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Article

Influence of Diabetes Mellitus on Changes in Intra-Operative Decision Making in Coronary Artery Bypass Grafting

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Abstract

Background: We evaluated whether patients with diabetes mellitus experienced more surgical strategy changes than patients without diabetes when undergoing coronary artery bypass graft surgery utilizing a protocol for intraoperative high frequency ultrasound and transit-time flow measurement. **Methods**: Outcomes of coronary artery bypass grafting (CABG) patients with and without diabetes enrolled in the multicenter prospective Registry for Quality Assessment with Ultrasound Imaging and TTFM in Cardiac Bypass Surgery (REQUEST) study were retrospectively compared. The primary endpoint was frequency of intraoperative surgical strategy changes. We also evaluated the differences in patient characteristics and operative characteristics including graft configuration. **Results**: We compared 614 non-diabetic patients with 402 diabetic patients, among whom 128 were insulin dependent. Patients with diabetes had higher rates of surgical strategy change for the aortic component of the operation (10.2% *vs*. 6.4%, odds ratio (OR) = 1.67; 95% confidence interval (CI) = 1.06–2.65; p = 0.026). Surgical strategy changes related to *in-situ* conduits were more common in on-pump procedures in comparison to off-pump in diabetics (4.0% *vs*. 0%; p = 0.007). Diabetes was associated with less frequent use of bilateral internal mammary arteries (BIMA) (25.6% *vs*. 33.7%; p = 0.006), more frequent use of radial artery (31.3% *vs*. 16.9%; $p < 0.001$) and multi-arterial configuration (48.3% *vs*. 39.9%, p = 0.009), and more total grafts (3.1 ± 1.1 *vs*. 2.8 ± 0.9; $p < 0.001$). **Conclusions**: When performing isolated CABG on diabetic patients, surgeons were more likely to change surgical strategy for the aortic component of the operation based on high-frequency ultrasound (HFUS), and more likely to make a change related to *in-situ* conduits in on-pump procedures in diabetics. Among diabetic patients, there was less frequent use of BIMA, more frequent use of radial artery, more frequent multi-arterial configuration, and more total grafts.

Keywords

coronary artery disease; diabetes; coronary artery bypass grafting; high frequency ultrasound; transit time flow measurement

Introduction

Patients with diabetes mellitus present several unique challenges to surgeons treating coronary artery disease (CAD). Cardiovascular disease is the leading cause of morbidity and mortality in diabetic patients [1]. Death from cardiovascular disease, death from CAD, and incidence of nonfatal myocardial infarction (MI) are higher in diabetic patients in comparison to the non-diabetic population [2]. The association between diabetes and CAD is so profound that some epidemiologic data has suggested that diabetic patients with no history of MI have the same cardiovascular risk as non-diabetic patients with prior MI [3]. Patients with diabetes also have higher incidence of other risk factors for the development of CAD such as obesity, hyperlipidemia, heart failure, peripheral vascular disease, and chronic kidney disease. Diabetics experience accelerated atherosclerosis leading to more complex CAD and greater atherosclerotic disease burden of the aorta [4–7]. Diabetic patients have worse outcomes after revascularization with coronary artery bypass grafting (CABG) in comparison to non-diabetics, a disparity that has been attenuated but not eliminated in recent years by improvements in surgical technique, cardiac anesthesia, and cardiac critical care. Indeed, diabetic patients have greater likelihood of stroke, renal failure, deep sternal wound infection, and death within 30-days, as well as worse all-cause mortality at five years after CABG [8–10]. Despite these worse outcomes, it has been well demonstrated that diabetic patients do better with CABG in comparison to percutaneous coronary intervention (PCI), making CABG as the preferred revascularization strategy for diabetic patients with multivessel CAD [11–13].

Transit-time flow measurement (TTFM) and epiaortic and epicardial high-frequency ultrasound (HFUS) allow surgeons the opportunity to objectively assess potential sites of aortic cross-clamp, proximal anastomosis, coronary targets, conduits, and completed grafts. The 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization state that intraoperative graft flow assessment with TTFM may be a useful intra-operative quality control measure to assess the presence or absence of a technical graft problem, however this recommendation is based on weak evidence [14]. Routine use of HFUS/TTFM by experienced surgeons using a prespecified protocol has been demonstrated to result in more frequent intraoperative surgical strategy changes and graft revisions in comparison to visual or manual assessment, and such changes are more common in patients with chronic kidney disease [15,16]. Given the greater complexity of CAD and CABG in diabetic patients, we sought to investigate differences in rates of surgical strategy changes between diabetic and nondiabetic patients undergoing CABG with an intraoperative assessment protocol using HFUS and TTFM.

