The reduction in all-cause hospital admissions with digoxin persisted through 60 days (HR, 0.76; 95% CI, 0.63 to 0.91; p=0.003) and 90 days (HR, 0.75; 95% CI, 0.63 to 0.88; p<0.001) post randomization. This suggests that the early benefit of digoxin was not achieved at the cost of harm at a later time.

In the 30 days following randomization, digoxin significantly reduced the risk of hospital admission due to cardiovascular causes by 47% (HR, 0.53; 95% CI, 0.38 to 0.72; p<0.001) and due to worsening HF by 60% (HR, 0.40; 95% CI, 0.26 to 0.62; p<0.001). Differences between 30-day mortality outcomes for all-cause and cardiovascular mortality were not significant between the digoxin and placebo groups. A favorable trend toward less frequent progression of HF (HR, 0.22; 95% CI, 0.05 to 1.04; p=0.056) was observed with digoxin.

Since these results were derived from post hoc subgroup analyses, the findings should be considered hypothesis-generating that require confirmation in prospective studies. Clinicians should be cautious about generalizing these results to patients in clinical practice, in part because the study was conducted in the early 1990s when current background therapies were either not standard-of-care (eg, β-blockers, spironolactone) or unavailable (eg, angiotensin receptor blockers).

If these findings can be replicated in current older HF patients on guideline recommended background therapy, digoxin may be a low-cost option to reduce 30-day all-cause readmissions and avoid penalties imposed by CMS.

Early Fibrinolysis as Effective as Primary PCI When Reperfusion Delay Is Long

Written by **Wayne Kuznar**

Fibrinolytic therapy coupled with timely coronary angiography results in effective reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) who cannot undergo primary percutaneous coronary intervention (PCI) within 1 hour of presentation, said Frans Van de Werf, MD, PhD, University of Leuven, Leuven, Belgium, who presented the results of the Strategic Reperfusion (With Tenecteplase and Antithrombotic Treatment) Early After Myocardial Infarction trial [STREAM; Armstrong PW et al. *N Engl J Med* 2013].

Although prompt delivery of primary PCI is the preferred strategy to treat patients with acute STEMI, delays in performing PCI are common when patients present to emergency medical services or hospitals without the capability for catheterization. The delay in reperfusion that results from long transfer to a hospital for primary PCI increases the rates of morbidity and mortality.

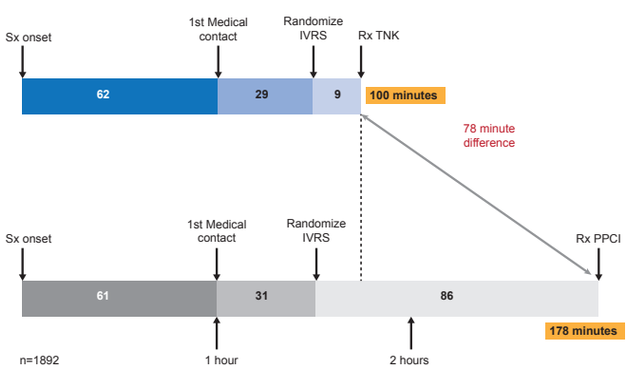
In STREAM, patients with STEMI (≥2 mm ST elevation in 2 contiguous leads) who presented within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact were randomized to 1 of 2 strategies: 1) early fibrinolysis followed by coronary angiography in 6 to 24 hours or rescue PCI, if needed, or 2) standard primary PCI. Patients from 99 sites in 15 countries were included in this trial.

In the early fibrinolysis group, patients received a weight-based bolus of tenecteplase along with aspirin, clopidogrel, and enoxaparin in the ambulance or emergency department. Rescue intervention was performed if there was <50% ST-segment resolution in the single lead of an electrocardiogram or clinical evidence of failed reperfusion within 90 minutes after fibrinolytic therapy. In the primary PCI group patients received antiplatelet and antithrombin treatment according to local guidelines, and underwent standard primary PCI.

The trial was designed as a proof-of-concept study where all statistical tests were of an exploratory nature. The primary endpoint was a composite of death, shock, congestive heart failure, or reinfarction at 30 days [Armstrong PW et al. *N Engl J Med* 2013].

After 20% of the planned recruitment into the study, the bolus dose of tenecteplase was halved in patients aged ≥75 years to reduce the risk of intracranial bleeding. A total of 1892 patients were randomized. The median time from symptom onset to the start of reperfusion therapy was 100 minutes in patients randomized to the early fibrinolysis group versus 178 minutes in the primary PCI group (Figure 1).

Figure 1. Median Time to Treatment: Early Fibrinolysis Versus Primary PCI



IVRS=interactive voice response system; PPCI=primary percutaneous coronary intervention; TNK=tenecteplase.

