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Diabetes in Coronary Artery Disease: Implications for Revascularization

ABSTRACTS & COMMENTARY

Synopsis: *Multiple analyses support the recommendation of the initial NHIBI clinical alert recommending surgery over angioplasty in diabetics with both 2 and 3 vessel disease.*

Sources: Ledru F, et al. *J Am Coll Cardiol.* 2001;37:1543-1550; Detre KM, et al. *N Engl J Med.* 2000;342:989-997; Niles NW, et al. *J Am Coll Cardiol.* 2001;37:100-115.

It is well known that diabetics have a greater risk of death and a shortened survival following myocardial infarction (MI); and patients with diabetes who undergo revascularization have a less optimal outcome than nondiabetics. In 1996, the BARI Trial, a comparison of coronary artery bypass surgery (CABG) with angioplasty in subjects with multivessel disease, reported that the diabetic cohort enrolled in the trial had a considerably lower 5-year mortality rate in those randomized to CABG (19.4% vs 34.5% with percutaneous intervention [PCI]; P = .003). An NHLBI clinical alert was issued recommending CABG over PCI in diabetic patients. Subsequently, analyses of other comparative revascularization trials and databases have demonstrated conflicting results as to whether diabetics with multivessel disease have a worse prognosis with PCI vs. CABG. Three recent reports bring information to this controversy; all appear to support a strategy of bypass surgery for the diabetic with 2 and 3 vessel coronary disease.

In an angiographic study from France, Ledru and colleagues confirm that diabetic subjects have more diffuse and extensive coronary atherosclerosis, a greater prevalence of mild, moderate, and severe stenoses, and a 2-fold higher vessel occlusion rate than patients without diabetes, after adjustment for multiple risk factors or clinical symptoms. Diabetics categorized into mild diabetes, with fasting plasma glucose in the lowest range, were more comparable to nondiabetics with respect to coronary anatomy and outcome. Four hundred sixty-six consecutive patients referred for coronary angiography were analyzed. Two-thirds of the patients presented with stable

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INSIDE

or unstable angina. Two independent angiographers analyzed the coronary anatomy lesion, an extent score, severity score, and atheroscrotic score. There were 93 diabetics who were older that had more hypertension and positive family history but otherwise presented with a similar clinical picture. Enrolled patients had no history of MI. Forty were newly diagnosed diabetics. Typical diabetic dyslipidemia was noted, with high TG, low HDL, and normal LDL cholesterol in the diabetic group as a whole. Analysis of the angiograms indicated substantially more multivessel disease, extent of CAD, atherosclerosis scores, numbers of diseased segments, and total occlusions, after adjustment for multiple risk factors. There was no difference in average stenosis severity between diabetics and nondiabetics. A step-wise assessment of hyperglycemic cohorts indicated an increasing atherosclerotic burden with higher plasma glucose; however, hyperglycemia was a less potent predictor of disease than LDL cholesterol, age, gender, or hypertension. There were more individuals with only mild (25-49%) coronary obstructions in the diabetic cohort; Ledru et al raise the question whether diabetics have more early or young vulnerable lesions susceptible to plaque rupture. They discuss multiple studies in the literature, and point out a variety of problems with interpretation of this data, including variable sample size, various methodologies of assessing CAD severity, and inclusion of only insulin dependent diabetics. They conclude that sustained hyperglycemia in diabetics results in substantially more severe coronary atherosclerosis. They speculate that in type 2 diabetics with relatively low fasting glucose, the somewhat greater prevalence of mild lesions may represent a surrogate for plaque vulnerability and potential rupture, leading to acute myocardial infarction (AMI).

Two other studies examine the relative advantage of CABG over angioplasty in subjects with multivessel coronary disease who are or are not diabetic. Detre and associates performed an analysis of the BARI cohort, with respect to the outcome of patients who had an AMI following the initial revascularization procedure, and provide evidence that CABG appears to protect the diabetic subjects with postrevascularization AMI compared to PCI, with no such differential in survival in the nondiabetics with an AMI after initial enrollment. The original BARI study, as well as the BARI registry cohort, were included in this analysis of 3603 patients, all of whom underwent revascularization. The primary end point was all-cause death; this analysis focused on spontaneous Q-wave MI (clinical or silent), in follow-up of all BARI patients. Diabetic patients randomized to CABG who had an AMI fared substantially better than those randomized to PCI with an AMI. At 5 years after revascularization, 64% of the diabetics and 58% of the nondiabetics had undergone a CABG. The incidence of spontaneous Q-wave MI was 4.8%; diabetics were 1.9 times as likely as nondiabetics to have an MI. There was no difference in the likelihood of Q-wave infarcts between the CABG and PCI patients. Overall mortality at 5 years was 8% for 2962 patients without diabetes and 20% for the 641 patients with diabetes, (P = < .001). The mortality in diabetics was 18% in those who had CABG and 25% in those who did not. In diabetics who had a subsequent MI, "the protection provided by CABG was dramatic;" mortality was 17% in those who underwent CABG vs. 80% in those who had a spontaneous Q-wave MI and underwent angioplasty. The mortality in the diabetic CABG patients was comparable to the nondiabetics. Thus, CABG in the diabetic cohort resulted in 81% risk reduction for death (P = .001) in those subjects who had a spontaneous Q-wave MI, and a 35% reduction in mortality (P = .02) in the diabetics who did not have a spontaneous infarct. Detre et al point out that relatively few diabetics subsequently had a spontaneous Q-wave MI, and most importantly, that CABG reduced mortality among the majority of diabetics who did not have an MI when compared to the angioplasty strategy. Nondiabetics who received a CABG did not have a statistically significant reduction in mortality with or without a subsequent Q-wave infarction. Detre et al emphasize the

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apparent benefit of using internal thoracic artery grafts as a primary CABG strategy. Patients who underwent angioplasty had substantially more jeopardized myocardium than those who had CABG. They suggest that the PCI strategy resulted in a greater burden of residual ischemic myocardium than with CABG.

A recent analysis of a large database from the New England Cardiovascular Disease Study Group supports the view that bypass grafting is a better strategy for multivessel revascularization in diabetics. Niles and colleagues evaluated a large number of diabetic patients who underwent coronary revascularization between 1992 and 1996 in 4 states, including Massachusetts. A complex statistical analysis and assessment of multiple variables, including the priority of need for revascularization, was included in this observational study. The study population consisted of 2756 patients with diabetes and multivessel disease. Seven hundred thirty-six underwent PCI and 2030 underwent CABG, all at the discretion of the physician. Primary outcome was all-cause mortality at 5 years. CABG patients had far more complete revascularization than PCI individual subjects, who tended to undergo a "culprit lesion strategy," with at least 75% of such individuals having incomplete revascularization. On the other hand, the PCI individuals were younger and healthier than the CABG cohort. Stents and IIb/IIIa drugs were not used in these patients. This was an observational study, it is not surprising that 56% of the CABG cohort had 3 vessel disease compared to 16% of PCI patients. The results, using adjusted survival outcomes, indicated a higher long-term mortality in the PCI patients, who were 49% more likely to die than those who received CABG (P = .037). Hospital mortality was similar; curve separation began at approximately 3 months. Triple vessel disease more than doubled the mortality risk for PCI vs. CABG. There was a 33% increase in mortality in the PCI patients with 2 vessel disease who received PCI compared to CABG. Niles et al reviewed 5 other cohorts, including the BARI patients. All studies demonstrated a trend favoring CABG over PCI, with the EAST trial insulin diabetics and the BARI randomized trial clearly favoring CABG. As mentioned, the long-term analysis of BARI, including the registry, demonstrates a major benefit for CABG. Furthermore, late analysis of the EAST trial also resulted in a favorable survival with CABG. Niles et al conclude that their analysis supports the recommendation of the initial NHIBI clinical alert recommending surgery over angioplasty in diabetics with both 2 and 3 vessel disease.

COMMENT BY JONATHAN ABRAMS, MD

The literature is rich with respect to reports on revascularization outcomes in diabetics. The subject is of considerable importance, in that approximately 6% of the US population has overt diabetes, with perhaps 2 times as many patients who do not know that they have diabetes or are prediabetic. Coronary disease accounts for 50-70% of the mortality in type 2 diabetics. The BARI observations have triggered multiple retrospective as well as prospective studies, culminating in these reports. Expert consensus guidelines, clinical trials, and prominent interventional clinical investigators, such as William O'Neil, support a preferential strategy of CABG for diabetics who have multivessel disease. The Northern New England Cardiovascular Disease Study Group report underlines the difficulty in carrying out such a blanket recommendation, by documenting that the large number of angioplasties performed in diabetics provide incomplete revascularization by addressing the lesion responsible for an AMI or acute coronary syndrome, leaving other obstructive lesions unprotected. The French angiographic study confirms multiple other reports that the degree of coronary atherosclerosis in the diabetic is more extensive, diffuse, and severe, making it difficult for multiple PCI interventions to "cure" or adequately treat the entire coronary circulation. Furthermore, there is evidence that multiple factors in the diabetic patient result in less good outcomes following angioplasty even with stenting. These include a prothrombotic-platelet-activated state, oxidative stress, and glycation of proteins. Stenting improves the outcomes in diabetics undergoing PCI, but this approach does not provide the diabetic with a comparable long-term outlook as the nondiabetic following PCI. Furthermore, other data from the Montreal Heart Institutes suggest that late stent stenosis, resulting in decreased LV function, may play a little recognized but important role in the adverse outcome of diabetics undergoing angioplasty with stenting.

Conclusions

The large database, in the aggregate, supports a generic recommendation for bypass grafting in the diabetic with severe 2 and 3 vessel disease warranting revascularization. Whether the widespread use of internal thoracic arteries is responsible for some or most of the protection with surgery is speculative; outcomes in nondiabetics in EAST, BARI, and other databases do not suggest a substantial outcome differential in the nondiabetic who receives a PCI vs. CABG. Physicians caring for diabetics who refer these patients for cardiac catheterization or interventions need to understand the robust data underlying the construct that bypass surgery is the optimal revascularization strategy for the diabetic with multivessel disease. ❖

Mitral Valve Replacement with the St. Jude Prosthesis

ABSTRACT & COMMENTARY

Synopsis: *Long-term results with the St. Jude valve for isolated mitral valve disease confirm excellent biocompatibility and durability, but these results demonstrate the difficulty of long-term anticoagulation therapy.*

Source: Remadi JP, et al. *Circulation*. 2001;103: 1542-1545.

Although the st. jude prosthesis has become the standard for mechanical valve replacement, there is little long-term data on its use in the mitral position. Thus, Remadi and colleagues reported on a 10-19 year follow-up of 440 patients operated upon between 1979-1989 for isolated mitral valve replacement. Slightly more were women and their mean age was 60 years. Rheumatic heart disease was the etiology in 60% and the number with predominant stenosis or regurgitation was about the same. A majority had atrial fibrillation (57%). A 29 mm prosthesis was most commonly used (range, 25-33) and the subvalvular apparatus was not preserved. Only 5% of the surgeries were considered urgent. All patients were put on lifelong warfarin beginning on day 4. Follow-up was 98% complete at 19 years.

The results demonstrated a 4% perioperative mortality and a subsequent survival of 61% at 19 years. Survival free of valve-related complications was 84%. The most common nonvalvular cardiac cause of death was heart failure. The most common valve-related cause of death was sudden death, followed by hemorrhage. With regard to valve-related complications, no structural dysfunction was observed. Anticoagulation-related complications occurred at a frequency of 1% per patient-year. Thrombosis was much less common at 0.2% per patient-year. At 19 years, freedom from endocarditis was 99%, thrombus 97%, perivalvular leak 94%, valve avulsion 90%, re-operation 90%, thromboembolism 82%, and hemorrhage 80%. Of those patients undergoing reoperation, 12 had perivalvular leak, 2 thrombosis, and 1 endocarditis. Remadi et al concluded that long-term results with the St. Jude valve for isolated mitral valve disease confirm excellent biocompatibility and durability, but demonstrate the difficulty of long-term anticoagulation therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

The St. Jude valve has become the most used prosthetic valve in the United States since Pfizer withdrew the Bjork-Shiley valve from the market. Consequently there is not much long-term data on this valve, especially in the mitral position. Therefore, these data from France are of interest. Although a small study by today's mega-trial standards, it demonstrates excellent long-term results with this valve. No structural failure was documented and valve thrombosis was rare. Almost all of the reoperations were for perivalvular leak. The data related to the prosthesis are impressive and justify Remandi et al's conclusions.

