ORIGINAL ARTICLE

Impact of early quantitative morbidity on 1-year outcomes in coronary artery bypass graft surgery

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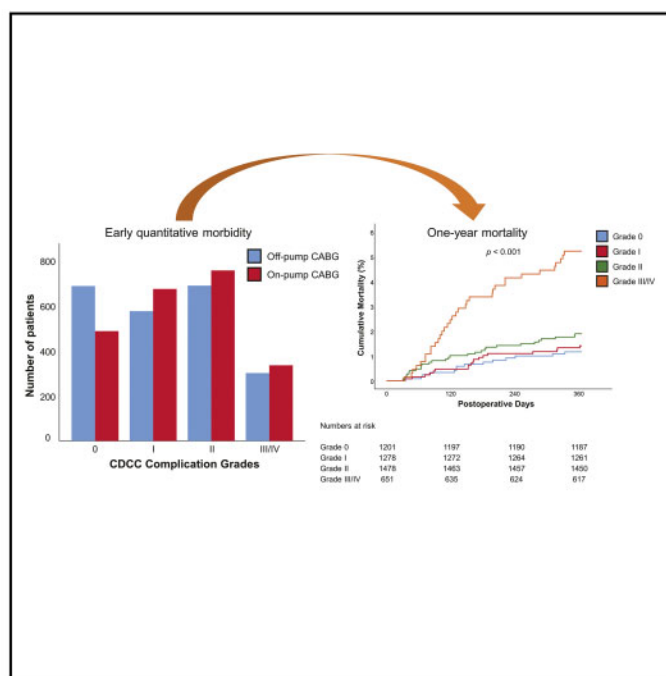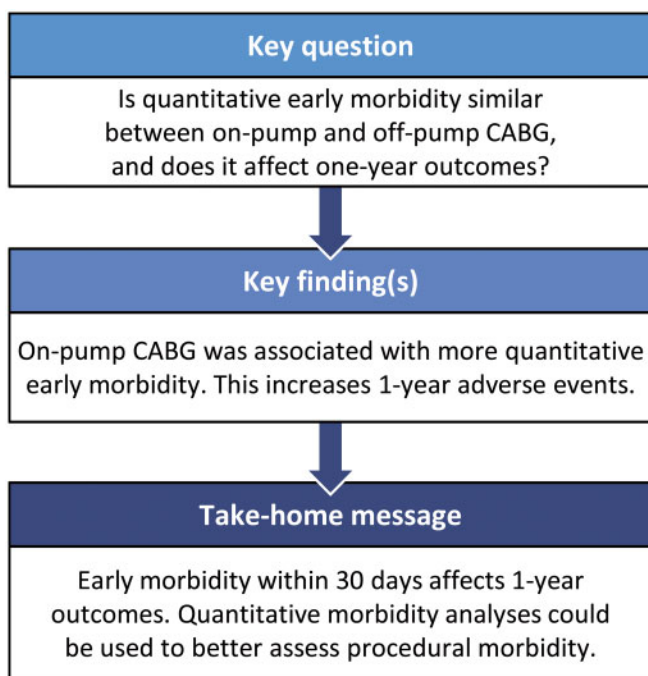
Abstract

OBJECTIVES: We applied the Clavien-Dindo Complications Classification (CDCC) and the Comprehensive Complication Index (CCI) to the CORONARY trial to assess whether quantitative early morbidity affects outcomes at 1 year.

METHODS: All postoperative hospitalization and 30-day follow-up complications were assigned a CDCC grade. CCI were calculated for all patients (n = 4752). Kaplan–Meier analysis examined 1-year mortality and 1-year co-primary outcome (i.e. death, non-fatal stroke, non-fatal myocardial infarction, new-onset renal failure requiring dialysis or repeat coronary revascularization) by CDCC grade. Multivariable logistic regression evaluated the predictive value of CCI for both outcomes.

RESULTS: For off-pump and on-pump coronary artery bypass graft surgery, median CDCC were 1 [interquartile range: 0, 2] and 2 [1, 2] ($P < 0.001$), while median CCI were 8.7 [0, 22.6] and 20.9 [8.7, 29.6], respectively ($P < 0.001$). In on-pump, there were more grade I and grade II complications, particularly grade I and II transfusions ($P < 0.001$) and grade I acute kidney injury ($P = 0.039$), and more grade IVa respiratory failures ($P = 0.047$). Patients with ≥IIIa complications had greater cumulative 1-year mortality ($P < 0.001$). The median CCI was 8.7 [0, 22.6] in patients who survived and 22.6 [8.7, 44.3] in patients who died at 1 year ($P < 0.001$). The CCI remained an independent risk factor for 1-year mortality and 1-year co-primary outcome after multivariable adjustment ($P < 0.001$).

CONCLUSIONS: On-pump coronary artery bypass graft surgery had a greater number of complications in the early postoperative period, likely driven by transfusions, respiratory outcomes and acute kidney injury. This affects 1-year outcomes. Similar analyses have not yet been used to compare both techniques and could prove useful to quantify procedural morbidity.

Clinical trial registration: https://www.clinicaltrials.gov/ct2/show/NCT00463294; Unique Identifier: NCT00463294.

Keywords: Coronary artery bypass graft surgery • Comprehensive Complication Index • Clavien-Dindo Complications Classification • Quantitative morbidity • Outcomes

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ABBREVIATIONS	
CABG	Coronary artery bypass graft surgery
CCI	Comprehensive Complication Index
CDCC	Clavien-Dindo Complications Classification
CORONARY	CABG Off- or On-Pump Revascularization Study

INTRODUCTION

Coronary artery bypass graft surgery (CABG) has been used for the past 50 years to improve mortality in patients with coronary artery disease [1]. Over the years in the USA, procedural in-hospital mortality has decreased from 5.5% to 3.1% between 1989 and 2004 [2]. There was a further decrease in operative mortality down to 2.3% in 2017 for isolated CABG [3]. Though a lower mortality rate must constantly be the primary objective, other outcomes could be examined as endpoints to better appreciate the differences in clinical results.

