Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200388.

Supplementary Appendix

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1- Inclusion and exclusion criteria

Inclusion Criteria

Patients were eligible if they:

1. provided written informed consent;
2. were >21 years of age;
3. required isolated CABG with median sternotomy;
4. had at least one of the following risk factors:

a) had peripheral vascular disease (previous peripheral bypass, amputation or ankle-branchial index <0.90),

b) had cerebrovascular disease (history of stroke, transient ischemic attach or carotid stenosis ≥70%),

c) had renal insufficiency (creatinine above upper limit of normal),

d) were ≥70 years of age, or

e) were between the ages of 60-69 with one of the following:

i. had diabetes and taking an oral hypoglycemic agent and/or insulin,

ii. required urgent revascularization (i.e., waiting in hospital for revascularization after an acute coronary syndrome),

iii. were a recent smoker (within 1 year of randomization), or

iv. had left ventricular ejection fraction ≤35%, OR

f) were between the ages of 55-59 with two of the following: i. Diabetes and taking an oral hypoglycemic agent and/or insulin,

ii. required urgent revascularization (i.e., waiting in hospital for revascularization after an acute coronary syndrome,

iii. were a recent smoker (within 1 year of randomization), or

iv. had a left ventricular ejection fraction ≤35%

Exclusion Criteria

Patients were excluded if they:

1. required a concomitant cardiac procedure associated with CABG;
2. had a contraindication to off-pump or on-pump CABG (e.g., calcified aorta, intramuscular left anterior descending artery, calcified coronaries, small target vessels);
3. had a concomitant life-threatening disease likely to limit life expectancy to less than 2 years;
4. were previously enrollment in the CORONARY Trial;
5. required emergency CABG surgery (i.e., immediate revascularization for hemodynamic instability); OR
6. required a redo CABG.

2- Definitions of Study Outcomes

Total mortality: all causes of death.

Stroke: a new acute focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours. Strokes were confirmed by a neurologist.

MI perioperative (within 72 hours of surgery): MI is defined by any of the following three criteria:

1) a CK-MB measurement ≥5 x 99th percentile upper reference limit (URL) without new pathological Q waves or new LBBB (non Q wave MI) or with new pathological Q waves or new LBBB (Q wave MI); 2) angiographic evidence of new graft or native coronary artery occlusion; or
3) imaging evidence of new loss of viable myocardium.

MI non-perioperative (later than 72 hours after surgery): Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

1) symptoms of ischaemia;
2) ECG changes indicative of new ischaemia [new ST-T changes or new LBBB];
3) development of pathological Q waves in the ECG; or
4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Post-PCI MIs are included in this group and are defined as an increase of biomarkers greater than 3 x 99th percentile URL.

Renal failure: requirement for renal replacement therapy (eg, dialysis, continuous hemofiltration, renal transplant). Hemofiltration or dialysis only during cardio-pulmonary bypass does not constitute a requirement for renal replacement therapy. Patients who receive dialysis within 1 month prior to the surgery are not eligible for this endpoint.

Repeated coronary revascularization: new CABG procedure or PCI associated with documented ischemia by stress testing (ECG, echocardiography, or nuclear) and graft failure or new culprit lesion (≥ 70% luminal stenosis).

Recurrence of angina: new onset of typical chest angina with documented ischemia by stress testing (ECG, echocardiography, or nuclear) or persistence of CCS grade ≥2 angina after the surgery.

Blood transfusions: all blood bank products transfused during the CABG surgery up to discharge.

Antifibrinolytics: use of antifibrinolytics and aprotinin perioperatively. (Subsequently, due to the withdrawal of aprotinin by its producer, antifibrinolytic therapy was defined as the use of tranexamic acid or epsilon amino caproic acid. Very few patients received aprotinin).

Cardiovascular death: all deaths in the first 30 days are considered to be cardiovascular deaths.

Respiratory complications: This included respiratory failure (i.e., requiring re-intubation and mechanical ventilation) and respiratory infection.

3- Event and Data Monitoring Strategies

Of all these components of the primary 30-day outcome, nonfatal myocardial infarction was the event that we believed had the most potential to go unrecognized by center investigators. We put in place the following monitoring strategy to avoid missing myocardial infarctions. CK-MB was measured on postoperative days one and two and recorded on case report forms. All these values were reviewed centrally. If a center did not submit a myocardial infarction case report form but their CK-MB measurement fulfilled our definition, the center was contacted to ensure that a myocardial infarction was not missed.

Data monitoring in CORONARY consisted of central data consistency checks, statistical monitoring, and on-site monitoring for centers that stood out on central data consistency checks or statistical monitoring. No center stood out on central data consistency checks. About ten centers stood out, however, during statistical monitoring. For the on-site monitoring, the central coordinator randomly selected participants with and without a perioperative complication, and independent monitors audited their hospital charts and all other supporting documents. On-site monitoring demonstrated no major discrepancies between the submitted data and the monitoring findings.

