Coronary Heart Disease

Two-Year Follow-Up of Tirofiban-Based Management of Non-ST-Elevation Acute Coronary Syndrome – A Single Center Study

Ho-Tsung Hsin,[1,2] Ai-Hsien Li,[3] Dong-Feng Yeih,[3] Chao-Lun Lai,[3] Yu-Wei Chiu,[3] Pen-Chih Liao,[3] Kuo-Chin Chen,[3] Hsein-Jung Lo,[3] Chi-Yu Yang[3] and Shu-Hsun Chu[3]

Background: The current practice guidelines suggest early and invasive strategies in treating patients of non-ST-elevation acute coronary syndrome (NSTEACS) with high-risk profiles. However, the definite benefit and treatment protocols are still under debate. We conducted a tirofiban-based follow-up study to assess the effects of early-invasive strategy in NSTEACS.

Methods: This was a prospective, open-label randomized trial. The study had a two-by-two factorial design, combining enoxaparin/unfractionated heparin and early-invasive/early-conservative strategies. The early-invasive arm mandated coronary angiography within 12 hours after randomization, while the counterpart took more than 48 hours. All enrolled patients received tirofiban at admission. The primary endpoint was composed of cardiovascular death, re-hospitalization due to recurrent angina, target vessel revascularization and unscheduled coronary bypass surgery in follow-up. The secondary endpoint concerned the bleeding complications.

Results: After a 2-year follow-up of 61 eligible patients, the early-invasive arm did not show benefit over the early-conservative arm (RR = 0.522, $P = 0.318$; Kaplan Meier (KM) log-rank $P = 0.36$) and enoxaparin was not superior to unfractionated heparin (RR = 0.319, $P = 0.079$; KM log-rank $P = 0.15$). From another viewpoint, updated strategies utilizing either enoxaparin or early catheterization were better than the conventional one, which adopted unfractionated heparin and delayed angiography (RR = 0.276, 95% CI 0.101-0.752, $P = 0.026$; KM log-rank $P = 0.0026$). There was no difference in bleeding complications.

Conclusion: The updated treatment should be superior to the most conventional protocol in treating NSTEACS. But, we cannot conclude that the early-invasive strategy benefits all NSTEACS patients more, especially when optimal adjunctive pharmacologic therapies are applied.

Key Words: Acute coronary syndrome • Early-invasive strategy • Myocardial infarction • Tirofiban

INTRODUCTION

The management of non-ST-elevation acute coronary syndromes (NSTEACS), including unstable angina and non-ST elevation myocardial infarction, has long been debated since the late nineties of last century. Two well-known studies discouraged early-invasive strategy for treatment. The Thrombolysis in Myocardial Infarction (TIMI) III B trial found similar clinical outcomes for both the early-conservative and early-invasive strategies.[1] The Veterans Administration Non-Q-Wave Infarc-

Received: November 3, 2009 Accepted: February 9, 2010

[1]Cardiovascular Intensive Care Unit, Far-Eastern Memorial Hospital, Taipei; [2]National Tainan Institute of Nursing, Tainan City; [3]Cardiovascular Center, Far-Eastern Memorial Hospital, Taipei, Taiwan.

Address correspondence and reprint requests to: Dr. Shu-Hsun Chu, Cardiovascular Center, Far-Eastern Memorial Hospital, 13F, No. 21, Sec. 2, Nan-Ya South Rd., Banciao City, Taipei County 220, Taiwan. Tel: 886-2-8966-7000 ext. 1602; Fax: 886-2-8966-5138; E-mail: cv@femh.org.tw

tion Strategies in-Hospital trial (VANQWISH) found a higher mortality in patients treated early-invasively.[2] However, the advent of newer interventional devices, techniques and pharmacological treatments has enabled definitive NSTEACS research studies to take place. Several milestone studies, such as TACTICS-TIMI 18,[3] FRISC-II,[4] and RITA-3[5] published at the dawn of the 21st century, have offered sound evidence that made early-invasive strategy prevail. The current ACC/AHA guidelines encourage treating NSTEACS early and invasively, especially for those patients with high-risk profiles.[6]

