charities; it was also welcomed by the major political parties. We hope that this widely supported model will not be pushed aside after the next general election. Moreover, we are encouraged that the recent *NHS Five Year Forward View*[6] from NHS England says it will build on the work of our Future Hospital report and recognises that no-one wants top down reorganisation of the NHS. Any change should be patient centred and clinicians must be listened to and allowed to lead. It is time for evidence-based policy making and physicians are ready for the challenge.

There are warning signs that the financial crisis is biting into the NHS.[7] A crisis in care can only be avoided by a substantial increase in health funding. Improved efficiency and reconfiguration will not deliver the savings we need, so we must invest now to save in the long term.

As a former Director of University College London Medical School, you would expect medical education to be close to my heart. Although medical education is fundamental to the future of our profession, it has been undervalued by both the NHS and academia. The next UK Government needs to recognise the importance of the direct link between educational excellence and high-quality health care, and ensure that training the next generation of doctors is part of all health-service planning and delivery.

Finally, the next UK Government must be more active in public health. Our progress in treating and managing disease is undermined by obesogenic environments that promote unhealthy foods and alcohol. The RCP's experience of campaigning on public health issues, particularly tobacco, has shown that national levers like legislation can change unhealthy behaviours.[8] Legislation—for example, the introduction of a minimum alcohol unit price of £0·50 and taxes on sugary drinks—should be combined with better local prevention and recovery services for patients already affected by non-communicable diseases.

The RCP's messages to the next UK Government are simple: no reorganisations of the NHS, support integration and education, and increase funding. I hope the politicians are listening.

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Dual antiplatelet treatment after stenting: is longer better?

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During the past decade, drug-eluting stents (DES) have emerged as a preferred and highly effective treatment for patients with symptomatic coronary artery disease. Stent thrombosis, the Achilles heel of DES implantation, continues to be a relevant issue that needs to be prevented with dual antiplatelet treatment (DAPT) consisting of aspirin and a $P2Y_{12}$ receptor inhibitor. Guidelines recommend (class IB) a DAPT duration of 6–12 months for stable patients with coronary artery disease[1] who are undergoing elective percutaneous coronary intervention (PCI) with a second-generation everolimus-eluting or zotarolimus-eluting DES, and a DAPT duration of 12 months (class IA) in patients with acute coronary syndrome[2] unless there are contraindications such as an excessive risk of bleeding. Such recommendations on DAPT duration are based on limited data from clinical trials. Extension of DAPT might mitigate risk of stent thrombosis or subsequent

thrombotic events elsewhere in the circulation. However, it will also increase bleeding risk and costs. Therefore, a key question that remained to be addressed by adequately powered clinical trials is whether or not extension of DAPT beyond 1 year after PCI provides any net clinical benefit.

In *The Lancet*, Jean-Philippe Collet and colleagues[3] report the results of the randomised, open-label, parallel-group ARCTIC-Interruption trial, which was a planned extension of the ARCTIC-Monitoring study.[4] In ARCTIC-Interruption, the investigators compared the outcomes of 1259 PCI-treated patients, who had received DAPT for 1 year, with either a continued single antiplatelet treatment including aspirin (n=624) or an extended DAPT regimen of 6–18 months (n=635). Their findings show no benefit of extension of DAPT beyond 1 year with respect to ischaemic complications including stent thrombosis (HR 1·17, 95% CI 0·68–2·03). Extension was, instead, harmful with respect to bleeding risk (0·26 for combined major or minor bleeding, 0·07–0·91). High platelet reactivity on thienopyridine treatment was associated with poor survival at the end of follow-up (5·07, 1·63–15·76) but there was no interaction between high platelet reactivity and outcome with respect to the mode of treatment (interruption *vs* continuation, p=0·78). Collet and colleagues are to be commended for providing solid evidence against a presumably unnecessary and even harmful extension of DAPT beyond 1 year after a PCI procedure. However, in interpreting the data, some issues and limitations merit mentioning.

First, patients not randomised in ARCTIC-Interruption were at higher risk than those randomised. Patients who had subsequent adverse events after the index PCI and patients for whom the treating physician considered extension necessary were excluded,[3] which can introduce a substantial selection bias. As a consequence, Collet and colleagues' findings might not be applicable to a high-risk cohort of patients. While a uniform duration period of DAPT irrespective of a patient's risk profile is to some extent encouraged by guidelines,[1,2] the optimum DAPT duration can vary from patient to patient and is likely to be determined by the individual combination of factors favouring longer DAPT and factors in favour of a shorter treatment (panel). Such factors include procedural issues, such as the stent type, lesion length or localisation, and the complexity of the procedure itself, as well as the clinical setting in which DES implantation was done and the presence or absence of comorbidities or co-medications.

Second, the investigators report an association of high platelet reactivity with mortality, but no interaction with respect to treatment strategy. However, this absence of interaction does not allow conclusions regarding the potential role of platelet function testing for guidance of antiplatelet treatment in general. In this context, the fact that overall results of ARCTIC-Interruption[3] were negative for treatment extension should be borne in mind, and in a scenario of very low event rates beyond 1 year after PCI, as in this trial,[3] any biomarker assessment is unlikely to be relevant for guidance of treatment options. Additionally, findings from previous studies[5,6] have shown that the presence of high platelet reactivity is highly predictive for early events after the procedure, whereas late events—such as those assessed in ARCTIC-Interruption—might have a different pathophysiological background beyond antiplatelet drug responsiveness. If high on-treatment platelet reactivity were to affect outcome late after PCI, it would not be likely to be high platelet reactivity with respect to the drug that is stopped ($P2Y_{12}$ inhibitor), but rather on-treatment platelet reactivity for aspirin, the antiplatelet agent that is maintained.

Third, ARCTIC-Interruption[3] provides important evidence for not extending DAPT beyond

***Panel:* Factors guiding the optimum DAPT duration**

Factors favouring a shorter duration of dual antiplatelet treatment (DAPT)

- Elective percutaneous coronary intervention (PCI) in stable coronary artery disease
- High bleeding risk or history of bleeding
- Need for oral anticoagulation
- Implantation of a second-generation drug-eluting or bare-metal stent*
- Old age, low body-mass index
- Planned major surgery

Factors favouring a longer duration of DAPT

- PCI for acute coronary syndrome
- Complex PCI (bifurcation or left main stenting, long lesions)
- Imperfect PCI procedure (stent malapposition, residual stenosis)
- History of stent thrombosis
- Morbidities with higher thrombogenicity
- Implantation of first-generation drug-eluting stent

*Although implantation of bare-metal stents requires DAPT for 1 month,[1,2] repeated revascularisation procedures due to restenotic lesions might extend the treatment duration.