4- **Reasons and timing of cross-overs in CORONARY**

Timing of cross-overs

184 patients crossed over from off-pump to on-pump CABG
- -12 prior to surgery
- -28 during anesthesia induction
- -81 during assessment of the heart
- -63 during coronary grafting

150 patients crossed over from on-pump to off-pump CABG
- -33 prior to surgery
- -25 during anesthesia induction
- -89 during assessment of the heart
- -2 during coronary grafting
- -1 missing

Reasons for cross-overs

The most frequent reasons for cross-overs from off-pump to on-pump were:
-hypotension: 31.2%
-small targets: 25.5%
-intra-muscular vessels: 22.3%
-ischemia: 18.5%

The most frequent reasons for cross-overs from on-pump to off-pump were:
-calcified ascending aorta: 64.7%
-patient co-morbidities: 7.7%

5- Table 1. Perioperative Events

Perioperative Outcomes	Off-pump Group N=2375 (%)	On-pump Group N=2377 (%)	Relative risk (95% CI)	P-Value
Cross-overs	184 (7.9)	150 (6.4)	1.23 (1.00-1.50)	0.06
Revascularization				
LIMA or RIMA	2199 (93.6)	2201 (93.4)		0.79
LIMA and RIMA	128 (5.4)	121 (5.1)		0.63
Radial artery	363 (15.5)	331 (14.0)		0.17
Total grafts performed (Mean, SD)	3.0 (0.95)	3.2 (0.92)		<0.001
Incomplete revascularization	278 (11.8)	236 (10.0)	1.18 (1.0-1.39)	0.05
Intra-aortic balloon pump	59 (2.5)	50 (2.1)	1.18 (0.81-1.71)	0.38
Bleeding				
Blood Transfusions *	1204 (50.7)	1505 (63.3)	0.80 (0.75-0.85)	<0.001
Antifibrinolytics †	620 (26.1)	879 (37.0)	0.71 (0.64-0.77)	<0.001
Re-operation for bleeding	34 (1.4)	56 (2.4)	0.61 (0.40-0.93)	0.02
Length of stay (median, Q1-3) ‡				
Operating room (hours)	4.0 (3.3-4.8)	4.2 (3.5-5.0)		<0.001
Initial ventilation (hours)	9.6 (5.7-16.8)	11.2 (6.0-17.7)		<0.001
ICU (days)	2 (1.0-3.0)	2 (1.0-3.0)		0.02
Ward (days)	5 (4.0-7.0)	5 (4.0-7.0)		0.44
Total (days)	8.0 (7.0-10.0)	8.0 (7.0-10.0)		0.27

*Patients who received at least 1 unit of blood products (red blood cells, whole blood, fresh frozen plasma, and platelets).
† Antifibrinolytic therapy was defined as the use of tranexamic acid or epsilon amino caproic acid.
‡ Means (SD) are 4.1 (1.2) and 4.3 (1.2) for operating room (hours), 16.4 (39.5) and 17.7 (48.4) for the initial ventilation time (hours), 2.9 (4.6) and 3.0 (4.0) for the ICU stay (days), 6.3 (6.4) and 6.2 (5.8) for the ward stay (days), 10.1 (8.6) and 10.2 (10.0) for the total stay (days).

6- AKIN and RIFLE classification for Acute Kidney Injury

AKIN Stage 1 or more	Evidence of an absolute increase in serum creatinine value ≥27 µmol/L OR an increase of ≥150 % from the baseline serum creatinine value
RIFLE Risk category	Evidence of an increase in serum creatinine value ≥150% (≥1.5-fold) from baseline
RIFLE injury category, AKIN stage 2	Evidence of an increase in serum creatinine value ≥200 % (≥2-fold) from baseline
RIFLE failure category, AKIN stage 3	Evidence of an increase in serum creatinine value ≥300 % (≥3-fold) from baseline OR an absolute serum creatinine ≥354 µmol/L with an increase ≥44 µmol/L from baseline. *Any patient who received acute dialysis is categorized in this category*

Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss and End-stage Renal Disease (RIFLE) classification systems. The categories are not mutually exclusive (i.e. patients who meet the criteria for RIFLE injury also meet the criteria for RIFLE risk).

Venkataraman R, Kellum JA: Defining acute renal failure: the RIFLE criteria. *J Intensive Care Med* 22:187-193, 2007.

Mehta RL, Kellum JA, Shah SV, et al.. : Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11:R31, 2007.

7- ROOBY Trial Outcomes definitions

The primary short-term composite end point was death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure requiring dialysis before discharge or within 30 days after surgery.

The primary long-term composite end point was death from any cause within 1 year after surgery, nonfatal myocardial infarction between 30 days and 1 year, and any revascularization procedure between 30 days and 1 year.

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