Regionalization of Care for Acute Ischemic Heart Disease
A Call for Specialized Centers
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The past 20 years have witnessed a dramatic evolution in medical care for patients with acute coronary syndromes (ACS). As the vast majority of hospitals lack tertiary invasive cardiac facilities, most therapeutic strategies for acute myocardial infarction have focused on pharmacological reperfusion with intravenous fibrinolytics. In addition, antiplatelet and anticoagulant therapies have gained evidence-based support for early use in patients with non–ST-segment elevation myocardial infarction. Despite the benefit derived from fibrinolysis in randomized clinical trials, many community hospitals in the United States have sought to implement primary angioplasty infarct reperfusion programs in the absence of elective provisions for percutaneous coronary intervention (PCI). In the context of new data from trials of infarct reperfusion, we should at this time examine the issues that have prompted hospitals of limited resources to provide tertiary cardiovascular services and the evidence-based provisions that must be placed on such strategies.

Unquestionably, the rapid restoration of normal coronary blood flow via pharmacological or mechanical recanalization of an occluded infarct-related coronary artery limits myocardial necrosis and reduces mortality. Only recently have the time-dependent efficacies for both mechanical and pharmacological reperfusion strategies been closely scrutinized and have relative differences between these treatment modalities become evident. Although the time from infarct symptom onset to initiation of fibrinolytic reperfusion is a critical determinant for successful recanalization as well as survival, the relationship of infarct duration before PCI recanalization with procedural success or survival is less direct.1 Remarkably, few patients receive PCI within 2 hours of symptom onset, even in highly experienced centers. Indeed, in the stent Primary Angioplasty in Myocardial Infarction Study (PAMI) trial only 5.9% of all patients were reperfused within 2 hours.2 Despite time delays incurred during provision of PCI, relative benefits accompany this therapy, including enhanced survival in a meta-analysis of randomized trials of PCI versus lysis.3 The authors concluded: “Based on outcomes at hospital discharge and 30 days, primary angioplasty appears to be superior to thrombolytic therapy for treatment of patients with acute myocardial infarction,” with an important proviso, “that success rates for angioplasty are as good as those achieved in these trials. Data evaluating longer term outcomes, operator experience, and time delay before treatment are needed before primary angioplasty can be universally recommended as a preferred treatment.”

These data prompted the Cardiovascular Patient Outcomes Research Team (C-PORT) pilot trial, which tested the feasibility of performing PCI for acute myocardial infarction in smaller community hospitals that did not perform elective PCI or have on-site coronary bypass facilities.4 C-PORT involved 11 participating community hospitals in Maryland and Massachusetts and randomly assigned 451 patients presenting with ST-segment elevation acute myocardial infarction to receive either PCI or lysis treatment “on site.” Extensive in-service training for the hospital staff, consignment inventory of angioplasty supplies, and performance of the PCI procedures by relatively high-volume operators from neighboring communities were notable features. Those patients randomly assigned to PCI experienced a lower incidence of...
of patient transport to a specialized regional center for all three of these trials, the randomized comparative strategy point of death, recurrent myocardial infarction, or stroke. In these trials, patients randomly assigned to fibrinolytic therapy experienced a 13% to 15% event rate for the composite clinical end point of death, reinfarction, and stroke at 30 days for the fibrinolytic (Lytic) and transport plus coronary intervention arms in 3 randomized trials. Data from references 5 to 7. DANAMI indicates the DANish multicenter randomized study on thrombolytic therapy versus coronary angioplasty in Acute Myocardial Infarction-2; PRAGUE-2, the PRimary Angioplasty in AMI patients from General community hospitals transported to PTCA Units versus Emergency thrombolysis trial; and Air PAMI, a randomized trial of transfer for Primary Angioplasty versus on-site thrombolysis in patients with high-risk Myocardial Infarction.

dearth, reinfarction or stroke at both 30 days and 6 months after treatment. Although the results of this pilot experience have enticed many community hospitals to follow suit in an attempt to recreate the C-PORT experience, extrapolation of these results to community hospital practice in the United States is questionable. In retrospect, the inclusion of a third randomized arm (transport to a high-volume center for PCI) as part of C-PORT would have been a very useful comparator for on-site community hospital PCI.

The importance of such a comparison looms large in the context of both the logistic considerations for PCI program proliferation in community hospitals and the results of three recent randomized trials that have challenged the use of on-site fibrinolysis when compared with immediate transport to a regional center for PCI. These trials, which enrolled patients with ST-segment elevation myocardial infarction (Figure 1), are particularly striking for the consistency and extent of clinical benefit derived by transporting the patient to a regional center for catheter-based reperfusion as compared with the on-site (community hospital) initiation of fibrinolytic therapy. In the DANish multicenter randomized study on thrombolytic therapy versus coronary angioplasty in Acute Myocardial Infarction-2 (DANAMI-2), the PRimary Angioplasty in AMI patients from General community hospitals transported to PTCA Units versus Emergency thrombolysis trial (PRAGUE-2), and A randomized trial of transfer for Primary Angioplasty versus on-site thrombolysis in patients with high-risk Myocardial Infarction (Air PAMI) trials,5–8 patients randomly assigned to fibrinolytic therapy experienced a 13% to 15% event rate for the composite clinical end point of death, recurrent myocardial infarction, or stroke. In all three of these trials, the randomized comparative strategy of patient transport to a specialized regional center for emergency angiography and coronary intervention yielded a composite event rate of \( \sim 8.0\% \) and thus, a consistent 40% reduction in adverse outcomes, with an almost identical intertrial point estimate. Furthermore, for patients who present with non–ST-segment elevation ACS (unstable angina, non–Q-wave myocardial infarction) 3 recent randomized trials compare an early invasive strategy of coronary angiography and revascularization with a more “conservative” approach employing medical therapy. In all 3 trials, Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II), Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombosis in Myocardial Infarction (TACTICS TIMI-18), and the Randomized Interventional Trial of Unstable Angina (RITA 3),9–11 the invasive strategy demonstrated superiority for reduction in the composite end point of death, recurrent infarction, or severe refractory angina. In TACTICS TIMI-18, particular benefit accompanied invasive therapy for patients at high risk as reflected by an elevated TIMI risk score, serum troponin I, or C-reactive protein. In aggregate, the results from recent trials of both ST-segment elevation myocardial infarction and non–ST-segment elevation ACS strongly support a revamped healthcare system to raise the bar for acute care in ischemic heart disease to a new standard. This situation is analogous to the emergency trauma system that currently exists in the United States that comprises regional centers of excellence to which patients who have experienced significant trauma are preferentially transported, and at which experienced staff are available on a continuous basis. For such a transformation in our process of acute care for ischemic heart disease to proceed, what barriers exist?

