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REPORT

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Adverse events while awaiting myocardial revascularization: a systematic review and meta-analysis

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Abstract

OBJECTIVES: The aim of the current study was to estimate adverse event rates while awaiting myocardial revascularization and review criteria for prioritizing patients.

METHODS: A PubMed search was performed on 19 January 2015, to identify English-language, original, observational studies reporting adverse events while awaiting coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Rates of death, non-fatal myocardial infarction (MI) and emergency revascularization were calculated as occurrence rates per 1000 patient-weeks and pooled using random-effects models.

RESULTS: The search yielded 1323 articles, of which 22 were included with 66 410 patients and 607 675 patient-weeks on the wait list. When awaiting CABG, rates per 1000 patient-weeks were 1.1 [95% confidence interval 0.9–1.3] for death, 1.0 [0.6–1.6] for non-fatal MI and 1.8 [0.8–4.1] for emergency revascularization. Subgroup analyses demonstrated consistent outcomes, and sensitivity analyses demonstrated comparable event rates with low heterogeneity. Higher urgency of revascularization was based primarily on angiographic complexity, angina severity, left ventricular dysfunction and symptoms on stress testing, and such patients with a semi-urgent status had a higher risk of death than patients awaiting elective revascularization (risk ratio at least 2.8). Individual studies identified angina severity and

left ventricular dysfunction as most important predictors of death when awaiting CABG. Adverse rates per 1000 patient-weeks for patients awaiting PCI were 0.1 [95% confidence interval 0.0–0.4] for death, 0.4 [0.1–1.2] for non-fatal MI and 0.7 [0.4–1.4] for emergency revascularization but were based on only a few old studies.

CONCLUSIONS: Rates of death, non-fatal MI and emergency revascularization when awaiting myocardial revascularization are infrequent but higher in specific patients. Countries that not yet have treatment recommendations related to waiting times should consider introducing a maximum to limit adverse events, particularly when awaiting CABG.

Keywords: Coronary artery bypass grafting • Percutaneous coronary intervention • Myocardial revascularization • Waiting • Wait list • Delay • Death • Myocardial infarction • Emergency revascularization

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of death in Western countries. If CAD is too severe or medical therapy falls short, treatment is based on myocardial revascularization performed by percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [1–3]. PCI has become the most frequently performed therapeutic intervention in medicine, while CABG is one of the most common surgical procedures [4, 5]. As a result, centres may have waiting lists in place for patients requiring myocardial revascularization, particularly for CABG. However, these patients are at risk for myocardial infarction (MI), urgent or emergency revascularization or death while awaiting (semi-)elective procedures [6].

To prioritize access to care for patients who are at risk for adverse events and in greater need for early revascularization [7], the Canadian Cardiovascular Society has introduced guidelines with maximum acceptable waiting times for patients requiring revascularization [8]. The recent 2014 ESC/EACTS guidelines for myocardial revascularization have adopted these prioritization criteria and for the first time provide a recommendation on the time frame in which patients in Europe should undergo revascularization. Accordingly, it is recommended that patients with severe symptoms or high-risk coronary anatomy should undergo revascularization within 2 weeks, while other patients with stable CAD should undergo revascularization within 6 weeks after diagnostic catheterization [3]. These recommendations pertain to patients with stable CAD referred for elective revascularization, whereas more stringent timelines are in place for patients undergoing revascularization in the context of acute coronary syndrome (ACS) [9, 10].

However, the debate on waiting lists for myocardial revascularization is still ongoing, as it remains unclear to what extent patients are at risk of adverse events and criteria for prioritizing patients have not been adequately reviewed and are contradictory. These data are crucial for patient care as well as for healthcare providers and insurance companies. Moreover, numerous countries, including the USA, do not have recommendations for maximum waiting times.

We have performed a systematic review and meta-analysis of observational studies to estimate adverse event rates while awaiting myocardial revascularization and review criteria for prioritizing patients.

MATERIALS AND METHODS

This study adheres to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria for meta-analysis of observational studies [11].

Search strategy

A search of the PubMed database was performed on 19 January 2015, to identify potentially relevant full-length English-language studies that reported adverse events occurring in patients awaiting coronary revascularization, either CABG or PCI. No year of publication exclusion was applied. A combination of the following keywords was used, which were related to treatment ('percutaneous coronary intervention', 'PCI', 'percutaneous transluminal coronary angioplasty', 'PTCA', 'coronary artery bypass', 'CABG', 'coronary artery revascularization', and 'coronary revascularization'), status ('waiting time', 'waiting list', 'wait time', 'priority', 'prioritizing', 'prioritization', 'delay', 'queueing', 'queued', 'queuing', 'queue', and 'rationing') and outcomes ('death', 'mortality', 'stroke', 'myocardial infarction', 'STEMI', 'acute coronary syndrome', 'unstable angina', 'heart failure', 'readmission', and 'rehospitalization') (Supplementary Material, Appendix). Reference lists of the included studies were hand-searched to determine that no potential articles were missed.

Study inclusion

The results of the literature search were screened in 3 phases: (i) an initial inspection of the study titles, (ii) a reading of the abstract and (iii) an in-depth screening of the full-text articles. Studies had to fulfil the following criteria to be included in the meta-analysis: (i) the population consisted primarily of adult patients undergoing myocardial revascularization, although <25% of patients awaiting valve procedures was allowed; (ii) the population had to consist of patients with CAD on a waiting list for myocardial revascularization, excluding studies exclusively on primary PCI for ST-elevation myocardial infarction, recent ACS or salvage/emergent procedures; (iii) adverse event rates were reported separately for CABG or PCI; and (iv) adverse event rates were reported as events per time interval (e.g. deaths per patient-weeks), or, alternatively, could be calculated to events per time interval. The screening and study selection was performed independently and in duplicate by 2 investigators (S.J.H and M.S.U.). Disagreement was resolved by consensus.

Data extraction

We collected a number of study characteristics to assess whether patient populations were overlapping by being included in multiple studies. If this was the case, only the study with the highest number of patients was included in the meta-analysis. Two researchers (S.J.H. and B.B.) extracted the data independently and in duplicate; in case of disagreement, consensus was reached by discussion.

For each study, the following patient characteristics were extracted: mean age, gender, left ventricular (LV) function, angina classification, and prevalence of diabetes, multivessel disease, and left main disease. The following outcome measures were extracted to allow appropriate analyses: mean or median number of days/weeks/months/years that individuals spent on the waiting list or the total number of days/weeks/months/years that the cohort spent on the waiting list, number of deaths while on the waiting list and number of non-fatal adverse events (MI or emergency revascularization) while on the waiting list.

For studies categorizing patients according to an urgency/priority scale, we collected the urgency/priority criteria (e.g. variables) and the waiting times and adverse events for each group separately. If rates were provided according to the Canadian criteria of prioritizing procedures using elective, semi-urgent A and semi-urgent B status based on clinical and anatomical variables (left main or complex multivessel disease), these rates were extracted separately [12]. Patients with a semi-urgent status are stable to be discharged home with a Canadian Cardiovascular Score I–III, and stratification takes place based on <2 metabolic equivalents on a stress test using the standard Bruce protocol (e.g. semi-urgent A) or 2–5 metabolic equivalents (e.g. semi-urgent B). Semi-urgent A patients also include those with more complex coronary disease as defined as left main disease, multivessel disease and involvement of the proximal left anterior descending artery.