There are two milestone drugs that caused the revolution toward the early-invasive strategy: low-molecular-weight heparin, especially enoxaparin, and glycoprotein IIb/IIIa inhibitors, such as tirofiban. In the TIMI-11B trial, enoxaparin showed superiority to conventional unfractionated heparin (UFH) in treating patients with NSTEACS,[7] and it is now the preferred drug of treatment by consensus. Tirofiban in adjunct with UFH facilitated the early-invasive strategy in the TACTICS-TIMI 18 trial.[3] So far, the practice guidelines have relegated tirofiban to assume a rescuing role for patients with refractory ischemic symptoms, or have regarded it as an adjunct to early coronary interventions. The writing committee did not conclude upon the appropriate timing for administering such agents in NSTEACS. Whether it is best to apply tirofiban for routine upstream or deferred selective use in acute coronary syndromes is still a matter of debate.[8,9]

The latest available large-scale NSTEACS studies adopting early-invasive strategy applied high percentage of Glycoprotein IIb/IIIa antagonists. Under such circumstances, we conducted this study to compare the efficacy and safety of early-invasive and early-conservative strategies in NSTEACS patients undergoing routine upstream usage of tirofiban. In addition, the difference between the aforementioned anti-coagulants, enoxaparin and UFH, was also addressed.

MATERIALS AND METHODS

Patients

This was a prospective, open-label randomized trial conducted at a single institution, which is a tertiary referring center. The study protocol was approved by the relevant institutional review boards, and written consent was obtained from all study participants. All patients older than 18 and younger than 85 years of either gender who presented to the hospital with acute coronary syndromes were enrolled. The diagnosis of acute coronary syndrome was defined by the following three criteria: (1) resting ischemic chest pain, or pain with increasing intensity, and occurrence of the last episode within a 24-hour period before randomization; (2) electrocardiographic (ECG) evidence of non-ST-segment elevation myocardial infarction; (3) elevated troponin-I (> 1 ng/ml) or other cardiac-specific enzymes (CK and CK-MB). Those who had any of the following conditions were excluded: (1) known or suspected pregnancy. (woman of childbearing potential were screened with a serum or urine beta-hCG test within 24 hours of initial examination); (2) an ECG showing ST-elevation myocardial infarction (STEMI) in the last 48 hours, mandating further reperfusion therapy; (3) hemodynamic instability, or overt heart failure that rendered randomization impossible; (4) contraindications to anticoagulants or increased bleeding risk; past or present bleeding disorder within 3 months prior to enrollment; gastrointestinal bleeding, gross hematuria, known coagulopathy, platelet disorder, or history of thrombocytopenia; significant retinopathy (i.e. hemorrhages or exudates); (5) any history of stroke or other intracranial pathology at any time; (6) transient ischemic attack within 1 year, or based on investigator's clinical judgments, when the benefit outweighed the risk for the study subject, (7) major surgery including CABG, (8) any ophthalmologic surgery or biopsy (non-cutaneous) within 1 month prior to enrollment, (9) severe physical trauma within 1 month, prolonged cardiopulmonary resuscitation within 2 weeks, acute pericarditis, (10) treatment with abciximab in the past 14 days; (11) allergy or intolerance to aspirin or heparin; (12) patients with abnormal lab data: serum creatinine > 2.5 mg/dL (> 220 μmol/L), hemoglobin < 11 g/dL or hematocrit < 34%, platelet count < 100,000/mm3, baseline prothrombin time > 1.3 times of control or an INR > 1.5; (13) patients suffering concomitant severe infection/sepsis; (14) patients unable to give informed consent (excepting those who are in the presence of legal delegates).

Procedures

Eligible patients were randomly assigned to either

the early-conservative arm or the early-invasive arm with the use of a computer-based randomization table. The early-invasive strategy required the performance of cardiac catheterization within 12 hours after initial randomization. The disposition after the diagnostic angiography, including percutaneous coronary intervention (PCI), coronary bypass surgery (CABG) or merely medical therapy, depended upon the coronary anatomy and the patient's preference. CABG would be recommended in the face of extensive 3-vessel disease or severe left-main disease, and the surgery would be done as soon as the patient agreed. Those patients allocated to the early-conservative arm would be managed medically and received cardiac catheterization routinely 48 hours after enrollment. The treatment policy after the angiography was the same as that of the early-invasive arm. In addition, patients in either treatment strategy would also receive either enoxaparin or UFH by randomization. Therefore, the two-by-two factorial design resulted in 4 treatment groups: A) UFH + cardiac catheterization within 12 hours; B) UFH + cardiac catheterization 48 hours later; C) enoxaparin + cardiac catheterization within 12 hours; D) enoxaparin + cardiac catheterization 48 hours later.

