Mortality rates for patients with acute myocardial infarction (MI) continue to decline as evidence-based therapies are implemented on a broader scale, invasive management and revascularization are more widely used, and reperfusion times for patients with acute ST-segment elevation myocardial infarction (STEMI) are shortened. Recent data from the Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines (ACTION Registry–GWTG) in the United States demonstrated that, by 2009, risk-adjusted in-hospital mortality had decreased to 5.5% among STEMI patients treated in routine practice. In addition, mortality rates through and beyond 1 year among STEMI patients treated with primary percutaneous coronary intervention (PCI) enrolled in recent clinical trials have declined by 3% to 6%. Yet, improvements in survival demonstrated with STEMI patients may be tempered by the consequent morbidity of postinfarction heart failure (HF), which, unfortunately remains a common clinical event. Acute STEMI is an independent predictor of HF at admission, and the development of HF among STEMI patients is associated with a much higher long-term mortality rate compared with patients who do not develop HF. Because mortality rates for STEMI patients have declined and reinfarction rates have been shown to be low with the widespread use of primary PCI, attention has shifted toward reducing postinfarction HF because this outcome is thought to reflect the downstream impact of acute therapies for STEMI.

There are multiple convergent trends that could contribute to the rising prevalence of HF after STEMI, including an aging population and a decrease in sudden cardiac death because of defibrillator therapy. Fortunately, though, HF hospitalizations are declining nationwide, partially because of a declining risk of postinfarction HF. Given that ischemic heart disease is the most common cause of HF, the relationship of improvements in upstream treatment of acute MI should be evaluated in terms of its impact on postinfarction HF. Unfortunately, the timing and scope of HF after presentation with STEMI have not been well defined. Unlike de novo MI and reinfarction, there is no universally agreed-upon definition of HF as a clinical outcome in the post-MI population. Consequently, there has been limited adoption of postinfarction HF as a clinical end point in trials or registries. Following the progress in reducing mortality from STEMI over the past 2 decades, reducing postinfarction HF events remains an important clinical need. In this review, we will explore the incidence of HF across previous STEMI trials, examine earlier experiences with the use and definition of HF end points for STEMI trials, and discuss options for developing a universal definition of post-STEMI HF that can be considered by regulatory bodies and clinical investigators to better delineate the impact of novel therapies for STEMI on myocardial salvage and subsequent downstream HF events.

Rationale for Collecting Heart Failure End Points in STEMI Trials

Since Braunwald and Maroko first described the time-sensitive nature of limiting infarct size, therapies that have targeted the early restoration of myocardial perfusion. Contemporary treatment strategies have moved beyond epicardial artery patency toward the restoration of microvascular flow and myocardial tissue perfusion to better preserve left ventricular function and reduce mortality. Heart failure on admission may reflect the extent of myocardial damage or decompensation already present in the setting of ongoing STEMI and often portends a worse prognosis proportional to the severity of HF as assessed by Killip class. In the Global Registry of Acute Coronary Events, for example, in-hospital mortality for Killip classes I, II, and III present on admission was 2.9%, 9.9%, and 20.4%, respectively (P<0.0001). The degree of HF after presentation anticipates a similar prognosis. Contemporary trials of acute coronary syndromes largely use thrombosis-related end points, such as cardiovascular death, MI, and stroke, but treatments that are specifically designed for STEMI care also need to be evaluated in the context of left ventricular dysfunction.
Several studies have explored the impact of post-STEMI HF. For example, an analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I (GUSTO-I) trial found that cardiogenic shock occurred in 7.2% of patients with STEMI but was responsible for 58% of deaths at 30 days.21 Mild-to-moderate HF (similar to Killip classes II and III at presentation) was a more common complication of STEMI in the early lytic trials. Among the patients enrolled in GUSTO-I, GUSTO-IIb, GUSTO-III, and the Assessment of the Safety of a New Thrombolytic-II (ASSENT-II) trials, 57.6% developed mild-to-moderate HF after STEMI. In a post hoc analysis, the incidence of death at 30 days was four times higher in patients with even mild-to-moderate HF compared with patients without HF (8% versus 2%).22 Therefore, the morbidity and mortality associated with developing HF after STEMI suggest that HF is an appropriate end point for the evaluation of novel treatments and reperfusion strategies for STEMI patients. With 30-day mortality rates decreasing in clinical trials to as low as 2.1% in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, it is increasingly difficult to show a mortality benefit that can be directly attributed to therapeutic impact on the index event of STEMI.23 Similarly, reinfarction rates have diminished considerably with broader use of PCI. Reinfarction within 30 days occurred in 4.2% of patients in GUSTO-III, whereas it occurred in 1.8% of patients in HORIZONS-AMI. It is a natural extension to consider composite end points for future STEMI trials that include HF as one of the key components of a composite primary end point.

