Faster, Safer, Better: The New Paradigm for Managing ST-Segment Elevation Myocardial Infarction
SUNIL V. RAO, MD

The Changing Landscape of the Healthcare System: Implications for STEMI Care
JOANE H. GOODROE, RN, BSN, MBA

Regional Systems of Care: An Interventional Laboratory Perspective
DANIEL MUÑOZ, MD; MAYME L. ROETTIG, RN, MSN; JAMES G. JOLLIS, MD

Unfractionated Heparin: Still Going Strong — Despite Limitations and Evidence
DAVID C. SANE, MD

Advances in Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction
JOSEPH R. ARAGON, MD, FACC, FSCAI, and MICHAEL M. SHENODA, MD

Preventing Radial Artery Occlusion and Anticoagulation in Transradial PCI
SAMIR B. PANCHOLY, MD, FACP, FACC, FSCAI

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Faster, Safer, Better: The New Paradigm for Managing ST-Segment Elevation Myocardial Infarction

Sunil V. Rao, MD

The decrease in 30-day mortality after myocardial infarction (MI) has been one of the most significant medical achievements of the last decade.\(^1\) This reduced mortality is down to advancements in both pharmacological treatments and their implementation. In other words, it was a combination of efficacy and effectiveness.

Pathophysiologically characterized by the presence of complete occlusion of an epicardial coronary artery, ST-segment elevation myocardial infarction (STEMI) accounts for approximately one-third of MI.\(^2\) The clinical priorities in STEMI are to re-establish coronary flow, salvage myocardium, and prevent downstream mechanical complications.

Previous randomized trials have established the efficacy of primary percutaneous coronary intervention (PCI) over fibrinolysis;\(^3\) however, timing is crucial in either strategy.\(^4\) This requires that multiple stakeholders — including emergency medical services, the emergency department, and the cardiac catheterization laboratory — coordinate.\(^5\) As such, a systems approach is essential to success. This supplement is dedicated to issues related to STEMI: systems of care and how they may evolve as the healthcare delivery changes, pharmacological approaches for improving primary PCI outcomes, and vascular access-site approaches that make primary PCI safer.

The issue begins with a glimpse into the future of healthcare and how this rapidly changing landscape may affect STEMI care. Joane H. Goodroe, RN, BSN, MBA, of Goodroe Healthcare Solutions has been at the forefront of healthcare reform; her insights into the direction of STEMI care will be valuable to physicians of all specialties.

As noted, multiple specialties must coordinate patient care to create successful STEMI programs. Drs. Jollis and Munoz and Mayme L. Roettig, RN, MSN, outline the importance of developing pathways of care and the role of regionalized specialty care for these complex patients. Such systems have been successful in North Carolina\(^6\) and Minnesota,\(^7\) and the article describes the elements necessary for efficient care.

The next three articles deal with pharmacological approaches associated with improved primary PCI outcomes. Antithrombotic therapy for primary PCI has evolved considerably. Unfractionated heparin had been the mainstay anticoagulant, with glycoprotein IIb/IIIa inhibitors (GPI) added to address the frequently present thrombus burden;\(^8\) however, the bleeding risks associated with this combination have led to interest in agents that preserve antithrombotic efficacy while minimizing hemorrhagic risks. Bivalirudin, a direct thrombin inhibitor, has now been studied in three large trials across the spectrum of patient risk from elective PCI to non-ST-segment-elevation MI to STEMI.\(^9\) The use of a bivalirudin strategy for primary PCI is associated reduced 30-day, 1-year, and 3-year mortality rates.

Dr. Sane discusses the limitations of unfractionated heparin and why an agent such as bivalirudin may be preferred in the primary PCI setting. Dr. Aragon reviews the combining of pharmacological and access-site approaches to optimize primary PCI outcomes.

The final two articles deal with two efficient-care strategies that may not be specifically related directly to STEMI care. The first is the concept of outpatient PCI. In this context, outpatient refers to same-day discharge of patients who underwent elective PCI (not primary PCI for STEMI). Dr. Gilchrist discusses why this strategy is attractive in selected patients, and which PCI pharmacological and access-site approaches can facilitate same-day discharge.

Candidates for same-day discharge after PCI are patients who have successful procedures without complications and have social support at home. A successful procedure is marked by the absence of both ischemic and bleeding complications — goals that can be readily achieved via radial access.

It’s important that the radial operator be aware of some important complications. Radial artery occlusion continues to limit transradial procedures, and Dr. Pancholy discusses the best way to reduce the risk of this complication. Drs. Gilchrist and Pancholy have published extensively on same-day discharge and radial artery occlusion, respectively, and the information they provide will be of interest to all practicing interventional cardiologists.

The Yogi Berra quote “It’s tough to make predictions … especially about the future” applies to interventional cardiology. The past decades’ advances have been alternatively iterative and novel. While improved outcomes are definitely good news, many patients still experience considerable morbidity and mortality after STEMI.

This supplement reviews the different aspects of STEMI care, as well as aspects of PCI in general, that will likely play roles in the future care of patients undergoing interventional procedures. I hope the articles herein will inform interventional cardiologists who are interested in providing safe, efficient care for their patients.
References
4. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the acc/aha 2004 guidelines for the management of patients with st-elevation myocardial infarction. A report of the american college of cardiology/american heart association task force on practice guidelines: Developed in collaboration with the canadian cardiovas-
The Changing Landscape of the Healthcare System: Implications for STEMI Care

Joane H. Goodroe, RN, BSN, MBA

For more than 10 years, physicians have been negatively affected by decreasing reimbursement. And, as fees have decreased dramatically in recent years, the future is more daunting. For two decades, forecasters have called for greater economic adjustment in healthcare, and this need extends beyond the physician fees. “The nation will face daunting long-term fiscal challenges posed by the aging of the population and rising costs for health care,” says the Congressional Budget Office 2011 report. Medicare spending represents 12% of the federal budget, and that figure continues to grow.¹

Although the Affordable Care Act appears to have instigated change, further examination demonstrates a long, detailed planning process has begun to transform patient care. This transformation will pose challenges and opportunities. The major implication for healthcare providers: The system of care will change from one driven by economic incentives for more patient services to one focusing on quality of care and the appropriate use of resources. Some of the evolution of economics related to the care of STEMI patients will be discussed.

The Medicare Reimbursement Model

To understand the future model of Medicare reimbursement, it is important to recognize the current system’s dilemmas. It does not seem possible that physicians’ fees could be decreased any further. Anyone examining the data can understand how great the problem really is.

In 1992, the payment system based on physicians’ charges was replaced by a fee schedule known as the Resource Based Relative Value Schedule (RBRVS). This method was designed to pay physicians by specialty—not to control costs. As the cost per Medicare beneficiary grew, Congress initiated the Sustainable Growth Rate (SGR) in 1998. The goal of SGR was to control spending on physicians’ services under Medicare Part B. The SGR process looks at the budget for spending, and payment rates are adjusted annually to reflect actual targeted spending. Under the first measure of Part B expenditures from 1997 through 2005, spending per Medicare beneficiary under the physician fee schedule grew by 65%.² Under SGR, this growth in expenditures per beneficiary is now adjusted annually in the proposed fee adjustments to the Medicare physician fee schedule.

Many would like to see the SRG methodology repealed because, each year, Congress adjusts the proposed fee schedule and, each year, the Medicare Part B deficit continues to grow.

An independent congressional agency, the Medicare Payment Advisory Commission, (MedPAC), was established to address issues affecting the Medicare program. In its September 2011 public meeting, MedPAC unveiled draft recommendations related to the unsustainable Medicare physician payment system. Although MedPAC focused on moving toward a system that rewarded quality of care, it recommended that most physician reimbursement be decreased annually for 3 years by 5.9%.³ As such, these recommendations highlighted the continued issue of healthcare costs and the unsustainability of existing reimbursement economics.

SGR and physician reimbursement do not address the central problem. Instead, they are symptoms of the underlying issue that is being addressed through new CMS efforts. The United States is spending a large portion of its budget on healthcare services, while quality and outcome statistics do not demonstrate a benefit to patients.

Experts have recognized since the 1980s that the financial incentives in healthcare do not encourage patient care coordination nor do they promote the best quality. Instead, the current physician payment system has led to duplicative and unnecessary services. For example, MedPAC estimated that, in 2005, 18% of Medicare beneficiaries discharged from a hospital were readmitted within 30 days, and that approximately 13% of the readmissions were preventable. The estimated cost of these readmissions is $12 billion.⁴

The Dartmouth Atlas published another well-known example regarding Medicare beneficiaries’ varying care.³ Researchers examined practice patterns in national, regional, and local markets, as well as hospitals and their affiliated physicians. Some interesting findings for interventional cardiology in 2007:

- Hawaii has the lowest PCI utilization, with a rate of 2.97 per 1000 Medicare patients.
- Arkansas has the highest utilization, with 14.26 PCI per 1000 Medicare patients.
- The national average was 9.89 PCI per 1000 Medicare patients (see Table 1).³

Published studies consistently demonstrate similar care-pattern variations, which are prone to creating waste in the healthcare system.

Fixing the System

Physicians are the key to ensuring healthcare quality while reducing system costs. “Doctors are key to cutting cost because their decisions control eighty-seven percent (87%) of personal health spending,” according to the Boston University School of Public Health.⁵

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1 Under SGR, this growth in expenditures per beneficiary grew by 65%.
2 As the cost per Medicare beneficiary grew, Congress initiated the Sustainable Growth Rate (SGR) in 1998.
3 The national average was 9.89 PCI per 1000 Medicare patients.
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5 Published studies consistently demonstrate similar care-pattern variations, which are prone to creating waste in the healthcare system.
Bundled Payments and Gainsharing

In August, CMS announced the request for proposals related to four bundled payment/gainsharing programs. CMS has a history of demonstration projects in this area, and its current efforts are built from the validated successes of other projects in bundled payments and gainsharing. It’s estimated that, in 2000, Medicare reimbursed hospitals approximately $5.8 billion on cardiac percutaneous cardiac interventions and another $7 billion on coronary artery bypass surgery. These amounts are staggering, and growing costs have made cardiac procedures an important target for the past 20 years of innovative, cost-decreasing, quality-assuring models.

The first cardiac bundled-payment demonstration project, which involved coronary artery bypass surgery, began in the early 1990s. This project demonstrated that bundled payments with gainsharing led to substantial savings for Medicare, higher profits for hospitals, better payment for physicians, higher quality of care, and improved patient satisfaction. According to the final report published by CMS contractor Health Economics Research, the physicians were most responsible for significantly decreasing variable costs.

The hospital with the greatest cost decreases was Saint Joseph’s Hospital of Atlanta (SJHA), which demonstrated a variable cost decrease of 25% in DRG 106 (coronary artery bypass graft with a cardiac catherization) and a 41% cost decrease in DRG 107 (coronary artery bypass graft without a cardiac catheterization). The largest components of variable cost reductions were seen in operating room and intensive care units and included staffing, drugs, and supplies. Although some fixed costs increased during this time, the substantial decreases in variable cost meant the hospital profited. Before the project, the net income per case for Medicare DRG 106 was $1,482 and, afterward, the net income was $2,126—a 43% increase 3 years into the project. DRG 107 showed even more favorable results: SJHA’s initial net profit of $891 per case grew to $3,513 per case.

SJHA implemented a gainsharing program that yielded similar positive results. Physicians supplemented their fees with 25% of the savings they generated. The cardiac surgeons’ reimbursement increased 28% from their original discounted rates, 3% more than their actual reimbursements at the time the project started. Both anesthesiologists’ and cardiologists’ reimbursements increased by more than 20%. CMS reported a $5.5 million savings from the SJHA project based on the discount given.

In 2009, CMS began the Acute Care Episode (ACE) Demonstration project. This project bundles hospital and physician payments for all cardiac and orthopedic procedures, and the gainsharing guidelines let the hospital pay physicians up to 25% of their total professional fees. There are no formal, published results on this project at this time, but the participating hospitals and physicians are reporting outcomes similarly positive to those of Medicare Coronary Artery Bypass Demonstration.

Initiatives Affecting STEMI Care

Reform of the current economic system for providers has several key goals: decreasing the variation in patient care practices, increasing documented quality, decreasing readmission rates, and decreasing the cost of care and the growth of costs. The future economic environment will reverse the incentives that reward volume-based care in favor of quality-based care. We have already seen new bundled-payment projects in acute and non-acute phases of care, penalties for high readmission rates, and alternative pay for performance models being implemented. Each of these affects how STEMI care is delivered and how providers will be paid in the future.