Materials and Methods

Ethical Statement

This study is a sub-analysis of the previously published Registry for Quality Assessment with Ultrasound Imaging and TTFM in Cardiac Bypass Surgery (REQUEST) study [15]. Institutional review boards at each participating center approved the trial, and all participants provided written, informed consent (IRB #01731; initial approval date 13 April 2015). The study was conducted in accordance with the principles of the Declaration of Helsinki. The REQUEST study was funded by MedStim ASA (Oslo, Norway). Principal investigators and authors had complete scientific freedom.

REQUEST Study

The REQUEST study was an international, multicenter, prospective observational registry designed to capture information on changes to preoperatively proposed surgical plans during CABG based on intraoperative assessment with HFUS and TTFM performed using (MiraQ) or (VeriQ C) devices (Medistim ASA, Oslo, Norway). Patients undergoing isolated CABG for ≥2-vessel CAD were enrolled. Exclusion criteria included emergency cases, concomitant surgical procedures, and comorbid muscle disorders or psychological, developmental, or emotional disorders.

All participating surgeons (n = 36) had performed >20 CABG cases with HFUS/TTFM. Surgeons and study coordinators were trained to use and interpret HFUS/TTFM results according to a structured study protocol. Preoperatively, surgeons formulated surgical plans using coronary angiography and other discretionary imaging modalities (e.g., computed tomography), which included proposed aortic cannulation, cross-clamp and proximal anastomosis sites, bypass conduits, number of anastomoses and coronary targets. Plans were later compared with actual operative conduct to determine occurrence of strategy changes. Protocol steps included HFUS assessment of (i) ascending aorta; (ii) *in situ* conduit arteries; (iii) location of anastomotic sites; and (iv) anatomy/flow in completed anastomoses/grafts. TTFM assessment was recommended at a mean arterial pressure of 80 mm mercury. Parameters prompting re-evaluation of completed grafts for possible revision typically included (i) low mean graft flow: arterial grafts <15 mL/min and venous grafts <20 mL/min; (ii) increased pulsatility index >5; (iii) decreased diastolic filling (<70% for left-sided and <50% for right-sided coronary vessels). Changes in plan and/or revisions were performed at the surgeon's discretion. Adherence to the HFUS/TTFM assessment protocol was highly recommended but was not mandatory. Surgeons provided detailed comments regarding any surgical changes performed including location and reasoning.

Study Population

Between April 2015 and December 2017, a total of 1046 patients undergoing isolated CABG for multivessel CAD at 7 centers in Europe and North America were enrolled in the REQUEST study. Specific inclusion and exclusion criteria have been described in detail elsewhere [15]. Thirty patients were excluded due to screening failure (n = 8), lack of training of all surgical team members according to the REQUEST study protocol (n = 11) or unavailability of HFUS/TTFM images for analysis (n = 11). All 1016 patients meeting inclusion criteria for the REQUEST study were included in the current study. Patients were stratified into 2 groups based on the presence or absence of a documented diagnosis of diabetes mellitus (DM).

Variables and Outcome Measures

Baseline patient and procedural characteristics, details of surgical changes, post-protamine TTFM parameters of completed grafts and in-hospital adverse events were collected prospectively. The primary outcome was frequency of intraoperative surgical strategy changes.

Surgical Strategy Changes: Definitions

Strategy changes were defined as any alterations from the preoperative plan. These changes could be based primarily on HFUS/TTFM use or visual/tactile inspection. Changes related to the aorta included changes to the cannulation site, cross-clamp site, or site for proximal anastomosis. Changes regarding *in situ* conduits occurred if an

Table 1. Demographic and clinical characteristics of patients with and without diabetes enrolled in the REQUEST study.

