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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Defining the Role of Low-Molecular-Weight Heparin in the Era of Early Invasive Management of Acute Coronary Syndromes: Late-breaking results of the SYNERGY trial

Originally presented by: KW Mahaffey, MD; JJ Ferguson, MD; SG Goodman, MD; EJ Topol, MD; RM Califf, MD

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Reported and discussed by:
HOWARD LEONG-POI, M.D.

Antithrombin therapy plays a critical role in the management of non-ST-segment elevation acute coronary syndromes (ACS), in combination with potent antiplatelet and anti-ischemic agents, and coupled with an early invasive treatment strategy. Randomized clinical trials comparing antithrombin regimens have demonstrated the superiority of the low-molecular-weight heparin (LMWH), enoxaparin, over unfractionated heparin (UFH) in the prevention of the composite of death or cardiac ischemic events in ACS patients. Despite these results, controversy still exists regarding which antithrombin agent should be used for the optimal management of ACS patients. The majority of trials comparing antithrombin regimens had relatively low rates of glycoprotein (GP) IIb/IIIa receptor inhibitor use and did not employ routine early catheterization. Thus, whether the improved outcomes with enoxaparin use seen in these studies translate into similar benefits in a contemporary clinical practice – that now includes both early catheterization and revascularization and the routine use of GP IIb/IIIa receptor antagonists – remains an unanswered question. This issue of *Cardiology Scientific Update* examines the role of the LMWH, enoxaparin, in the current era of early aggressive management of patients presenting with high-risk ACS, with a focus on the late-breaking results of the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) study.

Current evidence for LMWH in the management of ACS

For many years, UFH has been the standard antithrombin agent used in the treatment of ACS patients and during percutaneous coronary intervention (PCI). LMWH possesses several theoretical advantages over UFH, mainly more predictable antithrombin activity, a longer half-life, and greater bioavailability, thus allowing easier subcutaneous (SQ) rather than intravenous (IV) administration. LMWH obviates the need for routine therapeutic monitoring and, coupled with a lower incidence of heparin-induced thrombocytopenia, makes an appealing alternative to UFH. The emerging role of LMWH in the management of patients with ACS has been reviewed in a recent issue of *Cardiology Scientific Update*. The best evidence in favour of LMWH, in particular enoxaparin, comes from 2 large randomized clinical trials that compared enoxaparin to UFH in patients with ACS. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial[1] and the Thrombolysis in Myocardial Infarction (TIMI)-11B trial[2] demonstrated

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

the superiority of enoxaparin over UFH in preventing the composite of death and major cardiac events (myocardial infarction [MI], recurrent angina, urgent revascularization) without significant differences in the rates of major bleeding. A prospectively planned, systematic overview of the data from these 2 trials demonstrated a significant reduction in the combined endpoint of death or MI.[3] Despite these positive results, acceptance of enoxaparin as an alternative to UFH in the management of ACS has been limited, particularly in the United States. The main reasons cited have been the concern over combining LMWH with GP IIb/IIIa receptor antagonists (given that most trials showing the benefit of GP IIb/IIIa inhibitors in the setting of ACS used UFH as the antithrombin agent), and the reluctance to use LMWH during PCI due to a lack of therapeutic monitoring, the concern regarding PCI failures, and issues around sheath management. There are now 2 trials that address the first concern.

INTERACT

The Integrilin and Enoxaparin Randomized assessment of Acute Coronary Syndromes (INTERACT) trial[4] randomized 746 patients with ACS to either enoxaparin or UFH, with all patients receiving eptifibatide. Both the primary efficacy endpoint of ischemia, as demonstrated by continuous ECG monitoring, and the secondary efficacy outcome of combined death and MI at 30 days were significantly lower in the enoxaparin-treated group compared to the UFH-treated group. The primary safety outcome of incidence of non-coronary artery bypass graft (CABG) surgery-related bleeding at 96 hours favoured enoxaparin, while minor bleeding was more frequent in the enoxaparin-treated group. Interim long-term follow-up of the INTERACT study reveals that the event curves continue to diverge. At a mean follow-up of 2.4 years, the hazard ratio for the combined endpoint of death and MI is 0.53 (95% CI, 0.34-0.81, p=0.0027) favouring enoxaparin.

