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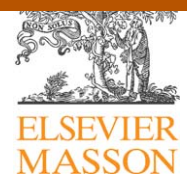

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CLINICAL RESEARCH

A prospective observational study of treatment practice patterns in acute coronary syndrome patients undergoing percutaneous coronary intervention in Europe

Une étude observationnelle prospective sur les schémas de prise en charge thérapeutique des patients avec un syndrome coronarien aigu traités par angioplastie coronarienne percutanée en Europe

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KEYWORDS
Acute coronary syndrome;

Summary
Background. — The AntiPlatelet Therapy Observational Registry (APTOR) was a prospective observational study of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) in France, Spain, and the UK.

Abbreviations: ACC, American College of Cardiology; ACE, Angiotensin-converting enzyme inhibitor; ACS, Acute coronary syndrome; AFSSAPS, *Agence française de sécurité sanitaire des produits de santé*; AHA, American Heart Association; APTOR, AntiPlatelet Therapy Observational Registry; ARB, Angiotensin 2 receptor blocker; BMI, Body mass index; BMS, Bare metal stent; CABG, Coronary artery bypass grafting; CHD, Coronary heart disease; CI, Confidence interval; CRO, Contract research organisation; DES, Drug eluting stent; ESC, European Society of Cardiology; GPI IIb/IIIa, Glycoprotein IIb/IIIa inhibitor; IQR, Interquartile range; MI, Myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction; OR, Odds ratio; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; T, Time; UA, Unstable angina; UK, United Kingdom.

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Percutaneous coronary intervention;
Stents;
Antiplatelet therapy;
Aspirin;
Clopidogrel

Aims. — To evaluate patterns of ACS healthcare use, focusing on APTOR results from France.
Methods. — Consecutive presenting ACS patients requiring PCI were recruited between January and August 2007. Treatments and outcomes were recorded from the qualifying ACS event to 12 months follow-up.
Results. — In France, qualifying diagnosis was unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) in 255 (53%) patients and ST-segment elevation myocardial infarction (STEMI) in 228 (47%) patients. Ninety-six percent underwent PCI with stent implantation. Drug eluting stents were used less frequently in France (22%) than Spain (54%) or the UK (42%). In France, antiplatelets were more frequently received in the ambulance (21%); a 200—299 mg aspirin-loading dose was most frequently received (50%) and more than a third of patients received a clopidogrel-loading dose of over 300 mg (34%). At 12 months in France, 86% were still receiving aspirin, 75% clopidogrel, and 73% combination treatment.
Conclusion. — There was considerable country-variation in ACS management. These results provide a benchmark of physician practice to compare with guidelines.

MOTS-CLÉS
Syndrome coronarien aigu ;
Angioplastie coronarienne percutanée ;
Stents ;
Anti-agrégants plaquettaires ;
Aspirine ;
Clopidogrel

Résumé
Contexte. — AntiPlatelet Therapy Observational Registry (APTOR) était une étude observationnelle prospective des patients avec un syndrome coronarien aigu (SCA) traités par angioplastie coronarienne percutanée (ICP) en France, Espagne et Angleterre.
Objectifs. — Évaluer les tendances d'utilisation de soins pour les SCA, plus précisément les résultats d'APTOR en France.
Méthodes. — Les patients consécutifs se présentant avec un SCA nécessitant une ICP ont été inclus entre janvier et août 2007. Les traitements et les événements cliniques ont été collectés entre le SCA initial et le suivi à 12 mois.
Résultats. — En France, le diagnostic initial était un angor instable/infarctus du myocarde sans sus-décalage du segment ST (UA/NSTEMI) pour 255 (53 %) patients et un infarctus du myocarde avec sus-décalage du segment ST (STEMI) pour 228 (47 %) patients. Quatre-vingt seize pour cent ont eu une ICP avec implantation de stent. Les stents actifs étaient moins souvent utilisés en France (22 %) qu'en Espagne (54 %) ou qu'en Angleterre (42 %). En France, les traitements antiplaquettaires étaient plus souvent prescrits dans l'ambulance (21 %) ; la dose de charge d'aspirine 200-299 mg était la plus souvent prescrite (50 %) et plus d'un tiers des patients ont reçu une dose de charge de clopidogrel supérieure à 300 mg (34 %). À 12 mois en France, 86 % des patients prenaient toujours l'aspirine, 75 % le clopidogrel et 73 % l'association des deux.
Conclusion. — D'importantes disparités existaient entre les pays pour la prise en charge des SCA. Ces résultats permettent d'illustrer les pratiques des médecins et de les comparer aux recommandations.

Background

ACS is an umbrella term for a set of pathophysiological cardiovascular signs and symptoms and is a leading cause of morbidity and mortality in Western Europe responsible for considerable healthcare costs [1]. ACS symptoms can be seen as a continuum ranging from UA to NSTEMI to STEMI. Treatment of ACS typically begins in the acute phase and includes interventional therapy with PCI or CABG as well as antithrombotic treatment. The oral antiplatelets aspirin and clopidogrel are considered the baseline standard of care.

The ACC/AHA and ESC guidelines recommend early diagnostic cardiac catheterisation and PCI within 2 hours for STEMI patients and 72 hours for NSTEMI patients, together with dual antiplatelet therapy for at least 12 months [2—6]. Despite the availability of guideline recommendations, variation in ACS management and PCI practice patterns are evident between countries. Although a number of studies on ACS management have been published, specific details on European patient management strategies, particularly beyond hospital discharge, are lacking.

The APTOR was a 12-month, prospective, observational study of ACS patients undergoing PCI between January and August 2007 in three European countries: France, Spain, and the UK. The main purpose of APTOR was to provide 'real world' information on country-specific patterns of healthcare use in ACS patients, to provide a benchmark for comparison with current guidelines and therefore ultimately direct future patient care. The researchers were also interested in exploring variations between countries. The purpose of this current manuscript is to evaluate treatment practice patterns in ACS patients undergoing PCI, focusing on APTOR study results from France.

