Non-cardiac surgery in patients with coronary stents: the RECO study

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Accepted 15 June 2011
Published Online First 26 July 2011

ABSTRACT

Context Interruption or maintenance of oral antiplatelet therapy (OAT) during an invasive procedure may result in ischaemic and/or haemorrhagic complications. There is currently a lack of clear guidance regarding the issue of treatment interruption during surgical procedures.

Objective To evaluate the rate of major adverse cardiac and cerebrovascular events (MACCEs) and major or minor bleeding complications and their associated independent correlates in coronary stented patients undergoing urgent or planned non-cardiac surgery.

Design, setting, and patients Prospective, multicentre, observational cohort study of 1134 consecutive patients with coronary stents.

Main outcome measures The co-primary endpoints consisted of the incidence of MACCE and major bleeding within the first 30 days of an invasive procedure.

Results MACCE and haemorrhagic complications were observed in 124 (10.9%) and 108 (9.5%) patients, respectively, within an average time delay from invasive procedure to event of 3.3±3.9 and 5.3±5.3 days. Independent preoperative correlates for MACCE were complete OAT interruption for more than 5 days prior to surgery, preoperative haemoglobin <10 g/dl, creatinine clearance of <30 ml/min and emergency or high-risk surgery. Independent factors for haemorrhagic complications were preoperative haemoglobin <10 g/dl, creatinine clearance between 30 and 60 ml/min, a delay from stent implantation to surgery <3 months and high-risk surgery according to the Lee classification.

Conclusions Patients with coronary stents undergoing an invasive procedure are at high risk of perioperative myocardial infarction including stent thrombosis irrespective of the stent type and major bleeding. Interruption of OAT more than 5 days prior to an invasive procedure is a key player for MACCE.

Clinical Trial Registration NCT01045850.

INTRODUCTION

Although there are clear risks associated with a complete interruption of oral antiplatelet therapy (OAT) in patients with coronary stents, a careful assessment of the relative risks of ischaemic and bleeding events is necessary to determine whether continuation or withdrawal is most appropriate to perform safely invasive or surgical procedures.[1–4] A decision regarding treatment interruption may be complicated by the existence of risk factors that are associated with both ischaemic and bleeding events, but because many of these shared risk factors are exclusion criteria in clinical trials, it may not be possible to make an evidence-based decision in some patients.[5] A multidisciplinary approach may be indicated in these complex cases, allowing careful risk stratification.[6]

There is currently a lack of clear guidance regarding the issue of treatment interruption during surgical procedures and of dual antiplatelet therapy discontinuation per se.[7 8] This is particularly so in the setting of drug-eluting stents (DES), for which it has been shown that management of OAT interruption in patients with intracoronary stents requiring invasive procedures that are potentially haemorrhagic depends mostly on the physician involved and type of practice rather than on a carefully weighted assessment of ischaemic/bleeding risk.[9] Stent implantation remains a sensitive situation, given the established catastrophic outcome of stent thrombosis (ST) following an invasive procedure[1 2 10 11] and the critical role of OAT interruption whatever the stent type (bare metal (BMS) or DES).[12]

Current guidelines suggest that OAT should be interrupted from 5 to 7 days prior to non-cardiac surgery and resumed within 2 days with loading doses, unless the procedure carries a low haemorrhagic risk and can be performed under OAT.[5 13] However, there is no evidence to suggest that such strategies are effective in preventing bleeding or cardiovascular events.

This present investigation aimed to evaluate the rate and preoperative risk factors of major cardiovascular events and major bleeding in a cohort of patients with coronary stents undergoing non-cardiac surgery.

METHODS

Study design

This multicentre, prospective, observational study was conducted from April 2007 to April 2009 in 47 centres in France. Participating centres prospectively enrolled consecutive patients with coronary stents who underwent elective or urgent non-cardiac surgery or another invasive procedure. Invasive procedure was defined as all non-cardiac surgeries including diagnostic endoscopy and all procedures requiring anaesthesia.

