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Regionalization of Acute Coronary Syndrome Care: More Evidence is Needed

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Introduction

There is a growing movement advocating the treatment of patients with acute coronary syndromes (ACS) at regional centers with dedicated facilities.[1, 2] Proponents contend that regionalized ACS care will save lives by improving access to new technologies, specialist physicians, and higher quality care not available at other centers.[1, 2] The state of Maryland has already begun planning for regionalized care for patients with ACS.[3] Recent enthusiasm for this movement has focused on its potential benefits. We present concerns about the rationale for regionalized ACS care, and outline some potential unintended consequences.

The Reported Benefits of ACS Centers

Recent articles arguing for the implementation of ACS regionalization have discussed three principal benefits.[1, 2]

Benefit 1: Transfer for primary percutaneous coronary intervention is more effective than on-site management with fibrinolytic therapy

Five randomized trials -- the DANish multicenter randomized study on fibrinolytic therapy versus coronary angioplasty in Acute Myocardial Infarction-2 (DANAMI-2),[4] the Primary Angioplasty in AMI patients from General community hospitals transported to PTCA Units versus Emergency thrombolysis trials (PRAGUE-1,[5] PRAGUE-2[6]), A randomized tRial of transfer for Primary Angioplasty versus on-site Thrombolysis in patients with high-risk Myocardial Infarction (Air PAMI),[7] and a single center randomized trial based in Maastricht, Netherlands[8] -- provide evidence for transferring patients with ST-elevation ACS for primary PCI in lieu of on-site fibrinolytic therapy. A recent meta-analysis suggests that such policies may result in as much as a 40% relative reduction in adverse outcomes.[9] However, these studies have notable limitations. DANAMI-2, the largest study, reported a benefit for transferring for primary PCI primarily on the basis of a lower rate of reinfarction.[4] The adverse event rate in DANAMI-2's on-site fibrinolytic arm, however, was nearly double that of contemporary studies of fibrinolytic therapy, which may reflect a bias introduced by the study protocol. Specifically, DANAMI-2 did not include peri-procedural reinfarctions in patients undergoing primary PCI in its outcome assessment, used higher than currently recommended doses of

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unfractionated heparin (thus increasing the risk of strokes), and required use of repeated fibrinolytic therapy as opposed to rescue PCI for patients experiencing recurrent ischemia.[10]

More important than study-specific limitations is the generalizability of these data to current practice in the United States. Three of the five studies (PRAGUE-1, PRAGUE-2, Air-PAMI) utilized streptokinase whereas other fibrinolytic agents are used in the United States. These studies likely represent selected populations in that patients considered "unsafe" for transfer for primary PCI or those requiring longer transfer times were excluded. Four studies (DANAMI-2, PRAGUE-1, PRAGUE-2, Maastricht) were conducted in small regions within centralized European hospital systems, which differ markedly from the United States, where populations are often dispersed and emergency medical services more heterogeneous. Results from the only study to enroll US patients (Air-PAMI) should be interpreted cautiously, because of insufficient subject enrollment and no statistically significant benefit for its primary endpoint of major adverse cardiac events at 30-days.[7] Air PAMI's enrollment of only 83 patients with ST-elevation ACS at US sites over 3 years (approximately 1 patient every 4 months from the 9 participating US centers) also raises concerns about patient selection.

Data comparing the benefits of fibrinolytic therapy with primary PCI suggest transferring all patients with ST elevation ACS for primary PCI may not be warranted. Although primary PCI may yield better clinical outcomes than fibrinolytic therapy in general, the largest part of this difference reflects a reduction in reinfarction.[11] Recent studies also indicate no difference in outcomes between fibrinolytic therapy and primary PCI for patients who present within two[12] or three hours[6] of symptom onset. A meta-regression based on 10 reperfusion therapy trials found that treating only the 39% of patients at highest risk with primary PCI would achieve similar outcomes to adopting a population-wide primary PCI strategy.[13] This underscores the point that the relative risk reduction associated with primary PCI is unlikely to improve outcomes meaningfully when applied to low risk patients who are candidates for both therapies and may result in poorer outcomes compared with on-site fibrinolysis because of the delayed time to reperfusion. Further, the continued evolution of fibrinolytic, adjuvant antithrombotic, and antiplatelet therapies and promising findings regarding pre-hospital fibrinolytic therapy suggest that transferring patients for primary PCI versus providing immediate pre-hospital fibrinolytic treatment will require frequent reassessment.

