et al. *N Engl J Med*. 2014]. The components of the primary outcome, as well as the secondary outcome of all-cause mortality, were also significantly reduced.

New results from analyses of prespecified outcomes showed that HF progression is attenuated and fatal and that nonfatal worsening heart failure (WHF) is delayed or prevented with LCZ696 when compared with enalapril, according to John J. V. McMurray, MD, University of Glasgow, Glasgow, Scotland, UK. LCZ696 combines a neprilysin inhibitor prodrug (sacubitril) and the angiotensin receptor blocker valsartan, thereby blocking both the AT_1 receptor and inhibiting the enzyme neprilysin, which breaks down natriuretic peptides and other vasoactive substances with beneficial effects in HF, to obtain incremental benefits beyond blockade of the renin angiotensin system alone.

In the original study, the median follow-up was 27 months, and the average daily dose at the last visit was LCZ696, 375 mg, and enalapril, 18.9 mg. The patients were aged 63.8 years; 22% were women; 60% had ischemic cardiomyopathy; and the mean left ventricular ejection fraction was about 29%.

Based on patient and physician assessments, the proportion of patients with WHF at month 8 was lower with LCZ696 vs enalapril [Packer M et al. *Circulation*. 2014]. For each domain measured by the Kansas City Cardiomyopathy Questionnaire, fewer patients in the LCZ696 group reported ≥5 points in deterioration (level considered to be clinically meaningful). Regarding change in NYHA class from baseline, more patients in the LCZ696 group improved (16.7% vs 14.9% with enalapril; $P=.0015$), and fewer patients progressed to a higher NYHA class (5.4% vs 7.0%, respectively), while 78% of each group had no change.

LCZ696 had a favorable influence on a number of parameters that are a measure of WHF—including reductions in treatment failure (as measured by the need for treatment intensification), emergency department visits for HF, hospitalization for HF, intensive care unit admission, and use of inotropic drugs (Table 1).

The need for devices, ventricular assist devices, or heart transplant for WHF was numerically lower with LCZ696 vs enalapril (Table 2).

Notably, all-cause hospitalization was reduced with LCZ696 as compared with enalapril, at about 110 fewer hospitalizations per 1000 patients, stated Prof McMurray. The number of admissions for any cause, including repeat episodes, was reduced (RR, 0.84; 95% CI, 0.78 to 0.91; $P<.001$), as was the proportion of patients hospitalized (HR, 0.88; 95% CI, 0.82 to 0.94; $P<.001$).

The rate of death for WHF was lower with LCZ696 vs enalapril (HR, 0.79; $P=.34$) and was significant for all-cause death (HR, 0.84; $P<.001$), CV death (HR, 0.80; $P=.00008$), and sudden death (HR, 0.80; $P=.008$).

Table 1. Effect of Enalapril and LCZ696 on Outcomes Associated With Heart Failure Progression

	Enalapril (n = 4212)	LCZ696 (n = 4187)	HR (95% CI)	*P* Value
Treatment intensification, %	14.3	12.4	0.84 (0.74 to 0.94)	.003
Patients with HF ED visit, %	3.6	2.4	0.66 (0.52 to 0.85)	.001
ED visits for HF, no.	208	151	0.70 (0.52 to 0.94)[a]	.017
Patients hospitalized for HF, %	15.6	12.8	0.79 (0.71 to 0.89)	< .001
Hospitalizations for HF, no.	1079	851	0.77 (0.67 to 0.89)[a]	< .001
Patients requiring ICU, no.	623	549	0.87 (0.78 to 0.98)	.019
ICU stays, no.	879	768	0.82 (0.72 to 0.94)[a]	.005
IV inotropic drugs in ICU, %	5.4	3.9	0.69 (0.57 to 0.85)	< .001

ED, emergency department; HF, heart failure; ICU, intensive care unit; IV, intravenous.

[a]Rate ratio.

Source: Packer M et al. *Circulation*. 2014.

Table 2. Rate of Device Implantation, Ventricular Assist Device Insertion, and Transplant for Worsening Heart Failure

	LCZ696 (n = 4187)	Enalapril (n = 4212)	*P* Value
CRT-D	54 (1.3)	77 (1.8)	.052
CRT-P	34 (0.8)	31 (0.7)	.710
VAD	12 (0.29)	19 (0.45)	.280
Transplant	1 (0.02)	4 (0.09)	.375

Data are presented as no. (%).

CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; VAD, ventricular assist device.

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PreSERVE-AMI: CD34+ Cells Improve Cardiac Function, Reduce Events After STEMI

Written by Mary Mosley

The intracoronary (IC) infusion of bone marrow mononuclear cells after an STEMI improved cardiac function, including left ventricular ejection fraction (LVEF), infarct size, and end-systolic volume, and major adverse cardiac events (MACEs) [Huikuri HV et al. *Eur Heart J*. 2008; Martin-Rendon E et al. *Eur Heart J*. 2008; Schachinger V et al. *N Engl J Med*. 2006]. A phase 1 study

demonstrated the feasibility and safety of IC infusion of autologous CD34+ cells after an acute STEMI, and a dose-dependent improvement in perfusion [Quyyumi AA et al. *Am Heart J*. 2011].