Most of the morbidity and one-quarter of the valve related deaths were related to anticoagulation problems. Despite more than 10 years of experience, poor anticoagulation control was demonstrated in 20% of the patients. Therefore, the major limitation to the use of this valve seems to be the need for anticoagulation. Some have suggested that if the patient is in sinus rhythm, the INR could be run at a lower level than the level of 3-4 used in this study. However, there are no data that this would reduce the number of anticoagulation-related problems and not result in more valve thrombosis. Also, many patients with mitral prostheses have atrial fibrillation and require anticoagulation for that reason.

The major cardiac nonvalvular cause of death was heart failure, which accounted for 38% of all deaths. This seems high in a group in which half had mitral stenosis. One potential reason for this finding was that chordal preservation was not used in these patients because they were all operated on in the 1980s before this had become common practice. Had chordal preservation techniques been used, heart failure related mortality may have been lower. ❖

Prediction of Operative Mortality with Valve Replacement Surgery

ABSTRACT & COMMENTARY

Synopsis: *The information in this paper provides benchmarks for assessing your institution's surgical results and a tool for assessing the relative risk in individual patients.*

Source: Edwards FH, et al. *J Am Coll Cardiol*. 2001; 37:885-892.

Risk assessment is a critical component of cardiothoracic surgery, but there is limited information

about the prediction of risk in valve replacement surgery. Therefore, Edwards and associates analyzed the Society of Thoracic Surgeons national cardiac surgery database for the outcome of patients with isolated aortic or mitral valve replacement surgery and valve replacement surgery plus coronary artery bypass surgery (CABG). The database was started in 1986 and now contains more than 1 million patients from 487 hospitals in 47 states and Canada. For the purpose of developing a risk model, 92,536 patients with either isolated aortic valve replacement (32,968), isolated mitral valve replacement (16,105), CABG plus aortic valve (32,528), or CABG plus mitral valve (10,925), operated on between 1994 and 1997 were analyzed. After development of the model, a validation sample of 51,492 patients operated on between 1998 and 1999 were used to test the model.

In general, patients with isolated valve replacement surgery were younger and had less CAD risk factors. Also, operative mortality and morbidity were greater for valve surgery combined with CABG vs. valve surgery alone. In addition, operative mortality and morbidity were higher for mitral vs. aortic surgery. Operative mortality was lowest for isolated aortic valve surgery and highest for mitral valve replacement plus CABG (*see Table*). Also, ceratin complications were more common with one type of surgery vs. the others.

Patient subgroup analysis showed that diabetes approximately doubles the risk of operative mortality. Renal dialysis increases risk 3-4 fold to 17-37%; peripheral vascular disease almost doubles the risk to 7-21%; and the presence of 3 vessel CAD increases risk to 10-16%. The presence of prior stroke, immunosuppressive therapy, and previous cardiac surgery increases operative mortality risk less than two fold. Systemic hypertension and chronic obstructive lung disease did not appreciably increase risk.

The validation sample analysis showed that the predicted operative mortality rate from the model was close to the observed rate: the overall rate for isolated valve replacement was 4.8% predicted vs. 4.7% observed; the overall rate for CAGB plus valve replacement was 8.6% predicted vs. 8.2% observed. Hameed et al concluded that they have developed a statistical model that accurately predicts operative mortality after valve replacement surgery.

Table

Perioperative Complications by Type of Surgery

	AVR	MVR	AVR+ CABG	MVR-CABG
Operative mortality (%)	4	6	7	13
Stroke (%)	2	2	3	4
Reoperation for bleeding (%)	4	5	6	6
Renal failure (%)	4	5	6	13
Infection (%)	0.5	0.3	0.7	0.8
Hospital stay (days)	11	13	13	16

COMMENT BY MICHAEL H. CRAWFORD, MD

Risk prediction models have been well worked out for CABG surgery, but little data exist for valve surgery. Thus, this report from the STS database is of interest. The strength of this database is that it includes a wide variety of public, government, and private hospitals. Consequently, Edwards et al suggest that this data can be used to form a national benchmark for valve replacement surgery. On the other hand, they do not believe their data can be used as a national standard, because of regional differences in practice and referral patterns. However, the data are useful for discussing the potential risk with patients if you do not have such data at your own institution.

Several things stand out in the results that are of interest to the clinician. Mitral valve replacement plus CABG surgery has the greatest operative mortality, the highest complication rate, and the greatest length of stay. The subgroup with the highest operative mortality is patients on renal dialysis (3-4 fold increase). Prior stroke and previous cardiac surgery have a modest effect on mortality (less than a 2-fold increase). Chronic lung disease has little influence on mortality. These results are useful for assessing risk in a particular patient. Thus, the information in this important paper provides benchmarks for assessing your institution's surgical results and a tool for assessing the relative risk in individual patients. ❖

Autonomic Tone Post MI

ABSTRACT & COMMENTARY

Synopsis: *Depressed baroreceptor sensitivity and the presence of nonsustained VT are independent risk factors for both cardiac mortality and arrhythmic events after MI.*

Source: LaRovere MT, et al. *Circulation*. 2001;103: 2072-2077.

The autonomic tone and reflexes after Myocardial Infarction (ATRAMI) project was a study that examined the predictive value of analysis of autonomic nervous system function in survivors of acute myocardial infarction. The study, whose primary end

points were reported several years ago, enrolled 1284 patients younger than 80 years of age with a myocardial infarction within 1 month of enrollment.[1] This substudy reports the prognostic significance of the following variables in ATRAMI: left ventricular ejection fraction (LVEF), nonsustained ventricular tachycardia (VT), abnormal heart rate variability (HRV), and baroreceptor sensitivity. These definitions were used: nonsustained VT was present if 3 or more consecutive ventricular beats at a rate of over 100 beats per minutes were seen on a 24-hour holter recording. Abnormal HRV was defined as a standard deviation of normal-to-normal RR intervals less than 70 msec. Depressed baroreceptor sensitivity was present if there was less than 3 msec heart rate slowing per mm Hg blood pressure increase during a phenylephrine infusion. Patients were dichotomized at a LVEF of 35%. The end points analyzed were total cardiac mortality and a combined end point of sudden death and/or sustained VT. Associations were assessed with univariate and multivariate Cox analysis and relative risks calculated.

Complete data were available on 1071 patients. The mean age was 59 ± 10 years and the mean LVEF was 49 ± 11%. The LVEF was less than 35% in 157 patients (14.6%). During 21 ± 8 months of follow-up there were 43 cardiac deaths or nonfatal cardiac arrests and 5 episodes of sustained ventricular tachycardia.

Life-table analysis of mortality showed that patients with both nonsustained VT and depressed baroreceptor sensitivity had a higher mortality (21%) than those without either of these findings (2.4%). Patients with either nonsustained VT or depressed baroreceptor sensitivity, but not both, had an intermediate mortality of 7.5%. Almost identical observations were made for patients with abnormal HRV with an overall mortality of 29% for patients with nonsustained VT and abnormal HRV, a 2.5% mortality for those with neither finding, and a 6-7% mortality for those with 1 of the findings. Multivariate Cox analysis showed that the combination of nonsustained VT plus abnormal HRV increased the relative risk for cardiac mortality to 17, and the combination of nonsustained VT plus depressed baroreceptor sensitivity resulted in a relative risk of 9.6. In patients with all 3 of these findings, the relative risk for cardiac death was 22.2. The prognostic significance of these variables was also examined in the subgroup of patients with ejection fractions less than 35%. Both nonsustained VT and depressed baroreceptor sensitivity maintained an independent prognostic association with cardiac mortality in this group but this was not the case for abnormal HRV. In patients with an ejection fraction of less than 35% who did not have nonsustained VT, depressed baroreceptor sensitivity still influenced mortality risk with a relative risk of 4.1.

LaRovere and colleagues conclude that depressed baroreceptor sensitivity and the presence of nonsustained VT are independent risk factors for both cardiac mortality and arrhythmic events after MI. A reasonable compromise between sensitivity and specificity is achieved by combining reduced LVEF with the presence of either nonsustained VT or depressed baroreceptor sensitivity.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Effective identification of patients at risk for death after MI remains challenging. Ejection fraction and the presence of nonsustained VT are commonly used markers for an adverse prognosis. Recently, the Multicenter Automatic Defibrillator Implantation Trial directly, and the Multicenter Unsustained Tachycardia Trial indirectly indicated that implantable cardioverter defibrillator (ICD) therapy reduced total mortality, largely by preventing sudden death. However, ICD therapy is quite expensive using current systems; and more precise methods to identify the patients in whom prophylactic ICD therapy would be the most cost-effective are needed.

The ATRAMI study tested whether baroreflex sensitivity and heart rate variability would be effective predictors of mortality after myocardial infarction. Nonsustained VT is the most commonly used predictor of arrhythmic risk but use of nonsustained VT in decisions regarding an individual patient is limited by day-to-day variability in the postinfarction period. Baroreflex sensitivity, a test infrequently performed in North America, and heart rate variability are measures of autonomic nervous system tone that reflect sympathetic predominance. They should remain stable from day-to-day unless the patient's clinical status changes. This study shows that these 2 markers, particularly when combined with the presence of nonsustained VT and a low LVEF, can help identify a group of high-risk patients who would have a substantial probability of benefiting from ICD implant insertion.

Unfortunately, there was only a relatively small number of patients with low LVEF (157) and this resulted in large confidence intervals for any of the estimates given. However, it seems clear that patients with a low LVEF who have either nonsustained VT and abnormal baroreceptor sensitivity, or both, constitute a group in whom studies to assess the benefits of prophylactic ICD therapy would be appropriate.

Unfortunately, this paper does not contain data analyzing a number of other factors associated with out-

come after MI. Patients who had recurrent ischemia and underwent bypass surgery or patients with signs or symptoms of heart failure were excluded. In addition, the use of other drugs, including statins, ACE inhibitors, and beta blockers, which have been shown to favorably influence survival, is not discussed in this manuscript. It is likely that a much larger study population would be required to include these variables in a survival analysis when planning any clinical trials. ❖

Reference

1. LaRovere M, et al. *Lancet*. 1998;351:478-484.

VT from the Aortic Sinus of Valsalva

ABSTRACT & COMMENTARY

Synopsis: *A significant proportion of patients with outflow tract tachycardia have initiation from a site reachable from the aortic sinus of Valsalva. Map-guided radiofrequency ablation can effectively eliminate these arrhythmias.*

Source: Kanagaratnam L, et al. *J Am Coll Cardiol.* 2001;37:1408-1414.

Kanagaratnam and colleagues describe unusual electrophysiologic findings in a group of 12 patients with recurrent ventricular tachycardia (VT) arising from the left ventricular outflow tract who were referred to their laboratories for ablation.

The 12 patients described in this report comprised 18% of all patients who were referred for radiofrequency ablation for VT with a left bundle branch block morphology and inferior axis during the period of the study. At electrophysiologic study, pace mapping and activation mapping during ventricular tachycardia were performed first in the right ventricular outflow tract, the typical site of origin. If no successful ablation site was found, left ventricular outflow tract mapping was next performed. When the site of origin was still not identified, either epicardial mapping or supravalvular mapping in the region of the sinus of Valsalva was performed. When a paced QRS identical to the clinical VT was identified, radiofrequency ablation was then performed.