Methods

Ethical conduct of the study

The study was carried out in accordance with guidelines for Good Clinical Practice and Good Pharmacoepidemiology Practices. The study was approved wherever required by law by an independent ethics committee. All patients gave written consent to release information.

Study design

Full details of the APTOR methods and population are reported elsewhere [7]. Briefly, APTOR was a 12-month, non-interventional, prospective, observational, cohort study that enrolled patients presenting with ACS and requiring PCI between January and August 2007 at 122 sites in France (71 sites), Spain (22 sites), and the UK (29 sites). Data were collected about country-specific patterns of healthcare use in ACS patient management at teaching and non-teaching centres. In France, in order to get a broad representation of ACS patients, all interventional cardiologists from all coronary angioplasty units (approximately 1000) were solicited by mail to participate and were asked to enrol on an average of 10 consecutive presenting patients with no more than 30 patients per site. In the other countries, fewer sites were solicited and were asked to enrol more patients. Following enrolment, patient care and treatment strategies were at the discretion of the physician.

Study population

Patients were required to be at least 18 years of age with a diagnosis of ACS requiring PCI with either initiation or continuation of any antiplatelet therapy. Patients who were simultaneously participating in another study including an investigational drug or procedure were excluded from this study. Once the study was initiated at a site, all consecutive presenting ACS patients who were undergoing PCI with associated antiplatelet therapy were invited to join the study.

Outcome measures

The study design is shown in Fig. 1. Demographic characteristics, medical history, qualifying ACS diagnosis (UA, NSTEMI, or STEMI), clinical characteristics, medical treatments and procedures, and clinical outcomes were recorded for each patient using an electronic web-based data collection system at hospital admission (baseline), time of PCI, hospital discharge, and at follow-up at 3 months after hospital discharge and 12 months after PCI. In-hospital measures were collected by review of hospital records by trained nurses and physicians. Postdischarge data were collected by primary care physicians.

Statistical methods

The data were evaluated by standard exploratory and descriptive summary statistics: median, IQR, frequency, and percentage. *P* values, ORs, and 95% CIs are reported for comparisons between France and the two combined countries, Spain and the UK; these are taken from logistic regression models which adjusted the country difference by potential confounders (the models included age, type of qualifying ACS, weight, sex, and past medical history). Logistic regression models were run to compare country differences on use of drug eluting stents, time from ACS to PCI in STEMI and UA/NSTEMI patients, clopidogrel loading dose administered in the ambulance, clopidogrel use before ACS event, statin use before ACS event, and dual antiplatelet use at 12 months. Analyses were done using SAS version 9.1.

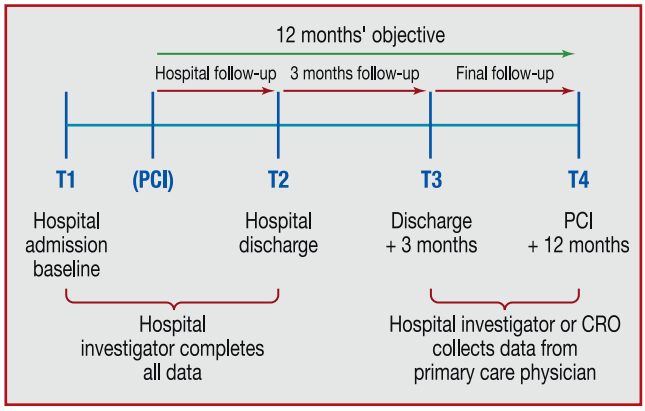

Figure 1. Study design. CRO: contract research organisation; PCI: percutaneous coronary intervention; T: time.

Results

Patients studied

One thousand five hundred and sixty-three ACS patients were enrolled into the full APTOR study; of these, 1525 patients (98%) were eligible for analysis. In France, 497 patients were enrolled by 59 interventional cardiologists from public university hospitals (36%), public non-university hospitals (45%), and private hospitals (19%). 483 patients (97%) were eligible for analysis. Of the 14 patients (3%) not eligible for analysis, the reasons for exclusion were: patient did not have an ACS diagnosis ($n = 11$), patient did not present within the normal course of care for PCI ($n = 9$), and patient did not provide consent to release information ($n = 3$); note: patients could have more than one reason for exclusion.

Demographic and baseline characteristics by qualifying ACS event and country are summarised in Table 1. The French cohort had a median age of 59 years compared with 62 years for both Spain and the UK. The French cohort also had the lowest number of female patients and rates of previous vascular events and procedures, MI, and stroke.

Among French patients, the qualifying ACS diagnosis was UA in 85 patients (18%), NSTEMI in 170 patients (35%), and STEMI in 228 patients (47%). A STEMI diagnosis was more common in France than in Spain or the UK, and in the overall APTOR population (38%). On average, STEMI patients had the lowest age and rate of cardiovascular risk factors including diabetes and previous MI compared with NSTEMI patients in France.

Table 1 Demographic and baseline characteristics.

	Qualifying ACS event	France		Other countries	
	UA/NSTEMI ($n = 255$)	STEMI ($n = 228$)	Total ($n = 483$)	Spain ($n = 538$)	UK ($n = 504$)
Qualifying ACS event, *n* (%)					
UA/NSTEMI	—	—	255 (52.8)	361 (67.1)	327 (64.9)
STEMI	—	—	228 (47.2)	177 (32.9)	177 (35.1)
Age, years					
Median (IQR)	61 (54, 72)	58 (50, 69)	59 (52, 71)	62 (53, 72)	62 (53, 70)
≥ 75 years, *n* (%)	51 (20.0)	36 (15.8)	87 (18.0)	99 (18.4)	70 (13.9)
Sex, *n* (%)					
Male	215 (84.3)	182 (79.8)	397 (82.2)	420 (78.1)	371 (73.6)
Female	40 (15.7)	46 (20.2)	86 (17.8)	118 (21.9)	133 (26.4)
Median (IQR) height, cm	—	—	170 (165, 176)	167 (160, 172)	170 (164, 178)
Median (IQR) weight, kg	—	—	79 (70, 90)	78 (70, 85)	81 (71, 92)
Median (IQR) BMI	27.0 (24.2, 29.7)	26.9 (24.6, 29.7)	27.0 (24.5, 29.7)	27.9 (25.7, 30.8)	27.7 (24.8, 30.7)
Previous diagnosis of vascular event, *n* (%)	—	—	123 (25.5)	236 (43.9)	197 (39.1)
Undergone previous vascular procedures, *n* (%)	—	—	83 (17.2)	113 (21.0)	98 (19.4)
Medical history, *n* (%)					
Diabetes	50 (19.6)	28 (12.3)	78 (16.1)	165 (30.7)	62 (12.3)
Previous MI	38 (14.9)	18 (7.9)	56 (11.6)	148 (27.5)	129 (25.6)
Previous stroke	4 (1.6)	3 (1.3)	7 (1.5)	13 (2.4)	13 (2.6)

