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Time from adenosine di-phosphate receptor antagonist discontinuation to coronary bypass surgery in patients with acute coronary syndrome: Meta-analysis and meta-regression

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ABSTRACT

Background: Adenosine di-phosphate receptor antagonists (ADPRAs) blunt hemostasis for several days after administration. This effect, aimed at preventing cardiac ischemic complications particularly in patients with acute coronary syndromes (ACS), may increase perioperative bleeding in the case of cardiac surgery. Practice Guidelines recommend withholding ADPRAs for at least 5 days prior to surgery, though with a weak base of evidence. The purpose of this study was to systematically review observational and experimental studies of early or late preoperative discontinuation of ADPRAs prior to coronary artery bypass grafting (CABG) for patients with ACS.
Methods: MEDLINE, EMBASE, the Cochrane Library databases up to December 2011; and reference lists. Observational and experimental studies that compared early ADPRA discontinuation with late discontinuation, or no discontinuation, in patients with ACS undergoing CABG.
Results: There were 19 studies, including 14,046 participants, 395 deaths and 309 reoperations due to bleeding. ADPRA late discontinuation up to CABG was associated with an increased risk of postoperative mortality (OR 1.46, 95% confidence interval (CI) 1.10 to 1.93) and reoperations due to bleeding (OR 2.18; 95% CI 1.47 to 2.62). Between-study heterogeneity was low. Meta-analysis limited to high quality or prospective studies gave consistent results. In most instances, the 95% prediction intervals for summary risk estimates confirmed the risk across study groups.
Conclusions: ADPRA late discontinuation prior to CABG is associated with an increased risk of death and reoperations due to bleeding in patients with ACS. The confidence in the estimates of risk for late discontinuation is moderate to high.

1. Introduction

The platelet adenosine di-phosphate receptor antagonists (ADPRAs) are extensively used in patients with coronary artery disease (CAD) [1]. In stable CAD, they are given in combination with aspirin in order to prevent stent thrombosis after elective angioplasty. In acute coronary syndrome (ACS), regardless of stent implantation, they have been shown to reduce the aggregate risk of cardiovascular death, myocardial infarction (MI) and stroke by almost 20% by acting on an activated thrombotic milieu [2–6].

Treatment prior to angioplasty is recommended by current guidelines in order to prevent early ischemic events [1]. However, since two of these agents (clopidogrel and prasugrel) exert an irreversible antiplatelet effect, and the third (ticagrelor) is a powerful, though reversible, blocker, an increased risk of perioperative bleeding exists in the case of urgent coronary artery bypass grafting (CABG). In this setting, preoperative ADPRA administration has been associated with increased rates of transfusion and re-operation to stop bleeding. Regardless of the antiplatelet regimen, reoperation due to bleeding is generally uncommon in patients undergoing elective CABG (about 1.5%) [7]. However this risk is increased in the case of urgent bypass surgery (4–15% among ACS patients) possibly due to preoperative antithrombotic treatments [8,9]. Reoperation to stop bleeding is associated with worse clinical outcomes and a 4.5 fold higher mortality [10,11]. On this basis, withholding ADPRAs prior to cardiac surgery might decrease re-exploration rate, chest tube drainage

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and post-operative mortality. Based upon multiple reviews and cohort studies, current guidelines recommend discontinuing ADPRAs for at least 5 days, and preferably 7 days, before CABG in order to reduce bleeding complications [12–16].

However, whereas this recommendation seems to be safe in elective CABG patients, the risk versus benefit of ADPRA discontinuation in ACS patients remains unclear.

Therefore, the aim of this meta-analysis was to determine whether early compared to late discontinuation of ADPRAs affects the postoperative course of CABG in ACS patients, and to define the optimal timing of ADPRA discontinuation prior to surgery.

2. Methods

2.1. Eligibility

This meta-analysis has been registered with PROSPERO—the NHR International Prospective Register of Systematic Reviews (CRD42011001865) [17]. We followed a priori study eligibility criteria for study selection. We included any observational and experimental study that compared any early discontinuation of ADPRA drugs to later discontinuation treatment or no discontinuation for patients with ACS referred to CABG surgery. We excluded studies with fewer than 50% of patients with ACS, those without a comparison group and those published in languages other than English.

Evidence from observational studies was included because it is unlikely that patients were randomized to receive immediate or postponed surgery after ADPRA administration to obtain evidence of the mortality-delay association. Furthermore observational studies may provide important additional information to RCTs with regard to specific populations, administration modes, and outcomes, especially mortality.

We did not define a priori an optimal time for ADPRA discontinuation but accepted what the authors claimed as the reference point between early and late discontinuation, within an interval of maximum seven days.

2.3. Search strategy

Studies were identified by searching electronic databases and scanning reference lists of articles. This search was applied to Medline, and adapted for EMBASE and the Cochrane Library [i.e. Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE)] for studies published in English between January 2001 and December 2011. The strategy was developed using the search terms "clopidogrel", "thienopyridine", "ticagrelor", "prasugrel", ADP receptor antagonist", "antiplatelet therapy", "coronary artery bypass", "coronary artery bypass graft", "graft occlusion", and "graft patency". The reference lists of relevant papers, including other systematic reviews focusing on this topic, and abstracts presented at the European and American Cardiology Congresses (2006–2012) were also searched.

2.4. Data extraction

The primary outcome was postoperative mortality (<30 days) and the secondary outcome was re-operation due to bleeding.

The exposure under consideration was ADPRA administration during 2–7 days preceding CABG. The control group was defined as any other antiplatelet treatment during 2–7 days preceding CABG, such as aspirin or no treatment.

We developed a data extraction sheet, pilot-tested it on five randomly-selected studies, and refined it accordingly. One review author (NM) extracted the following data from studies included and entered in the data extraction form: patient demographics and baseline characteristics, the ADPRA loading dose, the number of ADPRA-free days before surgery, the perioperative use of antifibrinolytic drugs, primary and secondary endpoints. A second author (JAO) checked the extracted data to ensure quality. Disagreements were solved by discussion between the two review authors; if no agreement was reached, a third author (VR) could decide.

For all studies, we recorded the number of treated-patients, the number of non treated-patients and the number of events in each group in order to estimate the odds ratios (OR) and corresponding 95% confidence intervals (CI).

Data concerning transfusion requirements, myocardial infarction, chest-tube drainage, and the duration of hospitalization were not included because of the heterogeneity of definitions, indications and measures applied in the different studies.