1 year in event-free patients. The results are in line with those from other studies,[7,8] with majority use of first-generation DES (sirolimus-eluting or paclitaxel-eluting). Further evidence for the value of extended (>1 year) DAPT is to be expected from the ongoing DAPT trial[9] that seeks to enrol more than 20 000 patients with stent implantation. One question not addressed by ARCTIC-Interruption or the DAPT trial, however, is the potential clinical benefit of a reduced rather than an extended DAPT. This issue is of increasing importance because second-generation DES platforms are now routinely used. These stents are characterised by an improved and accelerated endothelial coverage of stent struts, reduced thrombogenicity, and stent thrombosis rates below those of bare-metal stents.[10] With increasing use of second-generation DES, even shorter durations (3–6 months) of DAPT than those tested in ARCTIC-Interruption or the DAPT trial might be feasible. Indeed, evidence is accumulating that a shorter DAPT duration could have the potential to decrease bleeding risk without increasing the risk of stent thrombosis.[11,12] Solid evidence for the value of a shortened DAPT will come from the ongoing ISAR-SAFE trial,[13] which aims to compare 6 months versus 12 months of DAPT.

So, should duration of DAPT be the longer the better? The answer is no on the basis of available evidence,[3,7,8,10–12] and when a DAPT extension beyond 1 year is planned in event-free low-risk patients after DES implantation. With routine use of second-generation DES and increasing use of potent antiplatelet agents including prasugrel and ticagrelor in patients with acute coronary syndrome, in whom bleeding risk is an issue especially during long-term chronic treatment,[14] all efforts should now be undertaken to seek evidence for the feasibility of shorter DAPT durations of 3–6 months. The increasing use of bioresorbable vascular scaffolds will require a separate investigation on the optimum duration of DAPT for this specific platform. In addition to the results of randomised trials, the decision about the best timepoint to stop DAPT after coronary stenting must always consider factors (panel) that affect the individual patient's risk of thrombosis or bleeding.

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Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial

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Summary

Background Optimum duration of dual antiplatelet treatment (DAPT) after coronary stenting remains uncertain, with an unknown efficacy to safety ratio of extended treatment leading to discrepancies between international guidelines and clinical practice. We assessed whether DAPT continuation beyond 1 year after coronary stenting is beneficial.

Methods This analysis was a planned extension of the previously published ARCTIC-Monitoring trial, in which we randomly allocated 2440 patients to a strategy of platelet function testing with antiplatelet treatment adjustment or a conventional strategy after coronary stenting with drug-eluting stent (DES). We recruited patients (aged 18 years or older) scheduled for planned DES implantation at 38 centres in France. After 1 year of follow-up, patients without contraindication to interruption of DAPT were eligible for a second randomisation to this second phase of the study (ARCTIC-Interruption). Using a computer-generated randomisation sequence (1:1; stratified by centre), we allocated patients to a strategy of interruption of DAPT where the thienopyridine was interrupted and single aspirin antiplatelet treatment was maintained (interruption group) or a strategy of DAPT continuation for 6–18 months (continuation group). The primary endpoint was the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularisation, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00827411.

Findings Between Jan 4, 2011, and March 3, 2012, 1259 eligible patients were randomly allocated to treatment in ARCTIC-Interruption: 624 to the interruption group and 635 to the continuation group. After a median follow-up of 17 months (IQR 15–18), the primary endpoint occurred in 27 (4%) patients in the interruption group and 24 (4%) patients in the continuation group (hazard ratio [HR] 1·17 [95% CI 0·68–2·03]; p=0·58). STEEPLE major bleeding events occurred more often in the continuation group (seven [1%] patients) compared with the interruption group (one [<0·5%] patient; HR 0·15 [0·02–1·20]; p=0·073). Major or minor bleedings were also more common in the continuation group compared with the interruption group (12 [2%] patients *vs* three [1%] patients; HR 0·26 [0·07–0·91]; p=0·04).

Interpretation Our finding suggests no apparent benefit but instead harm with extension of DAPT beyond 1 year after stenting with DES when no event has occurred within the first year after stenting. No conclusion can be drawn for high-risk patients who could not be randomised. The consistency between findings from all trials of such interruption suggests the need for a reappraisal of guidelines for DAPT after coronary stenting towards shorter duration of treatment.

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Introduction

The recommended duration of dual antiplatelet treatment (DAPT) for elective coronary implantation of a bare-metal stent is at least 1 month on the basis of observational data.[1] Concerns about a potential increased risk of stent thrombosis with drug-eluting stents (DESs)[2–4] led to extension of DAPT from 2 months to 6–12 months.[5,6] However, new analyses of data from randomised trials[7] and data from studies of the newer generations of DESs have not substantiated any increased risk, but have instead shown a lower risk of stent thrombosis in higher risk clinical situations such as in ST-elevation myocardial infarction.[8–10]

Findings from several randomised studies and large observational registries have challenged the recommendation of 6–12 months of DAPT treatment after implantation of a DES in stable patients, although duration in the control groups of these studies was variable and not always reflecting the 12-month recommendation of DAPT duration after DES implantation.[11–20]

The ARCTIC (Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting)-Interruption trial is the second phase of the previously published ARCTIC-Monitoring study,[21,22] in which we randomly allocated 2440 patients to either platelet function testing with antiplatelet treatment adjustment or conventional antiplatelet treatment after coronary stenting with a DES.

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After 1 year of follow-up, we invited patients without major events and who were treated with clopidogrel or prasugrel in addition to aspirin to enrol in a second randomisation to either interruption of DAPT as recommended by international guidelines or continuation of DAPT for a further 6–18 months.[6,23] All patients participated in the first phase of the ARCTIC study, which served as a screening log book for the second randomisation 1 year later to assess this second hypothesis about DAPT duration.