To analyse the risk factors for adverse events when waiting for myocardial revascularization, we collected outcomes of multivariable analyses identifying independent predictors of adverse events, with corresponding point estimates (odds ratio, hazard ratio and rate ratio) for different characteristics.

Statistical analysis

Analyses were performed with studies evaluating adverse events when awaiting CABG and PCI separately because of severely different characteristics of patients referred to CABG and PCI in these observational studies; no comparisons were made between the treatment strategies.

We calculated the rate of events per patient-week of observation time and used log transformation before pooling of estimates using a random-effects model. If the total number of patient-weeks on the waiting list was not provided, it was recalculated using the total number of patient-days/patient-years. If the total number of days/weeks/months/years on the waiting list was not provided, it was calculated through ['median/mean number of waiting time in weeks × number of patients']. In case of zero events, we derived the upper end of the 95% confidence interval (CI) of the rate as described by Hanley and Lippman-Hand [13] and used a continuity correction of 0.01 at the level of events and denominator population to derive a rate. Log rates and corresponding limits of the 95% CI were back transformed to rates per 1000 patient-weeks throughout. Results were summarized in forest plots. To estimate whether the average waiting time had an impact on the death rate per study, a scatter plot was constructed with the coefficient of determination, also known as R^2.

Heterogeneity across studies was explored using the Tau [2] statistic, with their prediction intervals calculated taking into account the between-study variance [14]. Since there was considerable heterogeneity between studies, we calculated 95% prediction intervals in addition to conventional intervals to reflect residual uncertainty [15]; performed analyses stratified by study design (prospective vs retrospective), year of initiation of patient recruitment (before 1999 vs 1999 or later), geographic location of patient inclusion, urgency of procedure (exclusively elective vs not exclusively elective patients), number of patients included in the study (<700 vs ≥700) and mean length of waiting time (<10 vs ≥10 weeks); and identified studies that contributed most to statistical heterogeneity by *z*-tests for the difference between the estimated log rate of a specific study and the pooled estimate of remaining studies. In sensitivity analyses, we excluded the studies with the highest *z*-values deemed to contribute most to heterogeneity. For the analysis of CABG patients, we cumulatively excluded the top 3 studies and for the analysis of PCI patients, which included few studies only, we excluded a single study with the highest *z*-value. Additional sensitivity analyses were performed by calculating within-study death rates for each status of the Canadian criteria of prioritizing procedures (i.e. elective, semi-urgent A and semi-urgent B) and calculated rate ratios (RRs) to compare death rates across different status of prioritizing of procedures. We subsequently pooled log RR using inverse variance random-effects meta-analysis and exponentiated pooled log RR and 95% CI; a log RR is statistically significant if the 95% CI does not include 0. All analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

RESULTS

The database search yielded 1323 articles (Fig. 1). Based on the first screening of the titles, 105 potentially relevant articles were deemed eligible. During the second screening of the abstract, an additional 60 articles could be excluded. As a result, the full texts of 45 potentially relevant articles were read, after which 22 articles were included in the pooled analysis. The majority of studies reported adverse events while awaiting CABG. Only 3 dedicated studies were published on events awaiting PCI. Two studies reported adverse events awaiting both PCI and CABG.

Study characteristics as well as patient baseline characteristics are reported in Table 1. The total number of patients from all included studies amounted to 66 410 and a total time on the waiting list of 607 675 patient-weeks. Characteristics of waiting times and adverse events within the individual studies are summarized in Table 2.

Coronary artery bypass grafting

Adverse events while awaiting revascularization. There were 19 studies that could be pooled to estimate rates among patients awaiting CABG (Fig. 2; Table 3). Death occurred at a rate of 1.1 (95% CI 0.9–1.3) per 1000 patient-weeks when awaiting CABG, derived from 579 584 patient-weeks. A non-fatal MI occurred at a rate of 1.0 (95% CI 0.6–1.6) per 1000 patient-weeks, derived from 187 000 patient-weeks. Emergency revascularization occurred at a rate of 1.8 (95% CI 0.8–4.1) per 1000 patient-week derived from 4182 patient-weeks (Supplementary Material, Fig. S1).

In an analysis to determine whether the risk of death increases with longer waiting times, there was no correlation between the length of the average waiting time and the death rate, as indicated by an R^2 of 0.0045 (Supplementary Material, Fig. S2).

Adverse events according to urgency or priority. Nine studies reported on what basis the decision was made to prioritize patients or categorize them according to urgency. Urgency/

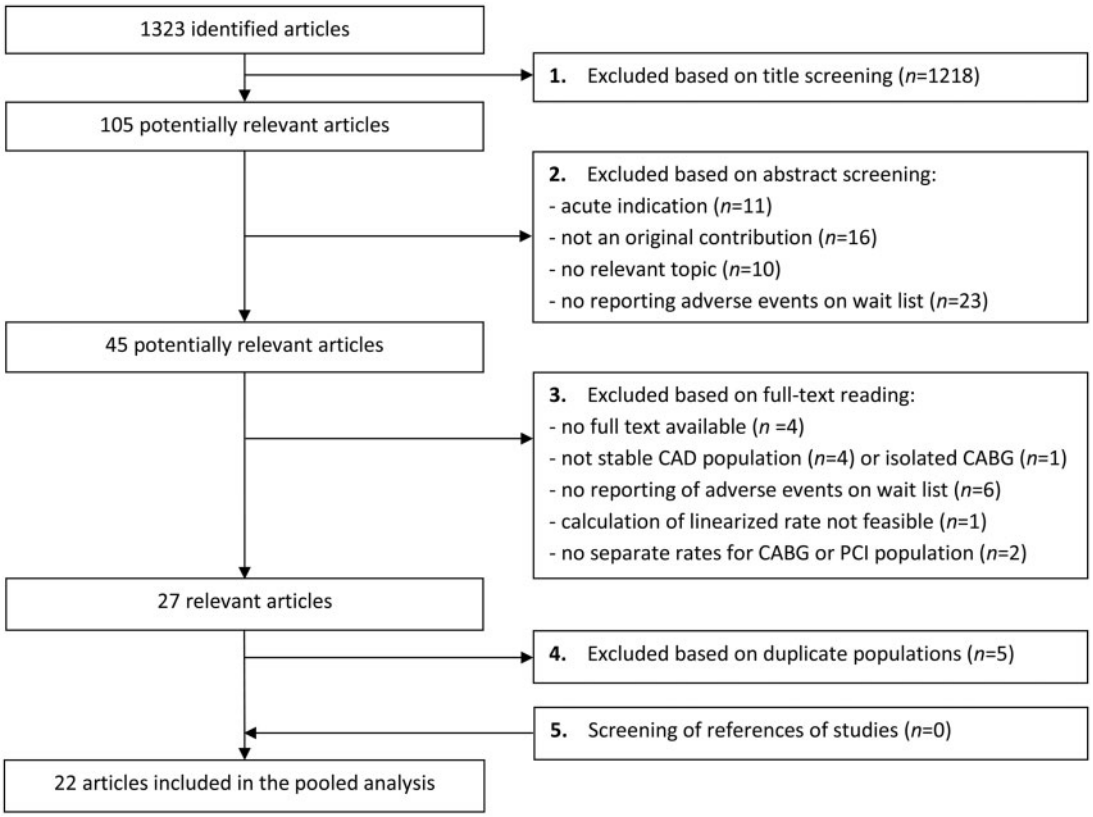

Figure 1: Study flow chart. CABG: coronary artery bypass grafting; CAD: coronary artery disease; PCI: percutaneous coronary intervention.

priority was based on the extent of CAD ($n = 9$ studies), severity of angina ($n = 9$ studies), LV dysfunction ($n = 8$ studies), exercise stress/non-invasive testing ($n = 6$ studies), ability to work ($n = 2$ studies) and the response to medical treatment ($n = 2$ studies).

