Assessing the role of eptifibatide in patients with diffuse coronary disease undergoing drug-eluting stenting: The INtegrilin plus STenting to Avoid myocardial Necrosis Trial

Giuseppe Biondi-Zoccai, MD,[a] Marco Valgimigli, MD, PhD,[b] Massimo Margheri, MD,[c] Antonio Marzocchi, MD,[d] Corrado Lettieri, MD,[e] Amerigo Stabile, MD,[f] A. Sonia Petronio, MD,[g] Giorgio Binetti, MD,[h] Leonardo Bolognese, MD,[i] Pietro Bellone, MD,[j] Gennaro Sardella, MD,[k] Marco Contarini, MD,[l] Imad Sheiban, MD,[m] Sebastiano Marra, MD,[n] Federico Piscione, MD,[o] Francesco Romeo, MD,[p] Antonio Colombo, MD,[q] and Giuseppe Sangiorgi, MD[p] ***Rome, Gussago, Ravenna, Bologna, Mantova, Palermo, Pisa, Pesaro, Arezzo, Savona, Siracusa, Turin, Naples, and Milan, Italy***

Background The optimal antiplatelet regimen in elective patients undergoing complex percutaneous coronary interventions (PCIs) is uncertain. We aimed to assess the impact of glycoprotein IIb/IIIa (GpIIb/IIIa) inhibition with eptifibatide in clinically stable subjects with diffuse coronary lesions.

Methods Patients with stable coronary artery disease undergoing PCI by means of implantation of >33 mm of drug-eluting stent were single-blindedly randomized to heparin plus eptifibatide versus heparin alone. The primary end point was the rate of abnormal post-PCI creatine kinase–MB mass values. Secondary end points were major adverse cardiovascular events (MACEs) (ie, cardiac death, myocardial infarction, or urgent revascularization) and MACE plus bailout GpIIb/IIIa inhibitor use.

Results The study was stopped for slow enrollment and funding issues after including a total of 91 patients: 44 were randomized to heparin plus eptifibatide, and 47, to heparin alone. Analysis for the primary end point showed a trend toward lower rates of abnormal post-PCI creatine kinase–MB mass values in the heparin-plus-eptifibatide group (18 [41%]) versus the heparin-alone group (26 [55%], relative risk 0.74 [95% CI 0.48-1.15], $P = .169$). Similar nonstatistically significant trends were found for rates of MACE, their components, or MACE plus bailout GpIIb/IIIa inhibitors (all $P > .05$). Notably, heparin plus eptifibatide proved remarkably safe because major bleedings or minor bleeding was uncommon and nonsignificantly different in both groups (all $P > .05$).

Conclusions Given its lack of statistical power, the INSTANT study cannot definitively provide evidence against or in favor of routine eptifibatide administration in stable patients undergoing implantation of multiple drug-eluting stent for diffuse coronary disease. However, the favorable trend evident for the primary end point warrants further larger randomized studies. (Am Heart J 2012;163:835.e1-835.e7.)

Intravenous glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors have been proved as a safe and effective treatment in patients undergoing percutaneous coronary intervention (PCI) by means of balloon-only percutaneous transluminal coronary angioplasty.[1] Several seminal randomized, controlled trials have also established the superior risk-benefit ratio of GpIIb/IIIa inhibitors in patients undergoing bare-metal stent (BMS) implantation.[1-3] The benefit of GpIIb/IIIa inhibition in low-risk patients adequately pretreated with clopidogrel and aspirin has, however,

From the [a]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Italy, [b]Institute of Cardiology, University of Ferrara, Ferrara, and Cardiovascular Research Center, Salvatore Maugeri Foundation, IRCCS, Gussago, Italy, [c]Division of Cardiology, Ravenna Hospital, Ravenna, Italy, [d]Division of Cardiology, S. Orsola-Malpighi Hospital, Bologna, Italy, [e]Cardiology Department, Carlo Poma Hospital, Mantova, Italy, [f]Unit of Interventional Cardiology, ARNAS, Palermo, Italy, [g]Division of Cardiology, University of Pisa, Pisa, Italy, [h]Division of Cardiology, S. Salvatore Hospital, Pesaro, Italy, [i]Division of Cardiology, S. Donato Hospital, Arezzo, Italy, [j]Division of Cardiology, S. Paolo Hospital, Savona, Italy, [k]Cardiovascular, Respiratory, Geriatric and Nephrologic Sciences Department, Umberto I Hospital, Sapienza University of Rome, Italy, [l]Division of Cardiology, Umberto I Hospital, Siracusa, Italy, [m]Division of Cardiology, University of Turin, Turin, Italy, [n]Division of Cardiology, S. Giovanni Battista "Molinette" Hospital, Turin, Italy, [o]Division of Cardiology, Federico II University, Naples, Italy, [p]Institute of Cardiology, Tor Vergata University, Rome, Italy, and [q]Interventional Cardiology Unit, San Raffaele Hospital and EMO GVM Columbus, Milan, Italy.