The protocol required the immediate oral loading of 300 mg aspirin and 300 mg clopidogrel at randomization to the entire patient population. The patients received daily aspirin (100 mg) and clopidogrel (75 mg) thereafter, unless contraindicated. The duration of daily clopidogrel in follow-up period conformed to contemporary treatment guidelines and the regulations of the Taiwanese National Health Insurance Bureau. Those randomized to UFH (Groups A and B) would receive an intravenous bolus of 4000 units of unfractionated heparin, followed by an infusion at a rate of 1000 U per hour for 48 hours. Groups C and D received enoxaparin (1 mg/kg twice daily) subcutaneously for 48 hours. The "48-hour" duration of anticoagulant was based on the current guidelines, which state "Discontinue anticoagulant after PCI in uncomplicated cases."[6] The maintenance of anticoagulants for more than 48 hours, such as in post-PCI patients, was up to the interventionist's discretion. In addition, all of the enrolled patients received an intravenous infusion of tirofiban, with a loading dose of 0.4 micrograms per kilogram of body weight per minute for a period of 30 minutes, followed by a maintenance infusion of 0.1 microgram per kilogram per minute for 48 hours or until revascularization occurred.[10] The tirofiban would be continued for at least 12 hours after percutaneous coronary revascularization procedures, or discontinued at least 4 hours before CABG. Medical therapy with beta-blockers, nitrates, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and lipid-lowering agents was administered to all patients as soon as possible unless contraindicated.

Blood samples were obtained at the time of randomization, and creatine kinase (CK), the MB isoform of creatine kinase (CK-MB), and troponin I were measured on site every 6 hours for 48 hours after randomization in order to detect episodes of recurrent angina suggestive of myocardial infarction, and after all revascularization procedures. The normal range of the laboratory kit for troponin-I in this institute was 0.0-0.4 ng/ml. However, we defined troponin-I > 1 ng/ml as "elevated troponin-I" in this study, in order to comply with the TIMI scoring system. The TIMI risk score for unstable angina and myocardial infarction without ST-segment elevation[11] was determined at admission. The prognostic test evaluates patients for the presence or absence of seven risk factors for death and ischemic events, which include: age greater than 65 years, more than 3 risk factors for coronary artery disease (CAD), documented CAD, aspirin use within 7 days (meaning aspirin failure), severe angina within 24 hours, an increase of more than 1.0 ng/ml in troponin-I levels, and a deviation of the ST-segment by more than 0.5 mm. A TIMI score of 0, 1, or 2 is regarded as low risk (14-day all-cause mortality < 10%); patients with a score of 3 or 4 are considered to be at intermediate risk (14-day all-cause mortality 10-20%); and those with a score of 5, 6, or 7 are thought to be at high risk (14-day all-cause mortality >20%).[11]

Follow-up and endpoints

Patients were frequently followed as outpatients at weeks 2, 4, and 8, and further follow-up was arranged at the interval of 3 months, conforming to the current pattern of medical practice in this nation. For long-term follow-up, patients were contacted by telephone between one year and two years after enrollment. All contributing drug regimens and potential outcome events were recorded and scrutinized. In the case of re-hospitalization, the follow-up information was obtained from hospital re-

cords, with the patient's or the family's permission. All hospitalizations were recorded unless the patient or the records indicated that the admission was definitely due to non-cardiovascular indications. If the patient could not be reached, the information came from the patient's family, the attending cardiologist, and/or related hospital records.

