

Interventional Cardiology

Benefit of bolus-only platelet glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention: Insights from the very early outcomes in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial

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Background Platelet glycoprotein IIb/IIIa inhibitors are administered during percutaneous coronary intervention as a bolus followed by infusion. The need for an infusion was established by the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial conducted during the percutaneous transluminal coronary balloon angioplasty (PTCA) era, when the threat of acute thrombotic complications prevailed over concerns regarding bleeding, and stenting was considered an adverse event.

Methods The EPIC trial randomized high-risk PTCA patients to 3 arms: placebo, abciximab bolus only, and abciximab bolus plus infusion. The present analysis of the EPIC outcomes was done at 6-hour intervals during the first 24 hours after PTCA to identify any early benefit derived from the abciximab bolus-only arm.

Results At 6 hours after randomization, the primary composite end point of death, myocardial infarction, or urgent intervention was significantly reduced by 46% with abciximab bolus-only compared with placebo (2.9% vs 5.3%; $P = .022$), which is mainly due to a reduced rate of urgent intervention. There was also a numerical but not statistically significant reduction in myocardial infarction rate using abciximab bolus-only compared with placebo. A lower bleeding rate in the bolus-only arm compared with bolus plus infusion has been reported.

Conclusions As stenting and thienopyridine use have become routine, there has been a decrease in the incidence of acute closure and an increasing concern for bleeding complications after percutaneous coronary intervention, which potentially may be addressed by adopting a bolus-only glycoprotein IIb/IIIa inhibitor strategy. The early protective ischemic effect of abciximab bolus-only observed in the EPIC trial may be relevant in this regard. (*Am Heart J* 2006;152:876-81.)

During the initial experience with percutaneous transluminal coronary balloon angioplasty (PTCA), the importance of preventing early thrombotic complications was paramount because arterial dissection with subsequent abrupt closure and the need for emergency coronary artery bypass surgery (CABG) were not uncommon.¹ The intravenous glycoprotein (GP) IIb/IIIa inhibitors were first used in the setting of PTCA in an attempt to reduce abrupt vessel closure and urgent

revascularization. Over the last decade, improvements in mechanical therapies, in particular the stent, as well as improvements in the methods of stent deployment have radically reduced the acute thrombotic complications associated with coronary intervention. In addition, the development of a new pharmacologic class of oral antiplatelet agents in percutaneous coronary intervention (PCI), specifically the thienopyridines, has resulted in an extremely low incidence of abrupt closure and acute thrombotic complications. It is in this setting that the need for routine GP IIb/IIIa inhibition has come into question,²⁻⁴ particularly as the deleterious effects of periprocedural bleeding become more apparent.⁵ However, acute dissections and embolization of plaque content resulting in significant creatine kinase MB (CK-MB) isoform release still occur at the time of stent deployment, supporting the idea that at least during the procedure, potent intravenous antiplatelet therapy is

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likely to be protective. Based on these technological advances and theoretic considerations, we believe that a bolus-only GP IIb/IIIa strategy may now be most appropriate. The most compelling data to refute the idea of such a strategy are the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, in which an infusion after the abciximab bolus was needed to demonstrate superiority over placebo at the prespecified 30-day end point.⁶ In light of the recent developments discussed above (ie, stents and thienopyridines), the very early periprocedural outcome data from the EPIC trial may now be of interest.

To determine whether data from the EPIC trial could support a bolus-only GP IIb/IIIa strategy, we reexamined the EPIC database for outcomes over the first 24 hours after PTCA.