Methods

Study design and population

ARCTIC was a multicentre, prospective open-label study with parallel trial arms and double randomisation. Between Jan 26, 2009, and Jan 5, 2011, we recruited patients (aged ≥18 years) scheduled for planned DES implantation at 38 centres in France.[21] We excluded patients with primary percutaneous coronary intervention for ST-elevation myocardial infarction, planned use of glycoprotein IIb/IIa inhibitors, chronic anticoagulation treatment, or bleeding diathesis. Results from the first phase (ARCTIC-Monitoring) have been published previously.[22] In the first phase, we randomly allocated eligible patients to either platelet function assessment with adjustment of antiplatelet drugs and doses in patients with inadequate platelet inhibitory response (monitoring group) or treatment without platelet function assessment (conventional group)—we saw no difference between the two groups after 1 year of follow-up.[22]

At the end of this follow-up period, and in the absence of contraindication to interruption of DAPT, patients were re-randomised from Jan 4, 2010, to March 3, 2012, to interrupt or to continue thienopyridine according to the initial signed consent form.

In the interruption group, the thienopyridine (clopidogrel or pradugrel) was interrupted and aspirin was maintained as single antiplatelet treatment. The final clinical assessment was done 6 months after the second randomisation of the last patient. In the continuation group, clopidogrel or prasugrel were maintained until the end of the study, with a minimum additional follow-up of 6 months for the last randomised patient, whereas all preceding patients had an accrual follow-up (last follow-up in Jan 26, 2013). In the continuation group, DAPT was maintained at the same dose regimen as during the first year of follow-up.

Exclusion criteria for the second randomisation were the occurrence of any ischaemic event of the primary

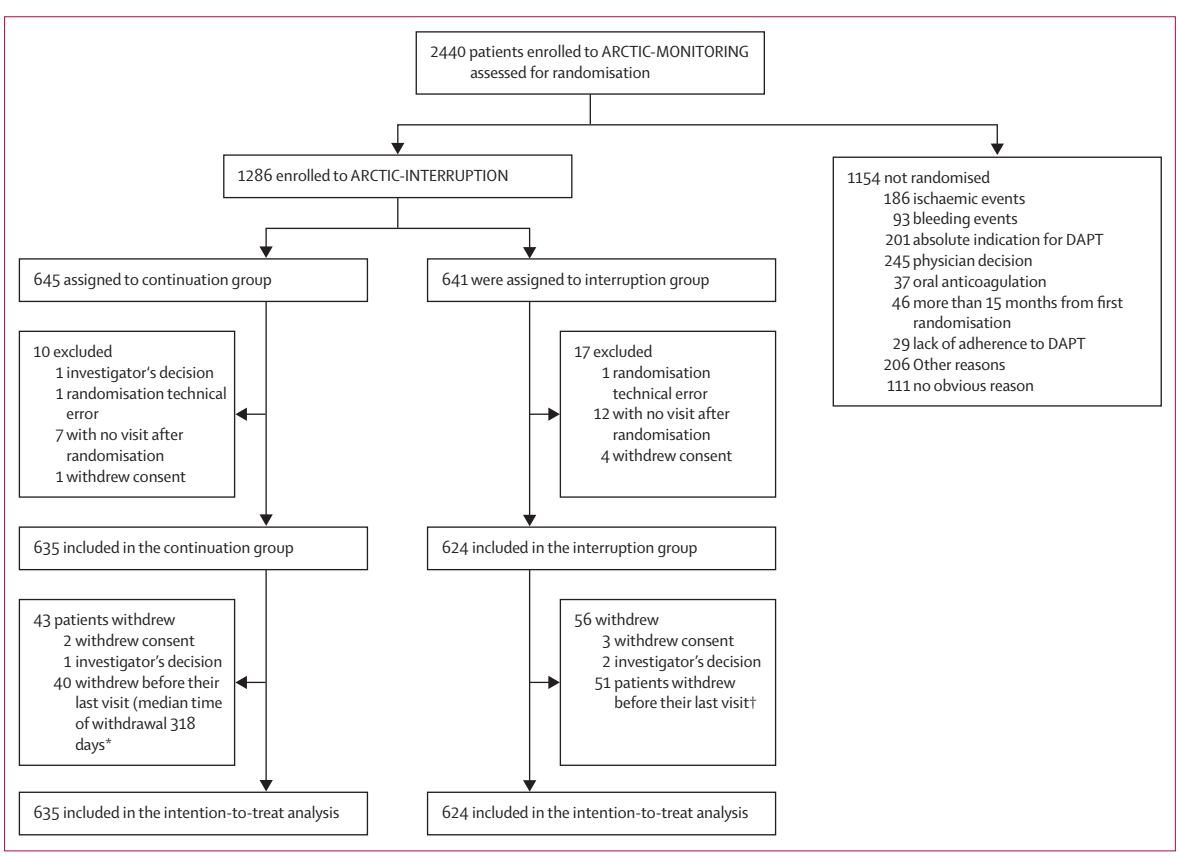

Figure 1: **Trial profile**
*Median time to withdrawal 318 days (IQR 189–392). †Median time to withdrawals 315 days (189–380).

	Continuation (n=635)	Interruption (n=624)
Age in years	64 (57–73)	64 (57–73)
Older than 75 years	117 (18%)	103 (17%)
Women	127 (20%)	121 (19%)
Body weight index (kg/m²)	27 (25–29)	27 (25–30)
Diabetes	198 (31%)	222 (36%)
Dyslipidaemia	428 (67%)	426 (68%)
Hypertension	376 (59%)	388 (62%)
Current smoker	147 (23%)	152 (24%)
High on-treatment platelet reactivity*	100 (19%)	81 (16%)
Prior stroke	28 (4%)	38 (6%)
Prior heart failure	20 (3%)	23 (4%)
Prior myocardial infarction	197 (31%)	186 (30%)
Prior percutaneous coronary intervention	273 (43%)	249 (40%)
Prior coronary artery bypass graft	47 (7%)	35 (6%)
ACE inhibitors	334 (53%)	322 (52%)
β blockers	389 (61%)	364 (58%)
Statin	428 (67%)	416 (67%)
Proton-pump inhibitors	208 (33%)	183 (29%)
Calcium-channel inhibitor	150 (24%)	116 (19%)
Drug-eluting stent implanted	623 (98%)	618 (99%)
First-generation stent†	270 (43%)	250 (40%)
Second-generation stent	392 (62%)	396 (64%)
Stented vessel		
Left main	18 (3%)	23 (4%)
Left anterior descending	342 (54%)	325 (52%)
Circumflex	209 (33%)	181 (29%)
Right coronary artery	191 (30%)	222 (36%)
Coronary artery bypass graft	7 (1%)	6 (1%)

Data are mean (IQR) or n (%). ACE=angiotensin-converting-enzyme. *Platelet reaction unit of 235 or more using the VerifyNow-P2Y$_{12}$ assay. †Paclitaxel and sirolimus drug-eluting stent.