The primary endpoint was a composite one, consisting of cardiovascular death, re-hospitalization due to recurrent angina, target vessel revascularization and unscheduled coronary bypass surgery in the follow-up. The secondary endpoint concerned the bleeding complications. Patients were monitored for bleeding for 24 hours after the cessation of anti-coagulants. Major bleeding was defined as a decrease in the blood hemoglobin level of at least 5 g/dL, an existing need for transfusing 2 or more units of blood, the need for corrective surgery for hemorrhage, the occurrence of an intracranial or retroperitoneal hemorrhage or cardiac tamponade, or any combination of these events.[12,13]

Statistical analysis

Cumulative event rates for the primary outcome were calculated according to the Kaplan-Meier method, and the event-timing was illustrated by Kaplan-Meier plots. Comparison between treatment groups was done by log-rank tests without adjustment for covariates. The comparison of strategies concerned three aspects. In the first place, groups A, C and D received therapy complying with updated guidelines and were allocated to the "updated strategy". Group B was designated as the "conventional strategy", which delayed the coronary angiography and used unfractionated heparin. Secondly, treatment groups A and C were compiled as the early-invasive arm, while the combination of groups B and D denoted early-conservative arm. Thirdly, groups A and B together contrasted with groups C and D, in the aspect of comparing different anti-coagulants (unfractionated heparin versus enoxaparin). Proportional hazards assumptions were verified by graphical examination of the partial residuals and by testing the significance of the interaction between treatment and time.

The TIMI risk score for unstable angina and myocardial infarction without ST-segment elevation was used for initial risk stratification, as described in the Procedures section. The baseline characteristics were compared with Chi-square test for categorical variables, and the comparison of continuous variables was done by ANOVA test. One interim efficacy analysis was carried out by the hospital's data and safety monitoring board.

All statistical tests were two-tailed, and a P value less than 0.05 was deemed significant. The analysis was done with Statistical Package for the Social Sciences software (SPSS 12.0 for Windows).

RESULTS

From Dec. 2004 to Nov. 2005, there were 133 patients who presented with NSTEACS to our institute. However, only 61 of them were eligible for enrollment. There were 72 patients who were excluded, because of concomitant systemic infection (25 patients), abnormal baseline renal function (18 patients), abnormal baseline level of hemoglobin or platelet (10 patients), pre-randomization anticoagulation in primary-care hospitals (15 patients), and their family's objection (4 patients). The enrolled 61 patients were randomly allocated to treatment group A, B, C or D (Table 1). Patients among the four treatment groups were matched without statistical differences. Overall, female patients constituted 23% of our population. Almost 61% of our patients were diabetics before this ACS event. The ECG evidence of changes in the ST segment was present in 75% of the patients, and the initial levels of troponin-I were elevated (> 1 ng/ml) in 69% of the 61 patients. All of the patients received diagnostic coronary angiography at different times according to the study protocol. Those patients in the early-invasive arms (A and C) underwent cardiac catheterization at a median of 8.6 hours after randomization. On the other hand, it took a median 67.3 hours for those in the early-conservative arms (B and D) to receive diagnostic angiography. The angiographic data and subsequent procedures of revascularization are illustrated in Table 2. Seven patients (11%) had left-main disease, and 2 patients were proved to have patent coronary arteries. All of the patients with significant coronary artery disease were given recommendations to receive revascularization after the diagnostic angiography. Those 7 patients with left-main disease received CABG. Twenty-four patients (40%) had three-vessel disease, and 3 of them received CABG, while the other favored PCI or mere medical treatment.

Table 1. Basic demographics of the patients enrolled in the study

	A^+	B^+	C^+	D^+	*P* value
Patient no.	14	17	17	13	
Male/Female	10/4	12/5	14/3	11/2	NS
Age	67.0 ± 11.2	67.1 ± 11.2	66.5 ± 11.7	66.8 ± 12.0	NS
Diabetes mellitus	8 (57%)	11 (64%)	10 (58%)	8 (61%)	NS
Hypertension	9 (64%)	14 (82%)	10 (59%)	11 (84%)	NS
Hyperlipidemia	5 (36%)	4 (24%)	9 (52%)	7 (53%)	NS
Smoking	9 (64%)	8 (47%)	10 (58%)	7 (54%)	NS
Past CABG	1 (7%)	1 (6%)	1 (6%)	1 (8%)	NS
ST deviation > 1 mm	12 (86%)	14 (82%)	11 (61%)	9 (69%)	NS
TIMI score	3.6 ± 1.1	3.6 ± 1.1	3.6 ± 1.1	3.6 ± 1.0	NS
Chest pain to randomization (hrs)	7.3 ± 13.9	5.6 ± 5.1	11.6 ± 18.1	8.1 ± 12.4	NS
Medication at enrollment					
Aspirin	14 (100%)	16 (94%)	14 (82%)	12 (92%)	NS
Clopidogrel	14 (100%)	17 (100%)	17 (100%)	13 (100%)	NS
Statins	4 (28%)	4 (24%)	5 (29%)	4 (30%)	NS
Beta-blocker	8 (57%)	9 (53%)	8 (48%)	7 (54%)	NS
Tirofiban	14 (100%)	17 (100%)	17 (100%)	13 (100%)	NS

