ORIGINAL ARTICLE

Long-term clinical outcome of patients with diabetes proposed for coronary revascularisation

J.R. Timmer[1], A. Breeman[1], J.P. Ottervanger[1*], E.P. de Kluiver[1], P.W. Boonstra[2], F. Zijlstra[3]

[1]Department of Cardiology, Isala Klinieken, Zwolle, the Netherlands, Departments of [2]Thoracic Surgery and [3]Cardiology, Thoraxcentre, University Medical Centre Groningen, the Netherlands, [*]corresponding author: tel.: +31 (0)38-424 21 98, fax: +31 (0)38-424 32 22, e-mail: v.r.c.derks@isala.nl

ABSTRACT

Background: The optimal method of revascularisation in diabetic patients with coronary artery disease (CAD) remains controversial. It was our aim to evaluate long-term outcome in diabetic patients with CAD in daily practice, in whom an invasive approach was considered.

Methods: A prospective follow-up study of patients with CAD in whom a coronary revascularisation procedure was considered. Follow-up data were obtained on the vital status up to ten years after inclusion.

Results: Of the 872 included patients, a total of 107 patients (12%) had diabetes. Patients with diabetes were older and more frequently female. Long-term mortality was higher in diabetics than nondiabetics (36 *vs* 25%, p=0.01). This association was observed in both medically treated patients (65 *vs* 31%, p=0.01) and in those treated by percutaneous coronary intervention (41 *vs* 24%, p=0.02). There was, however, no difference in mortality in diabetes *vs* nondiabetes patients after coronary artery bypass grafting (24 *vs* 24%, p=0.89). Multivariate analysis did not change these findings.

Conclusion: Diabetic patients with significant CAD had a higher long-term mortality compared with patients without diabetes. In patients with diabetes, survival was highest after coronary artery bypass grafting and appeared to be comparable between diabetic and nondiabetic patients. Complete revascularisation may decrease the influence of diabetes on survival.

KEYWORDS

Diabetes, CABG, revascularisation

INTRODUCTION

Diabetes is associated with impaired outcome after coronary revascularisation.[1,2] The optimal method of revascularisation remains controversial. In the BARI trial, coronary artery bypass grafting (CABG), when compared with percutaneous coronary intervention (PCI), was associated with a significant seven-year mortality reduction in patients with diabetes.[3] However, this long-term benefit was not confirmed by other randomised trials.[4,5] Furthermore, patients in daily practice may differ from those included in randomised trials, as was shown in the registry of the BARI trial.[6] To evaluate the long-term outcome of diabetic patients with coronary artery disease (CAD) in daily practice in whom an invasive approach was considered, we carried out a follow-up study of patients included in the DUCAT (Dutch Inventory of Invasive Coronary Atherosclerosis Treatments) study.

PATIENTS AND METHODS

The DUCAT study was initiated in 1992 with the purpose to determine how appropriate treatment decisions are concerning invasive treatment of patients with CAD.[7] Assessment of appropriateness of medical decisions was achieved using the RAND/UCLA method.[8] Six cardiothoracic surgeons and six interventional cardiologists from 12 heart centres in the Netherlands were asked to participate in a panel to determine appropriateness of treatment decisions in all consecutive patients presented to ten heart teams, consisting of at least one surgeon and one interventional cardiologist. This panel method has been proven to be consistent and reliable in assessing appropriateness.[8]

Enrolment began in February 1992 for a period of three months. Each case was presented by a clinical cardiologist in person or by letter, fax, or telephone, and eventually led to an intention-to-treat decision in favour of PCI, CABG, or medical treatment. All presentations were based on clinical data and coronary angiographic results. Enrolment was approved for all patients with significant CAD, defined by the DUCAT panel as a minimum of 50% narrowing of the left main coronary artery, or at least one artery with 70% narrowing and other arteries with 50% narrowing in multivessel disease, and one artery with 70% narrowing in one-vessel disease. Patients who had previously had CABG or in whom CABG was to be combined with other surgery (cardiac or general) were excluded. During presentation to the heart team, several variables were collected, including demographics, medical history, risk factors for CAD, symptomatology, ischaemia detection tests, coronary angiographic evaluation, left ventricular function tests, urgency status and intention of treatment. The main findings of the DUCAT study have been published previously.[7,8] In summary, 3646 consecutive patients were included. Unstable angina was the most appropriate clinical status for intervention, whereas asymptomatic coronary disease was the least.

