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Review Article

Early Invasive Versus Conservative Management for Non-ST-Segment Elevation Acute Coronary Syndromes

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Abstract

There is debate about routine early invasive treatment compared with conservative treatment in non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Current guidelines recommend an early invasive approach in high-risk patients with acute coronary syndromes without ST-segment elevation. Over the past 10 years, there have been nine trials which randomized approximately 10,000 NSTE-ACS patients into an early invasive or conservative treatment strategy. In these trials, early invasive treatment was not associated with a reduction in mortality after 1 year of follow-up. However, early invasive treatment was associated with a borderline statistically significant reduction in the composite endpoint of death or nonfatal myocardial infarction compared to conservative treatment. In addition, rehospitalization and refractory angina were less frequent in the early invasive strategy groups. Although the optimal timing of angiography and subsequent revascularization, if appropriate, remains controversial, we believe that for patients with NSTE-ACS, an early invasive strategy should be strongly considered during initial hospitalization in high-risk patients and in cases of medical therapy failure to reduce angina symptoms and rehospitalization, without increased risk of death or myocardial infarction. (*Tzu Chi Med J* 2008;20(1):19–24)

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1. Introduction

Patients with acute coronary syndromes without ST-segment elevation are at risk of adverse cardiac events (1). Over the past decade, two distinct approaches have emerged in the management of patients with non-ST elevation acute coronary syndromes (NSTE-ACS): (1) a *routine early invasive* strategy that consists of routinely referring patients with NSTE-ACS for coronary angiography during the first days after admission (in the majority of patients, cardiac catheterization is performed within 72 hours) and if necessary, revascularization as soon as possible thereafter; and (2) a *conservative* strategy (also referred to as a selective invasive or ischemic-guided strategy). In this strategy, patients are initially treated with pharmacological therapy, after which coronary angiography and revascularization, if appropriate, are

performed only for those with recurrent symptoms or objective evidence of inducible ischemia on noninvasive tests. The American College of Cardiology–American Heart Association and the European Society of Cardiology recommend an early invasive approach in high-risk patients with acute coronary syndromes without ST-segment elevation [2,3]. A number of randomized trials describe potential benefits of routine early invasive strategy for all patients with NSTE-ACS regardless of their initial risk stratum. Is this an appropriate and rational approach? We undertook a review of the literature to examine this question.

2. Randomized trials

Over the past 10 years, there have been nine trials which randomized approximately 10,000 NSTE-ACS patients into an early invasive or conservative treatment strategy [4–11] (Table 1).

In the Thrombolysis In Myocardial Infarction (TIMI-IIIB) trial, the early invasive strategy was associated with a shorter hospital stay, fewer readmissions and less need for anti-angina medications, but there was no significant difference in cardiac events [4].

In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial which included people with non-Q-wave myocardial infarction (MI), patients randomized to early invasive treatment had significantly higher 1-year event rates compared to conservatively managed patients (22.1% *vs.* 14.2%; odds ratio [OR], 1.7; 95% confidence interval [CI], 1.2–2.4). High perioperative mortality was observed in the invasive arm compared to the conservative treatment arm (11.6% *vs.* 3.4%; OR, 0.37; 95% CI, 1.0–3.6) [6].

However, the TIMI-IIIB and VANQWISH trials were conducted in the pre-glycoprotein IIb/IIIa inhibitor therapy era and before the widespread use of stents.