RCT reg no. NCT01454440.

Submitted November 27, 2011; accepted February 5, 2012.

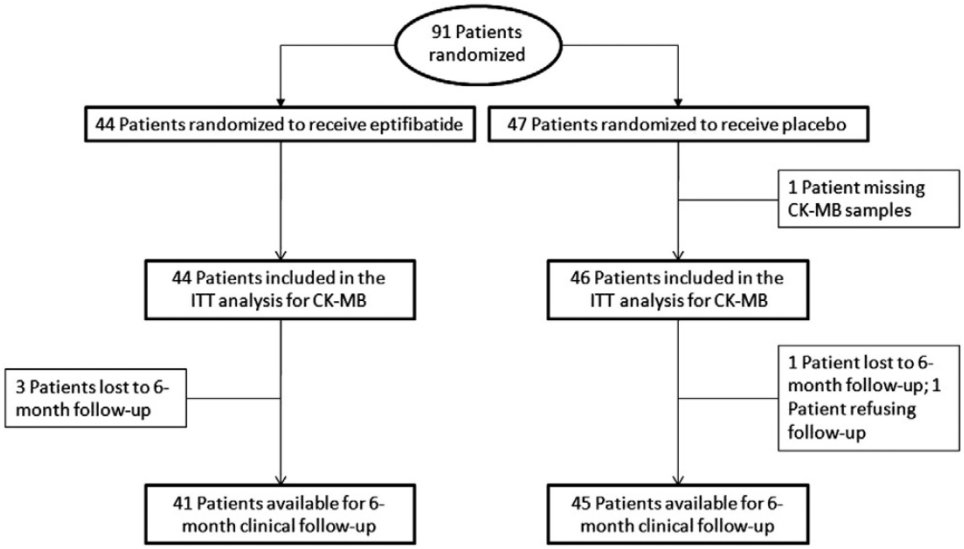
Reprint requests: Giuseppe Biondi Zoccai, MD, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Corso della Repubblica 79, 04100 Latina, Italy.

E-mail: gbiondizoccai@gmail.com

0002-8703/$ - see front matter

doi:10.1016/j.ahj.2012.02.009

Figure 1



Flow diagram of the study.

been challenged and is a subject of ongoing research, with recent data in support of more selective anticoagulation by means of bivalirudin rather than with heparin and GpIIb/IIIa inhibitors.[4-8] Indeed, the ISAR-REACT trials have shown that abciximab does not provide statistically significant benefits on top of optimal double antiplatelet therapy in stable patients and in low-risk unstable patients, whereas the opposite is true in higher risk unstable patients. However, the ISAR-REACT studies were all limited by an emphasis on risk-defining features based only on patient presentation, thus not giving any weight to coronary anatomical features. Accordingly, no subgroup of patients with clinically stable but anatomically complex coronary disease could be easily identified. Moreover, most comparative placebo-controlled trials of GpIIb/IIIa inhibitors were conducted in the percutaneous transluminal coronary angioplasty or BMS era, and few randomized trials have tested their role with drug-eluting stents (DESs).[9,10]

Although GpIIb/IIIa inhibitors are still used electively on a case by case basis or as bailout in stable patients with complex lesions and routinely in high-risk patients with acute coronary syndromes, there is a lack of prospective clinical trial data available on the role of GpIIb/IIIa inhibitors in patients treated with DES and high-loading clopidogrel. Specifically, consensus is building on the favorable results provided by GpIIb/IIIa inhibitors in high-risk patients, including those with multivessel coronary lesions or diffuse single-vessel disease.[11-13] Yet, there is no controlled study available in support of this approach combining both high-dose clopidogrel pretreatment and GpIIb/IIIa inhibition in patients with complex coronary lesions.