2.5. Methodological quality

Methodological quality was independently assessed by two review authors (NM and AS). The Newcastle–Ottawa (NOS) scale for cohort and case-control studies was used [18,19]. This scale has three groups of items: selection, exposure/outcome and comparability. A study can be awarded a maximum of one star for each numbered item in 'patient selection' (four items) and 'exposure or outcome' (for case-control or cohort studies respectively) (three items) and a maximum of two stars in the 'comparability of study groups' (two items), for a total of nine stars. Since we were interested in mortality of operated patients, we expected three items would be scored positively across all studies, specifically ascertainment of exposure (secure ADPRA administration), demonstration that outcome of interest was not present at the start of the study, and assessment of outcome (record linkage). The same three items were verified for studies reporting only the secondary endpoint. In fact, in our meta-analysis, the NOS scale could have ranged between three and nine. For randomized controlled trials (RCTs) we summarized the risk of bias for mortality within study across the following specific domains: sequence generation, allocation concealment, and incomplete outcome data [18]. We decided a priori that only observational studies that met eight or nine of the Newcastle–Ottawa Scale criteria were to be considered of high quality, whereas RCTs were considered of high quality if they satisfied two or more components. The Newcastle–Ottawa quality scoring assessment is reported in Appendix, Table 1.

2.6. Statistical analysis

We did an overall quantitative synthesis using all ORs for mortality computed from the frequencies obtained from each study. The results were pooled using the Mantel–Haenszel random effects model described by DerSimonian and Laird [20] and ordered by study year. Random effects model was used to synthesize data rather than the fixed effects model because they incorporate within- and between-study variability. This model was selected a priori as the meta-analysis was expected to include primarily observational studies with inherently more variability than RCTs. A Mantel–Haenszel estimate was also computed and compared to the DerSimonian and Laird estimate to investigate any influence of small study effects on the pooled OR, since the DerSimonian and Laird methods tend to attribute greater weight to small studies with increasing heterogeneity. The heterogeneity across studies was assessed by the I-squared statistic and corresponding p-value. We explored meta-analytic prediction intervals as means for providing a clear, appropriate and robust future treatment summary reflecting current estimates [21]. The prediction interval estimates the possible treatment effect in a future study, and if it includes the null value of one it is possible that the direction of the treatment effect in a single study may not be the same as that from the meta-analysis.

Pooled estimates were computed for each stratum of time from ADPRA discontinuation to surgery. Pooled ORs were obtained even for the secondary endpoints throughout the same approach. We also computed the predictive interval for the approximate predictive distribution of a future trial, based on the extent of heterogeneity, for both outcomes. Sensitivity analysis was performed to account for differences between the studies. Data were synthesized for study design (RCT, prospective and retrospective studies), for study quality (high and low qualities), for time from ADPRA discontinuation to surgery (<3, <4, <5, <7 days), and percentage of diabetic patients (>30% and <30%).

The extent to which study-level variables explained heterogeneity in predicting mortality and re-operation due to bleeding was explored by fitting random effect meta-regression models to account for the time from ADPRA discontinuation to surgery (<3, <4, <5, <7 days). We checked for potential publication and small study effects by the visual inspection of contour enhanced funnel plot [22,23], and the test proposed by Harbord [24].

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines in order to rate the quality of evidence [25]. Factors that affect the confidence in the estimate of effect include risk for bias (also known as detailed design and study limitations), imprecision, indirectness (directness in the GRADE approach includes generalizability and applicability), inconsistency of results (heterogeneity), publication bias, dose–effect responses, magnitude of effect, and issues of residual plausible confounding. The confidence in the estimate of effect is categorized into 4 levels, ranging from very low to high. The completed evidence summaries and GRADE assessments were discussed by several investigators and reviewed by the methodological and clinical senior investigators. Evidence summaries were prepared for each research question by using GRADE Profiler, version 3.6 (McMaster University, Hamilton, Ontario, Canada).

All statistical calculations were performed using Review Manager (RevMan), version 5.0.24 and STATA version 11.1.

3. Results

3.1. Search results

Database searches yielded 602 references, whereas one reference was yielded through other sources ("Prasugrel as an anti-thrombotic therapy in patients with ACS", presented to the Cardiovascular and Renal Drugs Advisory Committee, 3 February 2009) (Fig. 1). After screening the abstracts, 62 full-text articles were assessed for eligibility. The final meta-analysis was based on 19 articles [8,26–42], including 13 observational studies [8,28–30,32,34–37,39–42], two randomized clinical trials (RCTs) [27,33], and four post hoc analyses of RCTs [26,31,38,43]. Although the latter derived from RCTs, in this meta-analysis they are classified as observational since the randomization explored a subject different from the optimal timing of discontinuation. The other 43 full-text articles were excluded because they included patients with stable coronary artery disease (21 studies), or due to incomplete data availability in order to estimate the primary and secondary endpoints (19 studies), or due to unknown

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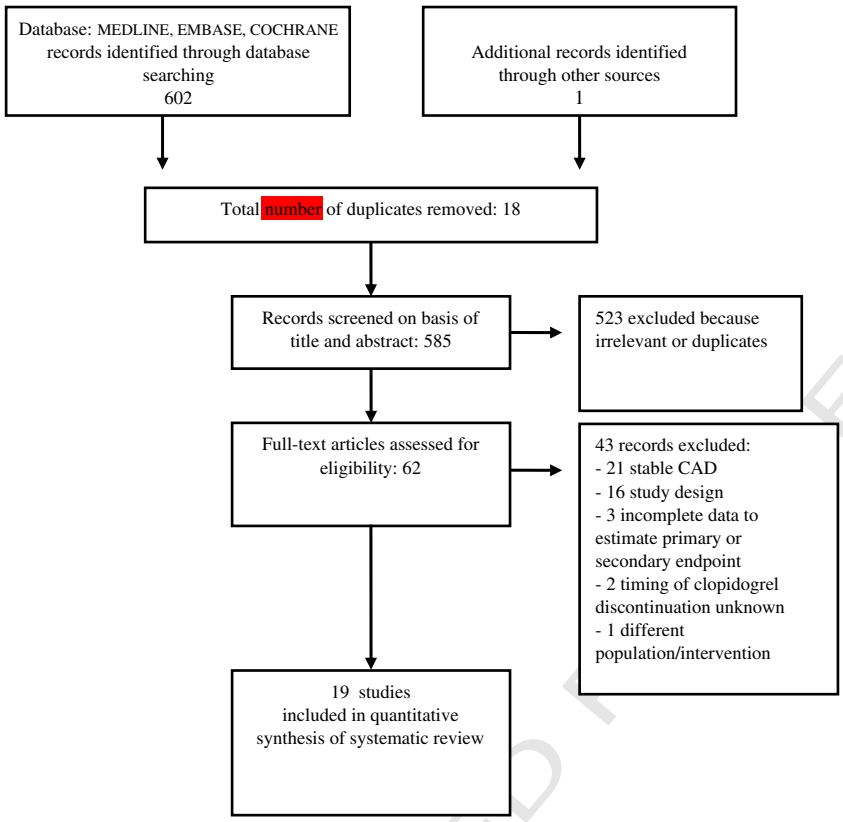

Fig. 1. Selection for studies exploring the association between post-operative outcome (mortality and reoperation due to bleeding) and optimal time to cardiac surgery in patients treated with ADPRA therapy.

timing of ADPRA discontinuation (2 studies) or, finally, different population/intervention (1 study).