Separate analyses with 12 studies could be pooled to generate rates of patients that were on the elective/routine waiting list (Table 3). The analysis of death included 104 371 patient-weeks during which 121 deaths occurred, calculating to a rate of 1.1 (95% CI 0.8–1.4) per 1000 patient-weeks. There were 30 608 patient-weeks during which 19 patients suffered a non-fatal MI, calculating to a rate of 0.7 (95% CI 0.4–1.1) per 1000 patient-weeks. Only a single study evaluated emergency revascularization when awaiting elective/routine CABG, occurring at a rate of 1.1 (95% CI 0.4–3.5) per 1000 patient-weeks.

For patients awaiting CABG, there were 3 studies that reported deaths of patients on a semi-urgent B and semi-urgent A waiting list, which could be pooled. When compared with patients awaiting elective/routine CABG, patients with a semi-urgent B status had an increased risk of death (log RR = 2.8, 95% CI 0.6–14.3). Patients with an even higher semi-urgent A priority status had an increased risk of death when compared with patients with an elective (log RR = 5.3, 95% CI 0.9–33.3) as well as semi-urgent B (log RR = 2.0, 95% CI 0.5–7.2) status.

Subgroup and sensitivity analyses. There were no significant differences in subgroup analyses for death and non-fatal MI (Table 4).

Sensitivity analyses by deleting studies contributing to heterogeneity demonstrated consistency in event rates of death and non-fatal MI when awaiting CABG while significantly reducing the degree of heterogeneity (Supplementary Material, Table S1).

Independent predictors of adverse events. Seven manuscripts reported the results of multivariable analysis of adverse events when awaiting CABG. Angina class appeared most often to be an independent predictor, followed by LV (dys)function or heart failure, male gender and time on the waiting list. Several other predictors have also been identified but have not been validated in other studies (Table 5).

Percutaneous coronary intervention

There were 5 studies that could be pooled to estimate rates among patients awaiting PCI (Fig. 3; Table 3). Death occurred at a rate of 0.1 (95% CI 0.0–0.4) per 1000 patient-weeks, derived from 28 001 patient-weeks. A non-fatal MI occurred at a rate of 0.4 (95% CI 0.1–1.2) per 1000 patient-weeks derived from 25 463 patient-weeks. Emergency revascularization occurred at a rate of 0.7 (95% CI 0.4–1.4) per 1000 patients-week derived from 13 428 patient-weeks (Supplementary Material, Fig. S1).

All studies evaluating adverse events awaiting PCI were performed on patients awaiting an elective procedure, and therefore the results did not change in the analysis of elective patients only (Table 3).

Sensitivity analyses to reduce heterogeneity and test consistency of death and non-fatal MI rates found similar event rates after deleting a single study contributing to heterogeneity (Supplementary Material, Table S1).

DISCUSSION

This systematic review and meta-analysis of 22 studies comprising 66 410 patients and a total time on the waiting list of 607 675

Table 1 Baseline characteristics of included studies

Author, year, ref.	Study design	Study location	Patient inclusion	Type of patients	Procedures	No. of patients (*n*)	Mean age (years)	Male (%)	DM (%)	LM disease (%)	Multivessel disease (%)	LV function	Angina class (%)
CABG													
Suttorp *et al.*, 1992 [6]	-	Netherlands	1985–1986	CAD	All CABG, irrespective of priority level	1124	-	-	-	-	-	-	-
Naylor *et al.*, 1995 [7]	Retrospective	Canada	1991–1993	CAD	All CABG, irrespective of urgency	8247	63[a]	79	-	15	~80	LV grade 3/4: 19%	CCS III: 40% CCS IV: 39%
Cox *et al.*, 1996 [12]	Prospective	Canada	1992	CAD	All CABG, irrespective of urgency	423	64	72	23	21	2VD: 26 3VD: 67	Mean EF: 62%	CCS III/IV: 91%
Maziak *et al.*, 1996 [16]	Prospective	Canada	1989–1994	Left main	All CABG	281	62	84	18	100	-	<60% EF: 39%	–
		-		No left main	All CABG	1864	61	83	21	0	-	<60% EF: 44%	–
Bernstein *et al.*, 1997[b] [17]	Prospective	Netherlands	1992	CAD	Elective CABG	980	-	78	-	16	2VD: 25 3VD: 54	-	CCS III/IV: 22%
	Prospective	Sweden	1994–1995		Elective CABG	1001	-	80	-	21	2VD: 23 3VD: 48	-	CCS III/IV: 40%
Morgan *et al.*, 1998 [18]	Prospective	Canada	1991–1995	CAD	All CABG, irrespective of urgency	22 655	62	79	-	16	78	LV grade 3/4: 23%	CCS IV-B/C: 16%
Jackson *et al.*, 1999 [19]	Retrospective	New Zealand	1994–1995	CAD	All CABG, irrespective of urgency	324	63[a]	73	15	24	~70	<50% EF: 25%	CCS III: 45% CCS IV: 39%
Seddon *et al.*, 1999 [20]	Retrospective	New Zealand	1993–1996	CAD	All patients on outpatient CABG waiting list, irrespective of urgency	701	62	71	16	15	~75	<50% EF: 21%	CCS III: 36% CCS IV: 30%
Arthur *et al.*, 2000 [21]	Prospective	Canada	1995–1997	CAD	Elective CABG	246	63	85	21	-	-	>40% EF: 100%	–
Koomen *et al.*, 2001 [22]	Prospective	Netherlands	-	CAD	All CABG (93%) with valve (7%), excluding those with an emergency indication	360	64	81	10	-	-	LVD: 16%	CCS III/IV: 15%
Ray *et al.*, 2001 [23]	Retrospective	Canada	1998–1999	CAD	Semi-urgent (A) iCABG (66%) with valve (14%) or other (20%)	437	67	65	33	-	-	Mean EF: 60%	CCS III/IV: 80
				-	Semi-urgent (B) iCABG (96%) with valve (2%) or other (2%)	576	64	78	31	-	-	Mean EF: 62%	CCS III/IV: 84
				-	Elective iCABG (96%) with valve (1%) or other (3%)	221	60	88	25	-	-	Mean EF: 65%	CCS III/IV: 19
Haddad *et al.*, 2002 [24]	Retrospective	Brazil	1993–1998	CAD	All CABG, excluding those with an emergency indication	484	61	70	-	-	-	-	-
da Rocha and da Silva, 2003 [25]	Retrospective	Brazil	-	Left main	All CABG	56	61	71	-	100	-	-	Unstable: 13
Cesena *et al.*, 2004 [26]	Prospective	Brazil	1998–2000	CAD	Elective CABG	516	61	72	37	-	58	Severe LVD: 22%	CCS III/IV: 30
Rexius *et al.*, 2004 [27]	Prospective	Sweden	1995–1999	CAD	Elective iCABG (89%) with valve (11%)	5864	66	78	18	17	-	Mean EF: 58%	CCS III/IV: 63
Légaré *et al.*, 2005[c] [28]	Retrospective	Canada	1999–2003	Left main	All CABG, irrespective of urgency	561	>70: 42%	76	37	100	-	<40% EF: 17%	CCS III/IV: 90
Sobolev *et al.*, 2006 [29]	Prospective	Canada	1991–2000	CAD	iCABG, irrespective of urgency	9233	>70: 32%	82	-	15	76	-	-
Henriksson *et al.*, 2010 [30]	Prospective	Sweden	2000–2005	CAD	All CABG, irrespective of urgency	9935	66	-	14	LM or 3VD: 79		-	-
CABG and PCI													

