electronic databases, manual reference search, and contact with investigators.

Review methods Two reviewers independently extracted data. Risk estimates for specific treatments were abstracted and pooled estimates derived by meta-analysis where appropriate.

Results Eight studies were included. Three of four studies found that insulin use was associated with increased risk for all cause mortality (odds ratio 1.25, 95% confidence interval 1.03 to 1.51; 3.42, 1.40 to 8.37 in studies that did not adjust for diet and antidiabetic drugs; hazard ratio 1.66, 1.20 to 2.31; 0.96, 0.88 to 1.05 in the studies that did). Metformin was associated with significantly reduced all cause mortality in two studies (hazard ratio 0.86, 0.78 to 0.97) compared with other antidiabetic drugs and insulin; 0.70, 0.54 to 0.91 compared with sulfonylureas); a similar trend was seen in a third. Metformin was not associated with increased hospital admission for any cause or for heart failure specifically. In four studies, use of thiazolidinediones was associated with reduced all cause mortality (pooled odds ratio 0.83, 0.71 to 0.97, $I^2=52%$, $P=0.02$). Thiazolidinediones were associated with increased risk of hospital admission for heart failure (pooled odds ratio 1.13, 1.04 to 1.22, $I^2=0%$, $P=0.004$). The two studies of sulfonylureas had conflicting results, probably because of differences in comparator treatments. Important limitations were noted in all studies.

Conclusion Metformin was the only antidiabetic agent not associated with harm in patients with heart failure and diabetes. It was associated with reduced all cause mortality in two of the three studies.

The role of antidiabetic agents in managing diabetes in patients with heart failure is uncertain,¹ and considerable controversy exists about their overall effect on outcomes in people with comorbid diabetes and heart failure.^{w1 w2} Some evidence also suggests that tight glycaemic control (glycated haemoglobin $\leq 7%$) may be associated with worse survival than less tight control in patients with heart failure, irrespective of the agent used.² We conducted a systematic review to examine the relation between antidiabetic treatment and outcomes in people with heart failure and diabetes.

METHODS

We used a comprehensive search strategy of various electronic databases from their date of inception until the week of 16 July 2007 for studies with contemporaneous comparison groups that evaluated the association between antidiabetic agents and clinical outcomes of hospital admission or mortality (or both) in patients with diabetes and heart failure (see bmj.com). We also manually searched reference lists from original studies and review articles and contacted experts and authors of included studies. The search was not restricted by language or quality of study.

Two reviewers independently identified relevant citations and included them if they described original research, included subjects with both diabetes and heart failure, evaluated the effects of antidiabetic drugs on health outcomes (mortality, all cause hospital admission, and hospital admission for heart failure), and included a contemporaneous control group for comparison. Discrepancies were resolved by consensus by a third investigator. All data were extracted and the two reviewers independently assessed the methodological quality of included studies using a validated quality checklist.³

Statistical analysis

We abstracted the 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. If appropriate, we then pooled data across studies using random effects models if excessive statistical heterogeneity did not exist (measured using the I^2 statistic and defined a priori as $P \leq 0.10$ or $I^2 \geq 50%$).

RESULTS

Our search yielded 10 091 citations. Eight studies met our inclusion criteria—one randomised controlled trial, two post hoc subgroup analyses from randomised trials, four retrospective cohort studies, and one prospective cohort study (see bmj.com).^{w1-w8} Inter-observer agreement was $\kappa=0.84$ for study inclusion. Of the eight studies, three had more than two comparison groups. As a result, four studies evaluated the effect of insulin treatment in patients with heart failure ($n=9104$), three examined metformin ($n=3327$), four evaluated thiazolidinediones ($n=3409$), and two studies ($n=8918$) compared sulfonylureas with other agents. See bmj.com for summary of the eight studies and their key findings. The table summarises the pooled statistical heterogeneity of the studies.