3.2. Characteristics of studies

We identified 19 studies including 14,046 participants (24.04% females), with a mean age of 64.5 years. All but two included participants who were receiving clopidogrel. Another study included clopidogrel and ticagrelor [26] and the last included clopidogrel and prasugrel [43]. For the purpose of our meta-analysis, the results of the two study populations were disaggregated and each analyzed independently.

Table 1 summarizes the characteristics of the studies included in the meta-analysis. Most studies (12 studies) [8,27–29,31,34–39,43] considered 5 days prior to surgery as cutoff for early vs late discontinuation, whereas the remainder used 3 days (4 studies) [32,33,40,41], 4 days (1 study) [30] and 7 days (1 study) [42]; only the PLATO (Platelet Inhibition and Patients Outcomes) –CABG trial used 5-day cut-off for clopidogrel administration and 3 day cut-off for ticagrelor administration [26]. Seventeen of the 19 studies included information about concomitant aspirin treatment [8,26–34,36–38,40–43], the daily doses of which were 80–150 mg in the RCTs, 75–325 mg in the post-hoc analysis of RCTs, and 75–325 mg in nine of the observational studies (in the other 26 the dose was not given). Thirteen studies (including the two RCTs) did not mention the concomitant administration of GPIIb/IIIa inhibitors [27–29,31–37,39,41,42]. Antifibrinolytic therapies such as tranexamic acid or aprotinin were not used in 3 studies [40–42], and not mentioned in 8 [26–29,31,34,36,38]. The administration of ADPRA loading dose was not specifically mentioned in 10 studies (two RCTs) [27,29,30,32,33,35,36,38,41,42]; in the remainder between 15.9% and 100% of the patients received a loading dose.

Three studies [27,34,35] did not mention the percentage of diabetic patients; in the others this value varied from 21% to 54%. Five studies (two RCTs) included only patients undergoing first time CABG [27,28,33,40,41], whereas 12 also included patients undergoing redo CABG (with percentages varying from 0.3% to 18.5%) [8,29–32,34,36–39,42], and 2 did not specify [26,35]. A high rate of internal mammary artery grafting was reported in about 80% of the studies. Two studies [40,42] (all observational) included only off-pump procedures, and 6 (two RCTs) only on-pump procedures [27,33,35,37,39,41]; the others included both, with the rate of on-pump procedures ranging from 1% to 87%. Ten (one RCT) [8,30,32,36,39–42] considered isolated CABG and 7 (one RCT) [26,28,31,33–35,38] did not specify; the percentage of concomitant valve surgery in the remaining papers was between 6.6% and 19.5%.

3.3. Mortality

Seventeen studies considered the association between preoperative ADPRA administration and post-operative death, including 3869 patients with ADPRA early discontinuation (171 deaths) and 8975 patients with ADPRA late discontinuation (223 deaths). Late or no preoperative ADPRA discontinuation was associated with an increased rate of post-operative death (OR 1.46; 95% CI 1.10–1.93) (Fig. 2). The estimated predictive interval was 0.82–2.59, meaning that an adverse effect of early surgery after discontinuation might be a plausible finding in a new study. Between-study heterogeneity was low (I-squared 15.7%). The Mantel–Haenszel OR was 1.47 (95% CI, 1.16–1.86), suggesting an unlikely impact of small studies on the random effects estimate towards more beneficial values. Summary estimates for post-operative mortality across strata of study design, quality, time from ADPRA discontinuation to surgery, and percentage of diabetic patients are presented in Fig. 3. All of the strata were consistent with the overall pooled estimate, although the strata estimates were only significant for prospective (OR 1.69, 95% CI: 1.01–2.81) and high quality (OR 1.45, 95% CI: 1.06–1.99) studies, and for studies with percentage of diabetic patients >30% (OR 1.43, 95% CI: 1.08–1.88). Timing of discontinuation had a uniform impact,

Table 1
Study characteristics.

1st author, year	Period of inclusion	Trial type	No of subjects	Diagnosis	Outcome	Concomitant ASA	Concomitant Antifibrinolytic	REDO-CABG	Concomitant valve surgery
Gansera, 2003	2000–2002	Obs	64 Clo 64 Not Clo	ACS[e]	Death; re-op	Unknown	Unknown	Unknown	Unknown
Chu, 2004	1999–2001	Obs	41 Clo 271 Not Clo	ACS	Death; re-op	70%	76.5%	<1%	NO
Fox, 2004	1998–2000	Post-hoc	436 Clo 476 Not Clo	ACS	Re-op	100%	Unknown	4.6%	Unknown
Ascione, 2005	2001–2002	Obs	91 Clo 379 Not Clo	ACS	Death; re-op	47%	Unknown	NO	Unknown
Akowuah, 2005	2002–2003	RCT[g]	25 Clo 24 Not Clo	ACS	Death; re-op	100%	100%	NO	NO
Metha, 2006	2003–2004	Obs	739 Clo 113 Not Clo	ACS	Death	96%	Unknown	13.3%	Unknown
Berger, 2008	2007–2007	Obs	298 Clo 298 Not Clo	ACS	Death; re-op	91.9%	61%	5.0%	NO
Hyung-Jun-Kim, 2008	1999–2003	Obs	332 Clo 4462 Not Clo	Mixed	Death; re-op	76.7%	10.4%	21.9%	NO
Filsoufi, 2008	1998–2005	Obs	72 Clo 72 Not Clo	Mixed	Death; re-op	89%	100%	4.5%	NO
Song, 2008	2004–2006	Obs	70 Clo 102 Not Clo	ACS	Death; re-op	100%	NO	NO	NO
Tabary, 2008	2003–2006	Obs	154 Clo 136 Not Clo	ACS	Re-op	63%	NO	NO	NO
Blasco, 2009	2000–2003	Obs	194 Clo 1483 Not Clo	Mixed	Death; re-op	100%	Unknown	8%	6.4%
Ebrahimi, 2009	2003–2005	Post-hoc	524 Clo 249 Not Clo	ACS	Death; re-op	97.7%	Unknown	Yes, Unknown%	Unknown
Firanescu, 2009	2006–2007	RCT	80 Clo 38 Not Clo	Mixed	Death; Re-op	100%	100%	NO	Unknown
Vaccarino, 2009	2003–2006	Obs	123 Clo 981 Not Clo	Mixed	Death; re-op	100%	NO	4.7%	NO
Nesher, 2010	2005–2008	Obs	189 Clo 262 Not Clo	ACS	Death; re-op	Unknown	100% Clo; %unknown not Clo	0.3%	NO
Mariscalco, 2011	2005–2010	Obs	225 Clo 225 Not Clo	Mixed	Death; re-op	100%	100%	1%	19.5%
Held, 2011	2008–2008	Post-hoc	Clo:412vs217 Tica:304vs328	ACS	Death	100%	Unknown	Unknown	Unknown
Smith, 2012	2004–2007	Post-hoc	Clo:91vs97 Pra:72vs105	ACS	Death	100%	Unknown	2.9%	NO

[a]Obs = observational studies; [B]re-op = reoperation for bleeding; [c] Clo = clopidgrel group; [d]Mixed = studies with unknown percentage of unstable coronary syndrome or with percentage >50% but <100%; [e]ACS: acute coronary syndrome; [f,h] = studies including 2 different comparisons; [g]RCT = randomized controlled trial.

although the majority of studies considered five days as cut-off (OR 1.45, 95% CI: 1.01–2.08).