Continued

Table 1 Continued

Author, year, ref.	Study design	Study location	Patient inclusion	Type of patients	Procedures	No. of patients (n)	Mean age (years)	Male (%)	DM (%)	LM disease (%)	Multivessel disease (%)	LV function	Angina class (%)
Lim *et al.*, 1991 [31]	Retrospective	England	1988	CAD	Elective CABG or PTCA	CABG, *n* = 85 PTCA, *n* = 39	58	88	-	13	3VD: 70	LVD: 35%	-
PCI													
Chester *et al.*, 1995 [32]	Prospective	England	1989–1990	CAD	Routine PCI, not emergent or urgent	215	57	100	11	-	2VD: 42 3VD: 11	-	Unstable: 16
Koch *et al.*, 1997 [33]	Prospective	Netherlands	1990–1992	CAD	Elective PTCA	817	64	72	14	-	-	-	-
Bernstein *et al.*, 1997[b] [17]	Prospective	Netherlands	1992	-	Elective PTCA	869	-	71	-	<1	2VD: 36 3VD: 10	-	CCS III/IV: 80
	Prospective	Sweden	1994–1995	-	Elective PTCA	423	-	76	-	<1	2VD: 30 3VD: 7	-	CCS III/IV: 54
Talwar *et al.*, 2005 [34]	Prospective	England	1998–1999	CAD	Elective PCI	145	60	80	10	1	29	-	-

2VD: two-vessel disease; 3VD: three-vessel disease; iCABG: (isolated) coronary artery bypass grafting; CAD: coronary artery disease; CCS: Canadian Cardiovascular Score; DM: diabetes mellitus; EF: ejection fraction; LM: left main; LV(D): left ventricular (dysfunction); PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty.
[a]Median instead of mean.
[b]Same study but results were reported for CABG and PCI separately.
[c]Includes 408 patients with an emergent or in-hospital waiting status because baseline characteristics were not reported separately.

patient-weeks provides, for the first time, a systematic analysis of an underappreciated topic: adverse events, including death, while awaiting myocardial revascularization. Although many consider waiting times to be an issue of the past, nearly all studies in this analysis, including more recent studies, had average waiting times longer than suggested by the recent guidelines. The key findings of the present study are the following. First, death and non-fatal MI occur at a rate of 1.1 and 1.0 per 1000 patient-weeks when awaiting CABG. Second, separate analysis of prioritized patients awaiting CABG shows that patients with an elective status versus those with a semi-urgent status have lower rates of death, justifying prioritizing according to status and anatomy. In this regard, the most powerful clinical predictors of death appear to be severity of angina and LV dysfunction, which were independent predictors in ≥4 studies. Third, death and non-fatal MI occur at a rate of 0.1 and 0.4 per 1000 patient-weeks, respectively, when awaiting PCI. However, this rate is derived from only a few old studies.

While the benefits and risks of myocardial revascularization among patients with stable CAD are well established, the consequences of untimely access to revascularization have not been subject to a thorough investigation. Therefore, our results have several important implications on a clinical, logistic and regulatory level.

The benefit of shorter waiting times is multifactorial. When analysing deaths that occurred when awaiting CABG, Plomp and co-authors reported that 181 of 224 deaths (80.8%) were considered waiting-list related [37]. Of these, 137 (61.1% of total) deaths were sudden, while another 20 (8.9% of total) and 15 (6.7% of total) were the result of MI or heart failure, respectively. As suggested by the authors, these deaths may have been avoidable had there been unrestricted surgical capacity. Second, patients with an indication for myocardial revascularization have an impaired quality of life that is only declining when waiting times are prolonged, while a remarkable quality of life increase is seen shortly after revascularization [38–40]. Therefore, shortening waiting times will likely have a great impact not only on the rates of death, but also on increasing quality-adjusted life-years by lowering rates of non-fatal MI. Third, studies have reported a decline in LV function while awaiting revascularization, which may in part explain the impaired quality of life. In addition, a recent non-fatal MI or ACS, as well as preoperative LV dysfunction and a higher New York Heart Association classification are all predictors of operative mortality, and could potentially be avoided by reducing events when shortening waiting times [41]. Indeed, Sobolev and co-authors found that patients with waiting times longer than recommended had an operative risk of death that was about 50% higher than that of patients with waiting lists within the recommended maximum time [42], extending the benefit of shorter waiting times to an improvement in postoperative outcomes.

Several studies have suggested that the risk of adverse events increases with longer waiting times [25, 35]. However, other studies have contradicted this finding and reported that rates of death were particularly high within the first weeks on the wait list for patients awaiting CABG. Morgan and co-authors reported that death rates were highest in the first 2 weeks and occurred randomly thereafter [18]. We found that there was no correlation between the average waiting times and death rates per study. However, the cumulative risk of an adverse event for a certain patient does increase with longer waiting times.