There is an ongoing debate on the relative risks and benefits between on-pump and off-pump CABG. On-pump CABG relies on the use of the cardiopulmonary bypass to ensure perfusion while the heart is stopped. Off-pump CABG aims to reduce the morbidity associated with cardiopulmonary bypass by performing the graft anastomoses on a beating and non-supported heart. Each technique has its proponents, and both have been compared in large randomized controlled trials, including the CABG Off- or On-Pump Revascularization Study (CORONARY) trial [4–7], the Randomized On/Off Bypass trial [8–10], the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients trial [11, 12] and the Danish On-pump versus Off-pump Randomization Study trial [13]. Despite more than 10 000 combined randomized patients, short- and long-term studied outcomes have found debatable results between the 2 techniques. This is in part due to variable technique between trials and variable experience with the techniques at a surgical and organizational level.

The application of classification scales to quantify procedural morbidity with a simple metric may be of interest. The Clavien-Dindo Complications Classification (CDCC) [14] grades the severity of the worse complication based on invasiveness of treatment, and the Comprehensive Complication Index (CCI) [15] adds the weighted CDCC grades to reflect the overall morbidity burden in individual patients. It has been used for the past 20 years in numerous other surgical specialties and is now considered a gold standard of outcome reporting [16, 17]. This was recently adapted for and validated in cardiac surgery using a comprehensive clinical cardiac surgery registry [18] but has never been applied to a large clinical trial.

To better characterize the early morbidity in off-pump CABG and on-pump CABG, the CDCC and the CCI were applied to the CORONARY trial cohort. The impact of early morbidity on long-term survival was also assessed.

PATIENTS AND METHODS

Trial design

The CORONARY trial was a randomized controlled trial with blinded adjudication of outcomes comparing isolated off-pump and on-pump CABG. The primary hypothesis was that off-pump CABG would be associated with fewer early major clinical events (30 days) than on-pump CABG and that the benefits of off-pump CABG would be maintained long term at 5 years. We have previously published the trial design, and the results at 30 days [5], 1 year [6] and 5 years [7].

Ethical statement

This trial was approved by the ethics committee at each participating centre and was funded by the Canadian Institutes of Health Research. Patients provided written informed consent and the study was conducted in accordance with the ethical standards of the Helsinki Declaration. The authors vouch for the accuracy and completeness of the data and take responsibility for its integrity and the data analysis.

Study patients and follow-up

As previously described, patients who were scheduled to undergo CABG were eligible to participate in the trial if they required isolated CABG with median sternotomy, provided written informed consent and had one or more of the following risk factors: an age of 70 years or more, peripheral arterial disease, cerebrovascular disease or carotid stenosis of 70% or more of the luminal diameter or renal insufficiency. Patients 60–69 years of age were eligible if they had at least one of the following risk factors (and patients 55–59 years of age were eligible if they had at

least 2): diabetes requiring treatment with an oral hypoglycaemic agent or insulin, the need for urgent revascularization after an acute coronary syndrome, a left ventricular ejection fraction of <35% or a history of smoking within 1 year before randomization.

Study personnel conducted in-person or telephone follow-up with patients or their next of kin (if patients were not available) at 30 days and at 1 year after the procedure and on a yearly basis until the end of the trial. If a patient indicated that any outcome event had occurred, the patient's physician was contacted to obtain source documents regarding the event.

Assessment of postoperative complications

The early morbidity assessed in this study encompassed complications collected as part of the CORONARY trial during the immediate postoperative hospitalization and at 30-day follow-up. These complications were graded according to the CDCC, adapted and validated for cardiac surgery [18], presented in Table 1, while the complications recorded in the trial are reported in Table 2. The CDCC is a method of grading complication severity based on the treatment invasiveness required to correct the complication. Early morbidity complications were assigned a CDCC grade according to the usual complication treatment. When assigning the overall CDCC grade to a single patient, the most severe complication grade seen in the patient is used.

The CCI was also used to quantify procedural morbidity in each patient [15]. It uses the complications occurring in a single patient and adds the weights of these complications to produce a sum over 100. The maximum score of 100 is reserved for the death of a patient.

The composite outcome used as CORONARY trial's co-primary outcome (i.e. death, non-fatal stroke, non-fatal myocardial infarction, new renal failure requiring dialysis or repeat coronary revascularization either by percutaneous coronary intervention or redo CABG) was also used in this analysis at 1-year post-randomization instead of 5 years to specifically examine the impact of early morbidity at 1 year. One-year outcomes were

chosen given that we hypothesize that it would more likely be affected by morbidity in the first 30 days compared to 5-year outcomes.

Statistical analysis

All analyses were conducted as intention-to-treat. Continuous non-normally distributed variables are expressed as median with first and third quartiles, while categorical variables are presented as absolute numbers and percentages (%). The CDCC grades were considered ordinal variables, while the CCI was considered a continuous non-normally distributed variable. Chi-squared, Mann–Whitney U and Kruskal–Wallis tests were used to compare differences in CDCC grade and CCI relative to other variables.

