

Advanced Symptoms in Diabetics Mitigates Early Benefits of Coronary Artery Bypass Grafting: Analysis of Over 10,000 Patients

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Abstract

Objectives: Coronary artery bypass grafting (CABG) is the preferred revascularisation option for diabetics with multivessel coronary artery disease, in current guideline recommendations. Not infrequently, coronary artery disease causes minimal symptoms in diabetic patients, so they present late for surgery and this could have implications for clinical outcomes. We sought to examine differences in symptom severity between diabetics and non-diabetics at presentation for CABG, and the impact on in-hospital outcomes. Methods: We retrieved prospectively collected data for all patients who had CABG between January 2000 and December 2022. Perioperative variables were compared between diabetic and non-diabetics. The association between in-hospital major adverse cardiac and cerebrovascular events (MACCE) and perioperative variables was determined using multivariate analysis. Results: Of 10,834 patients, diabetics constituted 24.8% (n = 2687) with mean age 66.4 ± 8.7 years compared to non-diabetics 65.9 ± 9.4 , p = 0.02. More diabetics (p < 0.001) had unstable symptoms (31% vs 25%), heart failure (15.5% vs 8.5%), previous myocardial infarction (54.2% vs 46.2%), prior coronary stenting (19% vs 15.8%), left ventricular systolic ejection fraction < 0.5 (33.8% vs 23.8%), triple vessel coronary disease (73.8% vs 70%) and frequently underwent non-elective CABG (32.3% vs 27.6%). Operative mortality (2.3% vs 1.5%, p = 0.004) and MACCE rates (4.7% vs 2.9%, p < 0.001) were higher in diabetics. Diabetes, however, was not an independent predictor of MACCE, but non-elective operation (HR1.4, 95% CI 1.11 - 1.77, p < 0.001) and NYHA class III/IV (HR1.03, 95% CI 1.32 - 1.70, p = 0.03) were. Conclusions: Diabetics more often presented for non-elective CABG with advanced symptoms, impaired left ventricular function, prior myocardial infarction and coronary stenting. Advanced symptoms contributed to higher MACCE rates in diabetics. Diabetic patients should be referred early for surgery.

Keywords

Coronary Artery Disease, Diabetes Mellitus, Advanced Cardiac Symptoms, Coronary Artery Bypass Grafting, Major Adverse Cardiac and Cerebrovascular Event

1. Introduction

Diabetes mellitus is a risk factor for coronary artery disease (CAD) [1] and its prevalence in the general population is on the rise [2]. Registration figures from Diabetes UK for 2021-2022 showed that 4.3 million people suffer from diabetes, an increase of 148,951 from 2020-2021 [2]. Coronary artery disease in people with diabetes mellitus is often multi-vessel, typically diffuse, and frequently associated with microvascular involvement [3], and not frequently associated with typical symptoms.

Coronary artery bypass grafting (CABG) is recommended by current guidelines as the preferred revascularisation strategy for diabetics with multi-vessel CAD because of better long-term outcomes, compared to PCI [4]-[6]. Following CABG, diabetic patients experience higher rates of postoperative infections [7]-[9], renal and neurological complications [10] [11] which adversely affect outcomes. We have also previously reported higher rates of non-infective complications in diabetic patients that was not due to diabetes per se [12]. It is, however, still unclear if diabetic patients are at greater risk of major adverse cardiac and cerebrovascular events (MACCE) after CABG because of their diabetes or due to advanced cardiac symptoms.

This study is therefore designed to examine the prevalence of advanced symptoms in diabetic patients undergoing CABG, in comparison to non-diabetics, and the influence on in-hospital MACCE.

2. Materials and Methods

2.1. Patient Population

This study was approved by the local ethics committee on December 7th, 2022 and individual patient consent was waived; approval number LA.2022.005. The clinical data for all patients undergoing cardiac surgery at our institution is prospectively collected and stored in a database that is maintained by a trained database manager. We retrieved pre-, intra-, and post-operative clinical data for all patients who underwent isolated CABG at our institution between January 2000 and December 2022. We excluded those with unknown diabetic status (n = 98) and those who underwent redo CABG (n = 203). We divided the patients into diabetic and non-diabetic groups (see Figure 1), and compared peri-operative data between the two groups.