Each site had a designated individual who entered raw data into an electronic case report form, allowing immediate and continuous monitoring of its completeness and accuracy (ClinInfo S.A., Lyon, France). The Institutional Review Board (IRB) (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale: Lyon B,

reference: QH03/2006) approved the study. Oral consent was obtained from patients. Written informed consent of the patients to participate was not necessary according to the French law regarding observational study.

Patient characteristics

The type (DES or BMS) and number of coronary stents and the delay from stent placement to invasive procedure were recorded. The procedural related risk was classified according to Lee *et al*.[14] High-risk surgery was defined as suprainguinal vascular, thoracic or intraperitoneal surgery.

Patients with missing baseline haemoglobin and creatinine values were considered as normal given that these parameters are not mandatory prior to an invasive procedure in routine practice.

Perioperative management of OAT

A detailed description of perioperative management of OAT was obtained for both aspirin and clopidogrel, that is, delay from interruption to invasive procedure and from invasive procedure to reintroduction and, finally, use of bridging therapies. Complete interruption of OAT was defined as a discontinuation of all antiplatelet drugs. In patients treated with clopidogrel alone, clopidogrel was replaced with aspirin. These patients were considered as being treated without interruption.

Clinical outcome definitions

The primary outcome measure was any major adverse cardiac and cerebrovascular event (MACCE) or haemorrhagic complication from preoperative visit to 30 days following surgery. The secondary outcome was death (from any cause) within 30 days.

Any postoperative myocardial infarction (MI), ST, stroke, heart failure, significant arrhythmia or cardiogenic shock was considered as MACCE. MI was defined according to European Society of Cardiology (ESC) / American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) / World Heart Federation (WHF) Task Force[15] as follows: detection of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following: new symptoms of ischaemia, electrocardiographic changes indicative of new ischaemia or development of new pathological Q waves in the electrocardiogram; sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation or new left bundle branch block, or evidence of fresh thrombus on coronary angiography or autopsy. Stent thromboses were either definite, probable or possible according to the Academic Research Consortium definitions.[16]

Haemorrhagic complications were defined according to the International Society of Thrombosis and Haemostasis.[17] Major bleeding included fatal bleeding, clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 g/l compared with the preoperative level (when available), clinically overt bleeding leading to the transfusion of two or more units of whole blood or packed cells, critical bleeding (intracerebral, intraocular, intraspinal, pericardial or retroperitoneal), bleeding warranting treatment cessation and bleeding at the surgical site leading to further surgery or medical procedures (eg, haematoma drainage or aspiration at the surgical site, transfer to intensive care unit). In other circumstances, bleeding was considered minor. Minor bleeding included abnormal bleeding as assessed by the surgeon or the physician performing the procedure.

Statistical analysis

Descriptive results were expressed as frequency and percentage for categorical variables and were compared using the χ^2 test (or Fisher exact test for small samples). For continuous variables, statistics were expressed as mean±SD and were analysed using a t test. We performed multivariate logistic regression to estimate the adjusted ORs and the corresponding 95% CIs associated with each risk factor for cardiovascular and haemorrhagic complications. For each multivariate logistic regression, patients without complications served as the reference category. The fit model contained all variables with $p<0.20$ at univariate analysis, and we used a descendant method to finally have a model with only statistically significant variables ($p<0.05$). The Lee score and the American Society of Anaesthesiologists (ASA) physical status classification were not included in the multivariate analysis, since each component was specifically tested. Statistical analyses were performed using the Stata software (V.10.0; Stata Corp.).

RESULTS

Baseline characteristics and invasive procedures

Forty-seven centres recruited 1134 patients. The delay from preoperative visit to surgery was 10±11 days. Preoperative baseline characteristics are summarised in table 1.

The majority of patients had BMS only (54.9%), and 32.4% had DES (±BMS). Stent type was not available in 12.7% of patients. The average number of stents per patient was 1.8±1.2. Patients with only BMS were older (69.5±10.4 vs 66.6±10.5 years, $p<0.001$), were less frequently diabetic (22% vs 33%, $p<0.001$) and had a lower number of stents per patient (1.6±0.9 vs 2.3±1.4, $p<0.001$). They were less frequently treated with dual OAT (22.3% vs 53.7%, $p<0.001$) and underwent fewer invasive procedures during the first year after stent placement (14.6% vs 24.6%, $p<0.001$) compared to patients with DES. No significant differences were observed with regard to preoperative OAT management (interruption or bridging) and surgery (high-risk and emergency procedures) with respect to stent type.