The study group included 7 women and 5 men with a mean age of 27 ± 10 years. Structural heart disease had been excluded in all patients. The ECG had a left bundle branch block pattern with small R waves in V^1 and an early transition to a dominant R in V^2 or V^3. Isoproterenol and/or phenylephrine infusion was required for VT initiation in all patients. Mapping in the right ventricular outflow tract and in the left ventricular outflow tract below the aortic leaflets failed to show a perfect QRS match. Although early activation times could be found using epicardial mapping, mapping in the region of the aortic sinus of Valsalva showed the earliest local activation times and the best pace maps. However, once the appropriate site was identified, a single radiofrequency application effectively eliminated the arrhythmia. Follow-up showed that all 12 patients remained tachycardia free over a period of 8 ± 2.6 months. No complications from the procedures were noted.

Kanagaratnam and colleagues conclude that a significant proportion of patients with outflow tract tachycardia have initiation from a site reachable from the aortic sinus of Valsalva. Map guided radiofrequency ablation can effectively eliminate these arrhythmias.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Radiofrequency ablation has become the therapy of choice for highly symptomatic patients with normal hearts and several types of ventricular tachycardia. The most common type has a left bundle branch block morphology and an inferiorly directed axis. The second most common pattern of VT in patients with normal hearts has a right bundle branch block pattern with left axis deviation and arises from the inferior left ventricular septum. A small number of patients with VT with a morphology resembling left bundle branch block with an inferior axis have been reported in whom successful ablation from the right ventricular outflow tract has not been possible. Some of these patients have left ventricular outflow tract sites of origin but in other cases, ablation using standard techniques in that region have not been successful. Some authors have reported successful ablation of this form of VT with epicardial lesions placed either directly or using a branch of a small cardiac vein.

In this paper, Kanagaratnam et al show another approach for ablating VT in these patients. They have excellent success and eliminated tachycardia in all 12 patients by delivering energy in an aortic sinus of Valsalva.

Patients in this series were highly symptomatic and failed multiple attempts of therapy. Kanagaratnam et al were fortunate in that they did not have any complications related to their procedure. Ablation in or above in the area of the aortic valve entails a significant possibility for creating valvular damage, atrioventricular block by damaging the bundle of His which runs through this area,

or coronary artery occlusion if energy is delivered in a coronary orifice. Any of these complications could be catastrophic. Therefore, despite the excellent results reported here, the procedure should be reserved for only extremely highly symptomatic patients in whom the risk is justified. ❖

CME Questions

21. Which of the following predicts cardiac mortality after myocardial infarction?
a. Nonsustained ventricular tachycardia
b. Depressed baroreceptor sensitivity
c. Abnormal heart rate variability
d. All of the above

22. Radiofrequency ablation from which sites have been successful for preventing ventricular tachycardia?
a. Right ventricular outflow tract
b. Left ventricular outflow tract
c. Aortic sinus of Valsalva
d. All of the above

23. Diabetic patients with symptomatic multivessel CAD should have:
a. PCI of the culprit lesion.
b. multivessel PCI.
c. staged PCI.
d. CABG surgery.

24. Long-term follow-up of the St. Jude mechanical valve in the mitral position shows:
a. frequent anticoagulation problems.
b. a high incidence of valve thrombosis.
c. a 30% reoperation rate at 10 years.
d. considerable valve dysfunction.

25. A national database of valve replacement surgery shows that operative mortality and morbidity:
a. doubles in renal dialysis patients.
b. quadruples in prior stroke patients.
c. triples in COPD patients.
d. is highest with mitral valve replacement plus CABG.

Attention Subscribers

Enclosed with this issue is a special report on Acute Coronary Syndromes. This report was originally published in *Emergency Medicine Reports*, December 4, 2000, volume 21, number 25, and we thought it would be of interest to our readers. *Emergency Medicine Reports* is edited by Gideon Bosker, MD, FACEP, Special Clinical Projects and Medical Education Resources; Assistant Clinical Professor, Section of Emergency Services, Yale University School of Medicine; Associate Clinical Professor, Oregon Health Sciences University. As always, we welcome your questions and comments. ❖

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A monthly update of developments in cardiovascular disease

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Acute Coronary Syndromes: An Evidence-Based Review and Outcome-Optimizing Guidelines for Patients With and Without Procedural Coronary Intervention (PCI)

Part III: Fibrinolytic Therapy, Procedural Coronary Intervention, Multi-Modal Approaches, and Medical Prophylaxis with Low Molecular Weight Heparins

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Series Editor's Note: *Gideon Bosker, MD, FACEP*

Editor's note—if only one could go with the flow, but no such luck. the appropriate strategy for managing patients with acute coronary syndromes (ACS) seems to change as rapidly as any therapeutic area in the field of acute care medicine. Part of the problem in identifying the outcome-optimizing approach to managing patients with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (MI) is the sheer number and combinations of pharmacological and procedural options available for reducing morbidity and mortality in ACS.

And not every institution is equipped to apply the interventional strategies that clinical trials suggest represent the best approach to managing these patients, which complicates both the development and application of national guidelines. In particular, landmark studies conducted at teaching institutions confirm the value of using percutaneous transluminal coronary angioplasty (PTCA) or stent insertion in patients with ST-elevation MI. However, the majority of American hospitals do not have the human or technical resources for managing patients using these techniques, which require prompt application (i.e., no more than 90 minutes from presentation to balloon catheter inflation across the culprit coronary lesion) in order to maximize clinical outcomes. In such institutions, clinicians may have to "default" to thrombolytic therapy as the mortality-reducing procedure of choice.

Then again, recent trials have demonstrated the potential value of using procedural coronary intervention (PCI) in combination with other pharmacological modalities, including glycoprotein (GP) IIb/IIIa inhibitors, thrombolytics, and low molecular weight or unfractionated heparins (UFH). The strategy of combining the two modalities is characterized as

"facilitated" perfusion. The combination may be cost-effective if a pharmacologic regimen decreases the need for early mechanical intervention or improves the results of PCI. Moreover, patients may be more stable in the catheterization lab after thrombolysis. In particular, patients arriving with more patent arteries due to earlier reperfusion are less likely to be in shock or to suffer dysrhythmias. Finally, the technical success of the procedure may be enhanced by the ability to better visualize distal vessels. Even when pharmacological therapy is the foundation of management, newer trials are assessing the efficacy and safety of using multi-modal approaches—a cocktail of anti-thrombotic, antiplatelet, and fibrinolytic agents administered in less than full doses—to improve patient outcomes.

Against the backdrop of rapid change and new data also is the emergence of paradigm shifts within therapeutic classes. For example, studies suggest that new thrombolytics such as tenecteplase (TNK/t-PA) may reduce the rate of non-cerebral hemorrhage and transfusion requirements following thrombolysis, enoxaparin is superior to heparin for patients with UA and NQMI, enoxaparin can be safely used as an anti-thrombin agent in the setting of PCI, and abciximab may produce better results in patients who are destined to have PCI.

The purpose of this evidence-based review is to evaluate the latest efficacy and safety trials that have been designed to measure the cardioprotective benefits of acute, procedural, and pharmacological interventions in patients with ACS. Then, based on a comparative assessment of such trials, and with the AHA/ACC recommendations for UA and NSTEMI as a platform, the author generates a detailed, practical, and evidence-based set of treatment guidelines that can be applied by emergency physicians and cardiologists to maximize clinical outcomes in patients with ACS. **—gideon bosker, md**

Thrombolytic Therapy

In appropriately selected patients with acute myocardial infarction, (AMI) early administration of thrombolytic agents reduces mortality and is associated with improved short- and long-term clinical outcomes. From a pathophysiological perspective, prompt restoration of patency in the infarct-related artery reduces infarct size and minimizes the extent of myocardial damage, preserves left ventricular function, reduces morbidity, and prolongs survival. Compared to standard therapy, thrombolysis is associated with a 21% reduction in 30-day mortality.[1] However, these agents also are associated with intracranial hemorrhage in about 0.5-0.9% of patients. In addition, only 30-60% of patients achieve TIMI 3 (normal) flow in the affected epicardial artery within 90 minutes.[1] Because of these drawbacks, safer and more effective fibrinolytic therapies have been developed through bioengineering techniques on the t-PA molecule. In addition, the role of combination therapy with adjunctive agents such as GP IIb/IIIa inhibitors is emerging.

Mechanism and Efficacy. From an outcome point of view, it should be stressed that mortality is affected by factors other than epicardial vessel flow. In this regard, reperfusion at the tissue level may be a critical factor in myocardial salvage and this does not necessarily correlate with epicardial vessel flow. Patients with documented TIMI 3 epicardial flow, but poor TIMI myocardial perfusion (TMP) grades (TMP 0 or 1), had a higher mortality rate (5.4%) than those patients with adequate (TMP grade 2 flow) or complete tissue perfusion (TMP grade 3 flow; 2.9% and 0.7%, respectively).[2] Therefore, while survival in studies has been correlated with epicardial vessel flow, there is still much to be deciphered about perfusion characteristics and predictors of mortality.

The ideal fibrinolytic agent provides rapid lysis, enhances tissue-level perfusion, reduces intracranial and systemic hemorrhage, has a long half-life enabling single-bolus administration, has no antigenicity, and has a low reocclusion rate. Enhanced fibrin specificity also is desirable because it permits preferential activation of fibrin-bound plasminogen at the clot surface; this has the

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potential to increase patency and produce higher initial patency rates, and may be associated with fewer bleeding complications. Greater fibrin specificity also decreases activation of circulating plasminogen and degradation of fibrinogen, resulting in less bleeding and reducing the need for transfusion. Plasminogen activator inhibitor-1 (PAI-1) inhibits thrombolysis. Greater resistance to the action of PAI-1 would increase the potency of fibrinolytic agents.

Streptokinase. Streptokinase was the first fibrinolytic to be extensively used in the setting of AMI. The benefits associated with intravenous streptokinase were clear, as was established by the GISSI-1 and ISIS-2 trials. These trials demonstrated a mortality reduction of 23% and 30%, respectively, in patients with AMI who received this therapy within six hours of symptom onset compared with placebo.[1] The current dose is 1.5 million units given intravenously over 60 minutes. Streptokinase can cause allergic reactions, and it is recommended that this fibrinolytic not be administered to patients with a history of recent streptococcal pharyngitis or who have received streptokinase within 12 months.[1] Streptokinase has been associated with a lower risk of intracranial hemorrhage than other thrombolytics.[1]

Alteplase. Alteplase (recombinant t-PA) is cloned from endogenous human t-PA, and it has become a standard against which other agents are compared. It has a short, 4- to 8-minute half-life, is administered as an initial intravenous bolus followed by a 90-minute intravenous infusion (accelerated regimen), is a direct activator of plasminogen, and is nonimmunogenic. Alteplase yields patency (TIMI 2/3 flow) rates of 70-85% at 90 minutes.[1] It has been shown to reduce mortality in various trials, including when used vs. placebo in the Anglo-Scandinavian Study of Early Thrombolysis (ASSET-1),[3] and vs. streptokinase in the Global Utilization of Streptokinase and t-PA in Occluded Arteries (GUSTO-I) trial.[4] Its clinical benefit is evident even when administered up to 12 hours following symptom onset.[5]

Reteplase. The first fibrinolytic to be bioengineered from the t-PA molecule, r-PA, like alteplase, is a direct plasminogen activator and is non-immunogenic. However, its longer half-life permits administration as two bolus injections given 30 minutes apart.[1] Its efficacy in comparison to alteplase was demonstrated in the GUSTO-III trial.[6] In this trial, r-PA and t-PA had similar 30-day mortality rates (7.5% and 7.2%, respectively).

Tenecteplase. Tenecteplase (TNK-tPA) has been bioengineered to have a relatively long half-life of approximately 20 minutes, enabling it to be administered as a single bolus injection. Unlike t-PA and r-PA, its administration is weight-based. It has a 14-fold greater fibrin specificity than t-PA in in-vitro testing, which yields more potent fibrinolytic activity at the site of the clot and reduces systemic plasmin generation, potentially enhancing the speed to patency. It also is more resistant to PAI-1 compared with t-PA; this permits longer association of TNK-tPA with the fibrin-rich clot. It also may be associated with fewer procoagulant effects than are seen with other thrombolytics.