The present study is a two-centre follow-up study of all patients consecutively presented to the heart team of the heart centres of Zwolle and Groningen in the Netherlands. In these two centres, a total of 1047 patients were presented to the heart teams during the study period. Follow-up data were obtained on the vital status up to ten years after inclusion. Follow-up data were collected via the registry office, the general practitioner or via a direct contact with the patient or his relatives by telephone.

DEFINITIONS

Diabetes was defined as the use of oral hypoglycaemic agents, insulin, or a diabetes-related diet with diabetes documented in the medical history. The presence of hypertension and a positive family history were derived from the data in the medical history. Lipid disorder was present when lipid-lowering medication was used or when stated in the medical history. Peripheral vascular disease was defined as the presence of symptomatic claudication or a history of peripheral vascular surgery. Stroke was defined as either an ischaemic or a haemorrhagic cerebral vascular accident with permanent sequelae. Decreased LV function was defined as an ejection fraction ≤40%. Type C lesion was defined as a stenosis longer than 20 mm, or with rugged contours or tortuous shape, or located at spots not readily accessible for a catheter, or total vessel occlusions older than three months.

STATISTICS

Differences between group means were tested by two-tailed Student's t test. A χ^2 statistic was calculated to test differences between proportions. Survival functions were calculated, using the Kaplan-Meier product limit method. Mantel-Cox (or log-rank) test was applied to evaluate the differences between survival functions.

Multivariate Cox proportional-hazards regression analysis was applied to assess the independent relation between revascularisation strategy and ten-year survival after adjustment for baseline characteristics.

RESULTS

Patients
Of the 1057 included patients, ten cases were censored because they were presented to the heart team for the second time. Of the remaining 1047 patients, 877 (84%) met the inclusion criteria and were enrolled in the study. The diabetic status was unknown for five patients; these patients were not included in our analysis. Our analysis therefore consisted of 872 patients. A total of 107 patients (12%) had diabetes. Patients with diabetes were older (66 ± 8 *vs* 62 ± 10 year, p<0.001), were more frequently female (55 *vs* 21%, p<0.001) and had a higher prevalence of hypertension (46 *vs* 27%, p<0.001) when compared with patients without diabetes. Furthermore, patients with diabetes more often had multivessel CAD. Differences in baseline characteristics between patients with and without diabetes are shown in *table 1*.

Coronary revascularisation
In patients without diabetes, PCI was recommended in 333 patients (44%), CABG in 333 patients (44%) and a conservative approach was advised in 99 patients (13%). In patients with diabetes the type of revascularisation was comparable with those without diabetes, with percentages of patients recommended for PCI, CABG or conservative approach of 36, 48 and 16%, respectively. There were several differences between diabetic patients treated conservatively and those treated invasively. There were no differences in baseline characteristics between diabetic patients treated with PCI and those treated with CABG with regard to age, sex, risk factors, coronary history, comorbidity or left ventricular ejection fraction (LVEF). However, patients with diabetes treated with PCI more often had single-vessel disease (56 *vs* 4%, p<0.001) compared with those treated with CABG.

Long-term mortality
In the total study group, long-term mortality was associated with increasing age, no revascularisation, diabetes (36 *vs* 25%, p=0.01), peripheral artery disease

Table 1. *Baseline characteristics of all patients according to diabetic status*

	Diabetes (n=107)	Nondiabetes (n=765)	P value
Age in years (mean SD)	66 ± 8	62 ± 10	<0.001
Male	48 (44.9%)	601 (78.6%)	<0.001
Risk factors			
• Hypertension	49 (45.8%)	208 (27.3%)	<0.001
• Smoking	17 (18.9%)	209 (29.7%)	0.033
• Lipid disorder	35 (35.7%)	261 (37.1%)	0.786
• Family history	24 (28.9%)	278 (42.4%)	0.018
• Obesity	17 (21.3%)	77 (13.2%)	0.054
Coronary history			
• Previous myocardial infarction	35 (32.7%)	292 (38.3%)	0.266
• Previous PCI	13 (12.1%)	83 (10.9%)	0.694
Comorbidity			
• COPD	12 (11.2%)	66 (8.7%)	0.389
• Peripheral vascular disease	17 (15.9%)	70 (9.2%)	0.030
• Stroke	12 (11.2%)	41 (5.4%)	0.018
Vessels diseased			
• One vessel	28 (26.2%)	275 (35.9%)	0.047
• Two vessels	36 (33.6%)	214 (28.0%)	0.224
• Three vessels	37 (34.6%)	223 (29.2%)	0.250
• Left main coronary artery	6 (5.6%)	53 (6.9%)	0.610
• Type C lesion	58 (54.2%)	382 (49.9%)	0.408
LVEF 20 to 40%	17 (16.3%)	116 (15.6%)	0.843
<20%	5 (4.8%)	20 (2.7%)	0.218

