

Treatment disparities and effect on late mortality in patients with diabetes presenting with acute myocardial infarction: observations from the ACACIA registry

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Patients with diabetes have higher short-term and long-term mortality and morbidity rates after acute myocardial infarction (MI) than non-diabetic patients.¹⁻⁷ Proven risk-modifying treatments have shown equivalent or larger relative risk reductions in diabetic compared with non-diabetic patients with acute coronary syndrome (ACS).⁸⁻¹⁰ The absolute benefit of these treatments among diabetic patients with ACS is potentially greater owing to their higher baseline risk. This underscores the importance of physician adherence to evidence-based guidelines in the treatment of patients with diabetes who present with ACS. However, data from several international registries suggest that disparities in mortality rates and treatments have persisted among diabetic compared with non-diabetic patients following acute MI, despite broad acceptance of ACS treatment guidelines.³⁻⁷

We used data from a prospective national registry of patients with ACS to compare the use of evidence-based pharmacological and invasive treatments and 12-month mortality rates between patients with and without diabetes who present with acute MI. We also explored the relationship between these treatments and 12-month clinical outcomes.

METHODS

The Acute Coronary Syndrome Prospective Audit (ACACIA, sanofi-aventis study protocol number PML-0051) has been described previously.^{11,12} The trial was conducted between 1 November 2005 and 31 July 2007 and involved 39 hospitals across all states and territories of Australia. Hospitals were selected to be representative of rural (25%) and metropolitan (75%) centres, and of interventional (83%) and non-interventional (17%) centres.¹¹ The trial enrolled 3402 patients with suspected ST segment elevation MI (STEMI) or high-risk and intermediate-risk non-ST segment elevation ACS.¹³ This analysis was limited to the 1744 patients with a final discharge diagnosis of acute MI, determined by investigators at

ABSTRACT

Objectives: To compare the use of evidence-based pharmacological and invasive treatments and 12-month mortality rates between patients with and without diabetes who present with acute myocardial infarction (MI), and to explore the relationship between these treatments and late clinical outcomes.

Design and setting: Prospective, nationwide multicentre registry: the Acute Coronary Syndrome Prospective Audit (ACACIA).

Patients: Patients presenting to 24 metropolitan and 15 non-metropolitan hospitals with acute coronary syndrome (ACS) and a final discharge diagnosis of acute MI between November 2005 and July 2007.

Main outcome measure: All-cause mortality at 12 months.

Results: Nearly a quarter of 1744 patients with a final diagnosis of acute MI had a history of diabetes on presentation. Patients with diabetes were older, with a greater prevalence of comorbidities than non-diabetic patients, and were less likely to be treated at discharge with evidence-based medications (aspirin, clopidogrel, a statin and/or a β -blocker) or to receive early invasive procedures. After adjusting for baseline characteristics and therapeutic interventions, diabetes at presentation was independently associated with a higher mortality at 12 months after MI (hazard ratio, 1.79; 95% CI, 1.18–2.72; $P=0.007$). Early invasive management and discharge prescription of guideline-recommended medications were associated with a significantly reduced hazard of mortality at 12 months.

Conclusion: Patients with diabetes have a higher risk than non-diabetic patients of late mortality following an acute MI, yet receive fewer guideline-recommended medications and early invasive procedures. Increased application of proven pharmacotherapies and an early invasive management strategy in patients with diabetes presenting with ACS might improve their outcomes.

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each hospital site and confirmed by a centralised query process.¹¹

The trial was approved by the institutional ethics committee at each site. All patients included in the trial provided informed consent with the exception of those who died before consent was sought; access to their medical records was approved by the local ethics committees.

Clinical and treatment variables

Data were obtained from hospital medical records on demographic, clinical and procedural factors involved in the management of patients with ACS. Diabetes status at admission was based on a self-reported physician diagnosis and was further classi-

fied by treatment type as diet only, oral hypoglycaemic agent(s), or needing insulin therapy. Those who were insulin-dependent included patients with type 1 diabetes. The estimated glomerular filtration rate (eGFR) was obtained from serum creatinine measurements and the Modification of Diet in Renal Disease formula.¹⁴ The Global Registry of Acute Coronary Events (GRACE) risk score containing relevant prognostic factors was derived for each patient.¹⁵ A discharge prescription of aspirin, clopidogrel, a statin, β -blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor (AR) antagonist was recorded. Early invasive management was defined as angiography at any time during the acute hospital

stay, regardless of transfer between acute hospitals. The use of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) was also recorded. All data were collected by trained clinical coordinators.