No study has evaluated the immediate transfer of patients with non-ST elevation ACS from community-based hospitals to PCI-capable centers. Although non-ST elevation ACS patients managed with an early invasive strategy instead of medical therapy had superior outcomes overall, this benefit was not observed in low risk patients[14] and may not be realized by a majority of patients with non-ST elevation ACS.[15] No study has directly tested the hypothesis that routinely transferring these patients to obtain invasive treatment is superior to on-site management, leaving the utility of transfer in this population unclear.

Benefit 2: Treating patients at high volume hospitals will improve outcomes

There are limited data regarding the association between hospital ACS volume and outcomes.[16] Proponents of ACS regionalization have relied instead on studies of hospital PCI volume and outcomes[17] to suggest that restricting ACS patients who will likely need PCI to higher volume PCI centers will improve patient outcomes. However, all published studies of ACS or PCI volume and outcomes have used cross-sectional designs, which cannot ascertain causality.[18] It remains unproven whether reports of better outcomes at higher volume centers reflect a true volume-associated benefit or other factors.

More importantly, no empirical data support the assertion that shifting patients to higher volume facilities improves outcomes for either ACS or PCI. The anticipated survival benefits from ACS regionalization are based on assumptions about the "transferability" of the volume

effect, the comparability of patients across hospitals, and the ability of hospitals undergoing large volume increases to provide high quality care.

Moreover, recent evaluations of the PCI volume-outcomes relationship question the conventional wisdom that higher volume centers achieve superior outcomes. Given that hospital PCI volume-associated differences in mortality have decreased since the mid-1980s, [19] any volume-associated benefit may become too small to be clinically meaningful. In fact, a recent study of hospital PCI volume suggests that the hospital volume-associated mortality effect may already be negligible and that individual hospital PCI volume is not a reliable marker of hospital PCI outcomes.[20]

Benefit 3: ACS centers will provide access to state of the art care including specialists and new therapies

Proponents argue that regionalized ACS centers will drive the adoption of new drugs, devices, and interventions, and provide greater access to treatment by specialist physicians. Prior evaluations of ACS and general medical care suggest that more procedure-intensive treatment patterns provide no discernible improvements in mortality.[21, 22] Promoting the adoption of intensive, interventional ACS strategies belies the fact that many patients may not require or even benefit from such an approach.[15] For instance, ACS patients treated in areas with higher rates of cardiac catheterization have comparable outcomes to those treated in areas with lower rates of cardiac catheterization and optimal medical care.[23] As Stukel and colleagues' findings suggest, treating ACS patients with high quality medical care, which can be accomplished by all hospitals without additional facilities, may reduce the need for interventional procedures. Also, focusing on the adoption of newer therapies ignores the fact that many inexpensive, readily available, established therapies remain underutilized in ACS patients.

Increased access to cardiologists during hospitalization is another expected benefit of ACS regionalization. Although ACS patients treated by cardiologists reportedly have superior outcomes,[24] generalist physicians treat patients with more comorbidities than those treated by cardiologists, raising the possibility that such comparisons may be confounded by unmeasured differences in patient characteristics.[25] Similarly, while cardiologists' rates of evidence-based therapy use are higher than generalists', the absolute differences in treatment rates do not explain observed differences in outcomes and are smaller than the sizable shortfalls in quality of care observed among both specialist and generalist physicians.[26] Concentrating care with specialists overlooks reports of superior outcomes obtained from patients treated in collaborative care models using generalist and specialist physicians.[27] Moreover, there are alternative approaches to increasing access to physician specialty care during hospitalization – including use of community-based physicians, remote consultations, or otherwise "bringing the physician to the patient" – that would not require regionalization of ACS care.