The risk of postoperative mortality in patients who received new generation ADPRA therapy (prasugrel and ticagrelor) was not increased in patients with early discontinuation (OR 0.76; 95% CI 0.10–5.57) (Appendix Fig. 1).

3.4. Re-operation due to bleeding

Sixteen studies considered the association between preoperative ADPRA administration and the rate of re-operation due to bleeding, including 2883 patients with ADPRA early discontinuation (116 re-operations) and 8685 patients with ADPRA late discontinuation (193 re-operations). The frequency of re-operation in each study varied between 1.2% and 12.2% (median 3.2%). Later preoperative ADPRAs were associated with an increased risk of re-operation due to bleeding (OR 2.18; 95% CI 1.47–3.25) (Fig. 4). The estimated predictive interval was 0.72–6.62, meaning that no effect or an adverse effect of late discontinuation might be a plausible finding in a new study. Between-study heterogeneity was significant (p = 0.046) although modest (I-squared 41.7%). Seven studies were classified as high quality and meta-analysis limited to prospective studies gave consistent results. All the strata were consistent with the overall pooled estimate, although the strata estimates were only significant for prospective (OR 2.82; 95% CI 1.52–5.24) and low quality (2.49; 95% CI 1.53–4.07) studies, and for percentage of diabetic patients <30% (OR 3.59; 95% CI 1.63–7.89). Discontinuation gave similar benefit at all days although the majority of studies considered five days as cut-off (OR 1.77; 95% CI 1.20–2.62) (Appendix Fig. 2).

3.5. Meta-regression analysis

Time from ADPRA discontinuation to surgery studied with meta-regression yielded no significant effect on mortality or re-operation due to bleeding, being the p-values >0.20. Moreover, none of the ORs changed after adjustment for percentage of diabetic patients (Table 2).

3.6. Small study effects

Visual inspection of the contour-enhanced funnel plot (Fig. 5) indicated that pooled data did not appear to be heavily influenced by publication bias. This means that slight asymmetry of the plot is possible, with few studies insisting in the area of significance and the majority midway in the area of non-significance. The Harbord's test was not statistically significant (p = 0.167).

3.7. Summary findings

The summary findings following the GRADE guidelines are reported in Table 3. Postoperative mortality is increased by one-half whereas the risk of re-operation is approximately two times more likely for patients discontinuing ADPRAs later. This means that, out of 1000 patients discontinued from ADPRAs early, about 45 would die and about 40 would require re-operation for bleeding. However out of 1000 patients

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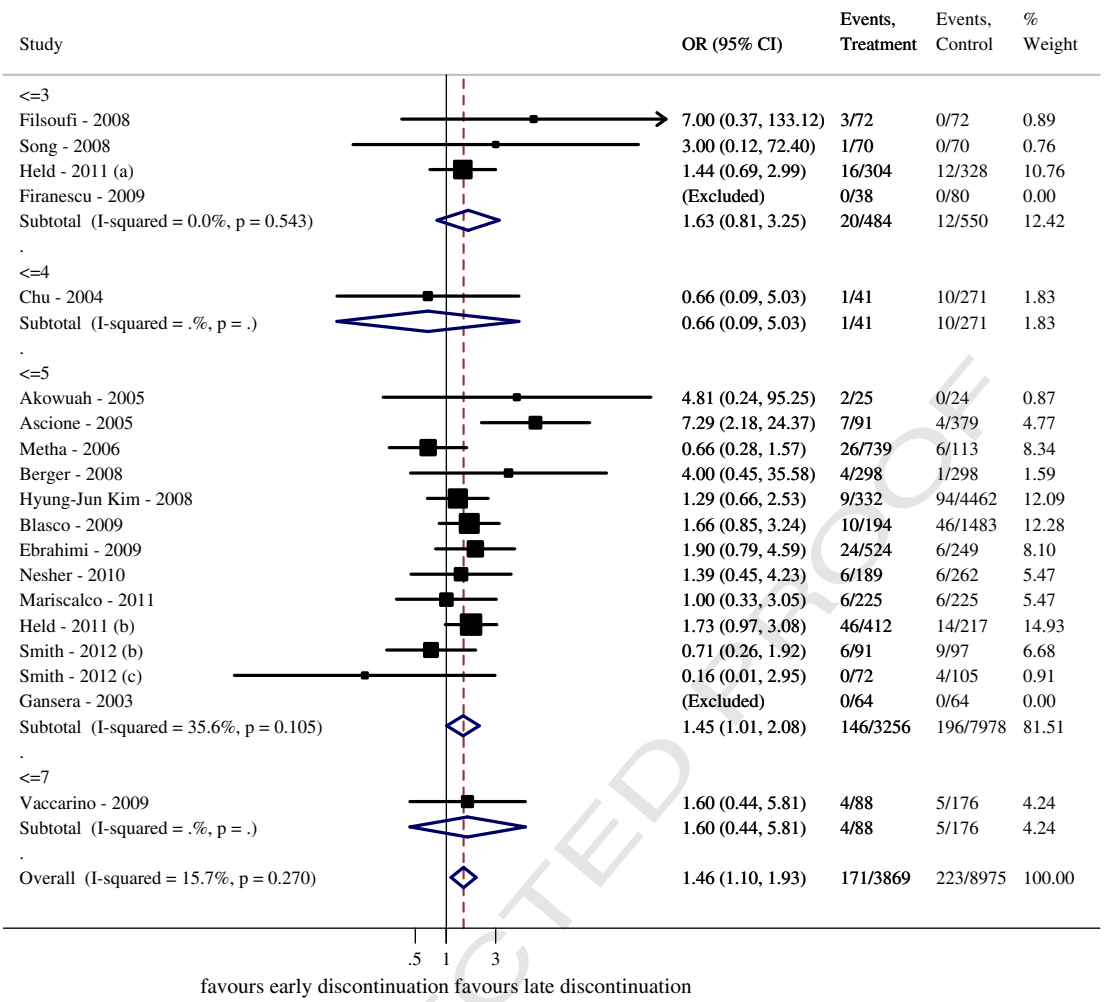

(a): Ticagrelor-assigned patients.
(b): Clopidogrel-assigned patients.
(c): Prasugrel-assigned patients.
ADPRAs: Adenosine diphosphate receptor antagonists.
CABG: Coronary artery bypass graft surgery.
Treatment: late-no discontinuation
Control: early discontinuation

Fig. 2. Risk of postoperative mortality in patients who received ADPRA therapy as compared to those who stopped before CABG, stratified according to the time to discontinuation. The combined OR and 95% CI were calculated using the random-effects models.

discontinued from ADPRAs later, about 70 (25 more patients) would die and 87 (47 more patients) would need to undergo re-operation to stop bleeding.