Figure 1 illustrates the type of surgery and the average time delay from stent implantation to invasive procedure. Urgent procedures represented 9.6% of all procedures. High-risk surgery represented 26.4% of all invasive procedures.

Perioperative OAT management

At the preoperative visit, 5.6% of the patients were not treated with any OAT, while other patients were treated with aspirin alone (39.6%), clopidogrel alone (21.7%) or dual therapy (33.1%). A complete interruption of OAT was observed in 28.9% of patients treated with aspirin alone and in 15.7% of patients treated with dual OAT. In patients treated with clopidogrel alone, 36.2% were bridged with aspirin, and 34.1% interrupted all OAT.

In case of a complete interruption of OAT, a bridge by low molecular weight heparin (LMWH) or flurbiprofen was done in 34.6%, 37% and 28.7% in patients treated with aspirin alone, clopidogrel alone and dual OAT, respectively.

Major adverse cardiac and cerebrovascular events

MACCEs occurred in 124 patients (10.9%) and were mostly MI (table 2). There was no event detected prior to invasive procedure, and delay from surgery to any event was short (3.3±3.9 days). The all-cause death rate in patients with MACCE was 14.5% (95% CI 8.8 to 22.0). The delay between stenting and surgery was not identified as a significant risk factor for MACCE.

Table 1 Univariate analysis of preoperative clinical and demographic characteristics associated with cardiac and haemorrhagic complications

	All patients n=1134	MACCE n=124	p	Bleeding complications n=108	p
Age (years)	68.4±10.5	70.7±9.9	0.009	68.9±11.1	0.593
Sex (% men)	80.3	78.2	0.549	78.7	0.672
Weight (kg)	78.4±14.6	77.3±16.9	0.372	75.7±14.1	0.040
Height (cm)	170±7.7	170±8.2	0.961	169±7.9	0.187
Hypertension (%)	62.1	62.1	0.997	65.7	0.410
Diabetes (%)	25.7	22.6	0.627	25.0	0.927
Stroke (%)	8.3	12.1	0.103	7.4	0.727
PVD (%)	81.0	79.8	0.738	75.0	0.098
Previous MI (%)	52.7	56.5	0.368	52.8	0.977
Congestive heart disease (%)	8.4	19.4	<0.001	16.7	0.001
Creatinine clearance (%)					
<30 ml/min	3.9	13.7	<0.001	10.2	<0.001
30–60 ml/min	18.4	24.2		32.4	
>60 ml/min	46.4	57.3		45.4	
Unknown	31.3	4.8		12.0	
Haemoglobin (g/dl)					
<10	3.3	9.7	<0.001	9.3	<0.001
10–12	10.5	16.1		21.3	
>12	46.5	37.1		49.1	
Unknown	39.4	37.1		20.4	
Coronary stents					
Number	1.8±1.2	2.0±0.12	0.130	1.8±0.1	0.933
Type (%)					
DES (±BMS)	32.4	29.0	0.184	34.3	0.222
BMS (only)	54.9	62.1		58.3	
Unknown*	12.7	8.9		7.4	
Treatment (%)					
β-Blockers	73.3	67.7	0.140	76.9	0.378
Statins	84.7	81.5	0.280	87.0	0.486
ACEI or ARB	43.7	41.1	0.549	46.3	0.560
NSAIDs	2.3	1.6	0.588	1.9	0.754
VKA	6.9	9.7	0.192	5.6	0.568
Nitrates	21.0	27.6	0.054	24.1	0.402
Antiplatelet agents (%)					
None	5.6	8.9	0.091	3.7	0.148
Aspirin alone	39.6	38.9		33.3	
Clopidogrel alone	21.7	17.7		20.4	
Dual therapy	33.1	38.5		42.6	
Preoperative management of OAT					
No interruption (%)	72.5	69.0	0.015	75.7	0.485
Total interruption ≤5 days (%)	13.5	8.9		9.7	
Total interruption >5 days (%)	14	22.1		14.6	
Delay between PCI and surgery (months)					
0–3	6.0	9.8	0.133	19.2	<0.001
4–6	5.2	7.7		5.8	
7–12	6.7	4.9		6.7	
>12	82.2	77.9		68.3	
Surgery					
Urgent	9.6	26.6	<0.001	19.4	<0.001
High risk	26.4	53.2	<0.001	56.5	<0.001
Lee score (%)					
II	65.9	58.8	0.119	58.3	0.023
III	27.3	30.7		28.7	
IV	6.9	10.5		13	
ASA classification (%)					
2	26.2	21.1	<0.001	20.6	0.175
3	69.2	67.5		72.0	
4–5	4.7	11.4		7.5	