All-cause mortality and time of death were determined to 12 months after the index hospitalisation. Vital status at 12 months could be confirmed in 99.9% (1741) of the cohort. Data on late non-fatal recurrent MI (re-MI), stroke and coronary revascularisation were obtained from hospital discharge summaries and diagnosis-related group (DRG) coding reports.

Statistical analysis

Normally distributed variables were expressed as mean (SD), variables with a skewed distribution as median (interquartile range [IQR]), and counts as number and percentage. Kaplan–Meier survival curves, stratified by diabetes treatment groups, were plotted and compared with the log-rank test.

The association between admission diabetes status and all-cause mortality and combined death, non-fatal re-MI or stroke at 12 months was assessed through Cox proportional hazards modelling, using robust sandwich standard error estimates to adjust for within-hospital clustering effects. The model was also adjusted for other significant clinical covariates, including age, prior MI, Killip Class, GRACE risk score, impaired renal function (eGFR < 60 mL/min/1.73 m²), need for dialysis, early invasive management, and discharge treatment with aspirin, clopidogrel, a statin, β -blocker or ACE-inhibitor/AR-antagonist. Diabetes status was entered into the model either as a binary variable or by category according to type of diabetes treatment.

As no interactions were observed between variables — including between diabetes status and rural/metropolitan hospital source — the simple models are presented. The proportional hazards ratio (HR) was assessed for each covariate. A probability <0.05 was considered statistically significant. All analyses were performed with Stata software, version 9.1 (StataCorp, College Station, Tex, USA).

RESULTS

Of the 1744 patients in the analysis, 24.3% (423) had a history of diabetes; about a third of these were treated with diet alone, a quarter required insulin therapy, and the remainder were taking oral hypoglycaemic

1 Patient characteristics, by diabetes history at admission*

Characteristic	No diabetes (n = 1321)	Diabetes (n = 423)
Mean age (years) (SD)	64.6 (13.6)	66.4 (11.9)
Male sex	936 (70.9%)	292 (69.0%)
Hypertension	706 (53.4%)	326 (77.1%)
Dyslipidaemia	640 (48.4%)	282 (66.9%)
Current smoking	385 (29.1%)	89 (21.0%)
Diabetes treatment		
Diet only	na	135 (31.9%)
Oral hypoglycaemic agent(s)	na	187 (44.2%)
Insulin	na	101 (23.9%)
Family history of coronary artery disease	444 (33.6%)	118 (27.9%)
Prior myocardial infarction	271 (20.5%)	114 (26.9%)
Prior percutaneous coronary intervention	151 (11.4%)	69 (16.3%)
Prior coronary artery bypass grafting	115 (8.7%)	67 (18.8%)
Prior atrial fibrillation	104 (7.9%)	57 (13.5%)
Prior cerebrovascular accident	60 (4.5%)	38 (9.0%)
Prior peripheral vascular disease	62 (4.7%)	45 (10.6%)
Admission diagnosis		
Acute STEMI	592 (44.8%)	133 (31.4%)
Non-ST segment elevation ACS	729 (55.2%)	290 (68.8%)
Killip Class II–IV [†]	254 (19.2%)	141 (33.3%)
eGFR < 60 mL/min/1.73m ²	333 (25.2%)	169 (39.9%)
Median GRACE score (interquartile range) [‡]	137 (12–167)	145 (119–171)

na = not applicable. STEMI = ST segment elevation myocardial infarction. ACS = acute coronary syndrome. eGFR = estimated glomerular filtration rate.

*Values are number of patients (%) unless otherwise indicated.

[†]Killip class (scale I–IV) is a risk stratification tool for patients after myocardial infarction; a low Killip class indicates a lower likelihood of death within the first 30 days than a high Killip class.