Figure 1. A flowchart depicting the selection of the study population.

2.2. Statistical Analysis

The primary outcome of this study was to examine the prevalence of advanced cardiac symptoms in diabetic and non-diabetic patients undergoing CABG, and the relationship with in-hospital major adverse cardiac and cerebrovascular event (MACCE). MACCE is defined as a composite of mortality, myocardial infarction, cardiac reintervention and stroke.

As secondary outcomes, we examined markers of advanced coronary artery disease, such as: frequencies of preoperative myocardial infarction, prior coronary artery stenting, impaired left ventricular ejection fraction, and urgency of surgery.

Absolute values and percentages are used for categorical variables. Continuous variables are presented as mean and standard deviation for variables with normal Gaussian distribution, and as median and interquartile range for variables with skewed distribution. Both categorical and continuous variables were compared between diabetic and non-diabetic patients using univariable analyses. Categorical variables were compared using the Pearson v2 test, while the analysis of variance was used for continuous variables with normal distribution and Kruskal–Wallis test was used for variables that are not summarized parametrically. Multivariable analyses were performed using stepwise logistic regression to determine the predictors for in-hospital MACCE. A 2-sided P-value of <0.05 was considered significant. Statistical analysis was performed using SPSS v.28.0.01.1.

3. Results

3.1. Baseline Characteristics

A total of 10,834 patients were included in the study; 2687 (24.8%) were diabetic and 8147 (75.2%) non-diabetic. Amongst the diabetics, 1349 (50.2%) were tablet controlled, 835 (31.1%) insulin controlled, and 503 (18.7%) diet controlled. The mean age for diabetics was 66.4 ± 8.7 compared to 65.9 ± 9.4 years for nondiabetics (p = 0.02). Diabetic patients were older, more often female and had higher mean body mass index (see Table 1). While multi-vessel disease was more prevalent in diabetics (n = 2605, 96.9% vs n = 7740, 95%, p < 0.001), non-diabetic patients had higher incidence of left main stem disease.

Other comorbidities more prevalent in diabetics (p < 0.001) included; hypertension 83.7% (n = 2238) vs 68.6% (n = 5562), renal dysfunction 2.8% (n = 75) vs 0.9% (n = 72), history of neurological disease 10.6% (n = 284) vs 5.6% (n = 450) and extracardiac arteriopathy 19% (n = 509) vs 10.9% (n = 888).

Table 1. Baseline characteristics of diabetic and non-diabetic patients undergoing coronary artery bypass grafting.

Variable	Diabetics $(n = 2687)$	Non-Diabetics (n = 8147)	P Value
Mean Age (years) ± SD	66.4 ± 8.7	65.9 ± 9.4	<0.02
Female, %, (n)	21.1 (568)	19.3 (1574)	0.040
Mean Body Mass Index (kg/m²) ± SD	30.4 ± 4.8	28.3 ± 4.3	<0.001
CCS class III or IV, %, (n)	49.0 (1317)	42.0 (3423)	<0.001
NYHA class III or IV, %, (n)	24.6 (662)	16.3 (1330)	<0.001
Unstable angina, %, (n)	31.0 (833)	25.0 (2033)	<0.001
Heart failure, %, (n)			<0.001
Never	80.3 (2158)	85.0 (6925)	
Current	8.4 (225)	4.6 (377)	
Past	7.1 (191)	4.9 (403)	
Number of Prior myocardial infarction, %, (n)			<0.001
0	45.8 (1226)	53.8 (4372)	
1	39.4 (1055)	37.1 (3009)	
2	14.8 (396)	9.1 (738)	
Number of Previous PCI, %, (n)			<0.001
0	81.1 (2173)	84.6 (6883)	
1	17.6 (472)	14.3 (1163)	
2	0.9 (25)	0.9 (70)	
3	0.4 (11)	0.3 (24)	
Hypertension, %, (n)	83.7 (2238)	68.7 (5563)	<0.001
Renal Dysfunction, %, (n)	2.8 (75)	0.9 (72)	<0.001
Previous TIA, %, (n)	6.3 (169)	3.8 (307)	<0.001
Previous Cerebrovascular accidents, %, (n)			<0.001
with full recovery	3.0 (80)	1.2 (95)	
with residual deficit	1.3 (35)	0.6 (48)	
Extracardiac arteriopathy, %, (n)	19.0 (509)	10.9 (888)	<0.001
Coronary artery disease, %, (n)			<0.001
Single vessel	3.0 (81)	4.9 (397)	
Double vessel	23.2 (623)	25.2 (2047)	
Triple vessel	73.8 (1982)	70.0 (5693)	