In the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II) trial, 2457 patients with unstable coronary disease were randomized after 48 hours to an invasive or noninvasive approach [7]. All patients were treated with aspirin, intravenous nitroglycerin, beta-blockers, and low-molecular-weight heparin (dalteparin) for 4–6 days until revascularization was performed in the invasive group, and for a similar duration in the noninvasive group. The invasive approach included catheterization followed by revascularization within 7 days. Patients in the noninvasive arm had angiography followed by revascularization if they had a marked positive exercise test, severe angina, or MI. At 6 months, the rate of death or MI was significantly lower in the invasive treatment group (9.4% *vs.* 12.1%; risk ratio [RR], 0.78; 95% CI, 0.62–0.98; $p=0.031$). There was a significant decrease in MI in the invasive group (7.8% *vs.* 10.1%; RR, 0.77; 95% CI, 0.60–0.99; $p=0.045$), while the difference in mortality was not significant. Invasive treatment provided the greatest advantages in older patients, in men, in those with chest pain at rest or longer durations of angina, and in patients with ST-segment depression. The 2-year follow-up of the FRISC II cohort showed a consistent reduction and continued separation of the event curves between the two strategies at 2 years. However, after enrolment, the prominent benefit between the two groups was most apparent within the first 6–12 months [12].

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS–TIMI 18) trial, 2220 patients with unstable angina or non-ST-elevation MI (NSTEMI) were randomized to an early invasive strategy (catheterization within 4–48 hours and revascularization) or a conservative strategy [9]. All patients received aspirin, beta-blockers, heparin, and tirofiban for 48–108 hours. At 6 months, the primary endpoint (death, MI, rehospitalization for an acute coronary syndrome) was significantly lower in the invasive strategy group than the conservative strategy group (5.9% *vs.* 19.4%; OR, 0.78; 95% CI, 0.62–0.97; $p=0.025$). The rate of death or non-fatal MI at 6 months was reduced in the invasive strategy group (7.3% *vs.* 9.5%; OR, 0.74;

Table 1 — Nine randomized trials comparing early invasive with conservative strategy in NSTE-ACS patients

Study	Year	Follow-up	Patients	
			Conservative	Invasive
TIMI IIIB	1994	6 wk	733	740
MATE	1998	21 mo	90	111
VANQWISH	1998	1 yr	458	462
FRISC II	2000	1 yr	1234	1222
TRUCS	2000	1 yr	72	76
TACTICS-TIMI 18	2001	6 mo	1106	1114
VINO	2002	6 mo	67	64
RITA 3	2002	1 yr	915	895
ICTUS	2005	1 yr	596	604
All			5271	5288

95% CI, 0.54–1.0; $p<0.05$). As in the FRISC II trial, the greatest benefit for the invasive strategy group was observed in patients with ST depression on the entry ECG, positive biomarkers, or ≥3 TIMI risk score. The clinical outcomes of patients with low risk did not differ between the invasive and conservative strategies.

The Randomized Intervention Trials of Unstable Angina (RITA 3) trial [11] showed that an interventional strategy was preferable to a conservative strategy in 1810 patients with NSTE-ACS (mean age, 62 years; 38% women). The difference was mainly due to a halving of refractory angina in the intervention group. Death or MI was similar in both treatment groups at 1 year (7.6% *vs.* 8.3%; RR, 0.91; 95% CI, 0.67–1.25; $p=0.58$).

In the Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial, 1201 NSTE-ACS patients with cardiac troponin T levels ≥0.03 μg per liter at admission were randomly assigned to an early invasive strategy (coronary angiography and subsequent revascularization within 24–48 hours) or to a selective invasive strategy [13]. Patients received aspirin daily, enoxaparin for 48 hours, and abciximab at the time of percutaneous coronary intervention. The protocol recommended intensive lipid-lowering therapy and the use of clopidogrel. Nonfatal MI was significantly increased in the early invasive group during the 1-year follow-up (15% *vs.* 10%; OR, 1.5; 95% CI, 1.1–2.0; $p=0.005$), but most events were procedure-related. The mortality rate was the same (2.5%). Rehospitalization was less frequent in the early invasive group (7.4% *vs.* 10.9%; OR, 0.68; 95% CI, 0.47–0.90; $p=0.04$).

In the FRISC II, TACTICS–TIMI 18, and RITA 3 trials, an early invasive strategy improved survival without recurrence of MI, readmission and urgent revascularization for severe angina (Table 2).