[‡]GRACE = Global Registry of Acute Coronary Events risk score.

agent(s) (Box 1). Patients with diabetes were older and more likely than non-diabetic patients to have a prior history of hypertension, dyslipidaemia, atrial fibrillation, established atherosclerotic vascular disease, and previous coronary artery revascularisation, but were less likely to be current smokers and to present initially with STEMI. During hospitalisation, those with diabetes were more likely to have Killip Class II–IV heart failure, renal impairment, and a higher GRACE risk score.

Guideline-recommended therapies and invasive management

Patients with diabetes were less likely than non-diabetic patients to be taking aspirin, clopidogrel, a statin or a β -blocker at hospital discharge, but were more likely to be taking an ACE-inhibitor or AR-antagonist (Box 2). Patients with diabetes were less likely to undergo early angiography than non-diabetic patients (67.6% versus

82.1%), and had a lower overall rate of any coronary revascularisation (PCI/CABG) (46.6% versus 61.3%).

Determinants of long-term outcomes

After 12 months, patients with diabetes had about twice the mortality rate of non-diabetic patients (16.3% versus 7.3%), and also about twice the rate of combined death, non-fatal re-MI or stroke (28.4% versus 16.4%) (Box 2).

Twelve-month survival curves by type of diabetes treatment are shown in Box 3. All groups of diabetic patients, regardless of therapy type, had worse survival than non-diabetic patients (log-rank $P < 0.001$).

Compared with non-diabetic patients, those with diabetes had an 80% higher adjusted hazard of 12-month mortality (HR, 1.79; 95% CI, 1.18–2.72; $P = 0.007$), with the highest hazard in those requiring insulin therapy (HR, 2.53; 95% CI, 1.50–4.28; $P = 0.005$) (Box 4). Invasive management and

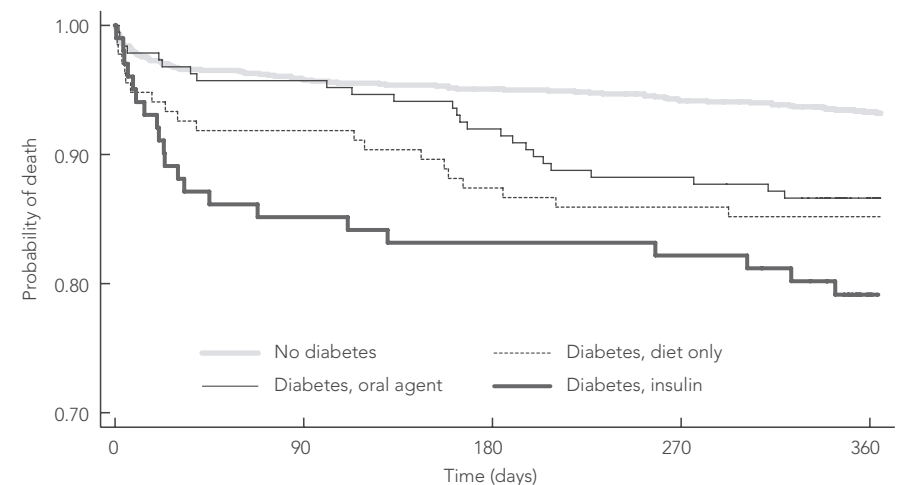
2 Use of clinical guideline-recommended treatments and 12-month clinical outcomes, by diabetes history at admission*

Outcome	No diabetes (n = 1321)	Diabetes (n = 423)
Drugs prescribed at discharge		
Aspirin	1181 (89.4%)	355 (83.9%)
Clopidogrel	932 (70.5%)	267 (63.1%)
Statin	1151 (87.1%)	353 (83.4%)
β-Blocker	976 (73.9%)	291 (68.8%)
ACE inhibitor/AR antagonist	973 (73.6%)	340 (80.4%)
Procedures		
Early angiography	1085 (82.1%)	286 (67.6%)
Percutaneous coronary intervention	711 (53.8%)	150 (35.5%)
Coronary artery bypass grafting	99 (7.4%)	47 (11.1%)
Clinical outcomes at 12 months		
All deaths	96 (7.3%)	69 (16.3%)
Death or non-fatal re-MI	205 (15.5%)	112 (26.5%)
Death, re-MI or stroke	217 (16.4%)	120 (28.4%)

ACE = angiotensin-converting enzyme. AR = angiotensin receptor. re-MI = recurrent myocardial infarction.

