

# Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery

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## Introduction

Coronary artery bypass grafting (CABG)-related bleeding complications and perioperative coronary events are strongly influenced by the management of antithrombotic therapy before and after CABG. Bleeding but also blood products transfusion increase the risk of death and compromise the long-term benefits of CABG.<sup>1</sup> The use of new P2Y<sub>12</sub> inhibitors, increasing pre-CABG percutaneous coronary interventions (PCI) with drug eluting stents (DES) requiring specific antiplatelet regimens, and advances in surgical technique has prompted the ESC Working Group on Cardiovascular Surgery and the ESC Working Group on Thrombosis to review the evidence of peri-CABG recommendations on antithrombotic management. Due to the paucity of randomized trials, most of the evidence is still derived from observational studies and expert consensus, further reinforcing the importance of a multidisciplinary consultation for optimal decision making.

## Risks and benefits of preoperative exposure to antiplatelet therapy

### Benefits of preoperative aspirin

Aspirin (acetylsalicylic acid, ASA) is recommended as secondary prevention therapy for all patients with proven coronary artery disease

(CAD) and without contraindications. Its indication is even stronger for post-CABG patients (recommendation IA).<sup>2</sup> The general consensus is that ASA treatment withdrawal has ominous prognostic implications in patients with CAD, especially in those with intracoronary stents, and should be advocated only when the bleeding risk clearly outweighs that of atherothrombotic events.<sup>3</sup>

The benefits of continuing ASA until the day of CABG ('preoperative ASA') are less clear and may explain the wide variability in the management of ASA therapy in the perioperative period and differences between guidelines endorsed by different professional and scientific societies (Supplementary material online, *Table S1*). This was based on the demonstration that ASA started the day before surgery was no more effective than ASA started 6 h after surgery at improving early (7- to 10-day) graft patency, but was associated with increased bleeding complications.<sup>4</sup> More recent evidence suggests, however, that ASA use within 5–7 days prior to CABG halves mortality without significant increase in haemorrhage, blood product requirements, or related morbidities<sup>5</sup> and reduces late infarction and repeat revascularization.<sup>6</sup> Retrospective data show consistent benefit of preoperative aspirin within 5 days of surgery, including a reduction in cerebrovascular events and 30-day mortality.<sup>7</sup>

### Risks of preoperative aspirin

Evidence that preoperative ASA increases the risk of transfusion, re-exploration rate, and chest tube drainage was derived from

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**Table 1** Management of antiplatelet therapy before coronary artery bypass grafting surgery

Assessment of the risk of bleeding and ischaemia is recommended when making the decision of CABG surgery (whether with aspirin or DAPT).	I	C	
Low-dose ASA (75–160 mg daily) should be maintained in patients undergoing CABG surgery.	I	C	3,5,10
In patients with increased bleeding risk and in those who refuse blood transfusion, cessation of ASA 3–5 days before surgery is recommended based on individualized assessment of ischaemic and bleeding risks.	I	C	10,11
In patients on P2Y <sub>12</sub> inhibitors who need CABG, it is recommended to postpone surgery for 5 days after interruption of ticagrelor or clopidogrel, and 7 days for prasugrel, unless the patient is at high risk of ischaemic events	I	B	12,13

randomized controlled trials (RCTs) conducted in the late 80s when blood conservation and cardiopulmonary bypass (CPB) techniques were very different, such as little off-pump CABG surgery and higher aspirin ASA dosage.<sup>8</sup> More recent analysis still suggests an increase in blood loss and more frequent use of blood products in patients exposed to ASA within 7 days of surgery.<sup>9</sup> However, the underpowered nature of subanalyses precludes any strong recommendation on the time delay from ASA discontinuation to CABG in those at high risk of bleeding.<sup>10</sup> Aspirin interruption 3 days prior to CABG may be considered in patients at very high risk for bleeding after individualized assessment or in patients who refuse blood transfusions<sup>11</sup> (Table 1).

## Overview of the net clinical benefit of dual antiplatelet therapy

Dual antiplatelet therapy (DAPT), the combination of ASA with a P2Y<sub>12</sub> inhibitor, namely clopidogrel, prasugrel, or ticagrelor (Table 1), has become the cornerstone of antiplatelet treatment before, during and after PCI, with significant reductions of stent thrombosis and ischaemic events compared with either aspirin alone or aspirin and anticoagulant drugs.<sup>14–16</sup> This combination increases the risk of major bleeding to an extent that appears to be associated with the degree of P2Y<sub>12</sub> inhibition achieved and all Phase 3 studies of P2Y<sub>12</sub> inhibitors vs. placebo or vs. clopidogrel, have excluded patients at high risk of bleeding. In the absence of contraindications, DAPT is currently recommended for 9–12 months following ACS based on evidence of enduring benefit over this time course in studies of clopidogrel, prasugrel, and ticagrelor.<sup>14–17</sup> There is no clear evidence for defining the optimal duration of DAPT after elective stenting. Indeed, none of the randomized trials were powered for ischaemic endpoints; all were open label and the time from stenting to randomization varied.<sup>18–21</sup> Therefore, weighing the quality of available evidence is difficult and these inferences need to be confirmed by ongoing mega trials. Usually, it is recommended to continue DAPT for 1 month after BMS implantation in stable angina,<sup>22</sup> 6–12 months after DES implantation in all patients,<sup>22</sup> and up to one 1 year in all patients after ACS, irrespective of revascularisation strategy.<sup>23</sup>

