Misurazione seriata di biomarcatori e rischio tromboembolico/emorragico nei pazienti con fibrillazione atriale

Sottanalisi del trial ENGAGE AF-TIMI 48

Background

- Circulating cardiovascular biomarkers may reflect underlying myocardial injury, hemodynamic stress, and inflammation that contribute to cardiac electrical and structural remodelling in patients with atrial fibrillation (AF).
- In the ENGAGE AF-TIMI 48 trial, a multimarker risk score incorporating cardiac troponin, NT-proBNP and D-dimer enhanced prognostic accuracy for stroke or systemic embolic events and death compared with the CHA_2DS_2-VASc score.
- When combined with clinical parameters in the **ABC-stroke** (age, prior stroke/TIA, hsTnT, and NT-proBNP) and **ABC-bleeding** (age, prior bleeding, haemoglobin, hsTnT, and GDF-15) risk scores, biomarkers improved prediction of stroke and bleeding risks, respectively.
- The ABC-stroke and ABC-bleeding scores were well calibrated and outperformed the CHA_2DS_2-VASc and HAS-BLED scores to predict stroke and bleeding, respectively, in this trial population.
- Few studies have examined the changes of these biomarkers in patients with AF over time, and the duration of follow-up in such analyses has been limited.

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Serial assessment of biomarkers and the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial

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Methods

- ENGAGE AF-TIMI 48 was a randomized trial of the oral factor Xa inhibitor edoxaban in patients with AF and a CHADS2 score ≥ 2.
- Nested prospective biomarker study in 6308 patients, analysing hsTnT, NT-proBNP, and GDF-15 at baseline and 12 months.
  - hsTnT was dynamic in 46.9% (≥ 2 ng/L change),
  - NT-proBNP in 51.9% (≥ 200pg/mL change),
  - GDF-15 in 45.6% (≥ 300pg/mL change) during 12months.