ACS: acute coronary syndromes; BMI: body mass index; IQR: interquartile range; NSTEMI: non-ST-segment elevation myocardial infarction; MI: myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina; UK: United Kingdom.

Table 2 Revascularisation and stent use, and timing of PCI relative to ACS event.

	France ($n=483$)	Spain ($n=538$)	UK ($n=504$)
PCI procedure, *n* (%)	481 (99.6)	533 (99.1)	489 (97.0)
With stent, n (%)	462 (95.7)	521 (96.8)	428 (84.9)
BMS	305 (63.1)	143 (26.6)	187 (37.1)
DES	104 (21.5)	290 (53.9)	209 (41.5)
BMS + DES	48 (9.9)	85 (15.8)	27 (5.4)
> 1 stent	165 (35.7)	245 (47.0)	179 (41.8)
Days from ACS event to PCI			
All patients, median (IQR)	1 (0, 2)	1 (0, 4)	4 (1, 8)
STEMI < 1 day, *n* (%)	136 (60.7)[a]	98 (57.7)	65 (39.2)
UA/NSTEMI ≤ 3 days, *n* (%)	202 (81.1)[b]	214 (64.9)	91 (31.6)

ACS: acute coronary syndromes; BMS: bare metal stent; DES: drug eluting stent; IQR: interquartile range; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina; UK: United Kingdom.

[a] France versus Spain and the UK: odds ratio 2.180; 95% confidence interval 1.462, 3.249; $p=0.0001$.

[b] France versus Spain and the UK: odds ratio 5.043; 95% confidence interval 3.515, 7.237; $p<0.0001$.

Revascularisation and stent use

In the APTOR study overall, 1504 patients (99%) underwent PCI and 1411 patients (93%) underwent stent implantation.

Revascularisation and stent use by country is shown in Table 2. In France, 96% of patients received stents compared with 85% in the UK and 97% in Spain. The use of DES was considerably lower in France (22%) than in Spain (54%) or the UK (42%; France versus Spain and the UK: OR 0.28; 95% CI 0.22, 0.37; $p<0.0001$). In France, and in the APTOR study overall, more than one stent was used in approximately one third of patients. Stent use was the same in UA/NSTEMI and STEMI patients in France (96%), but slightly higher in STEMI patients in APTOR overall (UA/NSTEMI: 91%; STEMI: 95%).

The number of STEMI patients who received their PCI on the same day as their qualifying ACS event was higher in France (60%) than in Spain (57%) and the UK (39%; France versus Spain and the UK: OR 2.18; 95% CI 1.46, 3.25; $p=0.0001$; Table 2). The number of UA/NSTEMI patients who received their PCI within 3 days of their qualifying ACS event date was also higher in France (81%) than in Spain (63%) and the UK (31%; France versus Spain and the UK: OR 5.04; 95% CI 3.52, 7.24; $p<0.0001$; Table 2).

Among STEMI patients, the median time from hospital admission to PCI was the day of admission in France (IQR 0, 1) and Spain (IQR 0, 2) compared with 1 day after admission (IQR 0, 4) in the UK. Among UA/NSTEMI patients, the median time from hospital admission to PCI was 1 day (IQR 1, 2) in France compared with 2 days (IQR 0, 4) in Spain and 5 days (IQR 2, 9) in the UK.

Admission and discharge cardiovascular medications

Cardiovascular medications administered before the qualifying ACS event and at hospital discharge are presented for France, Spain, and the UK in Fig. 2. Patients in France reported the lowest use of medications before the ACS event compared with Spain and the UK. Of particular note is the large difference in statin use between the countries (France 27%, Spain 39%, UK 45%; France versus Spain and the UK: OR 0.52; 95% CI 0.39, 0.70; $p<0.0001$). There was no difference in clopidogrel use before the ACS event between France and Spain and the UK (OR 0.76; 95% CI 0.54, 1.06; $p=0.1056$). Discharge medication rates were similar between the three countries.

Antiplatelet therapy and patterns of use

For most patients in France antiplatelet therapy was initiated with aspirin (91%) and clopidogrel (95%). Some patients also received tirofiban (18%), abciximab (16%), bivalirudin (3%), and eptifibatide (3%). Antiplatelet use was generally similar in the other countries; however, there were clear variations in location of administration, timing of administration, and dose. At hospital discharge, 92% of patients across all countries were prescribed dual antiplatelet therapy (aspirin and clopidogrel).