For survival, Kaplan–Meier analyses were used to plot the 1-year mortality based on early CDCC grades of patients who had survived the early period ($n = 4608$). For these analyses, patients who had a grade V complication (death) in the initial postoperative hospitalization or within 30-day follow-up were removed. Additional survival curves were made to plot 1-year mortality in patients by treatment group, as well as plot 1-year co-primary outcome in the overall cohort and by treatment group. When plotting the Kaplan–Meier curves for the co-primary outcome, patients who had the co-primary outcome within 30 days were excluded, since this was also taken into consideration by the CDCC grade. Log-rank tests were used to compare survival curves.

Receiver operating characteristic curves were plotted using the predicted probabilities generated through a multivariable logistic regression in the entire cohort for 1-year mortality or 1-year co-primary outcome. Age and sex were forced in the multivariable models due to their strong association with these outcomes. Other factors associated with the two 1-year outcomes were identified through logistic regression models using least absolute shrinkage and selection operator selection methods to identify candidate variables. To account for the effect of individual centres, multivariable analyses using mixed-effects regression models with logit link and a random effect of the centre were then conducted using variables identified through least absolute

Table 1: CDCC for cardiac surgery and CCI weights by complication grade

Grade	Weight	Definition
Grade I	300	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed treatments: antihypertensives, antiarrhythmics, vasopressors, vasodilators, antiemetics, antipyretics, analgesics, diuretics, electrolytes, physiotherapy, wound infections opened at the bedside and transfusion of 1 or 2 units of blood
Grade II	1750	Requiring pharmacological treatment with drugs other than those included for grade I complications, including blood transfusions ($\geq$3 transfusions) and total parenteral nutrition
Grade III		Requiring surgical, endoscopic or radiological intervention
Grade IIIa	2750	Intervention not under general anaesthesia
Grade IIIb	4550	Intervention under general anaesthesia
Grade IV		Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade IVa	7200	Single-organ dysfunction (e.g. liver failure, kidney failure with dialysis)
Grade IVb	8550	Multiorgan dysfunction
Grade V	N/A	Death of a patient

CCI formula: $CCI = \sqrt{\sum Weights_{comp}} \div 2$, where death is arbitrarily defined as 100.

CCI: comprehensive Complication Index; CDCC: Clavien-Dindo Complications Classification; CNS: central nervous system; IC: intermediate care; ICU: intensive care unit.

Table 2: Postoperative in-hospital and 30-day complications by treatment group in the CORONARY trial cohort based on the CDCC

Complication	Off-pump (n = 2375)	On-pump (n = 2377)	P-value
No complication	703, 30%	498, 21%	<0.001
Grade I	1093, 46%	1280, 54%	<0.001
Transfusion 1–2 units, or other products	897, 38%	1067, 45%	<0.001
Acute kidney injury, no dialysis	218, 9%	261, 11%	0.039
Angina without myocardial infarction	2, 0.1%	3, 0.1%	0.66
Grade II	903, 38%	1012, 43%	0.001
Transfusion ≥3 units	268, 11%	400, 17%	<0.001
Respiratory infection, no failure	72, 3%	93, 4%	0.097
PE, no failure	7, 0.3%	7, 0.3%	1.00
Deep vein thrombosis without PE	8, 0.3%	8, 0.3%	1.00
Wound infection	242, 10%	254, 11%	0.58
Atrial fibrillation, no failure	403, 17%	401, 17%	0.93
Myocardial infarction, no revascularization	143, 6%	159, 7%	0.35
Delirium	112, 5%	118, 5%	0.69
Heparin-induced thrombocytopaenia	3, 0.1%	0, 0%	0.083
Grade IIIa	16, 0.7%	6, 0.3%	0.032
Percutaneous coronary intervention	11, 0.5%	3, 0.1%	0.032
Grade IIIb	82, 4%	103, 4%	0.12
Reoperation for bleeding	34, 1%	56, 2%	0.019
Redo coronary artery bypass graft surgery	6, 0.3%	1, 0%	0.058
Mediastinitis	18, 0.8%	20, 0.8%	0.75
Grade Iva	302, 13%	341, 14%	0.10
Respiratory failure	238, 10%	281, 12%	0.047
Stroke	26, 1%	28, 1%	0.79
New-onset renal failure with dialysis	39, 2%	36, 2%	0.72
Heart failure requiring IABP or LVAD	70, 3%	56, 2%	0.20
Grade IVb	8, 0.3%	8, 0.3%	1.00
Low flow with renal failure	8, 0.3%	8, 0.3%	1.00
Grade V	70, 2.9%	74, 3.1%	0.74

CDCC: Clavien-Dindo Complications Classification; CORONARY: CABG Off- or On-Pump Revascularization Study; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device: PE: pulmonary embolism.

shrinkage and selection operator selection methods. Variables were manually excluded in a backward selection process until all variables in the final model were significant. A second mixed-effect multivariable model was created in which CCI was added to all the variables of the first multivariable model regardless of the changes in their regression coefficients or *P*-values. Since CCI was not normally distributed, the variable was categorized in 7 arbitrarily defined categories [CCI = 0 (*n* = 1299); CCI = 1–19 (*n* = 1401); CCI = 20–29 (*n* = 1109); CCI = 30–39 (*n* = 207); CCI = 40–49 (*n* = 380); CCI = 50–69 (*n* = 176); CCI = 70–100 (*n* = 146)]. The CCI in these cases excluded patients who had died within 30 days as to reduce incorporation bias. Likewise, patients who had died within 30 days or have reached the co-primary outcome at 30 days were excluded. Areas under the receiver operating characteristic curve with 95% confidence intervals were calculated for each model and compared. Assumptions for logistic regression were verified for all models and collinearity was excluded by assessing the correlation between variables which was shown to be minimal.

Statistical analyses were conducted with SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA) and statistical significance was set at α = 0.05.