A number of priority scores have been developed to assess which patients should receive myocardial revascularization within a certain

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Table 2 Waiting times and adverse event data of included studies

Treatment	Author, year, ref.	No. of patients (*n*)	Waiting time	Waiting period	Total waiting time (weeks)	Outcomes		
						Death	Non-fatal MI	Emergency revascularization
CABG	Suttorp *et al.*, 1992 [6]	CABG: 1124	Mean: 98 days	*Not provided*	15 736	26	-	-
	Naylor *et al.*, 1995 [35]	CABG: 8247	Mean: 34 days	Angio to revascularization	40 057	31	3	-
	Cox *et al.*, 1996 [12]	CABG: 423	Mean: 62.3 days	Assignment to revascularization	4655	5	0	-
	Maziak *et al.*, 1996 [16]	CABG: 281[a]	Mean: 38 days	Angio to revascularization	1525	0	4	4
	Bernstein *et al.*, 1997[b] [17]	CABG: 980	Median: 72 days	Angio to revascularization	10 080	11	8	-
		CABG: 1001	Median: 59 days	Angio to revascularization	8437	8	-	-
	Morgan *et al.*, 1998 [18]	CABG: 22 655	Mean: 38 days	Acceptance to revascularization	122 984	91	-	-
	Jackson *et al.*, 1999 [19]	CABG: 324	Mean: 232 days	Referral to revascularization	10 738	13	16	-
	Seddon *et al.*, 1999 [20]	CABG: 701	Median: 146 days	Acceptance to revascularization	14 621	18	16	-
	Arthur *et al.*, 2000 [21]	CABG: 246	Mean: 10.8 weeks	*Not provided*	2657	0	3	3
	Koomen *et al.*, 2001 [22]	CABG: 360	*Not provided*	Acceptance to revascularization	4316	8	3	-
	Ray *et al.*, 2001 [23]	Semi-urgent (A) CABG: 437	Median: 37 days	Angio to revascularization	2310	2	-	-
		Semi-urgent (B) CABG: 576	Median: 64 days		5266	6	-	-
		Elective CABG: 221	Median: 113 days		3568	1	-	-
	Haddad *et al.*, 2002 [24]	CABG: 484	Mean: 24 months	Acceptance to revascularization	50 336	54	-	-
	da Rocha, 2003 [25]	CABG: 56	Mean: 69 days	Angio to revascularization	552	1	6	-
	Cesena *et al.*, 2004 [26]	CABG: 516	Mean: 170 days	Referral to revascularization	12 531	12	5	-
	Rexius *et al.*, 2004 [27]	CABG: 5864	Median: 55 days	Acceptance to revascularization	46 074	67	-	-
	Légaré *et al.*, 2005[c] [28]	Semi-urgent (A) CABG: 91	Median: 30 days	Angio to revascularization	390	3	-	-
		Semi-urgent (B) CABG: 62	Median: 49 days		434	1	-	-
	Sobolev *et al.*, 2006 [29]	CABG: 9233	*No mean/median provided, only total wait time*	Acceptance to revascularization	137 139	92	-	-
	Henriksson *et al.*, 2010 [30]	CABG: 9935	Mean: 59 days	*Not provided*	83 738	83	84	-
CABG and PCI	Lim *et al.*, 1991 [31]	CABG: 85 PTCA: 39	Mean: 126 days	Angio to revascularization	CABG: 1530 PTCA: 702	0 0	1 0	6
PCI	Chester *et al.*, 1995 [32]	PCI: 215	Median: 7–8 months	Angio to revascularization	6988	1	4	-
	Koch *et al.*, 1997 [33]	PCI: 817	Mean: 8.8 weeks	Acceptance to revascularization	7190	0	0	5
	Bernstein *et al.*, 1997[b] [17]	PCI: 869	Median: 35 days	Angio to revascularization	4345	2	4	-
		PCI: 423	Median: 42 days	Angio to revascularization	2538	0	-	
	Talwar *et al.*, 2005 [34]	PCI: 145	Median: 10 months	Referral to revascularization	6283	0	1	5

CABG : coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty.
[a]Patients who did not have left main disease (see Table 1) were excluded because no adverse events on the waiting list were reported for those patients (*n* = 1864).
[b]Same study but results were reported for CABG and PCI separately.
[c]Patients who underwent CABG as an emergency or in-hospital urgent operation were excluded (*n* = 408).

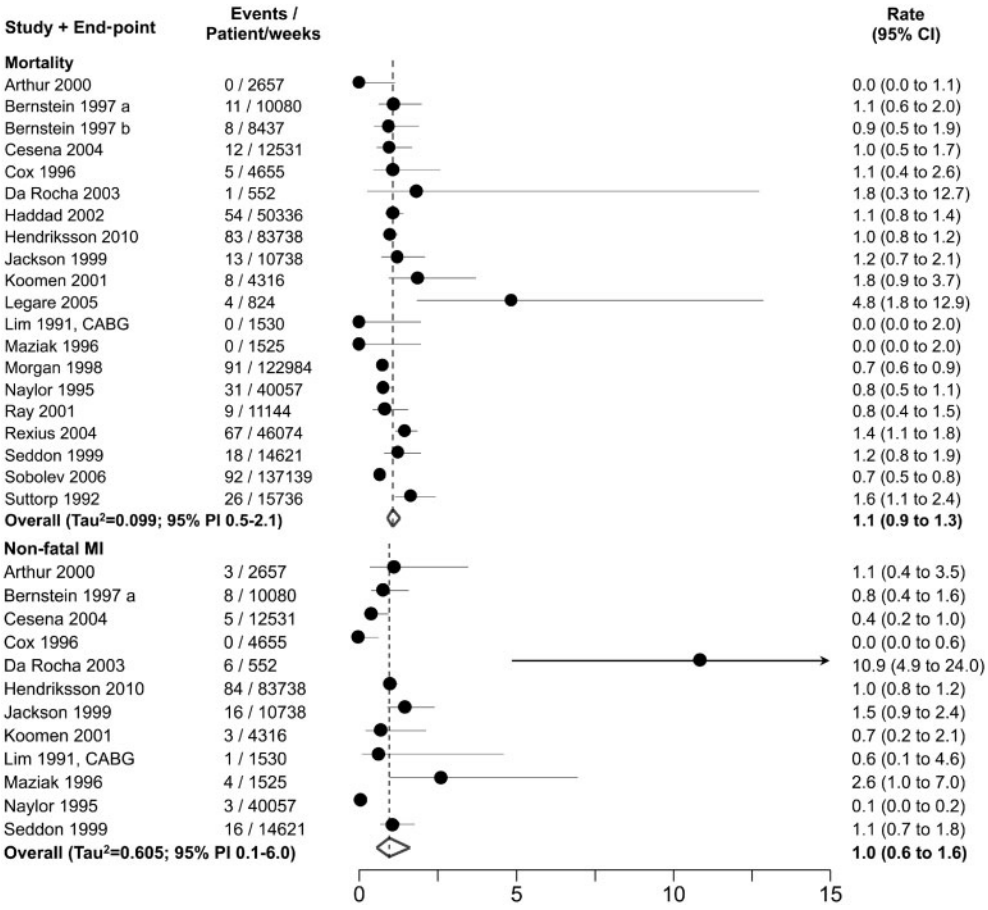

Figure 2: Pooled rate of death and non-fatal MI when awaiting CABG. Incidence estimated from log-transformed data; therefore, 95% CIs are asymmetrical. CABG: coronary artery bypass grafting; CI: confidence interval; MI: myocardial infarction.

time frame and which patients have a lower risk and can wait longer [7, 20]. These scores have largely been developed using the following variables: complexity of CAD, LV dysfunction, severity of angina and results on exercise stress/non-invasive test. Many of these factors have therefore been included in the most recent guidelines to perform revascularization within 2 instead of 6 weeks from coronary angiography [3]. Our subgroup analysis could not confirm the clinical impact of these variables on adverse events in patients awaiting revascularization. A meta-analysis with individual patient data would have the ability to perform specific subgroup and multivariable analyses to detect such differences. We did find that studies that identified predictors of death reported angina class and LV dysfunction as the most frequently occurring predictors. The complexity of CAD did not appear to be an independent predictor of adverse events in the individual studies, but it is unclear whether this is because it is not a predictor or because it often was not included as a variable. Moreover, it is not only the risk of an adverse event that warrants these patients to undergo earlier revascularization but also the risk of compromising the result of revascularization by the loss of viable myocardium when an event occurs in the left anterior descending coronary artery territory as opposed to an event in, e.g. the distal right coronary artery [43]. Furthermore, our analysis of prioritizing patients according to their extent of CAD, LV dysfunction, severity of angina and results on exercise stress/non-invasive testing did show that patients with a more urgent indication for revascularization had a higher rate of death while on the waiting list, suggesting that the waiting time should be minimized for these patients. In addition, data have shown that 38% of patients who have suffered an ACS (and would therefore have a high priority) were readmitted with further ACS while waiting [44].