A meta-analysis of the FRISC II, TRUCS, TACTICS–TIMI 18, VINO, and RITA 3 trials revealed a 28% reduction (and a 2.5% absolute reduction) in the composite endpoint of death or nonfatal MI in the early invasive strategy groups (7% *vs.* 9.5%; OR, 0.72; 95% CI, 0.6–0.86).

When all trials were considered, early invasive treatments were not associated with a mortality reduction after 1 year of follow-up (Table 3; Fig. 1). Early invasive treatment was associated with a borderline significant 12% relative reduction (and 1.1% absolute reduction) in the composite endpoint of death or nonfatal MI during the 1-year follow-up (8.7% *vs.* 9.8%; OR, 0.88; 95% CI, 0.77–1.0) (Table 3; Fig. 2).

In these trials, there was a high rate of crossover of patients from the conservative treatment group to the early revascularization group. Revascularization rates were high in the two treatment strategies as

Table 2 — Outcomes of three randomized trials comparing early invasive (Inv) with conservative (Cons) strategy in NSTE-ACS patients

Outcomes 6–12 mo	Death, MI, or severe angina leading to readmission/ revascularization (%)		Death or MI (%)		Death (%)		Spontaneous MI (%)		Procedure-related MI (%)	
	Cons	Inv	Cons	Inv	Cons	Inv	Cons	Inv	Cons	Inv
FRISC II	42.2	13.2	14.1	10.4	3.9	2.2	11.3	4.2	2.1	5.4
TACTICS	19.4	15.9	9.5	7.3	3.5	3.3	–	–	–	–
RITA 3	14.5	9.6	8.3	7.6	3.9	4.6	5.7	3.3	0.4	1.7

Table 3 — Outcomes during 1-year follow-up in randomized trials of invasive (Inv) versus conservative (Cons) treatment in NSTE-ACS patients

Study	Death (%)		Death or nonfatal MI (%)	
	Cons	Inv	Cons	Inv
TIMI IIIB	18 (2.5)	18 (2.4)	60 (8.2)	56 (7.6)
MATE	9 (10)	12 (10.8)	11 (12.2)	15 (13.5)
VANQWISH	37 (8.1)	61 (13.2)	65 (14.2)	102 (22.1)
FRISC II	48 (3.9)	27 (2.2)	143 (11.6)	105 (8.6)
TRUCS	9 (12.5)	3 (3.9)	12 (16.7)	6 (7.9)
TACTICS TIMI-18	39 (3.5)	37 (3.3)	76 (6.9)	53 (4.8)
VINO	9 (13.4)	2 (3.1)	15 (22.4)	4 (6.3)
RITA 3	36 (3.9)	41 (4.6)	76 (8.3)	68 (7.6)
ICTUS	15 (2.5)	15 (2.5)	NR	NR
All	220 (4.2)	216 (4.1)	458 (9.8)	409 (8.7)

NR = not reported.