RESULTS

Patients

The baseline characteristics of the CORONARY trial cohort have previously been described in detail [5]. From November 2006

through October 2011, a total of 4752 patients were enrolled from 49 hospitals in 19 countries and randomized in a 1:1 ratio to undergo off-pump (*n* = 2375) and on-pump CABG (*n* = 2377). At the end of the trial, mean follow-up was 4.8 years after randomization and data were available for 98.8% of patients.

Early morbidity by technique

The median CDCC complication grade was 1 [interquartile range: 0, 2] for off-pump CABG and 2 [1, 2] for on-pump CABG (*P* < 0.001). The median CCI was 8.7 [0, 22.6] for off-pump CABG and 20.9 [8.7, 29.6] for on-pump CABG (*P* < 0.001).

In off-pump CABG, more patients did not have any complications (off-pump: *n* = 703, 29.6% vs on-pump: *n* = 498, 21.0%; *P* < 0.001). In on-pump CABG, more patients had at least 1 grade I complication (off-pump: *n* = 1093, 46.0% vs on-pump: *n* = 1280, 53.8%; *P* < 0.001) and grade II complication (off-pump: *n* = 903, 38.0% vs on-pump: *n* = 1012, 42.6%; *P* < 0.001) (Fig. 1). There were 15.9% (*n* = 378) of patients experiencing complications of higher order (i.e. grades IIIa and greater) with off-pump CABG versus 17.5% (*n* = 417) in on-pump CABG (*P* = 0.133).

Among grade I complications, on-pump CABG patients had more transfusions of 1–2 red blood cell units (off-pump: *n* = 897, 37.8% vs on-pump: *n* = 1067, 44.9%; *P* < 0.001) and acute kidney injury without dialysis (off-pump: *n* = 218, 9.2% vs on-pump: *n* = 261, 11.0%; *P* = 0.039). Among grade II complications, transfusion of 3 or more red blood cell units differed (off-pump: *n* = 268, 11.3% vs on-pump: *n* = 400, 16.8%; *P* < 0.001), while respiratory infections without respiratory failure were similar (off-pump:
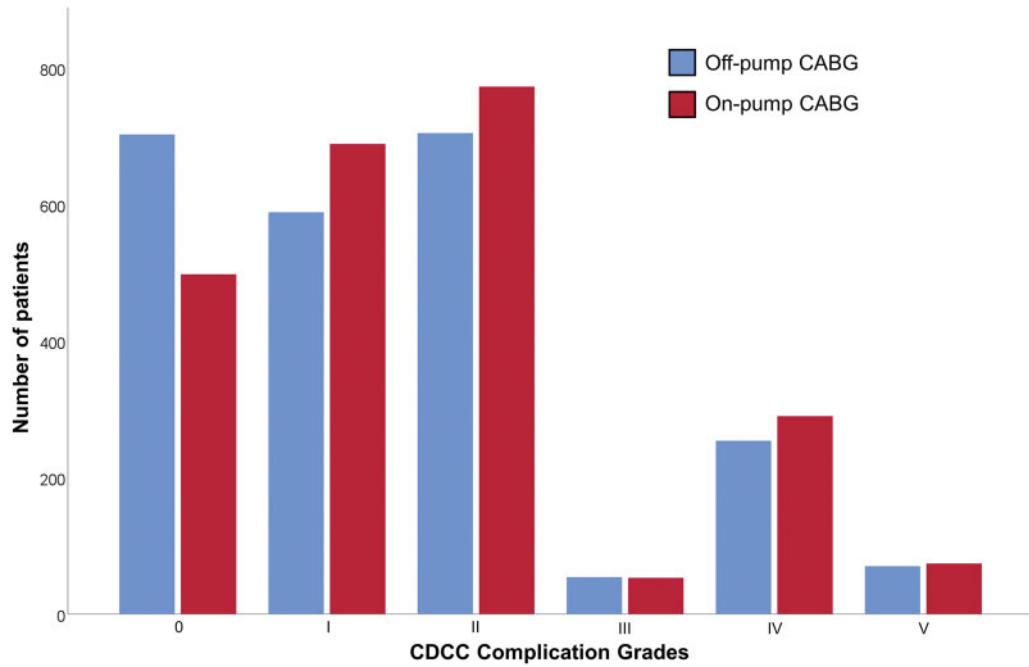
Figure 1: Distribution of CDCC grades for early postoperative morbidity in patients undergoing off-pump CABG and on-pump CABG. CABG: coronary artery bypass graft surgery; CDCC: Clavien-Dindo Complications Classification.
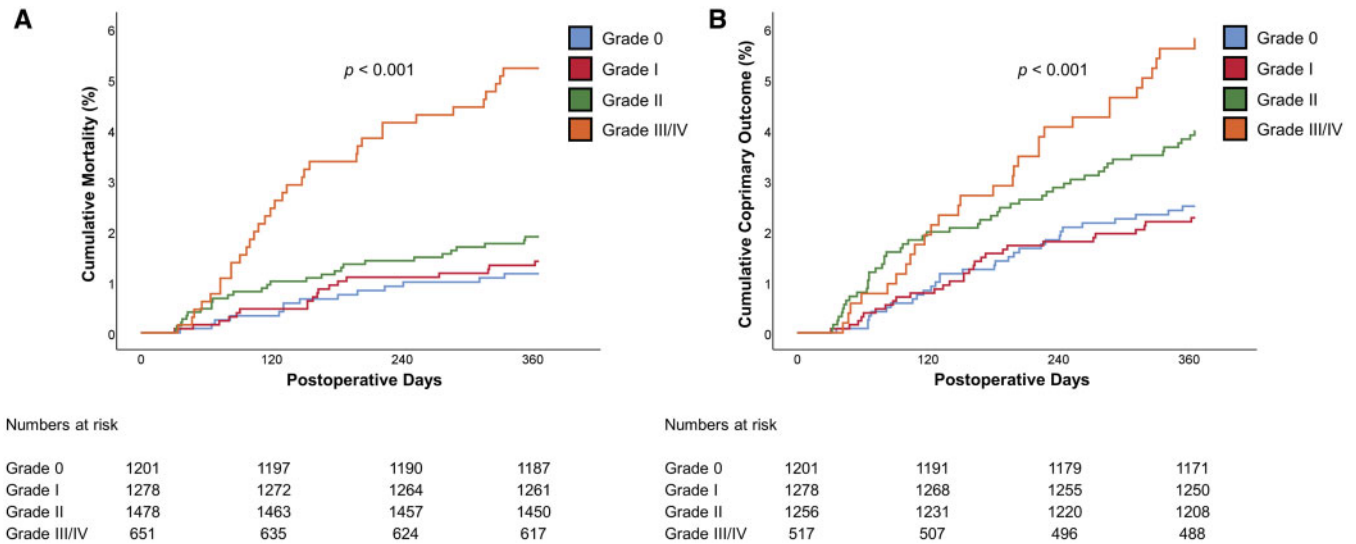