NS: not statistically significant.
+ A, UFH + cardiac catheterization within 12 hours; B, UFH + cardiac catheterization 48 hours later; C, enoxaparin + cardiac catheterization within 12 hours; D, enoxaparin + cardiac catheterization 48 hours later.

Table 2. Angiographic data and procedures of revascularization

	A^+	B^+	C^+	D^+	*P* value
Patient no.	14	17	17	13	
Door to cath (hr)	7.5	52.1	9.5	87.1	< 0.001
Vascular diagnosis					
Left-main disease	2 (14%)	2 (12%)	2 (12%)	1 (8%)	NS
3-vessel disease	5 (36%)	7 (41%)	6 (35%)	6 (46%)	NS
2-vessel disease	2 (14%)	4 (23%)	5 (29%)	3 (23%)	NS
1-vessel disease	3 (21%)	3 (18%)	2 (12%)	2 (15%)	NS
s/p CABG	1 (7%)	1 (6%)	1 (6%)	1 (8%)	NS
Interventions					
Balloon dilatation	1 (7%)	1 (6%)	1 (6%)	1 (8%)	NS
Stenting*	7 (50%)	6 (35%)	6 (35%)	4 (31%)	NS
CABG	2 (14%)	4 (24%)	5 (29%)	4 (31%)	NS

* During the study period (Dec. 2004-Nov. 2005), the stents deployed were all of bare metal, as the role of drug-eluting stent in emergent PCI was ambiguous and there was no reimbursement by the Taiwan National Health Insurance.
+ A: UFH + cardiac catheterization within 12 hours; B: UFH + cardiac catheterization 48 hours later; C: enoxaparin + cardiac catheterization within 12 hours; D: enoxaparin + cardiac catheterization 48 hours later.

End point follow-up

The primary composite end point consisted of cardiovascular death, re-hospitalization due to recurrent angina, target vessel revascularization and unscheduled CABG at follow-up (Table 3). There was no statistical difference between either treatment arm. The early-invasive arm (A, C) did not show significant benefit over the early-conservative arm (B, D) (Risk ratio (RR) = 0.522; 95% confidence interval (CI) 0.182-1.499 $P = 0.318$). Figure 1 shows the insignificant survival benefit. Re-

Table 3. Clinical variables of each treatment group during the two-year follow-up

	A+	B+	C+	D+
Patient no.	14	17	17	13
Duration of DAT (month)*	8.2 ± 1.7	7.8 ± 1.6	8.0 ± 1.3	7.9 ± 1.5
End Points				
Primary	2 (14.3%)	7 (41.2%)	2 (11.8%)	1 (7.7%)
Secondary	2 (14.3%)	1 (5.9%)	3 (17.6%)	2 (15.4%)

+ A: UFH + cardiac catheterization within 12 hours; B: UFH + cardiac catheterization 48 hours later; C: enoxaparin + cardiac catheterization within 12 hours; D: enoxaparin + cardiac catheterization 48 hours later.
* DAT: Dual anti-platelet therapy, no significant differences between groups.

garding the comparison of enoxaparin (C, D) and UFH (A, B), enoxaparin was not superior to UFH in this study (RR = 0.319; 95% CI 0.099-1.034 P = 0.079). The survival curve is illustrated by Figure 2, only revealing trend but not significance.