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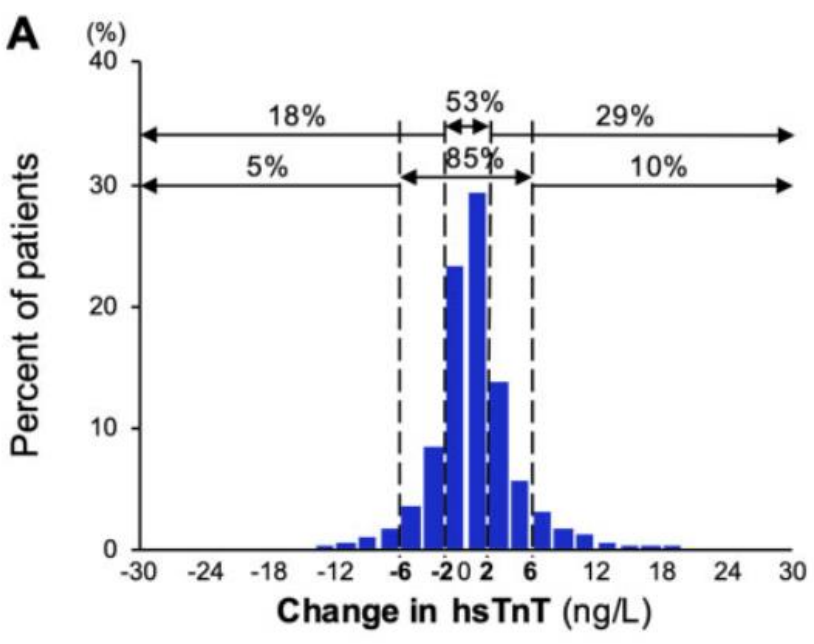
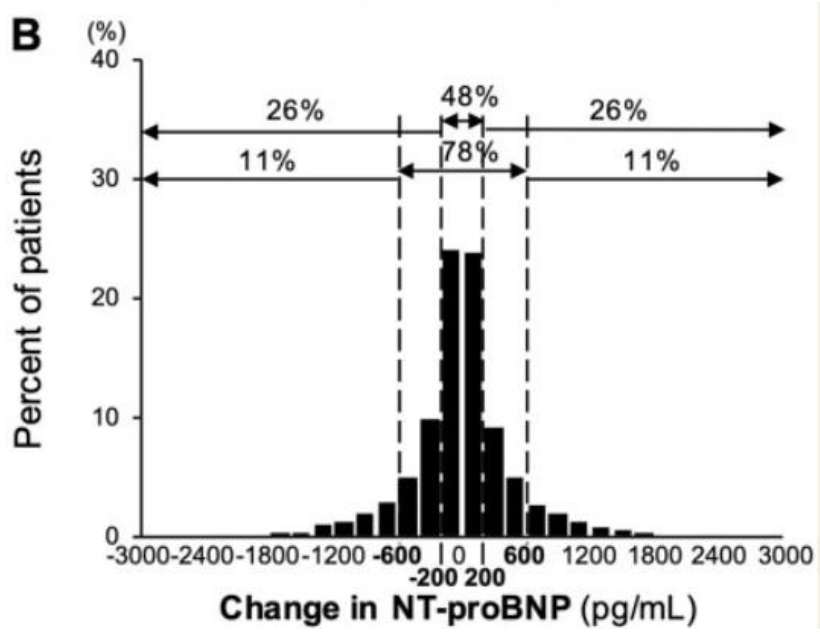
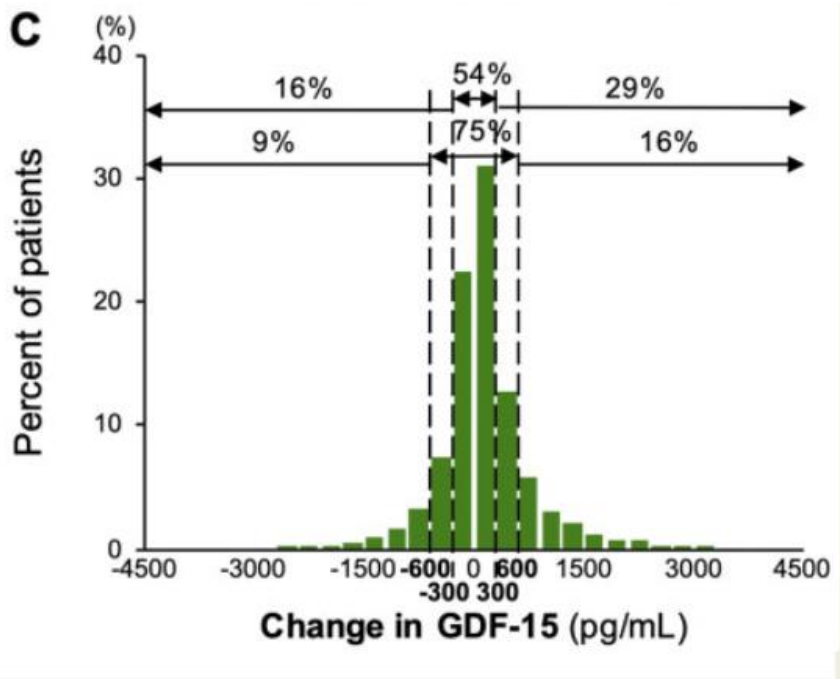
Distribution of patients by the absolute change in biomarker concentrations between baseline and 12 months