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Left main stem coronary artery disease, %, (n)	34.5 (925)	37.9 (3084)	0.001
Left ventricular ejection fraction, %, (n)			< 0.001
≥0.5	66.2 (1778)	76.2 (6207)	
0.31 to 0.49	27.0 (726)	19.6 (1593)	
≤0.3	6.8 (182)	4.2 (342)	
Mean EuroSCORE, % ± SD	4.08 ± 2.8	3.40 ± 2.6	< 0.001
Logistic EuroSCORE, % ± SD	4.71 ± 6.8	3.56 ± 4.9	< 0.001

Continued

CCS—Canadian cardiovascular society, EuroSCORE—European system for cardiac operative risk evaluation, PCI—Percutaneous coronary intervention with stenting, TIA—Transient Ischaemic Attack.

3.2. Advanced Symptoms at Presentation for Surgery

Diabetic patients had more significant cardiac history (**Table 1**); 31.0% presenting with unstable symptoms compared to 25.0% (p < 0.001) for non-diabetics. More diabetics had experienced 1 or 2 episodes of myocardial infarction, 39.4% and 14.8% respectively, in comparison to non-diabetics with corresponding rates of 37.1% and 9.1% (p < 0.001). Similarly, 18.9% of diabetics had been treated with, at least, one previous percutaneous coronary intervention and coronary artery stenting, in comparison to 15.5% of non-diabetics (p < 0.001).

Substantially more diabetic patients (33.8%) presented with Impaired left ventricular systolic ejection fraction less than 0.5 at the time of surgery compared to non-diabetic patients (23.8%, p < 0.001).

3.3. In-Hospital Outcomes

Table 2 compares in-hospital outcomes between the two groups. Diabetic patients had a substantially higher preoperative estimated risk of mortality using the European system for cardiac operative risk evaluation (EuroSCORE). Consistent with this, the observed in-hospital mortality was greater in diabetic patients than non-diabetic patients (2.3% vs 1.5%, p = 0.003). Postoperative complications in general, were more common in diabetic patients compared to non-diabetics (56.0%, n = 1506 vs 50.2% (n = 4095) p < 0.001. Infection rates were 9.5% for diabetics and 5.9% for non-diabetics p < 0.001. Amongst diabetics, 3.2% (n = 86) required readmission to intensive care versus 2.1% (n = 171) in non-diabetics.

Postoperative myocardial infarction and coronary re-intervention for graft failure (either by stenting or reoperation) were not statistically different between the two groups. Overall, MACCE rates were 4.7% for diabetics vs 2.9% for non-diabetics (p < 0.001).

3.4. Determinants of MACCE

Multivariate analysis identified preoperative factors that were independent predictors of MACCE, and these are depicted in **Table 3**. Diabetes was not a determinant of MACCE. However, preoperative parameters indicative of late presentation for CABG such as advanced cardiac symptoms (NHYA class III/IV), impaired left ventricular systolic ejection fraction and non-elective surgery (urgent and emergency operations), that were more prevalent in diabetic patients, significantly increased the risk of MACCE after CABG. Also, variables that are known indicators of complicated diabetes such as renal dysfunction, stroke, and extracardiac arteropathy independently increased the risk of MACCE.

Table 2. Comparison of perioperative details between diabetic and non-diabetic patients following coronary artery bypass grafting.