SD = standard deviation; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease.

and an LVEF ≤40%. As compared with revascularisation by either PCI or CABG, medically treated patients had an increased mortality. The increased mortality in patients with diabetes was observed in both medically treated patients (n=116) (diabetes 65 *vs* nondiabetes 31%, p=0.01) and in those who received PCI (n=372) (diabetes 41 *vs* nondiabetes 24%, p=0.02). There was, however, no difference in mortality between diabetes and nondiabetes after CABG (n=384) (24 *vs* 24%, p=0.89). Survival curves of patients with and without diabetes according to type of revascularisation are shown in *figures 1* to *3*.

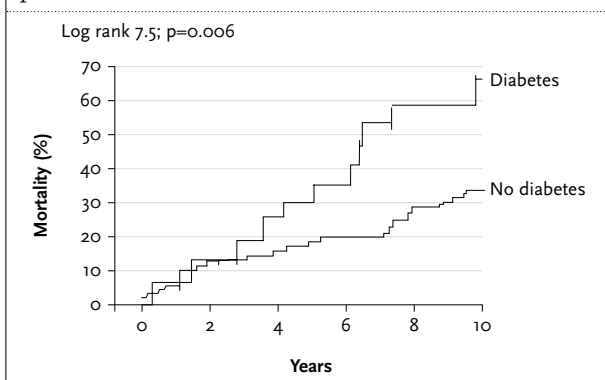**Figure 2.** *Ten years' follow-up of 372 PCI-treated patients*

Log rank 5.8; p=0.016

Figure 1. *Ten years' follow-up of 116 medically treated patients*

Log rank 7.5; p=0.006
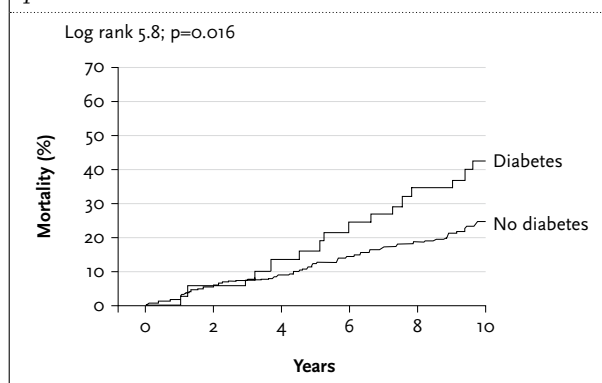
Figure 3. *Ten years' follow-up of 384 CABG-treated patients*

Log rank 0.02; p=0.90
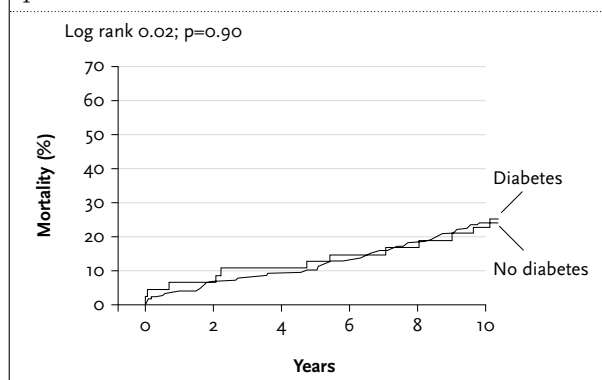
Multivariate analysis

To study the independent prognostic importance of diabetes on clinical outcome, multivariate analysis was performed. We included age, gender and all univariate predictors of long-term mortality in the multivariate model. After multivariate analysis increasing age, diabetes and a decreased LV function were independent predictors of long-term mortality (*table 2*). The independent predictive value of diabetes was most pronounced in patients treated without revascularisation and in those treated with PCI (OR 2.1, 95% CI 1.3 to 3.3). In patients treated with CABG, diabetes was not an independent predictor of long-term mortality (OR 1.2, 95% CI 0.6 to 2.4).