A-to-Z trial

The antithrombin arm of the Aggrastat to Zocor (A-to-Z) trial was recently presented at the 2003 Annual Scientific Session of The American College of Cardiology. This trial randomized 3,987 high-risk ACS patients to either enoxaparin or UFH, with all patients receiving tirofiban. The primary endpoint of death/MI/refractory ischemia was not significantly different between enoxaparin- and UFH-treated groups, but slightly favoured enoxaparin (8.4% vs 9.4%, respectively, p=0.23). Multiple secondary endpoints showed similar trends, favouring enoxaparin. Overall, there was a trend towards increased bleeding in the enoxaparin-treated group, which did not reach statistical significance. The results of these 2 trials demonstrate that the combination of enoxaparin and GP IIb/IIIa inhibitors was likely safe, with at least a trend toward reduced clinical events compared to the combination of UFH and GP IIb/IIIa inhibitors.

Summary

The lack of randomized data on LMWH use during PCI in the ACS setting remains an issue. Observational and registry data suggest that medical therapy with LMWH can be safely transitioned into the cath lab without necessitating a switch to UFH, with additional IV boluses if >8 hours after the last SQ dose. However, in randomized trials of LMWH versus UFH in ACS, such as ESSENCE and TIMI-11B, LMWH therapy was discontinued before catheterization and procedures were performed using UFH. These trials also did not employ routine early catheterization. Thus, given the benefit of an early invasive management strategy in non-ST elevation ACS patients, demonstrated in trials such as the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC-II) study[5] and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-Thrombolysis in Myocardial Infarction (TIMI) 18 trial,[6] the incremental clinical benefit of LMWH over UFH in the setting of early catheterization and revascularization remains as yet unproven.

The SYNERGY Trial

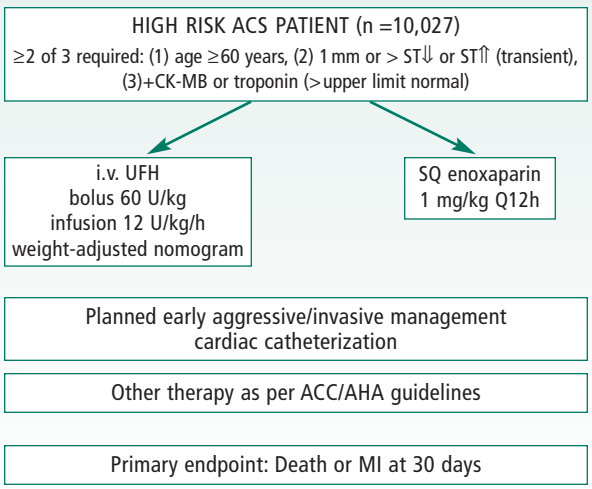
Study design and methods

The Superior Yield of the New strategy of Enoxaprin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial was a prospective, randomized, open-label, multi-centre trial comparing enoxaparin to UFH in non-ST-segment elevation MI ACS patients. SYNERGY was designed specifically to evaluate the efficacy and safety of enoxaparin versus UFH in high-risk ACS patients treated with an early invasive strategy and high rates of established therapy, including GP IIb/IIIa inhibitors. The rationale and design of SYNERGY has been published previously[7] and the study design is outlined in Figure 1. Study inclusion criteria included age >18 and ischemic pain at rest lasting ≥10 minutes and occurring within the previous 24 hours. Patients were required to have at least 2 of the following 3 high-risk markers:

- age ≥60 years
- ST-segment deviation, either new ST-depression of ≥1 mm, or transient ST-elevation of ≥1 mm in ≥2 contiguous ECG leads
- positive (>upper limit of normal) cardiac biomarkers, either CK-MB or cardiac troponin I or T.