In August, CMS announced two significant initiatives. One was the readmission rule, and the second related to a new, expanded-bundled payment initiative. Although they appear to be unrelated, their coexistence indicates where CMS payment changes will occur for hospitals and physicians. However, the lack of consistent language in these CMS initiatives confuses the future for hospitals and physicians.

This is an unintended consequence of the two payment systems—one for hospitals (Medicare Part A), one for physicians (Medicare Part B). For example, when hospital reimbursement is discussed, the term heart attack or myocardial infarction (MI)
The Changing Landscape of the Healthcare System: Implications for STEMI Care

is considered a category for patients. For physicians, MI covers a broad spectrum of patients, and a STEMI patient is a defined medical category. As CMS attempts to align the incentives of care between Medicare Part A and Part B reimbursements, the policies may be applied over a spectrum of patients instead of a particular category.

For example, a new CMS policy concerning hospital reimbursement penalizes hospitals who fall in the top 25% for readmissions within 30 days of discharge for heart attacks. According to the published methodology, patients have been risk-adjusted, so CMS is making comparisons between similar populations nationwide. This change is important to physicians, especially cardiologists, because it is the physician who controls patient care, not the hospital.

Variations in Patient Care

According to CMS, the average rate of readmission within 30 days of a heart attack nationally is 19.8%. This does not include planned coronary interventional readmissions. Currently, 50.4% of hospitals exceed this average. The data have been assessed on many levels, including urban compared to rural, teaching to non-teaching, among bed capacities, and hospital region; no correlation has been identified to delineate practice patterns (see Table 2).

It is this type of variation that is considered a waste of resources. As the care variations for heart attack patients for hospitals are published, the diversity of care in these patients will be examined, and physicians will need to adjust practice patterns that fall outside the norm. Although many are concerned that diverse patient populations are not accounted for when data are studied, there is no evidence that this is an accurate assumption.

Readmissions After Heart Attack

Researchers have actually found very few correlations on readmissions. One researcher’s work on understanding why readmissions differ concluded, “The study also demonstrated that many of the hospitals with higher readmission rates for patients with heart attack did not always receive information on what to do when they were discharged for recovery at home. Other county level predictors did not accurately predict readmission rates for heart attack and none were significant for heart failure and pneumonia diagnosis. Other factors which according to the literature affect readmission, such as gender and socioeconomic status were not significant at the county level.” Understanding the root causes of readmissions will be new information for physicians to use to determine where quality and cost can be improved.

In 2008, the Congressional Budget Office produced a report that highlighted the quality and economic opportunity of decreasing unnecessary readmissions. It estimated that reducing payments to hospitals with readmission rates above the 75th percentile compared with their peers would save $2.5 billion by 2014 and $8.1 billion by 2019. Importantly, the report stated that this approach would work especially well with a bundled payment system. This would economically align hospitals and physicians, which would lead to development of the best care pathway for patients.

Developing Payment Models

A week after the readmission penalty for hospital rule was finalized, CMS announced four new bundled payment/gain-sharing initiatives. These models let providers design their own
bundled payments and episodes of care, within parameters. Model 2 is described as the acute hospital stay plus the post-acute period to be defined by the provider. CMS suggests two post-hospitalization periods of a minimum of 30 days to more than 90 days of care.\(^{15}\) The care of a STEMI patient will be used as an example to demonstrate how this could benefit the patients, the providers, and CMS.

In the bundled payment project, CMS is looking for hospitals and physicians interested in accepting a discount on the current average total revenue per patient condition. It's hard to view the proposition of discounting revenue — when reimbursement has consistently decreased for 10 years — as an opportunity. In addition, these discounts carry no additional volume guarantee. However, the new bundled payment initiatives give hospitals and physicians the ability to reengineer the way care is provided to patients. This is validated by tremendous differences in practice patterns of the care for the same type of patient. Opportunities for decreasing excess costs occur during hospital admission and after the patient is discharged.

A STEMI patient receives care during an initial hospital stay, and the current reimbursement from CMS for a specific MS-DRG to the hospital is $15,000. During the same admission, the physician reimbursement is $3,000 — for all patients involved in the care of the patient, including services such as radiology and emergency room. In this scenario, the total bundled payment baseline is $18,000.

If this patient is readmitted to the hospital within 30 days, the total average for Medicare parts A and B could potentially double to $36,000, depending on the actual diagnosis and treatment during the second admission. If 20% of STEMI patients are readmitted within 30 days, CMS is paying the hospitals and physicians an average of $21,600 for initial and readmission care of the patient. This does not include any other services rendered outside the hospital. Under a bundled payment scenario, CMS would pay providers the average amount of reimbursement that is paid today for the care of these patients, minus a small discount. CMS has suggested a guideline of a 3% discount from Part A when providers agree to accept the risk of care for at least 30 days (Table 3).\(^{15}\)

Providers can propose an episode of care where they believe there is opportunity to ensure quality of care and decrease waste in the system. The example of heart attack readmissions can be tied to the bundled payment opportunity in Model 2. With the readmission rule, hospitals are already at risk for decreased reimbursement if their readmissions are in the uppermost quartile nationally. Under the bundled payment scenario, hospitals are allowed to pay physicians up to 50% of the base fee schedule based on the savings generated for these patients (Table 4). This is an excellent opportunity for providers who are willing to reengineer the way care is provided to patients. This is validated by tremendous differences in practice patterns of the care for the same type of patient. Opportunities for decreasing excess costs occur during hospital admission and after the patient is discharged.

In 2006, an American Heart Association initiative was adopted to improve and standardize the principles of STEMI care. This resulted in the development of “systems of care,” which included nine key recommendations in the treatment of STEMI patients (Table 5).\(^{15}\) It is this type of effort that would be used to examine quality and cost of all phases of STEMI

<table>
<thead>
<tr>
<th>Criteria for beneficiary inclusion in episode:</th>
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<tr>
<td>• Organized around reason for hospitalization (MS-DRG)</td>
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<tr>
<td>• Exact identification criteria to be proposed.</td>
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<tr>
<th>Episode anchor:</th>
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<tr>
<td>• Acute care hospital admission at awardee or bundled payment-participating organization for included clinical conditions (identified via MS-DRG)</td>
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<tr>
<th>End of episode:</th>
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<tr>
<td>• Option 1: Minimum 30 days post-hospital discharge; maximum 89 days post-hospital discharge</td>
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<tr>
<td>• Option 2: Minimum 90 days post-hospital discharge.</td>
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<th>Types of services included in bundle:</th>
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<tr>
<td>• Physicians’ services</td>
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<tr>
<td>• Inpatient hospital services (episode anchor)</td>
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<tr>
<td>• Inpatient hospital-readmission services.</td>
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<tr>
<td>• Long-term care hospital services</td>
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<tr>
<td>• Inpatient-rehabilitation facility services</td>
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<tr>
<td>• Skilled-nursing facility services</td>
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<td>• Home-health agency services</td>
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<td>• Hospital outpatient services</td>
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<td>• Independent outpatient therapy services</td>
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<td>• Clinical laboratory services</td>
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<td>• Durable medical equipment</td>
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<td>• Part B drugs</td>
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<th>Payment from CMS to providers:</th>
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<tr>
<td>• Traditional FFS (ultimate reconciliation with predetermined target price)</td>
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<tr>
<th>Expected discount provided to Medicare:</th>
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<tr>
<td>• Option 1: Minimum 3% discount on included Part A and Part B allowed charges for episodes that include a post-hospital discharge period of 30 days to 89 days</td>
</tr>
<tr>
<td>• Option 2: Minimum 2% discount on included Part A and Part B allowed charges for episodes that include a post-hospital discharge period of 90 days or longer</td>
</tr>
<tr>
<td>• Exact discount rate to be proposed under either option.</td>
</tr>
</tbody>
</table>

care, including medications, devices, lengths of admission, post-discharge follow-up care, complications, and criteria for readmission. When physicians and hospitals accept economic long-term risk for an episode of care, there is an additional opportunity to ensure outcomes post-hospitalization are also captured as part of the care decision-making process. Quality is measured first, then differences in costs are accessed. For example, one of the key data points about STEMI patients to uncover is the exact causes of readmissions.

**Conclusion**

Data for readmission of all types of patients is lacking the specificity of clinical information. This creates a dilemma in understanding the exact steps to be taken to decrease unnecessary readmissions. However, capturing data on the care of these patients post-hospital discharge will lead only to improved overall outcomes and decreased costs.

For example, the HORIZONS-AMI trial has examined stent types and the use of anticoagulants for long-term survival. Conclusions from this trial should be evaluated by clinicians to determine if practice patterns should be adjusted or if more data are needed. It is up to physicians to drive the best overall outcomes for patients, and the new market of care will economically reward them for quality of care rather than quantity of care.

Opportunities exist in every type of patient care scenario, including all treatment of cardiac patients. Many may argue this is just about costs, but delivery of care to all types of patients does differ. Studies consistently demonstrate these variances represent areas for improvement. Changing the system of care is hard work, however, and physicians must be reimbursed for the time and effort this requires. Data should include utilization, clinical, and cost comparisons that ensure accurate measurement and comparisons between patients, doctors, and hospitals. This would demonstrate where opportunities exist in current clinical practice to continually improve the quality of the outcome with a focus on the overall costs benefit.

Patients are not aware delivery of care varies so much. Many physicians believe they are providing the best standard of care. When the evidence is examined objectively, it is clear that there cannot be so many different ways to deliver the best patient care. The opportunity is to accept that our health system is moving from a volume payment system to a value-based payment system. The change is difficult, but one that will reward physicians who take the lead. There is a unique opportunity to be paid for determining the best practice of medicine — which includes identifying where the inefficiencies exist in our current health system.

**References**

mments/payment-care/BundledPayments-Request_for_Application_v4.pdf

Table 5. Development of systems of care for ST-elevation myocardial infarction: patient principles

| 1. Patient-centered care is the No. 1 priority. |
| 2. Care should be high-quality, safe, effective, and timely. |
| 3. Stakeholders come to consensus on systems infrastructure. |
| 4. Increase operational efficiencies. |
| 5. Use appropriate quality incentives, such as pay for performance, pay for value, or pay for quality. |
| 6. Devise measurable patient outcomes; measure patient outcomes. |
| 7. Use an evaluation mechanism to ensure that quality-of-care measures reflect changes in evidence-based research, including consensus-based treatment guidelines. |
| 8. Local community hospitals should play a role so as to avoid a negative impact that could eliminate critical access to local healthcare. |
| 9. Reduce disparities of healthcare delivery, such as those across economic, educational, racial/ethnic, or geographic boundaries. |

Source: http://circ.ahajournals.org/content/116/2/217.full
Regional Systems of Care: An Interventional Laboratory Perspective

Daniel Muñoz, MD; Mayme L. Roettig, RN, MSN; James G. Jollis, MD

Rapidly achieving coronary myocardial reperfusion in ST-segment elevation myocardial infarction (STEMI) depends highly on how emergency personnel act and what they decide long before patients reach the cardiac catheterization laboratory. Recognizing the importance of these early choices, percutaneous coronary intervention (PCI) hospitals have established relationships and protocols with referring hospitals and emergency medical services (EMS) that are designed to expedite primary PCI. The earliest arrangements involved coordination between a single large PCI center and referring hospitals in a hub-and-spoke model.

Moving From Hub-and-Spoke to Regionalized Systems

Based on the trauma prototype, the Minneapolis Heart Institute established one of the first and most successful systems, the Level 1 MI Program, led by Larsen, Unger, and Henry. This system that established standard protocols and expedited transfer to Abbott Northwestern Hospital from hospitals up to 120 miles away serves as a regional and national model that has been successfully emulated by many PCI centers.

The next advancement in rapid reperfusion involved the establishment of regional STEMI systems — defined as those that include all PCI hospitals within a region, establish common hospital and EMS protocols, and share common data. Although more challenging to organize than single-center arrangements, such a unified regional approach lets emergency physicians and paramedics promptly apply the same diagnostic and treatment algorithms independent of each patient’s final destination.

The most important element in timely emergency cardiac care involves the ability to follow a single, pre-established plan in which everyone knows their roles and steps can be executed in parallel. By removing as many decision points as is reasonably possible, treatment is greatly accelerated. Furthermore, referring hospitals and EMS agencies are more likely to be empowered by a unified message from all PCI centers, in contrast to the delay and fragmentation that results from protocol variability across receiving institutions.

Regional STEMI systems therefore bridge the substantial healthcare gaps between competing institutions and coordinate agencies that normally function under different leadership. The principles of regional STEMI systems have been codified by the American Heart Association (AHA) Mission: Lifeline project.