Methods

Study population, protocol, and end points

As previously reported,⁶ in the EPIC trial, 2099 patients scheduled to undergo high-risk coronary angioplasty were enrolled in 56 clinical centers throughout the United States. High-risk criteria were considered acute or recent myocardial infarction (MI), unstable angina, or complex target lesion angiographic morphology. Patients were randomized to 3 treatment arms: bolus and 12-hour infusion of placebo, abciximab bolus of 0.25 mg/kg plus 12-hour placebo infusion, and abciximab bolus plus 12-hour infusion (10 µg/min). Heparin was given as initial bolus of 10,000 to 12,000 units followed by bolus doses to keep the activated clotting time between 300 and 350 seconds during the intervention. In addition, patients received 325 mg of aspirin at least 2 hours before procedure and daily thereafter. Thienopyridines were not administered to patients in this study because at the time of the EPIC trial, these drugs were not indicated for PCI. Similarly, at the time patients were enrolled into the EPIC trial, the only coronary stent approved by the US Food and Drug Administration was the 20-mm Cook (Gianturco-Roubin) Flex Stent (Cook, Bloomington, IN), which was used in the EPIC study only to treat imminent or complete abrupt closure of the vessel undergoing angioplasty.⁶

The primary end point of the EPIC trial was a composite of death, MI, or urgent intervention during the first 30 days after randomization, with secondary end points of individual components.

Current data and statistical analysis

Patients enrolled in the EPIC trial were followed for prespecified clinical events and had blood samples drawn at various time points. The trial sponsor, Centocor, Inc (Malvern, PA), examined the available data and performed the statistical analysis for the current study. Although data were prospectively collected, this is a retrospective analysis of the early outcomes in the EPIC trial, at 6-hour intervals during the first day after randomization. The results at 48 and 72 hours as well as weekly to 30 days were also available and analyzed.

Composite and individual occurrences of death, MI, or urgent intervention were expressed as percentages at the

above time points. Pairwise comparisons of these values were performed between each abciximab group and the placebo group. Kaplan-Meier curves of the specified end points were generated for the first 24 hours after randomization. A *P* value of < .05 was considered statistically significant. There were no adjustments for multiple comparisons.

Results

The cumulative rates for the composite end point (death, MI, or urgent intervention) of the EPIC trial at 6-hour intervals during the first 24 hours, then at 48 and 72 hours, and weekly to 30 days are listed in Table I. For patients treated with abciximab bolus plus 12-hour infusion, a significant reduction in death, MI, or urgent intervention was seen at all time points compared with placebo. In contrast, patients treated with abciximab bolus-only demonstrated a statistically significant reduction in the composite end point at 6 hours only (46% reduction; *P* = .022). Beyond 6 hours, the event rates for the bolus-only arm were numerically lower than those associated with the placebo arm, but these differences were not statistically significant (Table I).

The rates for the individual components of the composite end point are presented in Table II. The significant reduction in the composite end point at 6 hours associated with the bolus-only arm was because of a nonstatistically significant 39% decrease in the rate of MI and a statistically significant 75% decrease in the rate of urgent intervention. The reduced rate of urgent intervention associated with the bolus only remained statistically significant throughout the first 24-hour observation period (Table II) and was sustained out to 7 days (4.3% vs 6.8% for bolus-only abciximab versus placebo, respectively; *P* = .045). The death rates were not different between the 3 groups at any time (Table II).

Kaplan-Meier curves were generated for the composite end point of death, MI, or urgent intervention and for the individual components of MI and urgent intervention during the first 24 hours after randomization (Figure 1). It is apparent from this figure that over the first 24 hours, the difference between abciximab bolus plus infusion versus bolus-only relates to the rate of MI. Specifically, whereas the rate of urgent intervention is identical (2% for both abciximab arms), the rate of MI is lower with patients receiving a 12-hour infusion. However, this difference of 2.4% versus 1.6% at 6 hours does not reach statistical significance.

