

Coronary artery disease

Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial

Gérard Helft^{1,2*}, Philippe Gabriel Steg^{3,4,5}, Claude Le Feuvre¹, Jean-Louis Georges⁶, Didier Carrie⁷, Xavier Dreyfus⁸, Alain Furber⁹, Florence Leclercq¹⁰, Hélène Eltchaninoff^{11,12}, Jean-François Falquier¹³, Patrick Henry¹⁴, Simon Cattan¹⁵, Laurent Sebah¹⁶, Pierre-Louis Michel^{17†}, Albert Tuambilangana¹⁸, Nadjib Hammoudi^{1,2}, Franck Boccara^{19,20}, Guillaume Cayla²¹, Hervé Douard²², Abdourahmane Diallo²³, Emmanuel Berman¹, Michel Komajda^{1,2}, Jean-Philippe Metzger¹, and Eric Vicaut^{23,24}, on Behalf of the OPTImal DUAL Antiplatelet Therapy Trial Investigators

¹Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie, boulevard de l'Hôpital, 75013 Paris, France; ²IHU, Institute of Cardiometabolism and Nutrition, Hôpital Pitié-Salpêtrière, Paris, France; ³DHU FIRE, Université Paris-Diderot, Sorbonne-Paris-Cité, Paris, France; ⁴Hôpital Bichat, Assistance Publique Hôpitaux de Paris, INSERM-U1148, Paris, France; ⁵NHLI, Royal Brompton Hospital, Imperial College, London, UK; ⁶Centre Hospitalier Versailles, Le Chesnay, France; ⁷Centre Hospitalier Universitaire Rangueil, Toulouse, France; ⁸Espace Médical Mounier, Grenoble, France; ⁹Centre Hospitalier Universitaire, Angers, France; ¹⁰Centre Hospitalier Universitaire, Montpellier, France; ¹¹Centre Hospitalier Universitaire, Rouen, France; ¹²INSERM U 1096, Rouen, France; ¹³Polyclinique de Bergerac, Bergerac, France; ¹⁴Hôpital Lariboisière, Assistance Publique Hôpitaux de Paris, Paris 7, Paris, France; ¹⁵Centre Hospitalier Intercommunal Le Raincy-Montfermeil, Montfermeil, France; ¹⁶Hôpital Privé de l'Ouest Parisien, Trappes, France; ¹⁷Hôpital Tenon, Assistance Publique Hôpitaux de Paris, Paris 6, France; ¹⁸Hôpital Cherbourg, Cherbourg, France; ¹⁹Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, Paris Pierre et Marie Curie, Paris, France; ²⁰INSERM UMR_S 938, Paris, France; ²¹Centre Hospitalier Universitaire Nîmes, Université de Montpellier, Nîmes, France; ²²Centre Hospitalier Universitaire, Bordeaux, France; ²³Unité de Recherche Clinique Lariboisière St Louis Hôpital Fernand Widal, Assistance Publique Hôpitaux de Paris, Université Paris-Diderot, Paris, France; and ²⁴PARTNERS/F-CRIN, Paris, France

Received 9 July 2015; revised 13 August 2015; accepted 24 August 2015; online publish-ahead-of-print 12 September 2015

See page 375 for the editorial comment on this article (doi:10.1093/eurheartj/ehv499)

Aim

This open-label, randomized, and multicentre trial tested the hypothesis that, on a background of aspirin, continuing clopidogrel would be superior to stopping clopidogrel at 12 months following drug-eluting stent (DES) implantation.

Methods and results

Patients ($N = 1799$) who had undergone placement of ≥ 1 DES for stable coronary artery disease or acute coronary syndrome were included in 58 French sites (January 2009–January 2013). Patients ($N = 1385$) free of major cardiovascular/cerebrovascular events or major bleeding and on aspirin and clopidogrel 12 months after stenting were eligible for randomization (1:1) between continuing clopidogrel 75 mg daily (extended-dual antiplatelet therapy, DAPT, group) or discontinuing clopidogrel (aspirin group). The primary outcome was net adverse clinical events defined as the composite of death, myocardial infarction, stroke, or major bleeding. Follow-up was planned from a minimum of 6 to a maximum of 36 months after randomization. Owing to slow recruitment, the study was stopped after enrolment of 1385 of a planned 1966 patients. Median follow-up after stenting was 33.4 months. The primary outcome occurred in 40 patients (5.8%) in the extended-DAPT group and 52 in the aspirin group (7.5%; hazard ratio 0.75, 95% confidence interval 0.50–1.28; $P = 0.17$). Rates of death were 2.3% in the extended-DAPT group and 3.5% in the aspirin group (HR 0.65, 95% CI 0.34–1.22; $P = 0.18$). Rates of major bleeding were identical (2.0%, $P = 0.95$).

* Corresponding author. Tel: +33 1 4216 2912, Fax: +33 1 4216 3034, Email: gerard.helft@aphp.fr

† Deceased.

Conclusions

Extended DAPT did not achieve superiority in reducing net adverse clinical events compared to 12 months of DAPT after DES placement. The power of the OPTIDUAL trial was however low and reduced by premature termination of enrolment.

ClinicalTrials.gov number

NCT00822536.

Keywords

Dual antiplatelet therapy • Drug-eluting stent • Randomized trial • Clopidogrel • Bleeding • Myocardial infarction