Establishing a Regional System

Successfully forming a regional system hinges on commitment to several fundamental elements: leadership, regional coordinators, data collection, and funding. Identifying effective regional leadership is crucial. Systems that cross institutions and encompass competing entities must be led by a broad vision of patient care that transcends the more-narrow interests of individual entities and stakeholders. Such leadership is critical in developing consensus, establishing policies, and supporting key front-line personnel with less cardiology expertise and system influence — personnel including EMS paramedics, nurses, and emergency physicians.

Leadership teams should span multiple disciplines and include interventional cardiology, emergency medicine, managers from the emergency department and catheterization laboratory, EMS directors, and quality improvement specialists. When initially establishing regional leadership, consider calling in select national STEMI-systems experts to guide leadership-team formation, inject neutrality into overcoming competitive obstacles, and provide strategic and tactical direction for early success.

After leadership, another key element of success involves data. Without access to timely, relevant information spanning the STEMI care process from symptom onset to device activation and hospital outcome, regional care cannot be meaningfully implemented. Fortunately, multiple data collection resources are widely available, and data plans that integrate a region’s hospitals and EMS agencies can be established.

In support of regional STEMI systems, the most widely applied registry is ACTION Registry-Get With The Guidelines (GWTG). This registry, maintained by the National Cardiovascular Data Registry (NCDR) and implemented in more than 500 hospitals, incorporates every data element essential to implementing timely primary PCI, including EMS and emergency department processes. Supported by the AHA Mission: Lifeline initiative, STEMI system reports are made available to regions on a quarterly basis (Figure 2). Alternative data sources include regional EMS registries and the NCDS CathPCI registry. The latter data, collected in the majority of tertiary care hospitals, does not include some data points important to system coordination, including first medical contact by EMS, transfer time for referring hospitals, and data regarding untreated eligible STEMI patients.

An integral component in building successful regional systems involves regional STEMI systems coordinators. Coordinators typically combine expertise in cardiac care, emergency care, and registry data, with the interpersonal skills necessary to engage a broad array of healthcare professionals. On a daily basis, coordinators actively implement coordinated STEMI care,
Regional Systems of Care: An Interventional Laboratory Perspective

Figure 1. Approach to establishing a regional ST-segment elevation myocardial infarction system.

1) Develop leadership, funding, data structure
2) Establish REGIONAL PCI CENTERS
   (primary, lytic ineligible, rescue)
3a) HOSPITAL by hospital establishment of STEMI plan
   (review, consensus, training)
3b) EMS by EMS establishment of STEMI plan
   (review, consensus, training)
4) Improve system
   Measurement & Feedback

educate regarding diagnosis and treatment, establish common protocols among hospitals and EMS agencies, troubleshoot systematic barriers, train hospital and emergency personnel, and review data with participants. When establishing a regional system, coordinators who are responsible for all PCI centers in a region are most effective in implementing care. Once a regional system is established, these duties may be assumed by emergency cardiac care coordinators or cardiology outreach personnel at individual hospitals.

Most of the elements needed for regional care are already in place and paid for with existing resources. A few elements, particularly those that span multiple health systems or support regional leadership require additional funding. While data collection efforts are often in place in many hospitals and EMS agencies, additional funding is required to support the development of system-wide data.

These funds mainly support:
- regional aggregation of data through an agreed-upon neutral intermediary; and
- performance of aggregate analyses and feedback to provide regional benchmarks, identify opportunities for improvement, and track progress.

Funding is also required to support the neutral regional STEMI systems coordinators and the STEMI region’s organizational activities including meetings, training materials and activities, and travel.

Numerous models for funding STEMI systems exist, including enlisting support from local or national foundations, individual philanthropy, large third-party payers, hospital associations, EMS agencies, participating PCI centers, and industry. Local AHA affiliates can be called upon to help obtain funding. Notable successful examples include funding of Mission: Lifeline interventions in Dallas County by the Caruth Foundation and South Dakota by the Helmsley Charitable Trust. Hospital systems may be induced to support STEMI systems by redirecting marketing and quality-assurance resources toward system development.5 Third-party payers have funded systems to improve care, obtain data, and manage costs on a regional or state level.11

Once funding has been obtained, and leadership, data plans, and regional coordinators are in place, regional systems should be implemented according to the approach outlined in Figure 1. Regional PCI hospitals should establish protocols for proving rapid primary PCI according to established standards: single phone-call activation, acceptance of all patients regardless of bed availability, catheterization laboratory availability within 30 minutes of activation, participation in STEMI system data registry, and support of a regional coordinator.

Supported by regional PCI hospitals, regional coordinators should then approach every hospital and EMS agency individually to establish a plan for promptly diagnosing and treating STEMI. Emergency medical systems plans should include a 12-lead ECG for every patient with suspected myocardial infarction (MI), paramedic or machine interpretation of that ECG, direct activation of the catheterization laboratory from the field, and diversion to a PCI hospital for patients who are not eligible for fibrinolysis and those who can be reliably intervened upon with 90 minutes of first medical contact. Emergency department plans should include a triage for chest pain before registration, a dedicated area for ECG performance, a structured process for handing every ECG to the emergency physician, and establishing a coronary reperfusion plan involving PCI or fibrinolysis to be initiated by the emergency physician.

Agreed-upon data elements should be collected immediately after interventions from participating hospitals and EMS agencies. While each PCI center should provide real time case-by-case feedback to system partners, the regional coordinators provide aggregate data to EMS and non-PCI centers in quality improvement meetings.

Accelerating Laboratory Activation and Improving Laboratory Door-to-Device Times

The ultimate goal of the regional STEMI system is to accelerate primary PCI, literally aborting MI in the fastest cases. With detailed attention to protocols and execution in the upstream setting, catheterization laboratory performance and, ultimately, patient outcomes can be greatly enhanced.1,3,12 The most important upstream processes can be categorized according to laboratory activation, patient transportation, treatment protocols, and laboratory organization. Figure 3 outlines key steps in the process of primary PCI and highlights important tactics for achieving shorter overall door-to-device times.

In the case of laboratory activation, the criteria for emergent coronary angiography should be clearly defined, uniform, and well supported by training and ongoing feedback, particularly for paramedics. The presence of characteristic symptoms and an ECG with ST-segment elevation of 1 mm in at least two contiguous leads represents a diagnostic starting point.

Systematically, potential activations take on one of two forms, according to “definite” or “possible” ECG findings. Activation should focus on patients with clear diagnoses, based either on convincing ECG findings or, in the case of EMS, high-likelihood ECG “machine interpretations” such as “***acute MI suspected***.” For patients in the category of “possible” MI, further diagnostic consideration should occur via mechanisms such as ECG transmission to a cardiologist or emergency physician.

To encourage paramedics and emergency physicians to call routinely, a certain rate of over-triage is to be expected, generally on the order of 5% of cases for emergency physicians and 20%
of cases for paramedics.\textsuperscript{13,14} Protocols should also specify patients deemed inappropriate for urgent coronary angiography, including those unwilling to consent to the procedure and those with definite contraindication such as active profuse bleeding. In all cases, involving the interventional cardiologist in early review of critical patient data most efficiently enhances system performance.

Depending on the region and PCI hospital, more than half of patients directed to a busy interventional laboratory require inter-hospital transport. Efficient transfer can greatly enhance laboratory performance. Whenever possible, hospitals should use locally available transportation options, including the ambulance that originally took the patient to the first hospital, for transferring patients. Patients with suspected MI should remain on the EMS stretcher while being evaluated for rapid transfer. Unless remotely and strategically located, air transport rarely accelerates transfer, as the faster travel time is offset by the time required to deploy air crews to remote locations.\textsuperscript{15} Transfer should not be delayed for the copying of patient records and forms. Such data can be electronically delivered directly to the receiving laboratory while the patient is in transport.

Catheterization laboratories should take advantage of the transport delay to prepare for rapid intervention upon patient arrival. Patients should be pre-registered or assigned a dummy registration number similar to trauma patient processes so as to not delay treatment on arrival. Whenever possible, patients should proceed directly to the table on arrival.

From an Emergency Transportation and Labor Act (EMTALA) standpoint, urgent coronary angiography should be considered in a framework similar to that of pregnant women’s proceeding directly to labor and delivery without the

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Sample Mission: Lifeline Systems Report performance by hospital.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Anatomy of a primary percutaneous coronary intervention system. ACC = American College of Cardiology, AHA = American Heart Association, CP = chest pain, ECG = electrocardiogram, EMS = emergency medical system, ER = emergency room, IV = intravenous catheter, MD = medical doctor, PCI = percutaneous coronary intervention, t = time from patient arrival to initial hospital.}
\end{figure}
need for emergency physician evaluation. The intervention- 
al cardiologist serves as the physician of recording in provid- 
ing the EMTALA-mandated medical evaluation.

If the catheterization laboratory is not ready due to short 
transport times and off-hours activation delays, the emer- 
gency department remains an important stopping point 
while awaiting laboratory availability. Whenever possible, 
critical care transport crews should prepare patients by

* establishing a working intravenous line in the left arm 
  with tubing compatible with the receiving hospital,
* removing patient’s clothing, and
* preparing the femoral access site when appropriate.

Timely, coordinated coronary intervention depends 
highly on treatment protocols that are standardized and 
simple. Establishing a single, widely accepted plan that can 
be rapidly instituted across emergency departments and 
EMS agencies should take precedence over protocols cus- 
tomized according to the receiving interventional cardio- 
lgist or laboratory.

In the case of EMS, aspirin and a load-and-go approach 
should be sufficient. In the case of emergency departments, 
aspirin, heparin bolus, and a standard p2y12 antagonist 
regimen (e.g., clopidogrel 600 mg) should be sufficient. 
Upon catheterization laboratory arrival, bivalirudin should 
generally be administered.16,17 The interventional cardiolo- 
gist can further refine treatment regimens according to their 
expertise and preference. Continuous infusion drips should 
be avoided whenever possible, as they significant delay tub- 
ing-set changes and limit some EMS agencies’ abilities to 
transport patients.

Protocols for treating simultaneous STEMI patients 
should established in a prospective fashion. These may in- 
clude activation of a second laboratory team, staging pa- 
tients according to procedural complexity and expected 
completion time, and initiation of fibrinolysis for patients at 
lower risk of bleeding who would otherwise be significantly 
delayed for coronary intervention.

Crucial to rapid coronary intervention is developing 
catheterization laboratory teams that are highly organized 
and efficient in providing primary PCI. The team should 
map every process and capitalize on every opportunity to 
save time or improve efficiency. As a national standard, me- 
dian laboratory door-to-device times are approaching 24 
minutes, and the best systems intervene within 20 minutes 
for the most straightforward cases.10

Teams of nurses and technicians can be trained to func- 
tion in a coordinated fashion — everyone knows their roles 
in preparing the facility and treating the patient. Whenever 
possible, the processes required for intervention should be 
performed in parallel, rather than sequentially. Focusing on 
laboratory readiness within 20 minutes, staff should have 
designated parking immediately adjacent to the laboratory 
and on-site sleeping facilities whenever possible.18 To the 
greatest extent possible, laboratory equipment and devices 
should be pre-set before activation.

In the absence of a prominent murmur or unexplained 
shock, ventriculography should be delayed to the end of the 
case. Some interventionalists choose to open the infarct-re- 
lated artery before taking diagnostic images of the remaining 
coronary tree.

Most importantly, every aspect of system performance, 
from laboratory activation to procedure performance, 
should be measured and reviewed on an ongoing basis. Im- 
mmediately after PCI completion, the communication center 
that initially received the call should put the interventional 
cardiologist in contact with the referring physician or EMS 
agency. Procedure summaries including actual and target 
performance should be circulated within 24 hours for review 
and comment, with particular attention to systematic pro- 
cesses that may be improved. Data should also be reviewed 
in monthly meetings that include EMS, emergency depart- 
ment, catheterization laboratory colleagues, and hospital 
administrators who have the ability to change processes and 
 improve the system.