## Coronary artery bypass grafting-related risk on Clopidogrel

Clopidogrel is a second-generation thienopyridine characterized by a large interindividual variability in pharmacodynamic response that has a significant impact on clinical outcomes<sup>24</sup> (Supplementary material online, Table S2). This is because clopidogrel is a prodrug that requires biotransformation into its active metabolite.<sup>25</sup> Polymorphisms in genes encoding the cytochrome P450 (CYP) system, especially CYP2C19, are key players and clopidogrel-treated PCI patients who carry genetic variants associated with CYP2C19 loss-of-function have a three- to six-fold higher risk of stent thrombosis.<sup>26</sup> However, polymorphic variation in CYP2C19 explains <20% of the response variability with clopidogrel, leaving variation in bioactivation of clopidogrel largely unexplained. So far, there is no convincing evidence that genetic testing or functional platelet assays that measure platelet reactivity may improve clinical outcomes in clopidogrel-treated patients undergoing PCI.<sup>27,28</sup>

### Observational studies

Observational studies have demonstrated that the increase in post-operative chest tube drainage, transfusion, reoperation rates, hospitalization stay, and mortality observed when DAPT (aspirin and clopidogrel) is maintained during CABG<sup>29–37</sup> is blunted when DAPT is stopped 5 days or more prior to CABG.<sup>38,39</sup> Shorter windows of clopidogrel interruption have been suggested but time delay alone does not solely account for the difference in the observed magnitude of clopidogrel effect on bleeding. Differences in patient response to P2Y<sub>12</sub> inhibitors, outcome definitions, transfusion triggers, use of antifibrinolytics, and surgeon-related factors may have been sources of bias. Few studies have reported on ischaemic event rates in ACS patients waiting for CABG. In the CURE trial, patients exposed to clopidogrel had a non-significantly lower MACE rate than the placebo group (2.9 vs. 4.7, 1.8% ARR, RR: 0.56, 95% CI: 0.29–1.08).<sup>40</sup> Overall, current evidence suggests that clopidogrel should be stopped 5 or more days prior to CABG to avoid bleeding complications that may increase perioperative mortality except if there is uncontrolled ischaemia (Table 1).

### Meta-analysis data

Higher blood loss, transfusion, and reoperation rates associated with pre-CABG clopidogrel exposure <5 days have been confirmed by five meta-analyses<sup>41,42</sup> (Supplementary material online, Table S3). Mortality is increased in observational studies except in patients with ACS,<sup>12,13</sup> although patient status (stable vs. ACS), type of surgery (urgent vs. elective), and the absence of appropriate study matching may confound the effect of recent clopidogrel exposure (Table 2). Importantly, discontinuation of clopidogrel for 5–7 days before operation does not seem to confer increased cardiac risk.

## Coronary artery bypass grafting-related risk on prasugrel

Prasugrel is the third generation oral thienopyridine with faster onset and a more consistent irreversible platelet P2Y<sub>12</sub> blockade than the second-generation oral thienopyridine clopidogrel. This pharmacodynamic advantage over clopidogrel translated into a 19% relative risk reduction in ischaemic events in ACS patients undergoing PCI

**Table 2 Bridging therapies and platelet function monitoring**

The risks of bleeding and thrombosis and decision-making regarding DAPT and timing of surgery should be assessed by the heart team prior to CABG surgery	I	C	
Bridging with cangrelor, if available, is recommended in high-risk patients	I	B	43
Bridging with short-acting intravenous GPIIb/IIIa inhibitors may be considered in patients at high risk for ischaemic events	IIb	C	44
It is reasonable to base timing of surgery on <b>platelet function monitoring</b> rather than arbitrary use of a specified period of delay in patients on DAPT.	IIa	B	45

at the expense of increased major and fatal bleeding<sup>15,46</sup> (Supplementary material online, *Table S2*). Prasugrel (60-mg loading dose, 10-mg daily dose) in addition to aspirin is recommended over clopidogrel in P2Y<sub>12</sub> inhibitor-naïve ACS patients undergoing PCI with no history of prior stroke/TIA and in whom coronary anatomy is known.<sup>23,47</sup> A lower maintenance dose of 5 mg is recommended in patients <60 kg or >75 years.<sup>48</sup> In the TRITON-TIMI 38 study, a total of 368 (2.7%) ACS patients received at least one dose of study medication and subsequently underwent CABG surgery out of a total of 13 608 patients.<sup>49</sup> Despite an increase in observed TIMI major bleeding (OR: 4.73, CI: 1.9–11.8), platelet transfusion and surgical re-exploration for bleeding, prasugrel was associated with a lower rate of death after CABG compared with clopidogrel (2.3 vs. 8.7%; OR<sub>adj</sub> 0.26; *P* = 0.025). More than 60% of patients received the last dose of study medication 5 or more days prior to CABG surgery, with the imbalance in the number of deaths attributable to patients who received last dose of study medication 4 or more days prior to surgery. It is recommended to discontinue prasugrel 7 days prior to CABG surgery, but it is also recognized that the level of platelet inhibition during prasugrel maintenance therapy tends to be less and more variable than in the days following a loading dose,<sup>50,51</sup> raising the question as to whether platelet function testing may be useful under some circumstances to guide timing of cessation prior to surgery.