Background

Drug-eluting stents (DES) have substantially improved the outcomes of patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).¹ After implantation of a DES, patients are treated with dual antiplatelet therapy (DAPT) in which a P2Y₁₂-receptor inhibitor is combined with aspirin to reduce the risk of stent thrombosis and minimize adverse cardiac outcomes.² Although stent thrombosis related to DES has become relatively rare with newer generation DES, it remains a life-threatening event.³ Dual antiplatelet therapy is currently recommended for at least 6–12 months after implantation of a DES.^{4,5} However, the optimum duration of this therapy remains a matter of debate. Evidence from initial studies^{6–9} has suggested that extending the duration of DAPT increases the risk of bleeding but does not reduce the risk of thrombotic events. Likewise, data from some randomized studies have shown that shortening the duration of DAPT (to 3–6 months) is associated with similar rates of major cardiovascular events but lower rates of bleeding compared with more-prolonged DAPT (i.e. 12–24 months)¹⁰; the median follow-up of these studies was 16.8 months. More-recent trials failed to demonstrate a benefit of prolonged DAPT after DES implantation: the ISAR-SAFE¹¹ and ITALIC¹² studies found no difference in net clinical outcome between 6 months and 12 months of clopidogrel therapy. However, the large DAPT trial¹³ has shown that compared with aspirin therapy alone, prolonging DAPT for 18 months, 1 year after placement of a DES, reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding. There was also a signal of increased all-cause mortality, driven by greater non-cardiovascular mortality due to bleeding, trauma, or cancer. Reconciling these results is difficult and underlines the need for more data regarding the appropriate duration of DAPT after stent implantation. In particular, few studies have addressed the specific question of very long-term DAPT, but their results suggest that the long-term risk of very late stent thrombosis is somewhat linear and low, particularly with the use of newer generations of stents^{13–15}; consequently, if there is a benefit of extended DAPT in preventing late stent thrombosis, there is no particular reason to expect the risk to abate after 12 or 18 months. We therefore sought to explore the value of very long-term DAPT in improving clinical outcomes in this setting. The OPTIDUAL antiplatelet therapy (OPTIDUAL) trial was designed to test whether prolonging clopidogrel after PCI would result in superior net clinical outcomes

compared with stopping clopidogrel 12 months after PCI in patients who received a DES.

Methods**Study design**

OPTIDUAL was an investigator-initiated, multicentre, open-label, randomized trial, with the aim of comparing the benefits and risks of DAPT continued for either 12 or 48 months after coronary stenting.¹⁶

The investigators (listed in Supplementary material online, *Appendix S1*) are solely responsible for the design and conduct of the trial, for the data analyses, and for writing the manuscript and for its final content. The study protocol was approved by an independent ethics committee before study initiation (CPP 34-2008). The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable local laws and regulations.

Study population

Eligible patients had symptoms of stable angina, silent ischaemia, or acute coronary syndrome (i.e. unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction) with ≥ 1 lesion with stenosis $>50\%$ located in a native vessel ≥ 2.25 mm in diameter and who were implanted with ≥ 1 DES of any type. The major exclusion criteria included requirement for oral anticoagulation, DES implantation in an unprotected left main coronary artery, and malignancies or other coexisting conditions associated with a life expectancy of <2 years (Supplementary material online, *Appendix S2*). Patients implanted with a bare-metal stent during the same procedure were permitted to enrol in the study. All patients provided written informed consent.

Intervention

At 12 ± 3 months after DES implantation, patients who were receiving DAPT (clopidogrel + aspirin) and who had remained free of major cardiovascular and cerebrovascular events or major bleeding were randomly assigned (1:1) to receive clopidogrel 75 mg daily (extended-DAPT group) for a further 36 additional months (total treatment duration with DAPT: 48 ± 3 months) or to discontinue clopidogrel (aspirin group). Post-procedure use of aspirin (75–160 mg daily according to local standards) was prescribed indefinitely. Patients who had received prasugrel ($n = 18$, 1.3% of the randomized patients) instead of clopidogrel at the time of PCI were eligible for randomization provided they had been switched to clopidogrel ≥ 6 months before randomization. Randomization was stratified by centre using an interactive voice response system.

Clinical follow-up

Patient baseline characteristics, clinical and procedural information were captured at the time of the randomization. All patients were scheduled to undergo clinical follow-up every 6 months, from a minimum of 6 months to a maximum of 36 months after randomization; consequently each patient attended between one and six follow-up visits, at least one of which was at an office. Attendance at the office was not possible for 60.9% of follow-up visits; these were replaced by telephone calls done by dedicated and trained study coordinators/clinical research assistants who were experienced in reporting all hospitalizations and/or major events. The final follow-up visit was a clinical visit with the investigator.

Outcomes and definitions

The primary outcome was net adverse clinical events defined as the composite of all-cause mortality, non-fatal myocardial infarction, stroke, or major bleeding. Myocardial infarction was defined as the presence of clinical or electrocardiographic changes consistent with myocardial ischaemia in the setting of increased cardiac biomarkers above the upper limit of normal in accordance with the universal definition.¹⁷ Strokes were categorized as ischaemic or haemorrhagic depending on the results of cerebral imaging. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) classification¹⁸ (fatal bleeding, and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in haemoglobin level of ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells) (defined in Supplementary material online, *Appendix S3*). Secondary outcomes were the individual components of the primary outcome; stent thrombosis (defined according to the Academic Research Consortium [ARC]¹⁹); repeat revascularization of the treated vessel; and bleeding, defined according to the ISTH,¹⁸ Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)²⁰ (moderate or severe), Thrombolysis In Myocardial Infarction (TIMI)²¹ (major and minor), and Bleeding Academic Research Consortium (BARC)¹⁹ type 2, 3, or 5 classifications.

All events occurring after randomization were adjudicated by an independent clinical event committee (Supplementary material online, *Appendix S1*), blinded to randomization assignment. Detailed definitions of outcomes are available in Supplementary material online, *Appendix S3*.

Statistical considerations

The trial was designed as a superiority trial: a sample size of 983 patients per arm was calculated to provide 80% power to demonstrate a significant reduction in the primary composite outcome at 3 years post-randomization from 7% with aspirin alone to 4% with prolonged DAPT, using survival analysis based on a Cox model and a 5% two-sided significance level.¹⁶

In July 2014, owing to lack of resources and slower enrolment than anticipated, the executive committee recommended termination of follow-up at the end of September 2014.