Regional STEMI system development offers multi-di-

Regional Systems of Care: An Interventional Laboratory Perspective

Conclusions

Many decisions and processes that occur long before a 
patient reaches the interventional catheterization laboratory 
have substantial influence on laboratory performance and 
time to treatment. The most effective approach to expediting 
care and effectively providing coronary artery reperfu- 
sion involves establishing regional STEMI systems. Defined 
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Conclusions

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establishes common hospital and EMS protocols, and 
shares common data, these organizations let emergency phy-

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11


Unfractionated Heparin: Still Going Strong — Despite Limitations and Evidence

David C. Sane, MD

Heparin was discovered by a medical student, J. McLean, in 1916 while he was searching for a coagulant in canine liver and has been used therapeutically since clinical trials in the 1930s. Today, heparin remains widely used both in cardiovascular therapy and throughout broader medical practice. Heparin's chief attributes include practitioner familiarity, availability of intravenous and subcutaneous administration, ability to monitor with the aPTT, reversibility with protamine, and lack of adjustment required in patients with renal failure.

Nevertheless, an accumulating body of evidence has highlighted the limitations of heparin and the benefits of alternative anticoagulants. Indeed, considerable literature points to superior outcomes with low molecular weight heparins, the synthetic pentasaccharide fondaparinux, and parenteral direct thrombin inhibitors, especially bivalirudin. Furthermore, with the early clinical trials success of oral direct thrombin and factor Xa inhibitors, and the early clinical trials success that these agents have demonstrated, it is time to update the concerns about unfractionated heparin (UFH) and to re-examine its place for therapy of patients with cardiovascular disease.

Heparin Mechanisms of Action

Heparin alone has no anticoagulant activity. Brinkhous and colleagues demonstrated in 1939 that the anticoagulant effect of heparin requires a plasma cofactor, subsequently called antithrombin (AT) III. The mechanism by which heparin catalyzes the inhibition of thrombin by ATIII was described in the 1970s. UFH binds to ATIII (now referred to simply as antithrombin/AT), causing a conformational change that renders AT a much more efficient inhibitor of the serine proteases thrombin (factor IIa), causing a conformational change that renders AT a much more efficient inhibitor of the serine proteases thrombin (factor IIa), factors IXa, Xa, XIIa, and kallikrein.

Heparin is a heterogeneous mixture of sulfated glycosaminoglycans with a mean molecular weight of 15 kilodaltons (kDa) but a broad range of 3–30 kDa. A pentasaccharide sequence, present in only about one-third of all UFH molecules, shows high affinity for AT, and can induce the structural change. For catalysis of Factor Xa inhibition, this conformational change in AT is sufficient.

For inhibiting thrombin (factor IIa), heparin must bind to both AT and thrombin, generating a ternary complex that unites the serine protease and its inhibitor. For this effect, a saccharide unit of 18 or longer is required. UFH contains lower molecular weight components with predominantly anti-factor Xa activity, along with higher weight components with both anti-IIa and anti-Xa activities. Overall, UFH catalyzes the inhibition of factors IIa and Xa with similar efficacies. Lower molecular weight heparin (LMWH) has a molecular weight (MW) of ~5 kDa and less than half the molecules can form the ternary complex of factor IIa, heparin, and AT. Consequently, LMWH has more anti-Xa than anti-IIa activity (typically by a ratio of 2–3:1), depending on the exact chain length.

Fondaparinux, the synthetic pentasaccharide sequence, has exclusively anti-Xa inhibition. UFH has at least two other anticoagulant effects:

- At high concentrations, it activates the anti-thrombin activity of heparin cofactor II, although HC-II may function primarily at extravascular sites.
- It releases TFPI from endothelial cells (EC), which then blocks factor Xa and, subsequently, the factor VIIa-tissue factor complex.

Unfractionated Heparin Has Complex Pharmacology

UFH has unpredictable pharmacology with variable half-life and coagulation effect, especially after subcutaneous administration. Heparin's half-life is dose-dependent, with a longer half-life for IV doses. There is an initial, rapid, saturable clearance phase due to reversible binding to cells, including EC and macrophages. After these binding sites are saturated, the slower clearance phase predominantly reflects renal clearance. Cellular binding is greater with longer-chain heparin molecules. Macrophages internalize UFH and depolymerize it, releasing fragments that are cleared by the kidneys. These smaller heparin fragments and the shorter, native, infused-heparin molecules are cleared more slowly, have more anti-Xa than anti-IIa activity and, therefore, are not as readily detected by the aPTT assay.

One of the major determinants of variability in anticoagulant response to UFH is binding to plasma proteins with concentrations that vary in different patients. The longer-MW UFH molecules bind more readily than LMWH to plasma proteins. Consequently, LMWH and fondaparinux have more predictable, less-variable anticoagulant responses after fixed dose. At the extreme, plasma heparin-binding proteins can completely neutralize the UFH's anticoagulant effect, producing heparin resistance. Protein binding also generates paradoxical pro-thrombotic responses to heparin.
by eliciting PF4/heparin antibodies or activating platelets, as discussed later.

Bivalirudin has more predictable pharmacology, with few or no protein-protein interactions other than its target (thrombin) and, therefore, its activity is not neutralized by proteins such as PF4. Its short half-life of about 25 minutes allows a quick return to baseline hemostatic activity upon discontinuation. Unlike heparins, bivalirudin does not activate platelets. Because it lacks the strong ionic charge of heparin and does not require cofactors, it is able to inhibit clot-bound thrombin.17

Heparin Resistance in ACS

Rich et al examined anticoagulant response variability and plasma heparin resistance in normal volunteers, patients with stable CAD, and patients with ACS (unstable and acute MI, STEMI and NSTEMI).18 They compared anticoagulant responses when fixed doses of either UFH or bivalirudin were spiked into these plasmas with monitoring of aPTT. The aPTT decreased significantly with increasing severity of manifestations of CAD. In normal volunteers the aPTT was 443 ± 137% of baseline, while in patients with acute MI the value was significantly reduced to 230 ± 120% of baseline.18

In contrast, the aPTT did not differ significantly in the four groups of plasmas treated with bivalirudin. Furthermore, there was significantly more variability in the aPTT achieved in plasma from normal volunteers with UFH (standard deviation about 30% of the mean) compared with bivalirudin (standard deviation about 12% of the mean). The reduction in heparin activity in ACS patients did not correlate with levels of antithrombin or PF4. However, the authors concluded that other, as-yet-unidentified high-affinity heparin-binding proteins were responsible for this effect, because the addition of low affinity heparin could recover the anticoagulant activity of UFH by displacing it from binding to these plasma proteins.18

Among the known UFH binding proteins are von Willebrand factor, histidine rich glycoprotein, fibronectin, P-selectin, thrombospondin, vitronectin and platelet factor 4.19–20 Some of these proteins are acute-phase reactants that are elevated in sick patients with ACS and other acute medical illnesses. Patients with medical conditions causing platelet activation, such as ACS, or medical devices, such as IABP or cardiopulmonary bypass membranes, will have elevated levels of PF4. PF4 is a basic, positively charged protein that neutralizes heparin and in some patients generates the antigen for anti-PF4/heparin antibodies, the instigator of the HIT syndrome. Activated endothelial cells release vWF. Thus, sick patients, especially those with thrombotic conditions, may have disease-related mechanisms that generate heparin resistance. The very patient in whom an anticoagulant effect is desirable may be the most resistant.

Heparin Resistance in Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) is a condition accompanied by acute-phase reactant-protein expression and activation of platelets, which leads to the release of the heparin-binding protein PF4. Heparin resistance during CPB has been defined as the requirement for > 35,000 units of heparin over 24 hours to achieve a therapeutic aPTT ratio and is seen in up to 20% of patients having CPB.20 Risk factors for heparin resistance in this setting include age > 65 years, platelet count > 300,000/ mm3, and pre-operative AT level < 80% of normal.21 Of interest, recent heparin exposure is a risk factor for heparin resistance during CPB with at least one mechanism being through the acquisition of AT deficiency. However, the impact of acquired AT deficiency in heparin resistance during CPB is still debated. Garvin et al. have found no relationship between pre-operative AT activity and response to heparin using measures of the heparin dose response or the heparin sensitivity index.21

Heparin Activates Platelets

Heparin enhances the responsiveness of platelet to stimuli such as adenosine 5'-diphosphate.22–24 The activation of platelets is strongly correlated with chain length, with decreasing activation from UFH to dalteparin to enoxaparin.25 Recently, the mechanism for heparin-induced platelet activation was elucidated in greater detail than previously understood.

Gao and colleagues demonstrated that functional glycoprotein IIb/IIIa (GpIIb/IIIa or αIIbβ3) is required for heparin to promote platelet reactivity.26 Multivalent heparin was shown to interact with the receptor at or near its ligand binding site, resulting in clustering of fibrinogen receptors on the platelet surface, with subsequent outside-in platelet activation activation of src-family kinases and other downstream signaling pathways.20 Soluble heparin required a co-stimulator agonist to induce platelet aggregation, whereas immobilized heparin could activate platelets more potently via this mechanism,20 a concern for heparin-coated catheters and other devices.

Because the fibrinogen receptor has a central role in UFH-induced platelet activation, GpIIb/IIIa inhibitors are able to block this effect. Heparin also binds to other cell surface proteins including G6b, a novel inhibitory platelet receptor,27 as well the vitronectin receptor αvβ3 and the fibrinectin receptor α5β1,28 but the effects of these interactions are currently unknown.

Thrombocytopenia With Heparin: Not Always HIT, But Strongly Associated With Increased Mortality

Thrombocytopenia (TCP) due to heparin has historically been classified as HIT1 or HIT2. HIT1, or non-immune thrombocytopenia, occurring a few days after heparin and resolving with heparin discontinuation, was felt to be associated with few or no thrombotic risks, a view that is probably incorrect. Instead, mild non-immune thrombocytopenia occurring during UFH treatment may be due to platelet activation and, as a corollary, be predictive thrombotic events.

The high incidence of thrombocytopenia and the strong correlation between TCP and adverse events during heparin therapy has not been widely appreciated. This issue was studied carefully in the CATCH registry among more than 2400 patients with cardiac and non-cardiac illnesses in the medical
and surgical settings. More than one-third of patients (36.4%) treated with heparin for 4 days or more developed TCP, defined as an absolute platelet count of less than 150 X 10^9/L, or a reduction in count of 50% or more from admission level. The risk of TCP increased 4% per day beyond 4 days of heparin exposure.

In CATCH, the median time from initial heparin exposure to the diagnosis of TCP was 55 hours, with this early time frame perhaps explaining why less than 10% of patients in the CATCH registry were suspected of having HIT. TCP was associated with a 3.4-fold odds ratio for death, 2.1 for MI, and 1.3 for heart failure. If the platelet count fell by > 70% from baseline, the odds ratio for death was 13.4, and this was the strongest independent predictor of death.

TCP was more closely associated with UFH use, but also occurred with LMWH administration, especially if there had been prior UFH exposure. Less than 10% of patients in the CATCH registry were suspected of having HIT; among those who were tested for HIT, almost one-third were positive for PF4/heparin antibodies, heparin-induced platelet aggregation, or heparin-induced serotonin release. Extrapolating these data to the entire CATCH registry, the authors estimated that the overall incidence of HIT could be in the range of 10% in that population.

At 6 months' follow-up, mortality in the heparin-treated thrombocytopenic patients remained high. Thus, thrombocytopenia is strongly associated with adverse events even if the PF4/heparin antibody assay is negative. In light of this report, it is likely that thrombocytopenia occurring in this setting represents clearance of platelets that are non-specifically activated by heparin binding; any platelet activation occurring in a patient with ongoing thrombosis (e.g., ACS) increases the risk of recurrent or new events.

**HIT and HIT Antibodies**

As noted, the overall rate of HIT in medical patients treated with UFH may be as high as 10%. Patients with multiple episodes of ACS or having repeated diagnostic cardiac catheterizations or bypass surgeries may have even higher rate due to repeated exposure. Of even greater concern, several recent studies have shown that patients may develop PF4/heparin antibodies in the absence of prior heparin exposure.

In a survey of almost 4,000 blood donors, PF4/heparin antibody was detected in 4.3–6.6%, although 80% of these responses were in the low-positive range (OD 0.40–0.59). Antibody with ODs of > 1.0–1.4 are more likely to be associated with HIT. About 30% of the seropositive donors in the study had antibodies of intermediate or high positivity (OD > 0.60). Because the American Red Cross excludes patients who have been recently hospitalized or have had indications for UFH, it is likely that some of the donors developed PF4/heparin autoantibodies. Although low-level antibody titers — especially in the absence of thrombocytopenia — are less likely to be associated with clinical HIT; a growing body of evidence has linked antibody status to adverse outcomes even when the platelet count remains in the normal range.

The predominant form of antibodies to the PF4/complex is IgG, which is unusual for a primary immune response (usually IgM). Serum from healthy subjects can have PF4/heparin antibodies, and cases of spontaneous HIT without prior heparin exposure have been reported. Recently, an explanation for formation of PF4/heparin antibodies without heparin exposure has emerged.

