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THE EPILOG TRIAL

Abciximab prevents ischemic complications during angioplasty

ABSTRACT

The EPILOG trial showed that the platelet glycoprotein IIb/IIIa inhibitor abciximab, together with heparin in a low, weight-adjusted dose, markedly reduced the risk of acute ischemic complications during percutaneous coronary revascularization, without increasing the risk of hemorrhage.

DURING AND AFTER percutaneous coronary revascularization, a number of acute ischemic complications can happen if the vessel closes abruptly, such as transmural (Q-wave) and non–Q-wave myocardial infarction (MI) and even death.[1–3] Platelet aggregation is an important mechanism in causing the intracoronary thrombosis that is thought to cause abrupt vessel closure after coronary intervention.[4] Thus, strategies to prevent these complications include antagonism of the platelet surface-membrane glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation.

EARLIER STUDIES SET THE STAGE

An earlier trial (EPIC—*E*valuation of 7E3 for the *P*revention of *I*schemic Complications) found that abciximab, a murine monoclonal antibody against the glycoprotein IIb/IIIa receptor, reduced acute ischemic events in patients undergoing "high-risk" percutaneous coronary revascularization by 35%.[5] To qualify as "high-risk," patients had to have acute MI, unstable angina with ischemic electrocardiographic changes, or complex coronary arterial lesions.

However, the advantage came at a price of a doubling of the rate of bleeding complications, possibly because patients receiving abciximab also received heparin in a standard high dose.[6]

A subsequent study suggested that hemorrhagic complications could be markedly reduced, with no loss in the reduction of ischemic endpoints, by using lower doses of heparin with abciximab and by removing the vascular sheath early after completing the revascularization procedure.[7] (The EPIC study investigators had left the vascular introduction sheath in place for the entire 12 hours of the abciximab infusion, out of concern that abciximab would cause uncontrolled bleeding at the insertion site if the sheath were removed sooner. However, in light of the subsequent study, this precaution was unnecessary and may have actually had the opposite effect.)

The stage was thus set for the EPILOG trial (*E*valuation in *P*TCA to *I*mprove Long-Term Outcome with Abciximab GP IIb/IIIa Blockade).

The EPILOG study was ended early because abciximab was clearly beneficial

DESIGN OF THE EPILOG TRIAL

EPILOG was a double-blind, randomized, placebo-controlled trial conducted at 69 sites in the United States and Canada. It was designed to test two questions:

- Whether abciximab would be beneficial in all patients undergoing percutaneous revascularization, not just patients at high risk.
- Whether bleeding complications could be reduced by using lower doses of heparin.[8]

TABLE 1

Effect of using abciximab plus heparin in high or low doses during angioplasty on efficacy endpoints within 30 days

EFFICACY ENDPOINT	PLACEBO + STANDARD-DOSE HEPARIN (N = 939)	ABCIXIMAB + LOW-DOSE HEPARIN (N = 935)	ABCIXIMAB + STANDARD-DOSE HEPARIN (N = 918)
Death	0.8%	0.3%	0.4%
Myocardial infarction	8.7%	3.7%*	3.8%*
Q-wave	0.8%	0.4%	0.5%
Non–Q-wave	7.9%	3.2%*	3.4%*
Death or myocardial infarction	9.1%	3.8%*	4.2%*
Urgent revascularization	5.2%	1.6%*	2.3%†
Repeat PTCA	3.8%	1.2%*	1.5%†
Coronary artery bypass grafting	1.7%	0.4%†	0.9%
Death, myocardial infarction, or urgent revascularization	**11.7%**	**5.2%***	**5.4%***

*$P < .001$ compared with placebo; †$P < .01$ compared with placebo

SOURCE: ADAPTED FROM THE EPILOG INVESTIGATORS, REFERENCE 8

Earlier, abciximab caused a doubling of the bleeding rate

Patients

In all, the study included 2,792 patients undergoing elective or urgent percutaneous revascularization with angioplasty (95% of patients) or directional coronary atherectomy (5% of patients). Patients with acute MI or unstable angina with ischemic electrocardiographic changes within the previous 24 hours were excluded.

Study protocol

Patients were randomly assigned to receive one of three regimens:

- **Abciximab plus standard-dose heparin.** The abciximab dosage was a 0.25 mg/kg bolus followed by a 0.125 µg/kg/minute infusion for 12 hours; the standard heparin dosage was a 100 U/kg bolus plus additional boluses as necessary to achieve a procedural activated coagulation time (ACT) of at least 300 seconds.
- **Abciximab plus low-dose heparin.** The abciximab dosage was the same as above; the heparin dosage was a 70 U/kg bolus with additional boluses as necessary to achieve an ACT target of at least 200 seconds.
- **Placebo plus standard-dose heparin.** The heparin dosage was as listed above.

All patients received aspirin before the procedure and then daily. Heparin was discontinued immediately after the procedure was completed, and the vascular sheaths were removed when the ACT was adequately low.