* Values are number of patients (%).

3 Kaplan–Meier survival curves to 12 months, by type of diabetes therapy



Oral agent = oral hypoglycaemic agent. Log-rank P value < 0.001.

the prescription at discharge of aspirin, a statin, β-blocker and/or ACE-inhibitor/AR-antagonist were each associated with a significantly reduced hazard of late mortality (Box 4). However, clopidogrel use was associated with an increased mortality hazard. These same treatment covariates, with the exception of a β-blocker and ACE inhibitor/AR-antagonist, were also independent predictors of a reduction in combined death, re-MI or stroke (Box 4). When analysis was confined to the subgroup with diabetes, the discharge prescription of a statin (HR, 0.27;

$P < 0.001$), β-blocker (HR, 0.34; $P < 0.001$), or ACE-inhibitor/AR-antagonist (HR, 0.30; $P < 0.001$) were each independent predictors of reduced 12-month mortality. Invasive management was also associated with a reduced hazard of death (HR, 0.56; 95% CI, 0.28–1.14), although this did not reach a conventional level of statistical significance ($P = 0.11$). Nevertheless, the observed 5%–15% differences in rates of individual therapies, including invasive management, between patients with and without diabetes accounted for little of the excess mortality

hazard associated with diabetes, with an HR of 1.84 (95% CI, 1.29–2.64), decreasing to 1.79 (95% CI, 1.18–2.72) when the model was adjusted for all therapies.

DISCUSSION

Our study shows that a substantially higher burden of late morbidity and mortality persists among patients with diabetes who present with acute MI, compared with non-diabetic patients, despite advances in the treatment of ACS. Although much of this excess mortality is explained by diabetes itself, a failure to use evidence-based pharmacotherapies and invasive treatment may also contribute.

A history of diabetes was present in nearly a quarter of patients who presented with acute MI, consistent with results of previous investigations of patients with ACS.^{2–4,6,7,16} Similarly, we found that patients with MI who have diabetes have an inherently higher cardiovascular risk than those without diabetes because of their older age, and higher prevalence of coronary risk factors, established cardiovascular disease and comorbidities, including heart failure and chronic renal impairment.^{2–4,6,7} However, despite controlling for these risk factors and comorbidities in our analysis, diabetes remained a strong independent predictor of late mortality. Although diabetic patients as a group had a worse late clinical outcome, those needing insulin appeared to be at highest risk. This contrasts with a previous investigation, which found that insulin dependence did not portend a worse long-term outcome after controlling for differences in risk characteristics, such as advanced age, longer duration of diabetes and the more severe disease in those who required insulin.¹⁷

Treatment practices: It has been shown that patients with diabetes and ACS derive even greater benefit than their non-diabetic counterparts from proven risk-modifying therapies.^{8–10,18} Despite this, we found that, within contemporary Australian clinical practice, there remains a disparity in the use of guideline-recommended treatments to the disadvantage of patients with diabetes (Box 2). As a group, diabetic patients at discharge were less likely than non-diabetic patients to be receiving long-term treatment with aspirin, clopidogrel, a statin or a β-blocker, although they were more likely to be receiving an ACE-inhibitor or AR-antagonist.

4 Diabetes and other independent predictors of 12-month all-cause mortality and death, myocardial infarction and stroke events