Concerns about ACS Centers

In addition to limited evidence for the proposed benefits of regionalization of ACS care, there are notable risks and potential unintended adverse consequences. We present six potential areas of concern that should be a part of the discussion of an ACS regionalization policy.

Concern 1: What is "regionalization"?

There is no clear consensus on the specific nature of ACS regionalization. Will ACS regionalization require the transfer of ACS patients to PCI-capable hospitals, or instead establish the cardiovascular equivalent of regional trauma centers with ACS patients bypassing closer hospitals for direct admission to designated centers? Will this policy focus only on confirmed ST elevation ACS, as Maryland is currently planning,[3] or instead encompass all

patients with suspected ACS? Will ACS centers be selected through an external review process or will an "ACS center" designation be offered to all hospitals meeting structural standards for technological capabilities and/or minimum volumes? The costs and benefits of ACS regionalization will obviously depend on the specifics of the policy and the areas in which it is implemented.

Concern 2: What are the potential risks to patients?

Under any ACS regionalization policy, some patients will forego part or all of their care at closer hospitals for treatment at ACS centers. The potential risks of this requirement have not been adequately assessed in randomized trials evaluating patient transfer Although published studies suggest a 1% to 2% risk of ventricular arrhythmias or death during transfer to an ACS center,[4, 6] this may reflect the small numbers and selected nature of randomized trial populations, and is unlikely to be a reliable estimate of risk due to longer travel times and the use of ACS transfer outside of randomized trials. Transferring patients for primary PCI in Air-PAMI added on average more than 100 minutes to patients' time to treatment after initial arrival at an emergency room (155 minutes vs. 51 minutes, $P<0.0001$).[7] Data from the National Registry of Myocardial Infarction (NRMI) 2 and 3 report a median door to balloon time of 195 minutes for patients transferred for primary PCI in the United States,[28] nearly double the time reported in DANAMI-2[4] and PRAGUE-2.[6] This is notable, because differences in time to reperfusion therapy >60 minutes negate the incremental benefit of primary PCI compared with fibrinolytic therapy for the average patient.[29] Data from NRMI 4 suggest that only 5% of transferred PCI patients in the United States currently satisfy this criterion.[30]

Concern 3: Are regional ACS centers viable?

Essential details concerning the feasibility of ACS regionalization have not been addressed. It is unclear how hospital capacity will be re-allocated given that fewer than 1 in 5 United States hospitals perform cardiac catheterizations.[31] Will ACS centers reduce their management of patients with other medical conditions or will they instead need to add facilities and staff to support their new ACS patients? How many patients will be reallocated to regional ACS centers? How will patients' access to care be maintained given the limitations associated with regionalization? What will the societal costs of this process be, and how will they be funded?

Current data offer some insight into the possible scope of required changes. Restricting the treatment of ACS patients to hospitals with PCI services and on-site coronary bypass surgery back-up would have required the transfer of nearly 65% of Medicare beneficiaries hospitalized for MI nationwide in 1994–1996.[32] Extrapolating these data to the 768,495 patients hospitalized for MI in the United States in 2000[33] suggests that approximately 497,000 patients would have needed to undergo treatment at different hospitals. This is a crude estimate and does not include ACS patients who did not have a MI. The feasibility of moving such a large number of patients is unclear. Although a study of Florida, Pennsylvania, and New York hospitals suggested that most patients may not need to travel additional distances if PCI were regionalized, this study relied on straight-line distances rather than travel time estimates and may not be generalizable to other areas.[34] It is apparent, however, that ACS regionalization will likely require a national redistribution of cardiovascular resources.

Concern 4: Is the direct admission of ACS patients feasible?

A key component of some regionalization proposals is the direct admission of ACS patients to dedicated centers, potentially bypassing closer hospitals. Some have suggested that ACS should be thought of as trauma, and like trauma care should be regionalized.[2] However, ACS is distinct from trauma in that frequently ACS is not an obvious diagnosis, and there is no valid, widely used ACS field triage capacity or experience in the United States. Moreover, most ACS patients in the United States present directly to the hospital without utilizing emergency

medical services.[35] A directed admission policy is unlikely to be relevant to patients with non-ST elevation ACS, who may display biomarker or electrocardiographic features of ACS only after serial measurements.