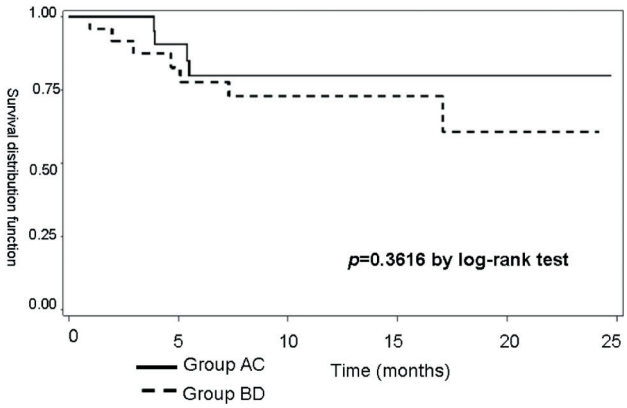

Figure 1. *Kaplan-Meier plots of primary endpoints-free survival in early-invasive versus early-conservative strategies (Groups AC vs. BD) (p = 0.3616 by log-rank test).*

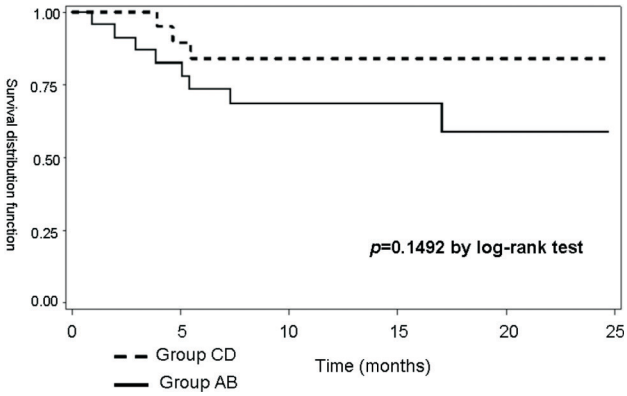

Figure 2. *Kaplan-Meier plots of primary endpoints-free survival in enoxaparin versus UFH (Groups CD vs. AB) (p = 0.1492 by log-rank test).*

Referring to the comparison between strategies, the "updated strategy" groups (A, C and D) were significantly better than the "conventional" group B (RR = 0.276, 95% CI 0.101-0.752, P = 0.026). In Figure 3, the ACD updated strategy rendered better survival than the group B conventional one.

In the aspect of secondary endpoint concerning the bleeding complications, the rate is illustrated in Table 3. Protocol-defined bleeding occurred in 13% of the study population. There was no statistical difference between each treatment arm. But the enoxaparin (C and D) groups were inclined to have more protocol-defined bleeding in comparison with the UFH groups (A, B), though insignificantly (RR = 1.722, P = 0.473).

DISCUSSION

After a 2-year follow-up in our study, the "updated

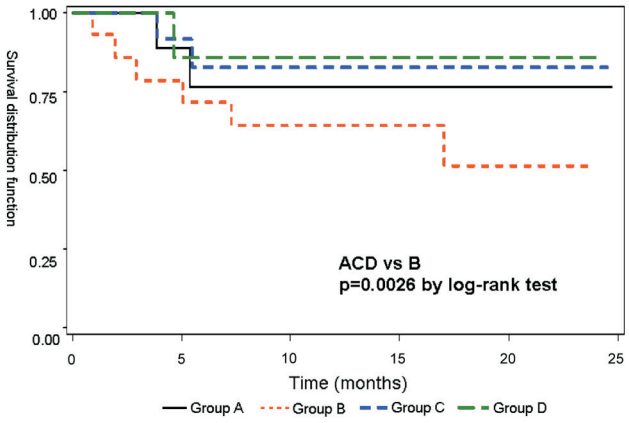

Figure 3. *Kaplan-Meier plots of primary endpoints-free survival in all groups. Significant difference exists between "updated" and "conventional" strategies (Group ACD vs. B) (p = 0.0026 by log-rank test).*