Current guideline recommendations do not take into account whether a patient is awaiting CABG or PCI [3]. According to our results, the impact of waiting times and the guideline recommendations may be more relevant for patients awaiting CABG than for those awaiting PCI, although the data on adverse events when awaiting PCI were scarce and conclusions related to PCI should be considered hypothesis generating. For CABG patients on a wait list who develop an acute indication, primary PCI and the subsequent need for complete revascularization with CABG increases complication rates, challenges hospital logistics and thus significantly increases health care costs. Diffusion of cardiac catheterization and PCI facilities have decreased bottlenecks related to access to interventional care. Moreover, the option of *ad hoc* PCI, supported by current guidelines [3] in patients with less complex CAD despite optimized medical therapy [45, 46], is probably one of the reasons why we could include only 5 studies that reported adverse events for patients awaiting PCI. These were particularly older studies with only a single study performed after 2000 [17, 31–34, 47, 48], which could reflect the progressive increase in *ad hoc* PCI [49]. Although PCI practice has since changed significantly, adverse event rates are still particularly relevant for patients with more complex and diffuse disease in whom *ad hoc* PCI is not advised by clinical guidelines and a Heart Team discussion should take place [3, 50]; these patients can

Table 3 Pooled data of adverse events when awaiting (elective) CABG or PTCA/PCI

Cohort	Outcome	Treatment	No. of studies[a]	No. of patients	Total waiting time (weeks)	No. of events	Pooled rate (per 1000 patient-weeks)	95% CI
Entire cohort	Death	CABG	19	64 002	579 584	533	1.1	0.9–1.3
		PTCA/PCI	5	2508	28 001	3	0.1	0.0–0.4
	Non-fatal MI	CABG	12	22 254	187 000	149	1.0	0.6–1.6
		PTCA/PCI	5	2085	25 463	9	0.4	0.1–1.2
	Emergency revascularization	CABG	2	527	4182	7	1.8	0.8–4.1
		PTCA/PCI	2	360	13 428	10	0.7	0.4–1.4
Elective/routine revascularization	Death	CABG	9	10 029	104 371	121	1.1	0.8–1.4
		PTCA/PCI	5	2508	28 001	3	0.1	0.0–0.4
	Non-fatal MI	CABG	6	2082	30 608	19	0.7	0.4–1.1
		PTCA/PCI	5	2085	25 463	9	0.4	0.1–1.2
	Emergency revascularization	CABG	1	246	2657	3	1.1	0.4–3.5
		PTCA/PCI	2	360	13 428	10	0.7	0.4–1.4

CABG: coronary artery bypass grafting; CI: confidence interval; MI: myocardial infarction; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty.
[a]The sum of the number of separate studies on CABG or PTCA/PCI patients does not add up to the 'all treatments' results, as some studies did or did not provide separate results for each treatment.

Table 4 Subgroup analyses of CABG studies

Death				Non-fatal MI			
	Rate	95% CI	*P*-value for interaction		Rate	95% CI	*P*-value for interaction
Study design							
Prospective	1.0	0.8–1.3	0.55	Prospective	0.9	0.6–1.4	0.73
Retrospective	1.1	0.8–1.6		Retrospective	1.1	0.3–3.6	
Years of patient inclusion							
Inclusion before 1999	1.0	0.8–1.3	0.64	Inclusion before 1999	0.8	0.4–1.6	0.89
Inclusion since 1999	1.2	0.7–2.0		Inclusion since 1999	0.7	0.3–1.7	
Geographic location of study			0.14				0.93
Canada	0.9	0.6–1.2		Canada	0.4	0.0–2.9	
Brazil	1.1	0.8–1.4		Brazil	2.1	0.1–51.4	
England	0.0	0.0–2.0		England	0.7	0.1–4.6	
Netherlands	1.5	1.1–2.0		Netherlands	0.8	0.4–1.4	
New Zealand	1.2	0.9–1.7		New Zealand	1.3	0.9–1.8	
Sweden	1.2	0.9–1.6		Sweden	1.0	0.8–1.2	
Study size							
Number of patients <700	1.3	0.8–2.0	0.28	Number of patients <700	1.3	0.5–3.1	0.33
Number of patients ≥700	1.0	0.8–1.2		Number of patients ≥700	0.6	0.3–1.2	
Urgency							
Exclusively elective patients	1.1	0.9–1.3	0.78	Exclusively elective patients	1.1	0.6–2.1	0.72
Not exclusively elective patients	1.1	0.8–1.6		Not exclusively elective patients	0.7	0.4–1.2	
Waiting time							
Average waiting time <10 weeks	1.0	0.8–1.4	0.76	Average waiting time <10 weeks	0.9	0.2–4.1	0.91
Average waiting time ≥10 weeks	1.1	0.8–1.5		Average waiting time ≥10 weeks	1.0	0.7–1.4	

CABG: coronary artery bypass grafting; CI: confidence interval; MI: myocardial infarction.

therefore be exposed to waiting times. Nevertheless, medical therapy while awaiting myocardial revascularization has significantly improved, potentially reducing the occurrence of adverse events. Our subgroup analysis according to patient inclusion before and after 1999 did not show a significant difference in terms of adverse event rates. Despite these results, it is anticipated that the use of more potent (dual) antiplatelet therapy while awaiting revascularization would significantly reduce adverse events. Individual studies did not report any information on the use of medical therapy, and this hypothesis could therefore not be tested.