*At the time of preoperative evaluation.
ACEI, ACE inhibitors; ARB, angiotensin receptor antagonists; BMS, bare metal stent; DES, drug-eluting stent; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; OAT, oral antiplatelet therapy; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; VKA, vitamin K antagonist.

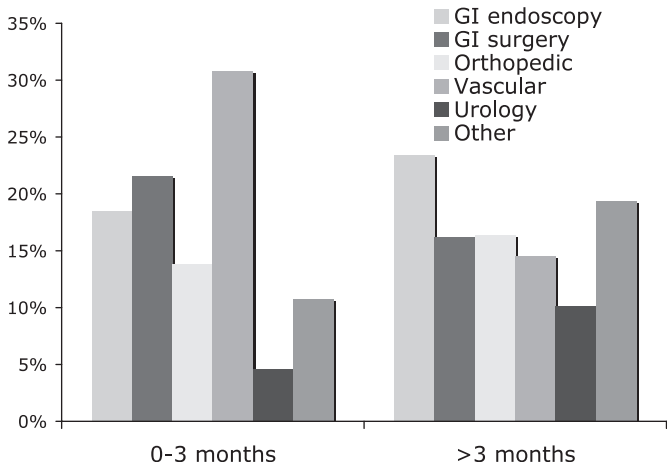

Figure 1 Distribution and type of surgery or invasive procedure according to the delay between stenting and surgery.

After multivariable analysis, independent correlates for MACCE were complete OAT interruption for more than 5 days, preoperative haemoglobin <10 g/dl, creatinine clearance <30 ml/min and high-risk and urgent invasive procedures (table 3).

As shown in figure 2, in patients with DES or BMS only, particularly in high-risk surgery, MACCEs were more frequent in patients in whom OATs were completely interrupted.

Stent thrombosis

Overall, 17 cases of ST were observed (1.5%, 95% CI 0.79 to 2.21) including 10 definite ST, 3 probable ST and 4 possible ST. Preoperative factors associated with ST were congestive heart failure (29.5% vs 8.1% in patients with no ST, p=0.01) and ASA score (p<0.001). When surgery was performed within the first 12 months after stent insertion, the ST rate was 2.5% and 1.3% (p=0.47) for procedures performed after the 12-month period. The rate of ST did not differ significantly with respect to the type of stent. Death occurred in five (29.4%) patients with ST.

Bleeding complications

Major and minor haemorrhagic complications were observed in 108 (9.5%) patients with an average delay from surgery to bleeding of 5.3±5.3 days (table 2). Most bleedings were at the surgical site (85.2%) and were associated with repeat surgery in 18.5% of patients. The death rate in patients with bleeding complications was 12.0% (95% CI 6.6 to 19.7). The independent preoperative risk factors for major and minor haemorrhagic complications were preoperative haemoglobin <10 g/dl, preoperative creatinine clearance between 30 and 60 ml/min, a short time delay from stent implantation to surgery (<3 months) and high-risk surgery. Of note, complete OAT interruption was not identified as an independent correlate for major bleeding.