Pre-operative Patient Variables	Non-Diabetic (n = 614)	Diabetic (n = 402)	*p*
Age (years)	66.1 ± 9.8	65.6 ± 9.1	0.358
Sex (female)	67 (10.9)	76 (18.9)	<0.001**
[Sex (male)]	547 (89.1)	326 (81.1)	-
BMI (kg/m^2) [a]	27.3 (24.9, 30.4)	28.7 (25.8, 32.5)	<0.001**
Prior myocardial infarction	193 (31.4)	138 (34.3)	0.336
History of coronary revascularization	127 (20.7)	105 (26.1)	0.044*
Prior CABG	2 (0.3)	5 (1.2)	0.120
Prior PCI	125 (20.4)	104 (25.9)	0.040*
Stroke history	34 (5.5)	28 (7.0)	0.353
Hypertension	389 (63.4)	335 (83.3)	<0.001**
Hyperlipidemia	301 (49.0)	257 (63.9)	<0.001**
COPD	38 (6.2)	39 (9.7)	0.039*
History of carotid/peripheral vascular intervention	28 (4.6)	17 (4.2)	0.802
CKD/ESRD	45 (7.3)	50 (12.4)	0.006*
Atrial fibrillation	20 (3.3)	13 (3.2)	0.984
LVEF <30% [b]	6/587 (1.0)	18/391 (4.6)	<0.001**
Missing	27	11	-
CCS angina classification III–IV [b]	239/582 (41.1)	164/390 (42.1)	0.760
Missing	32	12	-
NYHA classification III–IV [b]	109/558 (19.5)	81/377 (21.5)	0.467
Missing	56	25	-
Left main involvement [b]	273/491 (55.6)	164/306 (53.6)	0.580
Missing	123	96	-

PCI, percutaneous coronary intervention; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CKD/ESRD, Chronic Kidney Disease/End Stage Renal Disease; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society grading of angina pectoris; NYHA, New York Heart Association functional classification of heart failure. Data are presented as number and percentage, mean ± standard deviation, or median (interquartile range). *$p < 0.05$. **$p < 0.01$. [a] BMI was unknown for 1 patient. [b] Patients with missing data for a given variable were not considered when calculating percentages or performing group comparisons for these specific variables.

alternative conduit was used. Changes to coronary targets included different locations of anastomoses due to calcification or insufficient caliber, detection of intramural vessels or need for endarterectomy. Changes to completed grafts were defined as primary anastomotic revision (i.e., revision of the proximal and/or distal anastomosis due to technical problems), secondary anastomotic revision (revision of the proximal or distal anastomosis due to graft kinking or inadequate length but not an issue with the anastomosis itself), primary conduit revision (without revision of either proximal/distal anastomosis) or the need for additional grafts.

Statistical Analyses

Preoperative demographic and clinical variables, procedure variables and incidence of surgical changes were compared between cohorts using the χ^2 and the independent samples *t*-test for categorical and continuous variables, respectively. The Fisher's exact test was used in place of the χ^2 test when >25% of expected cell counts were <5. Normality was assessed using the Kolmogorov–Smirnov test. The Kruskal–Wallis test was used in place of the *t*-test if the continuous variable distribution was nonparametric. Incidence of surgical changes were presented as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA); *p*-value of <0.05 was considered statistically significant.

Results

Patient Demographics and Comorbidities

There were 402 (39.6%) patients with diabetes and 614 (60.4%) without diabetes. The cohort of patients with diabetes included more women than the cohort without diabetes (18.9% *vs.* 10.9%, $p < 0.001$) and had a higher average body mass index (BMI) (28.7 *vs.* 27.3; $p < 0.001$). Diabetic patients were more likely to have associated comorbidities such as hypertension (83.3% *vs.* 63.4%, $p < 0.001$), hyperlipidemia (63.9% *vs.* 49.0%, $p < 0.001$), chronic ob-

Table 2. Rates of surgical changes from preoperative plan in patients with and without diabetes.

