Original articles

Drug therapy during percutaneous coronary interventions in stable and unstable coronary artery disease: the Italian Drug Evaluation in Angioplasty (IDEA) study

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Coronary angioplasty; Drugs; Registries.

Background. **Although periprocedural drug therapy has been shown to improve the outcome of percutaneous coronary intervention (PCI), information regarding its use in daily clinical practice is limited.**

Methods. **We conducted a national survey on periprocedural drug therapy across the spectrum of PCI practice in Italy. Seventy-nine centers (41% of the Italian interventional cath labs) with a fair distribution across the country volunteered to enroll consecutive patients undergoing PCI for any indication from September 15 to 29, 2003.**

Results. **Of the 1517 patients enrolled, 745 (49%) had stable coronary disease and 772 (51%) acute coronary syndromes (ACS): 457 without and 315 with ST-segment elevation. Stenting was used in 89% of cases. N-acetylcysteine was used in 23% of the patients with preexisting renal dysfunction. Thienopyridine (63% clopidogrel) pretreatment was given in 49% of the cases and, at logistic regression analysis, was independently associated with prior myocardial infarction ($p < 0.001$), prior PCI ($p = 0.007$), stable coronary disease ($p = 0.005$), and treatment in northern Italy ($p < 0.05$). Platelet glycoprotein (GP) IIb/IIIa receptor blockers (50% abciximab, 50% tirofiban) were used in 22% of the stable patients and 40% of those with ACS, a proportion increasing to 62% when PCI was undertaken as an emergency procedure. Off-label use of these drugs was frequent (direct cath lab use of tirofiban in 55% of the cases; bailout use: 16% with abciximab and 26% with tirofiban). At logistic regression analysis, independent predictors of GP IIb/IIIa receptor blocker use were emergency procedure (odds ratio 3.6, 95% confidence interval 2.6 to 5.0, $p < 0.0001$) and treatment for an ACS (odds ratio 1.6, 95% confidence interval 1.3 to 2.1, $p = 0.0002$). An emergency procedure was the only independent predictor for the use of abciximab instead of tirofiban (odds ratio 4.1, 95% confidence interval 2.6 to 6.5, $p < 0.0001$). Triple periprocedural antiplatelet therapy, including aspirin, a thienopyridine and a GP IIb/IIIa receptor blocker was administered in only 21% of cases. At discharge, all stented patients received aspirin and a thienopyridine. Despite complete procedural success in > 90% of cases, 50% of the patients were discharged on symptomatic anti-ischemic therapy.**

Conclusions. **A wide gap exists between guideline recommendations and periprocedural drug therapy in PCI, the only exception being full prescription of aspirin and a thienopyridine at discharge after stenting. In patients with ACS, thienopyridine pretreatment is often used as a surrogate for GP IIb/IIIa blockade, whose use rather is associated with emergency procedures. Off-label use of drugs is not uncommon.**

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Introduction

Percutaneous coronary intervention (PCI) requires an integrated mechanical and pharmacological approach in order to minimize the thrombogenic risk of intravascular manipulation and stent implantation and preserve arterial patency. Periprocedural drug therapy has become even more important since PCI has become the preferred approach to acute coronary syndromes (ACS), both with and without ST-segment elevation, where the thrombogenic potential is increased by plaque inflammation[1,2] and activation of the coagulation cascade[3]. Coronary stenting also re-

quires systematic and careful antiplatelet therapy in order to prevent thrombotic occlusion[4-6]. Moreover, concomitant drug therapy has been shown to improve the therapeutic potential of PCI in the growing population of high-risk patients, such as those with diabetes[7] or renal insufficiency[8], and also to reduce the risk of postprocedural myocardial infarction and long-term mortality[9,10]. Guidelines for drug therapy concomitant to PCI have been issued in recent years[11], but the extent to which recommended treatments are applied in clinical practice has not been investigated in this particular setting.

The aim of the present study, promoted by the Italian Society of Invasive Cardiology, was to monitor the use of pharmacological therapy in a representative sample of the Italian interventional cath labs. The methodology is similar to that followed in a recent survey of acute myocardial infarction[12], consisting of a registry of consecutive patients undergoing PCI during 15 days in a large number of cath labs across the whole country. Subsequent surveys are planned at 2-year intervals.

Methods

Organization of the survey. An invitation to participate in the survey was mailed by the board of the Italian Society of Invasive Cardiology to all the cath labs included in the 2002 registry of the Society plus any additional cath lab that had contacted the Society prior to the issue of the invitation. The Ethics Committee of each participating center was notified about the study protocol, case record form and informed consent form: the Italian regulations do not require formal Ethics Committee approval for any observational registries promoted by recognized scientific societies. The enrolling period lasted from September 15 to 29, 2003.

Data collection. A 4-page case record form including information about the patient's demographic and clinical data, primary indication for PCI, angiographic and procedural data as well as any in-hospital ischemic events and postprocedural complications was prepared. Medications given prior to and during the procedure, as well as those prescribed at hospital discharge, were to be reported in the case record form with special emphasis on antithrombotic treatments, type and duration of any thienopyridine pretreatment, glycoprotein (GP) IIb/IIIa therapy prior to and during PCI, antithrombin therapy using either unfractionated or low-molecular-weight heparin and type and prospected duration of thienopyridine therapy at discharge.