All analyses were performed according to the intention-to-treat principle, with the inclusion of all randomized patients according to the original group allocation. The primary and secondary outcomes related to time to an event were analysed in a survival analysis based on a Cox model. In case of missing values regarding the occurrence of events, patients were censored at the time of their last date of follow-up. The survival status during follow-up is described using Kaplan–Meier curves. In addition, since it cannot be excluded that patients who were censored differed from those who were still being followed (informative censoring), thus possibly inducing a bias, we performed an additional ‘inverse probability of censoring’ weighted analysis that

incorporates confounders to account for potential imbalances due to censoring patterns.^{22,23} Other secondary outcomes were analysed with the chi-square or Fisher’s exact test. The two-sided significance level was fixed at 5%. As the present study was not blinded, it was important to assess the effect of compliance with the randomized treatment on our results. Thus, we also performed sensitivity analyses: (i) a per-protocol analysis (treatment as attributed by randomization taken until the last follow-up visit, no premature discontinuation of the study); (ii) an ‘as treated’ analysis with all randomized patients analysed as a function of the treatment really taken (i.e. a patient randomized in the aspirin group but who received clopidogrel during their follow-up was considered to be in the extended-DAPT group). All tests were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patients and procedures

Between January 2009 and January 2013, 1799 patients who had undergone DES implantation and were receiving DAPT were enrolled in the study. The majority of the patients ($n = 1396$) were included just after DES implantation, the remainder at 12 ± 3 months after DES implantation. At 12 ± 3 months after DES implantation, 401 of the 1396 patients included just after PCI were not randomized. At randomization (mean \pm SD 12 ± 3 months later), 1398 patients who were on DAPT and were free of myocardial infarction, stroke, or major bleeding in the intervening period were randomly assigned to receive a further 36 months of DAPT with clopidogrel (75 mg/day) plus aspirin (extended-DAPT group) or aspirin alone (aspirin group) (75–160 mg/day). *Figure 1* summarizes the study flow. Thirteen patients (six assigned to the extended-DAPT group and seven to the aspirin group) could not be analysed (2 patients withdrew consent, and no information was available for 11 patients).

Both baseline and procedural characteristics were well balanced between the two groups with the exception of age >75 years and LAD as the target vessel for revascularization, which were both significantly higher in the aspirin group (*Table 1*). The mean \pm age of the overall population was 64.1 ± 11.1 years; 31.4% of the patients had diabetes mellitus, 17.4% had a clinical history of myocardial infarction, and 26.4% had a previous PCI. Overall, 5014 patients (36.24%) presented with an acute coronary syndrome, whereas PCI was elective in the remaining 63.86% of patients. Regarding baseline lesion and angiographic characteristics, 54.7% of the patients had multivessel disease. The left anterior descending coronary artery was the target vessel for revascularization in 60.2% of the patients. On average, each patient received 1.5 ± 0.8 DES and mean total stent length was 18.72 ± 7.45 mm per patient. The mean \pm SD diameter of the stent was 3.01 ± 1.35 mm. First-generation DES (sirolimus-eluting and paclitaxel-eluting stents) were used in 34.3% of patients, and second-generation DES (zotarolimus-eluting, everolimus-eluting, or biodegradable polymer biolimus-eluting stents) in 65.7%. After the index procedure, the use of evidence-based medications was high: 93.9% of the patients were on a statin, 79.8% were on a β -blocker, and 74.7% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Proton-pump inhibitors were used in half of the patients (48.3%). All patients completed a minimum of 6 months follow-up. Maximal follow-up (36 months post-randomization) was achieved in 43.7% of the patients.