Surgical Changes	Non-Diabetic (n = 614)	Diabetic (n = 402)	Odds Ratio (95% CI)	*p*
Any strategy change	151/614 (24.6%)	105/402 (26.1%)	1.08 (0.81–1.45)	0.584
HFUS/TTFM	109/614 (17.8%)	88/402 (21.9%)	1.30 (0.95–1.78)	0.103
Visual/tactile	28/614 (4.6%)	16/402 (4.0%)	0.87 (0.46–1.63)	0.657
Unclassified	28/614 (4.6%)	10/402 (2.5%)	0.53 (0.26–1.11)	0.089
Changes related to the aorta				
Any surgical change (all patients)	39/614 (6.4%)	41/402 (10.2%)	1.67 (1.06–2.65)	0.026*
HFUS	34/614 (5.5%)	40/402 (10.0%)	-	-
Visual/tactile	3/614 (0.5%)	1/402 (0.2%)	-	-
Unclassified	2/614 (0.3%)	0/402 (0.0%)	-	-
Changes related to *in situ* conduits				
Any surgical change (all patients)	9/614 (1.5%)	9/402 (2.2%)	1.54 (0.61–3.91)	0.361
HFUS	5/614 (0.8%)	5/402 (1.2%)	-	-
Visual/tactile	3/614 (0.5%)	3/402 (0.7%)	-	-
Unclassified	1/614 (0.2%)	1/402 (0.2%)	-	-
Changes related to coronary targets				
Any surgical change (all patients)	71/614 (11.6%)	38/402 (9.5%)	0.80 (0.53–1.21)	0.288
HFUS	42/614 (6.8%)	31/402 (7.7%)	-	-
Visual/tactile	9/614 (1.5%)	2/402 (0.5%)	-	-
Unclassified	21/614 (3.4%)	6/402 (1.5%)	-	-
Changes related to completed grafts				
Any surgical change (all patients)	50/614 (8.1%)	29/402 (7.2%)	0.88 (0.55–1.41)	0.589
HFUS/TTFM	33/614 (5.3%)	18/402 (4.5%)	-	-
Visual/tactile	16/614 (2.6%)	11/402 (2.7%)	-	-
Unclassified	5/614 (0.8%)	1/402 (0.2%)	-	-

Note: One individual patient can have one or more surgical changes. Data are presented as number of patients with surgical change/number of patients undergoing intraoperative assessment (%). *$p < 0.05$. HFUS, high-frequency ultrasound; TTFM, transit-time flow measurement; CI, confidence interval.

structive pulmonary disease (COPD) (9.7% *vs.* 6.2%, p = 0.039), chronic kidney disease or end-stage renal disease (12.4% *vs.* 7.3%, p = 0.006), and left ventricular ejection fraction less than 30% (4.6% *vs.* 1.0%, $p < 0.001$). There were no differences between cohorts in prior MI or history of revascularization, Canadian Cardiovascular Society angina classification, New York Heart Association classification of heart failure, or left main disease. Specific proportions and statistics are displayed in Table 1.

Changes in Surgical Strategy

Patients with diabetes had more changes in surgical strategy related to the aorta (10.2% *vs.* 6.4%, OR = 1.67, 95% CI = 1.06–2.65; p = 0.026), almost all of which were made after evaluation with HFUS (40/41 in diabetics, 34/39 in non-diabetics), as shown in Table 2. The most common surgical strategy change related to the aorta was the site of the proximal anastomosis, however changes to the site of aortic cannulation and cross-clamp were also noted.

Among diabetic patients, there were more surgical changes related to *in-situ* conduits in on-pump procedures compared to off pump (Table 3, 4.0% *vs.* 0%, p = 0.007); however this difference was not present in non-diabetics (2.1% *vs.* 0.4%, OR = 0.21, 95% CI 0.03–1.70, p = 0.107).

There were no differences between diabetic and non-diabetic patients in surgical strategy changes related to coronary targets or completed grafts (Table 4).

Operative Variables

The presence of diabetes was associated with less frequent use of bilateral internal mammary arteries (BIMA) (Table 5, 25.6% *vs.* 33.7%; p = 0.006) and more frequent use of radial artery (31.3% *vs.* 16.9%; $p < 0.001$). A multi-arterial configuration was more common in diabetics (48.3% *vs.* 39.9%, p = 0.009); however there was no difference in the utilization of complete arterial revascularization (25.1% *vs.* 26.7%, p = 0.574). Diabetics had more total grafts per patient (3.1 $\pm$ 1.1 *vs.* 2.8 $\pm$ 0.9; $p < 0.001$). Operative time was longer in diabetics (258 minutes *vs.* 235 minutes, $p < 0.001$).