Table I. Baseline patient characteristics

	Eptifibatide (n = 44)	Placebo (n = 47)	*P*
Age (y)	67.3 ± 11.2	63.7 ± 9.2	.099
Female gender	9 (20.5%)	8 (17.0%)	.675
Weight (kg)	74.6 ± 11.4	79.6 ± 13.3	.057
Hypercholesterolemia	31 (70.5%)	34 (72.3%)	.842
Hypertension	33 (75.0%)	34 (72.3%)	.773
Family history of coronary artery disease	16 (36.4%)	14 (29.8%)	.505
Previous coronary artery bypass grafting	5 (11.4%)	4 (8.5%)	.734
Previous PCI	15 (34.1%)	13 (27.7%)	.506
Current or previous smoking	21 (47.7%)	28 (59.6%)	.257
Previous MI	13 (29.5%)	14 (29.8%)	.980
Diabetes mellitus	14 (31.8%)	14 (29.8%)	.834
Acute coronary syndrome at admission	18 (40.9%)	19 (40.4%)	.963

We hypothesized that GpIIb/IIIa inhibition may provide significant benefits on top of high-dose clopidogrel pretreatment in stable patients undergoing PCI by means of implantation of ≥2 DES in a single coronary lesion because of diffuse disease. The aim of the INSTANT was, thus, to assess, in a multicenter, randomized, single-blinded, controlled trial enrolling patients undergoing DES implantation for diffuse coronary artery disease, the efficacy and safety of GpIIb/IIIa inhibition by means of eptifibatide.

Table II. Medical therapy

	Eptifibatide (n = 44)	Placebo (n = 47)	P
Preprocedural medications			
Aspirin	44 (100%)	45 (95.7%)	.494
Ticlopidine	6 (13.6%)	4 (8.5%)	.513
Clopidogrel ongoing	25 (56.8%)	31 (66.0%)	.371
Clopidogrel loading	15 (34.1%)	16 (34.0%)	.996
Statins	30 (68.2%)	38 (80.9%)	.164
Postprocedural medications			
Aspirin	43 (97.7%)	45 (97.8%)	1.0
Clopidogrel	38 (86.4%)	44 (95.7%)	.305
Statins	39 (88.6%)	39 (84.8%)	.441
β-Blockers	36 (81.8%)	35 (76.1%)	.397
Nitrates	7 (15.9%)	13 (28.3%)	.176

Table III. Procedural and lesion characteristics

	Eptifibatide (patients = 44, lesions = 53)	Placebo (patients = 47, lesions = 77)	P
Target vessel			.807
Left anterior descending or its branches	32 (72.7%)	34 (72.3%)	
Left circumflex or its branches	4 (9.1%)	6 (12.8%)	
Right coronary artery or its branches	8 (18.2%)	7 (14.9%)	
Bifurcation	27 (61.4%)	30 (63.8%)	.807
Calcification	8 (18.6%)	10 (21.7%)	.711
>45° angulation	3 (6.8%)	4 (8.5%)	1.0
Thrombus	1 (2.3%)	0	.483
Predilation	37 (69.8%)	59 (76.6%)	.385
Stents	97	138	–
Stents per patient	2.7 ± 1.0	3.4 ± 1.4	.003
Multiple stents	33 (62.3%)	47 (61.0%)	.887
Stent type			.041
Paclitaxel-eluting stents	37 (31.4%)	65 (41.1%)	
Sirolimus-eluting stents	32 (27.1%)	50 (31.6%)	
Other DESs	49 (41.5%)	43 (27.3%)	
Stent length (mm)	22.8 ± 7.5	23.4 ± 7.6	.353
Stent diameter (mm)	2.92 ± 0.64	2.93 ± 0.43	.465
Maximum dilation pressure (atm)	16.6 ± 2.6	16.4 ± 3.3	.626
Postdilation	28 (52.8%)	39 (51.3%)	.806