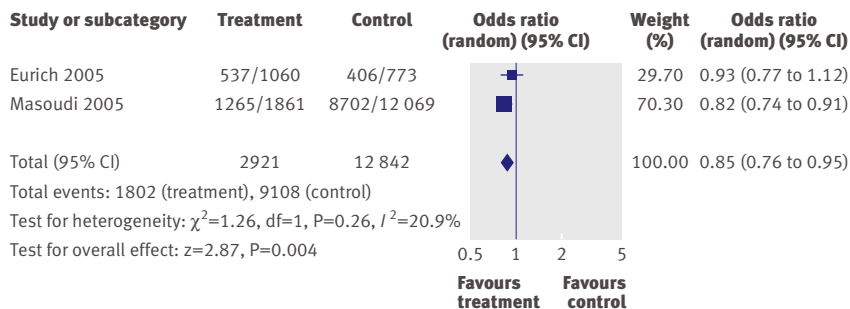


Fig 1 | Pooled odds ratio for metformin compared with other treatments for all cause hospital admission at one year. The data for Eurich 2005 were pooled from the metformin monotherapy group and combination therapy group (pooled test for heterogeneity $P=0.70$; $I^2=0\%$)

Insulin

Outcomes with insulin were evaluated in a subgroup analysis of 496 patients with diabetes and left ventricular dysfunction (ejection fraction <40% after acute myocardial infarction) from the survival and ventricular enlargement (SAVE) trial.^{w6} After multivariate adjustment, compared with 328 patients not treated with insulin (but treated with diet, sulfonylurea, or metformin), the 168 patients treated with insulin had significantly increased risk of all cause mortality (adjusted hazard ratio 1.66, 95% confidence interval 1.20 to 2.31), and cardiovascular morbidity (hospital admission for heart failure or prescription of an open label angiotensin converting enzyme inhibitor, or myocardial infarction) and mortality (1.38, 1.06 to 1.80).

The effect of insulin was also evaluated in the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) study.^{w4} Although insulin was not directly compared with other antidiabetic agents in adjusted analyses, unadjusted risk ratios calculated from the raw data presented in the paper suggest that treatment with insulin is associated with an increased risk of all cause mortality (risk ratio 1.25, 1.03 to 1.51) and death from cardiovascular disease or hospital admission for heart failure (1.55, 1.29 to 1.86) compared with other forms of treatment in patients with diabetes.^{w4}

Outcomes with insulin were also assessed in 554 consecutive patients referred to a university medical centre

for management of heart failure.^{w5} Of these patients, 132 (24%) had diabetes and were prospectively followed for 11.7 months. Although insulin and non-insulin treatments were not directly compared in patients with diabetes, extrapolation from the raw data suggests an unadjusted risk ratio for all cause mortality of 3.42 (1.40 to 8.37) at one year and 2.20 (0.96 to 5.03) at two years.

The effects of insulin on mortality were also evaluated in a retrospective cohort study of 16 417 Medicare beneficiaries with diabetes who were discharged from hospital with a primary diagnosis of heart failure.^{w1} This study found no association between the use of insulin and mortality (adjusted hazard ratio 0.96; 0.88 to 1.05) compared with patients receiving metformin, thiazolidinediones, sulfonylureas, non-sulfonylurea insulin secretagogues, or alpha glycosidase inhibitors.^{w1}

Oral antidiabetic agents

Metformin

Outcomes with metformin were evaluated in a retrospective cohort study of Medicare beneficiaries with diabetes discharged after hospital admission for acute myocardial infarction.^{w3} Subgroup analysis of the patients with diabetes and moderate to severe impaired left ventricular systolic function (n=2875) suggested that after multivariate adjustment, treatment with metformin was not associated with any risk of all cause mortality at one year compared with patients receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glycosidase inhibitors, and insulin (n=406; 0.92, 0.72 to 1.18).^{w3}

The study of Medicare beneficiaries with diabetes discharged with a primary diagnosis of heart failure also evaluated the effect of metformin on all cause mortality at one year.^{w1} After multivariate adjustment, compared with patients not receiving insulin sensitizers (n=12 069), all cause mortality was significantly lower in patients treated with metformin (n=1861; 0.86, 0.78 to 0.97), as well as in patients treated both with metformin and thiazolidinediones (n=261; 0.76, 0.58 to 0.99). In addition, no difference was seen in the risk for all cause hospital readmissions for patients receiving metformin (0.94, 0.89 to 1.01) and a lower risk was seen in patients treated with both metformin and thiazolidinediones (0.82, 0.69 to 0.96). A lower risk was also seen for metformin users with respect to heart failure related readmissions (0.92, 0.86 to 0.99) and a trend towards reduction in patients receiving both metformin and thiazolidinediones (0.85, 0.71 to 1.01).