In France, patients were treated quickly with both aspirin and clopidogrel. Aspirin loading and maintenance doses at hospital discharge are shown in Table 3. Most patients received their aspirin-loading dose in the ambulance (26%), the intensive care unit (25%), or the emergency room (24%). Aspirin was more likely to be given in the ambulance in STEMI (39%) rather than UA/NSTEMI (15%) patients. Compared with France, the rates for receiving aspirin in the ambulance were lower in Spain (6%) but slightly higher in the UK (32%). 83% of patients in France ($n=355$) received aspirin before PCI (Table 3). Patients in France most frequently received a 200—299 mg loading dose of aspirin (50%) and a ≤ 100 mg maintenance dose (57%; Table 3). Patients in France were more likely to receive a high aspirin discharge maintenance dose (≥ 150 mg) compared with Spain and the UK; this was mainly accounted for by doses of 160 mg (UA/NSTEMI: 39%; STEMI: 30%) with only one STEMI

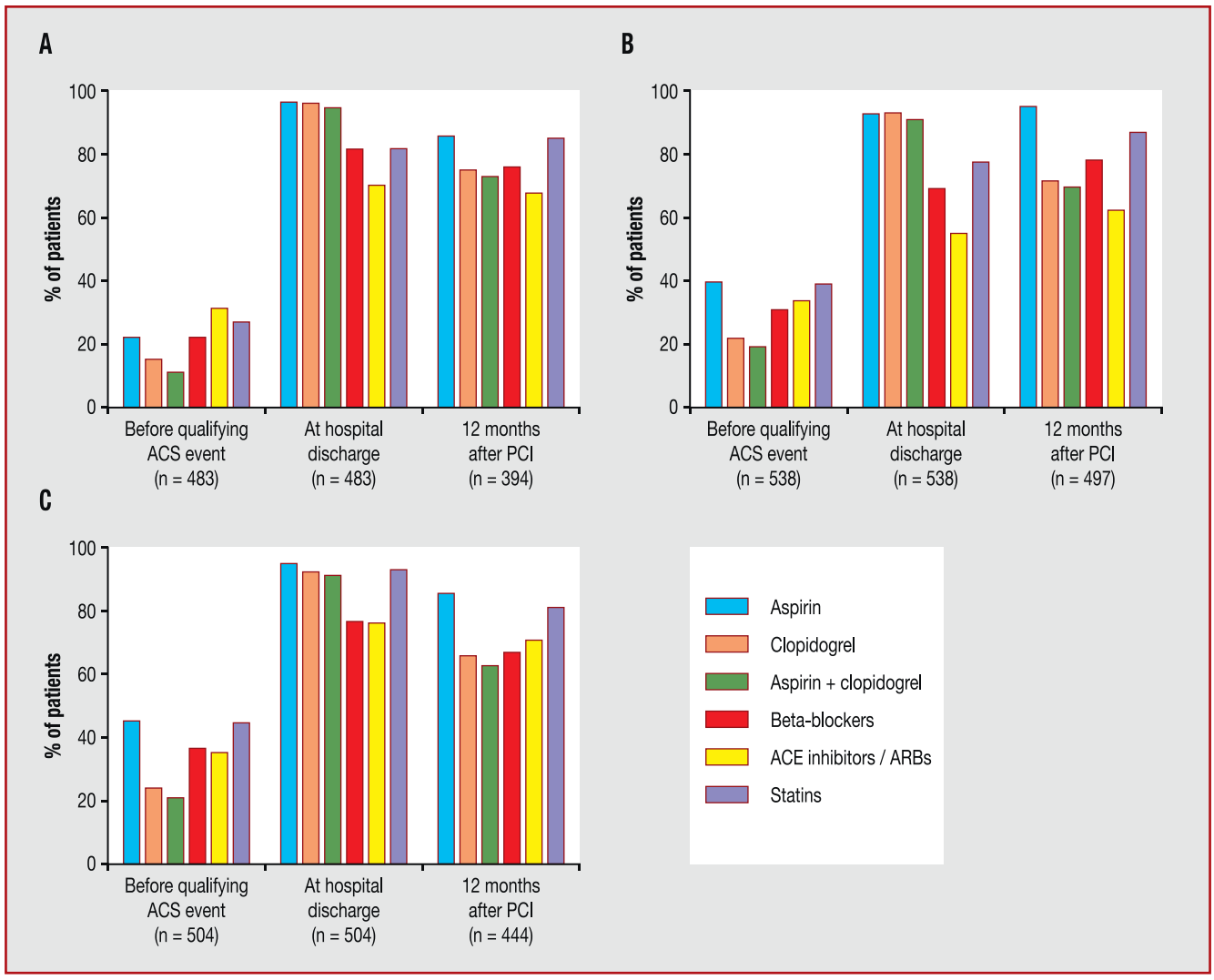

Figure 2. Cardiovascular medications at admission, discharge, and 12 months after PCI in France (A), Spain (B), and the UK (C). ACE: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin 2 receptor blocker; PCI: percutaneous coronary intervention; UK: United Kingdom.

patient receiving the highest dose of 300 mg. In addition, non-diabetic patients were more likely to receive higher aspirin discharge doses; for example, the one STEMI patient in France who received the highest aspirin discharge dose was non-diabetic, and more non-diabetic versus diabetic patients received the highest dose in both Spain (7% versus 4%) and the UK (7% versus 6%).

In France, 87% of patients ($n = 393$) received their clopidogrel loading dose before PCI; either in the intensive care unit (32%), the emergency room (24%), or the ambulance (21%; Fig. 3). The rates for receiving the drug in the ambulance were notably higher in STEMI (32%) than UA/NSTEMI (11%) patients in France, and lower in the total population in Spain (2%) and the UK (< 1%; France versus Spain and the UK: OR 24.64; 95% CI 12.15, 49.95; $p < 0.0001$). Distribution of dose data in Table 3 shows that patients in France most frequently received a 300 mg loading dose (on label dosage) of clopidogrel (53%), one third were treated with a loading dose greater than 300 mg (34%), and 14% received a loading dose lower than 300 mg. For chronic treatment, three quarters of the patients received a 75 mg maintenance dose (77%; on label dosage) and the remaining patients (23%) received a 150 mg maintenance dose. More French patients received higher loading (> 300 mg) and maintenance (150 mg) doses than the Spanish and UK patients; in fact, only one patient in each of Spain and the UK received the 150 mg clopidogrel maintenance dose.

Glycoprotein IIb/IIIa inhibitor (GPI IIb/IIIa) use is shown by country in Fig. 4. 172 patients (36%) in France received GPI IIb/IIIa; this was slightly lower in Spain and the UK. Tirofiban was the GPI IIb/IIIa used most frequently in France (18%) followed by abciximab (16%) and eptifibatide (3%). Abciximab was more frequently given in Spain and the UK followed by tirofiban and eptifibatide. The highest rate of abciximab use was observed in STEMI patients.

