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

Table 1. Patient Characteristics by Age in ENGAGE AF-TIMI 48

	< 65 y (n = 5497)	65-74 y (n = 7134)	≥ 75 y (n = 8474)
Women, %	27	39	45
Warfarin time in therapeutic range, %	67	69	70
$CHADS_2$ score, mean	2.6	2.7	3.2
HAS-BLED score ≥ 3, %	16	57	56
Creatinine clearance, mL/min, median	98	74	56
Weight, kg, median	91	83	76
Dose reduction at randomization, %	10	18	41

P < .001 for all.

ENGAGE AF-TIMI 48, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation.

Haemostasis (ISTH) major bleeding criteria, and intracranial hemorrhage (ICH; *P* < .001 for all). In the ≥ 75 and < 65 age groups, the absolute risk difference was 4% for stroke/SEE and 8% for ISTH at 3 years (*P* < .001 for both), underscoring the strong relation between age and risk, which was amplified for bleeding.

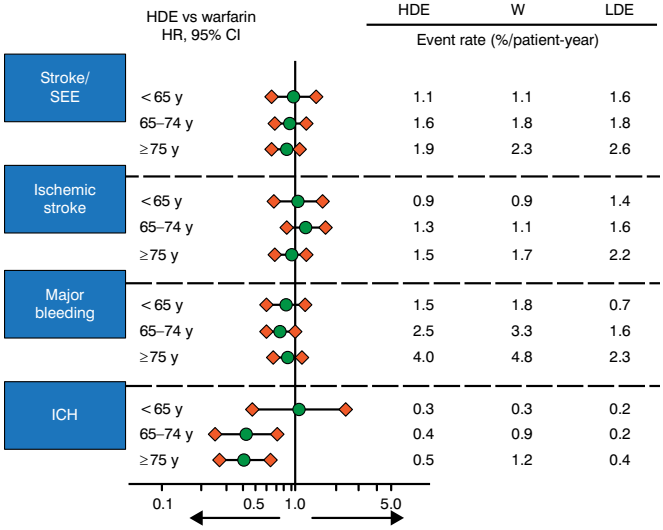
The risk of events was increased with age for all outcomes and all treatments (Figure 1). HDE provided a greater reduction in ICH in patients aged > 65 years, while HDE and warfarin had a similar effect on stroke, SEE, IS, major bleeding, and ICH in most other groups. LDE reduced major bleeding and ICH but increased this risk of stroke/SEE and IS. There was no evidence that age modified the effectiveness of treatment with edoxaban on stroke/SEE or any other outcome ($P_{Interaction} > .05$).

In the efficacy analysis of edoxaban vs warfarin, the absolute risk reduction (ARR) showed that HDE reduced stroke/SEE in all age groups but was more pronounced in patients aged ≥ 75 years (–40 events per 10 000 patient-years vs –6 and –20 for the < 65 and 65-74 age groups). It also reduced ICH in patients aged ≥ 75 years but not the other age groups (–18 events per 10 000 patient-years vs +2 and +17 for the < 65 and 65-74 age groups). LDE did not reduce stroke/SEE or IS.

The safety analysis showed a dramatic ARR with HDE and LDE for ISTH major bleeding in all age groups and for ICH in patients aged > 65 years (Table 2).

The prespecified primary net clinical outcome (approved by the Food and Drug Administration when designing the trial) comprising stroke/SEE, major bleeding, or all-cause death was reduced with HDE and LDE in all age groups, with a more marked ARR in the ≥ 75 age group (–144 and –251, respectively, vs –5 and –35 for the < 65 age group and –93 and –90 for the 65-74 age group).

Figure 1. Risk of Events by Age and Treatment in ENGAGE AF-TIMI 48



ENAGE AF-TIMI 48, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; HDE, high-dose edoxaban; ICH, intracranial hemorrhage; LDE, low-dose edoxaban; SEE, systemic embolic event; W, warfarin.

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Table 2. Safety Analysis: Absolute Risk Reduction With Edoxaban vs Warfarin[a]

	ISTH Major Bleeding			Intracerebral Hemorrhage		
Edoxaban	< 65 y	65-74 y	≥ 75 y	< 65 y	65-74 y	≥ 75 y
High dose	–34	–84	–82	+1	–55	–73
Low dose	–108	–171	–257	–10	–73	–85

ISTH, International Society of Thrombosis and Haemostasis.

[a]Events per 10 000 patient-years.

In conclusion, this analysis from ENGAGE-TIMI 48 showed that increasing age was associated with the risk of stroke/SEE, IS, ISTH major bleeding, and ICH and that the increased risk for ISTH major bleeding and ICH were more marked. Age did not affect outcomes with edoxaban vs warfarin. Edoxaban reduced the absolute risk of ISTH major bleeding and ICH and provided a superior net clinical benefit vs warfarin by decreasing the bleeding risk, particularly in patients aged ≥ 75 years. The absolute benefits with edoxaban vs warfarin were greater in patients aged ≥ 75 years because of their higher risk for stroke and bleeding.