## Coronary artery bypass grafting-related risk on ticagrelor

Ticagrelor is a direct-acting and reversible inhibitor of the P2Y<sub>12</sub> receptor and is additionally an inhibitor of adenosine reuptake (Supplementary material online, *Table S2*). Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with clopidogrel leading to a better outcome in ACS patients, irrespective of revascularization strategies, including a mortality benefit.<sup>16</sup> Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy and including those pretreated with clopidogrel.<sup>23,47</sup> In addition, it has a more rapid and consistent offset of action related to its reversible receptor binding and plasma half-life of 6–12 h.<sup>52</sup> In patients with stable CAD, recovery of platelet

aggregation is almost complete at 5 days after cessation of ticagrelor, with substantially more recovery than seen with good responders to clopidogrel.<sup>53</sup> For patients in the PLATO study who underwent CABG surgery within 7 days of the last dose of study medication, there was evidence of early mortality reduction in the ticagrelor group and this was accounted for by fewer deaths associated with bleeding and infection as well as ischaemic events (4.6 vs. 9.2%; *P* = 0.0018).<sup>54,55</sup>

The strategies to reduce bleeding during CABG surgery have been added as Supplementary material online, *Table S5*.

## Risk stratification, bridging therapies, and platelet function monitoring

The need for urgent CABG on DAPT arises in ACS patients or after recent stent PCI. In the absence of robust evidence from RCTs, the key issues are<sup>(i)</sup> individual risk stratification of bleeding vs. ischaemia according to patient clinical characteristics and<sup>(ii)</sup> time interval from treatment interruption to CABG with or without bridging therapy.

### Risk stratification

In urgent CABG indications, exposure to the full effect of DAPT may lead to increased major bleeding, a complication that is associated with poor outcome due to haemodynamic instability, need for reoperation, or red blood cell transfusion-related inflammation and ischaemia.<sup>56</sup> Red blood cell transfusion during CABG is associated with a two-fold increase in 5-year mortality rates and with significantly more frequent sternal wound infection, severe sepsis, and renal dysfunction.<sup>1,57,58</sup>

Risk factors for increased perioperative bleeding and transfusion during CABG have been identified:<sup>(i)</sup> upstream antithrombotic therapy,<sup>(ii)</sup> patient nongenetic factors (age, female gender, small body size, preoperative anaemia, and comorbidities including COPD, liver disease, cardiac failure, and renal insufficiency),<sup>(iii)</sup> patient genetic factors (variability in clopidogrel response, hereditary deficiencies in coagulation factors/platelet function), and<sup>(iv)</sup> surgical factors (complex/redo procedures, urgent/emergent procedures).<sup>45,59,60</sup> However, there is no easy-to-use scoring system available and the surgeon performance is not taken into account, although it has been shown to be of importance.<sup>61</sup> In addition, although severity of CAD, clinical presentation, and patient co-morbidities may assist in risk stratification for ischaemic events, no available scoring systems for ACS presenters undergoing PCI or medical management have ever been tested in CABG-eligible patients. It appears reasonable to recommend the use of scores which encapsulate the common comorbidities of the CABG-eligible population to better risk stratify (*Table 1*). The combination of the GRACE and the CRUSADE risk scores appears relevant in such context.

Premature interruption of DAPT is the most important risk factor for early stent thrombosis.<sup>62–64</sup> In addition to comorbidities (diabetes, renal failure), the initial clinical presentation, stent length, stent undersizing, complex and/or bifurcation lesions, coronary dissection, genetic factors influencing clopidogrel metabolism,

and high platelet reactivity have all been associated with stent thrombosis.<sup>65,66</sup>

## Bridging therapy and timing of cessation

### Time delay from oral antiplatelet treatment cessation to coronary artery bypass grafting surgery

The rate of ischaemic events occurring from P2Y<sub>12</sub> inhibitor interruption prior to CABG has never been estimated precisely and the safety of delaying surgery to allow for the washout of P2Y<sub>12</sub> inhibitors is uncertain. As a consequence, the time delay from P2Y<sub>12</sub> inhibitor interruption to CABG is best determined by multidisciplinary clinical judgment based on risk assessment and pharmacodynamic studies.<sup>22,23,47,50,52,53</sup>

### Bridging therapies

Bridging may provide an optimal platelet inhibition up to the day of CABG surgery using short-acting drugs started after oral P2Y<sub>12</sub> inhibitor interruption several days before (Table 2). This may prevent not only ischaemic events between discontinuation of P2Y<sub>12</sub> inhibitors and surgery but also bleeding events or the use of transfusion. The intravenous (i.v.) GPIIb/IIIa antagonists eptifibatid and tirofiban were studied in ACS patients eligible for CABG surgery and in whom coronary stents were recently implanted.<sup>44</sup> These feasibility studies demonstrated that a 'bridging strategy', using i.v. tirofiban in patients with a recently implanted DES and high-risk characteristics for stent thrombosis needing urgent surgery, allowed temporary withdrawal of oral clopidogrel without increasing the risk of perioperative bleeding.