The ASSENT-2 trial compared the 30-day mortality of accelerated t-PA with TNK-tPA. Mortality rates were similar (6.15% and 6.18%, respectively), as were intracranial hemorrhage rates (0.94% and 0.93%, respectively).[7] Interestingly, the rate of noncerebral bleeding was significantly lower for TNK-tPA compared with t-PA (26.4% vs 29%; $P < 0.0003$), as was the need for blood transfusion (4.25% vs 5.49%; $P < 0.0002$). The lower rate of noncerebral bleeding might be attributed to the higher fibrin specificity of the TNK-tPA. The greater fibrin specificity also may lead to enhanced dissolution of older fibrin clots, which may produce a better clinical outcome in patients who present late (i.e., after 3 or 4 hours of chest pain) in the clinical course of AMI.[7] It also was noted that patients who were treated more than four hours after symptoms onset exhibited a statistically better outcome (30-day mortality) with TNK-tPA compared with t-PA ($P = 0.018$).[7]

Primary Percutaneous Transluminal Coronary Angioplasty (PTCA)

ST-Segment Elevation Myocardial Infarction. "Primary" PTCA is the use of standard balloon angioplasty as the initial approach to coronary reperfusion. The main benefits as compared with thrombolysis include the potential for improved patency with avoidance of life-threatening hemorrhagic complications. There are no randomized, controlled trials comparing primary PTCA with no reperfusion. Primary PTCA has been compared with thrombolysis in several small, randomized studies. Most trials reflect that use of PTCA results in either a statistically significant improvement or at least a trend toward reduction of in-hospital or 30-day mortality, while reducing hemorrhage and stroke.[8,9]

Other studies have shown that primary PTCA is as, or more, cost effective than thrombolysis because it reduces early and late recurrent ischemic events and, as a result, facilitates earlier discharge.[8,10,11] It must be recognized that trials comparing PTCA with thrombolysis do not include patients who have contraindications to thrombolysis. Moreover, from a real world perspective, thrombolysis will continue to be the workhorse strategy for dissolving clots and establishing coronary artery patency in the setting of AMI because only approximately 20%

of U.S. hospitals maintain catheterization capabilities and a smaller percentage have the resources required to perform PTCA.[12]

The authors of the 1999 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines outlining management of patients with AMI expressed "serious concern" that PTCA should be done only by experienced physicians and teams in facilities where many such interventions are performed. They recognized that the PTCA trials generally were conducted by physicians with special interest and skills in PCI and that the results may not be applicable to all institutions. They stressed that thrombolysis should not be delayed for the purpose of enabling transfer of patients to a facility that can perform a PCI.[13]

Despite the advantage of mechanical perfusion, angioplasty is associated with restenosis in up to 50% of vessels, and there is a need for repeat target-vessel revascularization in 20% of patients. Intracoronary stents appear to reduce restenosis, and advances in antiplatelet therapy prevent subacute thrombosis. Three small trials in patients with AMI with vessels suitable for stenting have demonstrated a significant reduction with stenting in early (in-hospital or less than 1 month) recurrent ischemic events and in a late composite end point of death, recurrent AMI, or repeat target-vessel revascularization by six months.[8,9] Another recent trial, and the largest to date, was the Primary Angioplasty Myocardial Infarction (PAMI) stent trial. The rate of death, recurrent AMI, and target-vessel revascularization was reduced from 20% with PTCA to 13% with stent implantation in 900 patients.[13] Therefore, based on early data with primary stent implantation, that this technique may emerge as the PCI of choice in a large subset of patients. Optimization of this technique will require an appropriate—and as yet to be defined—combination of antiplatelet and antithrombin therapy.

Unstable Angina or NSTEMI. Various trials have compared the benefit of conservative (medical management) vs. early cardiac catheterization in order to determine the appropriate mode of revascularization (PCI or coronary artery bypass graft [CABG]). Data from the three primary trials have reflected mixed results.

The TIMI IIIB trial assessed the effects of thrombolysis with t-PA followed by randomization to conservative medical therapy vs. early invasive therapy in patients with UA or NSTEMI.[14] There were no significant differences in the rates of death or recurrent AMI at six weeks among the 1473 patients with ACS or in the subgroup of 476 patients with NSTEMI who were randomly assigned to an invasive (18 events) or to a conservative strategy (22 events).[14] The authors concluded that the two approaches were comparable. It must be noted that this trial was performed before the use of GP IIb/IIIa inhibitors, low molecular weight heparins (LMWHs), or stent implantation.

The Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH) trial randomized 920 patients with non-Q wave MI to either early conservative or early invasive management. The incidence of death or AMI during the median follow-up of 23 months was comparable between groups (26.9% in early medical therapy arm vs 29.9% in the early invasive arm; $P = 0.35$).[15] As with TIMI IIIB, the trial was mostly conducted before the widespread use of GP IIb/IIIa inhibitors, LMWHs, or stents. Because the early invasive group had more deaths and recurrent MIs at one year and the outcomes at the end of the follow-up period were comparable, the authors concluded that an initial medical-therapy approach was appropriate in patients with non-Q wave MI and that an early invasive approach may be dangerous.[15]

The FRISC II (Fragmin During Instability in Coronary Artery Disease II) trial, in addition to comparing chronic dalteparin administration vs. placebo as noted above, also compared an early invasive with a nxon-invasive treatment strategy in 2457 patients with UA or NSTEMI.[16] The primary end point was the composite of death or AMI at six months. The early invasive and early medical management groups had angiography performed in 96% and 10% of the patients within seven days and revascularization performed in 71% and 9% within 10 days, respectively. At six months, the composite end point was decreased from 12.1% in the non-invasive group to 9.4% in the early invasive group ($P = 0.031$). The greatest advantages were seen in patients who were at high risk, with electrocardiographic changes and/or elevated biochemical markers of myocardial damage.[16]

In summary, the three trials produced somewhat conflicting, inconsistent results, which might be explained by the variation in study design and the proportion of each group that actually underwent revascularization. In this regard, the FRISC II trial used more modern catheterization techniques, including stents and GP IIb/IIIa inhibitors. Even though the trials designated some patients to undergo early catheterization, patients from both early catheterization and early medical management underwent revascularization. Interestingly, in the TIMI IIIB and VANQWISH trials, the difference between the groups in those undergoing revascularization was only 6% and 11%, respectively. Conversely, 38% more patients in the early invasive group of the FRISC II trial underwent revascularization.

Combinations of Procedural Coronary Intervention, Thrombolysis, GP IIb/IIIa Inhibitors, and Low Molecular Weight Heparins

At the same time that the advantages of primary angioplasty and/or stenting were becoming more apparent, the benefit of aggressive antiplatelet and antithrombin therapy during these procedures also was emerging. Put simply, mechanical recanalization or surgical revascularization will only provide optimal efficacy and safety if combined with appropriate pharmacotherapy. Medical management may be best used to stabilize lesions until revascularization can be performed or to treat the most significant complications of angioplasty (acute and subacute vessel closure and restenosis). The full range of synergies between pharmacotherapeutic and procedural interventions is still being defined through many ongoing studies.

Primary PTCA vs. Thrombolysis in AMI With ST-Segment Elevation. The benefits of primary PTCA as compared with thrombolysis in AMI characterized by ST-segment elevation include the potential for improved patency and fewer hemorrhagic complications. However, primary PTCA is available only in a minority of U.S. hospitals. Numerous comparisons of PTCA with thrombolysis have been performed, and most suggest that PTCA is superior relative to reinfarction rates, stroke rates, 30-day mortality, and long-term benefits.[9]

Despite the apparent advantage of mechanical reperfusion, primary PTCA is associated with angiographic restenosis in up to 50% of vessels and the need for repeat target-vessel revascularization in 20% of patients.[8] It appears that stents reduce restenosis and new antiplatelet therapy prevents subacute thrombosis. Thus, recent trials have compared PTCA with stenting. Various, small trials have demonstrated that stenting reduced early (in-hospital or less than 1-month) recurrent ischemic events and the late composite end point of death, recurrent AMI, or repeat target-vessel revascularization by six months.[9]

The largest of these trials was the PAMI stent trial. The rate of death, recurrent AMI, and target-vessel revascularization was reduced from 20% with PTCA to 13% with stent implantation in 900 patients.[13] The benefit of stents was further evidenced by the Stenting vs. Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOP-AMI) trial in which 140 patients were randomized to receive thrombolysis or primary stenting plus abciximab. The stent plus abciximab group developed a significantly smaller infarct than did the thrombolysis group (14.3% vs 19.4% of the left ventricle; P = 0.02). The cumulative incidence of death, reinfarction, or stroke at six months was lower in the stent group than in the alteplase group (8.5% vs 23.2%; P = 0.02).[17]

Thrombolysis Combined With PTCA (Facilitated PCI). Clinical trials in the 1980s that evaluated the efficacy of early PTCA followed by full-dose thrombolysis (TAMI, ECSG, and TIMI IIb) found that PTCA after thrombolysis offered no advantage over t-PA alone and suggested that the combination may be harmful.[10,18,19] At that time, these approaches were viewed as competitive and mutually exclusive.

However, medical management of AMI has changed significantly since the 1980s, especially with the introduction of antiplatelet agents, new dosing schedules, and multi-modal options for thrombosis management. For example, thrombolytics are no longer given as extended infusions, aspirin is now regularly used, anticoagulation is better monitored within the catheterization lab, and new adjunctive agents are available. It also has been recognized that the success of PTCA directly correlates with vessel patency before the procedure begins: that is, patients with vessels with initial TIMI 2-3 flow have better outcomes than those with vessels with starting TIMI 0-1 flow.[11]

Accordingly, the strategy of combining the two modalities has been rekindled and is referred to as "facilitated" perfusion. The combination may be cost effective if an improved pharmacologic regimen decreases the need for early mechanical interventions. In addition, patients may be more stable in the catheterization lab after thrombolysis. In particular, patients arriving with more patent arteries due to earlier reperfusion are less likely to be in shock or to suffer dysrhythmias. Finally, the technical success of the procedure may be enhanced by the ability to better visualize distal vessels.[11]

To evaluate these possibilities, the recent PACT trial randomized 606 patients to reduced-dose thrombolysis (tissue plasminogen activator, 50 mg) or placebo followed by immediate angiography with PTCA if needed.[20] Patency was higher with fibrinolytic administration and ejection fraction was highest with either successful thrombolysis or early PTCA. Most importantly, unlike the earlier trials, this trial demonstrated no adverse risk associated with early intervention.[19]

Thrombolysis Combined With a GP IIb/IIIa Inhibitor. The concept of combining more effective antiplatelet therapy with thrombolysis is attractive because platelet activation and aggregation are increased during an ACS. Various studies investigated the combination of GP I,[21] IMPACT-AMI,[22] and PARADIGM.[22] The TAMI 8 trial involved 70 patients in a dose-escalation study using abciximab in combination with full-dose t-PA. The infarct-related coronary artery was patent in five of nine (56%) of the control patients and in 34 of

37 (92%) of the patients who received abciximab. Major bleeding was comparable between the groups.[21]

The IMPACT-AMI trial evaluated 132 patients who received full-dose, accelerated t-PA plus placebo or one of several different doses of eptifibatide. Sixty-six percent of the patients in the highest-dose eptifibatide group had 90-minute TIMI 3 flow vs. 39% of the placebo group (P = 0.006).[22] Severe bleeding complications also were equal among groups.[22] Patients in the PARADIGM trial all received full-dose t-PA or streptokinase and were randomized to receive lamifiban or placebo. The time to resolution of the ST-segment elevation, a clinical marker of reperfusion, was significantly decreased in those who received lamifiban. More major bleeding occurred in the lamifiban group.[23] These trials were not powered to enable determination of clinical outcomes. In addition, there was an overall trend toward increased bleeding in the GP IIb/IIIa groups. However, the combination of GP IIb/IIIa inhibitors with thrombolytics resulted in significantly more rapid and more complete reperfusion than with thrombolysis alone.

