Heart Failure Hospitalization and Mortality in Non-Valvular Atrial Fibrillation
The ENGAGE-AF TIMI 48 Trial

Riccardo M. Inciardi [1], Robert P. Giugliano [2], Francesco Nordio [2], Christian T. Ruff [2], Elliott M. Antman [2], Howard Rutman [3], Eugene Braunwald [2] and Scott D. Solomon [1].

[1] Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [2] TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3] Daiichi Sankyo, Inc., Global Clinical Development Department, Basking Ridge, United States of America

Purpose

- Atrial Fibrillation (AF) is associated with an increased risk of hospitalization for heart failure (HF) and mortality.
- Little is known about the pathophysiological mechanisms leading to these events, and a need exists to identify high-risk patients.
- We aim to identify clinical predictors and characterize the additional value of cardiac biomarkers on HF hospitalization and mortality in patients with history of non-valvular AF enrolled in the ENGAGE-AF TIMI 48 trial.

Methods

- The ENGAGE-AF TIMI 48 trial was a multinational, randomized, double-blind, noninferiority design trial comparing the efficacy and safety of edoxaban versus warfarin in 21105 patients with a history of non-valvular AF and CHADS2 score ≥ 2 (Figure 1).
- We assessed the rate of the composite endpoint of HF hospitalization, death due to HF or SCD among patients without investigator identified history of HF at baseline (8981 patients).
- Cox proportional hazards clinical model was developed using a stepwise selection analysis.
- We further assessed the association between biomarkers [N-terminal (NT)-pro hormone BNP (NT-proBNP) and Troponin I) in 1997 patients with available data, adjusting for the significant clinical risk factors.

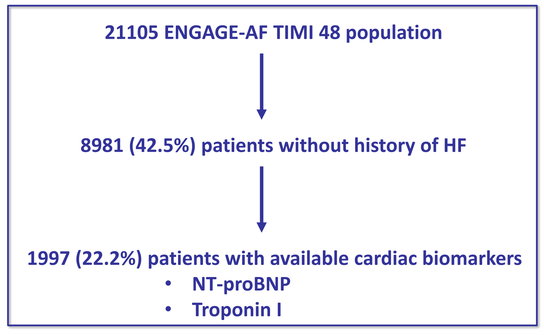


Figure 1. ENGAGE-AF TIMI 48 study population

Results

Among 8981 patients, the mean age was 72.7±8.8 years, 5517 (61.4%) were male, 7115 (79.2%) were white and 597 (9.8 %) had an LVEF <50%.

Table 1. Rates of the composite endpoint and its components

	N (%)	Event-rate 100 patient-years
HF Hospitalization or death due to HF or SCD	592 (6.6%)	2.4
- HF Hospitalization	367 (4.1%)	1.5
- Death due to HF	76 (0.8%)	0.3
- SCD	203 (2.2%)	0.8

Median follow-up 2.8 years; overall Stroke or Thromboembolic events were 450 (5.0%), event rate of 1.84 per 100 patient-years.

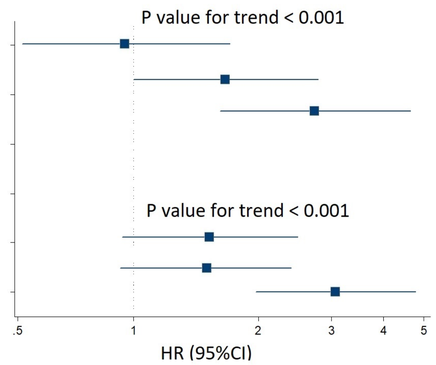
Table 2. Multivariable clinical predictors of HF hospitalization, death due to HF or SCD

Parameter	Hazard Ratio	95% CI	X^2	P-value
Age (per 10 years)	1.50	1.31 - 1.72	35.0	<0.001
ClCr ≤ 50 ml/min	1.48	1.23 - 1.78	16.6	<0.001
LVEF < 50%	1.73	1.32 - 2.28	15.3	<0.001
Diuretics use	1.36	1.15 - 1.61	13.3	<0.001
Heart rate (bpm)	1.01	1.00 - 1.02	11.0	<0.001
History of Diabetes	1.29	1.08 - 1.53	7.8	0.005
History of Heart Valve Disease	1.32	1.07 - 1.62	6.7	0.009
History of Stroke or TIA	1.25	1.05 - 1.50	6.0	0.014
History of Coronary Artery Disease	1.24	1.04 - 1.48	5.4	0.019
History of Hypertension	1.70	1.08 - 2.70	5.1	0.022

Stepwise selection entry p = 0.30, retention p = 0.05. Variables included in the stepwise analysis included: Age, Sex, BMI, Diabetes, Hypertension, Clearance Creatinine (ClCr) ≤50 ml/min, Heart Valve Disease, Previous Stroke/TIA, Coronary Artery Disease, AF type (paroxysmal vs. permanent/persistent), LVEF, ACEi/ARB, Beta Blocker, Use of Diuretics, Amiodarone, Aspirin, Lipid Lowering Medication, Heart Rate, Randomization group. 95%CI, Confidence interval

Figure 2. Adjusted association of cardiac biomarkers and the composite endpoint of HF hospitalization, death due to HF or SCD

Cardiac Biomarkers	Hazard Ratio	95% CI
NT-proBNP, pg/ml		
Q1: 0-370 REF	REF	REF
Q2: 371-776	0.96	0.54 – 1.71
Q3: 777-1360	1.67	1.00 – 2.79
Q4: 1361-18993	2.74	1.62 – 4.65
TnI-Ultra, ng/ml		
< LOD: < 0.006 REF	REF	REF
T1: 0.006-0.008	1.53	0.94 – 2.49
T2: 0.009-0.014	1.50	0.93 – 2.40
T3: 0.015-0.039	3.07	1.97 – 4.78



Hazard ratios for cardiac biomarkers are adjusted for the reported significant clinical predictors in Table 2. 95%CI, Confidence interval; Q, quartile; T, tertile; NT-proBNP, N-terminal pro-B-type natriuretic peptide. LOD, level of detection.

Table 3. Discrimination and Reclassification for HF hospitalization, death due to HF or SCD

Risk Models	C-statistics (95%CI)	NRI (95%CI)	IDI (95%CI)
Clinical Risk Model	0.67 (0.62 - 0.71)	REF	REF
Clinical Risk Model + NT-proBNP	0.70 (0.65 – 0.74)	0.40 (0.23 – 0.56)	0.015 (0.007 - 0.024)
	p < 0.001	p < 0.001	p < 0.001
Clinical Risk Model + Troponin I	0.70 (0.66 – 0.75)	0.43 (0.27 – 0.60)	0.033 (0.020 - 0.045)
	p < 0.001	p < 0.001	p < 0.001

NRI, net reclassification improvement; IDI, integrated discrimination improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 95%CI, Confidence interval.

Conclusions

- HF hospitalization and mortality are frequent complications in AF patients without a history of HF.
- High-risk clinical factors such as age, cardiovascular risk factors (hypertension, diabetes, heart valve disease), history of stroke and coronary artery disease, impaired renal function, heart rate at baseline and diuretic use are associated with increased risk of events.
- Cardiac biomarkers (NT-proBNP and troponin I) are also associated with worse outcome on top of the clinical predictors.
- The complementary use of high-risk clinical factors and cardiac biomarkers may enhance risk estimation and improve risk stratification for HF events and mortality.