Study exclusion criteria included thrombolytic therapy or PCI within 24 hours prior to enrollment, known bleeding

Figure 1: SYNERGY study design and primary endpoint[7]



diathesis, renal failure (creatinine clearance <30 mL/min), and a previous serious intracranial event (eg, infarct, hemorrhage, aneurysm, or tumour). Sample size calculations were performed on the basis of an expected 30-day control group event rate of 15%, with a 90% power to detect a clinically meaningful 17% relative risk reduction in event rates with a 2-sided type 1 error of 5%.

Patients enrolled in the study were randomized to receive in an open-labeled fashion either SQ enoxaparin 1 mg/kg every 12 hours, or an IV bolus of UFH 60 U/kg followed by an initial infusion of 12 U/kg/hour. Subsequent dose adjustments for UFH were made via a weight-adjusted nomogram, with a target aPTT of 50 to 70 seconds. An early invasive management strategy was strongly encouraged, with early cardiac catheterization and revascularization as required. In patients receiving enoxaparin, cardiac catheterization could be performed anytime after the last dose. If PCI was performed 8 to 12 hours after the last dose of enoxaparin, an IV bolus of 0.3 mg/kg was given. No additional doses were given for PCI within 8 hours of the last dose. Enoxaparin was discontinued for 8 hours prior to elective CABG surgery and stopped immediately if surgery was urgent. In patients treated with UFH, the drug was continued during catheterization. For PCI, the UFH infusion was discontinued, and IV boluses of UFH were administered to achieve an activated clotting time (ACT) of 250 seconds. Other medical therapy was to be administered as per ACC/AHA guidelines, at the discretion of the treating physician, including clopidogrel and GP IIb/IIIa receptor antagonists.

The primary efficacy endpoint was death and non-fatal MI at 30 days, using an intention-to-treat analysis.

The primary safety endpoint was major bleeding and stroke.

Table 1: Baseline characteristics

Characteristic	Enoxaparin (n = 4,993)	UFH (n = 4,985)
Median age (y)	60	60
Female (%)	34	34
History of diabetes (%)	29	30
History of hypertension (%)	68	68
Hypercholesterolemia (%)	58	59
Family history of CAD (%)	46	45
History of CHF (%)	9	9
Prior MI (%)	29	28
Prior stroke (%)	5	5
Peripheral vascular disease (%)	10	10
Prior PCI (%)	21	21
Prior CABG (%)	16	17

Secondary endpoints included combined all-cause mortality, non-fatal MI, stroke, or recurrent ischemia necessitating revascularization; individual components of the composite at 14 and 30 days after randomization; death or non-fatal MI at 14 days and 6 months; and death at 1 year.

Study results

A total of 10,027 high-risk ACS patients from 467 centres worldwide were enrolled into the study. Baseline characteristics of the two treatment groups are shown in Table 1. Treatment groups were well-matched, with a median age of 68 years, and one-third of participants were female. Table 2 shows use of concomitant medications in both groups. Overall, there were high rates of medication use recommended by ACC/AHA guidelines, including GP IIb/IIIa receptor inhibitor use in 57% of all patients. Data on rates and timing of catheterization and revascularization are shown in Table 3. As per study mandate, rates of catheterization were very high. Approximately half of all patients underwent PCI, with approximately 20% of patients undergoing CABG surgery. The median time to catheterization and revascularization with PCI was <24 hours for both treatment groups,

Table 2: Concomitant medication use

Medication	Enoxaparin (n = 4,993)	UFH (n = 4,985)
Aspirin (%)	95	95
Beta-blocker (%)	86	86
ACE-inhibitor (%)	64	62
Statin (%)	69	70
Clopidogrel (%)	62	63
GP IIb/IIIa receptor blocker (%)	56	58