The Thrombolysis in Myocardial Infarction (TIMI) 14 trial was a phase 2 trial with 888 patients randomized within 12 hours to receive either t-PA alone, abciximab alone, half-dose t-PA with abciximab, or half-dose streptokinase with abciximab.[24] The group treated with reduced-dose streptokinase and abciximab showed only a modest improvement in TIMI 3 flow at 90 minutes compared with abciximab alone, and showed an increase in bleeding complications. However, in patients given t-PA and abciximab, TIMI 3 flow was achieved in 77% of patients at 90 minutes compared with 62% with t-PA alone (P = 0.02). Rates of major hemorrhage were 6% in patients receiving alteplase alone, 3% with abciximab alone, 10% with streptokinase plus abciximab, and 7% with 50 mg of alteplase plus abciximab and low-dose heparin, and 1% with 50 mg of alteplase plus abciximab with very-low-dose heparin. Another phase of TIMI 14 used either full-dose, double-bolus of reteplase or half-dose, double-bolus of reteplase plus abciximab. While not reaching statistical significance, a trend toward higher TIMI 3 flow was observed in the reteplase plus abciximab group.[24]

The Strategies to Promote Early Reperfusion in the Emergency Department (SPEED) trial functioned as a pilot trial for the GUSTO 4 AMI trial. It enrolled 530 patients with AMI to receive either abciximab alone or abciximab and single or double boluses of r-PA. The primary end point was TIMI 3 flow at the 60-90 minute catheterization. The first phase of the study determined the appropriate dose of r-PA to be 5 units followed by another 5 units plus abciximab. In the second phase of the trial, 54% of those who received half-dose reteplase plus abciximab attained TIMI 3 flow vs. 47% of those who received full-dose reteplase alone. Flow rates were improved by using a 60 U/kg heparin bolus vs. a lower dose. Major bleeding rates were comparable between groups.[25]

Results from the SPEED and TIMI 14 trials, along with the three smaller studies noted above, suggest improved TIMI 3 perfusion when abciximab is combined with a fibrinolytic agent in patients with AMI. While none of the studies was powered to examine major bleeding complications, more minor bleeding and venous access site bleeding occurred with the combination therapies. Full-dose streptokinase with abciximab produced an unacceptably high rate of major hemorrhage.[24] Clinical outcomes will be compared in the GUSTO 4 AMI trial, a phase III study that will randomize more than 16,000 patients to receive full-dose reteplase or reduced-dose reteplase and abciximab.

Thrombolysis Plus a GP IIb/IIIa Inhibitor Followed by PCI. The little data that exist on this combination have been pulled from the PCI subsets of the TIMI 14 and SPEED trials. In TIMI 14, PCI was discouraged and was done only in 133 patients (11%) after the 90-minute angiograms. In patients who received PCI after lysis, resolution of ST-segment elevation increased from 8% in patients treated with either alteplase or reteplase to 49% in patients treated with a combination of a fibrinolytic and abciximab (P = 0.002). This difference was most prevalent in patients who had attained TIMI 3 flow before PCI.[24] In the SPEED trial, early PCI was encouraged and was done in 323 patients (61%) at a median of 62 minutes after initiation of reperfusion therapy. Patients receiving early PCI had fewer ischemic events and bleeding complications (15%) than patients not undergoing early PCI (30%, P = 0.001). Patients receiving abciximab with reduced-dose reteplase (5 U double bolus) had the highest TIMI 3 flow on initial angiography compared with other treatment regimens, and achieved 86% TIMI 3 flow at 90 minutes with a trend toward improved clinical outcomes.[25]

PTCA Combined with a GP IIb/IIIa Inhibitor in AMI. While numerous trials have assessed the efficacy of combining a GP IIb/IIIa inhibitor with PTCA in the setting of NSTEMI or UA, little information exists on this combination in patients with AMI. The RAPPORT trial randomized 483 patients with AMI to abciximab or placebo before PTCA.[26] The primary end point was the composite of death, reinfarction, or any (urgent or elective) target vessel revascularization at six months. There was no significant difference between groups relative to this composite end point. However, abciximab did sig-

nificantly reduce the composite of death, reinfarction, or need for urgent revascularization at six months (from 17.8% to 11.6%; P = 0.05).[26] A similar 52% reduction in a combined end point was observed in the Abciximab before Direct Angioplasty and Stenting in Acute Myocardial Infarction Regarding Acute and Long-Term Follow-Up (ADMIRAL) trial, which also allowed stent implantation.[27]

Low Molecular Weight Heparins Combined with Thrombolysis or PCI plus a GP IIb/IIIa Inhibitor in ACS. Heparin has been the standard antithrombin agent in the management of AMI, particularly in the peri-PCI or thrombolytic period. However, much of the data in support of it are non-randomized and retrospective.[28] The role of LMWHs in this setting now is being explored. There has been concern about performing PCI in patients treated with LMWH for UA or NSTEMI. The concerns are now being allayed as new study data emerge. Preliminary data from multiple trials evaluating the use of enoxaparin in the setting of thrombolysis or PCI were released at the 2000 Congress of the European Society of Cardiology. These trials primarily focused on the safety of enoxaparin in these clinical settings. Some of the trials also assessed the safety of enoxaparin in combination with different GP IIb/IIIa inhibitors. While each of the trials involved only a few hundred patients, they consistently suggested that enoxaparin was safe in patients undergoing PCI as well as in those undergoing thrombolysis or treated with a GP IIb/IIIa inhibitor. These results are undergoing additional confirmation in larger trials.

Two of the recent trials evaluated the efficacy and safety of enoxaparin in patients with ST-segment elevation MI who were managed with thrombolysis. The Hypertension Audit of Risk Factor Therapy (HART) II trial compared enoxaparin with heparin as adjunctive antithrombin therapy for 400 patients receiving front-loaded t-PA for ST-segment elevation AMI.[29] In this study, enoxaparin was administered intravenously (30 mg), followed by the standard subcutaneous regimen. The primary end points were infarct-related patency at 90 minutes after initiation of thrombolytic therapy, reocclusion at 5-7 days, and safety. The TIMI grade 2 or 3 flow was comparable between groups: 80.1% with enoxaparin and 75.1% with heparin. Reocclusion within one week occurred in 9.1% of the patients who received heparin and in only 3.1% of those who received enoxaparin (P = 0.1). Bleeding complications were comparable between groups.[29] Menown and associates assessed the efficacy and safety of enoxaparin vs. heparin in 300 patients with AMI who received thrombolytic therapy. The enoxaparin group received a 40 mg intravenous bolus followed by subcutaneous injections, while the heparin group received a 5000 unit bolus plus 30,000 units per 24 hours with adjustment to maintain an appropriate activated partial thromboplastin. The triple end point of death, AMI, or readmission with UA at three months occurred in 36% of those who received heparin and in 26% of those who received enoxaparin (P = 0.04). Major bleeding was comparable between groups.[30]

In addition, five recent trials assessed the safety of enoxaparin in the setting of PCI not associated with ST-segment elevation MI. The National Investigators Collaborating on Enoxaparin (NICE)-3 trial evaluated the incidence of bleeding while performing catheterization in 661 patients with ACS, all of whom received enoxaparin plus a GP IIb/IIIa inhibitor (either abciximab, eptifibatide, or tirofiban).[31] At the time of catheterization, enoxaparin (0.3 mg/kg intravenously) was administered if it had been more than eight hours since the last subcutaneous dose. The combination of enoxaparin with different GP IIb/IIIa inhibitors resulted in similar clinical outcomes and bleeding frequency in comparison to those seen in the large GP IIb/IIIa inhibitor trials.[31]

The National Investigators Collaborating on Enoxaparin (NICE)-4 trial combined enoxaparin with abciximab during PCI.[28] Enoxaparin was given as a 0.75 mg/kg intravenous bolus while abciximab was administered in its usual fashion. Data from the first 310 patients who received enoxaparin and abciximab revealed that the incidence of major non-CABG bleeding and transfusion in this group was 0.6%, which favorably compared with an incidence of 2.7% in patients receiving abciximab and low-dose heparin in the EPILOG trial.[28] Another group assessed the safety and outcomes in patients with UA or NSTEMI.[32] Of the 451 patients, a non-randomized 293 underwent catheterization within eight hours of the morning enoxaparin injection, which was followed by immediate PCI in 132 patients (28%). The procedures were done without additional heparin or enoxaparin. Major bleeding occurred in 0.8% of those who received catheterization, comparable to the 1.2% in those who were not studied.[32]

Another group performed a randomized comparison of peri-procedural heparin vs. enoxaparin in 200 patients receiving elective PCI after three days of aspirin and tirofiban. Clinical outcomes and major bleeding were comparable between the groups at 30 days.[33] Although this study is not in the PCI setting, the pharmacokinetics, pharmacodynamics, and safety of the combination of tirofiban with enoxaparin vs. heparin in non-Q wave myocardial infarction was addressed in a 55-patient series. As with most studies, more minor bleeding occurred with the enoxaparin combination, while major

bleeding was comparable. The combination of tirofiban and enoxaparin resulted in a more consistent inhibition of platelet aggregation and lower adjusted bleeding time than did the combination with heparin.[34]

The FRISC II trial assessed the role of three months of dalteparin therapy after the use of PCI in patients with UA or NSTEMI or after the use of thrombolysis in AMI. While the initial randomization compared three months of dalteparin vs. placebo, a second randomization, in a 2-by-2 design, compared the use of early PCI with more conservative (less aggressive) use. At six months, the composite of death or AMI was decreased by early PCI from 12.1% to 9.4% in those with less aggressive use (P = 0.031). Dalteparin decreased adverse coronary events during the three-month administration primarily in patients who received conservative use of PCI. It also was observed that there was no benefit from the three-month dalteparin administration in patients who were in the non-invasive segment of the study.[16]

Congestive Heart Failure in ACS: Considerations for Reducing the Burden of Venous Thrombosis

There is increasing awareness that seriously ill, hospitalized medical patients are at increased risk for sustaining deep venous thromboembolism (DVT). The potential complications, cost, and morbidity associated with DVT in this patient population can be significant, and may include pulmonary embolism, prolonged hospitalization, and in some cases, sudden death. In this regard, it should be stressed that immobilized patients with such conditions as congestive heart failure (CHF), in particular—as well as patients with chronic respiratory failure, serious pulmonary and systemic infections, and underlying malignancy—are at greater risk for the morbid sequelae and complications associated with DVT. Accordingly, the threshold for empirical prevention of DVT in CHF patients must be balanced against the relatively low risk of serious complications associated with antithrombin-mediated prophylaxis.

From a clinical perspective, perhaps the most important issue is for hospital-based clinicians to recognize those patient subgroups who are at significant risk for acute DVT. Although numerous trials have identified specific medical disorders that, when they afflict acutely hospitalized, immoblized patients, increase the risk of acquiring acute DVT, there is no single patient profile that mandates medical prophylaxis. Rather, the clinician must weigh all the relevant risk factors—among them, respiratory status, cardiovascular function, presence of infection, history of previous venous thromboembolic disease (VTED), patient age, underlying malignancy, and others—based on clinical judgment determine whether the risks of prophylaxis for VTED outweigh the risks. When patients are selected in a systematic way that accounts for all the risks and benefits, DVT prophylaxis will be outcome-effective.

Fortunately, the safety and effectiveness of medical prophylaxis has been carefully analyzed in recent clinical trials. In this regard, a recent landmark study (MEDENOX) has confirmed the effectiveness of at least one LMWH (enoxaparin, Lovenox®) in preventing VTED in seriously ill medical patients, including those with stage III-IV CHF. Risk-stratification strategies that identify those subgroups most suitable for prophylaxis using enoxaparin will expand awareness of the risks of VTED in this patient population, and will make medical prophylaxis against DVT in eligible cardiac patients a mandated clinical strategy for a broad range of hospitalized patients with decompensated heart failure. The ultimate goal is to make patients with coronary heart disease and/or CHF "thrombosis-free," as this relates to both the coronary arterial vascular bed as well as the systemic venous system.