Table 2. *Independent predictors of mortality*

	OR	95% CI
Male gender	1.36	0.98 to 1.89
Age (per year)	1.09	1.07 to 1.12
Conservative treatment[#]	1.24	0.86 to 1.79
Diabetes	1.46	1.01 to 2.13
Peripheral vascular disease	1.28	0.85 to 1.91
Decreased left ventricle function	1.58	1.15 to 2.18

[#]As compared with revascularisation by either PCI or CABG. Adjusted for differences in the other variables. OR = odds ratio; CI = confidence limit.

DISCUSSION

In patients with coronary artery disease in whom an invasive approach was considered, diabetes was associated with increased long-term mortality. However, in patients treated with CABG this association was not observed. Our analysis reflects real-world clinical practice and has additional value regarding the still ongoing debate about the optimal method of revascularisation for patients with diabetes.

Diabetes *vs* nondiabetes

Patients with diabetes had a higher long-term mortality compared with patients without diabetes. This could be due to differences in baseline characteristics. In general, patients with diabetes were older, were more often female and had a higher prevalence of hypertension. However, after multivariate analysis diabetes was still a significant predictor of mortality. There may be several mechanisms for this increase in mortality. A procoaguable state and more unfavourable lipid levels in diabetic patients might play a role.[9,10] Atherosclerotic coronary abnormalities may be more progressive in diabetes. Furthermore, pre-existing left ventricular failure, either diastolic or systolic, may contribute to an increase in mortality.[11] Moreover, glycometabolic disturbances during acute coronary events

increase infarct size and might predispose to ventricular arrhythmias.[12] Interestingly, in patients with extensive CAD, who are generally treated with CABG, the difference in mortality between diabetes and nondiabetes seems to be much less clear.[13]

PCI as revascularisation strategy

Mortality was higher in PCI-treated patients with diabetes compared with those without diabetes. There may be several explanations for this difference. Patients with diabetes have smaller calibre vessels and higher rates of restenosis than patients without diabetes.[14] Furthermore, more progressive atherosclerosis in diabetes may also affect coronary segments not significantly stenosed at the time of the initial decision to perform revascularisation. As diabetic patients already have a comprised LV function, display impaired preconditioning and have glycometabolic disturbances potentially increasing ischaemic myocardial damage, they might be more prone to die when suffering subsequent coronary events.[11,15]

CABG as revascularisation strategy

There was no difference in mortality in diabetic patients treated with CABG compared with nondiabetic patients treated with CABG. Previous studies show conflicting results. Several studies report that diabetes is associated with a worse outcome after CABG.[1,16] The randomised EAST trial and the recently published study by Calafiore *et al.*, however, did not find an association between diabetes and a long-term adverse prognosis after CABG.[5,17]

Revascularisation in diabetes

In patients with diabetes, those treated medically had the highest mortality, whereas the lowest mortality was found in diabetic patients treated with CABG. Differences in baseline characteristics between medically treated patients and those undergoing revascularisation may partly explain the differences in outcome. Medically treated patients were older and had a higher prevalence of peripheral artery disease and COPD than those treated with coronary revascularisation. The improved prognosis after CABG in diabetic patients can be caused by the fact that PCI in diabetes is associated with a higher restenosis rate, whereas graft patency after four years between patients with and without diabetes may be comparable.[18] Also, incomplete revascularisation might be detrimental in diabetic patients treated with PCI. Coronary artery bypass grafting may be superior in reaching complete revascularisation leaving PCI-treated patients with an increased area at risk for future ischaemic events.[19] Furthermore, there seems to be a protective effect from the use of an internal thoracic artery (ITA) in CABG, especially in patients with diabetes.[20] The mortality risk after myocardial infarction in diabetic patients without