DISCUSSION

This prospective observational study found that postoperative MACCE occurred in 10.9% of patients with coronary stents who underwent non-cardiac surgery or other invasive procedure. These complications were associated with five preoperative risk factors: preoperative anaemia, severe renal failure, urgent surgery, high-risk surgery and the interruption of antiplatelet treatment for more than 5 days preoperatively. The type of stent

Table 2 Complications

	All patients (n=1134)	MACCE (n=124)	Bleeding complications (n=108)
Cardiovascular complications, n (%)			
Stroke	–	1 (0.8)	–
Pulmonary oedema		20 (16.1)	
Cardiogenic shock		14 (11.3)	
Significant arrhythmia		16 (12.9)	
Acute limb ischaemia		2 (1.6)	
Myocardial infarction		71 (57.2)	
ST		17 (13.7)	
Definite		10	
Probable		3	
Possible		4	
Time to ST (days)		2 (0–8)	
Death (associated with ST)		5 (29.4)	
Bleeding complications, n (%)			
Site			
Surgical	–	–	92 (85.2)
Gastrointestinal			7
Retroperitoneal			1
Other			3
Repeat surgery to treat bleeding			20 (18.5)
Transfusion, n (%)	143 (12.6)	33 (26.6)	84 (77.8)
Erythrocytes		33 (26.6)	84 (100)
Plasma		5 (4)	9 (8.3)
Platelets		5 (4)	9 (8.3)
Major bleeding complications			92 (85.2)
Timing of complication			
After procedure (%)	–	100	84
Time after surgery (days)		3.3±3.9	5.3±5.3
Death rate, n (%) (95% CI)	25 (2.2) (1.4 to 3.2)	18 (14.5) (8.8 to 22.0)	13 (12) (6.6 to 19.7)

MACCE, major adverse cardiac and cerebrovascular events; ST, stent thrombosis.

Table 3 Independent preoperative risk factors for cardiovascular and haemorrhagic complications

	MACCE		Bleeding complications	
	OR (95% CI)	p	OR (95% CI)	p
Complete OAT interruption				
No interruption	Reference		Reference	
≤5 days	0.67 (0.32 to 1.37)	0.272	0.72 (0.35 to 1.47)	0.366
>5 days	2.11 (1.23 to 3.63)	0.007	0.93 (0.48 to 1.79)	0.826
Preoperative haemoglobin				
>12 g/dl (or missing)	Reference		Reference	
10–12 g/dl	1.13 (0.62 to 2.08)	0.691	1.37 (0.75 to 2.48)	0.308
<10 g/dl	3.00 (1.23 to 7.29)	0.016	2.61 (1.04 to 6.55)	0.041
Creatinine clearance				
>60 ml/min (or missing)	Reference		Reference	
30–60 ml/min	1.32 (0.79 to 2.21)	0.287	1.96 (1.19 to 3.24)	0.008
<30 ml/min	3.51 (1.54 to 8.04)	0.003	1.96 (0.76 to 5.03)	0.162
Time between PCI and surgery				
0–3 months	0.97 (0.45 to 2.07)	0.938	2.91 (1.53 to 5.52)	0.001
4–6 months	1.11 (0.48 to 2.58)	0.803	0.96 (0.38 to 2.44)	0.928
7–12 months	0.70 (0.28 to 1.73)	0.437	1.07 (0.46 to 2.52)	0.874
More than 12 months	Reference		Reference	
Urgent surgery	3.08 (1.74 to 5.47)	<0.001	1.77 (0.94 to 3.31)	0.075
High-risk surgery	3.59 (2.34 to 5.51)	<0.001	3.31 (2.11 to 5.18)	<0.001

MACCE, major adverse cardiac and cerebrovascular events; OAT, oral antiplatelet therapy.

was not identified as a risk factor. Bleeding events occurred in 9.5% of the procedures and were associated with four preoperative risk factors: moderate renal failure, a short delay between stenting and surgery, preoperative anaemia and high-risk surgery.

Patients with coronary stents are at high risk of postoperative cardiovascular complications.[1 2 18 19] However, the majority of these cardiac events are not related to ST. This study shows that a complete interruption of OAT before surgery independently predicts subsequent cardiovascular complications in patients with coronary stents. Moreover, as illustrated in figure 2, the longer the interruption, the higher the rate of cardiovascular events.