4. Discussion

Our findings, derived from 19 randomized and observational studies of ADPRAs in patients with an ACS undergoing urgent CABG, indicate that surgery performed within five days of last drug administration is associated with increased mortality and reoperation due to bleeding. Despite the fact that the majority of the information originates from observational studies, our analysis provides a moderate to high confidence in the estimates of effect. Moreover, the amount of evidence from observational studies increased the precision of the estimates we found in the RCTs, with consistent direction and size of the effects. The prediction interval also suggests that further studies are likely to confirm that longer time of discontinuation is safer than later discontinuation. Unfortunately, we could not define the best time period for discontinuation, since the majority of the studies considered five-days as cutoff, and the evidence exploring other cutoff times was sparse and limited.

This conclusion is consistent with the pharmacology of currently available oral ADPRAs and reinforces present guideline recommendations of discontinuing these agents for at least five days prior to surgery [44,45]. The current recommendation of starting dual antiplatelet therapy with aspirin and an ADPRA in ACS patients immediately upon admission in order to prevent early ischemic events is based on the results of the CURE study [34], but this approach creates a clinical dilemma in those patients who will later show at coronary angiography an indication to CABG. From one side, withdrawal of ADPRA before surgery might expose the patients to ischemic events in the preoperative period; however, its continuation up to the time of surgery has been shown to increase postoperative bleeding. Surgeons have been persuaded to operate on aspirin therapy

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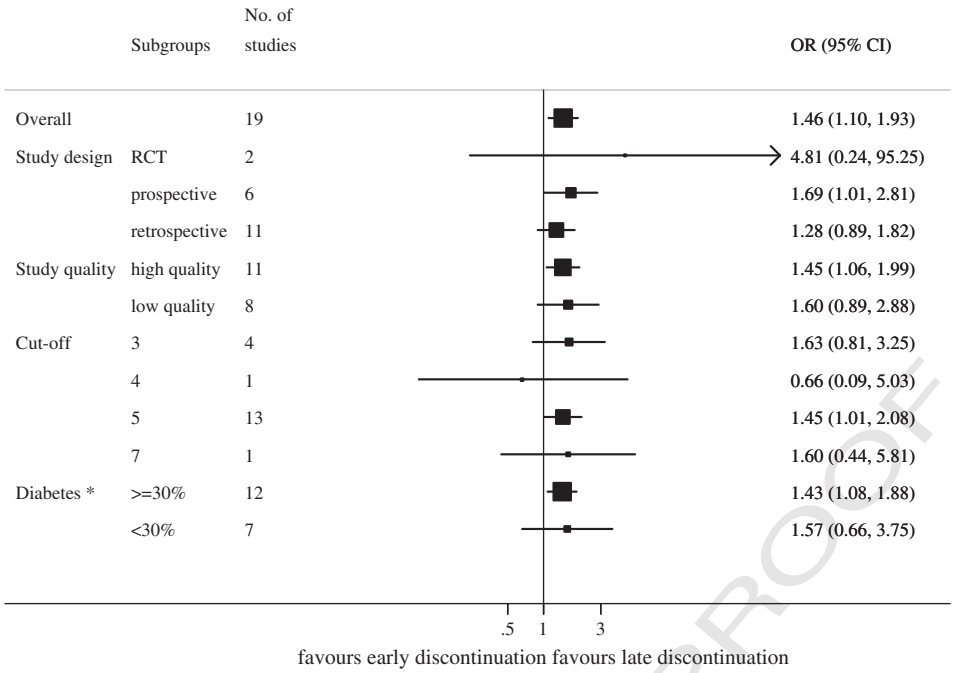

*The sum does not add up to the total because of missing values.
ADPRAs: Adenosine diphosphate receptor antagonists.
CABG: Coronary artery bypass graft surgery.

Fig. 3. Subgroup analysis for postoperative mortality in patients who received ADPRA therapy versus who stopped before CABG. The combined OR and 95% CI were calculated using the random-effects models.

since the convincing study by Mangano et al. has shown a 60 percent lower mortality and 50 percent reduction in ischemic complications without excess bleeding among patients receiving aspirin within 48 h after operation [46,47]. However, they are not similarly confident with ADPRAs due to the increased risk of bleeding complications and lack of evidence of a protective effect towards early post-operative ischemic events [48]. Antiplatelet therapy, especially with thienopyridines, may significantly contribute to cardiopulmonary bypass-induced platelet dysfunction, causing an increase in chest drain blood loss, utilization of blood products and incidence of re-explorations. Perioperative blood loss demanding transfusion has been shown to be associated with an eightfold increase of death after surgery [49], whereas re-exploration for bleeding after cardiac surgery is an independent predictor of adverse events such as sepsis, renal failure, acute respiratory distress syndrome and prolonged mechanical ventilation [50]. All these consequences can ultimately lead to death of patients as well as to increased hospital costs [51].

The landmark CURE study, which established the benefit of early clopidogrel use in addition to aspirin in the secondary prevention of ischemic events among patients with NSTEACS [34], is of little help for investigating the impact of this therapy in ACS patients undergoing urgent CABG. As clearly reported in the specific subanalysis of the study, the median time from index admission to CABG was 25.5 days, 93% of the patients who proceeded to CABG stopped clopidogrel before CABG, the median time off the study drug before CABG was 17 days (interquartile range, 9 to 33) and the median time after CABG was 10 days (interquartile range, 6 to 25) [2,34].

A meta-analysis of 11 observational studies published by Purkayastha et al. [52] involved 4002 CABG patients: pre-operative continuation of clopidogrel was independently associated with a significant increase in major bleeding, reoperation due to bleeding and transfusion requirements. Similar results were reported by Pickard et al. [53]. Both meta-analyses had insufficient power to be conclusive about the risk of death, and suffered from heterogeneity between studies. Several other meta-analyses have been published on this issue over the last years, but they included both stable CAD and ACS patients, and showed conflicting results [10,48]. A recent meta-analysis [54], specifically focused on ACS patients, showed a trend towards increased mortality (HR 1.44, 95% CI 0.97–2.01, $p = 0.07$) and reoperation rates among patients undergoing CABG without clopidogrel discontinuation.

Recent data with the newer ADPRA, ticagrelor [26] and prasugrel [43] in patients with ACS show similar or slightly increased rates of bleeding and reoperation, however, with significantly reduced mortality as compared to clopidogrel. Also in the case of these agents, current guidelines recommend at least five days of discontinuation prior to surgery.