Table 3: Procedures performed in SYNERGY

Procedure	Enoxaparin (n = 4,993)	UFH (n = 4,985)
Catheterization during baseline hospitalization (%)	95	95
Time to cath (hours)-median Time to cath (hours)-25th, 75th percentile	22 [6,44]	21 [6,43]
Percutaneous coronary intervention (%)	46	47
Time to PCI (hours)-median Time to PCI (hours)-25th, 75th percentile	23 [6,49]	22 [6,48]
CABG surgery (%)	19	18
Time to CABG (hours)-median Time to CABG (hours)-25th, 75th percentile	91 [44,167]	89 [45,166]
Days hospitalized-median Days hospitalized-25th, 75th percentile	5 [3,8]	4 [3,8]

and could be as little as 6 hours after randomization. From the data presented, many patients underwent PCI at the same time as diagnostic coronary angiography, or shortly thereafter.

The main results of the study are shown in Table 4. There were no significant differences between treatment groups in the primary efficacy endpoint of death or MI at 30 days, with the hazard ratio for enoxaparin being 0.96 (95% CI, 0.87-1.06). The upper 95% confidence interval

Table 4: Study endpoints – 30 days

Endpoint	Enoxaparin (n = 4,993)	UFH (n = 4,985)	p value
Efficacy	%	%	
Composite death/MI	14.0	14.5	NS
Death	3.2	3.1	NS
MI	11.7	12.7	NS
Safety			
GUSTO-severe bleeding	2.9	2.4	NS
TIMI major bleeding (all)	9.1	7.6	0.008
TIMI major bleeding (CABG)	6.8	5.9	NS
TIMI major bleeding (non-CABG)	2.4	1.7	0.025
Any red blood cell transfusion	17.0	16.0	NS
Stroke	1.0	0.9	NS
Intracranial hemorrhage (ICH)	<0.1	<0.1	NS
H and H* drop/ICH	15.2	12.5	0.001

* hemoglobin and hematocrit (hemoglobin drop of >5 g/dL or hematocrit drop of >15%)
NS = not significant

Table 5: PCI results

Event	Enoxaparin	UFH
Abrupt closure (%)	1.3	1.7
Any unsuccessful PCI (%)	3.6	3.4
Emergency CABG (%)	0.3	0.3

was below the cut-off of 1.1, thus meeting the pre-specified criteria for non-inferiority of enoxaparin as compared to UFH. In-hospital cardiovascular events, including cardiogenic shock, cardiac arrest, and congestive heart failure were similar in both treatment groups. While GUSTO-severe bleeding (defined as severe bleeding leading to hemodynamic compromise or intracranial hemorrhage [ICH]) and requirements for blood transfusions were similar in both treatment groups, the rates of all TIMI-major bleeding were significantly greater in the enoxaparin-treated group compared to the UFH-treated arm. There were no significant differences in CABG-related bleeding between treatment groups. PCI-related outcomes are shown in Table 5. There were no differences between treatment groups in rates of abrupt closure, failed PCI, or the need for emergency CABG surgery.

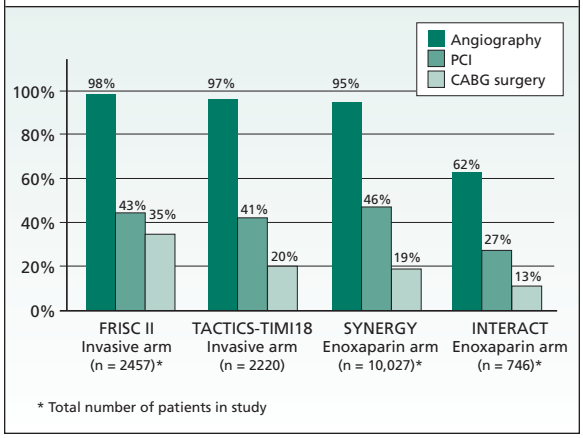
Subgroup analyses were performed, with patients grouped by whether they had received antithrombin therapy prior to randomization and, if they had, whether randomization was to the same antithrombin agent (consistent treatment), or to an alternate agent (treatment cross-over). These data are shown in Table 6. The group of patients who did not receive a pre-randomization antithrombin agent accounted for approximately 25% of the patients in the study. In this