In order to limit the percentage of missing data or misinterpretations, the first case record form filled in at each center, and including all in-hospital data, was to be faxed to the Study Coordinating Center within 24 hours of patient discharge, and checked by one of the study coordinators for data consistency and completeness. Any inconsistencies and missing data were reviewed with the investigators by telephone or via e-mail within 24 hours. After hospital discharge, all the case record forms were to be sent to the Coordinating Center for data input and statistical analysis. A copy of each patient's discharge summary was also to be sent to the Coordinating Center in order to check any major events. Queries were issued via e-mail or fax to the investigators in order to correct inconsistencies or missing entries.

Definitions. Formal definitions[13] of the characteristics or events to be entered in the case record form were reported in the "instructions for completion of the case record form". These included the following:

- diabetes mellitus: defined on the basis of either the clinical history (irrespective of treatment) or of the presence of fasting blood glucose levels > 110 mg/dl;
- renal insufficiency: serum creatinine levels > 1.5 mg/dl;
- systemic arteriopathy: symptoms of claudication or instrumental proof of a stenosis > 50% in one or more non-coronary arteries;
- prior myocardial infarction: any prior episode irrespective of ST-segment presentation or *post-hoc* recognition by electrocardiography, echocardiography or nuclear imaging;
- primary indication for PCI: stable coronary artery disease (CAD) or ACS (defined as symptoms and/or electrocardiographic signs of acute myocardial ischemia at rest), with further specification of non-ST-segment elevation (with or without elevation in the serum levels of the biochemical markers of myocardial damage) or ST-segment elevation;
- priority at PCI: "elective" when it was planned in a clinically stable patient; "urgent" when it had to be carried out prior to hospital discharge in a patient admitted due to an ACS; "emergent" when required immediately due to ongoing myocardial ischemia or hemodynamic instability despite optimal medical therapy;
- extension of CAD: number of coronary vessels with ≥ 50% angiographic stenosis by visual estimate, graded as single-vessel or multivessel or graft disease;
- pretreatment with a thienopyridine: was defined when ticlopidine had been administered for > 72 hours prior to the interventional procedure, whereas for clopidogrel any pre-lab administration was considered as pretreatment;
- successful lesion dilation: an absolute > 20% reduction in artery stenosis with final stenosis < 50%;
- successful procedure: either partial (some but not all attempted lesions successfully treated) or complete (all attempted lesions successfully treated) angiographic success without death, postprocedural myocardial infarction or emergency bypass surgery;
- postprocedural myocardial infarction: any[14] postprocedural elevation in the serum creatine kinase (CK)-MB levels above the upper limit of normal in the indi-

vidual laboratory if the preprocedural level was normal; a > 50% increase in CK-MB in case of elevated (but decreasing) preprocedural levels; a postprocedural infarction was not to be indicated if the preprocedural CK-MB levels were increasing or for primary angioplasty during an acute ST-elevation myocardial infarction;
• postprocedural renal deterioration: a postprocedural increase > 0.5 mg/dl in serum creatinine levels;
• vascular complication: any complication which was confirmed by a diagnostic examination or required surgical repair or prolonged hospital stay;
• major bleeding: a bleeding that was life-threatening or associated with a drop ≥ 5 mg in the hemoglobin levels or requiring blood transfusion;
• thrombocytopenia: a drop in the blood platelet count to < 50 000 per ml.

Outcome measures. Any death and the following postprocedural events occurring prior to hospital discharge were to be recorded:
• cardiac ischemic events: recurrent angina, myocardial infarction, and heart failure;
• coronary procedures: repeat angiography, repeat PCI, and urgent coronary artery bypass grafting;
• bleeding events: puncture site hematoma, minor bleeding, major bleeding, red blood cell transfusions, thrombocytopenia;
• procedural complications: vascular complications, renal function deterioration, stent thrombosis.

Statistical analysis. Descriptive statistics are reported as the mean ± SD or as the median with the minimum, maximum and interquartile (IQR) range depending on the distribution of each variable. Separate analyses were carried out according to whether PCI had been performed on patients with stable or unstable CAD and, among the latter, depending on the occurrence of ST-segment elevation.

Variables associated with preprocedural thienopyridine treatment were determined by means of logistic regression. Univariate statistics were run testing for significance by either the χ^2 or Student's t-test; all factors significant at the 0.1 level were entered in a backwards selection logistic model. Only factors significant at the 0.05 level at Wald's test were retained in the final logistic model. A separate model was run in the subgroup of patients with ACS in order to take into account the presence of ST-segment elevation. The same procedure was followed to detect factors associated with the procedural use of GP IIb/IIIa inhibitors. All analyses were performed using SAS system software (SAS Institute Inc., Cary, NC, USA), version 8.2.