How complex and confusing is this issue is demonstrated by an extensive review recently published by Burke et al. [55]. The authors underline how the ACC/AHA 2007 NSTEACS guidelines endorsed the use of clopidogrel upstream of coronary angiography in all patients irrespective of subsequent modality of treatment [56]. The updated ACC/AHA 2009 guidelines have modified this approach by stating that clopidogrel may be administrated "before or at the time of PCI", in patients with NSTEACS, but they do not give any new evidence to support this changing recommendation [57]. The same paper, revising data coming from the wide population included in the GRACE [58] and CRUSADE [59] registries, underscores that clopidogrel is underused in patients with NSTEACS, and especially in the high risk subgroup, probably because of concerns about CABG-related bleeding. In the CRUSADE study, in spite of the national guidelines, 87% of clopidogrel-treated patients underwent CABG within 5 days after discontinuation of treatment. Both the increasing hospitalization costs and the urgent underlying disease make often difficult to wait the suggested period. These facts cast doubt on the recommendation for a fixed safe waiting period following discontinuation of antiplatelet therapy.

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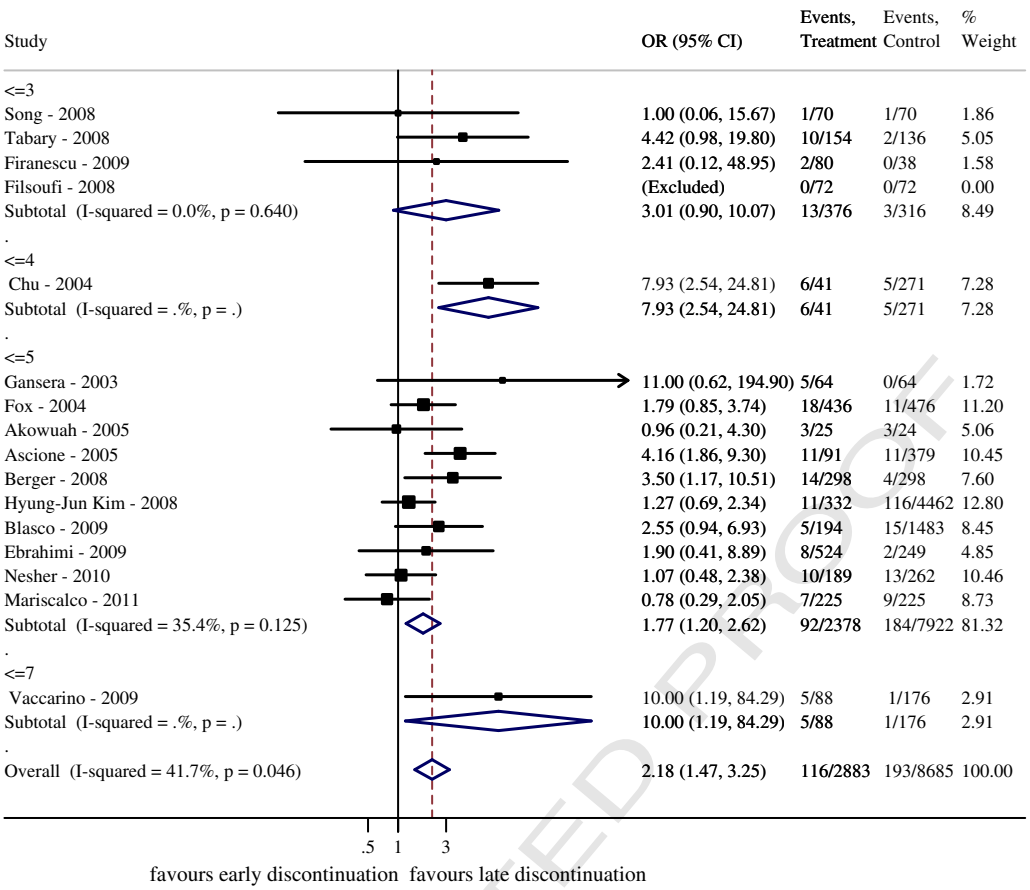

ADPRAs: Adenosine diphosphate receptor antagonists.
CABG: Coronary artery bypass graft surgery
Treatment: late-no discontinuation
Control: early discontinuation

Fig. 4. Risk of re-operation for bleeding in patients who received ADPRA therapy as compared to those who stopped before CABG stratified for the time to discontinuation. The combined OR and 95% CI were calculated using the random-effects models.

The strengths of our review include its focus on ACS patients, a comprehensive search methodology, inclusion of randomized as well as observational studies, and detailed assessment of the factors that influence the confidence in the results. It adds data on timing of interventions (such as early vs. late discontinuation), hard outcomes (mortality and re-operation due to bleeding), subgroups of patients (such as

Table 2
Random effects meta-regression analysis of postoperative mortality and re-operation for bleeding in patients who received ADP receptor antagonist as compared to those who stopped before CABG.

	No. of studies	No. of participants	OR (95% CI)	p-value	OR (95% CI) [a]	*rp*-value [a]
Mortality						
Cut-off						
≤3	4	1034	1[b]		1[b]	
≤4	1	312	0.38 (0.03–5.78)	0.46	0.33 (0.02–5.95)	0.42
≤5	13	11,234	0.85 (0.29–2.46)	0.75	0.83 (0.30–2.24)	0.68
≤7	1	264	0.94 (0.14–6.51)	0.97	0.72 (0.09–5.49)	0.73
Drug						
Ticagrelor/prasugrel	2	809	1[b]		1[b]	
Other	17	12,035	1.22 (0.46–3.24)	0.67	1.18 (0.46–3.02)	0.70
Re-operation for bleeding						
Cut-off						
≤3	4	692	1[b]		1[b]	
≤4	1	312	3.74 (0.45–30.92)	0.20	3.62 (0.36–36.46)	0.23
≤5	10	10,300	0.84 (0.18–3.87)	0.80	0.86 (0.16–4.62)	0.83
≤7	1	264	4.71 (0.25–87.79)	0.27	4.09 (0.17–98.59)	0.33

ADP: adenosine diphosphate.
CABG: coronary artery bypass graft surgery.
[a] Estimates adjusted for percentage of diabetes.
[b] Reference category.