Table 1: **Demographic, clinical, and procedural baseline characteristics**

	Continuation (n=635)	Interruption (n=624)	p value
Treatment at randomisation			
Clopidogrel maintenance dose	569 (90%)	562 (90%)	0·79
Clopidogrel maintenance dose of 75 mg	507 (89%)	482 (86%)	0·039
Clopidogrel maintenance dose of 150 mg	56 (10%)	78 (14%)	0·039
Clopidogrel maintenance dose greater than 150 mg	6 (1%)	2 (<0·5%)	0·039
Prasugrel maintenance dose of 10 mg	54 (9%)	53 (9%)	0·99
Aspirin maintenance dose	628 (99%)	622 (100%)	0·18
Treatment at last follow-up visit			
Clopidogrel maintenance dose	454 (72%)	95 (15%)	<0·0001
Aspirin maintenance dose	597 (94%)	605 (97%)	0·0121
Prasugrel maintenance dose of 10 mg	36 (6%)	14 (2%)	0·0019

Table 2: **Use of antiplatelet drugs during trial**

	Continuation (n=635)	Interruption (n=624)	Hazard ratio (95% CI)	p value
Any death, myocardial infarction, stent thrombosis, stroke or TIA, urgent revascularisation (primary endpoint)	24 (4%)	27 (4%)	1·17 (0·68–2·03)	0·58
Stent thrombosis (revascularised or not) or any urgent revascularsation (main secondary endpoint)	8 (1%)	10 (2%)	1·30 (0·51–3·30)	0·58
Any death, recurrent acute coronary syndrome , stroke or TIA	21 (3%)	24 (4%)	1·19 (0·66–2·13)	0·56
Death or resuscitated cardiac arrest	7 (1%)	9 (1%)	1·32 (0·49–3·55)	0·58
Death or myocardial infarction	14 (2%)	17 (3%)	1·26 (0·62–2·55)	0·52
Any death, myocardial infarction, stent thrombosis (revascularised or not), stroke or TIA, urgent revascularisation, TIMI major bleed (net clinical benefit)	30 (5%)	28 (5%)	0·97 (0·58–1·62)	0·90
Any death	7 (1%)	9 (1%)	1·32 (0·49–3·55)	0·58
Myocardial infarction	9 (1%)	9 (1%)	1·04 (0·41–2·62)	0·94
Stent thrombosis*	0 (0%)	3 (1%)		
Acute coronary syndrome	11 (2%)	13 (2%)	1·23 (0·55–2·74)	0·62
Stroke or TIA	6 (1%)	4 (1%)	0·69 (0·19–2·44)	0·57
Urgent revascularisation	8 (1%)	9 (1%)	1·17 (0·45–3·04)	0·74
Safety endpoints				
STEEPLE major bleed	7 (1%)	1 (<0·5%)	0·15 (0·02–1·20)	0·07
STEEPLE minor bleed	5 (1%)	2 (<0·5%)	0·41 (0·08–2·13)	0·29
STEEPLE major or minor bleed	12 (2%)	3 (1%)	0·26 (0·07–0·91)	0·04

Data are n (%) unless otherwise stated. *All three stent thromboses were definite . TIA=transient ischaemic attack. TIMI=thrombolysis in myocardial infarction.

Table 3: **Study endpoints during follow-up**

endpoint or any event of the primary safety endpoint during the first year of follow-up after the randomisation in the first phase of the study, any new revascularisation needing DAPT extension, any contraindication to aspirin continuation such as bleeding gastrointestinal ulcer, or aspirin resistance. Physician's choice not to randomise after 1 year was another exclusion criterion and was recorded in the case report form. We also recorded patients' last platelet function test (VerifyNowP2Y$_{12}$ assay, Accumetrics, CA, USA) done on the maintenance dose of thienopyridine as a baseline characteristic.

Randomisation and masking

The randomisation list was generated by an independent statistician according to the procedures of the Direction de la Recherche et du Développement de l'Assistance Publique des Hôpitaux de Paris with SAS software (version 9.2) and was stratified by centre. Group allocation was done using an interactive voice response system with a 1:1 ratio.

Outcomes

The main study objective was to show the superiority of continuation of DAPT beyond 1 year over a strategy of stopping thienopyridine. The primary endpoint was a composite of all-cause death, myocardial infarction, stroke or transient ischaemic attack, urgent coronary revascularisation, and stent thrombosis, the same endpoint as for the first phase of the study analysed by intention to treat. All definitions are described elsewhere.[21,22] The main secondary efficacy endpoint was the composite of stent

thrombosis (whether revascularised or not) and urgent revascularisation. We also analysed all the other protocol-specified study endpoints. The main safety endpoint was defined as major bleeding using the percutaneous coronary intervention-specific STEEPLE definitions.[24] All events were adjudicated by an independent clinical events committee (Pitié-Salpêtrière University Hospital, Institut de Cardiologie, Paris, France) unaware of treatment assignments. We assessed all interactions between high platelet reactivity during treatment with thienopyridine, defined as 235 or more platelet reaction units and treatment group for all pre-specified endpoints.