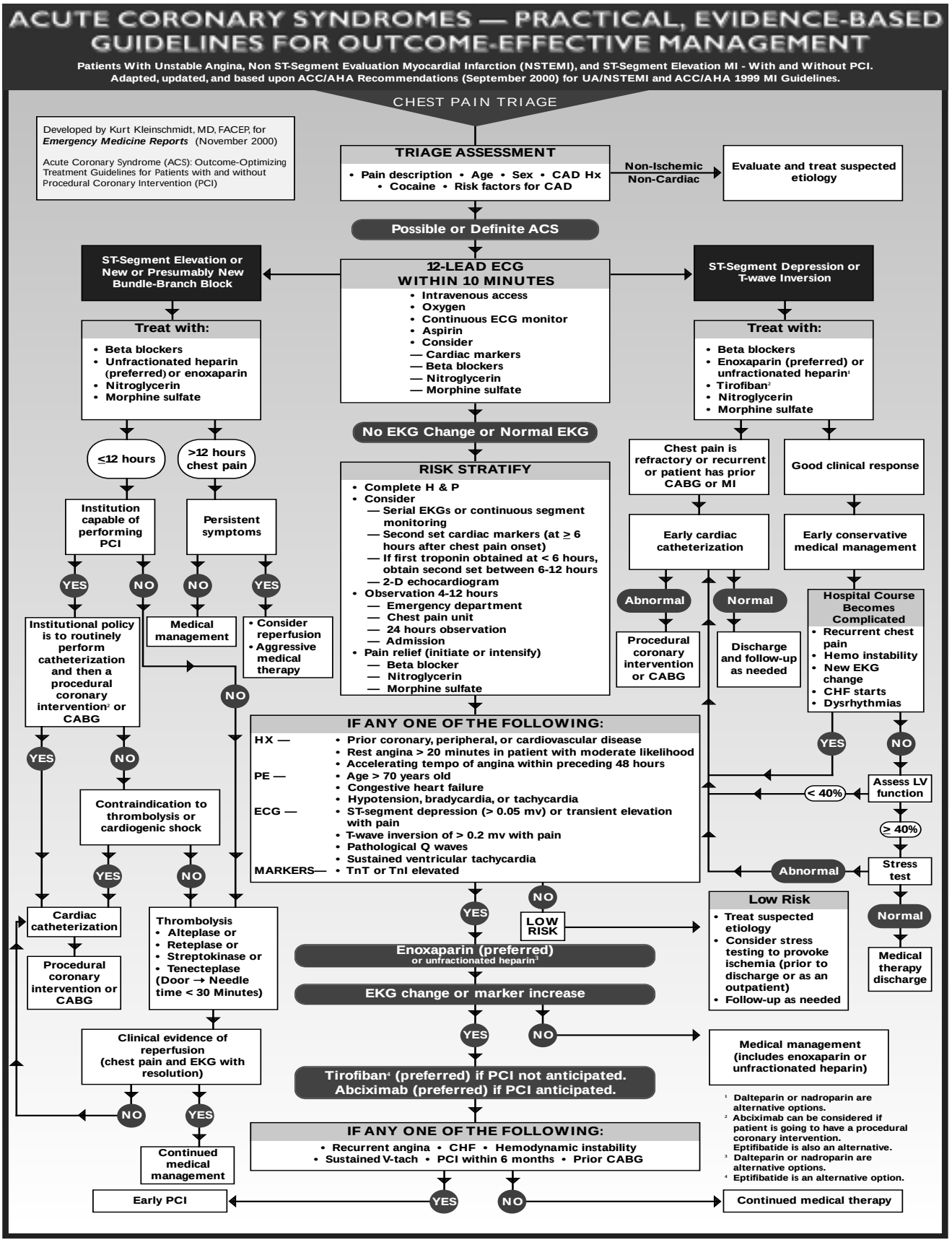
Medical Prophylaxis in Patients with Heart Disease. Venous thromboembolism (VTE) remains a major cause of mortality and morbidity in hospitalized patients with cardiac disease, despite the availability of effective prophylactic agents.[35] Interestingly, studies demonstrate that the majority of patients who suffer a fatal pulmonary embolism (PE) have not undergone recent surgery,[36] but PE is rarely suspected as a cause of death in non-surgical patients[37] and prophylaxis is infrequently used,[38] despite consensus statement recommendations.[39] The burden of venous thromboembolic disease in populations with heart disease is significant[39] with certain medical conditions—among them, severe congestive heart failure being associated with elevated risk for thromboembolic disease. A review of recent studies evaluating risk factors in individual patients clarifies the need for and value of thromboprophylaxis in clearly defined groups of medical patients.

It should be noted that much higher rates of VTE have been observed in specific groups that, accordingly, should be risk-stratified to receive thromboembolic prophylaxis when indicated.[40-46] In this regard, a recent study reported that up to one in 20 hospitalized medical patients with multiple problems and severe immobility may suffer a fatal PE.[47] However, it should be noted that current management practices in ACS emphasizing extensive use of thrombolytics, UFH, GIIB/IIIA inhibitors, LMWHs such as enoxaparin, and antiplatelet agents, may contribute to a reduction in the incidence of VTE, including PE.

continued on page 10

Figure.

Guidelines for Outcome-Effective Treatment of Acute Coronary Syndromes



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In light of the substantial burden of VTE in medical populations, current consensus statements on the prevention of VTE recommend assessment of all hospitalized patients, both medical and surgical, for thromboembolic risk, and use of appropriate prophylaxis. Specific prophylaxis recommendations have been made for patients with stroke and MI by the American College of Chest Physicians (ACCP)[48] and the International Consensus Conference.[41] Prophylaxis is also recommended for other groups of medical patients with clinical risk factors for VTE. However, recommendations are for poorly defined patient groups and vary among consensus documents.

Patient Risk Stratification and VTED Prophylaxis. From a clinical, need-to-prophylax perspective, a broad range of medical conditions are associated with an increased risk of VTE. Some of these have been stratified according to the level of risk they confer,[49] although classifications may vary depending on concomitant risk factors. In particular, stroke, critical care patients, and MI are strongly linked to thromboembolic events.

Although the current clinical condition is an important contributor to overall thromboembolic risk, underlying long-term risk factors appear to be at least as important in determining thromboembolic risk in medical patients.Risk factors are similar to those cited for surgical patients, but unlike surgical patients, in medical settings underlying factors may be even more important than the current medical condition in determining overall risk.[49] The THRIFT II report recommends clinical assessment and a series of blood tests to detect congenital and acquired molecular risk factors.[50] The International Consensus Statement suggests a similar series of blood tests for patients with a personal or family history of VTE.[41]

A number of clinical trials have demonstrated a reduction in the frequency of asymptomatic DVT in several medical populations through the use of pharmacological prophylaxis. Some of these studies[48] illustrate a substantial reduction in the rate of DVT in medical patients as detected by the fibrinogen uptake test, suggesting that prophylaxis with either UFH or LMWH may be of value in these groups.

Three large studies have assessed the effect of thromboprophylaxis on mortality in general medical patients[51-53]—all of which suggest the importance of risk-stratifying patients at risk for VTED. The venous thrombosis risk in non-surgical patients was evaluated in an epidemiological study (PRIME) that also assessed the efficacy and safety profile of enoxaparin. This was a multicentre, randomized, double-blinded comparison of enoxaparin (40 mg) vs. heparin (5000 U TID) in DVT prophylaxis. The 959 patients were expected to be immobilized for more than half of the daytime for the study period of 7 days and have at least one additional risk factor (age > 60, malignancy, obesity, previous VTE event, CHF, paresis, hemiplegia, or severe infection). New VTE disease occurred in 0.2% of the enoxaparin group and in 1.4% of the heparin groups (P = NS). Bleeding complications were comparable. The investigators concluded that enoxaparin is at least as efficacious as standard heparin in the prophylaxis of venous thrombosis.

MEDENOX Trial. In response to the need for evidence to clarify the role of prophylaxis in specific non-surgical patient subgroups, the MEDENOX trial was conducted using the LMWH enoxaparin in clearly identified risk groups. In contrast to previous investigations, the MEDENOX trial included a clearly defined patient population—patients immobilized with severe chest (cardiopulmonary) disease—and was designed to answer questions about the need for prophylaxis in this group of medical patients and to determine the optimal dose of LMWH.

The design of the MEDENOX trial included a placebo arm, allowing determination of the thromboembolic risk and the need for prophylaxis in the clearly defined patient group. According to the THRIFT II classification, the population would be expected to be at moderate risk of VTE, since low-risk patients and those with high-risk conditions (e.g., stroke or MI) were excluded.[50] However, the actual risk level for the defined population has not been confirmed in any previous trial. The use of systematic venography to detect DVT provided a reliable and accurate means of assessing prophylactic efficacy.

Inclusionary criteria for MEDENOX were intended to clearly define risk groups within the general medical population. Patients were considered eligible if they were 40 years of age or older, had been immobilized for less than 3 days, and were hospitalized due to a specific, acute medical condition—in particular, heart failure, respiratory failure, an infectious disease, or a rheumatic disorder. In this regard, it should be stressed that patients with congestive heart failure and/or pulmonary infections have been highlighted in the most recent ACCP consensus statement as a specific target group requiring thromboprophylaxis.[48]

Patients randomized in the MEDENOX trial had a projected hospital stay of at least 6 days. Patients with respiratory failure were considered eligible provided they did not require respiratory support. The primary exclusion criteria were: pregnancy or possible pregnan-

cy, breastfeeding, stroke, major surgery in the previous 3 months; contraindications to iodinated contrast media, thrombophilia, serum creatinine > 150 mmol/L, intubation, HIV infection, uncontrolled hypertension, conditions conferring risk of hemorrhage, abnormal clotting tests, or hypersensitivity to heparin.

Patients in the MEDENOX trial were randomized to receive enoxaparin, 20 mg or 40 mg subcutaneously, or placebo once daily, beginning within 24 hours of randomization. They were treated for 10 ± 4 days in the hospital and followed up in person or by telephone contact on day 90 (days 83-110). During follow-up, patients were instructed to report any symptoms or signs of VTE or any other clinical event. The primary and secondary efficacy end points for MEDENOX were chosen to allow an objective assessment of the risk of VTE in the study population and extent of any benefit of prophylaxis. The primary end point was any venous thromboembolic event between day 1 and day 14. All patients underwent systematic bilateral venography at day 10 ± 4, or earlier if clinical signs of DVT were observed. Venous ultrasonography was performed if venography was not possible. Suspected PE was confirmed by high-probability lung scan, pulmonary angiography, helical computerized tomography, or at autopsy.

The primary safety end points were hemorrhagic events, death, thrombocytopenia, or other adverse event or laboratory abnormalities. As the principal adverse event associated with anticoagulant therapy, hemorrhage was a key safety outcome. Major and minor hemorrhagic events occurring during treatment were recorded. Major hemorrhage was defined as overt hemorrhage associated with a need for transfusion of two or more units of packed red blood cells or whole blood, or a decrease in hemoglobin concentration of 20 g/L or more compared with baseline, or retroperitoneal, intracranial, or fatal bleeding. Overt hemorrhage that did not meet the criteria for major hemorrhage was defined as minor. Injection sites were checked daily for haematomas larger than 5 cm in diameter. Full blood counts were performed prior to treatment, then at 3-day intervals.

A total of 1102 patients were included in the MEDENOX trial, in 60 centers and nine countries. Overall, the mean age was 73.4 ± 10.5 years, the gender distribution was 50:50, and the mean body mass index was 25.0 ± 6.2 kg/m^2. The mean patient ages, gender distribution, and body mass index were similar in all three treatment groups; there were slightly more males than females in the placebo and enoxaparin 20-mg groups, and more females than males in the enoxaparin 40-mg group, but this difference was not significant. The reasons for hospitalization of randomized patients varied. The majority of patients were hospitalized for acute cardiac failure, respiratory failure, or infectious disease. The frequency of different reasons for hospitalization was similar across all treatment groups. The number of patients in each hospitalization group suggests that a high proportion of acutely ill medical patients have two or more concomitant conditions, each contributing to the overall thromboembolic risk.