Length of hospitalisation

In France, the median length of stay in hospital was 5 days (IQR 3, 7 days); this was primarily accounted for by time

Table 3 Antiplatelet treatment and time to stopping treatment in the 12 months following PCI.

	France ($n=483$)	Spain ($n=538$)	UK ($n=504$)
Aspirin			
Loading dose, *n* (%)			
0—199 mg	89 (21.7)	217 (47.7)	46 (10.7)
200—299 mg	205 (50.0)	31 (6.8)	3 (0.7)
300+ mg	116 (28.3)	207 (45.5)	381 (88.6)
Timing of loading dose relative to PCI, *n* (%)			
More than 24 hours before PCI	123 (27.8)	293 (59.9)	278 (62.6)
13 to 24 hours before PCI	59 (13.3)	35 (7.2)	27 (6.1)
7 to 12 hours before PCI	34 (7.7)	22 (4.5)	18 (4.1)
1 to 6 hours before PCI	139 (31.4)	79 (16.2)	106 (23.9)
At time of PCI	60 (13.6)	53 (10.8)	4 (0.9)
After PCI	27 (6.1)	7 (1.4)	11 (2.5)
Maintenance dose at hospital discharge, n (%)			
< 100 mg	265 (57.0)	2 (0.4)	444 (92.3)
100—150 mg	22 (4.7)	462 (93.0)	4 (0.8)
> 150 mg	178 (38.3)	33 (6.6)	33 (6.9)
Patients no longer taking aspirin 12 months after PCI, *n*	53	17	53
Median (IQR) time to stopping, days	30 (30, 128)	28 (1, 32)	98 (28, 175)
Clopidogrel			
Loading dose, *n* (%)			
< 300 mg	59 (13.5)	134 (27.7)	43 (9.3)
300 mg	230 (52.6)	273 (56.4)	324 (70.1)
> 300 mg	148 (33.9)	77 (15.9)	95 (20.6)
Timing of loading dose relative to PCI, *n* (%)			
More than 24 hours before PCI	134 (29.1)	231 (45.6)	289 (60.0)
13 to 24 hours before PCI	72 (15.7)	38 (7.5)	34 (7.1)
7 to 12 hours before PCI	36 (7.8)	16 (3.2)	22 (4.6)
1 to 6 hours before PCI	151 (32.8)	56 (11.0)	110 (22.8)
At time of PCI	49 (10.7)	153 (30.2)	20 (4.1)
After PCI	18 (3.9)	13 (2.6)	7 (1.5)
Maintenance dose at hospital discharge, *n* (%)			
75 mg	357 (77.3)	499 (99.6)	467 (99.8)
150 mg	105 (22.7)	1 (0.2)	1 (0.2)
Patients no longer taking clopidogrel 12 months after PCI, *n*	83	120	131
Median (IQR) time to stopping, days	90 (30, 182)	109 (30, 180)	84 (28, 177)

IQR: interquartile range; PCI: percutaneous coronary intervention; UK: United Kingdom.

spent in the coronary care unit. Median length of hospitalisation was generally similar among countries (5 days [IQR 3, 8 days] in Spain; 5 days [IQR 3, 9 days] in the UK) and between UA/NSTEMI (4 days [IQR 3, 7 days] in France, 5 days [IQR 2, 7 days] in Spain, and 6 days [IQR 3, 10 days] in the UK) and STEMI (5 days [IQR 4, 8 days] in France; 6 days [IQR 4, 8 days] in Spain, and 4 days [IQR 3, 8 days] in the UK) patients.

12-month follow-up

Follow-up data to 12 months were available for 394 patients (81%) in France compared with 497 patients (92%) in Spain and 444 patients (85%) in the UK. The most common reasons for discontinuation in France were patient lost to follow-up (9%) and physician decision (7%). Discontinuations mainly occurred during the final follow-up to 12 months post PCI. France had more patients lost to follow-up than either Spain (6%) or the UK (5%).

Most of the treatments received at hospital discharge for cardiovascular risk were maintained at 12 months (Fig. 2). Antiplatelet treatment continuation rates over 12 months are shown for France, Spain, and the UK in Fig. 5. In France, 337 patients (86%) were still receiving aspirin at 12 months, 297 patients (75%) were still receiving clopidogrel, and 287 patients (73%) were still receiving combination aspirin and clopidogrel. Continuation rates were higher for aspirin in Spain (95%) but similar in the UK (86%), slightly

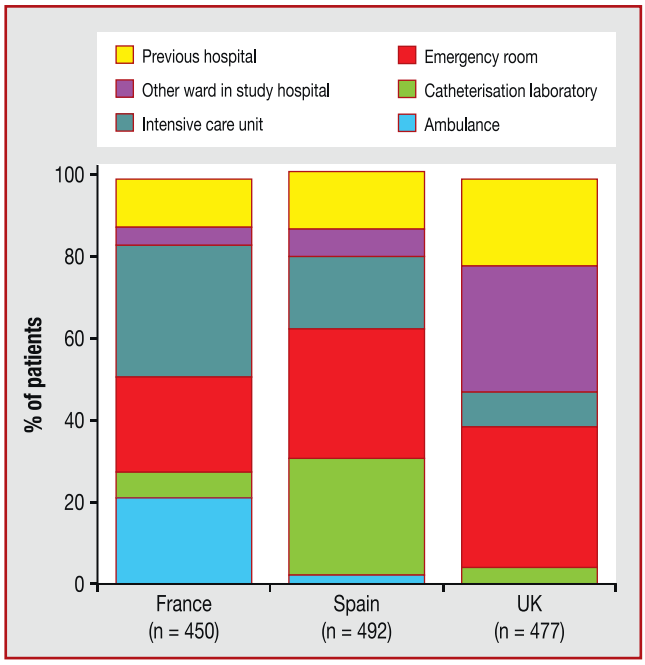

Figure 3. Location of clopidogrel loading dose in France, Spain, and the UK. UK, United Kingdom.