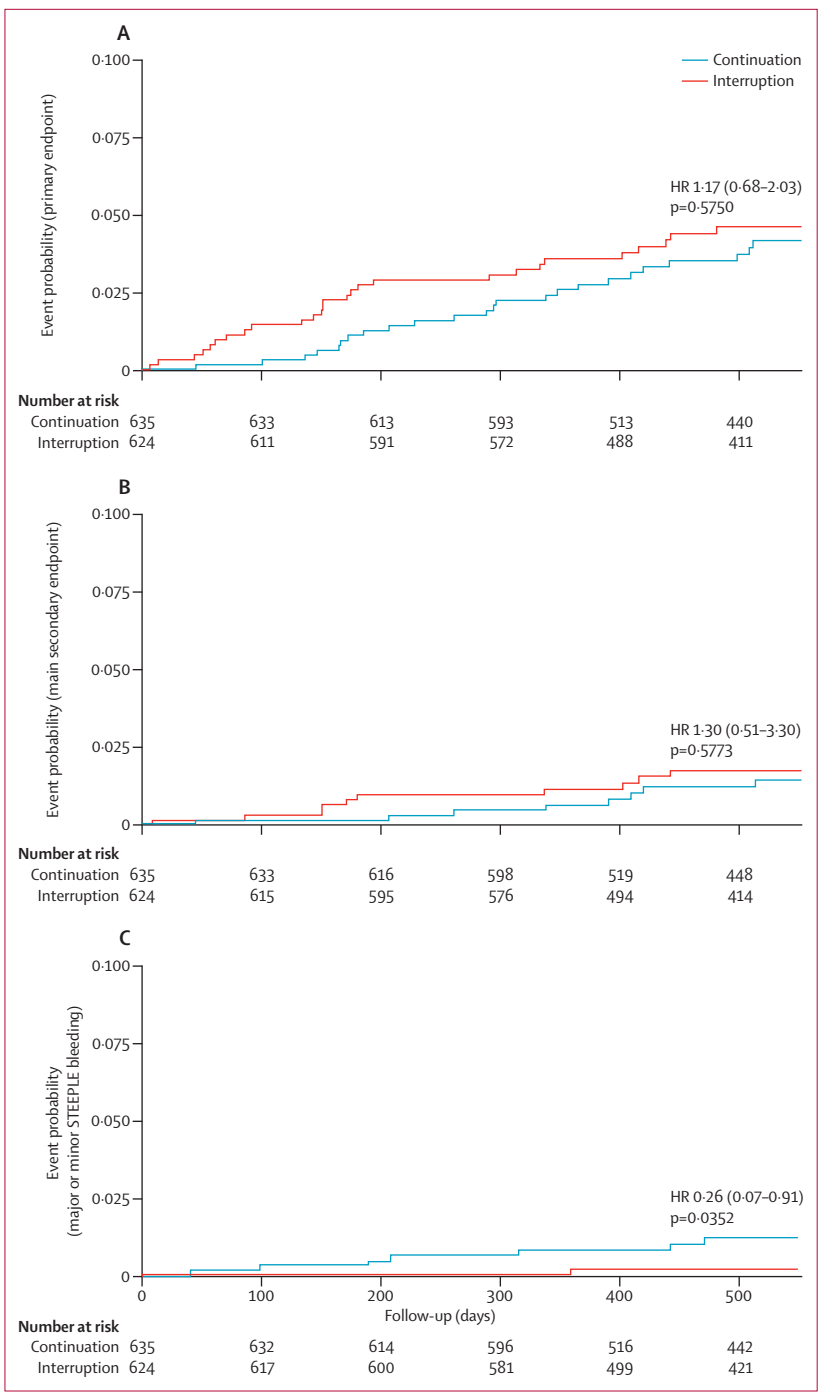

Figure 2: **Kaplan-Meier curves for the primary (A) and main secondary (B) endpoints and main safety endpoints (C)**

(A) The primary endpoint was death, myocardial infarction, stent thrombosis, stroke, or urgent revascularisation. (B) The main secondary endpoint was stent thrombosis or any urgent revascularisation. (C) The main safety endpoint was major and minor STEEPLE bleedings.

Statistical analysis

We hypothesised that the ischaemic event rate would be 6% within the first 6 months of interruption of DAPT. We calculated that we would need a sample size of 1492 patients to allow an 80% power to detect a 50% relative risk reduction by a 5% two-sided survival test based on a Cox model. The analysis was based on all events that occurred in the intention-to-treat population, defined as all randomly allocated patients who signed an informed consent form. In case of patients withdrawing consent during the study, only their data collected before the day of withdrawal were included in the database. We analysed the endpoints using a Cox model for survival analysis. We also tested outcomes for their association with high on-treatment platelet reactivity by linear regression using a codominant model after adjusting for clinical characteristics associated with high platelet reactivity at an α-level of <0·05. All patients were censored at the date of last available information. We summarised non-Gaussian variables as median (IQR) and compared them with the Mann-Whitney test. We used the χ^2 test for frequency comparisons. All subgroups presented were pre-specified. All tests were made at a two-sided 5% significance level. We also did on-treatment analyses by taking treatment exposition as a time-dependent covariate to assess the effect of patients who crossed over. We used SAS (version 9.2) for all statistical analyses.

The study protocol was registered at ClinicalTrials.gov, number NCT00827411.

Role of the funding source

The trial and the statistical analyses were done by the non-for-profit academic research organisation ACTION (Allies in Cardiovascular Trials, Initiatives and Organized Networks), based at Pitié-Salpêtrière Hospital). Research grants were obtained from Fondation de France, Sanofi-Aventis, Cordis, Medtronic, Boston Scientific, Fondation SGAM which had no involvement in the conduct of the study. GM and J-PC had full access to data and full responsibility for the decision to submit for publication.

Results

Of the 2440 patients originally enrolled in the ARCTIC-TRIAL, 1259 were enrolled into the ARCTIC-Interruption study, of whom 624 were assigned to the interruption group and 635 were assigned to the continuation group (figure 1). The baseline risk of the non-randomised study population (n=1181) differed