Figure 2: (**A**) Kaplan–Meier curves for cumulative mortality at 1 year in the entire cohort of patients who survived the early 30-day period based on postoperative Clavien-Dindo Complications Classification grade. (**B**) Kaplan–Meier survival curves for cumulative co-primary outcome (i.e. death, non-fatal stroke, non-fatal myocardial infarction, new-onset renal failure requiring dialysis or repeat coronary revascularization) at 1 year in the entire cohort of patients who survived the early 30-day period based on Clavien-Dindo Complications Classification grade. Patients with the occurrence of the co-primary outcome within 30 days were excluded.

$n = 72$, 3.0% vs on-pump: $n = 93$, 3.9%; $P = 0.097$). Among grade III complications, there were more percutaneous coronary interventions following off-pump CABG (off-pump: $n = 11$, 0.5% vs on-pump: $n = 3$, 0.1%; $P = 0.032$), while there were more reoperations for bleeding following on-pump CABG (off-pump: $n = 34$, 1% vs on-pump: $n = 56$, 2%; $P = 0.019$). There were more grade IVa respiratory failures after on-pump CABG (off-pump: $n = 238$, 10.0% vs on-pump: $n = 281$, 11.8%; $P = 0.047$). The detailed breakdown of all complications by grading is presented in Table 2.

Impact of early morbidity on survival and co-primary outcome

Survival curves differed significantly based on CDCC grade (Fig. 2A, $P < 0.001$). Between the 2 techniques, the impact of the grades III and IV complications on long-term mortality was similar (Fig. 3A for off-pump CABG and Fig. 3B for on-pump CABG). The quantitative early morbidity was lower in patients who survived at 1 year ($n = 4514$) with a median [interquartile range] CCI
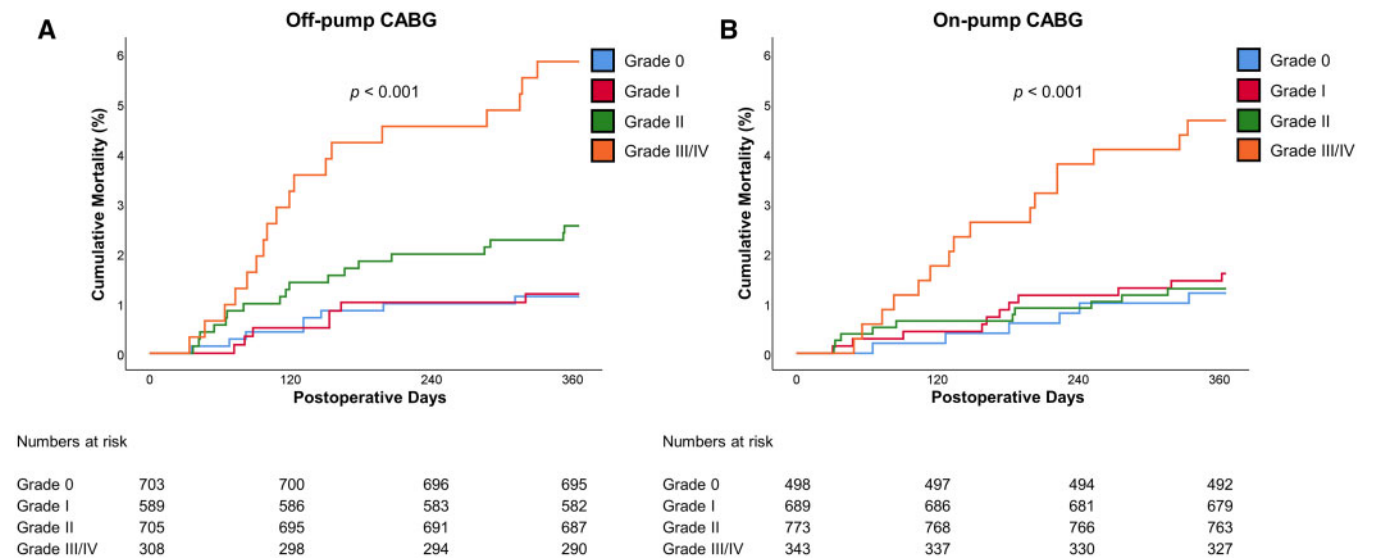
Figure 3: Kaplan–Meier survival curves for cumulative mortality at 1 year in patients who underwent (**A**) off-pump or (**B**) on-pump CABG and who survived the early 30-day period based on CDCC grade. CABG: coronary artery bypass graft surgery.
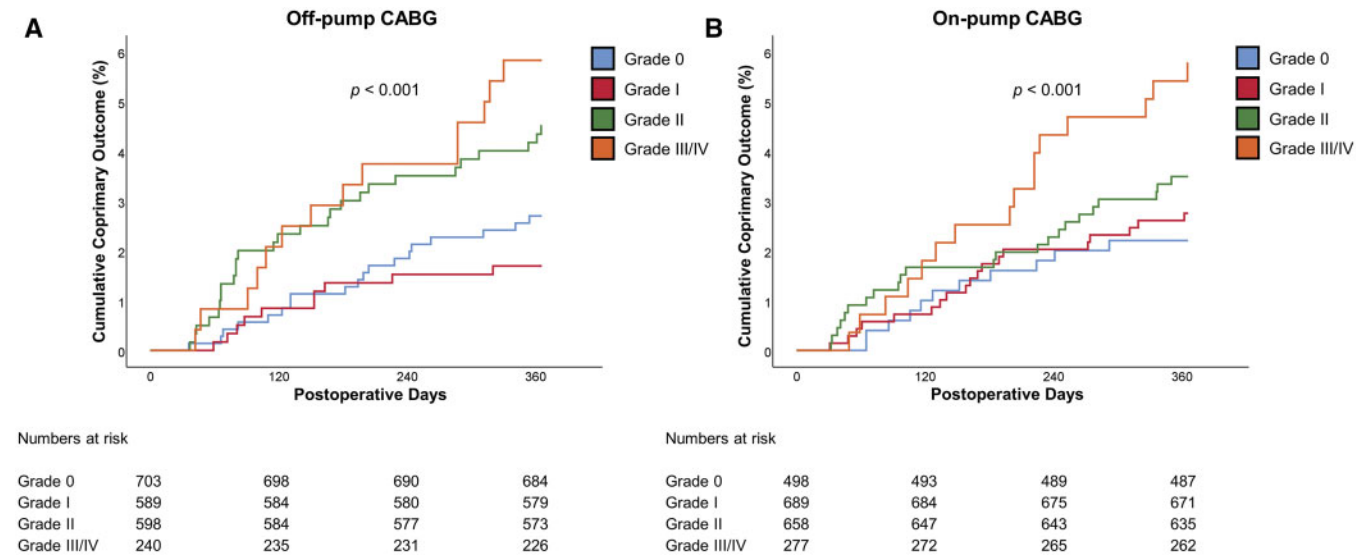