Variable	Diabetics N = 2687	Non-Diabetics n = 8147	p Value
Operative priority, % (n)			<0.001
Elective	67.7 (1819)	72.4 (5895)	
Urgent	31.1 (837)	26.6 (2168)	
Emergency	1.2 (31)	1.0 (84)	
Median Postoperative days (IQR)	8 (5 - 11)	7 (4 - 9)	<0.001
Infective complications, % (n)	9.5 (252)	5.9 (475)	< 0.001
Intra-aortic balloon pump, % (n)			0.004
No	94.1 (2525)	95.7 (7790)	
Preoperative	2.3 (61)	1.4 (114)	
Postoperative	3.5 (95)	2.9 (237)	
Reoperation for bleed or tamponade, % (n)	3.7 (97)	3.1 (249)	0.15
Coronary re-intervention, % (n)	1.1 (28)	0.9 (76)	0.58
Postoperative myocardial infarction, % (n)	1.2 (32)	1.2 (98)	0.97
Postoperative stroke, % (n)	2.2 (57)	1.1 (92)	< 0.001
In-hospital mortality, % (n)	2.3 (63)	1.5 (122)	0.003
MACCE, % (n)	4.7 (125)	2.9 (235)	<0.001

MACCE—major adverse cardiac and cerebrovascular event.

Table 3. Determinants of Major adverse cardiac and cerebrovascular events after coronary artery bypass grafting.

Variable	Odds ratio	95% Confidence interval	p value
Age	1.06	1.04 - 1.07	<0.001
New York Heart Association class III/IV	1.32	1.03 - 1.70	0.03
Preoperative renal dysfunction	2.07	1.21 - 3.53	0.008
Preoperative stroke	1.66	1.24 - 2.24	<0.001
Extracardiac arteriopathy	1.75	1.35 - 2.27	< 0.001
Triple vessel coronary artery disease	3.54	1.12 - 11.17	0.03
Left ventricular ejection fraction 0.3 - 0.49	1.50	1.17 - 1.93	0.002
Left ventricular ejection fraction < 0.30	3.48	2.50 - 4.86	<0.001
Urgent surgery	1.40	1.11 - 1.77	0.005
Emergency surgery	5.13	2.91 - 9.02	< 0.001

4. Discussion

Our study shows that diabetic patients undergoing CABG usually have multivessel

coronary artery disease and, compared to non diabetics more often experienced an in-hospital MACCE (composite of mortality, myocardial infarction, coronary artery re-intervention and stroke). Although there are no published series of MACCE after CABG in diabetic patients, operative mortality has been reported to be higher in diabetic patients [7] [13]. In a study of 5259 patients, Rajakaruna *et al.* [7] reported a higher rate for in-hospital mortality and neurological complications in diabetic patients, however they did not investigate postoperative myocardial infarction or coronary re-intervention. Similarly, a meta-analysis by Zhang and his associates [13] reported an increased risk of mortality and stroke in diabetic patients, but found no difference in the risk of postoperative myocardial infarction. We also did not find any difference between diabetic and non-diabetic patients for postoperative myocardial infarction, and coronary re-intervention. The difference in the MACCE outcome is driven by mortality and postoperative stroke. This is in keeping with other series.

4.1. Severity of Symptoms in Diabetic and Non-Diabetic Patients

Advanced cardiac symptoms such as Canadian Cardiovascular Society (CCS) angina class III/IV, New York Heart Association (NYHA) functional class III/IV, and unstable angina were more common in diabetic patients. Additionally, diabetic patients tended to present with impaired left ventricular ejection. This finding is similar to other reports [7] [14], implying that diabetic patients are undergoing surgery later in the course of their coronary artery disease. This is further highlighted by our findings of greater prevalences of prior myocardial infarction and coronary stenting, with higher requirement for urgent and/or emergency CABG amongst diabetics. This is an important finding that not been previously reported and deserves to be emphasised at heart team meetings, to perhaps encourage referral of patients at an earlier stage of their coronary artery dosease. Diabetic patients were higher risk for CABG at the time of surgery compared to non-diabetic patients so early referral for surgery before onset of advanced symptoms would help to mitigate the risk of CABG in diabetic patients.