Previously reported rates of bleeding were numerically lower with abciximab bolus-only compared with bolus plus 12-hour infusion, although these differences did not reach statistical significance.⁷ There was, however, a statistically significant difference in major bleeding rates between the bolus plus infusion group compared with placebo group (14% vs 7%; *P* < .001) that was driven by the difference in non-CABG-related major bleeding complications (10.6% for abciximab plus infusion vs

Table I. Cumulative rates for the composite end point of death, MI, and urgent intervention

Time after randomization	Placebo (n = 696)	Abciximab bolus only (n = 695)	P*	Abciximab bolus plus infusion (n = 708)	P†
6 h	37 (5.3)	20 (2.9)	.022	17 (2.4)	.005
12 h	46 (6.65)	33 (4.7)	.129	30 (4.2)	.047
18 h	52 (7.5)	40 (5.8)	.189	35 (4.9)	.047
24 h	58 (8.3)	44 (6.3)	.146	39 (5.5)	.035
48 h	67 (9.6)	55 (7.9)	.243	42 (5.9)	.009
72 h	74 (10.6)	56 (8.1)	.096	44 (6.2)	.003
7 d	80 (11.5)	63 (9.1)	.130	50 (7.1)	.004
14 d	84 (12.1)	69 (9.9)	.189	52 (7.3)	.003
21 d	86 (12.4)	71 (10.2)	.194	53 (7.5)	.002
30 d	87 (12.5)	73 (10.6)	.226	54 (7.6)	.002

Values are expressed as n (%).

*P value between the abciximab bolus only and placebo.

†P value between the abciximab bolus plus infusion and placebo.

Table II. Rates for the individual end points of death, MI, and urgent intervention at 6-hour intervals during the first day after randomization and at 30 days

Time after randomization	Placebo (n = 696)	Abciximab bolus only (n = 695)	P*	Abciximab bolus plus infusion (n = 708)	P†
Death					
6 h	1 (0.1)	0 (0)	.318	1 (0.1)	.990
12 h	1 (0.1)	1 (0.1)	1.00	1 (0.1)	.990
18 h	1 (0.1)	2 (0.3)	.563	1 (0.1)	.990
24 h	1 (0.1)	2 (0.3)	.563	1 (0.1)	.990
30 d	12 (1.7)	9 (1.3)	.510	12 (1.7)	.961
MI					
6 h	28 (4.0)	17 (2.4)	.098	11 (1.6)	.005
12 h	38 (5.5)	26 (3.7)	.126	24 (3.4)	.058
18 h	44 (6.3)	32 (4.6)	.158	27 (3.8)	.032
24 h	48 (6.9)	35 (5.0)	.142	30 (4.2)	.029
30 d	60 (8.6)	43 (6.2)	.083	37 (5.2)	.012
Urgent intervention					
6 h	20 (2.9)	5 (0.7)	.002	10 (1.4)	.058
12 h	24 (3.4)	11 (1.6)	.026	11 (1.6)	.023
18 h	25 (3.6)	12 (1.7)	.030	13 (1.8)	.042
24 h	29 (4.2)	14 (2.0)	.020	14 (2.0)	.017
30 d	52 (7.5)	37 (5.4)	.094	23 (3.3)	<.001

Values are expressed as n (%).

*P value between the abciximab bolus only and placebo.

†P value between the abciximab bolus plus infusion and placebo.