Table IV. Qualitative and quantitative coronary angiography

	Eptifibatide (n = 44)	Placebo (n = 47)	P
Baseline			
TIMI 3 flow	36 (81.8%)	38 (80.9%)	.906
Corrected TIMI frame count	21.5 ± 9.5	23.0 ± 10.8	.242
Myocardial blush grade >2	12 (27.2%)	12 (25.5%)	.850
Reference vessel diameter (mm)	2.67 ± 0.35	2.79 ± 0.36	.055
Minimum lumen diameter (mm)	0.75 ± 0.34	0.75 ± 0.31	.505
Diameter stenosis (%)	72.1 ± 12.3	73.5 ± 9.8	.276
Length (mm)	42.6 ± 13.5	46.5 ± 13.3	.085
Postprocedural			
TIMI 3 flow	41 (93.2%)	43 (91.5%)	1.0
Corrected TIMI frame count	18.1 ± 6.6	16.2 ± 6.1	.920
Myocardial blush grade 3	38 (86.4%)	30 (63.8%)	.055
Reference vessel diameter (mm)	2.79 ± 0.47	2.81 ± 0.44	.417
Minimum lumen diameter (mm)	2.13 ± 0.45	2.11 ± 0.47	.582
Diameter stenosis (%)	23.8 ± 8.8	25.0 ± 9.6	.267

Methods

Study design

This was a multicenter, randomized, single-blinded, parallel-group, investigator-initiated study.

Patient selection and study conduct

The study was approved by review boards of all participating centers and was registered on clinicaltrials.gov (NCT01454440), and its protocol has been reported in detail elsewhere.[14] Briefly, we enrolled consecutive patients with stable coronary disease and diffuse disease involving a major epicardial coronary vessel undergoing percutaneous treatment on a native coronary vessel with planned implantation of >33 mm of DES with a reference vessel diameter 2.25 to 4.0 mm and who agreed and provided written, informed consent and had no contraindications to a 6-month clinical follow-up.

Treatment assignment between eptifibatide and control treatment (normal saline) was determined by randomization in a ratio of 1:1 by means of an online randomization system. Enrolled patients were randomized in the catheterization laboratory, after the decision to perform PCI by means of planned implantation of DES >33 mm in length in the same coronary vessel, to intravenous normal saline or intravenous eptifibatide (double bolus [180 μg/kg] followed by infusion [2 μg/kg per minute] for 18-24 hours after the procedure). Concomitantly to study drug administration, an intravenous bolus of unfractionated heparin (60 IU/kg) was administered, and during the procedure, patients received intravenous boluses of heparin in sufficient doses to prolong the activated clotting time (≥250 seconds). A clopidogrel loading dose of 600 mg was recommended in all patients even if pretreated. In addition, aspirin was provided by either the intravenous or oral route to patients not previously treated. After the procedure, patients with an angiographically successful procedure continued daily lifelong aspirin plus clopidogrel 75 mg/d for 12 months. *Procedural success* was defined as an angiographic residual diameter stenosis <20% (visual estimation).

Clinical follow-up and end points

Patients underwent preprocedural 6 ± 2– and 12 ± 2–hour blood draws to measure creatine kinase (CK), CK-MB mass, and troponin measurement. In case of abnormal postprocedural CK-MB mass levels, blood draws were repeated every 6 to 8 hours

Table V. Cumulative clinical outcomes at 6 months of follow-up

	Eptifibatide (n = 44)	Placebo (n = 47)	*P*
Complete clinical follow-up	42 (95.5%)	46 (97.9%)	.608
Angiographic follow-up	2 (4.5%)	7 (14.9%)	.159
All-cause death	1 (2.3%)	1 (2.1%)	1.0
Cardiac death	0	1 (2.1%)	1.0
Noncardiac death	1 (2.3%)	0	.484
Any MI	9 (20.5%)	15 (31.9%)	.215
Fatal MI	0	1 (2.1%)	1.0
Nonfatal MI	9 (20.%)	14 (29.8%)	.305
Repeat percutaneous revascularization	1 (2.3%)	1 (2.1%)	1.0
Coronary artery bypass grafting	0	0	1.0
Urgent TVR	1 (2.3%)	1 (2.1%)	1.0
Bailout GpIIb/IIIa inhibitors	1 (2.3%)	0	1.0
Major bleeding	0	0	1.0
Minor bleeding	2 (4.5%)	2 (4.3%)	1.0
Patients with at least 1 MACE	10 (22.3%)	13 (27.7%)	.588
Total MACE (including multiple events in individual patients)	10 (22.3%)	16 (34.0%)	.181
Abnormal postprocedural CK-MB levels (primary end point)	18 (40.9%)	26 (55.3%)	.169
MACE plus bailout GpIIb/IIIa inhibitors (secondary end point)	10 (22.3%)	13 (27.7%)	.588

Major adverse cardiac events were defined as the composite of cardiac death, nonfatal MI, or urgent TVR.

until the peak CK-MB mass had been identified. Telephone-based interviews and office-based direct visits were to be performed at 1 and 6 months, respectively, for end point adjudication.