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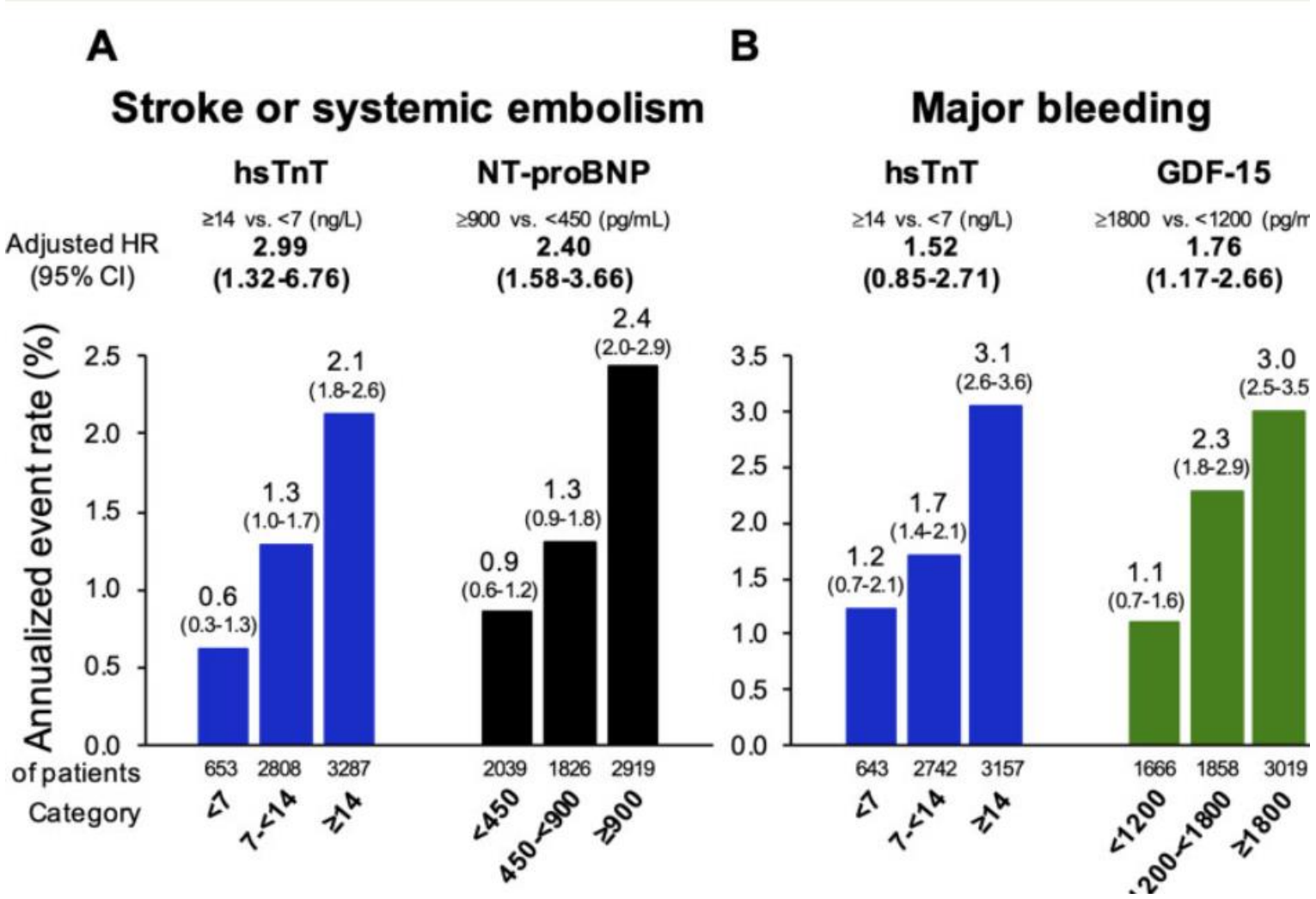
Biomarker values at 12 months and annualized subsequent event rates after 12 months



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Changes in biomarkers from baseline to 12 months and subsequent risks of clinical events

