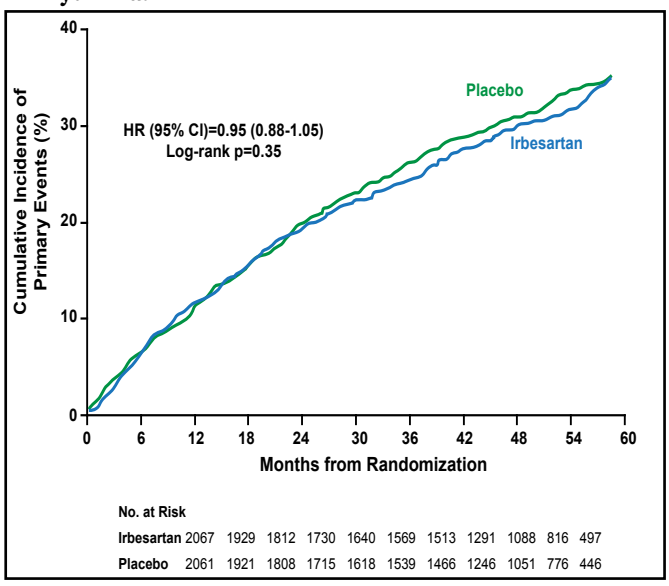
change in plasma NT-proBNP at 6 months; a vascular-event composite outcome that included death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke; and death from CV causes.

The population of I-PRESERVE was comprised of 4128 subjects (mean age 72 years; 60% women) with NY Heart Association class II, III, or IV HF and an EF ≥45%. Hypertension was present in 88% of subjects and was the primary cause of HFPEF in 63%. Subjects were randomly assigned to receive a target dose of 300 mg irbesartan (n=2067) or placebo (n=2061) daily using a forced titration protocol that began with 75 mg irbesartan at Week 1 and was increased every 2 weeks as tolerated. Follow-up continued at 4-month intervals until a total of 1440 primary endpoints occurred.

At the end of the titration phase, the mean dose of irbesartan was 275 mg/day. After a mean follow-up of 49.5 months, the primary composite endpoint occurred in 36% (742) of patients who were treated with irbesartan and 37% (763) of placebo-treated patients (HR, 0.95; 95% CI, 0.86 to 1.05; p=0.35; Figure 1). The absence of a treatment effect with irbesartan was consistent across all secondary endpoints as well as in all prespecified subgroups. Worse outcomes were seen among several prespecified subgroups, regardless of treatment, including subjects aged 75 years or older, males, subjects with EF ≤59% or diabetes, and those with an HF-related hospitalization within the prior 6 months.

Figure 1. Primary Endpoint: Death or Hospitalization for Heart Failure, MI, Unstable Angina, Stroke, or Arrhythmia.



Approximately 33% of subjects discontinued study participation in both treatment groups. Discontinuation of the study drug due to an adverse event was slightly more frequent in the irbesartan group compared with those who were randomized to placebo (16.1% vs 14.0%; p=0.07), although there was no significant difference in discontinuations due to serious adverse events. Patients who were randomized to irbesartan also were more likely to experience a doubling in serum creatinine (6% vs 4%; p<0.001) and an elevated potassium level >6.0 mmol/L (3% vs 2%; p=0.01).

The results of this trial were similar to those of other trials of renin-angiotensin receptor blockers in patients with HFPEF but stand in contrast to trials in patients with reduced EF. Dr. Carson commented, "In order for this field to move forward, we need a better understanding of the mechanism underlying this syndrome [HFPEF] and additional potential targets for treatment."

The results of the I-PRESERVE study are available online at www.nejm.org.

Mid-Regional Pro-Adrenomedullin Test Predicts 90-Day Mortality After Heart Failure

A novel biomarker, mid-regional pro-adrenomedullin (MR-proADM), has been shown to predict mortality among patients with heart failure better than the established biomarkers for prognosis that currently are available. The MR-proADM test is an indirect measure of adrenomedullin, a hormone that increases with blood vessel constriction and endothelial dysfunction, both of which frequently are present in patients with heart failure and are indicators of poor prognosis.

MR-proADM was compared with brain natriuretic peptide (BNP) and NT-proBNP (a biologic fragment associated with BNP) in the BACH trial (NCT00537628). BNP and NT-proBNP have been shown to be better predictors of mortality than clinical factors, such as age, gender, and renal function. The BACH trial is the largest biomarker study to be done in the setting of suspected heart failure, enrolling 1641 patients at 15 centers around the world. The patients all were evaluated for heart failure in the emergency department due to dyspnea that was unrelated to trauma or obvious myocardial infarction. Patients on dialysis were excluded

from this study. Acute heart failure subsequently was diagnosed in 568 of these patients, and 1073 patients had non-acute heart failure.