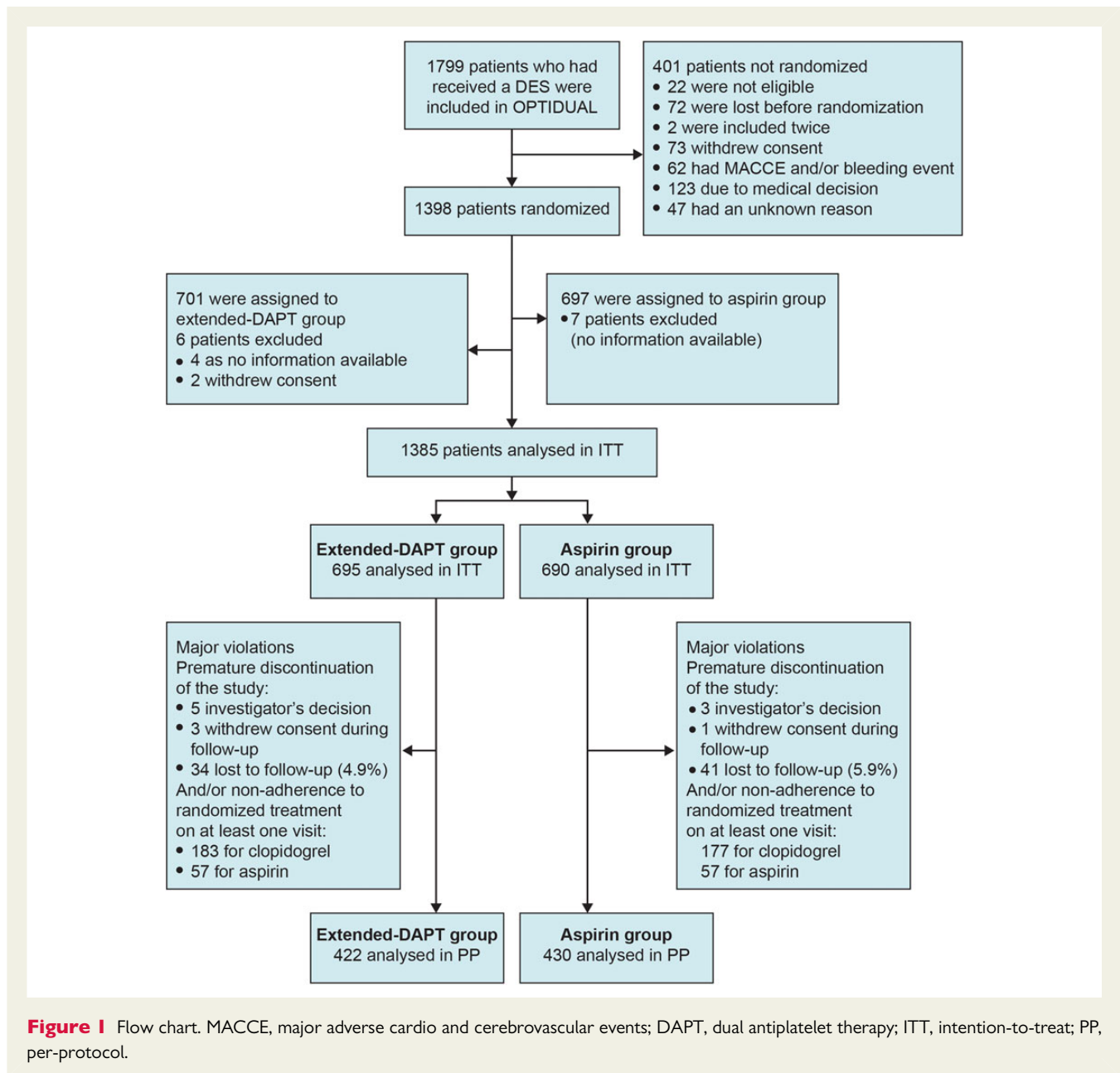


Figure 1 Flow chart. MACCE, major adverse cardio and cerebrovascular events; DAPT, dual antiplatelet therapy; ITT, intention-to-treat; PP, per-protocol.

Outcomes during follow-up

Median follow-up for the total population was 1017 days (quartile 1 to quartile 3: 567.0–1096.0). Estimates for the composite and individual endpoints are reported in Table 2. The primary composite outcome occurred in 40 patients in the extended-DAPT group vs. 52 in the aspirin group [5.8 vs. 7.5%; hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.50–1.28, $P = 0.17$] (Figure 2). All-cause mortality did not differ between the two groups (2.3% for extended DAPT vs. 3.5% for aspirin; HR 0.65, 95% CI 0.34–1.22, $P = 0.18$) (Figure 3A). There were numerically lower rates of stroke (Figure 3B) and myocardial infarction (Figure 3C) with extended DAPT, which did not achieve statistical significance.

Major ISTH bleeding occurred in 14 patients in both the extended-DAPT group and the aspirin group (HR 0.98, 95%

CI 0.47–2.05, $P = 0.95$) (Figure 3D). Bleeding events categorized according to the various classifications (TIMI, GUSTO, and BARC) are described in Table 3. Regardless of the classification used, there was no difference in bleeding rates between groups.

Results were similar and consistent when analyses taking into account informative censoring were made: HR 0.77, 95% CI 0.51–1.16, $P = 0.22$ for the primary composite outcome; HR 0.70, 95% CI 0.37–1.34, $P = 0.28$ for all-cause mortality; HR 0.80, 95% CI 0.24–2.61, $P = 0.71$ for stroke; HR 0.67, 95% CI 0.31–1.43, $P = 0.30$ for myocardial infarction; and HR 1.01, 95% CI 0.48–2.11, $P = 0.98$ for major ISTH bleeding.

The composite rate of death, myocardial infarction, or stroke (*post hoc* analysis) was 4.2% in the extended-DAPT group and 6.4% in the aspirin group (HR 0.64, 95% CI 0.40–1.02, $P = 0.06$)

Table 1 Patient baseline and procedural characteristics

Variable	Extended-DAPT group (N = 695)	Aspirin group (N = 690)	P-value
Age (years) mean \pm SD	64.1 \pm 10.8	64.2 \pm 11.5	0.88
>75 years	109 (15.7)	139 (20.1)	0.03
Women (%)	127 (18.3)	143 (20.7)	0.23
Diabetes mellitus (%)	213 (30.6)	222 (32.2)	0.54
Hypertension (%)	396 (57.0)	417 (60.4)	0.19
Current or recent cigarette smoker (%)	425 (61.2)	399 (57.8)	0.21
Family history of coronary artery disease (%)	195 (28.1)	224 (32.5)	0.07
Treatment at randomization (%)			
Statin	656 (94.4)	644 (93.3)	0.41
ACE inhibitor	522 (75.1)	512 (74.2)	0.71
Proton-pump inhibitor	346 (49.8)	323 (46.8)	0.27
β -Blocker	542 (78.0)	563 (81.6)	0.09
Calcium-channel inhibitor	215 (30.9)	200 (29.0)	0.43
Aspirin	695 (100)	687 (99.6)	
Daily dose of aspirin at the time of randomization (mg)			
\leq 100	545 (78.6)	537 (78.2)	0.84
101–300	148 (21.4)	150 (21.8)	
Medical history (%)			
Prior stroke or TIA	29 (4.2)	25 (3.6)	0.60
Congestive heart failure	4 (0.6)	8 (1.2)	0.24
Peripheral artery disease	34 (4.9)	45 (6.5)	0.19
Prior myocardial infarction	119 (17.1)	122 (17.7)	0.78
Prior PCI	180 (25.9)	186 (27.0)	0.66
Prior coronary artery bypass graft	37 (5.3)	35 (5.1)	0.83
Indication for PCI (%)			
ST-segment elevation myocardial infarction	74 (10.7)	82 (11.9)	0.47
Non-ST-segment elevation acute coronary syndrome	99 (14.2)	117 (17.0)	0.39
Unstable angina ^a	66 (9.5)	63 (9.1)	0.81
Stable angina	240 (34.5)	207 (30.0)	0.07
Silent ischaemia	138 (19.9)	151 (21.9)	0.35
Other	78 (11.2)	70 (10.1)	0.63
Number of vessels diseased (%)			
1	302 (43.5)	325 (47.1)	0.19
2	233 (33.6)	233 (33.8)	
3	159 (22.9)	132 (19.1)	
Type of DES at index procedure (%)			
Sirolimus stent	214 (19.9)	186 (17.5)	0.17
Paclitaxel stent	164 (15.2)	169 (16.0)	0.65
Zotarolimus stent	89 (8.3)	114 (10.8)	0.05
Everolimus stent	540 (50.2)	522 (49.2)	0.66
Other	69 (6.4)	69 (6.5)	0.93
Number of stents implanted	1.5 \pm 0.8	1.5 \pm 0.8	0.72
Minimum stent diameter (mm)			
<3	327 (47.7)	354 (52.1)	0.10
\geq 3	359 (52.3)	326 (47.9)	
Total stent length (mm)	18.70 \pm 7.51	18.73 \pm 7.40	0.94
Target vessel (%) ^b			
Left main	4 (<1)	2 (<1)	0.69

Continued

Table 1 Continued

Variable	Extended-DAPT group (N = 695)	Aspirin group (N = 690)	P-value
Left anterior descending	397 (57)	443 (64)	0.007
Right	280 (40)	268 (39)	0.58
Circumflex	225 (32)	214 (31)	0.59
Bypass grafting	6 (1)	8 (1)	0.60
Number of vessels treated during the index PCI (%)			
1	369 (61.2)	356 (60.5)	0.82
2	150 (24.9)	160 (27.2)	0.36
3	84 (12.9)	72 (12.3)	0.39

Data given as mean \pm SD or count (%).