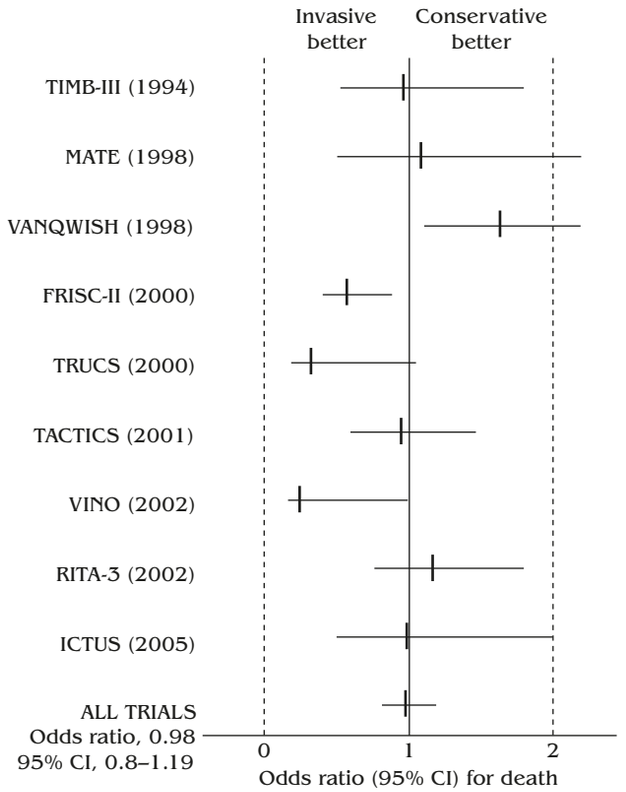

Fig. 1 — Odds ratio of mortality in nine randomized trials comparing invasive with selective invasive management of non-ST-elevation acute coronary syndromes. CI= confidence interval.

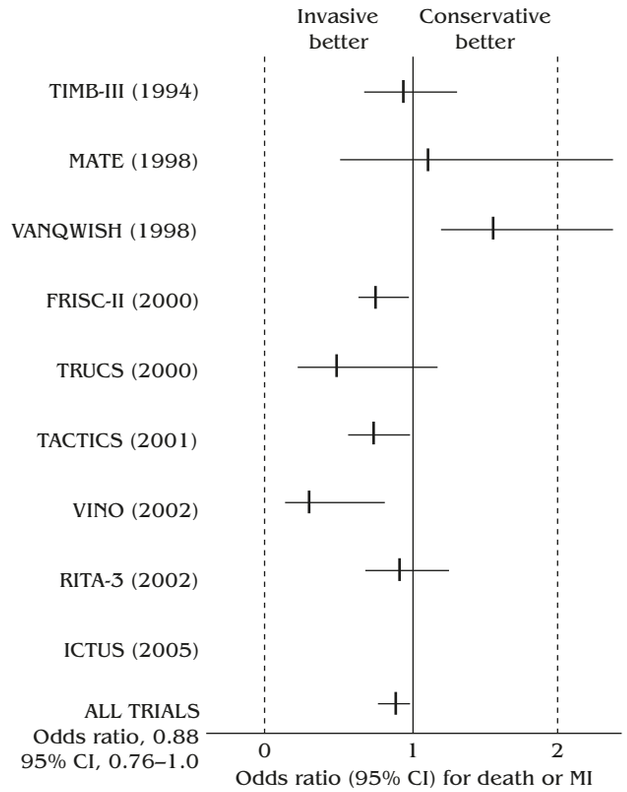

Fig. 2 — Odds ratio of the composite endpoint of death or nonfatal myocardial infarction (MI) in nine randomized trials comparing invasive with selective invasive management of non-ST-elevation acute coronary syndromes. CI= confidence interval.

follows: in TIMI-IIIB, 64% in the early invasive group and 58% in the conservative group at 1 year; VANQWISH, 44% *vs.* 33% at 23 months; FRISC II, 71% *vs.* 9% at 10 days and 77% *vs.* 37% at 6 months; TACTICS-TIMI 18, 61% *vs.* 44% at 6 months; RITA 3, 44% *vs.* 10% during the index admission and 57% *vs.* 28% within 1 year; and ICTUS, 76% *vs.* 40% during the initial hospitalization and 79% *vs.* 54% within 1 year [4,6,7,9,11,13]. The high crossover rate may underestimate the benefits of an invasive approach.

3. Timing of revascularization

In most trials, patients randomized to the invasive approach underwent cardiac catheterization within 72 hours and, if necessary, revascularization as soon as possible.