Figure 4: Kaplan–Meier survival curves for cumulative co-primary outcome (i.e. death, non-fatal stroke, non-fatal myocardial infarction, new-onset renal failure requiring dialysis or repeat coronary revascularization) at 1 year in patients who underwent off-pump or on-pump CABG who survived the early 30-day period based on Clavien-Dindo Complications Classification grade. Patients with occurrence of the co-primary outcome within 30 days were excluded. CABG: coronary artery bypass graft surgery.

of 8.7 [0, 22.6] compared to patients who did not survive at 1 year ($n = 94$) with a median CCI of 22.6 [8.7, 44.3] ($P < 0.001$).

In patients who did not reach the co-primary outcome within 30 days, there was significant increase in future occurrence of the co-primary outcome based on CDCC grade ($P < 0.001$). The co-primary outcome was reached in 2.5% (30/1201) of patients with no complications, 2.3% (29/1278) with grade I, 4.0% (50/1256) with grade II and 5.8% (30/517) with grade III/IV. The median [interquartile range] CCI was 8.7 [0, 22.6] in patients who did not reach the co-primary outcome between 30 days and 1 year compared to 20.9 [8.7, 32.0] in patients who did ($P < 0.001$). The risk of co-primary outcome was significantly higher with greater complication grades according to the Kaplan–Meier curves for the entire cohort (Fig. 2B), patients undergoing off-pump CABG (Fig. 4A) and patients undergoing on-pump CABG (Fig. 4B).

Using multivariable logistic regression, the CCI remained an independent risk factor for adverse outcomes at 1 year for both mortality and co-primary outcome (Table 3). It also increased the predictive value of the multivariable model based on the receiver operating characteristic curves for 1-year mortality (Fig. 5A, $P < 0.001$), but not for 1-year co-primary outcome (Fig. 5B, $P = 0.09$).

DISCUSSION

We have applied a quantitative morbidity analysis to the CORONARY trial by using the CDCC and the CCI to assess early morbidity. We have found that there were less patients in on-pump CABG without any complications and the early morbidity

Table 3: Logistic regression models for 1-year mortality and 1-year co-primary outcome with and without the CCI