Results

Ninety-five cath labs volunteered to take part in the survey, but only 79 actually joined in (41% of the total number of interventional cath labs included in the 2002 registry), whereas 16 could not participate due to administrative or logistic reasons. The geographic distribution of the participating cath labs reflects the actual share across the country: 41 (52%) centers in the north, 14 (18%) in the center, and 24 (30%) in the south or islands. All the participating cath labs had a coronary or intensive care unit on-site and 42 (53%) also had cardiac surgery facilities. A total number of 1517 patients were enrolled for a median of 16 per center (range 1 to 74, IQR 11-26). The patients' clinical characteristics are reported in table I. Approximately half of the pa-

Table I. Patient characteristics.

Variable	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Age (years)	64 ± 11	64 ± 10	65 ± 11	63 ± 12
> 70	30	28	35	28
Males	78	82	73	76
Caucasian race	> 99	> 99	> 99	> 99
Family history of CAD	36	38	34	35
Diabetes	26	27	26	23
Insulin-dependent	5.1	5.1	4.6	5.7
Non-insulin-dependent	21	22	21	17
Renal insufficiency*	6.3	7.4	5.9	3.8
Prior cerebrovascular event	4.7	5.6	3.9	3.5
Systemic arteriopathy*	11	12	11	6.0
Prior myocardial infarction	39	50	33	23
Prior CABG	10	11	12	3.8
Prior PCI	26	35	21	10
Elevated serum levels of CK-MB or Tn**	–	–	52	95

Numbers are percentages when not otherwise specified. CABG = coronary artery bypass grafting; CAD = coronary artery disease; CK = creatine kinase; NSTEACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction; Tn = troponin. * see text for definitions; ** preprocedural levels in patients with an ACS: no specific definition in the study protocol.

tients had stable and half unstable CAD. Of the 772 unstable CAD cases, 203 were primary angioplasties in patients with an acute ST-elevation myocardial infarction. The angiographic and procedural characteristics are reported in table II.

Preprocedural therapy. The preprocedural drug therapy is reported in table III. Pretreatment with a thienopyridine was used in 49% of cases, more frequently ($p < 0.05$) in northern regions, among men, in patients with prior myocardial infarction or PCI and in those with stable CAD. Prior myocardial infarction, prior PCI, stable CAD and intervention in northern Italy remained significant predictors of thienopyridine pretreatment at logistic regression analysis (Fig. 1). Among patients with an ACS, thienopyridine treatment was more frequent in patients without ST-segment elevation (56 vs 26% in patients with ST-segment elevation, $p < 0.0001$), and for whom a longer time had elapsed between the last ischemic episode and PCI

Table II. Procedural characteristics.

Variable	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Urgency of the procedure*				
Elective	62	97	36	14
Urgent	22	2	56	23
Emergent	16	1	8	64
CAD extension				
Single vessel	45	43	47	48
Multivessel	53	55	50	52
Graft lesion	1.5	1.5	0.7	2.2
No. lesions treated	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.8	1.4 ± 0.6
Stent deployment	89	87	91	93
No. stents	1.5 ± 0.8	1.5 ± 0.9	1.4 ± 0.8	1.4 ± 0.7
DES	22	26	22	10
Procedural outcome				
Success	94	93	93	95
Partial success	3.7	4	4	2.6
Failure	2.6	2.6	2.6	2.3

CAD = coronary artery disease; DES = drug-eluting stents; NSTEACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction. * see text for definitions.

Table III. Preprocedural drug therapy.

Drugs	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Aspirin	87	88	88	83
Ticlopidine	18	23	17	5.7
No. days (median, 25th-75th percentile)	5 (3-30)	7 (3-30)	4 (3-8)	5 (3-10)
Clopidogrel	31	31	39	19
No. days (median, 25th-75th percentile)	3 (2-7)	4 (2-15)	3 (1-5)	2 (1-5)
Oral anticoagulants	1.8	1.8	1.1	1.9
GP IIb/IIIa receptor blocker	10	1.3	16	22
Abciximab	3	0.7	1.8	14
Eptifibatide	0.3	0	0.7	0.3
Tirofiban	7	0.7	14	7.7
Unfractionated heparin	17	5	19	43
Low-molecular-weight heparin	19	7	41	16
Enoxaparin	16	4.4	34	14
Nadroparin	2.4	1.3	4.6	1.6
Dalteparin	0.8	0.8	1.3	0.4
Beta-blockers	52	53	59	38
N-acetylcysteine	1.5	1.7	1.8	0.3

Numbers are percentages when not otherwise specified. CAD = coronary artery disease; GP = glycoprotein; NSTEACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction.