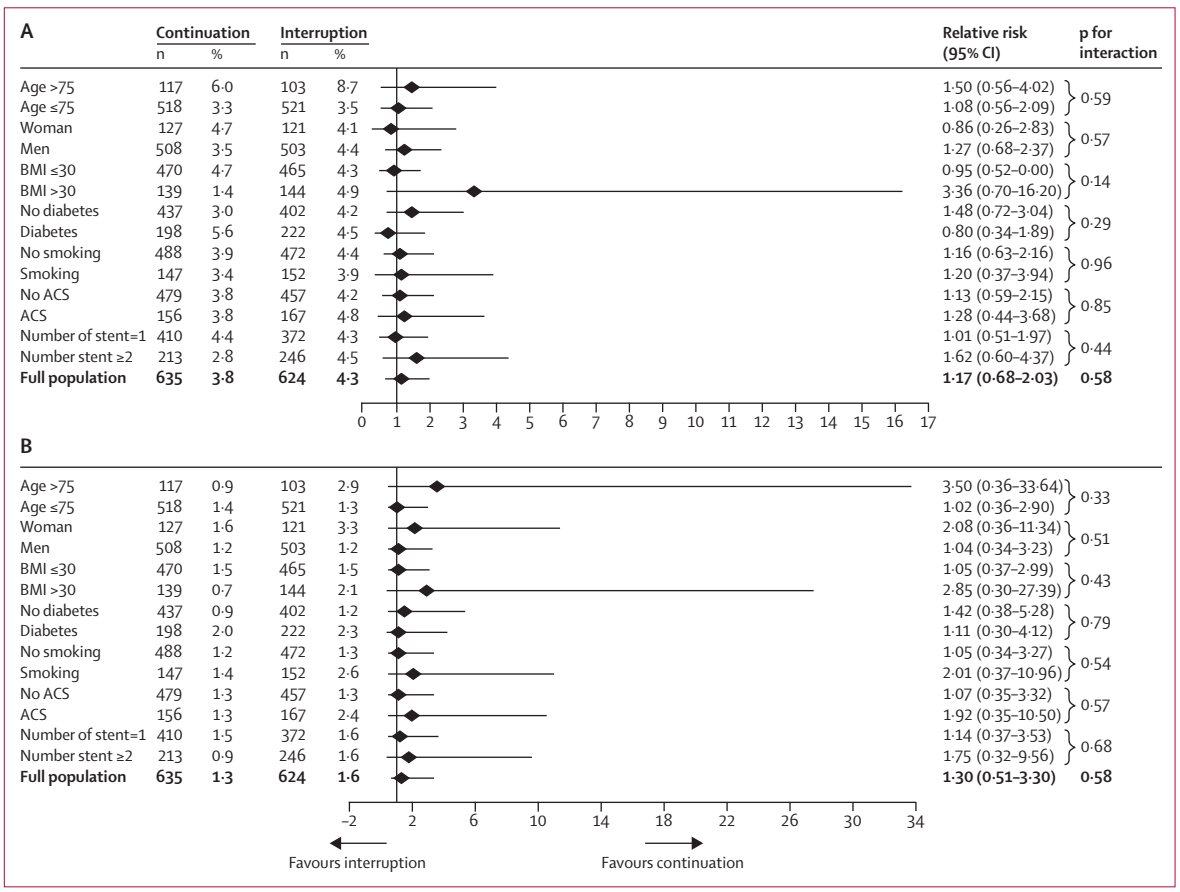

Figure 3: **Occurrence of primary (A) and secondary (B) endpoints in prespecified subgroups**
ACS=acute coronary stenting. BMI=body-mass index.

from the ARCTIC-Interruption population with a higher proportion of diabetes (469 [40%] of 1181 patients *vs* 420 [33%] of 1259 patients; p=0·0011), peripheral artery disease (167 [14%] patients *vs* 124 [10%] patients; p=0·0011; appendix), and higher platelet reactivity to adenosine diphosphate measured on thienopyridine maintenance treatment before interruption (158 [SD 92] *vs* 145 [88]; p=0·014). The main reasons for non-randomisation were physician's decision (n=671 [57%]), time from first randomisation greater than 15 months (n=253 [21%]), occurrence of major cardiovascular events or an absolute indication of extended DAPT (eg, new revascularisation; n=201 [17%]), lack of treatment adherence (n=29 [2%]), and the need for chronic oral anticoagulation (n=27 [2%]), baseline characteristics are reported in table 1). Use of antiplatelet treatment at the time of re-randomisation was well balanced between study groups except for clopidogrel 150 mg (table 2). Roughly 10% of patients were on prasugrel maintenance treatment and roughly 10% were on 150 mg clopidogrel maintenance treatment, with both treatments necessary because of previous treatment adjustment in patients initially randomly allocated to platelet function testing in the first phase of the study.

During the follow-up period, adherence to the assigned DAPT treatment progressively decreased in the continuation group while in the interruption group some patients had to be restarted on DAPT (table 2). Nevertheless, there was still a large difference between the two groups (table 2).

See Online for appendix

During the follow-up period of 17 months (IQR 15–18), 16 (1%) patients died, 18 (1%) had an acute myocardial infarction, 17 (1%) had an urgent revascularisation, three (1%) had a definite or probable stent thrombosis, and ten (1%) had a stroke. At the end of follow-up, we saw no between-group difference in the primary endpoint (table 3, figure 2). This finding was consistent for all the secondary endpoints (table 3, figure 2). We also saw no between-group differences across any subgroups for both the primary and main secondary endpoints (figure 3). High platelet reactivity to ADP during thienopyridine treatment prior to randomisation was associated with a higher mortality rate at the end of follow-up than that in patients without high platelet reactivity (six [3%] of 181 patients *vs* one (1%) of 181 patients; hazard ratio 5·07 [95% CI 1·63–15·76]; p=0·005). However, we detected no interaction between platelet reactivity to ADP and interruption or continuation of thienopyridine for

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the primary study endpoint (p=0·78; appendix) or for any other secondary ischaemic endpoint.

Overall, there were 15 bleeding events according to the STEEPLE definitions, of which eight were major and seven were minor (table 3). There was no statistically significant between-group difference in major bleeds (hazard ratio with interruption 0·15 [95% CI 0·02–1·20]; table 3). Analysis of both major and minor bleeds combined showed bleeding to be less frequent in the interruption group (0·26 [95% CI 0·07–0·91]; figure 2, table 3). No patient had a TIMI major bleed or a fatal bleed. We saw no interaction between platelet reactivity to ADP measured before randomisation and treatment group for safety outcomes (appendix). Sensitivity analyses taking into account the timing and the number of crossover patients showed similar results as the intention-to-treat analysis (appendix).

Discussion

Findings from ARCTIC-Interruption show no benefit with DAPT continuation beyond 1 year after coronary stenting, rather a harm of continued DAPT, with patients in the continuations group having more major or minor bleeding. They also show that 1 year after stenting, only half of patients are eligible for randomisation to thienopyridine interruption or continuation leading to the selection of a low risk population, and that strict adherence to the open-label treatment assignment of both single and dual antiplatelet treatment beyond 1 year after stenting was not possible in a quarter of patients, a rate that is consistent with observations in clinical practice.[25]