The relationship between interruption of OAT and adverse outcomes has been identified in several other situations. In a cohort of patients admitted for acute coronary syndrome, Collet *et al* described a subset of 5.4% of patients whose acute coronary syndrome was associated with an interruption in aspirin treatment.[20] The main hypothesis explaining this relationship between OAT interruption and cardiac events is that of a rebound platelet aggregation[21] associated with a prothrombotic state due to extensive surgery.[22] There is an established association between discontinuation of clopidogrel and a transient increase in platelet reactivity, although the precise mechanism is not known.[23] This transiently enhanced platelet aggregation may account for the known clustering of thrombotic events observed after clopidogrel discontinuation and is probably magnified by the simultaneous interruption of aspirin.[23] The potential role of the perioperative activation of haemostasis as a determinant of ST is unclear. Activation of haemostasis is associated with persistent high on-treatment platelet reactivity,[24] a well-known risk factor for ST.

As shown in previous studies, preoperative anaemia was also identified as an independent predictor of cardiovascular complications.[25] Anaemia may, however, also be a global marker of other medical conditions that confer an increased risk. The reasons for the increased morbidity with anaemia are multifactorial and complex. Anaemia per se is associated with an increased risk of adverse outcomes in patients with acute coronary syndrome (ACS) or undergoing coronary revascularization.[26–28] In addition, pre-existing anaemia is usually associated with a higher severity of illness such as older age and renal insufficiency, may also exacerbate the consequences of subsequent bleeding and certainly increases the probability of transfusion. The potential mechanisms for the detrimental effects of transfusions are also numerous,[29] including platelet activation and aggregation, impaired oxygen and nitric oxide delivery capabilities.[30] Finally, antiplatelet therapy such as aspirin and clopidogrel is frequently stopped in such context, and cardioprotective medications such as β-blockers may be also held.

A similar rate of ST was observed for both DES and BMS. This can be explained by the large difference in the characteristics of the two subgroups. Since DES patients were considered as higher risk at the preoperative assessment, they were more frequently treated with dual therapy, and antiplatelet agent was not stopped in 69.3% of cases (vs 62.3% for BMS patients). In the BMS group, there was a larger number of patients without OAT treatment (6.7% vs 2.7% in DES patients), and patients were more frequently treated with aspirin alone. Finally, there were no controls on the type of and indication for surgery.

Coronary artery disease patients, in particular, patients treated with antiplatelet agents, have a high risk of bleeding. However, further parameters may complicate these patients' care: increasing age, renal insufficiency and concomitant treatment with anticoagulants. These comorbidities and treatments are known to increase both the risk of thrombosis and the risk of haemorrhage. More attention is now given to the subsequent increase in the risk of thrombosis (causing STEMI or non-STEMI) in the bleeding patient.[28]

However, the risk of haemorrhage could be considered differently as far as aspirin or clopidogrel is concerned. Except for a limited number of neurosurgical procedures, stopping aspirin before surgery is no longer an issue. Even if bleeding does somehow increase, the transfusion rate is generally unchanged, and the consequences of bleeding are minor.

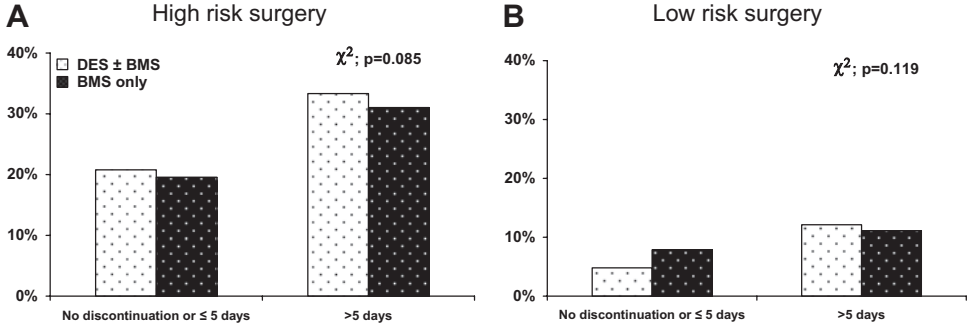

Figure 2 MACCE according to preoperative interruption in antiplatelet therapy in DES (±BMS) and BMS (only) stented patients in high- and low-risk surgery.