ACE, angiotensin-converting enzyme; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

^aThis category included patients with unstable angina without reported elevation of cardiac enzymes.

^bData regarding vessels treated were available for 616 patients in the group that was randomly assigned to extended DAPT and for 608 patients in the aspirin group.

Table 2 Clinical outcomes

Outcome, n (%)	Extended-DAPT group (N = 695)	Aspirin group (N = 690)	HR for extended DAPT (95% CI)	P-value
Primary composite outcome ^a	40 (5.8)	52 (7.5)	0.75 (0.50–1.28)	0.17
All-cause mortality	16 (2.3)	24 (3.5)	0.65 (0.34–1.22)	0.18
Cardiovascular mortality	10 (1.4)	14 (2.0)	0.69 (0.31–1.56)	0.37
Non-cardiovascular mortality	6 (0.9)	10 (1.4)	0.58 (0.21–1.61)	0.30
Non-fatal myocardial infarction	11 (1.6)	16 (2.3)	0.67 (0.31–1.44)	0.31
Non-fatal stroke	5 (0.7)	7 (1.0)	0.69 (0.22–2.18)	0.53
Ischaemic	4 (0.6)	4 (0.6)		
Haemorrhagic	1 (0.1)	2 (0.3)		
Uncertain	0 (0.0)	1 (0.1)		
Stent thrombosis				
Definite or probable	3 (0.4)	1 (0.1)	2.97 (0.31–28.53)	0.35
Definite	3 (0.4)	0 (0.0)		
Target-lesion revascularization	35 (5.0)	35 (5.1)	0.97 (0.61–1.55)	0.90
ISTH major bleeding	14 (2.0)	14 (2.0)	0.98 (0.47–2.05)	0.95

CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

^aNet adverse clinical events (composite of death, myocardial infarction, stroke, and major bleeding).

(Supplementary material online, Figure 1). Definite or probable stent thrombosis occurred in three patients in the extended-DAPT group (0.4%) and in one patient in the aspirin group (0.1%). Target vessel revascularization occurred in 5.0% in the extended-DAPT group and in 5.1% in the aspirin group (HR 0.97, 95% CI 0.61–1.55).

The number of patients who had stopped clopidogrel at least at one visit was 183 (26.3%) (Figure 1), and those who prematurely stopped clopidogrel during follow-up was 145 (20.9%) in the extended-DAPT group. Conversely, the number of patients who received clopidogrel or any other P2Y₁₂ blocker during follow-up in the aspirin group was 177 (25.7%, Figure 1); among those 92 (13.3%) were treated by clopidogrel at their last follow-up visit. Per-protocol and 'as treated' sensitivity analyses yielded results

consistent with the ITT analysis (Supplementary material online, Figure 2).

Discussion

This randomized, multicentre trial compared outcomes between patients in whom clopidogrel was stopped at 12 months or continued after DES implantation on a background of aspirin therapy. There was no reduction in net adverse clinical events in the group in whom clopidogrel was continued compared with that in whom it was stopped 12 months after DES placement. There was a nominally lower rate of ischaemic outcomes (combination of death, myocardial infarction, or stroke, which was not a pre-specified outcome),

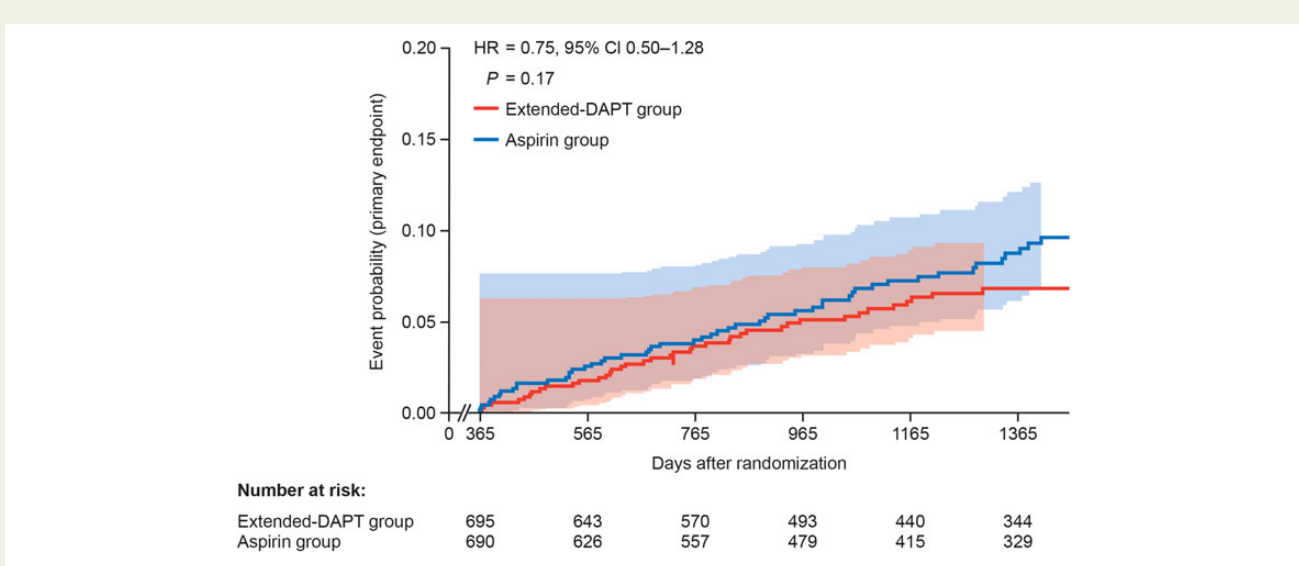


Figure 2 Kaplan–Meier curves for primary outcome of net adverse clinical events (defined as the composite of death, myocardial infarction, stroke, or major International Society on Thrombosis and Haemostasis bleeding). CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio.