In a retrospective analysis using administrative records, another study compared metformin alone, or combined with sulfonylurea, to sulfonylurea monotherapy in 1833 patients with newly treated diabetes and incident heart failure.^{w2} After multivariate adjustment, all cause mortality was significantly lower with metformin monotherapy (0.66, 0.44 to 0.97 at one year; 0.70, 0.54 to 0.91 after 2.5 years), or with combined treatment with metformin-sulfonylurea (0.54, 0.42 to 0.70 at one year; 0.61, 0.52 to 0.72 after 2.5 years). A reduction in the composite outcome of all cause mortality or hospital admission was also seen at the end of follow-up for the

Results of test for statistical heterogeneity

Antidiabetic drug	No of studies	Outcome assessed	P value for heterogeneity	I ² statistic
Insulin	4	All cause mortality	0.03	67.2%
	0	All cause hospital admission	Not determined	Not determined
	4	All cause mortality	0.10	52.3%
Thiazolidinediones	1	All cause hospital admission	Not determined	Not determined
	4	Heart failure related hospital admission	0.82	0%
Metformin	3	All cause mortality at 1 year	<0.001	83.5%
	2	All cause hospital admission at 1 year	0.26	20.9%
Sulfonylurea	2	All cause mortality at 1 year	<0.001	96.4%

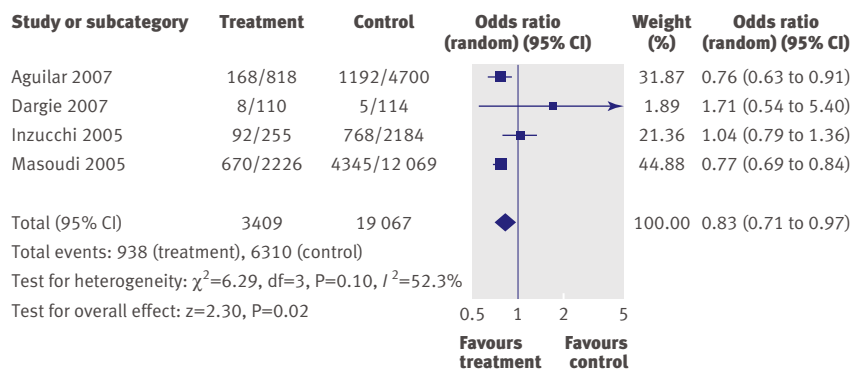


Fig 2 | Pooled odds ratio for thiazolidinediones compared with other treatments for all cause mortality

metformin monotherapy group (0.83, 0.70 to 0.99) and for combination therapy (0.86, 0.77 to 0.96).

The pooled effect of the studies assessing the effect of metformin on all cause hospital admission at one year suggests that treatment with metformin may be associated with reduced admission at one year compared with other treatments (pooled odds ratio 0.85, 0.76 to 0.95; $I^2=21\%$; $P=0.004$; fig 1).^{w1 w2}

Thiazolidinediones

In the previous Medicare study of patients with diabetes discharged after hospital admission for acute myocardial infarction,^{w3} after multivariate adjustment, the risk of all cause mortality at one year was no different for patients who received thiazolidinediones ($n=255$) than for patients treated with sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin (1.04, 0.83 to 1.31). There was a trend, however, towards an increased risk of readmission for heart failure associated with thiazolidinediones ($n=255$; 1.15, 0.97 to 1.38).^{w3}

In the second Medicare study of patients with diabetes discharged with a primary diagnosis of heart failure, after multivariate adjustment as above ($n=12 069$), all cause mortality at one year was significantly lower for patients treated with thiazolidinediones ($n=2226$; 0.87, 0.80 to 0.94).^{w1} This study also found no difference in the risk for all cause hospital readmissions for patients receiving thiazolidinediones (1.04, 0.99 to 1.10). However, a small increased risk of readmission for heart failure was seen in patients receiving thiazolidinediones (1.06, 1.00 to 1.12).