PF4 binds charge-dependent to various bacteria (e.g., *Staphylococcus*, *E Coli* and periodontal pathogens), and the bacteria/PF4 complex created an immune response, eliciting antibodies that bind to PF4/heparin. Thus, the primary immune response (IgM) may be to PF4-coated bacteria, with UFH treatment boosting the initial immune response with subsequent generation of IgG antibodies.

As support for this model, mice develop PF4/heparin antibodies in a model of polymicrobial sepsis, without heparin exposure. Boosting of preformed B cells by PF4/heparin exposure could explain why IgG antibodies occur early in some patients. Bacteria present in periodontitis may be the immunization infection, which generates PF4/bacterial antibodies that cross-react with PF4/heparin antibodies. Periodontitis and presence of PF4/heparin antibodies are strongly associated.

**Coagulant Activity Inaccessible to UFH**

Due to its size, negative charge and dependence on ternary complex formation for thrombin inhibition, UFH is an ineffective inhibitor of thrombus-bound thrombin factor Xa or factor Xa on the platelet surface (a component of the prothrombinase complex). Direct thrombin and factor Xa inhibitors are able to inhibit these heparin-resistant pro-coagulant activities. However, because both activities are present in the thrombus, highly specific direct Xa inhibitors have the limitation of failing to inhibit thrombin that has already been generated, probably explaining the increased occurrence of catheter-related thrombus observed in OASIS-5 and OASIS-6 trials using fondaparinux. This finding has led to the use of supplemental UFH as a source of an anti-thrombin agent at the time of PCI.

**Limitations of the aPTT Assay**

One of the reasons physicians choose UFH is the wide availability of the aPTT assay and their familiarity with it. However, the use of this assay is not based on randomized controlled trials and there is significant intra- and inter-patient variability. Artefactual heparin resistance is seen with elevated factor VIII levels in conditions such as pregnancy and burns; failure to recognize this effect can lead to overdosing. The aPTT is influenced by age, weight, smoking, and gender. At a therapeutic range of heparin — as determined by the factor Xa assay — the aPTT ratio (to normal control) has been reported to vary between 1.6–6.2.

**Clinical Trials Data: How Does UFH Compare With LMWH, Fondaparinux, and Bivalirudin?**

A. **LMWH tends to be better than UFH in NSTE-A CS patients.**

A meta-analysis of trials involving 21,946 patients with NSTE-ACS randomized to enoxaparin versus heparin showed
death at 30 days did not differ between the treatments, but there was a significant reduction in death or MI at 30-days in favor of enoxaparin (OR 0.91; 95% CI 0.83–0.99). No differences in blood transfusion or major bleeding were seen at 7 days after randomization.42

In a subsequent meta-analysis, the net clinical endpoint of death, MI, or major bleeding at 30 days was examined, and the entire ACS spectrum (NSTE-ACS and STEMI) was included. In 12 randomized trials of enoxaparin versus UFH in more than 49,000 STEMI or NSTE-ACS patients, death or MI was significantly reduced with enoxaparin compared to UFH OR 0.84, P < 0.001). Although major bleeding was higher with enoxaparin compared with UFH (OR 1.25; P = 0.019), the net clinical endpoint remained significantly lower with enoxaparin versus UFH for STEMI — although it was not significantly different for NSTE-ACS patients.43 Among STEMI patients, 21 deaths or MIs were prevented for every 1000 patients treated with enoxaparin, at the cost of four more non-fatal major bleeds.43 For NSTE-ACS patients, nine deaths or MIs were prevented for every 1000 patients treated with enoxaparin at the cost of eight more non-fatal major bleeds.43

The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial included more than 10,000 high risk patients undergoing consideration for early revascularization.44 Death nor MI did not differ at 30 days in the group treated with enoxaparin versus UFH. There was a statistically significant increase in TIMI major bleeding (9.1% versus 7.6%, P = 0.008) with enoxaparin, but only a trend toward increase in GUSTO severe bleeding. The higher bleeding rate was felt to be due to a high rate of prerandomization anticoagulant therapy with subsequent stacking of anticoagulants in the post-randomization period.

Thus, with the exception of the SYNERGY trial, the bulk of contemporary RCTs shows an edge for LMWH in treating NSTE-ACS patients.

B. Bivalirudin is preferable to UFH plus abciximab in NSTEMI.

The ISAR-REACT 4 trial randomized 1721 NSTEMI patients to UFH plus abciximab or bivalirudin before PCI. There was no difference in ischemic endpoints between the 2 groups, but UFH plus abciximab had a significantly higher rate of major bleeding (4.6% versus 2.6%, relative risk 1.84; 95% CI: 1.10–3.07; P = 0.002).45 The results of ISAR-REACT 4 support those of ACUITY, in which bivalirudin treatment rather than heparin plus GPIIb/IIIa had similar ischemic outcomes, but with lower bleeding and thrombocytopenia in the former. Coupled with the HORIZONS-AMI trial, bivalirudin may be the preferred agent in PCI in patients with acute MI (either STEMI or NSTEMI).

C. LMWH tends to be better than UFH in STEMI patients receiving primary PCI.

The ATOLL study randomized more than 900 patients with STEMI undergoing primary PCI to either intravenous enoxaparin or UFH.46 The enoxaparin group showed a strong trend toward benefit in all causes of death, which persisted to 6 months.46 The primary endpoint — the 30-day rate of death/MI complications/procedural failure/major bleeding — also trended strongly in favor of enoxaparin.

In a meta-analysis of 10 studies (including ATOLL) with more than 16,000 patients, LMWH (predominantly enoxaparin) was associated with an approximately 50% reduction in mortality (risk reduction 0.51; P < 0.001) and > 30% reduction in major bleeding (RR 0.68; P = 0.02) compared with UFH.47 Patients with higher baseline risk had greater relative benefit with LMWH.

However, in patients treated with PCI after having first received thrombolysis, there was no definite advantage of LMWH over UFH.47 It could be hypothesized that plasmin generation during thrombolytic therapy reduces heparin-binding and neutralization activities of some plasma proteins.48

D. LMWH is better than UFH in STEMI patients receiving thrombolytic therapy, but increases major bleeding.

In patients receiving thrombolysis for STEMI, enoxaparin given during the hospital course was superior to UFH for 48 hours in the Exenaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction 25 (EXTRACT-TIMI 25) study.49 Enoxaparin reduced the primary combined endpoint of death or nonfatal recurrent MI — but not mortality as a single endpoint. The primary endpoint was driven by a 33% reduction in non-fatal reinfarction at 30 days.49 Although UFH was given for the duration of hospitalization, a trend in favor of enoxaparin was already seen at 48 hours. However, major bleeding with enoxaparin was increased by 53%, despite adjustments in patients older than 75 years and those with chronic renal insufficiency. Nevertheless, enoxaparin was associated with a net clinical benefit when the efficacy and bleeding results were combined and, at 1-year follow-up, there was a sustained reduction in death or MI.50

E. Bivalirudin is better than UFH +/- GP IIb/III a inhibitors in STEMI.

The HORIZONS-AMI trial randomized 3602 STEMI patients to UFH plus provisional GP IIb/IIIa inhibitor or bivalirudin. Major bleeding was statistically lower in the bivalirudin patients, a durable effect to 3 years of follow-up.51 Both all-cause mortality and cardiac mortality were significantly lower in bivalirudin-treated patients at 1 year, an observation that also persisted at 3 years.51 Curiously, the event rates appeared to widen slightly with increased follow-up. Another interesting finding was that reinfarction rates were significantly lower in the bivalirudin-treated group at 3 years.51

Although stent thrombosis was slightly higher with bivalirudin within 24 hours, on longer-term follow-up, the rates of stent thrombosis in the UFH +/- GP IIb/IIIa group rose, neutralizing this early effect. Thus, overall, it appeared that UFH treatment was associated with a mild-but-prolonged prothrombotic risk relative to bivalirudin.51
Unfractionated Heparin: Still Going Strong — Despite Limitations and Evidence

The mechanism for the durable effect with widening of the curves and lower reinfarction rates is only speculative at present. One possibility is that UFH-treated group had a significant rate of PF4/heparin antibody development, which became increasingly clinically relevant upon subsequent hospital admissions for ACS, particularly upon re-exposure to heparin.

A Survey of UFH Use in Cardiology

UFH has limitations, and clinical trials demonstrate better outcomes with alternative anticoagulants; as such, one is struck by the ongoing dominance of UFH in cardiovascular medicine. In a 2003 analysis from the GRACE registry, UFH and LMWH (80% enoxaparin) were used with approximately equal frequency in patients diagnosed with unstable angina or NSTEMI, although UFH was used more two-thirds of the time in patients diagnosed with NSTEMI.52 Overall rates of in-hospital mortality, major bleeding, and stroke were significantly lower with LMWH than with UFH for both STEMI and NSTE-ACS after adjusting for co-

parts of the world, especially Europe.

or CABG) and treatment in the United States versus other parts of the world, especially Europe.53 In a more contemporary analysis of patients at 360 hospitals between January 2007 and June 2009, the NCDR ACTION Registry-GWTG found that UFH was used in 66% and 42% of STEMI and NSTEMI, respectively.54 There was an increase in bivalirudin use, especially over the last year of this report, but the rates of UFH use in STEMI were virtually the same as in the Grace registry from 2003.53

UFH in 2016

We can only speculate how, in 2016 — the 100-year anniversary of its discovery — UFH will be used in cardiovascular medicine. Over the next 5 years, expanded indications for oral and parenteral direct anti-thrombin and anti-Xa drugs will likely chip away at many of its current uses. It is likely that these agents will obtain FDA approval for VTE in the United States, as several have already acquired in Europe.

Furthermore, if direct thrombin inhibitors are extended to treating valvular disease including valvular atrial fibrillation, the role of UFH as a bridging agent will be diminished. UFH has been widely used in severe CKD, especially with GFR < 30 ml/min and will likely continue to be used for these patients. However, surprisingly, in a small subset of patients with moderate-to-severe renal dysfunction from the GRACE registry, bleeding complications were more common with UFH than with LMWH, especially when used in combination with GPIIIa inhibitors.54

UFH has been used when patients with ACS are treated with fondaparinux and a PCI is planned.55 Although this therapy is useful for providing an antithrombin effect — thereby reducing catheter thrombosis — there are theoretical advantages to using direct thrombin inhibitors instead, including thrombus penetration with better inhibition of cryptic thrombin activity. The role of UFH in cardiopulmonary bypass seems to be a stronghold for the foreseeable future. Indeed, limiting UFH use upstream for ACS patients will reduce the likelihood of heparin resistance or HIT in the peri-operative setting, thereby improving clinical outcomes for UFH in this setting.

The growing body of literature on thrombocytopenia and PF4/heparin antibodies casts a shadow over the future of UFH. Thrombocytopenia after heparin administration appears associated with adverse outcomes, especially when immune, but even when non-immune in origin. The presence of PF4/heparin antibodies may be associated with a worse prognosis, even in the absence of thrombocytopenia. Patients may be immunized to PF4/heparin without ever having been exposed to heparin. In patients with CAD, who often have recurring need for anticoagulants, these concerns, along with clinical trials data supporting alternatives, may reduce UFH use in the future.

References


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Advances in Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

Joseph R. Aragon, MD, FACC, FSACI, and Michael M. Shenoda, MD

Treating ST-segment elevation myocardial infarction (STEMI) requires a rapid and concerted effort from the health care delivery system. Given the incremental mortality benefit seen with shorter reperfusion times, it is imperative that patients presenting with a STEMI undergo swift and efficient reperfusion with minimal complications. Treatment advances such as rapid triage of STEMI patients, radial access, aspiration thrombectomy, bivalirudin administration, drug-eluting stents (DES), and more effective pharmacological therapy — including direct thrombin inhibition with bivalirudin and more potent P2Y12 inhibitors — can enhance safe, effective, prompt reperfusion. In the current era of primary percutaneous intervention (PCI) for the treatment of STEMs, employing these advances provides an opportunity to optimize results. This review examines the data supporting the use of these treatment advances in caring for this high-risk population.

Pre-Hospital Care

STEMI-receiving centers have significantly contribute to reduced ischemic times. The 2009 ACC/AHA focused update guidelines have recommended that each community develop a strategy to rapidly triage and transfer patients to PCI capable hospitals.1 Worldwide, communities have built on this by performing ECGs in the field, activating STEMI-receiving hospitals’ cardiac catheterization lab teams while en route and, in many cases, completely bypassing the emergency room and transferring patients directly to catheterization laboratories.

