An early invasive strategy reduced the incidence of major cardiac events in patients with unstable coronary syndromes

Cannon CP, Weintraub WS, Demopoulos LA, et al., for the TACTICS—Thrombolysis in Myocardial Infarction 18 Investigators. **Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban.** N Engl J Med. 2001 Jun 21;344:1879-87.

QUESTION

In patients with unstable coronary syndromes who are receiving the glycoprotein IIb/IIIa inhibitor tirofiban, is an early invasive strategy more effective than a conservative approach to reduce death, nonfatal myocardial infarction (MI), or rehospitalization for an acute coronary syndrome?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessors),* controlled trial with 6-month follow-up (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 [TACTICS–TIMI 18]).

SETTING

{180 sites worldwide}†.

PATIENTS

2220 patients (mean age 62 y, 57% men) who were ≥ 18 years of age and had electrocardiographic evidence of ischemia, elevated levels of troponin T (> 0.01 ng/mL), or documented coronary artery disease. Exclusion criteria included persistent ST-segment elevation, secondary angina, recent coronary revascularization, factors associated with increased risk for bleeding, left bundle-branch block or paced rhythm, severe congestive heart failure or cardiogenic shock, serious systemic disease, a serum creatinine level > 221 µmol/L, current warfarin use, or ticlopidine or clopidogrel use within the previous 3 days. Follow-up was > 98%.

INTERVENTION

Patients were allocated to an early invasive group (n = 1114) or to a conservative group (n = 1106). Patients in the invasive group had coronary angiography (CA) < 48 hours after randomization; the other group received medical treatment and a predischarge exercise-tolerance test. This group only received CA if they had objective evidence of recurrent ischemia or a positive result on a stress test before the end of the second stage of the Bruce protocol.

MAIN OUTCOME MEASURES

Combined end point of death, nonfatal MI, and rehospitalization for an acute coronary syndrome.

MAIN RESULTS

The combined incidence of death, nonfatal MI, or rehospitalization was lower in patients in the early-invasive-strategy group than in those in the conservative group at 30 days (P = 0.009) and 6 months (P = 0.025) (Table).

CONCLUSION

In patients with unstable coronary syndromes, an early invasive strategy was more effective than a conservative approach.

Source of funding: Merck.

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*See Glossary.

†**Cannon CP, Weintraub WS, Demopoulos LA, et al.** Am J Cardiol. 1998;82:731-6.

Early invasive vs conservative strategy for unstable coronary syndromes‡

Outcomes	Invasive	Conservative	RRR (95% CI)	NNT (CI)
Combined end point at 30 d§	7.4%	10.5%	30% (8 to 46)	32 (19 to 132)
Combined end point at 6 mo§	15.9%	19.4%	18% (2 to 32)	29 (15 to 265)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
§Combined end point = death, nonfatal myocardial infarction, or rehospitalization.

COMMENTARY

Previous randomized studies have failed to show that a routine invasive strategy has more benefit than a more selective invasive strategy (proceeding to CA for recurrent symptoms or when noninvasive testing identifies ischemia) in an unstable coronary syndrome. In contrast, Cannon and colleagues (TACTICS–TIMI 18) showed that in addition to standard medical therapy, IIb/IIIa inhibition with tirofiban and an early invasive approach led to substantially lower rates of the primary composite end point and 30-day and 6-month death or MI. These results support the findings of the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial, in which a greater reduction in death or MI during 6- to 12-month follow-up was shown with a routine invasive approach than with a conservative approach (1, 2). However, the apparent early hazard of the invasive strategy in FRISC II—an increased death or MI rate within the first week after percutaneous coronary intervention (PCI)—was not seen in TACTICS–TIMI 18. This leads to speculation that initial use of IIb/IIIa inhibition helped to passivate the platelet-rich thrombus that formed as a consequence of atherosclerotic plaque rupture or erosion. Such use may also help to mitigate against incomplete platelet inhibition, particularly with coronary stenting, which accounts for higher early event rates in previous studies.

Although TACTICS–TIMI 18 and FRISC II support a combined pharmacologic and routine invasive approach, appropriate patient selection by risk stratification should be done to identify which patients who have an acute coronary syndrome with non–ST elevation will benefit. For example, both studies showed that the benefit of the invasive strategy was greatest in intermediate- to high-risk patients (e.g., those with ST-segment depression or elevated troponin T levels). Furthermore, a routine invasive strategy is not synonymous with urgent PCI: Approximately 40% of patients had this procedure, 20% to 35% required bypass surgery as the method of revascularization (done at a median of 3.7 and 7 d in the TACTICS–TIMI 18 and FRISC-II trials, respectively), and 20% to 40% were managed medically after routine angiography. Thus, the results of these trials are not only applicable to those centers that can do early PCI.