The use of HF end points also makes sense from an economic standpoint, particularly in the contemporary era of unsustainable growth in healthcare spending. Prospective economic evaluations are increasingly used to justify the cost-effectiveness of novel therapies. To encourage the broad-scale addition of a new treatment, cost-effectiveness studies can show that a new therapy not only improves patient outcomes but also decreases downstream costs. In 2009, overall HF costs in the United States were an estimated $37.2 billion, of which $20.1 billion was attributable to inpatient care.24 As the use of device therapies (such as defibrillators and cardiac resynchronization therapy) for left ventricular dysfunction and HF grows, costs may continue to increase. Therefore, reducing the incidence of a resource-intensive complication such as HF after STEMI could justify the cost of a novel therapeutic agent for STEMI patients.

**Past Experience With HF End Points in STEMI Trials**

Despite the importance of HF as a consequence of STEMI, HF end points have not been consistently defined or systematically collected in previous STEMI trials. Several previous trials that have informed current treatment approaches for STEMI—Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) trial, many of the GUSTO trials, Trandolapril Cardiac Evaluation (TRACE) study, Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), and Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial, among others—demonstrated little consensus regarding the definition of HF end points and the optimal duration for the ascertainment of HF end points. As a result, recent STEMI trials that have captured and reported HF end points use different definitions (Table 1) and ascertainment time periods (Table 2), making it difficult to compare HF event rates across trials.

**Early Lytic Trials and Contemporary Primary/Facilitated PCI Trials**

Early lytic trials focused on HF as a dichotomous baseline covariate (either present or absent at the time of presentation with STEMI), rather than as a time-dependent clinical end point whose incidence could potentially be modified by the studied treatment.25,30–32 Analyses of these trials have defined HF as a sign or symptom of pulmonary congestion in the absence of a noncardiac cause. Although the criteria for HF as an end point are similar in more contemporary STEMI trials, there are several permutations of these criteria. The Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial, which found that the monoclonal antibody pexelizumab had no effect on mortality as an adjunctive therapy to STEMI patients undergoing primary PCI, exemplifies the subtle changes in the HF end point over time.26 Congestive HF was included in a composite secondary end point of death, cardiogenic shock, or congestive HF through 90 days. Similar to the early lytic trials, HF was defined on the basis of the physician’s decision to treat HF with an intravenous diuretic, inotropic agent, or vasodilator; yet fewer additional clinical criteria were needed to establish a diagnosis of HF, and the determination was not made at the time of STEMI presentation.