For the study population as a whole, the most prevalent risk factor in addition to the underlying illness was advanced age (50.4%), followed by varicose veins (25.4%) and obesity (20.2%). A similar number and proportion of patients in the three treatment groups exhibited each of the separate risk factors. Just more than one-third of patients in each group had chronic cardiac failure, and about one-half suffered from chronic respiratory insufficiency.

Many of the patients in all three treatment groups had multiple risk factors. Overall, 96.9% of the study population (1068 patients) had at least one additional risk factor for VTE, in addition to their qualifying medical condition (heart failure or acute respiratory failure). Only 31 patients (2.8%) had no additional risk factors, 335 (30.2%) had one risk factor, and 733 (66.7%) had two or more risk factors. This pattern was similar in all treatment groups. The mean number of risk factors per patient was 2.1 ± 1.1, 2.0 ± 1.1 and 2.1 ± 1.1 in the placebo group, enoxaparin 20-mg group, and enoxaparin 40-mg group, respectively. Therefore, multiple risk factors appear to affect a high proportion of patients with acute cardiopulmonary or infectious disease. Risk factors for VTE have a cumulative effect on total risk.

The mean duration of treatment in MEDENOX was approximately 7 days with a standard deviation of 3 days. Duration of treatment did not differ significantly among the groups. Overall, 16% of patients had less than 6 days treatment (i.e., less than the planned minimum period) and 26% had more than 8 days. No patients were treated for longer than 14 days as per protocol specifications. The use of the continuation of any anticoagulant therapy after the end of the treatment period was left to the individual investigator's judgment. Of the 1102 patients included in the study, 1073 received at least one dose of the study drug and were included in the safety analysis.

Of the 1102 patients enrolled, a total of 866 patients were assessed for primary efficacy at day 14. The incidence of total, proximal, and distal DVT was significantly reduced with enoxaparin 40 mg compared with placebo. By day 14, the incidence of VTE was 14.9% in the placebo group and 5.5% in the enoxaparin 40-mg group, representing a significant 63% relative risk reduction

(97% CI: 37-78%; P = 0.0002). Outcomes in the enoxaparin 20-mg group were not significantly different from placebo. A total of four symptomatic non-fatal PEs occurred—three in the placebo group and one in the enoxaparin 20-mg group. Finally, there was a trend toward mortality reduction with enoxaparin. By day 110, death had occurred in 50 (13.9%), 51 (14.7%), and 41 (11.4%) patients in the placebo group, enoxaparin 20-mg group, and enoxaparin 40-mg group, respectively. The 2.5% reduction in overall mortality in the enoxaparin 40-mg group was clinically meaningful but did not reach statistical significance.

By day 110,798 patients had been assessed for secondary efficacy. The significant reduction in total VTE and proximal and distal DVT observed in the enoxaparin 40-mg group was maintained at the 3-month follow-up. Relative risk reduction at 3-month follow-up—all VTE 59% and proximal DVT 66%. Four additional fatal PEs occurred during follow-up, one in the placebo group (3 weeks after the treatment period ended) and one and two in the enoxaparin 20-mg and 40-mg groups, respectively (2 months after the treatment period ended).

From a clinical safety perspective, there were no significant differences among the groups in the frequency of major or minor hemorrhage, thrombocytopenia, or any other adverse events. Major hemorrhage occurred in 11 patients during the treatment period; the fatal hemorrhage in the enoxaparin 40-mg group was considered unrelated to the study treatment by the investigators. Two additional fatal hemorrhages occurred during follow-up—one in the enoxaparin 20-mg group and one in the enoxaparin 40-mg group, 8 and 3 weeks after discontinuation of the study medication, respectively.

A total of 31 cases of thrombocytopenia occurred during the treatment period (13 cases in the placebo group, 10 in the enoxaparin 20-mg group and 8 in the enoxaparin 40-mg group). Fourteen of them were judged to be probably related to study medication, eight in the placebo group, four in the enoxaparin 20-mg group, and two in the enoxaparin 40-mg group. Remarkably, the three patients who experienced severe thrombocytopenia were all in the placebo group.

Evidence for VTED Prophylaxis in Cardiac Patients with CHF. The primary conclusions of the MEDENOX trial can be applied directly to clinical practice. First, acutely ill medical patients with congestive heart failure—especially if they are elderly or having concomitant cardiorespiratory diease—are at significant risk of VTE. Second, enoxaparin, given once daily at a dose of 40 mg for 6-14 days, reduces the risk of VTE in this population by about 63%; and third, the reduction in thromboembolic risk is achieved without increasing the frequency of hemorrhage, thrombocytopenia, or any other adverse event compared with placebo. This study strongly suggests that immobilized patients with Class III-IV CHF admitted to the hospital should, if there are no contraindications to the use of anticoagulants, be considered candidates for prophylaxis with enoxaparin, 40 mg SC qd upon admission to the hospital to prevent VTED.

Finally, it should be stressed that patients with ACS who are already being treated with other anticoagulant agents, fibrinolytics, anti-platelet agents, LMWHs, and/or are undergoing PCI should be evaluated on a patient-by-patient basis to determine their suitability for VTED prophylaxis. When these venous thrombosis prophylaxis strategies are applied to patients with ACS with CHF and/or other underlying risk factors for VTED, clinicians will be taking an important step toward making their hospital environments "thrombosis-free," and in the process, reducing overall costs, morbidity, and mortality associated with this at-risk population.

Basic Management Principles in ACS

The ACC/AHA have released clinical practice guidelines for the management of AMI, for UA, and for NSTEMI.[12,54] They have been incorporated into the overall management of ACS. (*See Figure*.) The following is an abridged summary of some of the recommendations from both of these clinical practice guidelines. The customary ACC/AHA classifications are used. Class I refers to conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II refers to conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa, the weight of evidence/opinion is in favor of usefulness/efficacy, while Class IIb is less well established by evidence/opinion.

Supplemental oxygen, intravenous access, and continuous electrocardiographic monitoring should be established (Class I).

Oxygen. Oxygen is recommended for pulmonary congestion, arterial oxygen desaturation (SaO_2 < 90%), cyanosis, or respiratory distress (Class I). It may be administered to patients with uncomplicated AMI during the first 2-3 hours (Class IIa).

Aspirin. All patients should receive 160-325 mg of aspirin (Class I). However, those with an aspirin allergy should receive dipyridamole, ticlopidine, or clopidogrel (Class IIb recommendation).

Nitroglycerin. Sublingual tablet or spray nitroglycerin is appropriate initial therapy. In the setting of AMI, intravenous nitroglycerin is recommended for the first 24-48

hours in patients with AMI and CHF, large anterior infarction, persistent ischemia, or hypertension (Class I). It is only a Class IIb recommendation for patients with uncomplicated AMI. It should be used with extreme caution in patients with suspected right ventricular infarction. Nitroglycerin should be avoided in patients with hypotension, bradycardia, and tachycardia (Class I), and in those who have had sildenafil (Viagra) within 24 hours (Class III).

Morphine Sulfate. Morphine sulfate is recommended intravenously when symptoms are not immediately relieved with nitroglycerin or when acute pulmonary congestion and/or severe agitation is present (Class I).

Thrombolysis. Thrombolysis is recommended if there is ST-segment elevation (> 0.1 mV, ≥ 2 contiguous leads), the time to therapy is 12 hours or less, and the age is younger than 75 years; or if there is a bundle-branch block and a history suggesting an AMI (Class I). It also can be used in those age 75 years old or older (Class IIa) or if the time of chest pain is between 12 and 24 hours (Class IIb). It is not recommended if the time to therapy is greater than 24 hours, the pain has resolved, or if there is only ST-segment depression. The guidelines stated that there was a serious concern that a "routine" policy for PTCA would result in unacceptable delays for many patients or in the procedure being done by less experienced personnel.

Primary Percutaneous Transluminal Coronary Angioplasty. Primary PTCA is recommended as an alternative to thrombolytic therapy if it can be done within 12 hours of onset of symptoms, performed in a timely fashion, done by persons skilled in the procedure, and supported by experienced personnel in an appropriate laboratory environment. It also is recommended if ischemic symptoms persist (Class I). It may be used as a reperfusion strategy in reperfusion candidates who have a contradiction to thrombolytic therapy (Class IIa). The guidelines noted that it was reasonable to further explore the combination of thrombolysis with PTCA.

It is widely accepted that the early restoration of perfusion in the AMI patient limits myocardial damage, preserves left ventricular function, and reduces mortality. Such restoration may be accomplished by either administration of a thrombolytic agent or performance of PTCA; in the rare case, emergent coronary artery bypass grafting is a third revascularization method.

Optimizing Outcomes. The rapid application of reperfusion therapy is mandatory in the patient with ST-elevation AMI. Many factors must be considered by both emergency and cardiovascular physicians regarding the early reperfusion treatment decisions when managing the AMI patient. While primary angioplasty may offer improved outcome over thrombolysis, PTCA must be applied early without prolonged delay. Should the catheterization laboratory activation delay either be anticipated or occur, the treating physician must proceed with thrombolysis if the patient is an appropriate candidate. Prior agreement between the ED and the cardiovascular physicians at institutions with angioplasty capability must be obtained so that consideration of PTCS will not introduce further delays in thrombolytic drug administration; such cooperation has been shown to limit additional delays in the administration of thrombolytic agents in patients who are considered for PTCA in AMI.

If applied without time delay in experienced hands, the data suggest that PTCA can produce improved outcomes in AMI. However, it must be stressed that although PTCA is felt to be superior in the treatment of AMI, this procedure must be initiated within 90 minutes of patient arrival at the hospital ED.[12] If the time required to mobilize staff and arrange for PTCA is prolonged (i.e., greater than 90 minutes to balloon catheter inflation across the culprit coronary lesion), then thrombolysis is the preferred mode of therapy.[55] Delays beyond this time period are unacceptable if the patient originally was considered to be a thrombolytic candidate.

Several issues must be considered by the emergency physician when evaluating the relative desirability of various therapeutic options. The literature base for answering questions related to therapeutic options is somewhat heterogeneous in construction (e.g., differing therapies, study sites, outcome measures, etc.). Therefore, making absolute, all-encompassing recommendations is impossible. Also, the question of technical expertise in performing PCI must be considered. In the GUSTO-IIb trial,[56] the vast majority of physicians performed at least 75 procedures per year; these results may not be generalizable to smaller-volume centers with less-experienced operators (i.e., less than 50 cases per year). Finally, another systems issue regarding time-to-arrival in the catheterization laboratory must be considered.

PTCA Availability and Patient Transfer. In certain centers, PTCA may not be available, necessitating rapid transfer to another facility; alternatively, in centers with PTCA capability, the catheterization laboratory may not be in operation at the time of the patient's arrival; this is likely to be a consideration at night and on weekends.

Indications for transfer of a patient with AMI to a regional tertiary care facility with angioplasty and cardiovascular surgery capabilities include patients with thrombolytic therapy contraindications who may benefit from PTCA or CABG, persistent hemodynamic instability, persistent ventricular dysrhythmias, or postinfarction

or postreperfusion ischemia. Hospital transfer for primary PTCA is required in patients with thrombolytic agent contraindications. The urgent transfer of a thrombolytic-eligible AMI patient for primary PTCA to another institution is not recommended until thrombolytic therapy is initiated; the delay in restoring perfusion in such a patient is not acceptable in most instances.

Beta-Adrenergic Blocking Agents. Beta blockers are recommended in patients without a contraindication if they are treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary PTCA. Beta blockers also are recommended for patients with continuing or recurrent ischemic pain or those with tachydysrhythmias (Class I). They can be used in patients with moderate left ventricular failure or with other contraindications if they can be monitored closely (Class IIb). Agents without intrinsic sympathomimetic activity are preferable.The recommendation for their use in high-risk patients with evolving pain is based on the demonstrated benefit in AMI patients.

Angiotensin-Converting Enzyme Inhibitors (ACEIs). In the setting of AMI, ACEIs are recommended in patients within the fist 24 hours of a suspected AMI with ST-segment elevation in two or more anterior precordial leads or with clinical heart failure in the absence of hypotension. They also are recommended for those with AMI and left ventricular ejection fraction of less than 40% or patients with clinical heart failure on the basis of systolic pump dysfunction (Class I). In the setting of UA/NSTEMI, they are recommended if hypertension persists despite treatment with nitroglycerin and a beta-blocker and in patients with left ventricular systolic dysfunction or congestive heart failure and in ACS patients with diabetes (Class I).