Table 3. Rates of surgical changes from preoperative plan in patients with diabetes: off versus on pump.

	Diabetic			
Surgical Changes	On-pump (n = 226)	Off-pump (n = 176)	Odds Ratio (95% CI)	*p*
Any strategy change	52/226 (23.0%)	53/176 (30.1%)	1.44 (0.92–2.25)	0.108
HFUS/TTFM	40/226 (17.7%)	48/176 (27.3%)	1.74 (1.08–2.81)	0.021*
Visual/tactile	12/226 (5.3%)	4/176 (2.3%)	0.42 (0.13–1.31)	0.112
Unclassified	6/226 (2.7%)	4/176 (2.3%)	0.85 (0.24–3.07)	0.807
Changes related to the aorta				
Any surgical change (all patients)	10/226 (4.4%)	31/176 (17.6%)	4.62 (2.20–9.71)	<0.001**
HFUS	9/226 (4.0%)	31/176 (17.6%)	-	-
Visual/tactile	1/226 (0.4%)	0/176 (0.0%)	-	-
Unclassified	0/226 (0.0%)	0/176 (0.0%)	-	-
Changes related to *in situ* conduits				
Any surgical change (all patients)	9/226 (4.0%)	0/176 (0.0%)	NE	0.007*
HFUS	5/226 (2.2%)	0/176 (0.0%)	-	-
Visual/tactile	3/226 (1.3%)	0/176 (0.0%)	-	-
Unclassified	1/226 (0.4%)	0/176 (0.0%)	-	-
Changes related to coronary targets				
Any surgical change (all patients)	26/226 (11.5%)	12/176 (6.8%)	0.56 (0.28–1.15)	0.111
HFUS	22/226 (9.7%)	9/176 (5.1%)	-	-
Visual/tactile	2/226 (0.9%)	0/176 (0.0%)	-	-
Unclassified	3/226 (1.3%)	3/176 (1.7%)	-	-
Changes related to completed grafts				
Any surgical change (all patients)	16/226 (7.1%)	13/176 (7.4%)	1.05 (0.49–2.24)	0.906
HFUS/TTFM	9/226 (4.0%)	9/176 (5.1%)	-	-
Visual/tactile	7/226 (3.1%)	4/176 (2.3%)	-	-
Unclassified	1/226 (0.4%)	0/176 (0.0%)	-	-

Note: One individual patient can have one or more surgical changes. Data are presented as number of patients with surgical change/number of patients (%). NE represent sample size small. *$p < 0.05$. **$p < 0.01$.

Adverse Events

In-hospital adverse events observed in patients with and without diabetes can be found in Table 6.

Discussion

In this study, surgeons were more likely to change strategy for the aortic component of isolated CABG operation based on HFUS. In addition, among diabetic patients, there was less frequent use of BIMA, more frequent use of the radial artery, more frequent multi-arterial configurations, and increased total number of grafts.

Diabetes has long been known as a risk factor for CAD and continues to contribute to the burden of CAD in the United States and worldwide [17–19]. Many randomized controlled trials have demonstrated the superiority of CABG in comparison to PCI in diabetic patients with multivessel disease. The diabetic population who underwent CABG in the Bypass Angioplasty Revascularization Investigation (BARI) demonstrated improved five-year survival in comparison with diabetic patients who underwent balloon angioplasty [20,21]. More recently, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial compared multivessel PCI with modern drug eluding stents to CABG in diabetic patients on optimal medical therapy and noted a reduction in all-cause mortality, fewer major adverse cardiac and cerebrovascular events, and fewer MIs among patients undergoing CABG, though stroke was more frequent in patients who underwent CABG [11]. These findings confirmed many of the observations made of the diabetic sub-populations in the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial and other studies [4,22,23]. Based on this evidence, CABG is recommend over PCI for diabetic patients with multivessel disease by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/ASCTS). The prevalence of diabetes among patients undergoing CABG has been increasing over the past several decades [9].

Unfortunately, diabetes is also associated with more technically complex coronary lesions. Diabetic patients in the SYNTAX trial, for example, had more total coronary lesions than non-diabetics [4]. Angiographic studies of patients with acute MI have demonstrated more dif-

Table 4. Rates of surgical changes from preoperative plan in patients without diabetes: off versus on pump.