The primary end point was the rate of elevated postprocedural peak CK-MB mass ratio values (ie, above the upper limit of normal [ULN], eg, 1.01 * ULN, according to each participating hospital laboratory). Secondary end points were the composite of cardiac death, nonfatal myocardial infarction (MI), urgent target vessel revascularization (TVR), and thrombotic bailout GpIIb/IIIa inhibitor therapy within 180 days: in-hospital 1- and 6-month *major adverse cardiovascular events* (*MACEs*), defined as the composite of cardiac death, nonfatal MI, or urgent TVR. Myocardial infarction was distinguished as new pathologic Q waves in ≥2 contiguous leads or non–Q wave MI (peak CK-MB mass >3 times the ULN together with abnormal CK). As additional safety and efficacy tertiary end points, we assessed the rate of major and minor bleedings (defined according to the thrombolysis in MI [TIMI] criteria). Events were adjudicated by an independent adjudication committee unaware of treatment assignment.

Statistical analysis and sample size calculation

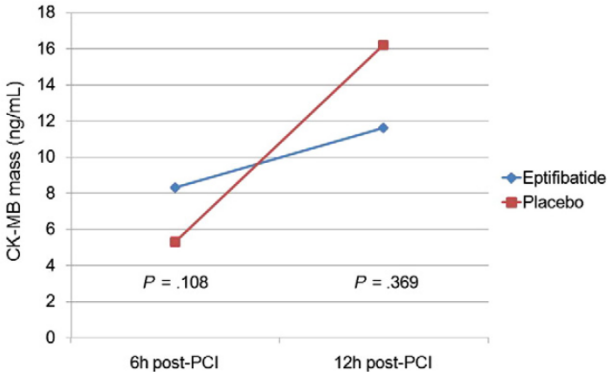
Continuous variables are reported as mean (SD) or median (interquartile range) and were compared by means of unpaired *t* or Mann-Whitney *U* test, when appropriate. Categorical variables are reported as raw numbers (n/N [%]) and were compared by means of Pearson χ^2, Fisher exact, or log-rank test, when appropriate. Survival analysis was conducted by means of both Kaplan-Meier method and Cox proportional hazard analysis.

Given an expected rate of abnormal postprocedural peak CK-MB ratio of 10% for the experimental group versus 25% for the control group,[7,18] aiming for a 5% α and 90% power, a total of 292 patients were deemed necessary (146 patients per group). This provisional sample was increased by 10% (leading to a total of 320 patients) to take into account potential losses to blood draw or follow-up.

Owing to difficulties in enrolling patients and funding issues due to the inability to meet enrollment milestones originally agreed upon with the sponsor, the study was prematurely stopped before any statistical analysis. At the time of study interruption, 92 patients had been randomized. Of these, 1 was erroneously randomized but not treated, leaving a total of 91 patients in the intention-to-treat population. With 45 patients in each treatment group, a difference of about 25% with a power of 80% at a statistical significance of 5% (2 tailed) could be demonstrated.

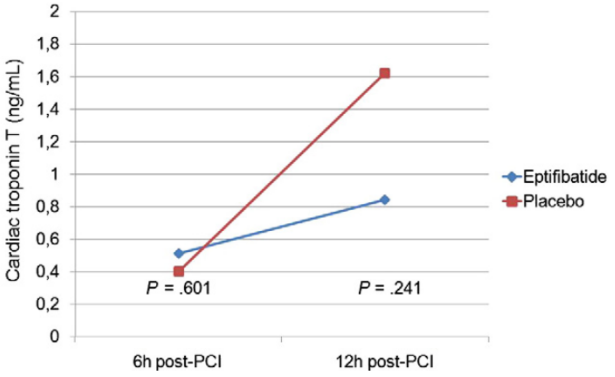
Funding for study conduct and drug preparation was provided by GlaxoSmithKline, Verona, Italy. No additional extramural funding