**Issues Confounding the Definition and Ascertainment of HF End Points in STEMI Trials**

Defining a temporal causal relationship between the incidence of postinfarction HF and the index STEMI event is particularly important, given the presence of many confounding factors. For example, the administration of intravenous contrast and fluids during primary PCI procedures may contribute to the development of early acute HF events, mostly because of volume overload or contrast nephropathy. To avoid such confounding and identify preventable events independent of the index event, trials such as APEX-AMI have only adjudicated HF events occurring >24 hours after randomization.28 Using a proper adjudication process to exclude clinical events that occur outside the timeframe for ascertainment is important to fully characterize treatment effect.33 Similar to distinguishing between the index acute MI and subsequent reinfection by trends in cardiac biomarkers, new-onset HF must be separated from perioperative circumstances that surround the index STEMI event. Beyond properly ascertaining HF events, an HF end point in STEMI trials must also minimize confounding from comorbidities and practice patterns. Both qualitative (dyspnea scales) and quantitative (measured hemodynamics with a pulmonary artery catheter) components of an HF definition are confounded by concomitant pulmonary disease (in the case of dyspnea scales) and large differences in the use of pulmonary artery catheters among post-MI patients across practices and regions.34
Radiographic evidence of pulmonary edema
Rales >1/3 of lung fields
PCWP >18 mm Hg with cardiac index <2.4 L/min per m²
Dyspnea, with documented PO² <80 mm Hg or O₂ saturation <90%, without known preexisting lung disease

Reinfarction at 90 days
Mortality at 30 days
All-cause mortality or severe HF at 30 days
All-cause mortality, cardiogenic shock, or HF at 90 days
Hospitalization for cardiogenic shock at 90 days
Rehospitalization for cardiogenic shock at 90 days
PCWP >25

Reinfarction at 90 days
Cardiogenic shock at 90 days
Rehospitalization for HF at 90 days
Cardiogenic shock at 90 days
Rales >1/3 of lung fields

Mortality at 30 days
Reinfarction at 30 days
Dyspnea, with documented PO₂
PCWP or LVEDP >18

Hospitalization for HF at 90 days
Reinfarction at 30 days
Dyspnea, with documented PO₂
PCWP >18

All-cause mortality, ventricular fibrillation >48 hours after randomization, cardiogenic shock, and HF requiring ED visit or rehospitalization at 90 days
Hospitalization for HF at 90 days

A standardized definition of HF as an end point is needed to ascertainable across different systems of care. A standardized definition for HF must be logistically feasible and broadly for HF.35,36 Given the global scale of STEMI trials, a standardized approach for standardization of the HF end point across clinical syndrome trials.37–40 Although the importance of using a similar approach for standardization of the HF end point across clinical trials is evident, several challenges exist, including generating consensus and implementing common end point definitions on a broad scale. Whether a standardized definition of HF could be properly integrated into trials for a single precursor disease state such as STEMI raises additional questions such as the following: (1) Will a standardized definition clarify the relationship between acute treatments administered for STEMI patients and downstream morbidity?; and (2) What would be the optimal duration of ascertainment for HF end points?

Many relevant efforts are already underway, which can inform the development of a tailored definition to describe the incidence of post-STEMI HF, both in-hospital and after discharge.
The Standardized Data Collection for Cardiovascular Trials Initiative is in the process of creating a standardized, multiple-component definition for HF events—an important step toward establishing a common framework for novel treatments in HF. The definition, which was posted for public review and is now being finalized, may serve as a template for a tailored multiple-component HF end point that can also reflect downstream morbidity. Such a multiple-component HF end point, which evaluates events beyond the index hospitalization, has been proposed for acute HF syndrome trials and could also be adapted for STEMI trials. A multiple-component HF end point, built using elements of these existing efforts, could provide a common platform upon which the efficacy of STEMI treatments could be compared based on overall rankings. In addition to the overall results from the multiple-component end point definition, the outcomes associated with each of the individual components of the end point definition used to form the overall definition could be reported in a consumer reports fashion, which has been done previously in non-ST-segment elevation acute coronary syndrome trials when reporting the different subclassifications of MI for reinfarction end points.

We propose that a composite end point of HF for STEMI trials meet these issues of generalizability by broadly capturing events during the initial hospitalization and beyond. At the same time, a standardized HF end point definition must define HF narrowly enough to capture clinically meaningful events while excluding confounding circumstances such as peri-procedural intravenous fluid administration and contrast-induced nephropathy. We propose a standardized multiple-component HF end point that adapts elements of the definition of HF requiring hospitalization from the Standardized Data Collection for Cardiovascular Trials Initiative while accounting for postdischarge events (Table 3).