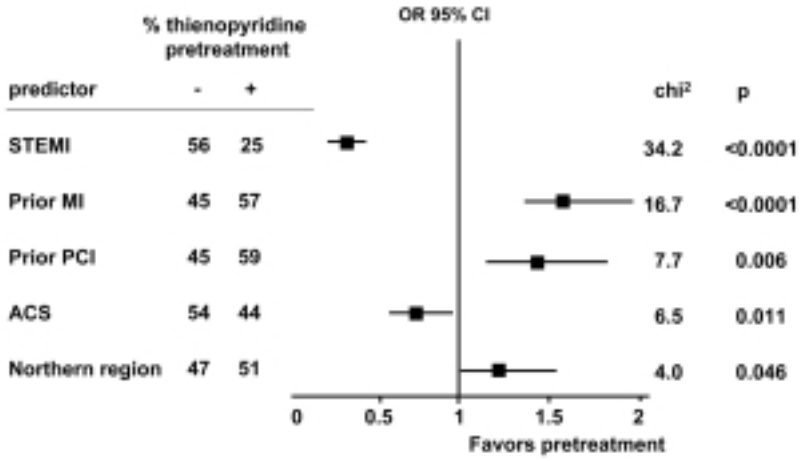

Figure 1. *Independent predictors of pretreatment with a thienopyridine (ticlopidine or clopidogrel) in the whole study population. Results of logistic regression analysis. ACS = acute coronary syndrome; CI = confidence interval; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.*

(median 86 vs 33 hours in non-pretreated patients, p < 0.0001). In this population, no ST-segment elevation (p < 0.0001), the time since the last ischemic episode (p < 0.0001), prior myocardial infarction (p = 0.0008) and treatment in northern regions (p = 0.03) were significant predictors of thienopyridine pretreatment at logistic regression analysis. Clopidogrel pretreatment was used with a similar frequency in patients with stable (32%) or unstable (30%) CAD whereas ticlopidine was used more frequently in stable patients (23 vs 15% for unstable subjects).

Pretreatment with a GP IIb/IIIa receptor blocker was used in 19% of the cases with an ACS and in 1.5% of those with stable CAD. Among the unstable patients, those with no ST-segment elevation were more frequently pretreated using tirofiban, whereas abciximab was more frequently used in those with ST-segment elevation. Unfractionated heparin was used in 5% of the patients with stable and in 29% of those with unstable disease, whereas low-molecular-weight heparin (83% enoxaparin) in, respectively, 7 and 32% of cases. Of the 96 patients with known renal insufficiency, 22 (23%) received N-acetylcysteine prior to the procedure at a mean dosage of 1076 mg (range 100 to 2400 mg).

Drug therapy during coronary intervention. The drug therapy administered in the cath lab is shown in table IV. A GP IIb/IIIa receptor blocker was used in 31% of cases, 16% abciximab, 14% tirofiban, and < 2% eptifibatide. The overall use of GP IIb/IIIa receptor blockers was similar in diabetic and non-diabetic patients (32 vs 31%). In the whole study population, the variables associated (p < 0.05) with more frequent GP IIb/IIIa inhibitor treatment were intervention in north-

Table IV. Drug therapy during the procedure.

Drugs	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Unfractionated heparin	95	97	95	87
Any GP IIb/IIIa receptor blocker	31	22	30	55
Abciximab	16	9.4	13	37
Predilation*	84	86	77	86
Bailout*	16	14	23	14
Ongoing from CCU*	17	7	10	28
Mean postprocedural duration (hours)	12 ± 0.8	12 ± 0.1	12 ± 0.1	12 ± 0.1
Tirofiban	14	12	15	16
Predilation*	74	62	84	86
Bailout*	26	38	16	14
Ongoing from CCU*	27	9	45	37
Mean postprocedural duration (hours)	17 ± 9	16 ± 6	17 ± 10	22 ± 13
Eptifibatide	1.4	0.6	2	2

Numbers are percentages when not otherwise specified. CAD = coronary artery disease; CCU = coronary care unit; GP = glycoprotein; NSTEACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction. * percent of total.

ern regions (34 vs 27% in non-northern regions), ACS (40 vs 21% in non-ACS patients), and intervention in an emergency setting (62 vs 25% in non-emergency); factors associated with less frequent GP IIb/IIIa usage were systemic arteriopathy (24 vs 32% in patients with no arteriopathy), prior myocardial infarction (27 vs 33% in those with no prior myocardial infarction), and prior PCI (24 vs 33% in those with no prior PCI). Among patients with an ACS, GP IIb/IIIa usage was more frequent ($p < 0.05$) in those with elevated biomarkers of myocardial damage (40 vs 26% in those with non-elevated biomarkers), ST-segment elevation (55 vs 30% in those with no ST-segment elevation), a shorter time since the last ischemic episode (median 54, IQR 36-72 hours in those treated vs 93, IQR 65-119 hours in those non-treated) and in those submitted to an emergency procedure (65 vs 31% in non-emergency procedures). As shown in figure 2, at logistic regression analysis (both in the whole study population and in ACS patients), the only significant predictors of GP IIb/IIIa usage were an emergency procedure and treatment for an ACS.

Among patients treated with a GP IIb/IIIa receptor blocker, tirofiban was used more frequently than abciximab in patients with peripheral vascular disease (61 vs 39%, $p = 0.055$), prior myocardial infarction (54 vs 46%, $p = 0.013$), prior PCI (55 vs 45%, $p = 0.039$) or prior coronary artery bypass grafting (66 vs 34%, $p = 0.0049$), whereas abciximab was preferred in patients with an ACS (60 vs 40%, $p = 0.0005$), in those with myocardial marker elevations (55 vs 45%, $p = 0.174$), and particularly in those with ST-segment elevation (70 vs 30%, $p < 0.0001$) or treated on an emergency basis (77 vs 23%, $p < 0.0001$).