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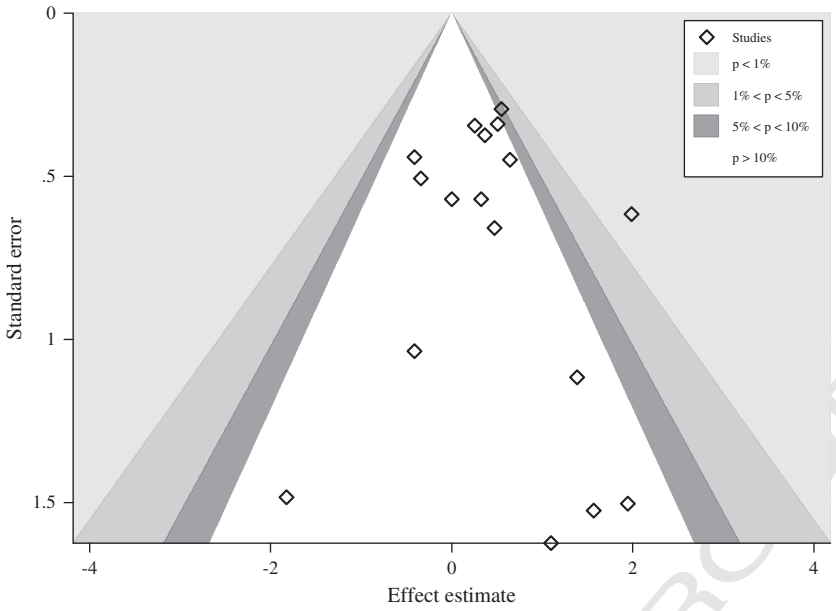

ADPRAs: Adenosine diphosphate receptor antagonists.
CABG: Coronary artery bypass graft surgery.

Fig. 5. Contour enhanced funnel plot of studies comparing patients who received ADPRA therapy versus who stopped before CABG for postoperative mortality.

diabetics) and use of newer agents (prasugrel and ticagrelor) that were not available from previous meta-analyses. Reporting and publication bias might be limited: the scientific community is alerted and the outcomes considered relevant.

Our review has limitations that deserve attention for both interpreting the results and conducting future research. The inclusion of observational studies increases the risk for bias due to the lack of control for confounders and covariates. We could not assess whether different cutoffs in discontinuation yielded different results. The majority of evidence is based on a five-day cutoff. The amount of risk might be variable with different length of drug discontinuation, with a skewed distribution of the difference between early and late discontinuation. Only few studies explored discontinuation at the extremes. Our meta-regression which considered cutoff discontinuation as a continuous outcome has advantages over subgroup analysis: it explores the covariate over an expanded range of values. The paucity of studies in some time intervals reduces the confidence in the absence of differences between alternative cutoff days. Observational studies can supplement this evidence by contributing data about special populations (e.g. high risk population, as diabetic patients).

4.1. Clinical implications

Risk stratification for both ischemic and bleeding events is recommended by current ACS guidelines, especially for patients presenting without persistent ST-segment elevation [60]. However, recommended risk scores and algorithms are of no help for estimating the probability of urgent CABG whose incidence is extremely variable across centers, and in clinical trials has been shown to range from 10 [31] to 16% [61,62]. Although the extent of ST-segment changes during acute ischemia have been shown to correlate with the presence of three-vessel

Table 3
Quality of the evidence according the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach.

ADPRA discontinuation compared to ADPRA continuation for patients with ACS undergoing CABG					
Bibliography:					
Outcomes	No. of participants (studies) follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Time frame is short-term mortality	
				Risk with ADPRA discontinuation	Risk difference with ADPRA continuation (95% CI)
Mortality	12489 (19 studies) 30 days	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.56** (1.2 to 2.03)	**Study population** **45 per 1000**	**25 more per 1000** (from 9 more to 46 more)
				High **100 per 1000**	**56 more per 1000** (from 20 more to 103 more)
Re-operation for bleeding	11568 (9 studies) 30 days	⊕⊕⊕⊖ **MODERATE**[1,2] Due to inconsistency	**RR 2.18** (1.47 to 3.25)	**Study population** **40 per 1000**	**47 more per 1000** (from 19 more to 91 more)
				High **100 per 1000**	**118 more per 1000** (From 47 more to 225 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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disease and left main disease [63], attempts to estimate the probability of early CABG in ACS have shown only moderate discriminative value [61]. The present data provides solid evidence that performing CABG without allowing at least five days off ADPRAs in ACS patients is associated with a significantly increased risk of reoperation to stop bleeding and mortality. In the lack of comparably solid evidence that administration of ADPRAs prior to angiography improves outcome in ACS, the present findings should suggest caution in recommending ADPRA administration prior to angiography, particularly within the current scenario of very early angiography across the ACS spectrum [64]. Estimating the probability of early CABG requires sound clinical judgment, and selective use of short acting GPIIb/IIIa receptor blockers in patients deemed at risk of urgent surgery may provide adequate antiplatelet protection, as well as reduction or perioperative ischemic risk, without paying the price of increased perioperative bleeding [65,66].

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2012.12.087.

References

[1] Levine GN, Bates ER, Blankenship JC, et al. ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44-122.

[2] Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.

[3] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

[4] Merlini PA, Bauer KA, Oltrona L, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation 1994;90:61–8.

[5] Cesari F, Marcucci R, Caporale R, et al. Relationship between high platelet turnover and platelet function in high-risk patients with coronary artery disease on dual antiplatelet therapy. Thromb Haemost 2008;99:930–5.

[6] Gori AM, Cesari F, Marcucci R, et al. The balance between pro- and anti-inflammatory cytokines is associated with platelet aggregability in acute coronary syndrome patients. Atherosclerosis 2009;202:255–62.

[7] 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;366:1489–97.

[8] Berger JS, Frye CB, Harshaw Q, Edwards FH, Steinhubl SR, Becker RC. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. J Am Coll Cardiol 2008;52:1693–701.

[9] Fox KA, Anderson FA, Dabbous OH, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart 2007;93:177–82.

[10] Biancari F, Airaksinen KE, Lip GY. Benefits and risks of using clopidogrel before coronary artery bypass surgery: systematic review and meta-analysis of randomized trials and observational studies. J Thorac Cardiovasc Surg 2012;143665–75 e4.

[11] Mehta RH, Sheng S, O'Brien SM, et al. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. Circ Cardiovasc Qual Outcomes 2009;2:583–90.

[12] Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.

[13] Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110:e340–437.

[14] Ferraris VA, Ferraris SP, Saha SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007;83:S27–86.

[15] Dunning J, Versteegh M, Fabbri A, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008;34:73–92.

[16] Fitchett D, Eikelboom J, Fremes S, et al. Dual antiplatelet therapy in patients requiring urgent coronary artery bypass grafting surgery: a position statement of the Canadian Cardiovascular Society. Can J Cardiol 2009;25:683–9.

[17] Morici N, Moja L, Rosato V, et al. Time from adenosine di-posphate receptor antagonists (ADPRAs) discontinuation to coronary bypass surgery in patients with Acute Coronary Syndrome (ACS). A meta-analysis and meta-regression. PROSPERO 2012; 2012 [http://wwwcrdyorkacuk/PROSPERO/full_docasp?ID=CRD42011001865].

[18] Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2008.

[19] Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2007.

[20] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7: 177–88.