Clinical practice guidelines are universal, independently of different local conditions and health care systems. However, depending on geographic, economic and social considerations, guideline adherence might vary across different countries. Notwithstanding, the recent 2014 ESC/EACTS guidelines for myocardial revascularization recommendations for a timely access to myocardial

Table 5 Independent predictors of adverse events

Characteristics	Point estimate	Outcome measure	Reference
Angina			
Unstable	OR = 6.4	Death	[6]
	HR = 2.5	Death/MI/UA	[22]
	OR = 8.4	Death/MI	[25]
	RR = 2.8	Death	[27]
Class III/IV	OR = 2.2	Death/MI/cardiac readmission	[20]
	HR = 2.3	Death/MI/UA/cardiac readmission	[26]
LV dysfunction			
LVEF per 10% decrease	RR = 1.3	Death	[27]
Class III/IV	OR = 2.5	Death	[18]
	HR = 2.4	Death/MI/UA/cardiac readmission	[26]
Male gender	OR = 2.0	Death	[18]
	RR = 2.4	Death	[27]
Waiting time			
Longer than recommended[a]	OR = 1.6	Death	[18]
Per month	RR = 1.1	Death	[27]
Urgency/priority			
Urgent	HR = 14.2	Death/MI/UA	[22]
Priority	RR = 2.0	Death	[27]
Age per 10 years	OR = 1.4	Death	[18]
Hypertension	OR = 1.8	Death/MI/cardiac readmission	[20]
Triglycerides <150 mg/dl (1.7 mmol/l)	OR = 1.8	Death/MI/UA/cardiac readmission	[26]
Smoking	OR = 8.7	Death	[6]
Positive exercise test	OR = 13.3	Death	[6]
Coumadin treatment	OR = 7.1	Death	[6]
Cardiac enlargement	OR = 14.4	Death	[6]
Cleveland Clinic risk score[b]	RR = 1.2	Death	[27]
Concomitant aortic valve disease	RR = 2.7	Death	[27]
Previous CABG	OR = 2.5	Death/MI/cardiac readmission	[20]

CABG: coronary artery bypass grafting; HR: hazard ratio; LV(EF): left ventricular (ejection fraction); MI: myocardial infarction; OR: odds ratio; RR: rate ratio; UA: unstable angina.
[a]According to Canadian guidelines for a patient's clinical profile.
[b]Cleveland Clinic risk score refers to Higgins and co-authors [36].

revascularization are the first cardiovascular guidelines to focus on the timing of myocardial revascularization [3]. European countries, therefore, now have been provided such guidance. However, other countries, such as the USA, do not have such recommendations. The present meta-analysis provides evidence to support maximum waiting times. Our findings that patients with CAD waiting for myocardial revascularization are at risk of death and other adverse events may contribute to health care systems reform that will ultimately benefit patients' access to cardiac care. However, dedicated registries and randomized controlled trials on the most optimal timing of revascularization after coronary angiography will be critical in complementing the information

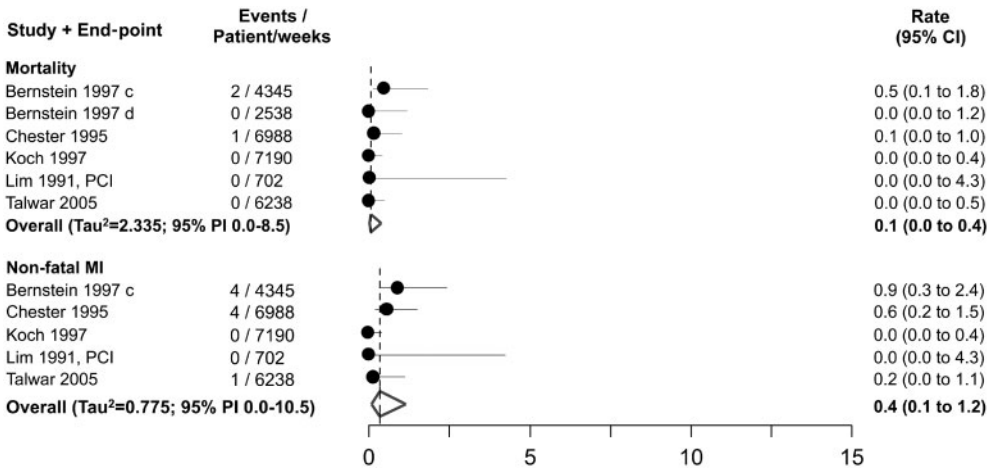

Figure 3: Pooled rate of death and non-fatal MI when awaiting PCI. Incidence estimated from log-transformed data; therefore, 95% CIs are asymmetrical. MI: myocardial infarction; PCI: percutaneous coronary intervention; CI: conficence interval.

gathered by this meta-analysis and are required to strengthen the evidence for guideline recommendations and provide insights into costs related to delayed revascularization.

Study limitations

Selection of manuscripts available in the literature may have introduced an entry bias, and it may therefore be unclear how these rates truly reflect clinical practice. Moreover, there were no randomized trials on the timing of revascularization that could be included. It is also possible that potentially relevant manuscripts were missed in the literature search. Furthermore, a publication bias might exist, and unpublished quality control data from health care systems might not be in the public domain or available only in closed fora or local languages.

Another important limitation of the current study is the heterogeneity in study designs and outcome data. The inclusion of studies with slightly different inclusion criteria is likely to be one of the reasons why there was a high heterogeneity in the analyses. Although most subgroup results did show consistency of adverse event rates, we could only perform such analyses with known factors, while unknown factors that could have an impact on adverse events could not be analysed. Furthermore, subgroup analyses according to patient characteristics, such as severity of angina and left ventricular dysfunction, could not be performed because no individual patient data was available. We did find that event rates remained consistent when deleting studies from the analysis, which significantly reduced the degree of heterogeneity.

The definition of waiting times was different among studies; it can be calculated from the time of registration to revascularization or the time between coronary angiography and revascularization [48]. Therefore, one of the problems we encountered was underappreciation of true waiting times due to a discrepancy between 'official' and real waiting times in relation to delay between angiography and registration for revascularization [28].

CONCLUSIONS

According to the results of this meta-analysis of observational studies, death and non-fatal MI occur at a rate of 1.1 and 1.0 per 1000 patient-weeks when awaiting CABG, respectively, with rates being dependent on the priority of patients according to their status and coronary anatomy. Angina class and LV function appear to be the most important predictors for adverse events when awaiting CABG. When awaiting PCI, rates are 0.1 and 0.4 per 1000 patient-weeks, respectively. Our study findings underscore the importance of recommendations on the maximum waiting time for revascularization provided by the recent guidelines, particularly for CABG. Countries that do not yet have such recommendations should consider introducing maximum waiting times to limit adverse events.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: Part 1–the evolution over the first 50 years. Eur Heart J 2013;34:2862–72.
[2] Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ *et al.* Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. Eur Heart J 2014;35:2821–30.
[3] Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V *et al.* 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2014;46:517–92.
[4] Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.
[5] Jha AK, Fisher ES, Li Z, Orav EJ, Epstein AM. Racial trends in the use of major procedures among the elderly. N Engl J Med 2005;353:683–91.
[6] Suttorp MJ, Kingma JH, Vos J, Koomen EM, Tijssen JG, Vermeulen FE *et al.* Determinants for early mortality in patients awaiting coronary artery bypass graft surgery: a case-control study. Eur Heart J 1992;13:238–42.
[7] Naylor CD, Baigrie RS, Goldman BS, Basinski A. Assessment of priority for coronary revascularisation procedures. Revascularisation Panel and Consensus Methods Group. Lancet 1990;335:1070–3.
[8] Graham MM, Knudtson ML, O'Neill BJ, Ross DB; Canadian Cardiovascular Society Access to Care Working Group. Treating the right patient at the right time: access to cardiac catheterization, percutaneous coronary intervention and cardiac surgery. Can J Cardiol 2006;22:679–83.
[9] Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
[10] Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2011;32:2999–3054.
[11] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al.* Meta-analysis of observational studies in epidemiology: a propsal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[12] Cox JL, Petrie JF, Pollak PT, Johnstone DE. Managed delay for coronary artery bypass graft surgery: the experience at one Canadian center. J Am Coll Cardiol 1996;27:1365–73.
[13] Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249:1743–5.
[14] da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;35:3336–45.
[15] Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaulation of random-effects meta-analysis. J R Stat Soc Ser Stat Soc 2009;172:137–59.
[16] Maziak DE, Rao V, Christakis GT, Buth KJ, Sever J, Fremes SE *et al.* Can patients with left main stenosis wait for coronary artery bypass grafting? Ann Thorac Surg 1996;61:552–7.
[17] Bernstein SJ, Rigter H, Brorsson B, Hilborne LH, Leape LL, Meijler AP *et al.* Waiting for coronary revascularization: a comparison between New York State, The Netherlands and Sweden. Health Policy 1997;42:15–27.
[18] Morgan CD, Sykora K, Naylor CD. Analysis of deaths while waiting for cardiac surgery among 29,293 consecutive patients in Ontario, Canada. The Steering Committee of the Cardiac Care Network of Ontario. Heart 1998;79:345–9.
[19] Jackson NW, Doogue MP, Elliott JM. Priority points and cardiac events while waiting for coronary bypass surgery. Heart 1999;81:367–73.
[20] Seddon ME, French JK, Amos DJ, Ramanathan K, McLaughlin SC, White HD. Waiting times and prioritization for coronary artery bypass surgery in New Zealand. Heart 1999;81:586–92.
[21] Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med 2000;133:253–62.
[22] Koomen EM, Hutten BA, Kelder JC, Redekop WK, Tijssen JG, Kingma JH. Morbidity and mortality in patients waiting for coronary artery bypass surgery. Eur J Cardiothorac Surg 2001;19:260–5.
[23] Ray AA, Buth KJ, Sullivan JA, Johnstone DE, Hirsch GM. Waiting for cardiac surgery: results of a risk-stratified queuing process. Circulation 2001;104:I92–8.