The primary endpoint of the trial was the comparison of the ability of MR-proADM and BNP to predict 90-day mortality. The researchers also evaluated the predictive value for MR-proADM and NT-proBNP, additive predictive value, and prognostic ability among all patients who were evaluated for dyspnea.

Stefan D. Anker, MD, PhD, Campus Virchow-Klinkum, Charite Medical Center, Berlin, Germany, co-principal investigator of the study, reported that the MR-proADM test had better prognostic accuracy for 90-day mortality than BNP (73.5% vs 60.8%; p<0.001). The novel biomarker also was significantly superior to NT-proBNP in predicting death within 90 days (73.5% vs 63.6%; p<0.001). The prognostic power of MR-proADM was even stronger for 30-day than for 90-day mortality (area under the curve [AUC], 0.739 vs 0.674). The corresponding AUC values were 0.555 versus 0.606 for BNP and 0.641 versus 0.664 for NT-proBNP.

Dr. Anker noted that the prognostic accuracy for 90-day mortality was improved by adding MR-proADM to BNP (chi^2 statistic 23.9; p<0.0001) or to NT-proBNP (chi^2 statistic 15.3; p<0.0001). In contrast, adding either BNP or NT-proBNP to MR-proADM did not increase the prognostic value (p=0.906 and p=0.291, respectively).

The MR-proADM test was also evaluated in terms of prognosis among all patients in the study who had visited the emergency room due to dyspnea. The prognostic accuracy of MR-proADM was significantly better than BNP or NT-proBNP (chi^2 statistic 129.5 for log MR-proADM vs 60.1 for log BNP and 83.7 for log NT-proBNP; p<0.0001). Dr. Anker pointed out that the prognostic ability of MR-proADM was in fact better among patients who did not have acute heart failure than among those who did (interaction p=0.005).

The better prognostic ability of MR-proADM makes it a superior risk stratification tool, which can help lead to better patient management, said Dr. Anker. However, because the 90-day mortality is high for all patients with heart failure, the biomarker actually distinguishes patients who are at very high risk from those who are at high risk. This fact, coupled with the lack of different treatment options for patients who are at very high risk of death after heart failure, makes it unclear whether the biomarker has true clinical utility.

Home Anticoagulation Monitoring is Safe for Patients with Atrial Fibrillation or Mechanical Heart Valves

For patients who are chronically taking the blood thinner warfarin, weekly home monitoring of the international normalized ratio (INR) is a safe alternative to monthly clinical monitoring, according to new results of The Home INR Study (THINRS; NCT00032591). Although more frequent home monitoring did not improve clinical outcomes compared with regular on-site clinic testing, the safety findings support its use, particularly among patients whose disabilities or geographic distance may limit access to a clinical lab for anticoagulation monitoring.

Warfarin is an effective therapy if it is managed well, which means maximizing the time that is spent at a therapeutic INR (range, 2.0-3.0) or time in the target range (TTR). When the intensity of anticoagulation exceeds the upper INR target, patients are at an increased risk for intracranial and other bleeding; when the anticoagulation intensity is below the INR target, the risk for ischemic stroke rises sharply. Therefore, carefully managed warfarin therapy can optimize the benefit of warfarin for prevention of thromboembolism. In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, a greater proportion of TTR was associated with a greater net clinical benefit – a composite of the number of thromboembolic events that is prevented by warfarin therapy minus the number of intracranial bleeds that is attributed to anticoagulation [Go AS American Heart Association Scientific Sessions 2007. Abstract 3590].

The goal of the THINRS trial was to assess whether increasing test frequency via home monitoring could further enhance the benefit of warfarin in patients who require chronic anticoagulation. Alan K. Jacobson, MD, Loma Linda University School of Medicine, Loma Linda, CA, presented results from THINRS at the American Heart Association Scientific Sessions meeting in New Orleans.

In THINRS, 2922 anticoagulated patients were randomly assigned to weekly home INR testing or monthly clinical monitoring. Prior to randomization, all patients received training on the home monitoring system and demonstrated proficiency following the testing protocol. All patients were taking warfarin to reduce the risk of thromboembolism that was related to atrial fibrillation or mechanical heart valves.