First, key practical issues such as time and transport must be acknowledged. In Denmark, where the DANAMI-2 trial was conducted in 5 specialized centers and 22 referring community hospitals that serve more than 3 million persons (\( \sim 60\% \) of Denmark’s population), the time delay for patient transport from community hospital to regional center for PCI (compared with time required to initiate on-site fibrinolysis) was only 10 minutes.5 Similarly, in the Czech Republic where the PRAGUE-2 trial was conducted country-wide, the relative time delay for transport and execution of PCI reperfusion was only 30 minutes (277 minutes for PCI versus 245 minutes for fibrinolysis).6 However, in the Air PAMI trial, in which the average distance between community and regional hospital was 32 miles, the time delay incurred by transport was 43 minutes.7 Unfortunately, time differences to coronary reperfusion between transport for PCI versus local thrombolysis (relief of chest pain or resolution of ST-segment elevation) are not discernible from these trials. As noted previously, although the time dependency of catheter-based reperfusion is substantially less than for pharmacological reperfusion, particularly for those patients who present beyond 3 hours of symptom onset, there is no reason to accept appreciable intrinsic delays in reperfusion therapy. Indeed,
the time from hospital presentation to balloon-catheter-mediated reperfusion (door-to-balloon time) is directly related to mortality after PCI for myocardial infarction, and door-to-balloon times of <120 minutes are associated with improved hospital survival. Interestingly, door-to-balloon times vary significantly with the time of hospital arrival (24-hour clock) and are inversely proportional to hospital volume of primary PCI procedures. Clearly, a more integrated system of community and regional hospitals to work efficiently in the care of patients with acute myocardial infarction would require exquisite cooperation between these facilities and emergency transport systems. The current default program of transporting patients with suspect myocardial infarction to the nearest hospital should be obsolete. Second, a direct relationship between hospital and operator PCI volumes and optimal clinical outcomes has been established for both elective and infarct PCI. Adverse outcomes, including death and the requirement for coronary bypass surgery, are lowest if primary PCI is performed by a high-volume operator at a high-volume center. In the national registry of myocardial infarction, US centers that performed >48 primary procedures yearly had the largest gradient for relative benefit of PCI over fibrinolytic therapy. In an editorial comment on this observation, Jollis and Romano stated “these data suggest that percutaneous interventions including primary angioplasty generally should not be conducted in low-volume hospitals unless there are substantial overriding concerns about geographic or socioeconomic access.” We agree and would further extend this premise: Even the most experienced sites and operators require continuous quality assurance, surveillance of door-to-balloon times, regularly scheduled morbidity and mortality conferences, as well as rigorous standards for postintervention medical therapy and risk factor modification. The need to assure true 24/7 coverage without lapse in responsiveness is emphasized by recent data from the NRMI 2, 3 registries that the ability of hospital staff and physicians to respond for PCI (door-to-balloon time) was dependent on hospital time of arrival and was <2.2 hours only between 8 AM and 5 PM.

Third, regional centers should have state-of-the-art equipment with high-quality digital radiographic imaging, hemodynamic monitoring systems, and a full inventory of guidewires, guiding.
and balloon catheters, and stent sizes. Intra-aortic balloon counterpulsation devices, as well as a staff trained to operate and troubleshoot this equipment, are necessary. Ideally, regional centers should have access to new technologies designed to limit myocardial injury and enhance functional recovery. Adjunctive novel pharmacotherapies or catheter-based technologies for distal atherothrombotic embolization protection are not likely to be employed by low-volume operators at community hospitals but instead should be the purview of regional centers. It remains unclear whether “facilitated” PCI with fibrinolytic therapy given as an early adjunct will be an advantage over current therapy, and trials are in progress to address this critical question.19

The time has come for a transformation in the care of patients presenting with acute myocardial infarction, which requires the establishment of centers of excellence. A mandate should come from both government and private health-care providers. The number of deaths in the United States from myocardial infarction exceeds (7-fold) that for all-cause mortality, requiring the establishment of centers of excellence. A managed-center approach for trauma has already been validated in the United States for improving clinical outcomes.21,22 The lack of specialized centers for acute ischemic heart disease is not commensurate with the magnitude of this public health problem. Indeed, such a system is now validated in both Denmark and the Czech Republic.5,6 Although a considerable investment of resources would be required, the return on investment should be a reduction in death, reinfarction, and stroke for patients with acute myocardial infarction. With myocardial infarction representing the most common cause of death and disability in our society today, the time for change is past due.

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_Circulation_. 2003;107:1463-1466
doi: 10.1161/01.CIR.0000063680.45780.A0
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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