Figure 2



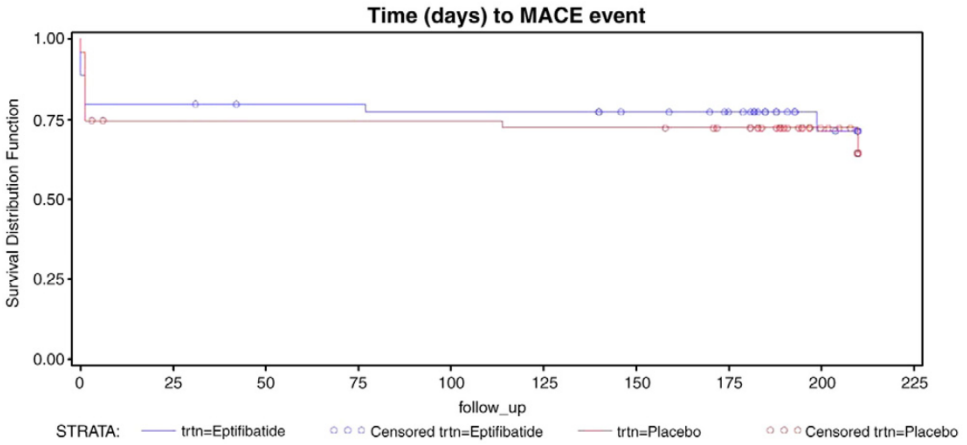
Changes in serum levels of CK-MB after PCI.

Figure 3



Changes in serum levels of cardiac troponin T after PCI.

Figure 4



Survival free from MACEs, showing similar results for the eptifibatide and placebo groups ($P = .7$ at log-rank test).

was used to support this work or the drafting of this report. The authors are solely responsible for the design and conduct of this study, the drafting and editing of the manuscript, and its final contents, with the notable exception of statistical analyses, which were conducted by an independent clinical research organization (Mediolanum Cardio Research, Milan, Italy).

Results

The study profile is reported in Figure 1. A total of 91 patients were randomized: 44 to heparin plus eptifibatide and 47 to heparin alone. Follow-up up to 6 months after the index procedure was available for 86 patients, as 4 were lost to follow-up, and 1 was contacted but refused further visits. Treatment groups were comparable at baseline (Table I), with an age of 67.3 ± 11.2 years in the heparin-plus-eptifibatide group and 63.7 ± 9.2 years in the heparin-only group ($P = .099$), female gender in 9 (20.5%) and 8 (17.0%, $P = .675$), and diabetes mellitus in 14 (31.8%) and 14 (29.8%, $P = .834$). Medical therapy (Table II), lesion, and procedural features were also similar in the 2 groups (Table III), with the notable exception of DES usage, as paclitaxel-eluting stents were used in 37 (31.4%) and 65 (41.1%), sirolimus-eluting stents in 32 (27.1%) and 50 (31.6%), and other DES in 49 (41.5%) and 43 (27.3%, overall $P = .041$). Postprocedural angiography also showed similar results in the 2 groups (Table IV), with final TIMI 3 flow in 41 (93.2%) and 43 (91.5%, $P = .0$) and corrected TIMI frames count of 18.1 ± 6.6 and 16.2 ± 6 ($P = .920$).

Appraisal of the primary end point of the study, that is, abnormal postprocedural CK-MB levels (Table V, Figures 2 and 3), showed a statistically nonsignificant trend in favor of the heparin-plus-eptifibatide group (18 [40.9%]) in comparison with the heparin-only group (26 [55.3%], relative risk 0.74 [95% CI 0.48-1.15], $P = .169$). Similar trends were found for MACE when analyzed as first MACE only (10 [22.3%] vs 13 [27.7%], $P = .588$) or multiple events (10 [22.3%] vs 16 [34.0%], $P = .181$) as well as the composite of MACE or bailout GpIIb/IIIa inhibitors (10 [22.3%] vs 13 [27.7%], $P = .588$) (Figure 4). Conversely, major and minor bleedings were similarly uncommon in both groups (respectively, 0 vs 0, $P = 1.0$, and 2 [4.5%] vs 2 [4.3%], $P = 1.0$).

Discussion

The INSTANT trial was designed based on the hypothesis that adjunctive GpIIb/IIIa inhibition could prove beneficial even in stable patients with complex or diffuse coronary artery disease undergoing PCI in the current dual antiplatelet era. Given the premature interruption of the study, all findings should be viewed only as exploratory and hypothesis generating. Notwithstanding this key limitation, we found a statistically non-significant trend in favor of the heparin-plus-eptifibatide regimen for the risk of postprocedural abnormal CK-MB values as well as for other clinical end points. Yet, CIs for the primary end point are wide (relative risk going from 0.48 to 1.15). Thus, pending further trials on the topic, we cannot provide statistical evidence to recommend routine use of eptifibatide in stable patients with complex or diffuse coronary artery disease undergoing PCI after adequate pretreatment or loading with dual antiplatelet therapy.