Patients in each treatment group were evenly matched for clinical characteristics, indications for percutaneous revascularization, and coronary artery disease risk factors.

Study endpoints

The primary endpoint was the total of three individual endpoints at 30 days:

- All-cause mortality
- Myocardial infarction
- Need for urgent revascularization (coronary artery bypass surgery or repeat angioplasty).

Secondary endpoints included death, infarction, and urgent or nonurgent revascularization for recurrent ischemia at 6 months. Safety outcome data on events such as major bleeding, transfusions, and thrombocytopenia were also collected.

RESULTS OF THE EPILOG TRIAL

Originally, the investigators estimated they would need a sample size of 4,800 patients, but the trial was terminated with only 2,792 patients enrolled because an interim analysis revealed an overwhelming benefit for patients treated with abciximab.

Results at 30 days

At 30 days, 5.2% of the patients who received abciximab plus low-dose heparin had either died, had an MI, or had undergone urgent revascularization, compared with 11.7% of the patients who received placebo plus standard-dose heparin, and 5.4% of the patients treated with abciximab plus standard-dose heparin ($P < .001$; TABLE 1). The benefit was evident in the first few days (FIGURE 1). Of the three individual endpoints, non–Q-wave infarctions and urgent revascularizations accounted for the largest differences among treatment groups.

Subgroup analyses revealed that abciximab was beneficial across diverse patient groups. Impressive reductions in the composite endpoint were seen not only in patients deemed to be at high risk (due to an MI within the previous 7 days or adverse lesion morphology on angiography), but in those at low risk as well, and in patients with stable or unstable angina. Moreover, there were no differences in the effect of abciximab according to age, gender, or weight.

Bleeding. Major bleeding was uncommon in all treatment groups, but minor bleeding occurred most often in patients who received abciximab plus standard-dose heparin (TABLE 2). In addition, the rate of minor bleeding with abciximab plus low-dose heparin was not significantly different from the rate with placebo plus standard-dose heparin, but the rate of transfusion was lower.

Results at 6 months

At 6 months, fewer patients in the abciximab groups than in the placebo group had suffered the composite endpoint of death, MI, or revascularization, but the difference was not as dramatic as at 30 days (TABLE 3).

The reductions in the rates of non–Q-wave MI and urgent revascularization were still statistically significant ($P < .05$) at 6 months, but the rate of nonurgent revascularization was actually higher in the abciximab groups (*P* NS). The investigators attributed the diminution of the overall benefit at 6 months to a lack of salutary effect of abciximab on nonurgent repeat revascularization (restenosis).

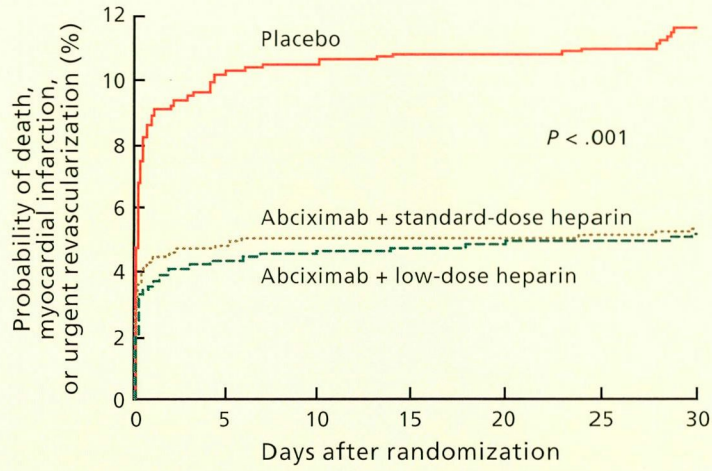

FIGURE 1. Kaplan-Meier estimate of the probability of the primary efficacy endpoints (death, myocardial infarct, or urgent repeated revascularization) within 30 days after randomization, according to treatment assignment.

SOURCE: FROM THE EPILOG INVESTIGATORS, REFERENCE 8

EPILOG included both high-risk and low-risk patients

IMPLICATIONS OF THE EPILOG TRIAL

By extending the use of abciximab to patients undergoing nonurgent, elective percutaneous coronary revascularization, the EPILOG investigators demonstrated that abciximab limits the development of important ischemic endpoints in patients undergoing routine coronary intervention.[8] Both the EPILOG and EPIC trials showed a substantial reduction in the incidence of nonfatal MI and in the need for emergent repeat revascularization procedures with abciximab use.[5,8] Likewise, preliminary reports from the RAPPORT trial, which compared abciximab and placebo with standard high-dose heparin in patients being treated with primary angioplasty for acute MI,

TABLE 2

Effect of using abciximab plus heparin, in high or low doses during angioplasty, on bleeding endpoints

BLEEDING ENDPOINT	PLACEBO + STANDARD-DOSE HEPARIN (N = 939)	ABCIXIMAB + LOW-DOSE HEPARIN (N = 935)	ABCIXIMAB + STANDARD-DOSE HEPARIN (N = 918)
Major bleeding	3.1%	2.0%	3.5%
Minor bleeding	3.7%	4.0%	7.4%*
Transfusion			
Red cells	3.9%	1.9%†	3.3%
Platelets	1.1%	0.9%	1.6%

*$P < .001$ compared with placebo; †$P < .05$ compared with placebo

SOURCE: ADAPTED FROM THE EPILOG INVESTIGATORS, REFERENCE 8

have shown a reduced need for emergent revascularization at 30 days.[9]

Confirming the results of prior pilot studies, the EPILOG trial also proved that the risk of bleeding from combined abciximab and heparin use could be decreased by using low-dose heparin without sacrificing any of the therapeutic benefits of abciximab.