At logistic regression analysis the only significant predictor for treatment with abciximab, as opposed to tirofiban, was an emergency procedure (odds ratio 4.1, 95% confidence interval 2.6 to 6.5, $p < 0.0001$).

Table V shows the use of thienopyridine pretreatment and GP IIb/IIIa receptor blockade according to the clinical syndrome and the urgency of the procedure: across the spectrum of PCI, approximately 30% of patients neither received thienopyridine pretreatment nor procedural GP IIb/IIIa receptor blockade. Thienopyri-

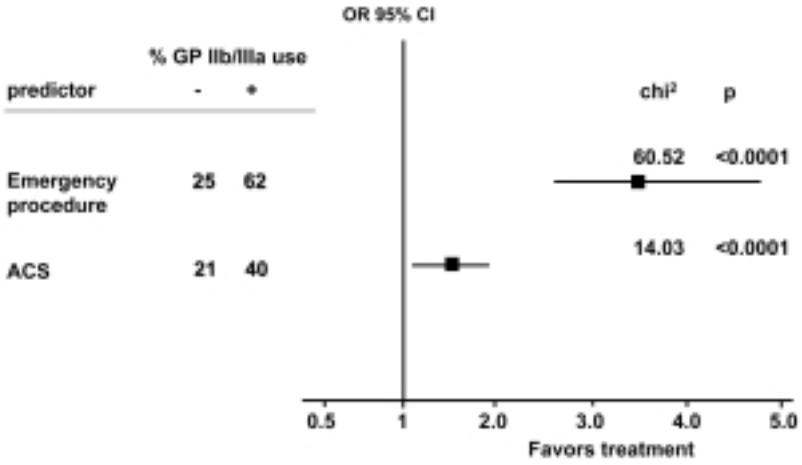

Figure 2. *Independent predictors of platelet glycoprotein (GP) IIb/IIIa receptor treatment in the whole study population. Results of logistic regression analysis. ACS = acute coronary syndrome; CI = confidence interval; OR = odds ratio.*

Table V. Thienopyridine pretreatment and glycoprotein (GP) IIb/IIIa receptor blockade according to clinical syndrome and urgency of the procedure.

	Thienopyridine pretreatment only	Thienopyridine and GP IIb/IIIa receptor blocker	GP IIb/IIIa receptor blocker only	Neither treatment
All patients (n = 1517)	38	21	11	31
Stable CAD (n = 745)	46	13	8.7	33
Unstable CAD (n = 772)	31	28	12	28
Non-ST-elevation (n = 457)	43	17	13	27
ST-elevation (n = 315)	13	45	12	30
Urgency of the procedure				
Elective (n = 939)	46	13	9.3	31
Urgent (n = 340)	36	17	16	30
Emergent (n = 238)	5.9	53	7.1	27

All numbers are percentages. CAD = coronary artery disease.

dine pretreatment alone was used more frequently in stable and elective patients, whereas the combination of thienopyridine pretreatment and GP IIb/IIIa receptor blockade was more common among unstable and emergent cases. GP IIb/IIIa receptor blockers were used alone only in 7 to 16% of cases.

Drug therapy at discharge. The drug prescription at discharge is shown in table VI. Ticlopidine or clopidogrel were prescribed to 94% of patients, in 89% of cases in combination with aspirin. The intended duration of prescription and the impact of drug-eluting stent implantation are shown in figure 3. Oral anticoagulants were always prescribed in combination with aspirin or a thienopyridine. Beta-blocker prescription increased by an absolute 10% compared to preprocedural values (Table III) with a very homogeneous distribution across stable and unstable CAD.

In-hospital outcome. The median postprocedural length of hospital stay was 3 (IQR 2-3) days in stable and 5 (IQR 3-7) days in unstable patients. The in-hospital events are reported in table VII. Fatal or severe complications were extremely rare in stable patients and slightly more frequent in patients with unstable CAD, particularly those with ST-elevation myocardial

Table VI. Drug prescription at discharge.

Drugs	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Aspirin	92	94	93	88
Aspirin + thienopyridine*	89	89	90	85
Ticlopidine	33	37	28	30
Intended duration (months)	2.7 ± 10	2.4 ± 7.2	4.7 ± 17	1.5 ± 1.2
Clopidogrel	61	57	69	60
Intended duration (months)	4.5 ± 6.1	4.8 ± 6.7	4.6 ± 6.6	3.6 ± 3.1
Oral anticoagulants	1.8	1.9	1.4	2.6
Oral anticoagulants + antiplatelets	1.8	1.9	1.4	2.6
Beta-blockers	65	64	67	66
Nitrates	46	50	47	34
Calcium antagonists	22	28	21	8.6
ACE-inhibitors	58	57	59	63
Angiotensin receptor blockers	7.4	8.4	7.2	5.3
Statins	74	75	76	67

Numbers are percentages when not otherwise specified. ACE = angiotensin-converting enzyme; CAD = coronary artery disease; NSTEACS = non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction. * ticlopidine or clopidogrel.