Evaluations of symptomatic patients hospitalized with suspected ACS raise additional concerns about the feasibility of directly routing suspected ACS cases to regional centers. In the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument trial, 83% of symptomatic patients did not have acute cardiac ischemia.[36] If these data are generalizable, regional ACS centers would likely be overwhelmed with patients with conditions other than cardiac ischemia. Accounting for the diversity of clinical conditions for which these non-ACS patients would require treatment may challenge the resources of dedicated ACS centers – and conceivably hamper the emergent treatment of ACS patients. It remains unknown whether ACS centers could handle the size and potential diversity of this population.

Concern 5: What are the economic implications?

Redistribution of ACS patients resulting from a regionalization policy would likely have severe financial consequences for hospitals not designated as ACS centers. A bellwether of such a change can be found in the recent experience of general acute care hospitals that lost substantial cardiovascular procedure market share, particularly for PCI, to newly opened heart hospitals.[37] The resultant decrease in revenue has caused financial strain, because cardiovascular services account for 35% of hospitals' revenue on average,[38] and other hospital services are typically cross-subsidized by cardiovascular procedure revenue. In the worst case, reductions in cardiovascular services at non-ACS centers could force these hospitals to cut other services or possibly to stop operating altogether.

Regionalization has potential economic implications that go beyond the distribution of procedures among hospitals. Although concentrating ACS care in fewer centers may result in lower hospital treatment costs through a combination of economies of scale and learning by doing, the evidence supporting this for PCI is only suggestive.[39] Even if regionalization reduces hospital costs for ACS treatment, it may have the offsetting effect of increasing hospital market power, thus enabling ACS centers to charge private payers more for ACS care and potentially leading to net increases in spending. Independent of the price effect, total spending on ACS may grow under regionalization because more cases may be treated with more intensive approaches than current practice.

Concern 6: The end of quality cardiovascular care at non-ACS centers?

The possible repercussions of an ACS regionalization policy on the management of cardiovascular care at non-ACS centers deserve consideration. Concentrating ACS care at regional centers will result in the movement of expertise from other centers, thereby reducing the ability of non-ACS centers to care for ACS patients and cardiovascular disease more broadly. This approach may result in poorer quality care and outcomes for patients at non-ACS centers, some of whom will require management of cardiovascular disease during hospitalizations for non-ACS conditions. Further, this approach fails to recognize that the greater shortfall in quality of ACS care concerns the 30% of eligible ST elevation ACS patients who do not receive reperfusion therapy, rather than the relative merits of PCI versus fibrinolytic therapy.[40]

Conclusion

This paper highlights important issues that deserve consideration in the discussion of treatment of ACS patients at dedicated regional centers. The evidence base supporting the adoption of ACS care regionalization and the transfer of ACS patients has significant limitations. Current

studies of transfer for patients with ST-elevation ACS have questionable applicability to the American health care system, and there is as yet no evidence to support the transfer of patients with non-ST elevation ACS. No study to date has provided convincing evidence that triaging patients to higher volume hospitals will actually reduce mortality. Hospital size, technology, and specialization do not guarantee high quality ACS care, just as the absence of these attributes does not preclude high quality ACS care. Moreover, recent studies question the marginal benefits of technologically sophisticated, resource intensive treatment for ACS. Generally absent from discussions of an ACS regionalization policy are the numerous potential problems that may accompany regionalization of care, including feasibility, potential risks to patients, economic costs, and the implications of regionalization policies for non-ACS centers.

We recognize that the absence of evidence of benefits from ACS regionalization is not the same as evidence of the absence of any ACS regionalization benefits. However, there is no definitive evidence to support ACS regionalization in the United States, and no current professional guideline endorses its implementation. Although ACS regionalization has its proponents and is a provocative topic for debate, the current data are insufficient to endorse a policy requiring such a fundamental change. Clear, compelling evidence of the benefits of ACS regionalization within the United States and a better understanding of its potential consequences are needed before implementing a national policy of regionalized ACS care.

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