Abciximab is expensive but may be cost-effective

Does abciximab confer long-term benefit?

Several previous studies showed that MI during coronary interventions is associated with adverse long-term outcomes. Likewise, the EPIC trial demonstrated a stepwise increase in long-term mortality with increasing levels of periprocedural creatine kinase elevation.[10–14] Abciximab treatment significantly reduced the rate of non–Q-wave infarctions in both the EPIC and EPILOG trials, which suggests that the patients treated in the EPILOG trial with abciximab may have a long-term mortality benefit similar to that seen in the EPIC trial.[10]

Although the EPIC trial demonstrated a 13.3% reduction in long-term target vessel revascularization with abciximab, the EPILOG trial did not duplicate this finding in its 6-month results.[7,8] Coronary stents may account for this difference. Few patients received stents in the EPIC trial, but 12% of the EPILOG patients received them for threatened abrupt closure after angioplasty.[8] Thus, stent use may have attenuated the effect of abciximab on repeat revascularization procedures.

The EPIC investigators recently examined their 3-year follow-up results, and found a persistent reduction of 13% in the composite endpoint of death, MI, or revascularization.[10] Abciximab treatment reduced the rate of mortality from 8.6% to 6.8%, repeat revascularization from 40.1% to 34.8%, and MI from 13.6% to 10.7%. Patients in the highest-risk subgroup of evolving MI or unstable angina tended to derive the most benefit from abciximab and had a 60% reduction in mortality.

Cost-effectiveness of abciximab

While abciximab has dramatic clinical effects in patients undergoing coronary interventions, it is expensive and may not be indicated for all patients.

In a formal economic analysis of the EPIC trial, the cost of a single abciximab dose was $1,407.[15] Further, patients who received abciximab incurred more costs due to bleeding episodes. However, they incurred less costs due to hospitalizations, repeat revascularizations, and ischemic events. Taking all these factors into account, the investigators found the net 6-month cost of abciximab to be only $293 per patient.

When the economic analysis of the EPILOG trial is published, the relative cost-effectiveness of abciximab treatment in all patients who undergo coronary interventions can be better evaluated. Given the decreased bleeding events seen with low-dose heparin, the shortened hospital stay with early vascular sheath removal, and the durable benefit of abciximab at 6 months in the EPILOG trial, greater savings are expected.

Unresolved questions

While abciximab has become the most important measure yet to improve the safety of percutaneous transluminal coronary angioplasty, important questions remain about which patients will benefit from it. High-risk patients with evolving MI or unstable angina have been shown to have impressive long-term benefits with abciximab, but which low-risk patients will show similar benefits has yet to be determined.

Additionally, the role of abciximab in the

TABLE 3

Effect of using abciximab plus heparin in high or low doses during angioplasty on efficacy endpoints at 6 months

EFFICACY ENDPOINT	PLACEBO + STANDARD-DOSE HEPARIN (N = 939)	ABCIXIMAB + LOW-DOSE HEPARIN (N = 935)	ABCIXIMAB + STANDARD-DOSE HEPARIN (N = 918)
Death	1.7%	1.1%	1.4%
Myocardial infarction	9.9%	5.0%*	5.3%*
Q-wave	1.6%	1.3%	1.4%
Non–Q-wave	8.4%	3.9%*	3.9%*
Repeat revascularization	19.4%	19.0%	18.4%
Urgent	6.7%	3.1%*	3.5%†
Not urgent	13.8%	16.7%‡	15.4%
Target-vessel	18.1%	17.0%	16.2%
Death, myocardial infarction, or urgent revascularization	14.7%	8.4%*	8.3%*
Death, myocardial infarction, or any revascularization	**25.8%**	**22.8%‡**	**22.3%†**

*$P < .001$ compared with placebo; †$P < .05$ compared with placebo; ‡$P = .07$

SOURCE: ADAPTED FROM THE EPILOG INVESTIGATORS, REFERENCE 8

contemporary "stent era" is unclear, since many patients undergoing coronary interventions now receive stents. The EPILOG-STENT trial will soon be completed and should help to determine which combination of mechanical and pharmacologic coronary intervention is most beneficial and cost-effective for patients undergoing percutaneous revascularization.

The role of abciximab in the "stent era" is unclear

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