Calcium Channel Blockers. Verapamil or diltiazem may be given to patients in whom beta-adrenoceptor blockers are ineffective or contraindicated (i.e., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation after AMI in the absence of congestive heart failure, left ventricular dysfunction, or atrio-ventricular block (Class IIa). Nifedipine generally is contraindicated because of its negative inotropic effect and the reflex sympathetic activation associated with its use. All calcium blockers are all contraindicated in the setting of MI and associated left ventricular dysfunction or CHF. They have not been shown to reduce mortality after AMI.

Intra-Aortic Balloon Pump. Counter pulsation is recommended for severe ischemia that is continuing or recurs frequently despite intensive medical therapy or for hemodynamic instability in patients before or after coronary angiography (Class IIa).

Early Invasive Strategy in Patients with UA/NSTEMI. An early invasive strategy is recommended in UA/NSTEMI patients who have any one of the following high-risk indicators (Class I):

- Recurrent angina/ischemia at rest or with low-level activities despite intensive medical management;
- Recurrent angina/ischemia with symptoms or CHF or new or worsening mitral regurgitation;
- Depressed left ventricular systolic function (ejection fraction < 40%);
- Hemodynamic instability;
- PCI within six months; or
- Prior CABG.

Management Summary and Critical Pathways: Acute Coronary Syndromes

Overview of Strategies. Optimizing future management of ACS will consist of identifying the highest benefit, lowest risk combination of pharmacotherapeutic agents, in conjunction with mechanical revascularization techniques. Outcome-enhancing choices among the myriad pharmacotherapeutic options for ACS are evolving at an extremely rapid pace. Unfortunately, even in the face of new investigational data, it is frequently difficult to compare clinical trials because trigger points for PCI and entry criteria for specific treatment modalities differ slightly among the trials, and head-to-head comparisons may be lacking.

Moreover, because so many combinations of LMWH, GP IIBA/IIIA inhibitors, fibrinolytic agents—with and without PCI—are possible for any ACS syndrome, it is unlikely that a "definitive" combination of specific agents will emerge that conclusively can be shown to provide the best results. In addition, each subgroup of patients with ACS (i.e., those with NSTEMI, UA, or T-segment elevation AMI) may eventually have a unique cocktail of antithrombin, antiplatelet, and antifibrin agents best suited for a specific patient population.

With these limitations in mind, a practical, heat-of-battle critical pathway of care for patients with acute coronary syndromes is presented in the ACS Treatment Pathway. (*See Figure*.) Although this pathway is based primarily upon the ACC/AHA guidelines, some modifications, updates, and refinements have been made, particularly as they relate to the role of the LMWH, enoxaparin vs. UFH and the relative indications of specific GP IIb/IIIa inhibitors. As would be expected, the standard, time-honored, clinically proven agents used for management of ACS (e.g., among them, aspirin, beta blockers, nitroglycerin, and analgesics) have been incorporated into the pathway.

Certain components of ACS management are, put simply, mandatory. For example, there is little debate about the importance of giving aspirin as soon as a patient is felt to have a possible or definite ACS. This occurs at the very beginning of our critical pathway. It also is important that patients with a possible or definite ACS have an EKG immediately upon arrival. Major treatment decisions and the critical pathways to be followed are based upon the results of the EKG. Risk stratification using observation, cardiac monitoring, serial EKGs, cardiac markers, and clinical response must be done for patients who don't have initial EKG changes. This evaluation can be performed in various settings, including the emergency department.

It is recognized that many treatment decisions will be made by local consultants, particularly relative to the role of PCI. However, emergency medicine providers must be aware of the general approach to management so optimal initial care is provided. It also is recognized that the use and timing of PCI in the setting of UA and NSTEMI is very controversial and that the decision often will vary among the institutions and cardiologists involved. The same can be said for the role of PCI vs. thrombolysis in patients with ST-segment elevation MI. Depending on the setting, assessment of ventricular function and/or stress testing could be done by emergency medicine providers as a part of a local comprehensive program.

Low Molecular Weight Heparins (LMWHs)—Enoxaparin. The precise indications for and potential advantage of LMWHs in patients with ACS is a somewhat controversial area that is in a state of flux. In this vein, the ACC/AHA guidelines for UA and NSTEMI present a somewhat mixed message in their prioritization of LMWHs vs. UFH. First, although the document provides data demonstrating superiority for enoxaparin in UA and NSTEMI, when issuing recommendations for use of LMWH in ACS, the guidelines lumped all LMWHs together. Specifically, the ACC/AHA guidelines suggest that heparin or a LMWH (in this order) may be used in high-risk patients. However, within the text of the document, it is stated that a "LMWH can be substituted advantageously" for heparin.[12] The term "advantageously" would seem to reflect superiority data, despite their recommendation that heparin be used over LMWHs.

The guidelines appropriately indicate that it is somewhat difficult to draw conclusions about the relative efficacy of one LMWH vs. the others, and that head-to-head trials are the only conclusive way to settle this issue. However, the ESSENCE and TIMI-11b data, in the defined high-risk populations they studied, both clearly demonstrated superiority of enoxaparin over heparin for the composite end points of death, AMI, and recurrent angina. It has been argued that the reason enoxaparin trials demonstrated superiority (as opposed to the FRIC and FRAXIS trials that did not) of other LMWHs over UFH, is because of differences in trial populations and study designs. For example, it is argued that the ESSENCE and TIMI-11b populations were at higher risk than those in the other trials and that the magnitude of benefit in randomized trials is generally greater in patients at high risk compared with those at low risk. Patients in these trials were at higher risk because: 1) they had to present within 24 hours of the chest pain episode while those in FRIC and FRAXIS presented in 72 and 48 hours, respectively; and 2) the definition of AMI was softer than in FRIC and FRAXIS.

However, patients with chest pain and a history of or previous CAD were included in ESSENCE and TIMI-11b. Many of the patients in these trials did not have elevation of markers or EKG changes. Conversely, patients in the FRIC and FRAXIS trials had to have EKG changes, which could reflect a higher risk group. The point is that while arguments relative to design and population are endless, the data for the high risk population defined in the ESSENCE and TIMI-11b trials clearly reflect enoxaparin superiority as compared to heparin. Interestingly, in their analysis of the LMWHs, the ACC/AHA guidelines for AMI, state that "enoxaparin for the acute management of patients with UA/non-Q wave MI has been shown to be superior to heparin for reducing death and serious cardiac ischemic events. This superiority is achieved without an increase in the rate of either spontaneous or instrumented major hemorrhage." Consequently, from a practical, clinical perspective, enoxaparin, specifically and uniquely, can and should be substituted "advantageously" for heparin in UA and NSTEMI. Data for substituting other LMWHs "advantageously" for heparin simply do not exist, and it is somewhat curious that this distinction was not emphasized in the "advantageous" designation advocating LMWH substitution for UFH.

Despite the evidence-based support of enoxaparin superiority, the ACC/AHA guidelines issue a potential cautionary note concerning use of LMWHs in the setting of PCI because of the theoretical risk of increasing bleeding complications that may be associated with prolonged anticoagulation. The authors of the ACC/AHA document appropriately noted that enoxaparin was stopped 6-12 hours prior to PCI in ESSENCE and TIMI-11b, and therefore, it was difficult to draw conclusions regarding its safety in the PCI patient population.

Enoxaparin Safety in PCI. It should be stressed that the recommendations of the ACC/AHA document were

generated prior to very recent studies, all of which suggest that enoxaparin can be used safely, without a heparin window, in the peri-PCI setting. As previously mentioned, the NICE-3 Trial assessed the incidence of bleeding while performing catheterization in 661 patients with ACS, all of whom received enoxaparin plus a GP IIb/IIIa inhibitor (either abciximab, eptifibatide, or tirofiban).[31] At the time of catheterization, enoxaparin (0.3 mg/kg intravenously) was administered if more than eight hours had elapsed since the last subcutaneous dose. NICE-3 provides compelling data that enoxaparin in combination with the different GP IIb/IIIa inhibitors produces similar clinical outcomes and bleeding frequency when compared to these end points reported in the large GP IIb/IIIa inhibitor trials.[31] Put simply, NICE-3 suggests enoxaparin plus GP IIb/IIIa inhibitors is as safe as UFH plus GIIb/IIIa inhibitors in the setting of ACS and PCI, a finding that should be applied clinically as indicated.

In addition, the NICE-4 trial combined enoxaparin with abciximab during PCI. Enoxaparin was given as a 0.75 mg/kg intravenous bolus while abciximab was administered in its usual fashion. Data from the first 310 patients reveal the incidence of major non-CABG bleeding and transfusion to be 0.6%, which compared favorably with the 2.7% occurring in patients receiving abciximab and low-dose heparin in the EPILOG trial.[28] It must be recognized that minor, but not major bleeding, does occur more frequently with enoxaparin. Based on enoxaparin superiority in UA/NSTEMI compared to heparin as well as recent confirmation of safety as it relates to bleeding complications in PCI (NICE-3 and NICE-4), the guidelines in this review prioritize enoxaparin as the preferred antithrombin agent in UA/NSTEMI patients, including those with PCI.

In the setting of ST-segment elevation MI, the ACC/AHA AMI guidelines recommend heparin for patients undergoing PCI or surgical revascularization and for patients undergoing reperfusion therapy with alteplase. However, the preliminary results of 700 patients in the HART II and Menown trials reflected excellent efficacy and safety of enoxaparin in comparison to heparin. In addition, more than 1600 patients were involved in trials discussed previously involving peri-procedural use of enoxaparin in ACS, also reflecting efficacy and safety. Our guidelines reflect that enoxaparin can be used as an alternate in patients with ST-segment elevation MI who are receiving thrombolysis or a PCI.

GP IIb/IIIa inhibitors. The GP IIb/IIIa inhibitors are recommended for all patients with high-risk UA/NSTEMI by the ACC/AHA guidelines. Our guidelines reflect a more specified population. According to the ACC/AHA guidelines, patients can be high risk because of either previous history of CAD, physical exam evidence of heart failure in the setting of ischemia, EKG changes, or cardiac marker elevations. However, these ACC/AHA high-risk criteria were not the inclusion criteria for the PURSUIT, PARAGON, PRISM, and PRISM-PLUS trials, where PCI was not mandated.

All patients in these trials had to have EKG changes (or cardiac marker elevation in the PRISM trial). A history of CAD or physical exam findings consistent with heart failure were entry criteria for these trials. Our guidelines reflect this. As with the LMWHs, the ACC/AHA guidelines for UA and NSTEMI use the generic recommendation of a "GP IIb/IIIa inhibitor." For patients who have UA or NSTEMI and for whom it is unknown if PCI will be performed, the best efficacy data exist for tirofiban (PRISM and PRISM-PLUS), followed by eptifibatide (PURSUIT). These are the patients who are seen in the emergency department.

However, it must be recognized that evidence in these trials pertaining to patients who do not receive a PCI is much less robust. The data for abciximab use in patients with UA or NSTEMI who are not undergoing a PCI are lacking. Conversely, the efficacy data for patients who are definitely going to have a PCI performed are excellent for abciximab. It is important to recognize that many of the patients, in the trials of GP IIb/IIIa inhibitors with mandated PCI, were not having an ACS and were often receiving elective PCIs. These trials involved a different population than that seen in the emergency department.

The ACC/AHA guidelines for AMI only mention GP IIb/IIIa inhibitors in the setting of NSTEMI. The role for these agents is evolving. Data from studies that have used reperfusion as the end point have been favorable when the GP IIb/IIIa inhibitor has been combined with a half-dose thrombolytic. The results of the large GUSTO 4 AMI clinical trial have not yet been released. Our recommendations do not yet incorporate a GP IIb/IIIa inhibitor in the setting of ST-segment elevation MI.

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