	Without Diabetes			
Surgical Changes	On-pump (n = 388)	Off-pump (n = 226)	Odds Ratio (95% CI)	*p*
Any strategy change	76/388 (19.6%)	75/226 (33.2%)	2.04 (1.40–2.96)	<0.001**
HFUS/TTFM	52/388 (13.4%)	57/226 (25.2%)	2.18 (1.43–3.31)	<0.001**
Visual/tactile	22/388 (5.7%)	6/226 (2.7%)	0.45 (0.18–1.14)	0.084
Unclassified	13/388 (3.4%)	15/226 (6.6%)	2.05 (0.96–4.39)	0.060
Changes related to the aorta				
Any surgical change (all patients)	11/388 (2.8%)	28/226 (12.4%)	4.85 (2.36–9.94)	<0.001**
HFUS	7/388 (1.8%)	27/226 (11.9%)	-	-
Visual/tactile	3/388 (0.8%)	0/226 (0.0%)	-	-
Unclassified	1/388 (0.2%)	1/226 (0.4%)	-	-
Changes related to *in situ* conduits				
Any surgical change (all patients)	8/388 (2.1%)	1/226 (0.4%)	0.21 (0.03–1.70)	0.107
HFUS	5/388 (1.3%)	0/226 (0.0%)	-	-
Visual/tactile	2/388 (0.5%)	1/226 (0.4%)	-	-
Unclassified	1/388 (0.3%)	0/226 (0.0%)	-	-
Changes related to coronary targets				
Any surgical change (all patients)	41/388 (10.6%)	30/226 (13.3%)	1.30 (0.78–2.14)	0.312
HFUS	26/388 (6.7%)	16/226 (7.1%)	-	-
Visual/tactile	7/388 (1.8%)	2/226 (0.9%)	-	-
Unclassified	8/388 (2.1%)	13/226 (5.8%)	-	-
Changes related to completed grafts				
Any surgical change (all patients)	28/388 (7.2%)	22/226 (9.7%)	1.39 (0.77–2.49)	0.271
HFUS/TTFM	16/388 (4.1%)	17/226 (7.5%)	-	-
Visual/tactile	12/388 (3.1%)	4/226 (1.8%)	-	-
Unclassified	3/388 (0.8%)	2/226 (0.9%)	-	-

Note: One individual patient can have one or more surgical changes. Data are presented as number of patients with surgical change/number of patients (%). $^{**}p < 0.01$.

fuse disease and smaller vessel lumen amongst diabetic patients in comparison to non-diabetics [24]. Ultrasound and cadaveric studies have demonstrated more extensive atherosclerosis, greater total atheroma volume, greater percent atheroma volume, and small vessel lumen among diabetic patients [5–7]. These factors may limit sites for potential distal coronary anastomoses and may contribute to incomplete revascularization. Within the context of our own study, for example, the more complex disease in this population may have contributed to the higher rates of multi-arterial configurations and total number of grafts used.

While CABG is the preferred revascularization strategy for diabetics with multivessel CAD, these patients have worse outcomes after revascularization than their non-diabetic peers [8,9,11–13]. This includes an increased risk of stroke [11]. It has been previously noted that the location and extent of atherosclerosis in the ascending aorta is strongly associated with post-operative stroke [25], and surgical manipulation of the aorta has been suggested as a contributing mechanism for thromboembolism leading to stroke [26,27]. Strategies to avoid surgical manipulation of the aorta may help prevent early stroke in CABG patients [28–30].

Identification of atheromas in the ascending aorta may allow surgeons to alter their surgical approach and minimize the risk of plaque disruption. Epiaortic ultrasound has been studied for this purpose and was found to identify more ascending aortic atheromas than digital palpation and transesophageal echocardiography, though this has not yet been associated with improved outcomes [31]. Multiple previous studies have noted the utility of epiaortic HFUS to identify aortic atheromatous plaques and guide selection of cannulation site, cross-clamp site, and proximal anastomoses when performing CABG, leading to the ESC/EACTS 2018 guidelines "to identify atheromatous plaques and select the optimal surgical strategy" [13,25,30,32]. In the present study, the majority of surgical strategy changes related to the aorta were made after evaluation with HFUS and only a small number after tactile or visual assessment. Surgical strategy changes were more frequent among diabetic patients in comparison to nondiabetics. This fits well with previous observations that diabetes is associated with more rapid progression of aortic wall calcification [33]. The use of epiaortic scanning has previously been associated with a lower risk of intraoperative adverse events leading to early post-operative stroke, and this may be attributable to decreased utilization of plaque-containing sites for cannulation, cross-

Table 5. Operative characteristics of patients with and without diabetes enrolled in the REQUEST study.