Early revascularization is associated with a higher risk of early death and MI because of procedure-related events. The TIMI-IIIB and VANQWISH trials showed an approximately 60% excess MI rate within the first 2 weeks with an early invasive approach in NSTE-ACS patients [4,6]. However, the TIMI-IIIB and VANQWISH trials were conducted in the pre-glycoprotein IIb/IIIa inhibitor therapy era, and before the widespread use of stents (Table 4). This rise in early in-hospital risk is compensated for by a lower risk of spontaneous events after revascularization, as in the FRISC II and RITA 3 trials [7,11]. In TACTICS-TIMI 18, the risk of procedure-related MI could have been reduced by routine glycoprotein IIb/IIIa inhibition, suggesting that glycoprotein IIb/IIIa inhibitor administration mitigates the adverse consequences of distal embolization and incomplete platelet inhibition associated with early intervention [9].

In the VANQWISH and GUSTO IV-ACS trials, an increase in mortality was found in patients with early coronary artery bypass graft (CABG) surgery [6,14]. In the FRISC II and TACTICS-TIMI 18 trials, the outcome was comparable between patients undergoing CABG and percutaneous coronary intervention (PCI) [7,9].

Possibly, when indicated, PCI should be performed as soon as possible after admission for ACS and only patients who might gain from early

Table 4 — Conservative versus invasive strategies in NSTE-ACS: six randomized trials

	Invasive arm			Conservative arm
	Medium time to cath	Stents	GP IIb/IIIa inhibitors	Threshold to cath
TIMI IIIB	1.5 d	0%	0%	Rec. Sx, ST Holter+ or TET/Tl201+
VANQWISH	2 d	0%	0%	Rec. Sx, or TET/Tl201+
FRISC II	4 d (2–7 d)	65%	10%	Rec. Refr. Sx, or TET+++ (3mm ST depression)
TACTICS	1 d	84%	100%	Rec. Refr. Sx, TET/Tc 99+, or stress echo+
RITA 3	2 d	88%	25%	Rec. Refr. Sx, TET/Tl201+, or stress echocardiography+
ICTUS	23 hr (1–2 d)	88%	94%	Rec. Refr. Sx, or TET+

+ = positive; +++ = markedly positive; Cath = coronary angiography; TET = exercise stress test; Rec. = recurrent; Refr. = refractory; Sx = symptoms.

revascularization should be referred for CABG. However, the appropriate timing of coronary angiography and revascularization remains controversial.

4. Subgroups of patients

Risk stratification remains an important part of optimal clinical decision making today because NSTE-ACS is heterogeneous, representing a spectrum of risk ranging from low to high.

The FRISC II and TACTICS-TIMI 18 trials did not demonstrate clear superiority for patients who were biomarker-negative and those without ST-segment depression [7,9].

In the FRISC II and RITA 3 trials, there were significant interactions with sex, with significant reductions of the composite of death and MI in men but trends to hazards in women [7,11]. But in the ICTUS trial, the relative risks were not different between genders [13].

Increasing age is an important risk factor for adverse outcomes in NSTE-ACS patients. Elderly patients are often managed conservatively. A subgroup analysis of patients in the FRISC II and TACTICS-TIMI 18 trials showed that an early invasive strategy can significantly improve outcomes in elderly patients [7,9].

Diabetes is an independent predictor of mortality in NSTE-ACS patients. However, in most studies, coronary revascularization in patients with diabetes and NSTE-ACS was as effective as in patients without diabetes.

5. Conclusion

When all trials were considered together, early invasive treatment was not associated with a mortality reduction after the 1-year follow-up. However, it was associated with a statistically significant reduction in the composite endpoint of death or nonfatal MI compared to conservative treatment. In addition, rehospitalization and refractory angina were less frequent with an early invasive strategy.

Thus, for patients with NSTE-ACS, an early invasive strategy should be strongly considered during initial hospitalization, especially in high-risk patients, such as older patients, men, and patients with diabetes, ST-segment depression, and intractable angina, with the aim of reducing angina symptoms and rehospitalization,without increased risk of death or MI.

The optimal timing of coronary angiography and subsequent revascularization, if appropriate, remains controversial, but possibly, PCI should be performed as soon as possible after admission, whereas CABG can be deferred until the patient is more stable.

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