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**Table 2. Incidence of Heart Failure in Selected STEMI Trials**

<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Date</th>
<th>Intervention</th>
<th>Ascertainment Time Period for HF Events</th>
<th>Incidence of HF Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lytic trial</td>
<td></td>
<td></td>
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<tr>
<td>GUSTO III</td>
<td>1997</td>
<td>Reteplase vs accelerated alteplase</td>
<td>30 days</td>
<td>17.2% in reteplase arm, 17.5% in alteplase arm</td>
</tr>
<tr>
<td>PCI trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE MI</td>
<td>2005</td>
<td>Facilitated PCI with eptifibatide-half-dose tenecteplase vs facilitated PCI with eptifibatide-plus placebo</td>
<td>30 days</td>
<td>6% in the eptifibatide-half-dose TNK group vs 3% in the facilitated PCI with eptifibatide-plus placebo group</td>
</tr>
<tr>
<td>ASSENT-4 PCI</td>
<td>2006</td>
<td>Facilitated PCI with full-dose tenecteplase vs standard PCI</td>
<td>90 days</td>
<td>12% in the TNK+PCI group vs 9% in the standard PCI group</td>
</tr>
<tr>
<td>APEX-AMI</td>
<td>2007</td>
<td>Pexelizumab vs placebo as adjunct to PCI</td>
<td>30 and 90 days</td>
<td>At 30 days: 4% in placebo group vs 4% in pexelizumab group At 90 days: 5% in placebo group vs 5% in pexelizumab group</td>
</tr>
<tr>
<td>FINESSE</td>
<td>2008</td>
<td>Combination-facilitated PCI vs abciximab-facilitated PCI vs primary PCI</td>
<td>In-hospital</td>
<td>HF during index hospitalization: 6.5% in combination-facilitated PCI group vs 5.5% in abciximab-facilitated PCI group vs 6.5% in placebo group</td>
</tr>
</tbody>
</table>

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**Figure.** Progression of HF post-STEMI. This figure displays the pathophysiological progression of heart failure following STEMI. HF indicates heart failure; LV, left ventricular; and STEMI, ST-segment elevation myocardial infarction.
Drawing from previous STEMI trials, such as APEX-AMI, we propose that HF events be ascertained only after the first 24 hours during the index STEMI hospitalization to minimize confounding from other treatment strategies specific to STEMI care. We propose that ascertainment for HF events extend well beyond the index hospitalization to reflect the full extent of the downstream morbidity post-STEMI. Ascertainment of HF events should extend to at least 30 days after discharge from the index event, allowing trials to assess the impact of a novel STEMI therapy on the hospital metric of 30-day readmission rates.

Such a composite definition could be integrated into a composite end point that accurately reflects competing risks. Comprehensively capturing morbidity and mortality will also align the objectives of a trial with outcomes important to patients. To do so, more reliable ascertainment of subjective components, such as in-hospital physical signs of HF, is needed. In addition, consensus among various stakeholders, such as academia, industry, and patients, is needed on other components, such as what constitutes significant titration of HF therapies.

**Conclusions**

The mortality rates for STEMI patients will likely continue to decline through more widespread and timely use of primary PCI and through the broad use of evidence-based secondary prevention therapies. Thus, a new approach needs to be developed, with particular attention paid to reducing the incidence of postinfarction HF, a typical complication seen among STEMI patients. As an initial step, we propose the development of a consistent, multiple-component HF end point definition that is relevant for post-STEMI patients and that can be used in future STEMI trials. A standardized HF end point for STEMI trials