Characteristic	One-year mortality		One-year co-primary outcome	
	Multivariable OR (95% CI), *P*-value	Multivariable + CCI OR (95% CI), *P*-value	Multivariable OR (95% CI), *P*-value	Multivariable + CCI OR (95% CI), *P*-value
Age, per 10 years	1.85 (1.35–2.52), **<0.001**	1.51 (1.11–2.05), **0.009**	1.56 (1.11–2.20), **0.01**	1.46 (1.04–2.07), **0.03**
Female sex	1.40 (0.90–2.18), 0.13	1.29 (0.80–2.10), 0.29	1.45 (0.87–2.41), 0.16	1.43 (0.85–2.42), 0.18
Insulin-dependent diabetes	1.82 (1.17–2.84), **0.008**	1.61 (0.95–2.73), 0.08	1.69 (1.09–2.62), **0.02**	1.63 (1.03–2.58), **0.04**
Peripheral artery disease	2.08 (1.21–3.58), **0.008**	2.12 (1.17–3.85), **0.01**	1.95 (1.12–3.41), **0.02**	2.02 (1.08–3.79), **0.03**
LVEF (REF: ≥50%)	Overall *P* < 0.001	Overall *P* < 0.001	Overall *P* = 0.003	Overall *P* = 0.02
LVEF 35–49%	2.96 (1.86–4.73), **<0.001**	2.96 (1.86–4.73), **<0.001**	2.26 (1.39–3.68), **0.001**	0.77 (0.49–1.19), **0.009**
LVEF <35%	4.20 (1.95–9.05), **<0.001**	4.20 (1.95–9.05), **<0.001**	2.66 (1.24–5.68), **0.01**	0.80 (0.51–1.25), **0.02**
eGFR (REF: ≥90)	Overall *P* = 0.01	Overall *P* = 0.31	Overall *P* = 0.03	Overall *P* = 0.04
eGFR 60–89	2.12 (0.96–4.69), 0.06	1.71 (0.76–3.83), 0.19	1.59 (0.81–3.34), 0.18	1.49 (0.75–2.98), 0.26
eGFR 30–59	2.14 (0.89–5.19), 0.09	1.89 (0.74–4.80), 0.18	1.71 (0.86–3.40), 0.12	1.73 (0.86–3.50), 0.13
eGFR <30	6.68 (2.28–19.55), **<0.001**	3.74 (1.06–13.16), **0.04**	3.84 (1.45–10.20), **0.007**	3.44 (1.25–9.50), **0.02**
Smoking (REF: never)			Overall *P* = 0.11	Overall *P* = 0.37
Recent smoker			0.70 (0.46–1.08), 0.11	0.77 (0.49–1.19), 0.23
Former smoker			0.72 (0.48–1.08), 0.11	0.80 (0.51–1.25), 0.31
EuroScore II (REF: 0–2%)			Overall *P* = 0.08	Overall *P* = 0.16
EuroScore II 3–5%			1.72 (0.95–3.08), 0.07	1.62 (0.90–2.93), 0.11
EuroScore II >5%			2.07 (1.09–3.91), **0.03**	1.91 (0.97–3.76), 0.06
CCI (REF: 0)		Overall *P* < 0.001		Overall *P* < 0.001
CCI 1–19		1.18 (0.53–2.63), 0.69		0.90 (0.47–1.70), 0.73
CCI 20–29		1.63 (0.70–3.79), 0.26		1.07 (0.55–2.08), 0.85
CCI 30–39		3.10 (1.25–7.70), **0.01**		2.00 (0.89–4.48), 0.09
CCI 40–49		2.06 (0.71–5.94), 0.18		1.37 (0.52–3.59), 0.52
CCI 50–69		4.02 (1.52–10.61), **0.005**		1.93 (0.73–5.09), 0.19
CCI 70–100		101.64 (39.19–263.61), **<0.001**		53.29 (15.33–185.28), **<0.001**

The models excluded patients who had reached the outcome within 30 days, and the CCI excluded the score of patients who had died within 30 days.
CCI: comprehensive Complication Index; CI: confidence interval; eGFR: estimated glomerular filtration rate in ml/min/1.73 m2; LVEF: left ventricular ejection fraction; OR: odds ratio.
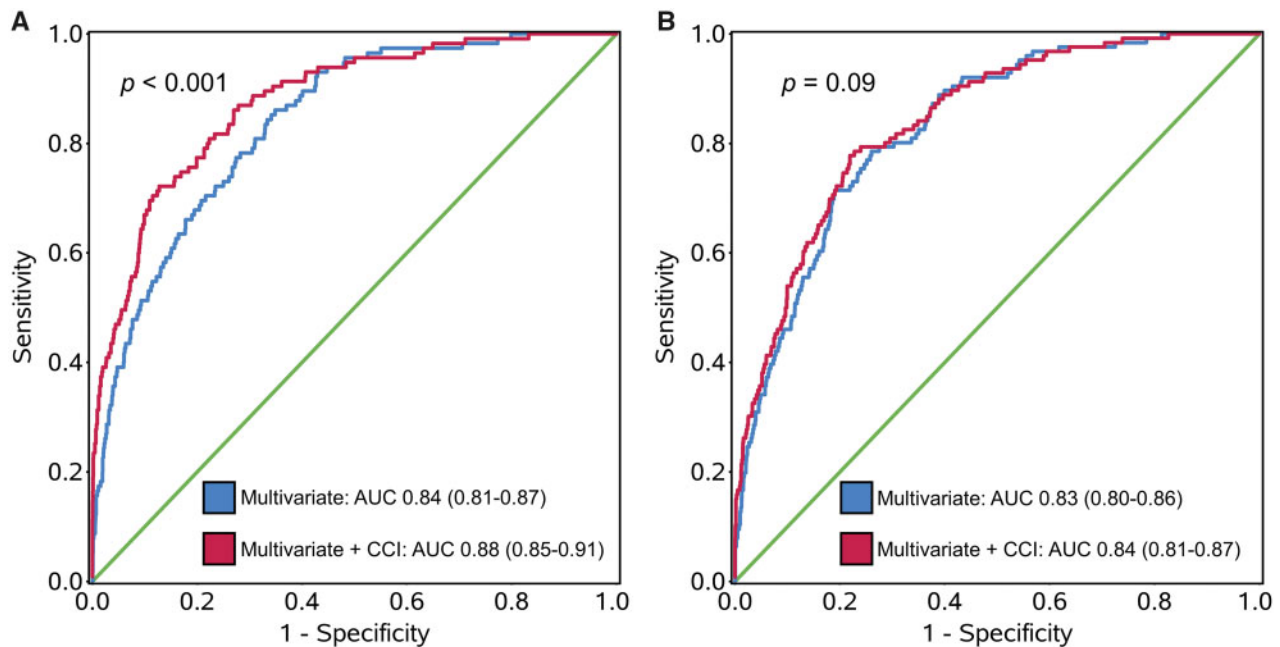

Figure 5: Receiver operating characteristic curves with area under the receiver operating characteristic curve and 95% confidence interval comparing the predictive ability of the multivariable logistic models with or without CCI for (**A**) 1-year mortality and (**B**) 1-year co-primary outcome. The models excluded patients who had reached the outcome within 30 days, and the CCI excluded the score of patients who had died within 30 days.

was greater in patients undergoing on-pump CABG than off-pump CABG. This early morbidity also translates in worse long-term outcomes.