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In the 36% of the patients who required rescue or urgent PCI the median time to PCI following bolus tenecteplase was 2.2 hours. In the remaining 64% a nonurgent angiography was performed after a median of 17 hours

Patients assigned to early fibrinolysis were more likely to have Thrombolysis in Myocardial Infarction (TIMI)-3 blood flow prior to PCI compared with the primary PCI group (58.5% vs 20.7%; p<0.001) but there was no significant difference in TIMI-3 blood flow after PCI (91.1 % vs 92.3%; p=0.41). Coronary artery bypass graft surgery was performed about twice as often in the early fibrinolysis versus the primary PCI group (4.7% vs 2.1%; p=0.002).

STREAM suggests that a strategy involving early fibrinolysis in appropriate patients on a background of contemporary antithrombotic therapy may be beneficial in patients with STEMI who present within 3 hours of symptom onset and who cannot undergo primary PCI within 1 hour of first medical contact. An important implication of STREAM is the key role of prehospital systems capable of early diagnosis, therapy, and triage at the first point of care. In addition, STREAM underscores the importance of efforts to improve the availability of primary PCI for patients presenting with STEMI.

Science Advisor's note: As specified in the methods the statistical testing was considered exploratory and therefore these findings should be considered hypothesis-generating.

New SAPIEN XT System Is Noninferior to and Safer Than Old SAPIEN System

Written by Phil Vinall

Results from the Placement of Aortic Transcatheter Valves 2 trial [PARTNER 2; NCT01314313] indicated that the new SAPIEN XT transcatheter heart valve (THV) system is noninferior to the old SAPIEN system when used in an inoperable cohort of patients. The new slimmer version was associated with improved procedural outcomes and reduced vascular complications, including major vascular bleeding. Martin B. Leon, MD, Columbia University Medical Center and New York-Presbyterian Hospital, New York, New York, USA, presented the results of PARTNER 2.

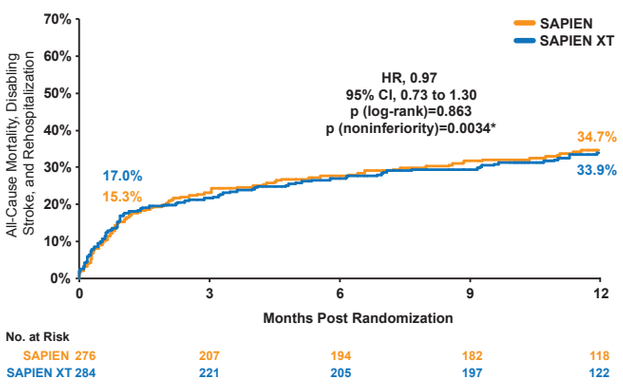
The objective of PARTNER 2 was to compare the safety and effectiveness of the new balloon-expandable SAPIEN XT with the old SAPIEN system in a randomized controlled trial of patients with symptomatic severe aortic stenosis who could not have surgery. The longer-profile SAPIEN XT incorporates important enhancements to the valve support frame, the valve leaflet geometry, the delivery system, and a significant reduction in sheath size designed to improve clinical outcomes.

This noninferiority trial included patients with severe aortic stenosis, NYHA Class ≥II and ≥50% risk of death or of serious irreversible morbidity as assessed by a cardiologist and 2 surgeons. After being assessed for inoperability and transfemoral access, patients (n=560) were randomly assigned 1:1 to THV replacement with either the SAPIEN XT or SAPIEN system. The primary study endpoint was a composite of all-cause mortality, disabling stroke, and rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure at 1 year.

Randomized patients (n=560) were 50% female, a mean age of 84 years, and had a mean Society of Thoracic Surgeons (STS) score of 10.3. More than half (59%) were deemed inoperable due to frailty.

At 12 months, SAPIEN XT was noninferior for the primary endpoint compared with SAPIEN (33.9% vs 34.7%; HR, 0.97; 95% CI, 0.73 to 1.30; p for noninferiority= 0.0034; p for superiority=0.863; Figure 1). There was no significant difference in all-cause mortality at 12 months between the SAPIEN XT and SAPIEN groups (22.5% vs 23.7%; HR, 0.93; 95% CI, 0.66 to 1.33; p=0.706; Figure 2). There were also no significant differences between the 2 groups in the number of disabling strokes or rehospitalization events.

Figure 1. All-Cause Mortality, Disabling Stroke, and Rehospitalization



*Preliminary based upon 100% CEC adjudication at 30 days and 89% CEC adjudication at 1 year.

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There were no significant differences between the SAPIEN XT and SAPIEN groups at 30 days for the primary endpoint (17.0% vs 15.3%; p=0.60), all-cause mortality (3.5% vs 5.1%; p=0.36), or disabling stroke (3.2% vs 3.0%; p=0.85).

There were lower rates of major vascular complications with SAPIEN XT (9.6% vs 15.5%;