Variable	All-cause mortality		Death, re-MI or stroke	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, per decade > 65 years	1.01 (1.00–1.02)	0.03	1.01 (1.00–1.01)	ns
Prior myocardial infarction	1.56 (1.10–2.20)	0.01	1.83 (1.43–2.30)	<0.001
Killip Class	1.42 (1.10–1.82)	0.006	1.45 (1.23–1.74)	<0.001
GRACE score				
< 100	1.00		1.00	
101–150	1.37 (0.37–5.06)	ns	1.16 (0.67–2.04)	ns
151–200	3.43 (0.74–15.93)	0.11	1.32 (0.70–2.50)	ns
> 200	6.08 (1.15–32.24)	0.03	1.61 (0.75–3.46)	ns
eGFR < 60 mL/min/1.73 m ²	1.26 (0.82–1.94)	ns	1.35 (1.07–1.72)	0.01
Dialysis	2.77 (1.32–5.79)	0.007	3.35 (2.23–5.03)	<0.001
Angiogram	0.56 (0.38–0.83)	0.004	0.68 (0.51–0.90)	0.007
Discharge medications				
Aspirin	0.58 (0.39–0.86)	0.006	0.59 (0.43–0.82)	0.002
Statin	0.29 (0.19–0.43)	<0.001	0.48 (0.35–0.65)	<0.001
β-Blocker	0.57 (0.41–0.79)	0.001	0.75 (0.55–1.04)	ns
ACE inhibitor/AR antagonist	0.49 (0.34–0.71)	<0.001	0.80 (0.59–1.04)	ns
Clopidogrel	1.90 (1.29–2.84)	0.001	1.45 (1.15–1.83)	0.001
No history of diabetes	1.00		1.00	
Diabetes present	1.79 (1.18–2.72)	0.007	1.44 (1.11–1.86)	0.005
No history of diabetes*	1.00		1.00	
Dietary treatment only	1.27 (0.69–2.34)	0.44	1.38 (0.90–2.12)	0.14
Oral hypoglycaemic agent	1.89 (1.21–2.94)	0.005	1.35 (0.99–2.58)	0.06
Insulin therapy	2.53 (1.50–4.28)	0.005	1.71 (1.13–2.58)	0.01

re-MI = recurrent myocardial infarction. ns = not significant.

GRACE = Global Registry of Acute Coronary Events. eGFR = estimated glomerular filtration rate.

ACE = angiotensin-converting enzyme. AR = angiotensin receptor.

* Separate model including all covariates but with diabetes grouped according to treatment type. ◆

Moreover, analysis showed that the discharge prescription of aspirin, a statin, β-blocker, or ACE-inhibitor/AR-antagonist were each associated with a significantly reduced hazard of late deaths and serious cardiovascular events, although prescription of clopidogrel was associated with an increased hazard (Box 4). The latter finding could have been the result of unmeasured confounding or reverse causality (ie, patients who are sicker and more likely to die are also more likely to be prescribed treatments), as clinical trial evidence consistently supports a benefit for clopidogrel in the treatment of high-risk patients with ACS, with or without PCl.^{19–22} However, an adverse effect of clopidogrel in some patient subsets cannot be excluded, as suggested for patients with diabetic nephropathy in a post-hoc analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and

Ischemic Stabilization, Management, and Avoidance) trial, which did not include patients with ACS.²³

A similar underutilisation of evidence-based pharmacotherapies among diabetic patients with ACS has been demonstrated by data from recent international registries.^{3–7} Discordance between the level of risk and intensity of evidence-based treatment in patients with ACS appears to be a widespread problem that will be overcome only with targeted strategies.²⁴

Invasive management: Diabetic patients who present with ACS are more likely than non-diabetic patients to have multivessel and more diffuse coronary artery disease, and to derive greater benefit from an early invasive strategy.^{10,18} However, invasive procedures are often reported to be less used in diabetic patients than in non-diabetic patients, despite current trends towards early revascularisation

for high-risk patients with ACS.^{5–7} This disparity was also seen in our study, where diabetic patients had a lower rate of early angiography and coronary revascularisation. Similar to the finding reported in the total ACACIA cohort,¹² our analysis confirms that a relative long-term mortality advantage is associated with the provision of invasive management among high-risk patients with ACS and documented MI.

A limitation of this study was that the diagnosis of diabetes was based on self-report, and we were unable to evaluate patients with previously unrecognised diabetes. However, the described differences in outcome might have been even more pronounced had we investigated more actively for diabetes. We did not ascertain the adequacy of metabolic control among the diabetic patients studied, but another recent clinical trial failed to show that intensive metabolic control by means of the acute introduction of long-term insulin had a positive effect on mortality and morbidity in patients with diabetes and acute myocardial infarction (DIGAMI 2).²⁵ Our results have to be interpreted cautiously as causal associations cannot be proven using observational data. Furthermore, we are unable to account for unmeasured factors that influence the clinical decision not to prescribe certain cardiac medications or undertake angiography, and these unmeasured factors may have had an important effect on late clinical outcomes.

A concerted effort must be made to optimise the application of evidence-based guideline treatments, including an early invasive management strategy in patients with diabetes who develop ACS.

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