Table 6: Subset analysis based on pre-randomization treatment and crossover

Endpoint	Enoxaparin	UFH	p value
Patients without pre-randomization antithrombin therapy			
30-day death/MI (%)	12.6	14.8	NS
GUSTO-severe bleeding (%)	3.1	1.8	Significant
TIMI major bleeding (%)	9.7	6.9	Significant
Patients on pre-randomization antithrombin therapy, who remained on the same regimen after randomization			
30-day death/MI (%)	13.3	15.9	Significant
GUSTO-severe bleeding (%)	3.1	2.2	Significant
TIMI major bleeding (%)	9.3	7.9	NS

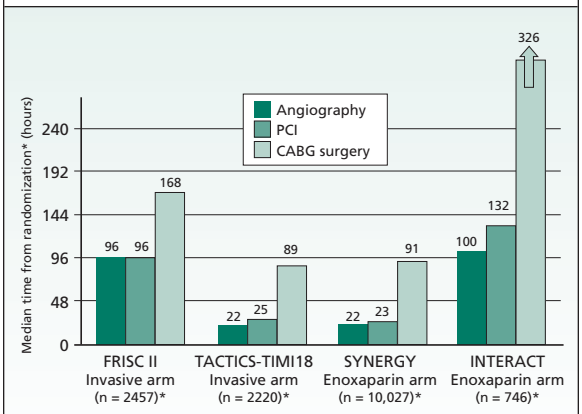
NS = not significant

Figure 2: Comparison of rates of procedures in specific arms of non-ST elevation ACS trials



* Total number of patients in study

Figure 3: Comparison of timing of procedures in specific arms of non-ST elevation ACS trials



* Randomization at various times after hospitalizations

group, there was a strong trend towards clinical benefit at 30 days in the enoxaparin-treated arm. The group that received antithrombin therapy prior to randomization and continued on the same regimen after randomization accounted for just over 60% of patients enrolled. This group showed a significant reduction in 30-day death/MI rates in the enoxaparin-treated as compared to UFH-treated arm. Bleeding endpoints remained increased with enoxaparin in both of these subgroups. Thus, it would appear that patients who crossed over to another therapy did worse with enoxaparin treatment compared to UFH.

Discussion

Overall, the results of SYNERGY demonstrated that enoxaparin was not superior to, but was at least as effective as UFH in the prevention of death or MI in high-risk ACS patients treated with an early invasive management strategy. Importantly, SYNERGY did show unequivocally that PCI in the setting of ACS can be safely performed using enoxaparin, with low rates of abrupt closure, failed PCI, and the need for urgent CABG surgery, and no differences between treatment groups. Treatment with enoxaparin was associated with a higher incidence of bleeding, but was not associated with higher rates of ICH, hemodynamic compromise, or requirements for blood transfusions.

There are several important aspects of the SYNERGY trial. First, it was the largest trial to compare different antithrombin regimens in ACS patients, with more patients enrolled than the ESSENCE and TIMI-11B studies combined. Second, SYNERGY was successful in identifying and enrolling a high-risk subset of ACS patients, with 30-day death/MI rates almost twice that of contemporary ACS trials of enoxaparin. Given the power of the study and the high clinical event rates, and considering evidence from previously published trials demonstrating the superiority of enoxaparin over UFH in the setting of ACS, the results were somewhat unexpected. Thus, unfortunately, the trial that was going to definitively define the role of LMWH in the current management of ACS may instead have led to further controversy and unanswered questions.