strategy" showed superiority to the "conventional" one. The updated treatment included either enoxaparin (groups C, D) or early cardiac catheterization (group A). The "conventional" B group offered the most traditional therapy, unfractionated heparin and delayed coronary angiography, with the only exception of tirofiban infusion. The result may imply that the "conventional" strategy is inferior in the face of any updated treatment, referring to either enoxaparin or early cardiac catheterization. On the other hand, our study indicated that the early-invasive strategy was not better than early-conservative treatment. In addition, enoxaparin does not seem to be superior to UFH in treating NSTEACS patients, though the Kaplan-Meier curves show an obvious trend favoring enoxaparin. In the perspective of strategy comparison, our data bears certain degrees of similarity to Mehta's meta-analysis, which included seven strategy trials.[14] Selective short-term studies such as TACTICS-TIMI 18 showed significant benefits when the patients were treated early and invasively.[3] However, when combining strategy trials that routinely used stents in PCI procedures, there was no difference in 6-month to 12-month mortality.[15,16] Moreover, the latest published follow-up trial ICTUS showed that the early invasive strategy might not be better than a more selective invasive strategy in patients with NSTEACS and an elevated cardiac troponin. The authors implied that implementation of either strategy might be acceptable.[17]

The meta-analysis based on 4- to 5-year mortality in the FRISC-II, RITA-3 and ICTUS trials disclosed only modest mortality benefit associated with early-invasive strategy, but the meta-analysis was limited by the following facts. In the first place, each individual trial was underpowered to address mortality. Secondly, heterogeneity of the revascularization rate in either treatment strategy among the three trials made the meta-analysis less persuasive. In our 2-year series, there was no case of death, though ours was a small study, which was not entitled to make such remarks. Interestingly, our Kaplan-Meier curves comparing the early-invasive and early-conservative strategies bear similarity to those of the ICTUS trial follow-up, which did not show a significant difference between the two arms.

The pharmacologic therapy we administered may make some difference. The first agent was tirofiban, which constituted our basic drug treatment. All of the enrolled patients received upstream tirofiban regardless of the risk stratifications. The universal administration of upstream tirofiban is different from current practice guidelines and most follow-up trials, such as FRISC II, and RITA-3. In the dalteparin-based FRISC II trial, there was no mention of applying glycoprotein IIb/IIIa inhibitors. The enoxaparin-based RITA-3 trial administered such agents by clinical appropriateness and physician's discretion. The exact rate was not available, either. We gave tirofiban to all treatment groups as soon as randomization was achieved. One hundred percent of our patients received tirofiban infusion for about 24 hours unless prematurely aborted by bleeding complications. Therefore, the universal application of tirofiban probably offsets the reported benefits of an early-invasive strategy over an early-conservative strategy, and to a lesser extent, the superiority of enoxaparin to UFH. Interestingly, there was no significant increase in major bleeding as compared to the other series.

The second drug that may play a vital role is clopidogrel. In the era when FRISC-II and RITA-3 trials were designed, clopidogrel was not commercially available. It wasn't until 2002 that clopidogrel was indicated for acute coronary syndrome. The oral antiplatelet treatment in the FRISC-II and RITA-3 trials merely incorporated aspirin. In the ICTUS trial, clopidogrel was added after stent placement, and early usage was encouraged as soon as the drug was available in the Netherlands. The exact percentage of prescribed clopidogrel in the ICTUS was not illustrated, but the add-on clopidogrel was believed to make the outcome of ICTUS different. In our trial, all patients received dual anti-platelet therapy (DAT), consisting of aspirin and clopidogrel, unless the patient was absolutely contraindicated to either agent. Overall, 87% of our patients received DAT, and 9% took only clopidogrel. In other words, clopidogrel was prescribed to 96% of our patients at admission and was continued according to contemporary treatment guidelines. In comparison with those trials without clopidogrel, our study and the ICTUS trial imply that the benefits of early-invasive strategy may be lessened by adequate anti-platelet therapy.

The high percentage of revascularization in the early-conservative group also contributed to our results. In those trials that favored the early-invasive strategies, the revascularization rate in the conservative arm was

relatively low. The exact statistics of revascularization in early-invasive vs. early-conservative treatment is listed: FRISC-II – 76% vs. 13%; TACTICS-TIMI 18 – 60% vs. 36%; RITA-3 – 44% vs. 10%. In the ICTUS trial, the revascularization rate was 76% vs. 40%. Our statistics were 70% vs. 67%. The only significant difference is the time from randomization to cardiac catheterization (door to cath time) and subsequent revascularization procedures: 8.6 vs. 67.3 hours. Quoting the words of ICTUS, we were actually comparing routine, early revascularization to less aggressive, delayed intervention, instead of comparing early-invasive to early-conservative strategy.