Cangrelor, a non-thienopyridine adenosine triphosphate analogue, is an i.v. antagonist of the P2Y<sub>12</sub> receptor characterized by rapid, potent, predictable, and reversible platelet inhibition with rapid offset of effect<sup>67</sup> (Supplementary material online, Table S1). It has been demonstrated to reduce the rate of ischaemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding as compared with oral clopidogrel in patients not pretreated prior to randomization at the time of PCI.<sup>68</sup> In the BRIDGE trial, the use of cangrelor compared with placebo maintained platelet inhibition in patients who discontinued thienopyridine therapy prior to cardiac surgery.<sup>43</sup> Excessive CABG surgery-related bleeding occurred in 11.8 (12 of 102) vs. 10.4% (10 of 96) in the

cangrelor and placebo groups, respectively (RR: 1.1 [95% CI: 0.5–2.5];  $P = .763$ ). There were no significant differences in major bleeding prior to CABG surgery. Cangrelor is not yet approved for bridging in CABG patients, nor for any other indication, but it has been submitted to FDA and EMA.

## Platelet function monitoring

The interindividual variability in pharmacodynamic response to clopidogrel leads to variability in the time taken to recover normal platelet reactivity following cessation of clopidogrel.<sup>50</sup> This is important because several studies have shown that the level of platelet reactivity at the time of surgery can predict the risk of CABG-related bleeding.<sup>69–71</sup> Although bedside platelet function testing has not, so far, been successful in guiding antiplatelet therapy during PCI to prevent ischaemic events,<sup>27,28</sup> treatment monitoring using bedside testing has been suggested as an option to guide treatment interruption rather than arbitrary use of a specified period of delay.<sup>72</sup> Platelet inhibitory response to clopidogrel determines CABG-related bleeding and a strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients led to ≈50% shorter waiting time than recommended in the current guidelines.<sup>72</sup> For these reasons, the 2012 Update of the Society of Thoracic Surgeons Guideline suggested that a delay of even a day or 2 is reasonable to decrease bleeding and thrombotic risk in ACS patients.<sup>73</sup> Point-of-care monitoring of platelet aggregation or whole-blood clot properties is associated with reduced perioperative bleeding and ischaemic complications especially during off-pump CABG surgery.<sup>69,70</sup> Bedside platelet function testing has been evaluated during clopidogrel exposure but might also be useful in prasugrel- or ticagrelor-treated patients, as recently shown for prasugrel.<sup>71</sup> A proposed strategy for preoperative management of P2Y<sub>12</sub> inhibitors and bridging is shown in Table 3. When the bleeding risk is low, short timing of cessation of P2Y<sub>12</sub> inhibitors prior to CABG surgery is encouraged in addition to bridging therapies that should be used when the thrombotic risk appears high. Platelet function testing may be used when the bleeding risk is low and the thrombotic risk is low. Evidence for PFT is derived from a single randomized study that was performed without point-of-care assay<sup>72</sup> and the interpretation of high platelet reactivity in patients at risk for bleeding remains unclear.

**Table 3** Proposed strategies for discontinuation of P2Y<sub>12</sub> inhibitors prior to coronary artery bypass grafting surgery

		Bleeding risk	
		High <sup>a</sup>	Low
Thrombotic risk	High <sup>b</sup> ACS or recent stent PCI	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 5 days before and bridge for 4 days. Prasugrel: stop 7 days and bridge for 5 days	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 3 days before and bridge for 2 days. Prasugrel: stop 5 days before and bridge for 3 days
	Low	Early Heart Team Consultation Clopidogrel/ ticagrelor: stop 5 days before. Prasugrel: stop 7 days prior to CABG	Clopidogrel/ticagrelor: stop 5 days before or less if indicated by platelet function test. Prasugrel: stop 7 days before or less if indicated by platelet function test.

<sup>a</sup>Examples of high-bleeding risk: renal or hepatic insufficiency, advanced age, anaemia, small body surface area, cardiac failure, and redo operation.

<sup>b</sup>Examples of high-thrombotic risk: haemodynamic instability, ongoing ischaemia, complex coronary anatomy, stenting < 1 month for BMS, and < 6 months for DES. CABG, coronary artery bypass grafting.