Eight characteristics of the study suggest that our findings are applicable to the general population of patients. First, before being regarded as eligible for interruption, patients underwent a first screening for the ARCTIC study and needed to be in stable condition and a candidate for coronary stenting with a DES.[22] Second, the patients were exposed to DAPT for 1 year after DES implantation, a duration recommended by clinical guidelines.[6,26] Third, only half the ARCTIC population was eligible for the second phase assessing thienopyridine interruption, a finding that is consistent with results of other studies—eg, in the prospective observational PARIS registry,[25] physicians discontinued DAPT 1 year after stenting in only 41% of patients. Fourth, by contrast with previous studies,[18–20] we randomly allocated patients for DAPT interruption not at the time of stenting but 1 year later, which better follows clinical practice. Subsequently, we restricted enrolment to patients who remained event-free 1 year after the index percutaneous coronary intervention and higher risk patients were likely to be excluded. Fifth, the global follow-up of our patients could be extended up to 30 months, a duration longer than what is usually seen in interventional studies. Sixth, event rates in ARCTIC-Interruption were within the ranges expected from registries, outlining that the study is relevant to real-world practice.[25] Seventh, the results of the ARCTIC-Interruption study were consistent irrespective of the timing and the number of crossover patients. Finally, the absence of benefit of extended DAPT reported in ARCTIC-Interruption lends support to findings from the randomised CHARISMA trial which was done in stable, at-risk patients who were medically managed (panel).[27]

Measurement of platelet reactivity was another unique aspect of the ARCTIC-Interruption trial. Although platelet reactivity was shown to be a risk marker in the first phase of the ARCTIC study, antiplatelet treatment adjustment in patients with persistent high on-treatment platelet reactivity did not improve outcome.[22] Whether platelet reactivity should be measured in specific situations is under debate.[30–32] In the ARCTIC-Interruption study, platelet reactivity to ADP was measured on $P2Y_{12}$ inhibitor maintenance dose and was regarded as a baseline characteristic. The finding that non-randomised patients had higher platelet reactivity substantiates the fact that platelet reactivity is a marker of the global vascular risk of patients. That platelet reactivity did not differ between the continuation and the interruption

Panel: Research in context

Systematic review

To further assess the effect of treatment duration on clinical outcome, we searched PubMed and the Cochrane databases from Jan 1, 2002, to Sept 1, 2013, using the following search terms: "dual antiplatelet therapy", "aspirin", "clopidogrel", "stent(s)", "drug-eluting stent(s)", "PCI" (percutaneous coronary intervention), and "randomized trial". We did not include studies with $P2Y_{12}$ inhibitors other than thienopyridine and included studies with a minimum follow-up of 3 months from randomisation. On the basis of this review we identified no clear effect of the duration of interruption. Indeed, there was one trial[16] with a 1-year minimum duration of DAPT. We did a meta-analysis of all randomised studies that assessed interruption of dual antiplatelet treatment (DAPT) after coronary stenting with drug-eluting stents (DESs). We included six randomised studies including the ARCTIC-Interruption study with a total of 12 536 enrolled patients, of whom 6252 were assigned to short DAPT duration defined as a minimum of 3 months.[16–20] Events were independently adjudicated in all studies and randomisation took place at the time of index PCI,[18–20] or 1 month[17] or 1 year later.[16] All cause death and major bleeding were the primary objectives of this meta-analysis. The endpoint definitions were those of each individual study. Two investigators (JPC and JS) independently assessed reports for eligibility on review of the title or the abstract (appendix). The study was done in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (appendix) and the protocol is available on request.

Interpretation

When pooling all the evidence, at a median follow-up of 17 months, continuation of DAPT did not reduce reduced all-cause mortality (figure 4), major adverse cardiac events (1·05 [95% CI 0·87–1·25]; p=0·62), or the net clinical benefit (1·07 [0·89–1·27]; p=0·48). None of the individual ischaemic endpoints was reduced by continuation of DAPT, including stent thrombosis (0·86 [0·53–1·39]; p=0·41), stroke (1·43 [0·93–2·21]; p=0·10), and myocardial infarction (1·03 [0·79–1·34]; p=0·84). Major bleeding was increased by two times (figure 4). These findings were consistent irrespective of the DAPT duration in the interruption group. Additionally, we saw no statistically significant heterogeneity and the sample size of this meta-analysis is in the range of the large ongoing trials assessing the effect of DAPT interruption (NCT00661206, NCT00977938).[28,29]