Procedure Variables	Non-Diabetic (n = 614)	Diabetic (n = 402)	p
Operative time (min) [a]	235 (190, 293)	258 (204, 326)	<0.001**
LIMA use	595 (96.9%)	388 (96.5%)	0.733
BIMA use	207 (33.7%)	103 (25.6%)	0.006*
Radial artery use	104 (16.9%)	126 (31.3%)	<0.001**
Multiarterial	245 (39.9%)	194 (48.3%)	0.009*
Complete arterial	164 (26.7%)	101 (25.1%)	0.574
Y or T configuration	218/1556 (14.0%)	180/1119 (16.1%)	0.137
Sequential grafts	118/1556 (7.6%)	101/1119 (9.0%)	0.180
Number of conduits			
Total	1556	1119	-
Per patient	2.5 ± 0.8	2.8 ± 0.9	<0.001**
Arterial — per graft	907/1556 (58.3%)	652/1119 (58.3%)	0.990
Venous — per graft	640/1556 (41.1%)	465/1119 (41.6%)	0.826
Arterio-venous — per graft [b]	9/1556 (0.6%)	2/1119 (0.2%)	0.111
Number of distal anastomoses			
Total	1727	1232	-
Per patient	2.8 ± 0.9	3.1 ± 1.1	<0.001**
Arterial — per patient	1.6 ± 0.9	1.8 ± 0.9	0.012*
Venous — per patient	1.2 ± 1.0	1.3 ± 1.0	0.069

LIMA, Left internal mammary artery; BIMA, Bilateral internal mammary artery. Data are presented as number (percentage), median (interquartile range), (count/total number of grafts within a cohort), and mean/patient +/– standard deviation. *$p < 0.05$. **$p < 0.01$. [a] First incision to gloves off. [b] If the arterial graft was too short to reach coronary target, a venous graft was added.

Table 6. In-hospital clinical outcomes for patients enrolled in the REQUEST study, stratified by diabetes status.

Adverse Event	Non-Diabetic (n = 614)	Diabetic (n = 402)	χ^2
MAACE	10/614 (1.6%)	10/402 (2.5%)	0.335
Death (a)	2/614 (0.3%)	4/402 (1.0%)	0.221
Stroke/TIA	6/614 (1.0)	4/402 (1.0%)	0.978
MI	2/614 (0.3%)	1/402 (0.3%)	1.000
Repeat Revascularization	0/614 (0%)	1/402 (0.3%)	0.396
Unplanned CT operation	8/614 (1.3%)	1/402 (0.3%)	0.080
Pacemaker implantation	0/614 (0%)	3/402 (0.8%)	0.062
AKI	8/614 (1.3%)	15/402 (3.7%)	0.011*
New hemodialysis	1/614 (0.2%)	2/402 (0.5%)	0.566
Sepsis	5/614 (0.8%)	9/402 (2.2%)	0.057
Pneumonia	18/614 (2.9%)	25/402 (6.2%)	0.011*
Unplanned reintubation	1/614 (0.2%)	3/402 (0.75%)	0.307
DVT/PE	4/614 (0.7%)	0/402 (0%)	0.157
Post-operative atrial fibrillation	97/614 (15.8%)	83/402 (20.6%)	0.048*
Wound infection/dehiscence	11/614 (1.8%)	9/402 (2.2%)	0.616

Abbreviations used: MACCE, major adverse cardiovascular and cerebrovascular events (composite of death, stroke/TIA, MI, and repeat coronary revascularization); MI, myocardial infarction; TIA, transient ischemic attack; CT, cardiothoracic; AKI, acute kidney injury; DVT, deep vein thrombosis; PE, pulmonary embolism. (a) Causes of death were cardiac arrest (2), sepsis (2), respiratory failure (1), and multifactorial shock (1). *$p < 0.05$.