ITA is much higher when compared with diabetic patients who had received revascularisation with an ITA. In our study the majority of patients were treated with an ITA. It is still unclear whether the type of antidiabetic treatment used interacts with the success of different revascularisation procedures. Although the use of drug-eluting stents has reduced the occurrence of restenosis in diabetic patients, diabetic patients using insulin still appear to be at an increased risk.[21,22] It is possible that particularly this patient group could benefit from surgical revascularisation compared with PCI.[23]

Other studies

In the BARI trial, 1829 patients with multivessel disease were randomised to CABG or PCI.[3] This study found a better seven-year survival in diabetic patients (n=353) treated with CABG compared with PCI (76 *vs* 56%). However, other randomised trials, as the CABRI trial and the EAST trial, did not find a significant beneficial effect after CABG compared with PCI in diabetic patients.[4,5] Moreover, the RITA trial including 62 patients with diabetes found a nonsignificantly worse outcome for diabetic patients randomised to CABG compared with PCI.[24] Observational studies also found contradicting evidence regarding the optimal method of reperfusion. The Duke and EMORY analyses did not find a benefit for CABG *vs* PCI in diabetic patients, although insulin-treated diabetes seemed to benefit from CABG.[1,2] The MAHI study found an unadjusted survival benefit of diabetic patients when treated with CABG compared with PCI.[25] Interestingly, in diabetic patients from the registry of the BARI trial there was no significant difference in mortality between the two revascularisation methods.[6] Niles *et al.*, however, did find a significant reduction in mortality in more than 7000 diabetic patients treated with CABG *vs* PCI after five years of follow-up.[26] Our study also found a survival benefit for diabetic patients when treated with CABG compared with PCI after a long follow-up period of ten years.

STUDY LIMITATIONS

This was an observational study without randomisation. This could have led to differences in unmeasured baseline characteristics for which no correction or adjustment could be made.

Unfortunately, no detailed information about medication use or the type of antidiabetic treatment was available. During the study period, intracoronary stenting and treatment with glycoprotein IIb-IIIa inhibitors or clopidogrel were not available. These new therapeutic modalities may well have a profound effect on clinical outcome and may, in particular, improve clinical outcome in patients with diabetes when treated with PCI.[27,28]

CONCLUSION

Diabetic patients with significant CAD had a higher long-term mortality compared with patients without diabetes. In patients with diabetes survival was highest after coronary artery bypass grafting and appeared to be comparable between diabetic and nondiabetic patients. Complete revascularisation may decrease the influence of diabetes on survival.

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ABOUT THE COVER

'Gedroogde inktvis'

Manuela Jalimsing
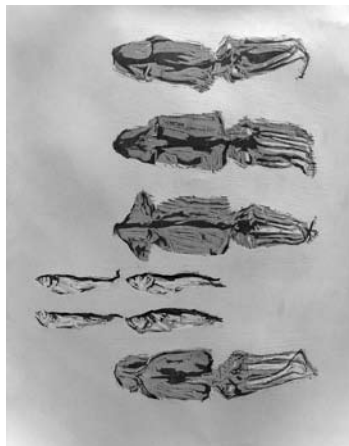
Manuela Jalimsing was born in 1971 in Paramaribo. She now lives and works in The Hague. Manuele attended the College of Art in Utrecht and the Royal Academy of Art in The Hague.

Her work can be seen in many group and solo exhibitions in the Netherlands.

With the shape of fish, she designs a composition on a surface. The expression of the fish and the transparency due to the drying in salt attract her. Every fish is put in its own position, thus creating a certain tension, trying to reach a balance. After observation the images are put onto paper. She often uses desiccated fish, bought at the Chinese supermarket.

Her passion for the wooden print is probably based on the fact that it is a near to nature and practical technique in the course of which you can create images without using lots of material.

In her childhood, fish was one of her main sources of inspiration. Her father was a fisherman on the Atlantic Ocean from the age of eleven, just as his father and his brothers. The many stories about the rough sea and his catches made a great of impression on her.

During her studies at the Academy of Art, Jalimsing was pregnant and she avoided the studios because of the chemical substances. When making wooden prints she only used a board, a wooden spoon and a gouge, and she experienced the natural art of wooden print.

Later, she attended a workshop by a Japanese master, who taught her how to use only pure materials.

An original print (71 x 100 cm) is available at a price of € 525 and can be ordered from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, e-mail: Galerie-Unita @planet.nl, www.galerie-unita.com.