In the United States, door-to-balloon times have been reduced over the last 10 years. This reduction in overall ischemic time for patients translates into better short- and long-term outcomes.2 A great deal of information must be obtained efficiently before STEMI patients are brought to the cardiac catheterization lab. In cases of direct ambulance transfer to the catheterization laboratory, the history and physical exam are usually performed while the patient is prepped for the cardiac catheterization procedure. This includes thoroughly assessing for dual anti-platelet candidacy, which is especially imperative in guiding an operator toward the appropriate intervention and coronary stent type.

Furthermore, informed consent must be obtained during this short time interval, without delaying reperfusion. It is therefore imperative that the additional procedural strategies selected can allow for rapid, efficient PCI with a high probability of success and maximum safety.

Procedural Care

The choice of access site significantly affects the probability of bleeding complications, which are known to increase mortality in ACS patients.3 The decision to pursue femoral or radial access is in many cases related to operator experience.

Data suggest that experienced radial operators can perform PCI rapidly via radial access. Pancholy et al have shown that radial access is not associated with longer door-to-balloon times and that vascular complications were significantly reduced in their center.4 Weaver et al also demonstrated significantly shorter door-to-balloon times for radial access in comparison to femoral access when experienced operators are involved.5

The opportunity to use a universal diagnostic catheter for both right and left coronaries theoretically reduces the time to placement of the guide catheter. Furthermore, universal guide catheters such as a Kimney (Boston Scientific, Natick, MA) or Ikari (Terumo, Somerset, NJ) let an experienced radial operator eliminate the need for a diagnostic catheter in the non-infract artery.

Many novice radial operators encounter issues with radial loops and brachiocephalic tortuosity when using the right radial artery. These issues can hinder the delivery of either diagnostic or guide catheters and may be magnified during a complex PCI if the guide catheter support is suboptimal. The use of the left radial artery in STEMI reduces the risk of anatomic variability and lets the operator use standard femoral diagnostic and guide catheter curves. However, current published data does not show procedural outcomes differ between left or right radial artery access.6 The left radial approach may be a more comfortable alternative for physicians in the beginning stages of transradial PCI, as catheter manipulation is similar to that with transfemoral catheters.7

The smaller radial artery size may limit the operator to 6 Fr or 7 Fr guide catheters. Nonetheless, the majority of STEMI PCIs can be performed via 6 Fr guiding catheters. Additionally, the use of sheathless guide catheters has been well described in transradial PCI.

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The data in support of radial access for STEMI is robust. Vascular complications and access-site bleeding are significantly lower with radial access. Furthermore, patient satisfaction is known to be higher with radial access. However, a consistent mortality benefit has not been definitively demonstrated. The RIVAL trial demonstrated a reduction in the endpoint of death, MI, and stroke in STEMI patients versus NSTEMI-ACS patients treated with transradial PCI versus femoral at 30 days. The overall primary endpoint of the trial did not show a difference in bleeding or mortality between the two groups, but did show an advantage for radial access in major vascular complications at 30 days. The trial was not sufficiently powered for the mortality endpoint identified and, therefore, this subgroup analysis can be seen only as hypothesis-generating. The overall rates of bleeding in the trial were low (0.7% versus 0.9%) and may be explained by the fact that the physicians involved were high-volume operators who were well-trained in radial and femoral access (median PCI volume of 300 cases per year).

In contrast, the recently presented SCAAR Registry Data demonstrated a significant reduction of mortality in STEMI patients at 30 days and 1 year. The mortality advantage was even greater in women and the elderly. These findings are confounded by the fact that transradial patients received bivalirudin more often, had less exposure to glycoprotein inhibitors (GPI), and underwent thrombectomy more frequently (P < 0.001 for all) in comparison to transfemoral patients. The rate of transradial PCI rose from 10% to 50% over the study period. The reported findings in this retrospective database reflect a transition in practice over a 5-year window to strategies that reduced bleeding complications in STEMI patients and translated into a mortality benefit in this Swedish population.

Advances in femoral access includes the use of the micro-puncture technique and a vascular ultrasound to assist with obtaining access. It is unknown if the use of these techniques will reduce vascular complications encountered with primary PCI via the femoral route. The combined use of vascular closure devices and bivalirudin has been shown to reduce bleeding in high-risk patients. However, they are not frequently offered to those at the greatest risk of bleeding.

**Procedural Techniques**

**Thrombus Aspiration**

The recent ACC/AHA focused guidelines consider aspiration thrombectomy for STEMI patients undergoing primary PCI a Class IIA recommendation. The use of manual thrombus aspiration has failed to show consistently reduce mortality in randomized trials. Several smaller studies have demonstrated a reduction in infarct size in comparison to conventional PCI and a subsequent reduction in MACE. Both the single-center TAPAS and the EXPIRA trials demonstrated a significant difference in ST-segment resolution and TIMI myocardial blush grade with aspiration thrombectomy. However, only the TAPAS trial demonstrated a 1-year mortality difference favoring the aspiration thrombectomy group (3.6% versus 6.7%, P < 0.02). Separate meta-analyses by Burzotta et al and Bavry et al found a significant mortality benefit with routine thrombus aspiration. A more recent Bayesian analysis failed to show a mortality reduction, but did improve post-procedure incidence of no-reflow, lower rates of distal embolization, and increase rates TIMI-3 flow post-PCI.

The potential for complications with thrombectomy have been described. Both manual and mechanical thrombectomy are associated with increased risk of stroke. A plausible explanation of this increased stroke risk may be cerebral embolization of coronary thrombus during withdrawal of the catheter (see Figure 1).

Theoretically patients with shorter ischemic times and visible thrombus will benefit from simple manual aspiration. Careful attention to the position of the guide catheter and preventing accidental air entry during withdrawal are simple strategies to minimize this risk. In the case of heavy thrombus burden or delayed presentation, where simple aspiration thrombectomy is unlikely to be effective, more aggressive treatment may be warranted with mechanical thrombectomy. Given the simplicity of manual aspiration, it should be the preferred method for rapid and efficient treatment of primary PCI for STEMI patients with visible thrombus and anatomy that allows for safe catheter delivery and withdrawal.

**Bivalirudin in PCI for STEMI**

The HORIZIONS-AMI trial demonstrated lower rates of bleeding in PCI for STEMI and a reduction in mortality. At 3 years, the mortality benefit was persistent and exposure to bivalirudin appears to be protective against reinfarction and very late stent thrombosis (Table 2). The use of bivalirudin in STEMI is considered an appropriate choice in the presence of...
Table 1. RIVAL and SCAAR mortality and bleeding data

<table>
<thead>
<tr>
<th></th>
<th>Transfemoral</th>
<th>Transradial</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIVAL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>30-day mortality (STEMI and NSTEMI)</td>
<td>1.5</td>
<td>1.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Major bleeding (STEMI and NSTEMI)</td>
<td>0.9</td>
<td>0.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>3.7</td>
<td>1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-day mortality STEMI only</td>
<td>3.2</td>
<td>1.3</td>
<td>0.006</td>
</tr>
<tr>
<td>30-day bleeding STEMI only</td>
<td>0.9</td>
<td>0.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Patient prefers next procedure radial</td>
<td>90.2</td>
<td>50.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2. HORIZONS-AMI 3-year outcomes according to pharmacologic randomization

<table>
<thead>
<tr>
<th></th>
<th>Heparin +GPI</th>
<th>Bivalirudin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all cause)</td>
<td>7.7%</td>
<td>5.9%</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>5.1%</td>
<td>2.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Bleeding TIMI major</td>
<td>6.1%</td>
<td>4.1%</td>
<td>0.007</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>5.1%</td>
<td>3.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>8.2%</td>
<td>6.2%</td>
<td>0.04</td>
</tr>
<tr>
<td>Stent thrombosis (ARC def)</td>
<td>4.1%</td>
<td>4.2%</td>
<td>0.87</td>
</tr>
<tr>
<td>Stent thrombosis (very late &gt; 1 year)</td>
<td>2.2%</td>
<td>1.1%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

P2Y12 inhibitors, with or without prior exposure to heparin, according to the ACC/AHA STEMI guidelines. The bleeding associated with PCI in ACS patients carries a higher mortality than re-infarction, congestive heart failure, and renal failure. Current data do not support a consistent mortality advantage for abciximab, and results with eptifibatide have been mixed in larger randomized PCI trials. Nonetheless, even in patients who do respond to clopidogrel, under-responsiveness to clopidogrel with high on-treatment platelet reactivity is associated with worse outcomes after PCI. The ability to overcome clopidogrel under-responsiveness in high-risk populations with larger thrombus burden and higher platelet activation may provide clinical benefit and perhaps even reduce the need for a GPI in STEMI. The pharmacodynamics of prasugrel and ticagrelor involve not only more bioavailability than clopidogrel, but the time to maximal anti-platelet effect is also shorter. Pretreatment with these agents in high-risk STEMI patients, along with the use of bivalirudin at the time of PCI, may negate the acute stent thrombosis risk associated with bivalirudin, while leading to decreased bleeding risk. Data from the currently enrolling BRAVE-4 trial should shed light into the possible benefit of combined bivalirudin and prasugrel use in this population.

Under-responsiveness to clopidogrel with high on-treatment platelet reactivity is associated with worse outcomes after PCI. The use of newer and more potent P2Y12 inhibitors may mitigate the risk of acute stent thrombosis in this setting. A reduction of stent thrombosis in ACS patients with these P2Y12 inhibitors has been demonstrated. Many critics of the HORIZONS-AMI data suggest that heparin alone or low-dose heparin (ACT 200–250) with a GPI could be considered in PCI for STEMI. Bangalore et al demonstrated a numerically higher rate of bleeding with both low-dose UFH and UFH with GPI treatment. To date, this hypothesis remains unconfirmed in randomized trials.

Rapid triage systems and shorter ischemic times may lead to a decreased thrombus burden that is more manageable without a GPI. In addition, more potent oral P2Y12 inhibitors such as prasugrel and ticagrelor may provide additional protection from stent thrombosis with bivalirudin in the first 24 hours, although this has yet to be proven.
DES in STEMI

The use of DES in STEMI has been debated extensively. The ACC/AHA 2009 Focused Update considers the use of DES in STEMI a Class IIB recommendation. This recommendation is based on early registry studies that reduced target-vessel revascularization and a mortality advantage in comparison to bare metal stents (BMS).24,35

Data from the HORIZONS-AMI trial did not show a difference between DES or BMS with regard to stent thrombosis or mortality, but was notable for a lower TVR rate in the DES arm. Recently published 3-year data from HORIZONS-AMI trial revealed that using DES in STEMI is not associated with any excess hazard of late stent thrombosis compared to BMS, although the overall rates of stent thrombosis in this trial were higher than in other randomized and observational studies (4.7% DES versus 3.2% BMS, \(P = NS\)).

It is unknown if a longer duration of dual anti-platelet therapy (DAPT) would provide additional protection from late stent thrombosis. The FDA mandated DES manufacturers’ DAPT registries should provide insight as to the benefit of DAPT for 36 months and clarify the advantages that second-generation DES may provide in terms of lower stent thrombosis risk.

Post-Procedural Care

Dual Anti-Platelet Therapy

The primary benefit of DES in STEMI is in the reduction of TVR. The critical issues with DES use in primary PCI for STEMI entails the short amount of time available to assess the patient and the financial and medical ability to comply with dual anti-platelet therapy for 6 to 12 months. STEMI transfer protocols and shorter door-to-balloon times will serve only to make this more of a challenge in the future.

Regardless of the stent type used, DAPT is recommended for up to 12 months for patients treated with PCI for STEMI.3 Newer agents such as prasugrel and ticagrelor are attractive alternatives for managing these patients. Both agents provide increased protection from the combined endpoint of death, myocardial infarction, and stroke in ACS patients.

In the TRITON-TIMI 38 STEMI sub-study, a reduction in the combined endpoint was achieved in patients treated with prasugrel in comparison to clopidogrel.44 This was driven by patients who presented with failed thrombolytic therapy. In contrast to NSTEMI patients, this STEMI subgroup analysis showed no increase in non-CABG bleeding risk.34 In the PLATO study, patients managed invasively had significantly reduced mortality, but this was seen primarily in the NSTEMI population.35 Protocol defined bleeding rates in the PLATO study were overall higher than previous ACS trials, but there was no difference in bleeding between ticagrelor and clopidogrel. TRITON-TIMI39 was notable for higher CABG-associated bleeding with prasugrel in STEMI patients. This is not seen with ticagrelor. An explanation for this difference is the shorter half-life of ticagrelor. After cessation of therapy, platelet aggregation returns to normal in 2 to 3 days.45 This makes ticagrelor an attractive option for pretreatment of patients with STEMI before angiography.