Several studies and meta-analyses have established the beneficial role of GpIIb/IIIa inhibition in patients undergoing balloon-only angioplasty, BMS implantation, or other types of PCI, such as directional coronary atherectomy. However, limited evidence on subjects receiving DES and dual antiplatelet therapy is available. Indeed, the recent studies suggested a paradoxical increase in clinical events with these drugs.[1] Although confounders might easily explain these findings, debate persists on the

usefulness of routine use of GpIIb/IIIa inhibitors in patients without acute or very recent MI.[4-5,8]

Indeed, several paradigm shifting changes have occurred in cardiovascular medicine since the introduction of GpIIb/IIIa inhibitors. The systematic adoption of dual antiplatelet therapy with aspirin and P2Y12 inhibitors,[15] new-generation thin-strut coronary stents,[16] and high-pressure dilation[17] has concomitantly brought major reductions in the early and late risks faced by patients with coronary artery disease undergoing PCI. Yet, most of the pivotal studies that provide the evidence base in favor of routine usage of GpIIb/IIIa inhibitors predate all the above milestones.[1-3,18] Thus, GpIIb/IIIa inhibitors are not used as frequently as recommended by some guidelines, especially in Europe, because physicians prefer ad hoc or bailout usage in several, if not most, cases.[19] Accordingly, the goal of our study was to provide further evidence in support or against of routine GpIIb/IIIa inhibition in stable patients but with clearly and explicitly identified anatomical complexity.

Our findings do not confirm previous reports on a potential paradoxical negative effect of GpIIb/IIIa inhibitors in patients receiving DES.[19] Yet, we found no statistical evidence in support of routine eptifibatide administration in stable patients with diffuse coronary artery disease. Although the primary end point was nonsignificantly but numerically lower in the eptifibatide group, lack of significant differences for post-PCI troponin and CK-MB levels confirms the overall study findings. Thus, also in keeping with results from the Munich and Ferrara group, we believe that it is appropriate to limit GpIIb/IIIa use to stable patients on a bailout setting unless antiplatelet unresponsiveness has been demonstrated.[4-5,8,20] Different results from the present ones might have been envisioned with a larger sample size or with adoption of more potent GpIIb/IIIa inhibitors,[21] but recent studies suggest noninferiority of eptifibatide in comparison with both abciximab and tirofiban in patients undergoing PCI.[22-27]

This work, despite being a randomized, controlled trial, has several limitations, including the choice of a surrogate as the primary end point. Indeed, the major drawback of the INSTANT study is the premature interruption of the study given slow enrollment, yielding a very small sample size. Thus, only hypothesis-generating analyses can be envisioned from the INSTANT trial. Decision makers must thus weigh the totality of available evidence when asking themselves on the risk-benefit balance of GpIIb/IIIa inhibition in patients with stable but complex coronary artery disease. Yet, our work does add to the current evidence base on GpIIb/IIIa inhibitors. Moreover, we agree with Guyatt et al[28] who emphasize that "given the primacy of systematic reviews—and the fact that individual clinical trials rarely provide definitive answers to a clinical research question—some commentators question whether the sample size calculation for an individual trial still matters."

Conclusions

Given its lack of statistical power, the INSTANT study cannot definitely provide evidence against or in favor of routine eptifibatide administration in stable patients undergoing implantation of multiple DES for diffuse coronary disease. However, the favorable trend evident for the primary end point warrants further larger randomized studies.

Disclosures

Conflicts of interest: Dr Biondi-Zoccai has lectured for AstraZeneca, Bristol Myers Squibb, Chiesi, Sanofi Aventis, and The Medicine Company.

Funding: Supported by an unrestricted grant from GlaxoSmithKline, Verona, Italy.