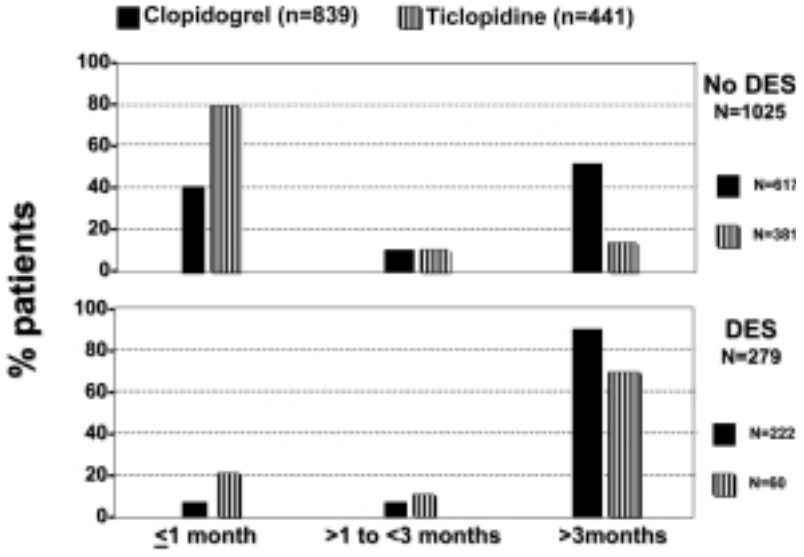

Figure 3. *Prescription of thienopyridines at discharge and the impact of drug-eluting stent (DES) implantation.*

Table VII. In-hospital outcome.

Variable	All patients (n = 1517)	Stable CAD (n = 745)	Unstable CAD	
			NSTEACS (n = 457)	STEMI (n = 315)
Death	1.5	0.5	1.1	4.3
Myocardial infarction	2.4	1.9	3.3	2.3
Enzyme elevation only*	1.8	1.5	2.6	1.6
ST-segment changes	0.4	0.3	0.6	0.7
New Q waves	< 0.01	0.01	0	0
Recurrent angina	1.6	1.1	2.4	1.6
Repeat angiography	1.8	0.8	2.6	3.0
Repeat angioplasty	0.7	0.3	0.9	1.6
Urgent CABG	0.4	0.5	0	0.7
Heart failure	1.6	0.4	1.1	5.6
Renal insufficiency*	1.6	1.1	1.1	3.6
Vascular complications	0.9	0.7	1.3	0.7
Subacute stent thrombosis	0.4	0.1	0.7	0.7
Bleeding events	4.8	3.1	6.4	6.9
Major bleeding*	0.5	0.1	0.4	1.3
RBC transfusion	1.1	0.4	0.9	3.0
Minor bleeding	0.9	0.3	1.3	1.6
Puncture-site hematoma	3.4	2.7	4.6	3.3
Thrombocytopenia*	0.4	0.1	0.9	0.3

All numbers are percentages. CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTEACS = non-ST-elevation acute coronary syndrome; RBC = red blood cell; STEMI = ST-elevation myocardial infarction. * see text for definitions.

infarction: in this latter group, renal insufficiency and heart failure were typically more frequent. Severe bleeding was a rare event for all patient groups.

Discussion

Guideline indications for periprocedural therapy in percutaneous coronary intervention. Periprocedural drug therapy has been shown to improve the safety and outcome of PCI by reducing the risk of acute coronary occlusion, stent thrombosis, and postprocedural myocardial infarction particularly in patients with ACS. Practice guidelines for drug therapy during PCI have been developed[11,15-19], with great emphasis on antithrombotic therapy. Among the antiplatelet agents, aspirin is recommended as a class IA drug for all indications[11,18,19]. The periprocedural use of the GP IIb/IIIa receptor blockers in patients with ACS has been graded as a class IA indication, though with different specifications for the small molecules and abciximab, whereas in stable patients undergoing elective PCI the evidence of benefit has been considered less compelling, with a class 2A indication[18]. The postprocedural administration of ticlopidine or clopidogrel in order to prevent subacute stent thrombosis has been recognized as a class IA indication[18,19], but treatment for a few days, or using a loading dose, prior to coronary angiography is generally recommended in order to enhance the antiplatelet effect at the time of the procedure[20-22]. Periprocedural antithrombin therapy using unfractionated heparin is the current standard of care with an empiric class I indication[15], whereas low-molecular-weight heparins are currently not recommended though they are used to some extent on the basis of the results of pharmacological studies and registries[23].

Recent surveys have shown underutilization of GP IIb/IIIa inhibitors in patients with ACS irrespective of concomitant PCI[12,24-26], but the use of these agents and of other antithrombotic therapies across the spectrum of PCI has not been reported.