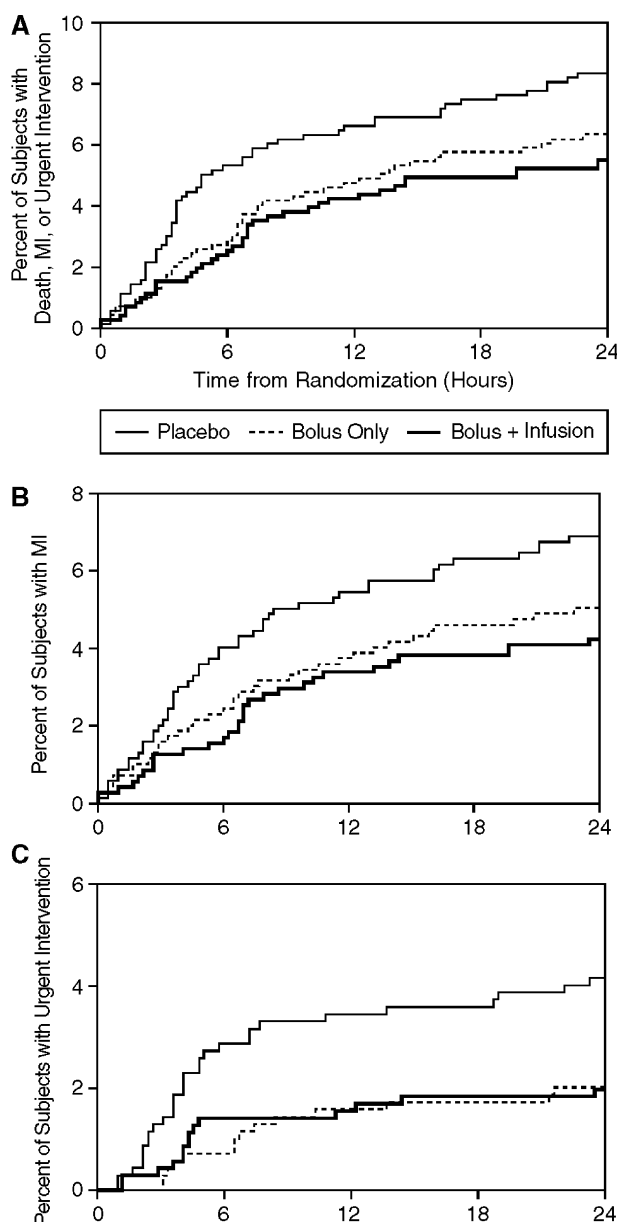
3.3% for placebo), whereas the CABG-related bleeding rates were similar between the 3 groups.⁷ Patients receiving abciximab bolus plus infusion had statistically significant more thrombocytopenia and required more blood transfusions than those treated with abciximab bolus only.⁸

Discussion

The present analysis of the early results in the EPIC trial demonstrates a significant reduction in the composite end point of death, MI, or urgent intervention at 6 hours in the abciximab bolus-only group compared

with the placebo group. After 6 hours and throughout the first 24 hours postprocedure, a numerical reduction is apparent, but statistical significance is not achieved. The fact that a bolus-only strategy appears to be effective in the first 6 hours may be relevant in the context of stenting and routine administration of a loading dose of clopidogrel.^{3,4,9} On the basis of a prespecified cutoff point for analysis, the Clopidogrel for the Reduction of Events During Observation study investigators initially reported that patients who had received clopidogrel at least 6 hours before PCI had a reduced rate of ischemic complications.⁹ Later analyses showed that with a loading dose of 300 mg, even a 6-hour interval was not

Figure 1



Kaplan-Meier curves for cumulative occurrence of death, MI, or urgent intervention (**A**) as well as for the individual occurrence of MI (**B**) and urgent intervention (**C**) during the first 24 hours after randomization.

sufficient, with efficacy becoming apparent at approximately 15 hours after clopidogrel ingestion.¹⁰ More recent studies have demonstrated that the administration of a higher loading dose (600 mg) appears to shorten the onset of clopidogrel's protective effects to within 2 to 3 hours, a range that is well within the

6 hours of abciximab's protective effect after bolus-only administration.^{3,4}

The improved outcomes at 6 hours associated with abciximab bolus-only versus placebo were predominantly because of a 75% reduction in the 6-hour urgent intervention rate, a benefit that was maintained over the first 24 hours after angioplasty. Although the reduction in urgent intervention over the first 24 hours with abciximab bolus-only therapy was equally profound to that seen with a bolus plus infusion strategy (Figure 1, C), at the prespecified study end point of 30 days, only the bolus plus infusion arm maintains statistical significance (Table II). Presently however, the rates of urgent intervention after PCI are extremely low due to stenting that has virtually eliminated abrupt closure.