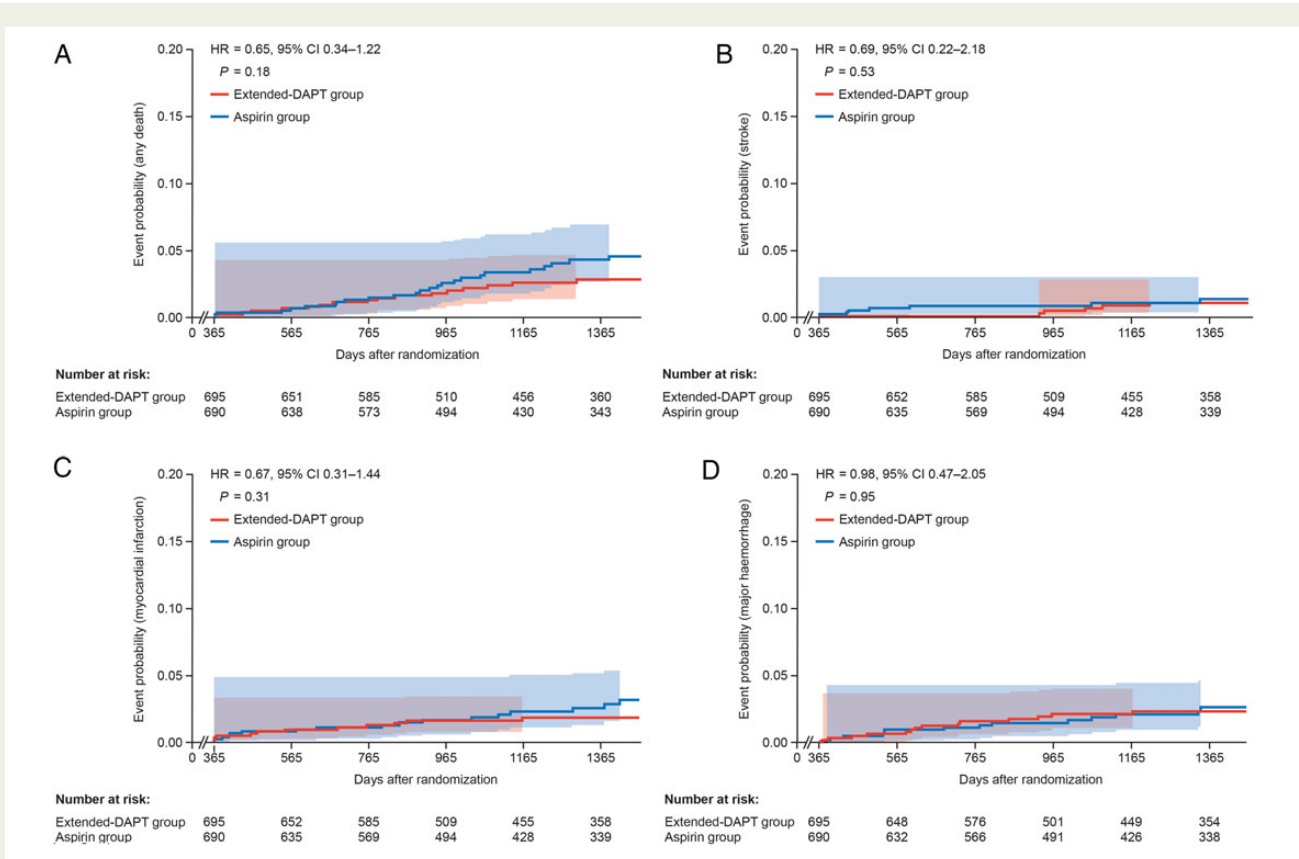


Figure 3 (A) All-cause mortality, (B) stroke, (C) myocardial infarction, and (D) major ISTH bleeding. CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

Table 3 Bleeding outcomes

Outcome n (%)	Extended-DAPT group (n = 695)	Aspirin group (n = 690)	Risk difference DAPT-aspirin (95% CI)	P-value ^a
GUSTO moderate or severe	13 (1.9)	12 (1.7)	0.1 (−1.3 to 1.5)	0.85
Moderate	11 (1.6)	8 (1.2)	0.4 (−0.8 to 1.7)	0.50
Severe	3 (0.4)	4 (0.6)	−0.2 (−0.9 to 0.6)	0.72
BARC type 2, 3, or 5	18 (2.6)	20 (2.9)	−0.3 (−2.0 to 1.4)	0.72
2	5 (0.7)	7 (1.0)	−0.3 (−1.3 to 0.7)	0.85
3	13 (1.9)	14 (2.0)	−0.1 (−1.6 to 1.3)	0.83
5	1 (0.1)	0 (0.0)	0.1 (−0.1 to 0.4)	1.00
TIMI major or minor	18 (2.6)	20 (2.9)	−0.3 (−1.4 to 2.0)	0.72
Major	4 (0.6)	4 (0.6)	0.0 (−0.8 to 0.8)	1.00
Minor	15 (2.2)	16 (2.3)	−0.1 (−1.7 to 1.4)	0.84
ISTH major	14 (2.0)	14 (2.0)	0.0 (−1.5 to 1.5)	0.98
ISTH moderate	6 (0.9)	7 (1.0)	−0.1 (−1.1 to 0.9)	0.77

^aP value for risk difference test

BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis In Myocardial Infarction.

which did not achieve statistical superiority, and appears related to consistently lower rates of all ischaemic components, with point estimates for the HR of 0.65 for all-cause mortality, 0.67 for myocardial infarction, and 0.69 for stroke. Importantly, there was no apparent difference in the rates of major bleeding, which were identical in both groups. However, given the power of the trial, we cannot rule out up to a 50% reduction or a 28% increase in the primary outcome with extended DAPT. Stent thromboses were rare and the rate did not differ between the two groups. In the DAPT trial,¹³ extended DAPT clearly reduced stent thrombosis rates, but the low rate of events in OPTIDUAL precludes conclusions. In terms of clinical efficacy, the OPTIDUAL results are consistent with the recent findings from the DAPT trial regarding the value of prolonging DAPT after DES placement, as the CI for the effects of extended DAPT on ischaemic outcomes includes the point estimate of 0.71 observed in the DAPT trial. With respect to all-cause mortality or bleeding, the confidence intervals of the effects observed in both trials largely overlap.