Thienopyridine therapy. The present registry documents a wide gap between guideline recommendations and their application in the PCI context, the only exception being the systematic postprocedural use of thienopyridines in combination with aspirin. This antiplatelet combination has been shown to be more effective than aspirin alone or aspirin plus warfarin for the prevention of stent thrombosis[4-6], the difference in terms of efficacy between ticlopidine and clopidogrel being marginal[27]. The 2:1 ratio of clopidogrel to ticlopidine observed at discharge in the present survey, is likely to be ascribed to better tolerability[28-30] and specific documentation on the long-term postprocedural efficacy[31] with clopidogrel; however, ticlopidine is still used in 30% of the whole stenting population, probably due to its much lower cost. Pharmacological studies[32] and non-randomized comparisons[33] have also suggested that thienopyridine treatment prior to PCI may lower the risk of postprocedural infarction and improve the long-term outcome[34], though the duration of pretreat-

ment and the loading dose needed to achieve the maximal antiplatelet effect allowed by this treatment are still ill defined. According to the present survey, pretreatment with ticlopidine or clopidogrel is being used in 50% of patients, including those with unstable CAD. Since these agents block only one of three distinct platelet adenosine diphosphate (ADP) receptors, at its best the combination of aspirin and a thienopyridine may provide no higher than 50 to 60% blockade of ADP-induced platelet aggregation[22,35], which is much lower than what has been shown necessary to prevent ischemic complications, at least in patients with an ACS[32]. Thus, although this double antiplatelet therapy has been shown to be adequate in low-risk patients[36], in higher-risk patients, such as those with diabetes or an ACS, the ADP-receptor blockers should be used in combination with a GP IIb/IIIa receptor inhibitor in order to achieve adequate platelet inhibition. In the present survey, full antiplatelet therapy including aspirin, a thienopyridine and a GP IIb/IIIa receptor blocker was used in only 17% of the patients with non-ST-elevation and in 45% of those with ST-elevation ACS, slightly more in patients treated on an emergency basis. Thus, particularly in non-ST-elevation ACS, thienopyridine pretreatment seems to be currently considered as a surrogate for GP IIb/IIIa receptor blockade. The intended duration of thienopyridine treatment was for several months after discharge, particularly for clopidogrel, with no difference between stable and unstable patients: this datum is probably the result of long-term prescription in patients with an ACS[29] and in those having undergone drug-eluting stent implantation, where the duration of double antiplatelet therapy has not yet been defined, but should probably be in the region of several months due to late stent endothelialization.

Glycoprotein IIb/IIIa receptor blockers. GP IIb/IIIa receptor blockers were used in 22% of the patients with stable and in 40% of those with unstable CAD, a proportion increasing to 62% when PCI was undertaken as an emergency procedure. Within the spectrum of ACS, GP IIb/IIIa antagonist use was higher in patients presenting with ST-segment elevation, particularly during primary angioplasty. The demonstration of a long-term mortality reduction even reaching 70% by using abciximab in diabetic patients[7,37] does not seem to have had an impact on clinical practice, since the use of these agents was exactly the same in diabetic and non-diabetic patients. Thus, in the operator's mind, the concept of full antiplatelet protection seems to be currently associated with the clinical evidence of acute ongoing myocardial ischemia (60% use), rather than with the biological evidence of plaque instability as would be generally indicated by the clinical syndrome of ACS (40% use) or by elevated levels of the biomarkers of myocardial damage (40% use). If a conclusion has to be drawn about operator indications for using a GP IIb/IIIa inhibitor during PCI, the present data seem to indicate that these agents are administered for preventing acute complications in emergency conditions rather than with the idea of improving the long-term outcome. As far as the relative use of abciximab and tirofiban is concerned (eptifibatide was not being promoted in Italy at the time of the survey), abciximab was used 4 times more frequently than tirofiban in emergency conditions; besides, this agent was used as a bailout medication only in 15% of cases. On the other hand, tirofiban use in PCI seems to be less clear, since this agent was used off-label (i.e. without pretreatment) in 55% of the patients with an ACS, and under bailout conditions in 38% of cases in stable patients, despite the fact that neither proof of efficacy nor definite dose recommendations have been issued regarding its use under these conditions.

N-acetylcysteine, anti-ischemic agents and statins. Among the medications given preprocedurally in order to reduce the procedural risk, N-acetylcysteine has been shown to prevent contrast nephropathy in patients with chronic renal dysfunction[8,38]. Whether this method of preventing postprocedural serum creatinine elevations may also improve outcome is yet unknown, but the fact that in the present survey only 23% of the patients with preexisting renal failure received the nontoxic and inexpensive N-acetylcysteine prior to the procedure reveals significant room for improving the quality of care in this growing patient population. Compared to preprocedural treatment, beta-blocker prescription at discharge increased by an absolute 12% in the whole population and by 24% for ST-elevation myocardial infarction patients, resulting in a value slightly higher than that reported in the recent BLITZ registry of acute myocardial infarction[12]. Surprisingly enough, despite having undergone revascularization, almost 50% of the patients were discharged on nitrates, a prescription difficult to justify since these agents should be indicated only in symptomatic patients or in those with contraindications to beta-blockers[39]. Statins were prescribed at discharge to 72% of the patients irrespective of clinical presentation, a figure much higher than previously reported for patients with myocardial infarction[12], but very close to the actual prevalence on hypercholesterolemia reported by epidemiological studies in the Italian population with CAD[40]. This high prescription rate may be also the result of the indication that patients with prior cardiac events, including coronary revascularization, should be treated with the primary goal of achieving LDL cholesterol levels < 100 mg/dl[11].