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**Table 3. Proposed Standardized Definition for HF in STEMI Trials**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria 1: Physical signs of HF, including at least 2 of the following:</th>
</tr>
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<tbody>
<tr>
<td>HF during the index hospitalization</td>
<td>Edema (&gt;2+ lower extremity)</td>
</tr>
<tr>
<td>Dyspnea, beginning or persisting &gt;24 hours after hospital admission, accompanied by both of the following:</td>
<td>Pulmonary crackles/rales greater than basilar</td>
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<td></td>
<td>Tachypnea (respiratory rate &gt;20 bpm)</td>
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<td>Rapid weight gain</td>
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<td>S3 gallop</td>
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<td>Increasing abdominal distension or ascites</td>
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<td>Hepatocellular reflux</td>
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<td></td>
<td>Radiological evidence of worsening HF</td>
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<td></td>
<td>A right heart catheterization showing a pulmonary capillary wedge pressure &gt;18 mm Hg or a cardiac output &lt;2.2 L/min per m²</td>
</tr>
<tr>
<td>HF after hospital discharge</td>
<td>Therapy initiation or significant augmentation in oral therapies for HF, including diuretics, ACE-I/ARB, vasodilators, or ARBs</td>
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<tr>
<td>New-onset dyspnea, persisting &gt; 24 hours, accompanied by at least 1 of the following criteria:</td>
<td>Initiation of intravenous diuretic, inotrope, or vasodilator therapy</td>
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<tr>
<td></td>
<td>Uptitration of intravenous therapies (diuretics, inotropes, vasodilators), if already treated with these therapies</td>
</tr>
<tr>
<td></td>
<td>Initiation of mechanical or surgical intervention, or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF</td>
</tr>
<tr>
<td>New-onset dyspnea, persisting &gt; 24 hours, accompanied by at least 1 of the following criteria:</td>
<td>A right heart catheterization showing a pulmonary capillary wedge pressure &gt;18 mm Hg or a cardiac output &lt;2.2 L/min per m²</td>
</tr>
</tbody>
</table>

STEMI indicates ST-segment elevation myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; HF, heart failure; and ARB, angiotensin receptor blocker.
should include both in-hospital events and postdischarge events to fully assess the impact of HF as a time-dependent covariate. To chart a path forward, stakeholders must generate consensus on how to define and how to ascertain individual components within a composite definition of HF. Through ongoing collaborative efforts, a relevant, consistent, and uniform HF end point definition can be refined to contribute to the comprehensive evaluation of promising new treatments for STEMI patients.

Acknowledgments

We thank Erin LoFrese for editorial contributions. She did not receive compensation for her assistance, apart from her employment at the institution where the study was conducted.

Sources of Funding

This work was supported by an award from the American Heart Association Pharmaceutical Roundtable and David and Stevie Spina. Dr Eapen received funding from an American Heart Association Pharmaceutical Roundtable outcomes training grant (0875142N).

Disclosures

Dr Tang reports research funding from Abbott Laboratories, and consulting or honoraria from Medtronic, St. Jude Medical. Dr Felker reports research funding from NHLBI, Amgen, Otsuka, BG Medicine, Critical Diagnostics, Roche Diagnostics, Johnson & Johnson; and consulting or honoraria from NHLBI, Amgen, Otsuka, BG Medicine, Critical Diagnostics, Roche Diagnostics, Johnson & Johnson, Medpace, Novartis, Geron. Dr Hernandez reports research funding from Johnson & Johnson, Proventys, Amylin; and consulting or honoraria from Medtronic, St. Jude Medical, LOP, Aumon MC, Budaj A, Goldberg RJ, Klein W, Anderson FA Jr; Global Registry of Acute Coronary Events Investigators. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004;109:494–499.


Defining Heart Failure End Points in ST-Segment Elevation Myocardial Infarction Trials: Integrating Past Experiences to Chart a Path Forward

Circ Cardiovasc Qual Outcomes. 2012;5:594-600
doi: 10.1161/CIRCOUTCOMES.112.966150
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/5/4/594