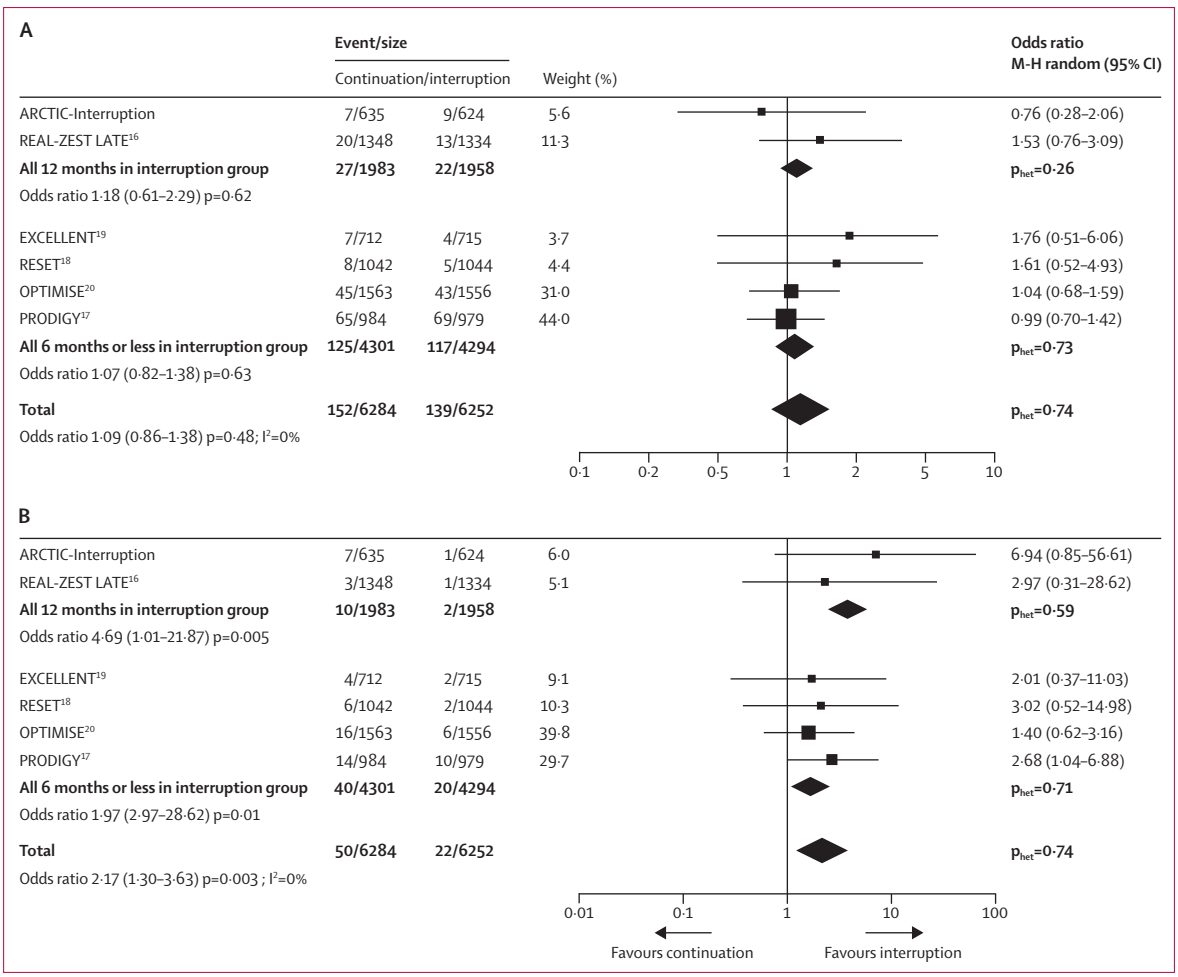

Figure 4: **Outcomes according to continuation or interruption of dual antiplatelet treatment after percutaneous coronary interventions**
Data are for death (A) or major bleeding (B). Analyses were dichotomised according to the minimum duration of dual antiplatelet treatment in the control group. M-H Random=Mantel-Haenszel Random. p_{het}=p for heterogeneity.

groups suggests that not only antiplatelet treatment but also response to treatment were well balanced in the two groups after randomisation in ARCTIC-Interruption. In this randomised population, we saw a strong relation between baseline platelet reactivity to ADP and survival, substantiating once more the prognostic value of this marker. However, the absence of statistically significant interaction between interruption and platelet reactivity on clinical outcomes validates further the main results of the first phase of the ARCTIC study. The results of ARCTIC-Monitoring and ARCTIC-Interruption emphasise that platelet reactivity is of restricted value to guide decisions of augmentation or interruption of antiplatelet treatment.

We acknowledge that the ARCTIC-Interruption trial enrolled a sample size smaller than anticipated, used power assumptions based on data from the era of first-generation of DESs, and did not enrol patients at very high thrombotic burden. These limitations further draw attention to the need for confirmatory data from ongoing larger studies with longer follow-up, stronger pharmacological intervention, and higher-risk patients (NCT00977938, NCT01225562).[33,34] Additionally, the absence of interaction between interruption and platelet reactivity on clinical outcomes should be viewed as merely hypothesis-generating.

The randomised ARCTIC-Interruption study and the meta-analysis suggest no apparent benefit, but instead harm, with extension of DAPT beyond 1 year after stenting with DES when no event has occurred within the first year of treatment.

Contributors

GM, J-PC, and EV designed the study and analysed and interpreted the data. GC, TC, SE, GR, J-PC, GM participated to the steering committee, contributed to implementation of the study, enrolment, and follow-up of patients, and revised the manuscript. HR and EV did all statistical analyses. GM and J-PC wrote the first draft and submitted the final version for publication. TC, GR, GC, SE, PH, DC, LB, EV, PA, JM, PS, SAO'C, JA, MK, CS-E, OB, FB, and JS participated to the study, commented on the manuscript, and approved the final version. All authors have seen the version of the Article and agree with the content and conclusions.

Declaration of interests

J-PC reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Medtronic, Boston Scientific, Cordis, Stago, Fondation de France, INSERM, Nanospheres, Fédération Française de Cardiologie and Société Française de Cardiologie; consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca. TC reports receiving a research grant from Eli Lilly; consulting fees from Daiichi Sankyo and Eli Lilly; support for travel to meetings from Eli Lilly Daiichi Sankyo; lecture fees from AstraZeneca, Eli Lilly, Sanofi, Abbott Vascular, Biotronik, Boston Scientific, Cordis, Edwards, Iroko Cardio, Medtronic, Servier; travel and meetings expenses from Abbott Vascular, AstraZeneca, Biotronik, Boston Scientific, Cordis, Daiichi Sankyo, Edwards, Eli Lilly, Iroko Cardio, Medtronic, and Servier. GC reports receiving a research grant from la Fédération Française de Cardiologie; consultant fees from Abbott Vascular, AstraZeneca, CLS, Behring, Daiichi Sankyo, and Eli Lilly; and lecture fees from Abbott Vascular, AstraZeneca, Biotronik, CLS Behring, Daiichi Sankyo, Eli Lilly, and Iroko Cardio. CP reports receiving research support and consulting fees from Sanofi-Aventis and The Medicines Company. PM has received consultancy fees from St Jude Medical and Terumo. PS reports receiving fees for board membership from Bristol-Myers Squibb; consulting fees from Daiichi Sankyo and Eli Lilly; and lecture fees from Merck Sharp and Dohme and Sanofi. SAO'C reports receiving grants from A Menarini and the European Society of Cardiology. JA reports receiving a grant from Fonds d'Etudes et de Recherche du Corps Médical (FERCM). MK reports receiving a grant from Fédération Française de Cardiologie. FB reports receiving grants from Pfizer, Brahms, and Fédération Française de Cardiologie; and lecture fees from Roche, Sanofi-Aventis, Pfizer, and Astellas. JS reports receiving research grants from Sanofi-Aventis, Daiichi-Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consulting fees from Daiichi-Sankyo and Eli Lilly; and speakers' honoraria from AstraZeneca, Daiichi Sankyo, Eli Lilly, and Servier. EV reports receiving research grants from Sanofi-Aventis, Medtronic, Cordis, Boston Scientific, Fondation SGAM, Fondation de France, ACTION and APHP; consulting fees from Pfizer, Eli Lilly, Sanofi, LFB, Abbott, Frensenius; grant from Boehringer-Ingelheim; and lecture fees from Merck and Pfizer. GM reports receiving grant support from Abbott Vascular, Boston Scientific, Cordis, Eli Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, ITC Edison, Medtronic, Pfizer, Sanofi-Aventis, Société Française de Cardiologie, and Stago; consulting or board fees and lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiovascular Research Foundation, Cleveland Clinic Research Foundation, Daiichi-Sankyo, Duke Institute, Eli Lilly, Europa, Lead-up, GlaxoSmithKline, Institut de Cardiologie de Montréal, Menarini, Nanospheres, Novartis, Pfizer, Portola, Sanofi-Aventis, The Medicines Company, and the TIMI study group.

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