One has to consider that most of the clinical benefits seen in previous trials comparing enoxaparin versus UFH in ACS were due to improved rates of MI, recurrent ischemia, and urgent revascularization, rather than lower rates of death. This beneficial effect may have been somewhat negated in the SYNERGY trial. Patients enrolled in SYNERGY had arguably the most current optimal management for non-ST-segment elevation ACS. There were high rates of proven medical therapy, including the use of GP IIb/IIIa receptor blockers (Table 2). The rates of catheterization and revascularization were higher than those seen in the INTERACT study and were comparable to studies showing the benefits of early invasive management (Figure 2). Similarly, timing of catheterization and revascularization was at least as good as that seen in FRISC II[5] and TACTICS-TIMI 18,[6] with median times of <24 hours, and as early as <6 hours after randomization. It should be noted that randomization in SYNERGY occurred an average of 20 hours after hospitalization. This contrasts with data from the INTERACT trial,[4] in which 64% of patients underwent catheterization within 30 days and median times to catheterization, PCI, and CABG surgery were 100, 132, and 326 hours, respectively (Figure 3). Thus, given the overall effectiveness and efficiency with

which patients were managed, it may not be that surprising that the choice of antithrombin agent used in this study did not significantly affect clinical outcomes, specifically non-fatal MI.

Bleeding outcomes in this study and their relevance will undoubtedly be debated. TIMI-major bleeding was significantly increased with enoxaparin as compared to UFH. Notably, this difference was not wholly attributable to increased CABG-related bleeding in the enoxaparin-treated group. However, despite this, there were no significant differences in the requirement for blood transfusions or in bleeding resulting in hemodynamic compromise. In addition, overall rates of ICH were low, without significant differences between groups. Thus, the true clinical relevance of the increased bleeding seen with enoxaparin remains unclear. It is hoped that further data, including procedure-related bleeding, may lead to further insights into the mechanisms and significance of bleeding events, that may need to be addressed in future studies.

The SYNERGY investigators have put forward an interesting theory that was derived from secondary subgroup analyses. In patients where the pre- and post-randomization antithrombin therapy was the same, meaning no treatment crossovers, they found a significant reduction in the primary efficacy endpoint with enoxaparin. In addition, patients randomized without previously being on antithrombin therapy showed a strong trend towards improved clinical outcomes with enoxaparin. This suggests that there may be a benefit of enoxaparin over UFH in the subgroup of non-crossover treatment patients. However, bleeding remained significantly greater with enoxaparin therapy in both of these subgroups, despite better efficacy outcomes. It seemed that patients who had their antithrombin treatment changed at the time of randomization had worse outcomes with enoxaparin treatment, suggesting that treatment crossovers led to worse outcomes with enoxaparin, and thus, should be avoided. However, these results, while provocative, remain hypothesis-generating rather than conclusive.

Conclusions

In summary, SYNERGY did not demonstrate the superiority of enoxaparin over UFH. However, it did show that enoxaparin is an effective alternative to UFH for the treatment of high-risk ACS patients managed with an early invasive treatment strategy and that patients with ACS can be safely and effectively transitioned to the catheterization laboratory for PCI. While bleeding rates were increased with enoxaparin and, given that there were no differences in transfusion requirements, hemodynamic instability, or ICH, the clinical relevance remains to be further defined. Data from previous clinical trials continue to demonstrate that in those ACS patients treated medically, or potentially in whom early catheterization and revascularization is delayed, enoxaparin is superior to UFH in preventing adverse cardiac events. While concerns have been raised regarding the clinical consequences of treatment crossovers in antithrombin therapy, this hypothesis remains to be further explored. The results of the SYNERGY trial are important; however, given the overall neutral results, its impact on current clinical practice is likely not high, and remains difficult to predict.

References

1. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight–heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. *N Engl J Med* 1997;337:447-452.
2. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI)-11B trial. *Circulation* 1999;100:1593-1601.
3. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI-11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602-1608.
4. Goodman SG, Fitchett D, Armstrong PW, et al. Integrilin and enoxaparin randomized assessment of acute coronary syndrome treatment (INTERACT) trial investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation* 2003;107:238-244.
5. FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomized multicentre study. *Lancet* 1999;354:708-715.
6. Cannon CP, Weintraub WS, Demopolous 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 glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-1887.
7. The SYNERGY executive committee. The SYNERGY trial: Study design and rationale. *Am Heart J* 2002;143:952-960.

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