It would also be considered appropriate to use prasugrel for STEMI before angiography in patients who do not have contraindications to the drug (age, previous stroke, low body weight) given the overall low risk of urgent CABG in STEMI patients. Those patients with contraindications and patients whom physicians clinically suspect may have multi-vessel disease (diabetes, shock, cardiac arrest, low ejection fraction) should be treated with ticagrelor, based on the PLATO study findings.

At this time there is insufficient evidence to recommend one agent over the other in STEMI patients. In PLATO, a significant number of patients changed platelet therapy due to drug-related dyspnea. This side effect appears to be due to the adenosine-like action of ticagrelor.45 Close monitoring of patients for compliance with ticagrelor is a key component to consistent clinical outcomes with this agent.

Platelet function Testing

The use of platelet-function testing may be considered useful to evaluate the response of patients who are on DAPT. For patients who are deemed non-responders to clopidogrel therapy, prasugrel and ticagrelor are both appropriate options.

Price et al demonstrated in GRAVITAS that there was no benefit in doubling the dose of clopidogrel to 150 mg daily for 6 months after PCI with a DES.46 Furthermore, over time, there was no improvement in high on-treatment platelet reactivity after prolonged exposure to clopidogrel 150 mg daily. Therefore, in STEMI patients previously loaded with clopidogrel for primary PCI, but later found to be non-responders with platelet-function testing, strong consideration should be made for changing therapy to prasugrel or ticagrelor post-PCI.

Conclusion

The rapid and efficient treatment of STEMI patients with primary PCI mandates the use of strategies that ensure a successful procedure with low complications rates. Currently, the use of radial access offers a safety advantage with no appreciable increase in procedural times for experienced operators. Aspiration thrombectomy has been shown to improve the angiographic outcomes in STEMI patients with minimal risk and a suggestion of possible long-term mortality advantage in recent meta-analysis.

The use of bivalirudin in STEMI offers a significant reduction in bleeding with a mortality advantage in the HORIZONS-AMI trial when clopidogrel is used. Selective use of DES in STEMI is safe and does not increase the risk of stent thrombosis, provided the patient can take dual anti-platelet therapy. Newer more potent P2Y12 antagonists offer anti-platelet therapy in primary PCI for STEMI that reduces death, MI, stroke, and stent thrombosis, with no appreciable increase in bleeding in randomized trials. In the ever-more scrutinized arena of quality assurance, operators and institutions that have higher rates of bleeding and worse outcomes will likely come under increased criticism.

Implementing treatment protocols that use these strategies should be considered to determine whether there is additive benefit for STEMI patients. At the present time, it is logical to offer patients a treatment strategy that maintains the speed of primary PCI for STEMI while enhancing its effectiveness and maximizes its safety.
References


Preventing Radial Artery Occlusion and Anticoagulation in Transradial PCI

Samir B. Pancholy, MD, FACP, FACC, FSCAI

Bleeding complications after percutaneous coronary intervention (PCI) can be categorized two ways: related to the access site, and occurring at sites away from the access site, which is termed non-access-site bleeding. Any major bleeding event — especially those necessitating blood transfusion after PCI — is probably the most potent predictor of adverse future prognostic events.1

Access-site bleeding can be decreased with a bivalirudin-based antithrombotic strategy during transfemoral PCI and nearly eliminated by using transradial access (TRA).2 TRA has equivalent procedural success to transfemoral access, and has broad applicability to the majority of the PCI subsets.

TRA has not been shown to decrease non-access-site bleeding, which accounts for more than 50% of post-PCI bleeding events.3 Non-access-site bleeding also more adversely affects prognosis compared to access-site bleeding. This does not decrease the importance of access-site bleeding; rather, it emphasizes the importance of the residual bleeding burden in a patient undergoing PCI using TRA.

Non-access-site bleeding is a function of the patient substrate, which is usually non-modifiable, and the adjunctive pharmacotherapy used during PCI. A post hoc analysis from the ACUITY trial demonstrated the extent of the antithrombotic strategy’s effect on the overall bleeding burden, even in the TRA cohort.4 In this analysis, bivalirudin decreased non-access-site bleeding compared to a heparin plus glycoprotein IIb/IIIa-inhibitor strategy. Based on this evidence, it’s reasonable to assume that a combination of TRA and a bivalirudin-based antithrombotic strategy would provide the best bleeding outcomes in patients undergoing PCI.

Radial Artery Occlusion

Radial artery occlusion (RAO), although asymptomatic, is an important consequence of transradial access, as it prohibits future ipsilateral radial access. Hence preventing RAO is eminently important, as most patients with ischemic heart disease require more than one procedure during their lifetimes. RAO risk increases with increasing sheath-to-artery ratio,5 repeated instrumentation of the radial artery, performance of procedure without anticoagulation,6 and absence of radial artery flow after procedure termination.7 Routinely using systemic anticoagulation7 and maintaining radial artery patency during hemostatic compression have been shown to significantly decrease the incidence of RAO.7

Unfractionated heparin has been shown to decrease the risk of RAO after TRA, with some evidence supporting better efficacy at higher doses (50–70 µ/kg) compared to lower doses.8 Multiple anticoagulants efficaciously prevent RAO.9,10 Anticoagulation’s protective effect to be systemic, as both intravenous and intra-arterial routes have similar efficacy in preventing RAO.11

As performance of radial access without anticoagulation carries a very high risk of RAO, administering anticoagulation is required, even for diagnostic procedures. For diagnostic procedures, unfractionated heparin is the most commonly used anticoagulant due to its proven efficacy and lower cost compared to other parenteral systemic anticoagulants. For interventional procedures, several anticoagulants may be used, including unfractionated heparin, bivalirudin, and enoxaparin.

Patients undergoing diagnostic coronary angiography typically receive unfractionated heparin at the beginning of the procedure. As a result, skilled and conscientious operators who choose TRA feel committed to using heparin-based antithrombotic strategies for ad hoc PCI because, after obtaining TRA, heparin is usually administered very early in the procedure, before coronary anatomy is defined. However, operators need not feel locked in to this anticoagulation strategy.

Strategies for Anticoagulation During TRA

There are several approaches during transradial diagnostic coronary evaluation that let an operator be flexible about the antithrombotic strategy most favorable for a given patient, if ad hoc PCI is contemplated, and prevent radial artery occlusion.

Change to bivalirudin

Use the usual dose of unfractionated heparin (50–70 µ/kg, administered intravenously or intra-arterially) at the beginning of the procedure. If ad hoc PCI is contemplated, proceed with the usual dose of bivalirudin instead of continuing to use a heparin-based anticoagulation strategy. The recent HORIZONS SWITCH analysis examined patients with acute ST-segment elevated myocardial infarction (STEMI) who received unfractionated heparin before reaching the cardiac catheterization laboratory.12 When these patients were given bivalirudin for the PCI procedure, they had lower bleeding rates compared to those given a heparin with glycoprotein IIb/IIIa receptor-antagonist combination. Bivalirudin strategy was also associated with lower mortality and lower re-infarction rates.13

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The Journal of Invasive Cardiology
Although this was a post hoc analysis, it highlights the safety of using bivalirudin in a systematically anticoagulated patient with prior administration of heparin. Extrapolating these results to a lower-risk PCI population will let operators safely administer full-dose bivalirudin in patients who have received heparin earlier in the procedure as a part of radial artery cocktail. A caution: This combination strategy may raise concerns in patients with increased risks of non-access-site bleeding, such as the elderly and those with multiple comorbidities.

Split-dose heparin

In a small pilot study, Venkatesh et al demonstrated the safety split-dose heparin for transradial procedures. Transradial patients were administered 1000 units of unfractionated heparin at the beginning of their procedures. If ad hoc PCI was contemplated, patients received bivalirudin; if PCI was not contemplated, patients received the remainder of the heparin dose (4000 IU) before procedure termination. Although small, only one patient in this evaluation developed acute RAO that required subsequent recanalization. There were no major differences in major adverse cardiac events.

In a larger study population presented by Plante et al, 400 patients were studied; 200 received 70 µ/kg, of unfractionated heparin at the termination of a diagnostic procedure performed transradially, versus usual dose bivalirudin, if ad hoc PCI was performed. No differences in RAO were noted between the heparin or bivalirudin groups. Procedure duration longer than 20 minutes was an independent predictor of RAO. This data establishes bivalirudin’s ability to prevent RAO after TRA, and lets the operator to administer an anticoagulant after coronary angiographic data are available (usually within 20 minutes of the introducer sheath’s introduction to the radial artery), then select the antithrombotic therapy of choice for PCI.

Our own data on 400 patients has revealed comparable RAO rates between up-front heparin administration and administration of heparin if needed, at the end of the diagnostic procedure. The patients were prospectively randomized to receiving either prior unfractionated heparin or provisional heparin at the end of the procedure, based on radial artery patency status. This finding corroborates, in a prospective model, the safety of using heparin at the end of the procedure. It should be noted that all 400 procedures were less than 20 minutes long and, therefore, heparin should be administered well before the 20-minute mark to prevent RAO.

Conclusion

Our standard practice is to administer heparin after the coronary anatomy is defined, if PCI is not contemplated, or if arterial dwell time exceeds 20 minutes (due to procedural complexity). In patients undergoing ad hoc PCI, bivalirudin is administered as soon as the decision to proceed with PCI is made. This provides an optimal balance of reducing the global bleeding burden and incidence of radial artery occlusion.

These variations from the best practice of prior anticoagulation should be instituted only after the operator has developed significant TRA expertise, with diagnostic cardiac catheterization procedure durations well within the 20-minute safety period. Ultimately, multiple strategies could be used to provide systemic anticoagulation during a diagnostic transradial procedure to prevent RAO and maintain the ability to choose the antithrombotic therapy for ad hoc PCI.

References

Elective revascularization of coronary artery disease has evolved from a procedure requiring 2 weeks in the hospital and several months of recuperation to a same day procedure with normal activity the following day. Modern stent procedures result in a vascular repair that can be so stable that inpatient admission is no longer supported by the U.S. reimbursement system simply for the performance of stent placement. While routine stenting can be safely done on an outpatient basis, collateral complications from vascular access and pharmacologic side effects can prevent safe discharge. This review will explore some choices of vascular access and pharmacology to promulgate practices consistent with outpatient PCI.

A well-placed stent mechanically stabilizes the artery, but the advantage can be fully manifested only with appropriate pharmacologic therapy and a stable vascular access site. The ideal stent procedure occurs when there is adequate inhibition of platelet function and control of the thrombosis. Too little effect, and the stent can become acutely thrombotic and risk ischemic complications. Too much anticoagulation, and bleeding at the access or non-access sites can complicate the procedure and reduce the chance for same-day discharge. In addition, unintended bleeding endangers long-term outcomes. The choice of access site interacts with this balance of anticoagulation and can play a role manifesting vascular complications.

**Access-site Considerations:**

Present PCI procedures can be done using either a radial or femoral approach. Both approaches are compatible with outpatient PCI procedures. The transradial approach to PCI was first introduced in the early 1990s in the same time frame as the early vascular closure devices.

Since then, transradial techniques slowly advanced primarily outside of the United States, while the promise of closure devices was chased by the U.S. cardiology community. Different iterations of closure devices have been developed, and they may be very valuable in the future for controlling large artery punctures used for percutaneous structural heart devices.

Unfortunately, cardiologists in practice have never been able to consistently demonstrate improved outcomes with closure devices over manual compression after the performance of routine PCI procedures. Whether this is due to an inherent design deficiency of closure devices or difficult learning curves in the hands of relatively low-volume operators, the promise of closure devices as a panacea for safe vascular closure has not yet been obtained.

Paralleling the advances and failures in the vascular closure-device industry, there has been progressive reduction in catheter and stent size that now permits much smaller catheters and vascular access sheaths. In addition, microvascular puncture techniques, ultrasound, and fluoroscopic localization of vascular entry sites have resulted in a better understanding and performance of more ideal femoral vascular access. When combined with respect for the negative outcomes that can result from bleeding, femoral vascular access can be done now more safely than previously reported when care and effort are taken.