In a retrospective cohort study of ambulatory patients followed through Veteran Affairs medical centres, after multivariate adjustment no differences were seen in all cause mortality at two years ($n=814$; 0.98, 0.81 to 1.17) or in hospital admission for heart failure (1.00, 0.81 to 1.24) in patients treated with thiazolidinediones compared with those not receiving insulin sensitisers ($n=4700$). However, in patients not receiving insulin, thiazolidinediones ($n=381$) were associated with an increased risk of hospital admission for heart failure compared with those not receiving insulin sensitisers ($n=2217$; 1.62, 1.15 to 2.29).^{w8}

The only randomised controlled trial evaluated the addition of rosiglitazone ($n=110$) or placebo ($n=114$) to existing antidiabetic drugs in patients with New York Heart Association class I or II disease.^{w7} Although not a specific end point of the study, after 52 weeks of treatment (compared with placebo) there was a trend towards an increased risk of all cause mortality for rosiglitazone (hazard ratio 1.50, 0.49 to 4.59) and in the proportion of patients with hospital admission for heart failure (relative risk 1.30, 0.35 to 4.82). A trend towards an increase in all cause mortality or worsening heart failure was also seen (hazard ratio 1.28, 0.51 to 3.21). The pooled effect of the four studies which assessed the effect of thiazolidinediones on all cause mortality^{w1 w3 w7 w8} suggests that treatment with thiazolidinediones may be associated with reduced all cause mortality compared with other treatments (pooled odds ratio 0.83, 0.71 to 0.97; $I^2=52\%$; $P=0.10$), although moderate heterogeneity was seen (fig 2). Similarly, the pooled effect on hospital admission for heart failure suggests that thiazolidinediones may be associated with an increased risk of such admissions compared with other treatments (1.13; 1.04 to 1.22; $I^2=0\%$; $P=0.004$; fig 3).^{w1 w3 w7 w8}

Sulfonylureas

Apart from the effect of sulfonylureas relative to the use of metformin already mentioned,^{w2} only one other study looked at sulfonylureas.^{w1} After multivariate analysis, no increased risk of mortality at one year was seen for patients receiving sulfonylureas compared with patients receiving other insulin secretagogues, alpha glucosidase inhibitors, metformin, thiazolidinediones, or insulin (0.99; 0.91 to 1.08).

DISCUSSION

Heart failure is a common comorbidity in patients with diabetes. Despite the high morbidity and mortality associated with the disease, our systematic review found few studies that formally compared antidiabetic agents in this population. Of the eight studies included, most were observational and there was only one randomised controlled trial, which was not designed to evaluate clinical outcomes. All studies were published in the past two years, and focused on use of insulin, thiazolidinediones, or metformin.

Insulin

In the four studies that specifically evaluated the use of insulin, three suggested an increase in mortality, and one reported no association with mortality. Statistical heterogeneity precluded formal meta-analysis. It is difficult to tell whether there is a true adverse effect of insulin or whether it is simply confounding by indication. Treatment with insulin in these studies may well have been a marker for more advanced diabetes or vascular disease (or both).^{w6}

Metformin

Our analysis revealed that treatment with metformin may be associated with lower mortality rates, although statistical heterogeneity precluded formal meta-analysis.