Conversely, very few reports describe the risk of haemorrhage during non-cardiac surgery in clopidogrel-treated patients. While some patients in the pivotal CAPRIE trial underwent emergency surgery, the data are not retrievable.[31] A unique direct comparison was performed by our group 17 years ago in pigs, before clopidogrel was marketed. Clopidogrel was responsible for a much more prolonged ear immersion bleeding time than aspirin.[32]

The limitations of this study are those inherent to any observational study: the necessary absence of a control group. Furthermore, some patients did not have a preoperative blood analysis as is often the case before minor surgery. Indeed, the riskiest situation is OAT interruption in patients scheduled with no blood evaluation for minor surgery, that is, ambulatory surgery. Patient characteristics and outcomes may be biased, and OAT management prior to surgery was not standardised. The duration of interruption was also not predefined. Surgical procedures with the highest risk of bleeding may have longer OAT withdrawal times. Time between stent implantation and surgery was not significantly associated to MACCE. The present study was started after the French guidelines on perioperative management of antiplatelet agents in patients with coronary stents were issued.[13] Physicians participating in this study were largely informed on the risk of MACCE and, particularly, ST if all OATs were eventually stopped. In contrast, this attitude may explain the high bleeding rate observed in our study when there was a short delay (less than 3 months) between the stent implantation and the surgery.

CONCLUSIONS

Patients with coronary stents undergoing non-cardiac surgery are exposed to a high risk of cardiovascular and haemorrhagic complications. These complications are associated with a high death rate. In this study, we identified several specific and common preoperative predictors of these complications. Maintaining OAT throughout surgical and invasive procedures is the key to avoiding cardiovascular complications without increasing haemorrhagic risk. If interrupting OAT treatment is absolutely essential (which is rare), a delay between interruption and surgery of <5 days is strongly advised for patients treated with aspirin, clopidogrel or both.

Author footnote:
RECO study participants: O Loutrel (Nantes); S Jaber, M Delay (Montpellier); S Pinchou (Maubeuge); C Blery (Cavaillon); M Spenle (Mulhouse); E Prévost (Rouen); E Samain (Besançon); D Gontier (Hyères); V Piriou, JP Vellard (Lyon-Sud); T Coste, R Leroy (Clermont-Ferrand); P Leroy, R Laplace (Lyon); H Dupont (Amiens); H Charbonneau (Créteil); G Scotto (Berck sur Mer); C Ceddaha (Paris); E Marret (Paris); H Le Hetet (Cesson Sevigne); G Milhem (Angers); A Desroy (Mantes la Jolie); JM Dombey (Marseille); P Bruchet (Avignon); J Bruna, P Balmette (Trélazé); JP Gayard (Voiron); D Blayac (Marseille); E Marcadella (Saint Dizier); JM Guerineau (Villeneuve sur Lot); D Merlin (Redon); G Massardier (St Etienne); M Levy (La Roche Sur Yon); MF Smati (Chalons en Champagne); T François (St Herblain); V Minville (Toulouse); JP Fontes (Castres) ; G Lohmann (Paris); E Gaertner (Nice); E Belaich (La Seyne sur Mer); P Marchesan (Perpignan); P Lavaud (Marseille); A Cherfa (Dracy le Fort); M Gentili (St Gregoire); L Habib (Aix en Provence); H Bouaziz (Nancy).

Acknowledgements We thank Carole Rolland for her help with data management and Alison Foote for editing the manuscript (Clinical Research Center, Grenoble, France).

Funding This study was supported by the French College of Anaesthesia and Intensive Care (Collége Français d'Anesthésie Réanimation) and by an unrestricted grant from Sanofi-Aventis. The funding source did not influence the study design, collection, analysis or interpretation of data; the writing of the report; nor the decision to submit this paper for publication.

Competing interests Drs Albaladejo, Bosson, Samama and Marret received honoraria from Sanofi-Aventis.

Ethics approval This study was conducted with the approval of the IRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale: Lyon B, reference: QH03/2006).

Contributors PA, EM, CMS and VP developed the study protocol. All authors except for JLB and SR participated in the study as clinical investigators. PA, JLB and SR performed all the statistical analyses. PA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

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Heart 2011 97: 1566-1572 originally published online July 26, 2011
doi: 10.1136/hrt.2011.224519