clamp, or anastomosis [34]. However, while the use of epiarotic scanning led to modifications in intraoperative surgical management in almost one-third of patients undergoing CABG surgery in the present study, a decreased stroke rate was not observed after changes in surgical strategy. This is consistent with other similar studies of the effects of epiaortic scanning on intraoperative surgical strategies [25]. Additionally, no differences were observed for in-hospital adverse events between groups, and outpatient follow-up data was not available. While this study therefore adds to the existing body of evidence supporting the utilization of epiaortic ultrasound for the identification of atheromatous plaques of the ascending aorta, it should not be used to draw conclusions about any positive or negative impact of these strategy changes.

The present study also demonstrated several differences in conduit choice when comparing diabetic patients to non-diabetics, including less frequent use of BIMA and more frequent use of the radial artery and multi-arterial configurations. Since diabetic patients are known to have more complex CAD, an increased number of grafts per patient or more diversity of graft choice and configuration is not unexpected [4]. The less frequent use of BIMA in diabetic patients in this study is likely secondary to concerns about deep sternal wound infection, which is increased in diabetic patients, particularly for those who are insulin dependent [8]. However, the rate of BIMA overall in this study was high in both patient groups (>25%) when compared to the approximate rate in other US cases (6.7%) [35]. This likely reflect surgeon preference at the specific centers involved in this study.

The present study also demonstrated an increased use of radial artery configurations in diabetic patients. While this should be interpreted as manifestation of surgeon preference, there is some evidence to suggest that radial artery use leads to improved outcomes in diabetic patients. In the US, approximately 9% of CABG cases use the radial artery [35]. Some studies have shown that while saphenous vein grafts are more likely to fail by one year in diabetic patients, use of the radial artery may decrease rates of graft occlusion in these patients [36,37].

Limitations

There were several limitations to this study. The REQUEST study was not designed to specifically evaluate patients with diabetes, although the proportion of diabetic patients was comparable to the CABG population at large [8,15]. Thus, specific data regarding the diabetic status of each patient, (i.e., hemoglobin A1C) were not available, and the post-hoc nature of the analysis necessitates a certain amount of caution when interpreting results. The rates of off-pump CABG, BIMA, and complete arterial revascularization in this study are greater than have been reported elsewhere, likely due to the experience and preferences of the specific centers enrolled in the study, and this potentially limits the generalizability of this dataset [35]. Additionally, it is important to consider that the group of diabetic patients demonstrated several baseline differences from the other group, including higher BMI and increased rates of hypertension, hyperlipidemia, and kidney disease. These comorbidities also have the potential to independently influence patient outcomes, and so caution should be taken when interpreting study results. The post hoc nature of our analysis also limits the strength of conclusions that can be drawn from the data, and it will be important to address these issues in our future research. Finally, because the REQUEST study was primarily intended to evaluate intraoperative events, no data is available regarding how surgical strategy changes affected outcomes after discharge.

Conclusions

Epiaortic HFUS may be a useful tool to guide the surgeon's selection of cannulation site, cross-clamp site, and proximal anastomoses when performing CABG on diabetic patients. However, the body of evidence remains limited. Additional studies of this population, ideally in a controlled and randomized setting, with extended patient follow up and reassessment using not only defined primary outcomes, but also additional secondary outcomes and imaging adjuncts, are warranted to delineate the influence of HFUS use and associated surgical strategy changes on outcomes, with particular focus on cerebrovascular accidents.

Availability of Data and Materials

Inquiries regarding availability of data and materals should be directed to the corresponding author.

Author Contributions

GDT and DPPT designed the study and collected data. ESR, JPD, ASP, JLA analyzed and interpreted the data. GDT, JLA, and JPD provided administrative support. All authors assisted in manuscript writing, final editing, and final approval. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All patients enrolled in the REQUEST study signed written informed consent before the surgical procedure. Each participating site received approval from their institutional review board or ethics committee before screening or enrollment of eligible patients (IRB #01731). The study is registered at ClinicalTrials.gov (NCT02385344).

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Conflict of Interest

The authors declares no conflict of interest. There is no conflict of interest between Medistim ASA company and the authors. GDT serves as editorial board member of this journal. GDT declares that he was not involved in the processing of this article and has no access to information regarding its processing.

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