This deviates from the previous reports of the trial which did not find significant differences between the 2 treatment groups at 30 days [5] and 1 year [6] for the first co-primary composite outcome of death, non-fatal myocardial infarction, non-fatal stroke or non-fatal new renal failure requiring dialysis. Other secondary outcomes such as cost per procedure and quality-of-life measures were not significantly different [7].

The likely cause for this new finding is that using a quantitative approach to morbidity increases the sensitivity of reported outcomes. The CCI provides a weighted sum of complications in every patient and therefore gives a better understanding of the total postoperative morbidity. Additionally, some early outcomes had already been reported less frequently in off-pump CABG, including rates of bleeding, acute kidney injury and respiratory complications [5]. When combining all early complications, these differences between procedures are made more apparent. The application of this exploratory *post hoc* analysis is not sufficient on its own to support prioritizing off-pump CABG over on-pump CABG as the major outcomes that have been extensively researched remain more clinically important and similar between both groups. Similarly, other considerations of surgical technique, centre expertise and patient profiles overweigh the significant differences in low-grade complications between both treatment groups.

The severity of the early morbidity also affected the 1-year survival. We expected to find increasing cumulative mortality rate with greater complication grades. The survival curves for both off-pump and on-pump CABG were consistent with this hypothesis. Complications of higher order were associated with a decreased survival at 1 year compared to lower-order complications in both treatment groups and the entire cohort with a greater than three-fold increase in 1-year mortality or co-primary outcome with grade III reinterventions or grade IV intensive care unit admissions for organ failures. This increase in risk is consistent with other studies which have applied the CDCC/CCI but may be even more marked in cardiac surgery. This could reflect the greater burden on patients who require this kind of postoperative management on long-term organ function. For instance, patients with high postoperative CCI ($\geq$26.2) following gastric cancer resection had a cancer-specific survival of 46.3% at 5 years, compared to 54.9% in patients with less postoperative morbidity ($P = 0.009$) [19]. In a cohort of patients following colorectal cancer surgery, the CCI was associated with an increase in mortality at 5 years with a hazard ratio of 1.22 ($P = 0.02$) [20].

The application of the CDCC/CCI to CORONARY demonstrates the potential for quantitative morbidity as an outcome measure in clinical trials. It can measure the number and severity of postoperative complications thereby giving a more accurate picture of procedural morbidity. It adds granularity by allowing different gradings for a same complication, depending on invasiveness of treatment. For instance, a wound infection requiring antibiotics is less severe than a wound infection requiring extensive debridement in the operating room which is in turn less severe than a wound infection causing septic shock. Finally, it gives a more holistic approach to defining clinical outcomes benchmarks for quality-of-care improvement initiatives.

Limitations

The main limitation is that the CORONARY trial was not originally designed using the CDCC/CCI for morbidity. Therefore, the sample size calculation was done using the co-primary outcomes as part of the original CORONARY trial design. Applying the CDCC/CCI as a *post hoc* analysis can therefore only be speculative and exploratory in its conclusions. Ideally, a system of complications grading would be implemented at the start of the trial to gather more granularity regarding the severity of each complication. As such, other complications that were not originally included in the study protocol (e.g. gastroenterological complications) could not be included in this analysis. In addition, the blinded adjudication of outcomes used in this trial was only applied to the components of the primary outcome and recurrent angina. This allows for different outcome reporting between centres in the study based on the local interpretation of study definitions, though this is unlikely to cause a differential bias between procedures given the treatment randomization which would have distributed patients evenly among centres.

An inherent component of the CDCC/CCI is the use of invasiveness of treatment to assess severity of a complication. As such, this introduces a medical decision bias that depends on the management method of certain complications between centres and between surgeons (e.g. dialysis in acute kidney injury, transfusions and repeat revascularizations). These outcomes were, however, used in the original trial and were therefore considered relevant to be included in this analysis. Given that the randomization in the CORONARY trial was done within each centre, this should also not produce a significant differential bias between both treatment groups but must be considered in the interpretation of the results.

The observation interval for the early complications was also arbitrarily defined as in-hospital and 30-day morbidity, though additional complications impacting long-term mortality may have occurred after this period. The method of follow-up based on interviews with patients or their next of kin at 30 days and 1 year can also introduce incomplete reporting of morbidity for which we could not account.

In conclusion, on-pump CABG seems to be associated with a greater number of complications in the early postoperative period, when using the CDCC and the CCI to measure the number and severity of complications. This is likely driven by increased transfusions, respiratory outcomes and acute kidney injury. This early morbidity within 30 days also seems to affect 1-year outcomes. The application of this quantitative morbidity approach has never been used in the debate between on-pump CABG and off-pump CABG. This also suggests a usefulness for the CDCC/CCI to better quantify procedural morbidity in clinical trials. The implementation of these systems in prospectively collected databases would allow further confirmation of the present findings.

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ADULT CARDIAC

AUTHOR CONTRIBUTIONS

Mélanie Hébert: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing. **André Lamy:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing. **Nicolas Noiseux:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review & editing. **Louis-Mathieu Stevens:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

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