[24] Haddad N, Bittar OJ, Pereira AA, da Silva MB, Amato VL, Farsky PS *et al*. Consequences of the prolonged waiting time for patient candidates for heart surgery. Arq Bras Cardiol 2002;78:452–65.
[25] da Rocha AS, da Silva PR. Can patients with left main coronary artery disease wait for myocardial revascularization surgery? Arq Bras Cardiol 2003;80:191–3, 187–90.
[26] Cesena FH, Favarato D, Cesar LA, de Oliveira SA, da Luz PL. Ontario score and cardiac risk during waiting for elective coronary bypass grafting. Int J Cardiol 2006;110:167–74.
[27] Rexius H, Brandrup-Wognsen G, Oden A, Jeppsson A. Mortality on the waiting list for coronary artery bypass grafting: incidence and risk factors. Ann Thorac Surg 2004;77:769–74; discussion 774–5.
[28] Légaré JF, MacLean A, Buth KJ, Sullivan JA. Assessing the risk of waiting for coronary artery bypass graft surgery among patients with stenosis of the left main coronary artery. CMAJ 2005;173:371–5.
[29] Sobolev BG, Levy AR, Kuramoto L, Hayden R, FitzGerald JM. Do longer delays for coronary artery bypass surgery contribute to preoperative mortality in less urgent patients? Med Care 2006;44:680–6.
[30] Henriksson M, Palmer S, Chen R, Damant J, Fitzpatrick NK, Abrams K *et al*. Assessing the cost effectiveness of using prognostic biomarkers with decision models: case study in prioritising patients waiting for coronary artery surgery. BMJ 2010;340:b5606.
[31] Lim R, Kreidieh I, Dymond DS. Do routine clinic visits prevent destabilization in patients awaiting coronary revascularization? J R Soc Med 1991;84:660–1.
[32] Chester M, Chen L, Kaski JC. Identification of patients at high risk for adverse coronary events while awaiting routine coronary angioplasty. Br Heart J 1995;73:216–22.
[33] Koch KT, Piek JJ, David GK, Mulder K, Peters RJ, Lie KI. Does a waiting time for elective coronary angioplasty affect the primary success rate? Heart 1997;77:432–6.
[34] Talwar S, Karpha M, Thomas R, Vurwerk C, Cox IC, Burrell CJ *et al*. Disease progression and adverse events in patients listed for elective percutaneous coronary intervention. Postgrad Med J 2005;81:459–62.
[35] Naylor CD, Sykora K, Jaglal SB, Jefferson S. Waiting for coronary artery bypass surgery: population-based study of 8517 consecutive patients in Ontario, Canada. The Steering Committee of the Adult Cardiac Care Network of Ontario. Lancet 1995;346:1605–9.
[36] Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. JAMA 1992;267:2344–8.
[37] Plomp J, Redekop WK, Dekker FW, van Geldorp TR, Haalebos MM, Jambroes G *et al*. Death on the waiting list for cardiac surgery in The Netherlands in 1994 and 1995. Heart 1999;81:593–7.
[38] Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P *et al*. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. N Engl J Med 2011;364:1016–26.
[39] Bengtson A, Karlsson T, Herlitz J. On the waiting list for possible coronary revascularisation. Symptoms relief during the first year and association between quality of life and the very long-term mortality risk. Int J Cardiol 2008;123:271–6.
[40] Underwood MJ, Firmin RK, Jehu D. Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting. Br Heart J 1993;69:382–4.
[41] Pitt M, Dutka D, Pagano D, Camici P, Bonser R. The natural history of myocardium awaiting revascularisation in patients with impaired left ventricular function. Eur Heart J 2004;25:500–7.
[42] Sobolev BG, Fradet G, Hayden R, Kuramoto L, Levy AR, FitzGerald MJ. Delay in admission for elective coronary-artery bypass grafting is associated with increased in-hospital mortality. BMC Health Serv Res 2008;8:185.
[43] Stone PH, Raabe DS, Jaffe AS, Gustafson N, Muller JE, Turi ZG *et al*. Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. J Am Coll Cardiol 1988;11:453–63.
[44] Voss J, Martin A, Caldwell I, Lee M, Kerr AJ. How long do acute coronary syndrome patients wait for reperfusion, diagnostic coronary angiography and surgical revascularization? N Z Med J 2013;126:38–48.
[45] Kolh P, Wijns W, Danchin N,D, Mario C, Falk V, Folliguet T *et al*. Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2010;38 Suppl:S1–52.
[46] Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG *et al*. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e652–735.
[47] Naylor CD, Morgan CD, Levinton CM, Wheeler S, Hunter L, Klymciw K *et al*. Waiting for coronary revascularization in Toronto: 2 years' experience with a regional referral office. CMAJ 1993;149:955–62.
[48] Bengtson A, Karlsson T, Hjalmarson A, Herlitz J. Complications prior to revascularization among patients waiting for coronary artery bypass grafting and percutaneous transluminal coronary angioplasty. Eur Heart J 1996;17:1846–51.
[49] Hannan EL, Samadashvili Z, Walford G, Holmes DR, Jacobs A, Sharma S *et al*. Predictors and outcomes of ad hoc versus non-ad hoc percutaneous coronary interventions. JACC Cardiovasc Interv 2009;2:350–6.
[50] Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR Jr *et al*. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 2013;34:2510–8.