4.2. Influence of Advanced Symptoms on In-Hospital Outcomes

Analysis of postoperative outcomes reveals that although higher rates for postoperative stroke, mortality, and consequently MACCE was observed in diabetics compared to on-diabetic patients, diabetes was not a determinant of these adverse outcomes. There are no published research that have investigated the association between diabetes and MACCE after CABG, but studies that have examined the impact of diabetes on in-hospital mortality, have not found any correlation [7] [14], like our study. Multivariate logistic regression modelling did not identify diabetes as an independent risk factor for MACCE, however, clinical and physiological markers of advanced cardiac symptoms and coronary artery disease, such as: NYHA functional class III/IV, impaired left ventricular ejection fraction and non-elective surgery were predictors for MACCE after CABG. Advanced cardiac symptoms increased the risk of MACCE by up to 32% while impaired left ventricular function, renal dysfunction, stroke and extracardiac arteriopathy substantially increased the risk for MACCE post-CABG. It is therefore arguable that there are potential outcome benefits to be gained by performing CABG in diabetics at an earlier stage of their cardiac disease, as well as in the diabetic disease process.

5. Study Limitations and Strengths

Retrospective studies can have the risk of implicit bias from the study design; for this study, data were recorded prospectively and the large sample size will minimise this effect.

The lack of data on HbA1c may attract criticism. This data is not routinely recorded in the database and was not available for analysis, but as the study focus was on impact of advanced symptoms of coronary artery disease on MACCE following CABG, the absence of this data does not affect the study findings. Moreover, HbA1c is a reflection of diabetic control in the preceeding 2 - 3 months and may not necessarily reflect many years of poor control in patients with diabetic nephropathy and neuropathy, who have achieved good control in the months preceeding the test. The influence of poorly controlled diabetes can be deduced from the comorbidities like chronic kidney disease, stroke and extracardiac arteriopathy which we have found to independently increase the risk of MACCE after CABG.

This is a single center study and may be considered not to represent a wider practice, however it spans over two decades and would capture changes in practice over the period.

On the other hand, the strengths of the study include its large sample size of over 10,000 patients. It also represents the "real world" experience of the surgical management of diabetic patients with coronary artery disease. An advantage of this single centre report is a limited variability in the perioperative care with few differences in management approach for both diabetic and non-diabetic patients within our centre. Importantly, this study addresses some of the challenges encountered in heart team meetings relating to decision-making for diabetic patients who require myocardial revascularisation.

6. Summary of Findings and Clinical Significance

Up to a quarter of patients undergoing CABG were diabetic (predominantly tablet-controlled) and often had higher BMIs. Compared to non-diabetics, at presentation for surgery more diabetics had suffered one or more myocardial infarctions and received percutaneous coronary interventions, and were experiencing advanced symptoms, with impaired left ventricular systolic function. They were more likely to have comorbidities that had prognostic implications, such as: renal impairment, neurological dysfunction and peripheral vascular disease. Operative mortality and MACCE were observed in more diabetics due to advanced symptoms, impaired left ventricular systolic function and co-morbidities, rather than the diabetes, itself. This undercores the importance of early referral of diabetics for CABG before they suffer multiple myocardial infarctions and impairment of left ventricular function, and develop advanced symptoms. Delaying surgery by performing percutaneous coronary interventions could contribute to adverse outcomes of CABG in diabetics.

7. Conclusions

Compared to non-diabetics, diabetic patients undergoing CABG are usually higher operative risk, and present with advanced symptoms, preoperative myocardial infarction, prior coronary stenting and impaired left ventricular function. They often require non-elective surgery and experience higher rates of major adverse cardiac and cerebrovascular events. Diabetes was not a predictor of MACCE but advanced cardiac symptoms, impaired left ventricular function and requirement for non-elective surgery significantly increased the risk of MACCE.

Early referral of Diabetic patients with multi-vessel coronary artery disease may mitigate the risk of CABG in diabetic patients.

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Ethical Approval

This study was approved by the Hull university teaching hospitals NHS Trust's clinical audit and clinical effectiveness committee on December 7th, 2022; approval number LA.2022.005.

Informed Consent

Individual patient consent was waived for this retrospective study.

Conflicts of Interest

The authors do not have any conflict of interest in relation to this paper.

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