An unresolved question is the ideal timing of the invasive component. The median time to angiography ranged from 22 hours (the target was 4 to 48 h in TACTICS–TIMI 18) to 96 hours (the target was ≤ 5 d in

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Abciximab was more effective than tirofiban in preventing ischemic events in patients having coronary stenting

Topol EJ, Moliterno DJ, Herrmann HC, et al., for the TARGET Investigators. **Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization.** N Engl J Med. 2001 Jun 21;344:1888-94.

QUESTION

In patients having coronary stenting, is tirofiban as effective as abciximab in preventing death, nonfatal myocardial infarction (MI), or urgent target-vessel revascularization (TVR)?

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians, patients, outcome assessors, and statisticians),* controlled trial with 30-day follow-up (Do Tirofiban and ReoPro Give Similar Efficacy Trial [TARGET]).

SETTING

149 hospitals in 18 countries.

PATIENTS

5308 patients who were having coronary stenting of a newly stenotic or restenotic atherosclerotic lesion in a native vessel or bypass graft. Exclusion criteria were lesions not amenable to stenting, cardiogenic shock, acute MI with ST-segment elevation, a serum creatinine level ≥ 221 µmol/L, or a bleeding diathesis. 4809 patients (91%) were included in the analysis (mean age 62 y, 74% men).

INTERVENTION

Patients were stratified by the presence or absence of diabetes and allocated to tirofiban (n = 2647) or abciximab (n = 2661) received intravenously just before revascularization. Tirofiban was given in a bolus of 10 µg/kg body weight and an infusion of 0.15 µg/kg per minute for 18 to 24 hours; abciximab was given in a bolus of 0.25 mg/kg and an infusion of 0.125 µg/kg per minute for 12 hours.

MAIN OUTCOME MEASURES

Combined end point of death, nonfatal MI, or urgent TVR within 30 days. Secondary outcomes were each component of the combined end point alone.

MAIN RESULTS

Analysis was by intention to treat. Patients in the tirofiban group had a higher incidence of the combined end point than did patients in the abciximab group (P = 0.038) (Table).

CONCLUSION

In patients having coronary stenting, abciximab was more effective than tirofiban in preventing ischemic events.

Source of funding: Merck.

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*See Glossary.

†Information provided by author.

Tirofiban vs abciximab in coronary stenting‡

Outcomes at 30 d	Tirofiban	Abciximab	RRI (95% CI)	NNH (CI)
Combined end point§	7.6%	6.0%	26% (2.3 to 56)	64 (34 to 654)
Death	0.5%	0.4%	21% (–47 to 172)	Not significant
Nonfatal myocardial infarction	6.9%	5.4%	28% (2 to 59)	68 (35 to 753)
Urgent target-vessel revascularization	0.8%	0.7%	12% (–41 to 113)	Not significant

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

§Combined end point = death, nonfatal myocardial infarction, or urgent target-vessel revascularization.

COMMENTARY

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FRISC II). It seems most appropriate to rapidly initiate aggressive medical therapy and referral for angiography simultaneously, with the latter done as soon as resources allow.

Randomized placebo-controlled trials have established the benefit of IIb/IIIa inhibition in patients having elective or urgent PCI (about 40% relative reduction and 3.5% absolute reduction in 30-d death or MI). However, 3 agents (abciximab, tirofiban, and eptifibatide) with distinct characteristics, differing specificity for the IIb/IIIa receptor, and different costs have been studied. Before the trial by Topol and colleagues (TARGET), however, a direct clinical outcome comparison between drugs had not been done. Although TARGET was intended to show similarity (noninferiority) between tirofiban and abciximab (which has the most definitive data supporting its use in PCI), abciximab was superior in protecting against 30-day major ischemic events after revascularization, including MI. Why was tirofiban, which has shown to benefit patients with an acute coronary syndrome with non–ST elevation (including those subsequently having PCI) inferior? Perhaps the dosing regimen was less than ideal, especially in the setting of coronary stenting in patients with an acute coronary syndrome who had inadequate pretreatment. Indeed, experience with eptifibatide has shown that identifying the dose that leads to an ideal degree of platelet inhibition may be difficult to establish, and a different dose and administration strategy in PCI may be required. Unfortunately, many potential explanations for the disparity between TARGET and previous placebo-controlled evaluations have been raised, but a paucity of unifying evidence exists. Furthermore, the benefit of the IIb/IIIa inhibitor class of drugs is evident in many different clinical settings, but TARGET highlights the importance of head-to-head assessments within the class before concluding that the effect of one agent is truly similar to another.

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References

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2. **Wallentin L, Lagerqvist B, Husted S, et al.** Lancet. 2000;356:9-16.