The optimal duration of DAPT is an important clinical issue, given the large number of patients treated with DES, the costs and risks of antiplatelet therapy, the potentially life-threatening consequences of stent thrombosis, and the potential benefits of antiplatelet therapy in preventing ischaemic outcomes beyond stent thrombosis. The rationale for a prolonged duration of DAPT is the prevention of stent thrombosis, but also the prevention of ischaemic events unrelated to the index coronary lesion.^{13,24} However, extending the duration of DAPT may also increase the risk of major bleeding.^{7,13} Recent randomized trials have explored shorter and longer durations of DAPT than 12 months. Shorter durations have been associated with lower bleeding rates but no clear difference in the rate of major adverse cardiac events.^{25,26} Conversely, treatment duration for >12 months appears to reduce rates of major adverse cardiac events and major adverse cardiac and cerebrovascular events, and rates of stent thrombosis, albeit at the expense of increased major

bleeding,^{13,26,27} a result driven largely by the large DAPT trial.¹³ In the DAPT trial, this finding was associated with a signal of increased mortality,²⁸ for which the mechanism remains debated.²⁹

Interestingly, in the OPTIDUAL trial, the rates of major bleeding were low and were very similar in both groups, regardless of the bleeding classification used. In addition, mortality was not increased with extended duration DAPT. In fact, the point estimate for the HR of all-cause mortality was 0.65 (95% CI 0.34–1.22). Since randomization was performed 12 months after PCI and only in patients who were event-free and on continued DAPT, OPTIDUAL may have selected a population at low risk of bleeding, particularly as DAPT is associated with a greater risk of bleeding in the first year after initiating therapy.^{30,31} However, given the relatively low event rate and wide CI, we cannot rule out an increase in bleeding risk of the same magnitude as that reported in the DAPT trial.¹³

Limitations

Several limitations must be considered when interpreting our results. First, termination of the trial before enrolment and follow-up were completed reduced the trial power. Our study was only powered to detect major differences in ischaemic and bleeding events and we absolutely cannot rule out clinically meaningful reductions in net adverse clinical outcomes, major adverse clinical outcomes, stent thrombosis, or mortality. In fact, there is a borderline but non-statistically significant reduction in ischaemic outcomes with extended DAPT. However, this pertained to an outcome which was not pre-specified and therefore this finding from a *post hoc* analysis can only be viewed as hypothesis generating. Secondly, the use of third-generation DES was not mandated by protocol and there is evidence that the type of stent may have a bearing on the value of extending DAPT duration. However, the latest generation DES, relying on zotarolimus and everolimus-eluting stents, were used in the majority of the OPTIDUAL population and the outcomes observed in OPTIDUAL appear consistent across the various types

of stents used. Third, the antiplatelet agents tested in OPTIDUAL were aspirin and clopidogrel. Recently, the PEGASUS trial³² has found that in patients with a remote history of myocardial infarction, DAPT using ticagrelor was associated with benefit compared with single-antiplatelet therapy with aspirin. Whether ticagrelor would have provided greater efficacy, greater bleeding, or both compared with what clopidogrel achieved in OPTIDUAL remains speculative.¹⁶ Fourth, the study was open-label, which is a less robust design than a double-blind trial, which requires substantially more resources for implementation. However, all clinical outcomes were adjudicated by an independent clinical event committee blinded to treatment assignment, and the components of the primary composite outcome all are objectively defined outcomes. Finally, a potentially important finding from the DAPT trial was the observation of an increased risk of stent thrombosis and major adverse cardiac outcomes in the weeks following discontinuation of clopidogrel, after both 12 and 30 months.¹³ Unfortunately, we did not monitor event rates after treatment discontinuation, and therefore cannot comment on whether the excess risk of stent thrombosis related to treatment discontinuation is present or attenuated after extended DAPT. In the aspirin-only group, the Kaplan–Meier estimates do not suggest a clear increase in ischaemic events in the first few weeks following randomization and rather suggest a linear accrual of events, but the present study is underpowered for reliably assessing such a transient effect.

Conclusions

Extending DAPT duration for a median 22 months did not achieve statistical superiority compared with stopping clopidogrel at 12 months, with regards to net adverse clinical outcomes in patients free of a major cardiovascular or cerebrovascular event and major bleed 12 months after stent implantation.

Supplementary material

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

Authors' contributions

E.V. and A.D.: performed statistical analysis. G.H., M.K., J-P.M., and C.L.F.: handled funding and supervision. G.H., P.G.S., C.L.F., J-L.G., D.C., X.D., A.F., F.L., H.E., J-F.F., P.H., S.C., L.S., N.H., A.T., F.B., G.C., H.D., and E.B.: acquired the data. G.H., C.L.F., J-L.G., D.C., X.D., A.F., F.L., H.E., J-F.F., P.H., S.C., L.S., A.T., N.H., F.B., G.C., H.D., M.K., J-P.M., and E.V.: conceived and designed the research. G.H. and P.G.S.: drafted the manuscript. G.H., D.C., X.D., F.B., S.C., G.C., H.D., A.F., N.H., H.E., P.H., M.K., F.L., J-P.M., L.S., E.V., P.G.S., and J-L.G.: made critical revision of the manuscript for key intellectual content.

Acknowledgements

We thank the Clinical Events Committee. We are very grateful to Vidhya Raghavan, Sofiane Djaileb, Florence Reboullet, and Véronique Jouis for their continuous support of the study and Sophie Rushton-Smith (MedLink Healthcare Communications) for reviewing the paper.