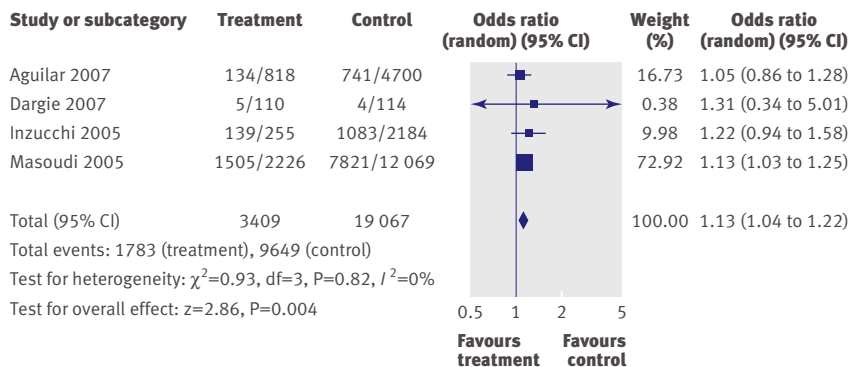


Fig 3 | Pooled odds ratio for thiazolidinediones compared with other treatments on hospital admission for heart failure

No study found an increase in adverse events with metformin. The results of both studies that evaluated all cause hospital admissions in metformin users suggested that this drug is associated with a lower rate of all cause hospital admission than other antidiabetic drugs.

Thiazolidinediones

The pooled effects for mortality suggest that thiazolidinediones may be associated with reduced mortality, although moderate statistical heterogeneity was present. The only randomised controlled trial showed a trend towards an increased risk of mortality with thiazolidinediones; however, the study was not specifically designed to assess clinical outcomes and 62 (28%) patients withdrew.^{w7} Data from one of the two large observational studies suggest that thiazolidinediones may be associated with lower mortality, whereas this was not seen in the other study.^{w1 w8} This discrepancy may be related to the lower severity of illness in the patients in the second study, the under-representation of female patients, or differences in the use of combination treatments between study groups.^{w8} All studies except for one reported higher numbers of hospital admissions related to heart failure for patients receiving thiazolidinediones.^{w1 w3 w7 w8} This risk was confirmed by formal pooling of data.

Although the lower mortality rates associated with use of metformin or thiazolidinediones are consistent with those seen in randomised controlled trials of insulin sensitisers in other populations with diabetes,⁴⁻⁶ none of the three included studies were randomised controlled

trials. The benefits of metformin and thiazolidinediones on mortality may be due to selection bias in these studies. Only one study specifically evaluated the effects of oral antidiabetic agents as monotherapy,^{w2} and contamination of comparison groups as a result of the use of multiple antidiabetic drugs is a possibility.^{w1 w3}

Sulfonylureas

Only two studies specifically evaluated sulfonylureas as an independent exposure.^{w1 w2} One found that sulfonylurea monotherapy may be associated with worse outcomes,^{w2} whereas the other did not.^{w1} The discrepancy may partly be due to the comparator groups used in the studies. Although these results are consistent with other studies evaluating sulfonylureas, a recent meta-analysis has indicated that these drugs are not associated with an increase in cardiovascular events.⁷ Given the current controversy surrounding the use of sulfonylureas in patients with pre-existing cardiovascular disease,⁸ more research is needed.

Limitations

Inherent to any systematic review is the potential for publication or selection bias, although our search strategy meant that any relevant articles are unlikely to have been missed. Secondly, the included studies were mainly observational and only one study randomised patients to different antidiabetic drugs. As a result, the effects of unmeasured confounding variables could not be fully explored and this may be a limitation of most of the reported studies.

Conclusions

Our results suggest that of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality. Given the large number of people affected with diabetes and heart failure and the fact that this population is expected to increase rapidly, evidence on how to optimally control glycaemic levels in this population is urgently needed. It is therefore imperative that further research is undertaken.

Contributors: See bmj.com.

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Competing interests: None declared.

Ethical approval: Not required.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Diabetes is a common comorbidity in people with heart failure and predicts worse outcome. The best way to achieve glycaemic control in patients with diabetes and heart failure is unclear.

WHAT THIS STUDY ADDS

Current evidence suggests that metformin is the only antidiabetic agent not associated with any measurable harm in patients with diabetes and heart failure.

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Outside the comfort zone

I realised that there might be more to this Afghanistan trip than I had supposed when my "dog tags" arrived. For several months, I had looked forward to it with all the anticipation of a trip to the car wash: it was simply an unknown, and I was therefore neither excited nor apprehensive at the prospect. That changed the moment those shiny metal discs fell from the envelope.