[21] Graham PL, Moran JL. Robust meta-analytic conclusions mandate the provision of prediction intervals in meta-analysis summaries. J Clin Epidemiol 2012;65:503–10.

[22] Palmer TM, Peters JL, Sutton AJ, Moreno SG. Contour-enhanced funnel plots for meta-analysis. Stata J 2008;8:242–54.

[23] Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991–6.

[24] Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006;25:3443–57.

[25] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

[26] Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011;57:672–84.

[27] Akowuah E, Shrivastava V, Jamnadas B, et al. Comparison of two strategies for the management of antiplatelet therapy during urgent surgery. Ann Thorac Surg 2005;80: 149–52.

[28] Ascione R, Ghosh A, Rogers CA, Cohen A, Monk C, Angelini GD. In-hospital patients exposed to clopidogrel before coronary artery bypass graft surgery: a word of caution. Ann Thorac Surg 2005;79:1210–6.

[29] Blasco-Colmenares E, Perl TM, Guallar E, et al. Aspirin plus clopidogrel and risk of infection after coronary artery bypass surgery. Arch Intern Med 2009;169: 788–96.

[30] Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? Ann Thorac Surg 2004;78:1536–41.

[31] Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol 2009;53:1965–72.

[32] Filsoufi F, Rahmanian PB, Castillo JG, Kahn RA, Fischer G, Adams DH. Clopidogrel treatment before coronary artery bypass graft surgery increases postoperative morbidity and blood product requirements. J Cardiothorac Vasc Anesth 2008;22:60–6.

[33] Firanescu CE, Martens EJ, Schonberger JP, Soliman Hamad MA, van Straten AH. Postoperative blood loss in patients undergoing coronary artery bypass surgery after preoperative treatment with clopidogrel. A prospective randomised controlled study. Eur J Cardiothorac Surg 2009;36:856–62.

[34] Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004;110:1202–8.

[35] Gansera B, Schmidtler F, Spiliopoulos K, Angelis I, Neumaier-Prauser P, Kemkes BM. Urgent or emergent coronary revascularization using bilateral internal thoracic artery after previous clopidogrel antiplatelet therapy. Thorac Cardiovasc Surg 2003;51:185–9.

[36] Kim JH, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. Am Heart J 2008;156:886–92.

[37] Mariscalco G, Bruno VD, Cottini M, et al. Optimal timing of discontinuation of clopidogrel and risk of blood transfusion after coronary surgery. Propensity score analysis. Circ J 2011;75:2805–12.

[38] Mehta RH, Roe MT, Mulgund J, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol 2006;48:281–6.

[39] Nesher N, Singh SK, Fawzy HF, et al. Impact of clopidogrel use on mortality and major bleeding in patients undergoing coronary artery bypass surgery. Interact Cardiovasc Thorac Surg 2010;10:732–6.

[40] Song SW, Youn YN, Yi G, Lee S, Yoo KJ. Effects of continuous administration of clopidogrel before off-pump coronary artery bypass grafting in patients with acute coronary syndrome. Circ J 2008;72:626–32.

[41] Tabary SZ. Does Plavix have any influences on postoperative bleeding and blood transfusion after urgent and emergent coronary artery bypass grafting. J Med Sci 2008;8: 293–7.

[42] Vaccarino GN, Thierer J, Albertal M, et al. Impact of preoperative clopidogrel in off pump coronary artery bypass surgery: a propensity score analysis. J Thorac Cardiovasc Surg 2009;137:309–13.

[43] Smith PK, Goodnough LT, Levy JH, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. J Am Coll Cardiol 2012;60:388–96.

[44] Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:53S–70S.

[45] Price MJ, Walder JS, Baker BA, et al. Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the Recovery trial. J Am Coll Cardiol 2012;59:2338–43.

[46] Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–17.

[47] Topol EJ. Aspirin with bypass surgery—from taboo to new standard of care. N Engl J Med 2002;347:1359–60.

[48] Au AG, Majumdar SR, McAlister FA. Preoperative thienopyridine use and outcomes after surgery: a systematic review. Am J Med 2012;125:87–99 e1.

[49] Karkouti K, Wijeysundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004;44:1453–62.

Please cite this article as: Morici N, et al, Time from adenosine di-phosphate receptor antagonist discontinuation to coronary bypass surgery in patients with acute coronary syndrome: Meta-analysis and meta-regression, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2012.12.087

[50] Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996;111:1037–46.
[51] Alstrom U, Levin LA, Stahle E, Svedjeholm R, Friberg O. Cost analysis of re-exploration for bleeding after coronary artery bypass graft surgery. Br J Anaesth 2012;108:216–22.
[52] Purkayastha S, Athanasiou T, Malinovski V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006;92:531–2.
[53] Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy 2008;28:376–92.
[54] Nijjer SS, Watson G, Athanasiou T, Malik IS. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. Eur Heart J 2011;32:2970–88.
[55] Burke MA, Lee R, Fintel DJ. Early clopidogrel use in non-ST elevation acute coronary syndrome and subsequent coronary artery bypass grafting. Am Heart J 2011;161:832–41.
[56] Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:e1-157.
[57] Kushner FG, Hand M, Smith SC, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205–41.
[58] Banihashemi B, Goodman SG, Yan RT, et al. Underutilization of clopidogrel and glycoprotein IIb/IIIa inhibitors in non-ST-elevation acute coronary syndrome patients: the Canadian global registry of acute coronary events (GRACE) experience. Am Heart J 2009;158:917–24.
[59] Alexander D, Ou FS, Roe MT, et al. Use of and in-hospital outcomes after early clopidogrel therapy in patients not undergoing an early invasive strategy for treatment of non-ST-segment elevation myocardial infarction: results from Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE). Am Heart J 2008;156:606–12.
[60] Hamm W, Bassand JP, Agewall S, 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.
[61] Sadanandan S, Cannon CP, Gibson CM, et al. A risk score to estimate the likelihood of coronary artery bypass surgery during the index hospitalization among patients with unstable angina and non-ST-segment elevation myocardial infarction. J Am Coll Cardiol 2004;44:799–803.
[62] White HD, Kleiman NS, Mahaffey KW, et al. Efficacy and safety of enoxaparin compared with unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial. Am Heart J 2006;152:1042–50.
[63] Savonitto S, Cohen MG, Politi A, et al. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. Eur Heart J 2005;26:2106–13.
[64] Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.
[65] Marso SP, Bhatt DL, Roe MT, et al. Enhanced efficacy of eptifibatide administration in patients with acute coronary syndrome requiring in-hospital coronary artery bypass grafting. PURSUIT Investigators. Circulation 2000;102:2952–8.
[66] Anderson JH, Wright RS, Adams CD, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012;60:645–81.

Please cite this article as: Morici N, et al, Time from adenosine di-phosphate receptor antagonist discontinuation to coronary bypass surgery in patients with acute coronary syndrome: Meta-analysis and meta-regression, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2012.12.087