**Table 4** Resuming antiplatelet therapy after coronary artery bypass grafting surgery

ASA 75–160 mg/day should be restarted within the first 24 h and preferably within 6 h after CABG surgery and maintained lifelong.	I	B	74–76
In case of aspirin intolerance or contraindication, a loading dose of clopidogrel 300 mg as soon as bleeding is controlled followed by 75 mg/day is recommended lifelong.	I	C	
DAPT with clopidogrel may be considered to be (re-) started after CABG surgery for stable CAD patients as soon as considered safe.	IIb	C	77,78
For patients who undergo CABG within 1 year of ACS, resumption of P2Y <sub>12</sub> inhibitor should be considered as soon as bleeding is controlled.	IIa	B	54,55
A 300 mg clopidogrel loading dose as soon as bleeding is controlled followed by a 75 mg clopidogrel maintenance dose in addition to aspirin is recommended in stable CAD patients with coronary stent in non-grafted territories for the duration intended following stent implantation.	I	C	77

## Postoperative management of antiplatelet therapy

### Single antiplatelet therapy

Early thrombosis is the major cause of vein graft attrition during the first month after CABG, with occlusion rates of between 5 and 26% at 1 year, and ASA has been shown to improve 1-year vein graft patency.<sup>74–76</sup> The role of ASA in graft patency becomes substantial when initiated prior to CABG and then restarted ~6 h after surgery.<sup>76</sup> The beneficial effect of ASA on vein graft patency appears attenuated after the first year due to lack of effect on intimal hyperplasia and vein graft atherosclerosis. Although there is no evidence for an effect of ASA on long-term internal mammary artery graft patency, it should be continued indefinitely after CABG given its benefit in preventing subsequent clinical events (Table 4).<sup>3</sup> Medium doses of ASA (300–325 mg daily) have not been shown to be more effective than low doses (75–160 mg daily) in preventing graft occlusion and adverse clinical events, although an indirect meta-analysis provided weak evidence that medium doses might be more effective.<sup>79</sup> Inhibition of platelet function by ASA may be impaired after CABG, with or without CPB, in one-third of patients, due to reduced absorption, drug interactions, systemic inflammation, and increased platelet turnover, and these factors may increase the risk of graft occlusion early after CABG.<sup>80,81</sup> This phenomenon is transient and may be addressed by early intravenous or rectal administration followed by oral twice-daily administration early postoperatively.<sup>82</sup> In case of ASA intolerance, clopidogrel is indicated for prevention of ischaemic events.<sup>83</sup>

### Dual antiplatelet therapy after Coronary artery bypass grafting surgery

Observational studies have demonstrated the safety of early postoperative clopidogrel use following CABG but a meta-analysis of

studies reporting on safety/efficacy of clopidogrel use with or without aspirin did not show a clear clinical benefit of clopidogrel when given in addition to aspirin after CABG.<sup>84,85</sup> Several randomized trials have compared the effect of DAPT vs. aspirin on graft patency with diverging results.<sup>86–89</sup> Two meta-analyses of observational studies and RCTs showed that the use of DAPT reduced early vein graft occlusion.<sup>77,78</sup> The meta-analysis by Deo *et al.* also showed, in the ASA-clopidogrel group, a decrease in hospital or 30-day mortality (0.8 vs. 1.9%,  $P < 0.0001$ ) compared with ASA alone and this effect was more pronounced in off-pump patients.<sup>77</sup>

The effects of prasugrel have not yet been studied following CABG surgery but the mortality data from TRITON is supportive of resuming prasugrel following CABG surgery (adj OR: 0.26; 95% CI: 0.08–0.85;  $P = 0.025$ ).<sup>49</sup> In the PLATO study, it was intended that study medication with ticagrelor or clopidogrel should be started as soon as possible after CABG surgery and prior to hospital discharge. Thirty-six percent of CABG patients in the study restarted study medication within 7 days of surgery, 37% did not restart study medication and the rest restarted study medication 7 or more days later. Postoperative mortality was lower in the ticagrelor group compared with the clopidogrel group (HR: 0.49; 95% CI: 0.32–0.77).<sup>54</sup> It is uncertain how much of the benefit of ticagrelor compared with clopidogrel related to preoperative compared with postoperative treatment and further studies will provide more evidence in this area.

### Conclusions

Antiplatelet therapy plays a major role in the treatment of CAD and is therefore implicated throughout the CABG pathway. Management of single and DAPT in patients undergoing CABG for ACS, previous PCI, or stable angina impacts on early and late outcomes. Risk stratification for bleeding and recurrent ischaemic events, heart team decision making for temporary interruption of antiplatelet therapy and bridging strategies, the use of platelet function monitoring, and blood sparing management strategies are the key steps to further improve clinical outcome in patients undergoing CABG surgery. Gaps in knowledge remain, especially with respect to identification of the optimal bleeding-thrombotic risk balance before and after surgery. Specific studies for patients undergoing CABG are mandatory.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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### References

- Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006;**34**:1608–1616.
- Antiplatelet trialists' collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
- Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, Testa L, Sheiban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;**27**:2667–2674.

4. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Kern KB, Sethi G, Sharma GV, Khuri S. Starting aspirin therapy after operation. Effects on early graft patency. Department of Veterans Affairs Cooperative Study Group. *Circulation* 1991;**84**:520–526.
5. Bybee KA, Powell BD, Valeti U, Rosales AG, Kopecky SL, Mullany C, Wright RS. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005;**112**:1286–1292.
6. Deja MA, Kargul T, Domaradzki W, Stęcel T, Mazur W, Wojakowski W, Gocot R, Gaszewska-Zurek E, Zurek P, Pytel A, Woś S. Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. *J Thorac Cardiovasc Surg* 2012;**144**:204–209.
7. Cao L, Young N, Liu H, Silvestry S, Sun W, Zhao N, Diehl J, Sun J. Preoperative aspirin use and outcomes in cardiac surgery patients. *Ann Surg* 2012;**255**:399–404.
8. Alghamdi AA, Moussa F, Fremes SE. Does the use of preoperative aspirin increase the risk of bleeding in patients undergoing coronary artery bypass grafting surgery? Systematic review and meta-analysis. *J Card Surg* 2007;**22**:247–256.
9. Jacob M, Smedira N, Blackstone E, Williams S, Cho L. Effect of timing of chronic preoperative aspirin discontinuation on morbidity and mortality in coronary artery bypass surgery. *Circulation* 2011;**123**:577–583.
10. Sun JC, Whitlock R, Cheng J, Eikelboom JW, Thabane L, Crowther MA, Teoh KH. The effect of pre-operative ASA on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J* 2008;**29**:1057–1071.
11. Jassar AS, Ford PA, Haber HL, Isidro A, Swain JD, Bavaria JE, Bridges CR. Cardiac surgery in Jehovah's Witness patients: ten-year experience. *Ann Thorac Surg* 2012;**93**:19–25.
12. Biancari F, Airaksinen KEJ, Lip GYH. 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;**143**:665–675.e4.
13. Nijjer SS, Watson G, Athanasios 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**:2970–2988.
14. The Clopidogrel in Unstable angina to prevent Recurrent Events Trials Investigators (CURE). 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.
15. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman E, The TRITON-TIMI 38 Investigators. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2007;**357**:2001–2015.
16. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
17. Mehta S, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, Di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KAA, Yusuf S, on behalf of the CURRENT Investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010;**376**:1233–1243.
18. Gwon H-C, Hahn J-Y, Park KW, Song YB, Chae I-H, Lim D-S, Han K-R, Choi J-H, Choi S-H, Kang H-J, Koo B-K, Ahn T, Yoon J-H, Jeong M-H, Hong T-J, Chung W-Y, Choi Y-J, Hur S-H, Kwon H-M, Jeon D-W, Kim B-O, Park S-H, Lee N-H, Jeon H-K, Jang Y, Kim H-S. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;**125**:505–513.
19. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, Han KH, Park SW, Yun SC, Lee SG, Rha SW, Seong IW, Jeong MH, Hur SH, Lee NH, Yoon J, Yang JY, Lee BK, Choi YJ, Chung WS, Lim DS, Cheong SS, Kim KS, Chae JK, Nah DY, Jeon DS, Seung KB, Jang JS, Park HS, Lee K. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 2010;**362**:1374–1382.
20. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Cucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short-versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;**125**:2015–2026.
21. Steinhubl SR, Berger S, Mann JT, Fry ETA, DeLago A, Wilmer C, Topol EJ, for the Credo Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. *JAMA* 2002;**288**:2411–2418.
22. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliquet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirelet C, Pomar JL, Reifart N, Ribichini FL, Schali J, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filipatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, EACTS Clinical Guidelines Committee, Kolh P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, Document Reviewers, Kearney P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozeman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010;**31**:2501–2555.
23. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;**32**:2999–3054.
24. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. *JAMA* 2011;**306**:1215–1223.
25. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Van de Werf F, Verheugt FW. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;**32**:2922–2932.
26. Mega JL, Simon T, Anderson JL, Bliden K, Collet J-P, Danchin N, Giusti B, Gurbel P, Horne BD, Kastrati A, Montalescot G, Neumann F-J, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. CYP2C19 genetic variants and clinical outcomes with clopidogrel: a collaborative meta-analysis. *Circulation*. 2009;**120**:S598–S599.
27. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon J, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ, for GRACIAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRACIAS randomized trial. *JAMA* 2011;**305**:1097–1105.
28. Collet J-P, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Montalescot G. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;**367**:2100–2109.
29. 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**:1210–1216.
30. Kapetanakis EI, Medlam DA, Boyce SW, Haile E, Hill PC, Dullum MK, Bafi AS, Petro KR, Corso PJ. Clopidogrel administration prior to coronary artery bypass grafting surgery: the cardiologist's panacea or the surgeon's headache? *Eur Heart J* 2005;**26**:576–583.
31. Kapetanakis EI, Medlam DA, Petro KR, Haile E, Hill PC, Dullum MK, Bafi AS, Boyce SW, Corso PJ. Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae?. *Circulation* 2006;**113**:1667–1674.
32. Hongo RL, Dick S, Yee R. The effect of clopidogrel in combination with aspirin when given before coronary bypass grafting. *J Am Coll Cardiol* 2002;**40**:231–237.
33. Herman CR, Butth KJ, Kent BA, Hirsch GM. Clopidogrel increases blood transfusion and hemorrhagic complications in patients undergoing cardiac surgery. *Ann Thorac Surg* 2010;**89**:397–402.
34. Filsoofi 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**:60–66.
35. Leong JY, Baker RA, Shah PJ, Cherian VK, Knight JL. Clopidogrel and bleeding after coronary artery bypass graft surgery. *Ann Thorac Surg* 2005;**80**:928–933.
36. Miceli A, Duggan SMJ, Aresu G, de Siena PM, Romeo F, Glauber M, Caputo M, Angelini GD. Combined clopidogrel and aspirin treatment up to surgery increases