Transradial procedures became popular outside of the influence of closure devices as an answer to concerns about vascular access complications and patient satisfaction. While femoral access can be done with low rate access complications by experienced operators with refined techniques, transradial techniques can result in near-elimination of vascular access concerns, even by early operators during their learning curves. Repeat comparison with transfemoral approach — with or without closure devices — shows a clear advantage to the transradial approach for minimizing vascular complications. This holds true even when experienced transfemoral operators are compared against relatively inexperienced transradial operators.

The simplest action to reduce vascular complications is to use transradial access. Both high- and low-volume operators can benefit from this technique. Recent trials such as the RI-VAL study have shown that, when done by high-volume operators, transfemoral procedures without closure devices can be done with vascular complication rates nearly as low as transradial. This needs to be tempered by the understanding that these results were obtained by operators who were significantly more active than the typical U.S. cardiologist. These results may not be as reproducible in low-volume femoral operators, as has been shown with transradial techniques. Despite similarly low access complications between experienced operators using either transfemoral or radial approaches, patients continue to overwhelmingly prefer transradial. In outpatient PCI, satisfied patients who are confident in their procedures tend to have positive attitudes, fostering early hospital discharge.

**Pharmacologic Considerations**

The pharmacologic therapy specific to outpatient PCI has never been formally studied, as most current compounds have undergone FDA testing in environments of inpatient procedures and under protocols for which early discharge was not a consideration. There appears to be little interest from a financial-reward basis for industry to formally test products for outpatient use. As such, many products are used in a fashion not formally approved
by the FDA. Instead, knowledge of the basic pathophysiology and pharmacology has been telescoped and combined with small proof-of-concept trials to formulate rational drug therapies that meet the demands of outpatient PCI.8

**Antiplatelet Agents**

**Aspirin.** Outpatient PCI represents elective or non-emergent procedures. Time should be available for adequate pharmacological preparation of the patient. Aspirin therapy forms a foundation of therapy to prevent coronary artery thrombosis in addition to long-term preventative therapy for coronary artery disease. Before consideration for outpatient PCI, patients need to be on aspirin therapy. Allergic patients can be desensitized before arrival for the PCI, or alternatively adequately covered with a substitute therapy such as chronic thienopyridine therapy. Angioplasty without adequate aspirin therapy or its substitute is associated with poor outcomes and should be remediated before proceeding.

P2Y12 adenosine diphosphate (ADP) receptor inhibition. Dual antiplatelet therapy at the time of stent implantation provides a microenvironment in the coronary vasculature associated with the best outcomes.9 Most patients being considered for outpatient procedures will tend to fall in those risk classes with minimal active thrombin generation and platelet activation. Patients with stable electrocardiograms and no cardiac-marker elevation can be managed through the PCI with dual antiplatelet therapy and anti-thrombin therapy without needing intravenous antiplatelet therapy, assuming they are adequately pre-treated.10

In institutions where there are concerns about the possible need for CABG and peri-operative bleeding, the initiation of ADP-receptor blockade may be delayed until the patient is on the table or immediately after the procedure. In low-risk patients, it is unlikely that a hazard can be measured, but in higher-risk patients such protocols may open the patient to gaps in ADP inhibition occur. It too can be rapidly activated and has a relatively rapid off-action that may be appealing under some circumstances.13 Both these newer agents appear to have pharmacokinetics that would greatly obviate the need for bridging with intravenous antiplatelet therapy in treatment-naive patients. Prasugrel and ticagrelor are both under patent protection and will be more expensive than the older thienopyridines that are coming off patent.

As more clinical data is accumulated, a better understanding of cost-effectiveness and differential effects may be defined. At present, it is clear that optimal PCI occurs under the influence of dual antiplatelet therapy defined in Table 1. Because outpatients remain on the lower end of the risk scale, differential outcomes will be difficult to define based on which agent is used, and an adequately powered three-way randomization is not available.14 The final choice of agent depends on multiple patient and operator factors. Patient bleeding risk and financial means might favor one of the older agents, while time factors might favor using more rapidly acting agents in the outpatient setting.

**Supplemental intravenous antiplatelet therapy.** Intravenous glycoprotein protein Iib/Illa receptor (GP Iib/Illa) antagonists were developed in the era of balloon angioplasty when prolonged infusions were felt necessary to pacify the thrombotic arterial surface. With stent technology, the arterial wall is mechanically stabilized, and the need for pacification has probably passed. Unfortunately, FDA-approved regimens reflect a past era and use of these agents in the present stent era is often off-label as described in this section and shown in Table 2.

With the time constraints of outpatient practice, adequate oral loading of dual antiplatelet therapy may not have occurred, or may not have had the opportunity to be in full effect at the time of PCI. This is primarily a concern with the older thienopyridines, clopidogrel and ticlopidine, as the newer P2Y12 inhibitors have a much shorter time to onset. The use of GP Iib/Illa therapy can bridge the gap in platelet-antagonist therapy that can occur when using older thienopyridine therapy by blocking the final common pathway in platelet aggregation.

There are multiple publications describing the use of eptifibatide,15,16 tirofiban,17 and abciximab18 in bolus or abbreviated fashion that appear to be quite adequate for bridging the gap in full dual antiplatelet therapy. Both eptifibatide and abciximab regimens use standard, label-approved bolus therapy but forgo the infusion; tirofiban therapy uses a higher dose than the FDA-label as the bolus to compensate for the inadequate
The Journal of Invasive Cardiology

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Table 1. Dual antiplatelet therapy to consider in the setting of PCI with stent*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Loading dose</th>
<th>Time needed for effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>300–600 mg</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Aspirin plus either</td>
<td>60 mg</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>180 mg</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

*Each drug has a different risk/benefit profile and drug interactions. These need to be considered and understood by the physician before prescribing to patients.

Table 2. Intravenous antiplatelet therapy options available to bridge suboptimal ADP-receptor inhibition due to inadequate time for oral inhibitors to have reached full effect

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bolus Dosage</th>
<th>Infusion Dosage</th>
<th>Duration of inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eptifibatide</td>
<td>180 µg/kg, repeated after 10 minutes</td>
<td>2 µg/kg/min</td>
<td>$T_{1/2} = 2$ hours</td>
</tr>
<tr>
<td>Tirofiban†</td>
<td>25 µg/kg</td>
<td>0.15 µg/kg/min</td>
<td>$T_{1/2} = 2$ hours</td>
</tr>
<tr>
<td>Abciximab‡</td>
<td>0.25 mg/kg</td>
<td>10 µg/min</td>
<td>&gt; 12 hours</td>
</tr>
</tbody>
</table>

*This is for illustrative purposes only. The actual dosage may differ, depending on patient characteristics. Infusions may not be necessary for short periods of bridging but shown for completeness.
†Tirofiban dosages are off-label.
‡Elimination times after discontinuing therapy are approximate for illustration purposes.

Table 3. Options for antithrombin therapy used with dual antiplatelet therapy*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bolus Dosage</th>
<th>Infusion Dosage</th>
<th>Terminal $T_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>100 U/kg or titrate to ACT</td>
<td>N/A</td>
<td>60 minutes</td>
</tr>
<tr>
<td>LMWH (e.g., enoxaparin)</td>
<td>.50 mg/kg</td>
<td>N/A</td>
<td>2 hours</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>0.75 mg/kg</td>
<td>1.75 mg/kg/hr</td>
<td>25 minutes</td>
</tr>
</tbody>
</table>

*This is for illustrative purposes only. Actual dosage may differ, depending on patient characteristics.

Anti-thrombin Therapy

In addition to antiplatelet therapy, suppression of the thrombin-associated clotting cascades is needed during stent placement. The classic and time tested approach uses heparin at a dose significant to raise the ACT to the 200–300-second range depending on the adjunctive therapy. While some data suggest high ACT may result in less ischemic complications, literature from the femoral approach also points to greater risk of bleeding complications at the access site.

Agents focused on specific points higher in the clotting cascade such as fondaparinux and the Xa inhibitors have been associated with the potential of clot formation on catheters and have not be advocated as stand alone anti-thrombin agents for PCI. These agents need to be supplemented by heparin or similar thrombin inhibitors. In the outpatient arena, it is not clear at this point that these more specific factor inhibitors will play a role in the PCI procedure. Low molecular-weight heparins might offer an alternative to heparin. The ability to titrate is not readily available, but in low-risk stent procedures, the reproducibility effects from standard dosing may be attractive.

The direct thrombin inhibitor, bivalirudin, has been found effective for PCI procedures and is widely used in the United States for interventional procedures. In trials dominated by femoral artery procedures, bivalirudin clearly reduces vascular and other bleeding complications when compared to heparin combinations. It has a shorter half-life and more predictable dosing effect than heparin and, as such, may be particularly appealing for femoral operators.

Transradial procedures are not likely to suffer catastrophic vascular access-site bleeding complications so the role of bivalirudin, or its value, in the radial community was initially underappreciated. Bleeding in non-access sites, similar to access-site bleeding, plays a prognostically important role, and radial access does not modify the risk of non-access site bleeding. This bleeding risk exceeds the access-site bleeding risk in some patient subsets and remains an important source of bleeding across the spectrum of patients undergoing PCI. Bivalirudin’s value in reducing non-access bleeding is equally important in the transradial and femoral subgroups. Considering the broad spectrum of effect, bivalirudin should be considered the antithrombin of choice for minimizing bleeding complications, regardless of access site.

Bivalirudin has a quicker off-time than heparin that may improve time to ambulation and reduce bleeding in femoral patients. For the radial patients, band times for hemostasis may also be shortened, and non-access-site bleeding may be

degree of protection provided from the initial agency approval. The several hours of inhibition from bolus GP IIb/IIIa therapy acting on platelet function fits well within the observation period otherwise used to ensure hemostasis and, at least mechanistically, should cover any gaps in antiplatelet therapy forged by time constraints.

While complete coverage of platelet activity can be obtained by adding bridging GP IIb/IIIa therapy, enthusiasm needs to be tempered by the recognition that these regimens have not been tested in appropriately powered trials and remain off label indications. While they may reduce the risk of an ischemic event, they may complicate the access-site management, especially in femoral patients. With longer infusions, the GP IIb/IIIa agents acting on platelet function fits well within the observation period otherwise used to ensure hemostasis and, at least mechanistically, should cover any gaps in antithrombin therapy forged by time constraints.

In the end, outpatient procedures should be as low-risk as possible. Although often framed in the setting of high-risk acute coronary syndromes, GP IIb/IIIa may play a role as bridging agents in outpatient procedures for which the risk/benefit ratio remains favorable after careful consideration.
reduced compared to heparin. Table 3 summarizes antithrombin agents.

**Summary**

Routine outpatient PCI is optimally performed by a transradial approach due to the ease in obtaining rapid and durable hemostasis. The transfemoral approach can alternatively be used in outpatient PCI with excellent results, but this requires attention to detail and has been demonstrated only by experienced, high-volume operators. How closure devices interact with the decision for outpatient management has yet to be determined and lacks convincing data.

All patients undergoing outpatient PCI need to be appropriately loaded with dual-antiplatelet agents and given adequate antithrombin therapy such that their procedures can be executed in a low-risk state and not compromised by time constraints of outpatient medicine (see Figure 1). Several ADP-receptor inhibitors that can be used with aspirin are now on the market and each, given in an appropriate dose with enough time to work, should offer similar outcomes in typical outpatients. The newer, short-acting agents may be more convenient for outpatient use and, cost issues aside, may have a growing role in outpatient procedures.

Gaps in antiplatelet therapy can occur when using older thienopyridine therapy as ad hoc PCI, and the time constraints of outpatient procedures may prevent adequate pretreatment. Bridging with IV GP IIb/IIIa inhibition is potentially one partially tested option, but the newer P2Y12 inhibitors may be especially attractive in the outpatient unit, due to their rapid onsets of action, which could avoid significant gaps in antiplatelet therapy. Antithrombin therapy should be limited to either one of the heparins or the direct thrombin inhibitor bivalirudin. For femoral patients, bivalirudin may be particularly attractive for ensuring fewer access-site bleeding complications and earlier sheath removal, but even transradial patients will derive a benefit from reduced hemostasis band time and less non-access-site bleeding.

Application of approaches and therapies that minimize bleeding complications while maintaining anti-ischemic/anti-thrombotic protection of modern pharmacology are key to successful outpatient PCI. Therapy should give the physician and patient confidence that they have had a procedure at least as safe as an inpatient procedure without the hazards of prolonged hospitalization. Finally, no outpatient procedure is complete without an adequate safety net. Predictable access-site bleeding complications and earlier sheath removal, but even transradial patients will derive a benefit from reduced hemostasis band time and less non-access-site bleeding.

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**References**


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29