Only a few weeks later I found myself facing something of a challenge, both surgically and ethically. My six week deployment as a Territorial Army maxillofacial surgeon began uneventfully enough. The multinational team of doctors were all suitably eminent and charismatic individuals. The hospital proved remarkably well equipped for a war zone, and, despite the dust and occasional rocket attacks by the Taliban, it functioned with the quiet efficiency of a banking house. If you imagine the film *M*A*S*H* but set in a high altitude desert surrounded by fairly impressive mountains, with occasional glimpses of the snow capped Himalayan foothills, and add the incessant beat of helicopter engines and the roar of high speed jets, then you may begin to conjure the atmosphere of the place.

A knock on the door of our billet at 6.30 one morning served to jolt us into action and to announce the imminent arrival of casualties from the crash in the mountains of a helicopter that had been carrying 22 men. The first five off the rescue helicopter were in body bags, apparently a feature of the loading priorities; they had put the sick on board first and the dead last.

One patient, a 29 year old, presented in the first wave of casualties at 7.30. He had been thrown clear of the wreckage and was deeply unconscious, with a Glasgow coma score of 4, but apparently otherwise uninjured. He had been intubated at the scene, and his initial clinical examination was unremarkable, although he had bradycardia of 50 beats/minute. Computed tomography, however, showed considerable bilateral intracerebral haemorrhage, with bleeding into the fourth ventricles, and extensive cerebral oedema.

Unable to monitor the patient's intracerebral pressure and without a neurosurgeon on site, we sought a neurosurgical opinion by telephone. A bleary voiced colleague, roused from sleep four time zones away, advised against decompressive craniotomy. We therefore managed conservatively, by means of intravenous 20% mannitol infusion and cooling by means of wet towels and ice. This dropped his temperature to 34°C. With head elevation and inotropic support to maintain his mean arterial pressure, he was maintained until 3.30 pm, by which time he had developed profound bradycardia at

35 beats/minute and had blown one pupil, although inotropic support meant his mean arterial pressure remained at 100 mm Hg.

At this point, some 14 hours after injury, the patient's evacuation flight was still not due to land for some two hours; after which, he could expect a flight time of a further seven and a half hours. Given this scenario, we felt that he was unlikely to survive without some form of surgical intervention. As the next best thing to a neurosurgeon, and having a degree of familiarity with the anterior cranial fossa acquired through working in a regional neurosurgical centre, I could scarcely shirk the responsibility.

He was a young, fit man. His outcome looked bleak without surgery; could it be any more bleak with it? If we knew anything, it was that serious head injuries often had unpredictable outcomes. Would it be better to allow him to die here in a foreign land with dignity, rather than preserve him, only to live out a vegetative existence? Or should we do what we could to keep him alive long enough for him to reach a neurosurgical centre and take his chances from there? After some discussion, the medical team agreed to adopt the latter course.

We performed a bifrontal, decompressive craniotomy relatively uneventfully—after a fruitless initial search to find a non-existent craniotome—and replaced the bone flap on the unopened dura to allow the already tense brain to expand further. After the procedure, the patient's pulse rose to a range of 50-65 beats/minute (my own pulse was considerably higher). The patient was finally evacuated by air, in a ventilated state, at about 10 pm, a journey which he survived.

At the time of writing, some two weeks after the event, he is still alive, but his outcome remains uncertain. At leisure again, we found support for our approach in the literature: bifrontal, decompressive craniotomy is recommended in cases of refractory intracranial hypertension (Bullock et al, *Neurosurgery* 2006;58 25-31).

As my return to the humdrum, target ridden, comfort zone of the NHS looms, I find myself once more unexcited. War surgery is a mixture of boredom alternating with frenetic activity; but, regardless of one's views on conflict, there can scarcely be a more needful or deserving group of patients than the courageous men who put themselves in harm's way for a living. As a doctor, waiting safe in hospital for the fruits of conflict, I found this contrast rather humbling.

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