In-hospital outcome and clinical implications. Among the possible reasons for the limited application of evidence-based treatments may be operator satisfaction with the extremely favorable in-hospital outcome of PCI. In line with the most recent reports[11,41], the overall rates of mortality and emergency bypass surgery or repeat angiography observed by the present survey are extremely low. However, two considerations

are suggested by the present data. First, postprocedural myocardial infarctions (or "enzyme elevations" as most interventionalists would prefer) go largely unreported. Although the study protocol mandated that "any postprocedural elevation in the serum CK-MB levels should be reported as a myocardial infarction", the rates of 2.4% for overall infarction, and 1.8 for enzyme elevations only, reported by clinicians in the present survey clearly underestimates the real size of the phenomenon as published in the literature[42]. A recently completed study of 4039 patients undergoing PCI at 17 Italian centers, with prospective blood sampling during the first 24 hours after PCI for CK-MB determinations at a core laboratory, showed that 8.6% of patients had CK-MB elevations > 2 times the upper normal limit, a proportion increasing to 16.2% when any elevations > upper normal limit were considered[43]. Second, the main impact of full antiplatelet protection during PCI has been shown to be on the long-term mortality, particularly in patients with ACS and in those with diabetes[7,9,10]. This is possibly mediated by prevention of postprocedural infarction or by any effect on the microcirculation. Since, in this case, the price of long-term benefit is all to be paid by higher hospital costs, the operator may be satisfied with the angiographic outcome of the procedure and reluctant to spend the extra money needed to provide long-term benefit. This reluctance seems to be much lower when it comes to prescribing posthospital medications, such as thienopyridines or statins, or even nitrates, whose costs do not impact on the hospital budget.

Study limitations. Among the study limitations is the lack of any check that the patients were actually enrolled consecutively. This may reduce the epidemiological value of the survey and lead to enrolment bias. Unfortunately, only a tiny minority of the centers complied with the explicit protocol requirement that a copy of the cath lab master book for the enrolment period should be sent to the Coordinating Center in order to check for consecutive enrolment, whereas the majority refused to do it due to privacy regulations. It should be considered, however, that most of the national registries, including the recent BLITZ surveys[12], though requiring consecutive enrolment did not check for it. This also applies for the Euro Heart survey[25] and other international registries. Despite these limitations, the short enrolment period should have facilitated enrolment of consecutive patients. In addition, two indirect proofs of "consecutive enrolment" are provided by the fact that the number of patients enrolled at each center quite reasonably reflects the total number of procedures reported for the year 2003 in the yearly PCI registry of the Italian Society of Invasive Cardiology[44], and by the ratio of elective vs emergency procedures, which was reasonably fair in most of the centers.

Due to the limited study budget, source data verification was carried out only by checking the patient discharge summaries. Therefore, the results rely mostly on the quality of reporting by the investigators. Also, little information is provided about drug dosage, information that was considered cumbersome to report in the study case record forms, and not reliable considering the incompleteness of source data verification. Self-referral of procedural success (however not the focus of the present registry) may have led to overestimation of the quality of the interventional results.

In conclusion, the efficacy of periprocedural drug therapy in reducing short-term complications and improving the long-term outcome of PCI are well documented by solid experimental evidence[18]. The IDEA registry represents the first attempt to survey periprocedural drug therapy for PCI. The findings of this survey suggest that some of the guideline recommendations have been well received by the Italian cardiologists, whereas others are applied with approximation or not at all, probably depending on the physician's perception of clinical risk and also on cost issues. Subacute stent thrombosis is adequately prevented by full prescription of aspirin and a thienopyridine after coronary stenting and is now a rare event. On the other hand, postprocedural myocardial infarction is clearly underreported and probably not perceived as a frequent clinical problem. Probably for this reason (but also owing to their impact on the hospital budget) GP IIb/IIIa agents, which act mainly by reducing the risk of postprocedural infarction, are underused, particularly in patients with ACS; the use of these agents is mainly associated with emergency procedures, where the angiographic evidence of an intracoronary thrombus and the risk of acute occlusion or of a suboptimal angiographic result is higher. Off-label use of drugs, using regimens of unproven efficacy, is not uncommon. Besides the antithrombotic drugs, N-acetylcysteine is used in a minority of patients with renal insufficiency; beta-blockers, statins and angiotensin-converting enzyme inhibitors seem to be administered according to guideline recommendations, whereas long-acting nitrates, which should be administered only to symptomatic patients, are probably overprescribed. The IDEA registry provides evidence in support of an educational effort aimed at promoting a more rational and cost-effective use of periprocedural drug therapy.

Appendix

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