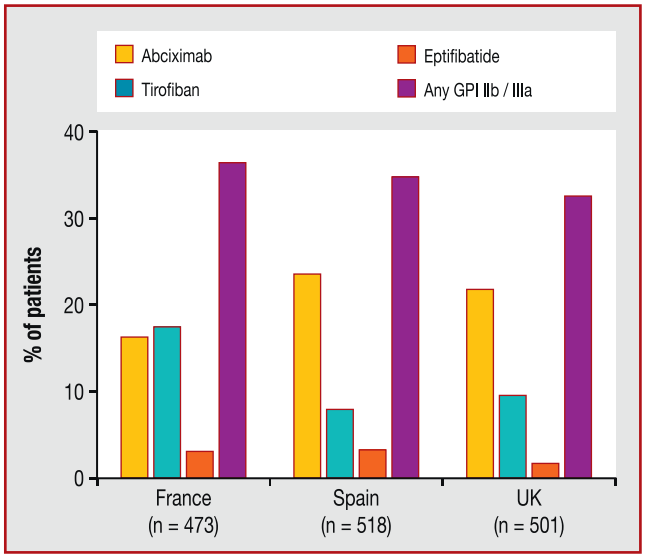

Figure 4. Glycoprotein IIb/IIIa inhibitors use in France, Spain, and the UK. GPI IIb/IIIa, glycoprotein IIb/IIIa inhibitor; UK, United Kingdom.

lower for clopidogrel in Spain (70%) and the UK (66%), and lower for combination treatment in both other countries (Spain, 68%; UK, 63%; France versus Spain and the UK: OR 2.06; 95% CI 1.51, 2.82; $p < 0.0001$).

In France, approximately two thirds of patients still receiving treatment at 12 months after PCI had no treatment interruptions (aspirin: 66%; clopidogrel: 65%). However, the proportion of patients with no interruptions was higher in Spain and the UK for both aspirin (Spain: 99%; UK: 88%) and clopidogrel (Spain: 99%; UK: 88%). Among French patients still treated with antiplatelets 12 months after PCI, most patients who received aspirin remained on the same maintenance dose; however, for clopidogrel, maintenance dose was decreased during follow-up for most patients ($n = 59$) receiving 150 mg at discharge and was not changed for most patients ($n = 220$) receiving 75 mg at discharge. In both Spain and the UK, 90% of patients remained on the same aspirin maintenance dose and 99% remained on the same clopidogrel maintenance dose (mainly 75 mg).

The median time to stopping aspirin and clopidogrel treatment is shown by country in Table 3. In France, among patients who stopped clopidogrel before 12 months, 48% discontinued during the first 3 months. Among patients no longer treated at 12 months after PCI, the median times to stopping treatment were 30 days for aspirin and 90 days for clopidogrel. Stopping times for clopidogrel were shorter for STEMI (median, 30 days; $n = 39$) than for UA/NSTEMI (median, 121 days; $n = 44$) patients. Results were similar in Spain and the UK for clopidogrel, but UK patients had a much longer median stopping time for aspirin compared with France and Spain. More patients with BMS stopped taking clopidogrel within 12 months (25%) compared with those who had DES (14%). This was also the case in Spain and the UK and in APTOR overall.

In France, 23 patients (6%) had planned hospital readmissions and in more than half of cases (52%) a PCI was done during these readmissions. Fifty-four patients (14%) had unplanned hospital readmissions due to cardiovascular events; 31 (57%) of these had a PCI, 3 (6%) had a CABG, and 13 (24%) were readmitted two or more times. Six patients (1%) had planned hospital readmissions in Spain and 42 (9%) had unplanned readmissions due to cardiovascular events, whereas in the UK, 13 (3%) and 45 (10%) patients had planned and unplanned readmissions, respectively. The overall death rate was low and comparable among the countries. In France there were 10 deaths (2%) compared with 14 deaths in Spain (3%) and 15 deaths in the UK (3%).

Discussion

This manuscript has described the results of the French cohort of APTOR, a large prospective observational study designed to provide long-term data on the treatment management practices of ACS patients undergoing PCI, and compared them with the cohorts from Spain and the UK.

Although baseline characteristics were generally comparable between the countries, some differences were noted; for example, the French population were younger, had more cases of STEMI, and had lower rates of prestudy cardiovascular events compared with Spain and the UK. A hypothesis to explain this could be the selection of the participating centres from among the more active centres which tend to recruit younger patients. Even so, before the qualifying ACS event, significant numbers of patients were taking cardiovascular medications and had experienced previous events, which suggests recurrent events still occur at a high rate despite the availability of treatments.

Most patients underwent PCI and stent implantation. DES, which are coated with an antiproliferative agent to help reduce the risk of restenosis, were implanted three times less than BMS in France, and were used much less in France