The phase 1 study suggested a threshold dose of 10 million CD34+ cells for bioactivity, stated Arshed A. Quyyumi, MD, Emory University School of Medicine, Atlanta, Georgia, USA, and provided the basis for the phase 2 NBS10 (Also Known as AMR-001) Versus Placebo Post ST Segment Elevation Myocardial Infarction trial [PreSERVE-AMI; NCT01495364].

The double-blind PreSERVE-AMI trial randomized patients to IC autologous CD34+ cells (NBS10) or matching placebo at days 6 and 11 after stent placement. The patients had an acute STEMI and were stented within 3 days of chest pain onset; had reduced LVEF (≤45% to 48%) and wall motion abnormality; and were NYHA class I, II, or III. An infusion was given to 78 of the 100 patients in the NBS10 arm and 83 of the 95 patients in the placebo arm.

The patients had a mean age of 57 years, and most were men (about 80%). The mean LVEF was 34%, and the mean left ventricular end diastolic and systolic volume indices were 92 (placebo) to 98 (treated) and 58 (placebo) to 61 (treated), respectively. The time from symptom onset to stent placement was significantly longer in the NBS10 vs placebo arm (mean 931 vs 569 minutes; $P = .041$). Serious adverse events (SAEs) were low and similar in both arms at bone marrow harvest and infusion.

There was a similar rate of the primary safety outcome of AEs (63%; $P = .89$) and SAEs (36%; $P = .97$) at the median 12-month follow-up. A dose-dependent reduction in the proportion of SAEs was seen with the higher doses of NBS10 vs placebo.

The primary outcome of MACEs, comprising cardiac death, recurrent myocardial infarction (MI), heart failure (HF) hospitalization, or coronary revascularization, was similar at 6 months at 19.2% and 16.9% of the NBS10 and placebo arms ($P = .66$). Mortality was significantly lower with NBS10 (0 vs 3 with placebo; $P = .04$). A nonsignificant dose-dependent reduction in MACEs was observed with the higher NBS10 doses (10% for >14 million cells; 7% for >20 million cells; 14% for placebo; 17% for <14 million cells).

The primary outcome of mean change in myocardial perfusion at 6 months was –142.7 with NBS10 and –149.6 with placebo (P = NS), measured by the single-photon emission computed tomography resting total severity score. A nonsignificant reduction was found for the secondary outcome of mean change in LVEF at 6 months (4.1% with NBS10 vs 4.9% with placebo). A dose-dependent improvement in LVEF was found with the higher doses of NBS10 vs placebo. A relation between greater improvement and the higher NBS10 doses was suggested by a multiple regression model adjusted for time from pain onset to stenting ($P = .045$).

PreSERVE-AMI showed IC NBS10 was well tolerated and safe in patients with an acute STEMI. Although there were no significant differences in the primary end point of cardiac death, recurrent MI, HF hospitalization, or coronary revascularization, there was evidence that higher doses of stem cells may improve LVEF. These findings provide some evidence that this therapy may be beneficial and should be further tested to determine if stem cells can improve outcomes in patients with acute MI.

ENGAGE AF-TIMI 48: Edoxaban Safe and Effective in Elderly Patients With AF

Written by Mary Mosley

Atrial fibrillation (AF) becomes more common with increasing age. Elderly patients are at greater risk of stroke while having a higher bleeding risk with anticoagulation. Data from an unpublished new analysis of the Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation [ENGAGE AF-TIMI 48; Giugliano RP et al. *N Engl J Med*. 2013] support edoxaban as an alternative treatment to warfarin in elderly patients who require anticoagulation therapy, stated Eri Toda Kato, MD, PhD, TIMI Study Group, Boston, Massachusetts, USA. She presented a prespecified analysis that evaluated the association of age on study outcomes and the efficacy and safety of edoxaban relative to warfarin in the elderly with AF.

The ENGAGE AF-TIMI 48 trial [Giugliano RP et al. *N Engl J Med*. 2013] established the noninferiority of high-dose edoxaban (HDE; 60 mg) and low-dose edoxaban (LDE; 30 mg) to warfarin for the primary outcome of stroke and systemic embolic event (SEE) in 21 105 patients with nonvalvular AF and a $CHADS_2$ score ≥2. The edoxaban dose was halved for patients having a creatinine clearance between 30 and 50 mL/min or a body weight ≤60 kg or for those taking potent P-glycoprotein inhibitors.

Their key characteristics in the prespecified age categories for the new analyses are detailed in Table 1.

The association of age on outcomes was determined by examining the event rate in the warfarin group, which eliminated the possible influence of the edoxaban dose adjustment. This analysis revealed a significant linear association between age and stroke/SEE, ischemic stroke (IS), International Society of Thrombosis and