The risk profiles may also dictate. Both the FRISC-II and RITA-3 trial showed benefit for an early-invasive strategy in patients with high-risk profiles. However, ICTUS did not indicate that an early-invasive strategy would prevent death or recurrent myocardial infarction. According to the treatment guidelines and some studies, the elevation of troponin-I or T should be regarded as the sole factor of high risk. Sixty-nine percent of our patients had elevated troponin-I (> 1 ng/ml), which is similar to those studies advocating early-invasive strategies. However, elevation of troponin-I is only one of the items in TIMI risk scoring system, which categorized 68.9% of our patients as intermediate risk (TIMI score of 3 and 4). The distribution of our score-based risk stratification is similar to that of the ICTUS trial, in which about 60% of the patients were considered to be intermediate risk according to FRISC score. Based on the incorporated scoring system, we may not argue that an early-invasive strategy failed to protect the high-risk patients. Instead, it could be reasonable to say that the benefit of an early-invasive strategy and the superiority of enoxaparin may be effaced by the intermediate risk profiles. In addition, our patient population consisted of a higher percentage of diabetics than other trials. (61% vs. 25-35%). The inherited poor prognosis of diabetics probably contributed to the higher MACE rate (about 20-40%) in the 1st-year follow up. The adverse impact cast by high percentage of diabetics may also make the beneficial effect of either enoxaparin or early-invasive strategy less prominent.

LIMITATIONS

This prospective randomized study is too underpowered because of its small scale to make remarks and determine hard endpoints. The subgroup analysis was also hampered by the small case number.

CONCLUSION

The current practice guideline has stated that the glycoprotein IIb/IIIa antagonist has been playing more important role in managing NSTEACS. Early-invasive treatment and enoxaparin has also been advocated. However, the longest follow-up study to date, the ICTUS trial, challenged this notion. The 100% usage of tirofiban, high percentage of revascularization in both treatment strategies, high proportion of dual anti-platelet therapy, and the intermediate risk profiles probably contribute to the differences between our study and other trials favoring early-invasive treatment. But our study did implicate that the NSTEACS patients may benefit more when we adopt either enoxaparin or early cardiac catheterization. We may not go so far with the last point, since it needs larger scale of study to confirm our preliminary results.

ACKNOWLEDGEMENT

We show our great gratitude toward Dr. Jou-Wei Lin in National Taiwan University Hospital and MSD Taiwan for their assistance with statistics. The study was also granted by a research project of Far-Eastern Memorial Hospital.

REFERENCES

1. Anderson HV, Cannon CP, Stone PH, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial: a randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q-wave myocardial infarction. *J Am Coll Cardiol* 1995;26:1643-50.
2. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med*

1998;338:1785-92.
3. Cannon CP, Weintraub WS, Demopoulos LA, et al. TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) -- 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;21:1879-87.
4. Lagerqvist B, Husted S, Kontny F, et al. Five-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998-1004.
5. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
6. Anderson JL (Chair), et al. ACC/AHA 2007 guidelines for the management of patients of unstable angina/non-ST elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:e1-133.
7. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischaemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
8. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. *JAMA* 2007;297:591-602.
9. Rasoul S, Ottervanger JP, de Boer MJ, et al. Routine upstream versus selective downstream use of tirofiban in non-ST elevation myocardial infarction patients scheduled for early invasive therapy: a randomized comparison. *J Thromb Thrombolysis* 2007;24:241-6.
10. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498-505.
11. Antman EM, Cohen M, Bernink PJ. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
12. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488-97.
13. Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149-56.
14. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908-17.
15. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48:1319-25.
16. Lagerqvist B, Husted S, Kontny F, et al. Five-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998-1004.
17. Hirsch A, Windhausen F, Tijssen JGP, et al. Invasive versus Conservative Treatment in Unstable coronary Syndromes [ICTUS] investigators. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. *Lancet* 2007;369:827-35.
18. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:e166-286.