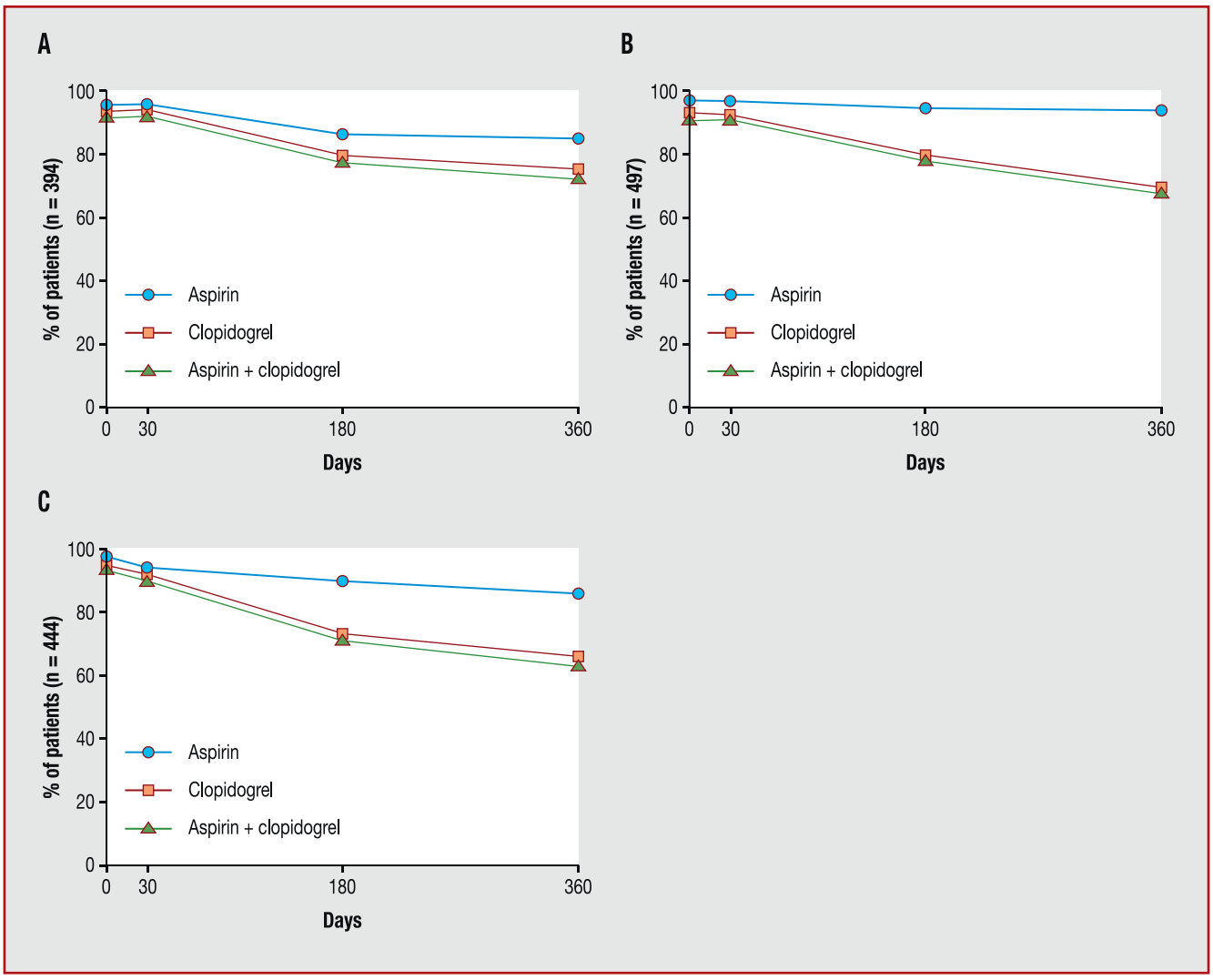

Figure 5. Antiplatelet treatments continuation rates over 12 months in France (A), Spain (B), and the UK (C). N is the total number of patients in each country with 12-month follow-up data. UK, United Kingdom.

compared with Spain and the UK. There has been a lot of worldwide discussion about the use of DES in recent years and doubts have been raised about the safety of these devices. This has been a particularly relevant issue in France because in 2008, after recruitment of the patients, the French Society of Cardiology reviewed the available data and accepted that although DES are effective in reducing the risk of restenosis, doubts persist regarding the possibility of late thrombosis. They recommended particular care in weighing up the risks and benefits for each patient when considering using a DES [8]. Moreover, lower use of DES could be explained by the non-recommendation of DES in STEMI patients by the French health authority at the time of recruitment and the higher rates of STEMI patients in the French cohort.

In France, the time between the occurrence of the qualifying ACS event and the patient undergoing PCI was short. This was especially evident in patients with STEMI, for whom a special process seems to be in place between the ambulance and the catheterisation laboratory. This could be related to the good availability of catheterisation laboratories in France; there are around 220 hospitals with catheterisation facilities in the country. In France, it seems that ESC and ACC/AHA guideline recommendations for the optimal treatment of acute MI, in terms of delay from symptom onset to treatment and access to interventional facilities, are followed. This is important as there is evidence that compliance with guidelines for early reperfusion therapy has a proven benefit in reducing mortality in patients with STEMI [9].

The rates and patterns of baseline medication use reflect the incidence of cardiovascular diseases in the different countries. The lower rate of previous statin use observed in France compared with the UK may reflect higher disease rates in the UK. Epidemiological studies repeatedly show higher rates (up to three times) of MI in the UK compared with France [10], which could possibly be related to differences in diet and lifestyle between these countries. There may also be the contextual effect of the 'French paradox'; the observation that despite a high intake of dietary cholesterol and saturated fat in France there is a low death rate from CHD. This is inconsistent with the known risk factors

for CHD and is thus paradoxical and therefore could suggest that there are protective behaviours specific to France that help reduce CHD incidence. The exact nature of these protective factors is under debate, although wine drinking and attitudes to food may be an important component [11]. On the other hand, the prescription of statins in France for primary prevention is limited by the AFSSAPS guidelines [12], whereas they are commonly used for primary preventative care in the UK. Furthermore, a selection bias of patients with a low history of previous MI in France may also be a further explanation of such findings.

Most patients received appropriate antiplatelet therapy following their qualifying ACS event. However, there was variation in the location of administration, the timing of administration, and dosing of aspirin and clopidogrel between the three countries. Antiplatelet therapy was much more frequently given in the ambulance in France than in Spain or the UK. This could be related to the system in France in which treatment starts quickly in the ambulance, or the nature of the ACS event as there were more STEMI cases in France, which requires rapid treatment initiation. Regarding the timing of antiplatelet treatment, patients were treated very quickly in France, this again seems to be related to the current system and facilities available. ESC guidelines recommend an aspirin-loading dose of 150—325 mg and a maintenance dose of 75—100 mg, and a clopidogrel loading dose of 300 mg and a maintenance dose of 75 mg. Despite this guidance, variation in practice was evident by country, including somewhat higher doses being used in France, particularly with aspirin. These practices could be related to the extensive use of antiplatelet resistance tests in France [13]. This is in contrast to the large observational PCI-CURE analysis in which lower doses of aspirin were found to be as effective as higher doses in preventing ischaemic events but with the advantage of fewer adverse bleeding events [14].