The rates of MI in the abciximab bolus-only group are numerically but not statistically significantly lower. In contrast, patients receiving abciximab bolus plus infusion have a lower rate of MI in comparison with placebo-treated patients at all time points. As previously reported,⁶ the difference between the abciximab groups was mainly because of the rate of small non-Q wave MI, whereas the rates of Q wave or large MI remained similar throughout the study period. Why the very early rates of non-Q wave MI should differ between bolus-only and bolus plus infusion is unclear but may relate to the fact that the bolus dosing of abciximab targets only 80% receptor occupancy.¹¹ Subsequent pharmacokinetic studies have demonstrated that optimal platelet inhibition is not achieved in up to 20% of patients with the dose of the abciximab bolus used in the EPIC trial.¹² Such patients would likely be most vulnerable to a lack of an infusion to maintain receptor occupancy at already borderline efficacious levels, potentially resulting in early periprocedural myonecrosis. Indeed, the GOLD study suggests that suppression of CK-MB release is best achieved with 95% inhibition of platelet aggregation at the time of PCI, and that the level of platelet inhibition in the later hours (12-16 hours after PCI) is less important when one takes into account the degree of intraprocedural inhibition.¹² Although variations in the dose of the abciximab bolus have not been investigated, several studies have been performed with small molecule GP IIb/IIIa inhibitors using 2- to 2.5-fold increases in the bolus dose.¹³⁻¹⁹

Previous reports from the EPIC trial have documented that the highest rates of major bleeding are seen in the abciximab bolus plus infusion arm (14%), with intermediate rates in the bolus-only arm (11%) and the lowest rate of major bleeding in the placebo arm (7%) ($P < .001$).⁷ In addition, a statistically significant increase in thrombocytopenia in the abciximab bolus plus infusion group (5.2%) compared with bolus-only (3.0%) and placebo group (3.3%) has been reported.⁸ Finally, a median maximum decrease in hemoglobin and hematocrit of 2.3 g/dL and 6.5%,

respectively, in the abciximab bolus plus infusion group was significantly greater than the 1.8 g/dL and 5.4% reductions seen in the placebo group; patients in the abciximab bolus-only group had intermediate values (2.2 g/dL and 6.5%).⁷ Recent multivariate analysis of the data from the REPLACE-2 trial suggests that periprocedural bleeding is a more powerful predictor of 1-year mortality than periprocedural CK-MB elevation.⁵ On the basis of these observations, some have argued that the higher rate of CK-MB elevation seen with the bivalirudin arm in comparison with the routine GP IIb/IIIa inhibitor arm is offset by the advantage of reduced bleeding. The reduced bleeding in the bivalirudin arm may in part reflect the absence of a postprocedural bivalirudin infusion. The observations we now report from the EPIC trial are potentially relevant because they point to a strategy that combines elements both to reduce periprocedural infarction (ie, full platelet blockade) and bleeding (ie, no postprocedural infusion). There is a potential to reduce even further the bleeding rates observed in EPIC by using lower doses of heparin that are more representative of contemporary practice.²⁰ In fact, bolus-only GP IIb/IIIa inhibition has been associated with excellent long-term outcomes²¹; the long-term follow-up of the EPIC trial demonstrates that the lowest mortality rate at 7 years is seen in the bolus-only arm (16.1% vs 20.1% for placebo and 17.3% for bolus plus infusion; data on file at Centocor).

Study limitations

The EPIC trial was designed for a 30-day composite end point analysis and not for early outcomes at 24 hours after randomization. However, we believe that the present analysis is relevant because the standard approach to coronary intervention has changed dramatically since the EPIC trial was conducted. Although insertion of a stent in the EPIC trial was considered an adverse event, presently, stent insertion with adjuvant thienopyridine therapy represents the standard of care. An additional limitation is that the time points for the analysis of bleeding complications and thrombocytopenia do not match those for ischemic outcomes.

Conclusion

An antiplatelet GP IIb/IIIa receptor bolus-only strategy in PCI is associated with an early protective anti-ischemic effect. In the current era of routine clopidogrel and stenting, this early effect may be sufficient to reduce the thrombotic complications of PCI with the potential advantage of a reduced rate of bleeding complications, reduced length of stay, and reduced costs. A randomized trial of bolus-only platelet GP IIb/IIIa inhibition versus the conventional bolus plus infusion, ideally with an additional arm of bivalirudin, would be of interest.

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