References

1. Karvouni E, Katritsis DG, Ioannidis JP. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. J Am Coll Cardiol 2003;41:26-32.
2. Topol EJ, Mark DB, Lincoff AM, et al. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicenter randomised trial. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Lancet 1999;354:2019-24.
3. O'Shea JC, Buller CE, Cantor WJ, et al. Long-term efficacy of platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention. JAMA 2002;287:618-21.
4. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. JAMA 2006;295:1531-8.
5. Kastrati A, Mehilli J, Schuhlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. N Engl J Med 2004;350:232-8.
6. Lotrionte M, Biondi-Zoccai G, Agostoni P, et al. Meta-analysis appraising high clopidogrel loading in patients undergoing percutaneous coronary intervention. Am J Cardiol 2007;100:1199-206.
7. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193-204.
8. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non–ST-elevation myocardial infarction. N Engl J Med 2011;365:1980-9.
9. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-17.
10. Valgimigli M, Campo G, Percoco G, et al, Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study (MULTISTRATEGY) Investigators. Comparison of angioplasty with

infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. JAMA 2008;299:1788-99.
11. Biondi-Zoccai GGL, Sangiorgi GM, Chieffo A, et al. Validation of predictors of intraprocedural stent thrombosis in the drug-eluting stent era. Am J Cardiol 2005;95:1466-8.
12. Orlic D, Bonizzoni E, Stankovic G, et al. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. J Am Coll Cardiol 2004;43:1154-60.
13. Tsagalou E, Chieffo A, Iakovou I, et al. Multiple overlapping drug-eluting stents to treat diffuse disease of the left anterior descending coronary artery. J Am Coll Cardiol 2005;45:1570-3.
14. Biondi-Zoccai GG, Valgimigli M, Sheiban I, et al. A randomized trial comparing eptifibatide vs. placebo in patients with diffuse coronary artery disease undergoing drug-eluting stent implantation: design of the INtegrilin plus STenting to Avoid myocardial Necrosis Trial. J Cardiovasc Med (Hagerstown) 2008;9:957-62.
15. Biondi-Zoccai G, Lotrionte M, Agostoni P, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol 2011;150:325-31.
16. Biondi-Zoccai GG, Agostoni P, Abbate A, et al. Adjusted indirect comparison of intracoronary drug-eluting stents: evidence from a metaanalysis of randomized bare-metal-stent-controlled trials. Int J Cardiol 2005;100:119-23.
17. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676-88.
18. Lengenfelder B, Stoerk S, Boes L, et al. Long-term reduction of mortality in the 4-year follow up of tirofiban therapy in elective percutaneous coronary interventions (TOPSTAR) trial. J Invasive Cardiol 2011;23:128-32.
19. Teirstein PS, Kao J, Watkins M, et al. Impact of platelet glycoprotein IIb/IIIa inhibition on the paclitaxel-eluting stent in patients with stable or unstable angina pectoris or provocable myocardial ischemia (a TAXUS IV substudy). Am J Cardiol 2005;96:500-5.
20. Valgimigli M, Campo G, de Cesare N, et al, Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) Investigators. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. Circulation 2009;119:3215-22.
21. Schiariti M, Saladini A, Cuturello D, et al. Long-term efficacy of high-dose tirofiban versus double-bolus eptifibatide in patients undergoing percutaneous coronary intervention. J Cardiovasc Med (Hagerstown) 2011;12:29-36.
22. Gurm HS, Tamhane U, Meier P, et al. A comparison of abciximab and small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention: a meta-analysis of contemporary randomized controlled trials. Circ Cardiovasc Interv 2009;2:230-6.
23. De Luca G, Ucci G, Cassetti E, et al. Benefits from small molecule administration as compared with abciximab among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-analysis. J Am Coll Cardiol 2009;53:1668-73.
24. Akerblom A, James SK, Koutouzis M, et al. Eptifibatide is noninferior to abciximab in primary percutaneous coronary intervention: results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). J Am Coll Cardiol 2010;56:470-5.
25. Ottani F, La Vecchia L, De Vita M, et al. Comparison by meta-analysis of eptifibatide and tirofiban to abciximab in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2010;106:167e1-74e1.
26. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. Eur Heart J 2010;31:35-49.
27. Zeymer U, Margenet A, Haude M, et al. Randomized comparison of eptifibatide versus abciximab in primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction: results of the EVA-AMI Trial. J Am Coll Cardiol 2010;56:463-9.
28. Guyatt GH, Mills EJ, Elbourne D. In the era of systematic reviews, does the size of an individual trial still matter. PLoS Med 2008;5:e4.