The length of patient hospitalisation was generally similar between the countries, which suggests that the observed differences in patient management strategies may not significantly impact the duration of in-hospital treatment needed. At hospital discharge, most patients received established therapies and almost all received antiplatelet treatments, but there were still between-country variations in dose; most notably, patients in France were more likely to have received higher discharge doses.

Most cardiovascular treatments received at hospital discharge were maintained over the 12 month follow-up. Patients in France had the longest length of clopidogrel therapy, although they also had more treatment interruptions. ESC guidelines recommend maintaining dual therapy with both clopidogrel and aspirin for at least 12 months. However, stopping medication is common in cardiovascular disease patients and has been linked to increased rates of ischaemic events and mortality [15,16]. One study evaluated medication patterns following MI and found that use of recommended medications, such as beta-blockers, aspirin and/or clopidogrel, statins, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in France is satisfactory, although not optimal [17]. In the current study, continued use of clopidogrel at 12 months was lower in patients who received BMS; however, guidelines recommend 12 months of clopidogrel in ACS patients treated with PCI irrespective of the type of stent used.

One other interesting finding was the absence of differences in the outcomes between countries despite the very different patient management practices. The low rate of clinical outcomes could be due to the data collection modalities used by physicians who may have missed some events and also because patients' deaths may have occurred outside the hospital [18].

APTOR is one of the first studies to provide data on ACS treatment practices in Europe. Non-experimental observational studies such as APTOR reflect real-life practice, help us to understand the natural history and impact of therapy, and are more reflective of the experiences of the patient. However, with observational studies, there is always a potential for bias (in the design, data collection, and analysis) and subjective interpretation of the data, which can undermine the quality of the results. ACS patients in the French APTOR study population were different from the Spanish and UK populations because they had a younger median age, more STEMI cases, and lower rates of vascular disease, diabetes, and previous medication use. Selection bias was highly probable in the APTOR study; there was a selection bias between countries as the selection of centres was different and thus there were differences in the baseline characteristics of the recruited patients, and the low mortality rate suggests a general selection bias of patients within the study. However, the demographic characteristics and clinical features of the French study population are in agreement with epidemiological results from the MONICA study of 2018 ACS patients hospitalised in three regions in France and the 2005 FAST-MI registry of 3059 acute MI patients [19,20]. In both of these studies, the study populations had a high rate of STEMI (MONICA, 60%; FAST-MI, 52%) and the MONICA study also had a population with a low age (mean of 57.2 years).

Conclusions

The long-term data supplied by this study reflect 'real world' treatment practice patterns of ACS patients managed by PCI in France, and provide a useful benchmark for comparison with data from other European countries and current guidelines. This in turn should help direct future patient care and strengthen efforts to achieve international best practice. An important finding is that there is considerable variation in the treatment of patients between the three European countries. The features of the treatment received by French patients is reflective of the system in France; for example, treatment is received quickly in France with the first doses of antiplatelet therapy often received in the ambulance and PCI typically carried out on the day of hospital admission. In addition, the lower use of DES in France could be related to recent concerns about their safety. This study suggests that standards in the current European guidelines for ACS management are generally being met in France.

Conflict of interest statement

JF has received research grants from AstraZeneca, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Pfizer, Sanofi-Aventis, and Solvay Pharma. MS, STL, and MB are

currently employees of Eli Lilly and Company, who funded and conducted the APTOR study.

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References

[1] Taylor MJ, Scuffham PA, McCollam PL, Newby DE. Acute coronary syndromes in Europe: 1-year costs and outcomes. Curr Med Res Opin 2007;23(3):495—503.

[2] Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116(7):e148—304.

[3] Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing committee. Circulation 2008;117(2):296—329.

[4] Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28(13):1598—660.

[5] Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29(23): 2909—45.

[6] Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The task force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26(8):804—47.

[7] Ferrières J, Bakhai A, Iñiguez A, et al. Treatment patterns in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Curr Med Res Opin 2010;26(9):2193—202.

[8] Danchin N, Blanchard D, Chevalier B, et al. Use of drug eluting stents: expert consensus of the French Society of Cardiology. Arch Cardiovasc Dis 2008;101(3):190—3.

[9] Charpentier S, Sagnes-Raffy C, Cournot M, et al. Determinants and prognostic impact of compliance with guidelines in reperfusion therapy for ST-segment elevation myocardial infarction: results from the ESTIM Midi-Pyrénées Area. Arch Cardiovasc Dis 2009;102(5):387—96.

[10] Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999;353(9164):1547—57.

[11] Ferrières J. The French paradox: lessons for other countries. Heart 2004;90(1):107—11.

[12] Agence Française de Sécurité Sanitaire des Produits de Santé. Prise en charge thérapeutique du patient dyslipidémique — recommandations. Mars 2005. www.afssaps.sante.fr.

[13] Collet JP, Montalescot G. Platelet function testing and implications for clinical practice. J Cardiovasc Pharmacol Ther 2009;14(3):157—69.

[14] Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. Eur Heart J 2009;30(8):900—7.

[15] Collet JP, Montalescot G, Steg PG, et al. Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial. Arch Cardiovasc Dis 2009;102(6—7):485—96.

[16] Amar J, Ferrières J, Cambou JP, Amelineau E, Danchin N. Persistence of combination of evidence-based medical therapy in patients with acute coronary syndromes. Arch Cardiovasc Dis 2008;101(5):301—6.

[17] Tuppin P, Neumann A, Danchin N, et al. Combined secondary prevention after hospitalization for myocardial infarction in France: analysis from a large administrative database. Arch Cardiovasc Dis 2009;102(4):279—92.

[18] Ferrières J, Arveiler D, Amouyel P, et al. Epidemiology of sudden coronary death in France (1985—1982). Arch Mal Coeur Vaiss 1997;90(4):483—7.

[19] Ferrières J, Ruidavets JB, Arveiler D, et al. Implementation of the ESC guidelines on the management of AMI in community hospitals. Eur Heart J 2009;30 [abstract supplement]:(337).

[20] Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. Arch Mal Coeur Vaiss 2007;100(6—7):524—34.