Funding

The sponsor was Assistance Publique-Hôpitaux de Paris (Département de la Recherche Clinique et du Développement). The study was funded by a grant from Programme Hospitalier de Recherche Publique-PHRC 2008 (Ministère de la Santé, N° AOM 08 080) and unrestricted research grants from Fédération française de Cardiologie, Cordis, Boston, Medtronic, Terumo and Biotronik.

Conflict of interest: G.H. reports grants from Fédération Française de Cardiologie, grants from Cordis, grants from Boston, grants from Medtronic, grants from Terumo, grants from Biotronik, during the conduct of the study; personal fees from Astra Zeneca, personal fees from Abbott, personal fees from Pfizer, personal fees from Boehringer-Ingelheim, personal fees from Bayer, outside the submitted work.

P.G.S. reports personal fees from Amarin, personal fees from Astra-Zeneca, personal fees from Bayer, personal fees from Boehringer-Ingelheim, personal fees from Bristol-Myers-Squibb, personal fees from Daiichi-Sankyo, personal fees from GlaxoSmithKline, personal fees from Lilly, personal fees from Merck-Sharp-Dohme, personal fees from Novartis, personal fees from Otsuka, personal fees from Pfizer, personal fees from Roche, personal fees from Medtronic, grants and personal fees from Sanofi, grants and personal fees from Servier, personal fees from Vivus, personal fees from Janssen, personal fees and non-financial support from The Medicines Company, personal fees from Orexigen, personal fees from Regado, outside the submitted work.

J.-L.G. reports grants from Astra Zeneca, outside the submitted work. A.F. reports personal fees from Servier, personal fees from Lilly, personal fees from Bayer, personal fees from Daiichi-Sankyo, personal fees from Sanofi, personal fees from Pfizer, personal fees from Astra Zeneca, personal fees from The Medicines Company, outside the submitted work.

H.E. reports grants and personal fees from Edwards Lifesciences, outside the submitted work.

F.B. reports personal fees from Amgen, Sanofi, AstraZeneca, ViiV Healthcare, Gilead, outside the submitted work.

G.C. reports personal fees from AstraZeneca, personal fees from Biotronik, personal fees from Eli Lilly, personal fees from Daiichi Sankyo, personal fees from Merk, personal fees from Medtronic, personal fees from Boston, personal fees from Abbott Vascular, outside the submitted work. E.V. reports grants from EU, during the conduct of the study; personal fees from Abbott, grants from Boehringer, personal fees from Bristol Myers Squibb, personal fees from Celgene, personal fees from European Cardiovascular Research Center, personal fees from Fresenius, personal fees from LFB, personal fees from Lilly, personal fees from Medtronic, personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, grants from Sanofi, outside the submitted work.

The other authors report no disclosures.

References

- Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;**356**:998–1008.
- Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;**356**:1020–1029.
- Claessen BE, Henriques JP, Jaffer FA, Mehran R, Piek JJ, Dangas GD. Stent thrombosis: a clinical perspective. *JACC Cardiovasc Interv* 2014;**7**:1081–1092.
- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 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. *Circulation* 2011;**124**:e574–e651.
5. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS 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) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
 6. 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.
 7. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubba MD, 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.
 8. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. 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.
 9. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y, RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;**60**:1340–1348.
 10. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. *Eur Heart J* 2012;**33**:3078–3087.
 11. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tolg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schomig A, Mehilli J, Kastrati A. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;**36**:1252–1263.
 12. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, Castellani P, Schneberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuyx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschhat J, Morice MC. 6- Versus 24-Month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents in Patients Nonresistant to Aspirin: The Randomized, Multicenter ITALIC Trial. *J Am Coll Cardiol* 2015;**65**:777–786.
 13. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
 14. Raber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Juni P, Serruys PW, Windecker S. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation* 2012;**125**:1110–1121.
 15. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Han S, Lee SG, Seong IW, Rha SW, Jeong MH, Lim DS, Yoon JH, Hur SH, Choi YS, Yang JY, Lee NH, Kim HS, Lee BK, Kim KS, Lee SU, Chae JK, Cheong SS, Suh IW, Park HS, Nah DY, Jeon DS, Seung KB, Lee K, Jang JS, Park SJ. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation* 2014;**129**:304–312.
 16. Helft G, Le Feuvre C, Georges JL, Carrie D, Leclercq F, Eltchaninoff H, Furber A, Prunier F, Sebah L, Cattani S, Cayla G, Vicaut E, Metzger JP. Efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent: the OPTimal DUAL antiplatelet therapy (OPTIDUAL) trial: study protocol for a randomized controlled trial. *Trials* 2013;**14**:56.
 17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, the Writing Group on behalf of the Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
 18. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
 19. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.
 20. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673–682.
 21. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial – phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.
 22. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;**11**:550–560.
 23. Harvard School of Public Health. Harvard School of Public Health Program on Causal Inference: Software—marginal structural Cox model in SAS. <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/148/2012/10/samplemsmcox.txt>. (10 August 2015).
 24. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
 25. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Mariani A, Della Riva D, Genereux P, Leon MB, Bhatt DL, Benedetto U, Rapezzi C, Stone GW. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. *J Am Coll Cardiol* 2015;**65**:1092–1102.
 26. Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M, Costa F, Kowalewski M, Parati G, Lip GY, Kelm M, Valgimigli M. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ* 2015;**350**:h1618.
 27. Giustino G, Baber U, Sartori S, Mehran R, Mastorisi I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2015;**65**:1298–1310.
 28. Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG, Kereiakes DJ, Yeh RW. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet* 2015;**385**:792–798.
 29. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet* 2015;**385**:2371–2382.
 30. Jeger RV, Pfisterer ME, Sorensen R, von Felten S, Alber H, Bonetti PO, Eberli F, Erne P, Pedrazzini G, Rickli H, Galatius S, Kaiser CA, BASKET and BASKET-PROVE investigators. Tradeoff between bleeding and stent thrombosis in different dual antiplatelet therapy regimes: Importance of case fatality rates and effective treatment durations. *Am Heart J* 2014;**168**:698–705.
 31. Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KA, Shao M, Brennan DM, Hacke W, Montalescot G, Steinhilber SR, Topol EJ, CHARISMA Investigators. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Circulation* 2010;**121**:2575–2583.
 32. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI Steering Committee Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–1800.