- the risk of postoperative myocardial infarction, blood loss and reoperation for bleeding in patients undergoing coronary artery bypass grafting. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2013;**43**:722–728.
37. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;**114**:774–782.
  38. Dasarathan C, Vaidyanathan K, Chandrasekaran D, Cherian KM. Does preoperative clopidogrel increase bleeding after coronary bypass surgery? *Asian Cardiovasc Thorac Ann* 2011;**19**:52–56.
  39. Karabulut H, Toraman F, Evrenkaya S, Goksel O, Tarcan S, Alhan C. Clopidogrel does not increase bleeding and allogenic blood transfusion in coronary artery surgery. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2004;**25**:419–423.
  40. Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. 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**:1202–1208.
  41. Purkayastha S, Athanasiou T, Malinovski V, Tekkis P, Foale R, Casula R, Glenville B, Darzi A. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. *Heart* 2006;**92**:531–532.
  42. Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. *Pharmacotherapy*. 2008;**28**:376–392.
  43. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutrya M, Welsby J, Voeltz MD, Chandra H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA J Am Med Assoc* 2012;**307**:265–274.
  44. Savonitto S, D'Urbano M, Caracciolo M, Barlocco F, Mariani G, Nichelatti M, Klugmann S, De Servi S. Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth* 2010;**104**:285–291.
  45. Ferraris VA, Saha SP, Oestreich JH, Song HK, Rosengart T, Reece TB, Mazer CD, Bridges CR, Despotis GJ, Jointer K, Clough ER. Society of Thoracic Surgeons. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;**94**:1761–1781.
  46. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM, TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;**373**:723–731.
  47. Steg PG, James SK, Atar D, Badano LP, Blömostrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zaher D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
  48. Roe MT, Goodman SG, Ohman EM, Stevens SR, Hochman JS, Gottlieb S, Martinez F, Dalby AJ, Boden WE, White HD, Prabhakaran D, Winters KJ, Aylward PE, Bassand J-P, McGuire DK, Ardissino D, Fox KAA, Armstrong PW. Elderly patients with acute coronary syndromes managed without revascularization insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel vs. standard-dose clopidogrel. *Circulation* 2013;**128**:823–833.
  49. Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, Lenarz LA. 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**:388–396.
  50. Price MJ, Walder JS, Baker BA, Heiselman DE, Jakubowski JA, Logan DK, Winters KJ, Li W, Angiolillo DJ. 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**:2338–2343.
  51. Kerneis M, Silvain J, Abtan J, Cayla G, O'Connor SA, Barthélémy O, Vignalou J-B, Beygui F, Brugier D, Martin R, Collet J-P, Montalescot G. Switching acute coronary syndrome patients from prasugrel to clopidogrel. *JACC Cardiovasc Interv* 2013;**6**:158–165.
  52. Storey RF, Bliden KP, Ecob R, Karunakaran A, Butler K, Wei C, Tantry U, Gurbel PA. Earlier recovery of platelet function after discontinuation of treatment with ticagrelor compared with clopidogrel in patients with high antiplatelet responses. *J Thromb Haemost JTH* 2011;**9**:1730–1737.
  53. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary disease: The ONSET/OFFSET Study. *Circulation* 2009;**120**:2577–2585.
  54. Held C, Bassand JP, Becker RC, Cannon CP, Harrington RA, Morrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Olofsson S, Scirica BM, Storey RF, Vintila M, Ycas J, Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO trial. *J Am Coll Cardiol* 2011;**57**:672–684.
  55. Varenhorst C, Alström U, Scirica BM, Hogue CW, Åsenblad N, Storey RF, Steg PG, Morrow J, Mahaffey KW, Becker RC, James S, Cannon CP, Brandrup-Wogensen G, Wallentin L, Held C. Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. *J Am Coll Cardiol* 2012;**60**:1623–1630.
  56. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;**116**:2544–2552.
  57. Bhaskar B, Dulhunty J, Mullany DV, Fraser JF. Impact of blood product transfusion on short and long-term survival after cardiac surgery: more evidence. *Ann Thorac Surg* 2012;**94**:460–467.
  58. Jakobsen C-J, Ryhammer PK, Tang M, Andreassen JJ, Mortensen PE. Transfusion of blood during cardiac surgery is associated with higher long-term mortality in low-risk patients. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2012;**42**:114–120.
  59. Mehta RH, Sheng S, O'Brien SM, Grover FL, Gammie JS, Ferguson TB, Peterson ED, Society of Thoracic Surgeons National Cardiac Surgery Database Investigators. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes* 2009;**2**:583–590.
  60. Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH, Sabik JF 3rd. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg* 2011;**91**:1780–1790.
  61. Kim JH-J, Newby LK, Clare RM, Shaw LK, Lodge AJ, Smith PK, Jolicoeur EM, Rao SV, Becker RC, Mark DB, Granger CB. Clopidogrel use and bleeding after coronary artery bypass graft surgery. *Am Heart J* 2008;**156**:886–892.
  62. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, Jesse RA, Rumsfeld JS. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008;**299**:532–539.
  63. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004;**110**:2361–2367.
  64. Iakovou I, Schmidt T, Bonizzi E, GE L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michei I, Corvaja N, Briguori C, Gercken U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–2130.
  65. Cayla G, Hulot J-S, O'Connor SA, Pathak A, Scott SA, Gruel Y, Silvain J, Vignalou J-B, Huerre Y, de la Briolle A, Allanic F, Beygui F, Barthélémy O, Montalescot G, Collet J-P. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. *JAMA J Am Med Assoc* 2011;**306**:1765–1774.
  66. van Werkum JW, Heestermaas AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 2009;**53**:1399–1409.
  67. Ferreira JL, Ueno M, Angiolillo DJ. Cangrelor: a review on its mechanism of action and clinical development. *Expert Rev Cardiovasc Ther* 2009;**7**:1195–1201.
  68. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimský P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Généreux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA. Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events. *N Engl J Med* 2013;**368**:1303–1313. 130310091208003.
  69. Poston R, Gu J, Manchio J, Lee A, Brown J, Gammie J, White C, Griffith BP. Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2005;**27**:584–591.
  70. Kwak Y-L, Kim J-C, Choi Y-S, Yoo K-J, Song Y, Shim J-K. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. *J Am Coll Cardiol* 2010;**56**:1994–2002.
  71. Ranucci M, Baryshnikova E, Soro G, Ballotta A, De Benedetti D, Conti D, Surgical and Clinical Outcome Research (SCORE) Group. Multiple electrode whole-blood

- aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg* 2011;**91**:123–129.
72. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ, Cho P, Sell J, Fan J, Antonino MJ, Tantry US, Gurbel PA. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012;**5**:261–269.
  73. Ferraris VA, Saha SP, Oestreich JH, Song HK, Rosengart T, Reece TB, Mazer CD, Bridges CR, Despotis GJ, Jointer K, Clough ER. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;**94**:1761–1781.
  74. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA J Am Med Assoc* 2004;**291**:1841–1849.
  75. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Doherty J, Read R, Chesler E, Sako Y. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation* 1988;**77**:1324–1332.
  76. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Doherty J, Read R, Chesler E, Sako Y. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. *Circulation* 1989;**80**:1190–1197.
  77. Deo SV, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA, Park SJ, Joyce LD. Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. *J Card Surg*. 2013;**28**:109–116.
  78. Nocerino AG, Achenbach S, Taylor AJ. Meta-analysis of effect of single versus dual antiplatelet therapy on early patency of bypass conduits after coronary artery bypass grafting. *Am J Cardiol* 2013;**112**:1576–1579.
  79. Lim E, Ali Z, Ali A, Routledge T, Edmonds L, Altman DG, Large S. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. *BMJ* 2003;**327**:1309.
  80. Wang G, Bainbridge D, Martin J, Cheng D. The efficacy of an intraoperative cell saver during cardiac surgery: a meta-analysis of randomized trials. *Anesth Analg* 2009;**109**:320–330.
  81. Zimmermann N, Kurt M, Wenk A, Winter J, Gams E, Hohlfeld T. Is cardiopulmonary bypass a reason for aspirin resistance after coronary artery bypass grafting? *Eur J Cardiothorac Surg* 2005;**27**:606–610.
  82. Capodanno D, Patel A, Dharmashankar K, Ferreiro JL, Ueno M, Kodali M, Tomasello SD, Capranzano P, Seecheran N, Darlington A, Tello-Montoliu A, Desai B, Bass TA, Angiolillo DJ. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. *Circ Cardiovasc Interv* 2011;**4**:180–187.
  83. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M, Dundar Y, Dickson R, Proudlove C, Fisher M. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. *Health Technol Assess Winch Engl* 2011;**15**:1–178.
  84. Halkos ME, Cooper WA, Petersen R, Puskas JD, Lattouf OM, Craver JM, Guyton RA. Early administration of clopidogrel is safe after off-pump coronary artery bypass surgery. *Ann Thorac Surg* 2006;**81**:815–819.
  85. Kim DH, Daskalakis C, Silvestry SC, Sheth MP, Lee AN, Adams S, Hohmann S, Medvedev S, Whellan DJ. Aspirin and clopidogrel use in the early postoperative period following on-pump and off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2009;**138**:1377–1384.
  86. Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery: a single-center, randomized, controlled trial. *J Am Coll Cardiol* 2010;**56**:1639–1643.
  87. Kulik A, Le May MR, Voisine P, Tardif J-C, Delarochelliere R, Naidoo S, Wells GA, Mesana TG, Ruel M. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. *Circulation*. 2010;**122**:2680–2687.
  88. Mannacio VA, Di Tommaso L, Antignan A, De Amicis V, Vosa C. Aspirin plus clopidogrel for optimal platelet inhibition following off-pump coronary artery bypass surgery: results from the CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) randomised study. *Heart Br Card Soc*. 2012;**98**:1710–1715.
  89. Sun J-C, Teoh KHT, Lamy A, Sheth T, Ellins ML, Jung H, Yusuf S, Anand S, Connolly S, Whitlock RP, Eikelboom JW. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: the Pre-operative Aspirin and Postoperative Antiplatelets in Coronary Artery Bypass Grafting study. *Am Heart J*. 2010;**160**:1178–1184.