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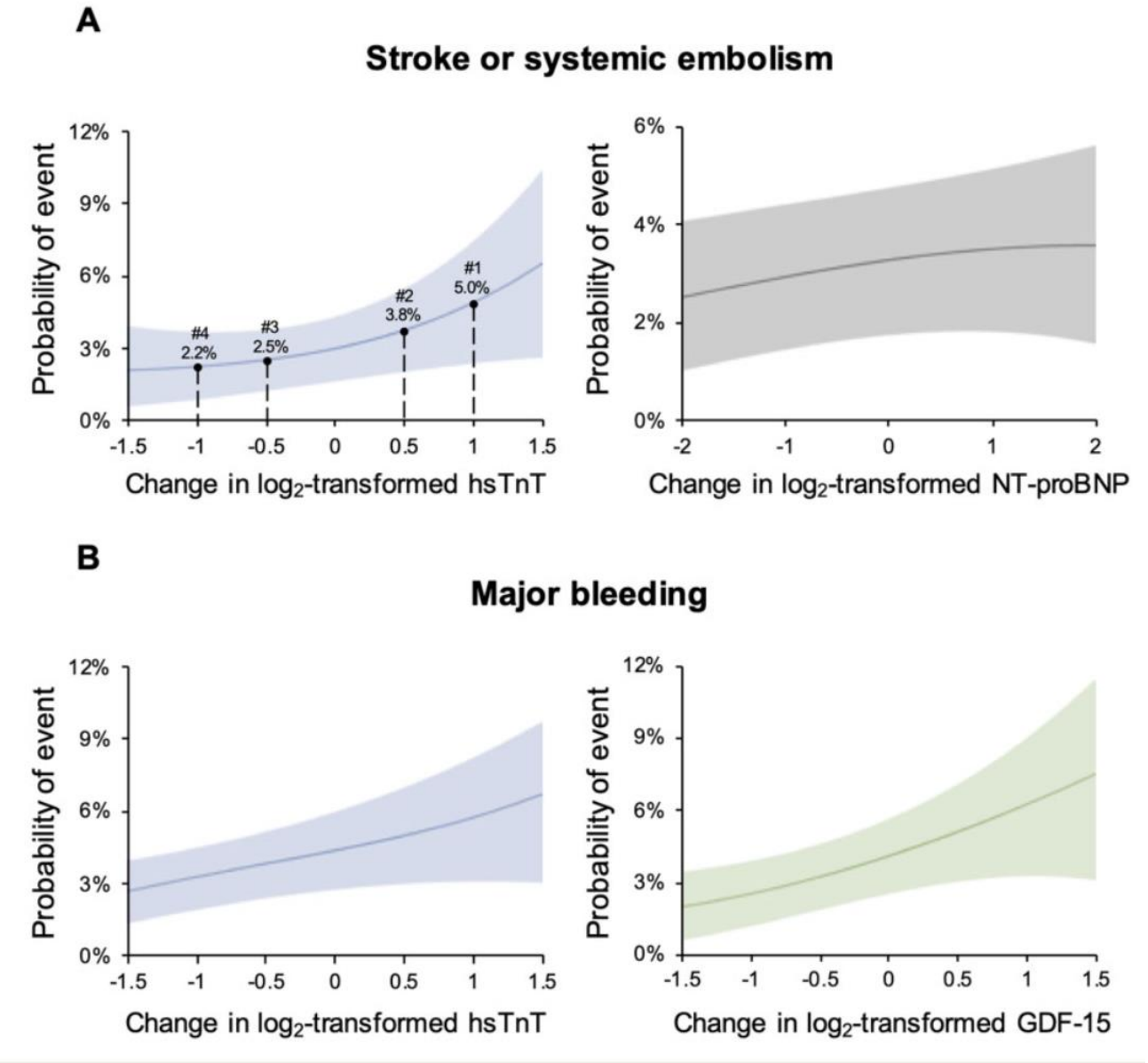
Example patients in panel A indicate specific changes in high-sensitivity troponin T;

#1 with 8 ng/L at baseline and 16 ng/L at 12 months,

#2 with 31 ng/L at baseline and 45 ng/L at 12 months,

#3 with 33 ng/L at baseline and 23 ng/L at 12 months,

#4 with 17 ng/L at baseline and 8 ng/L at 12 months



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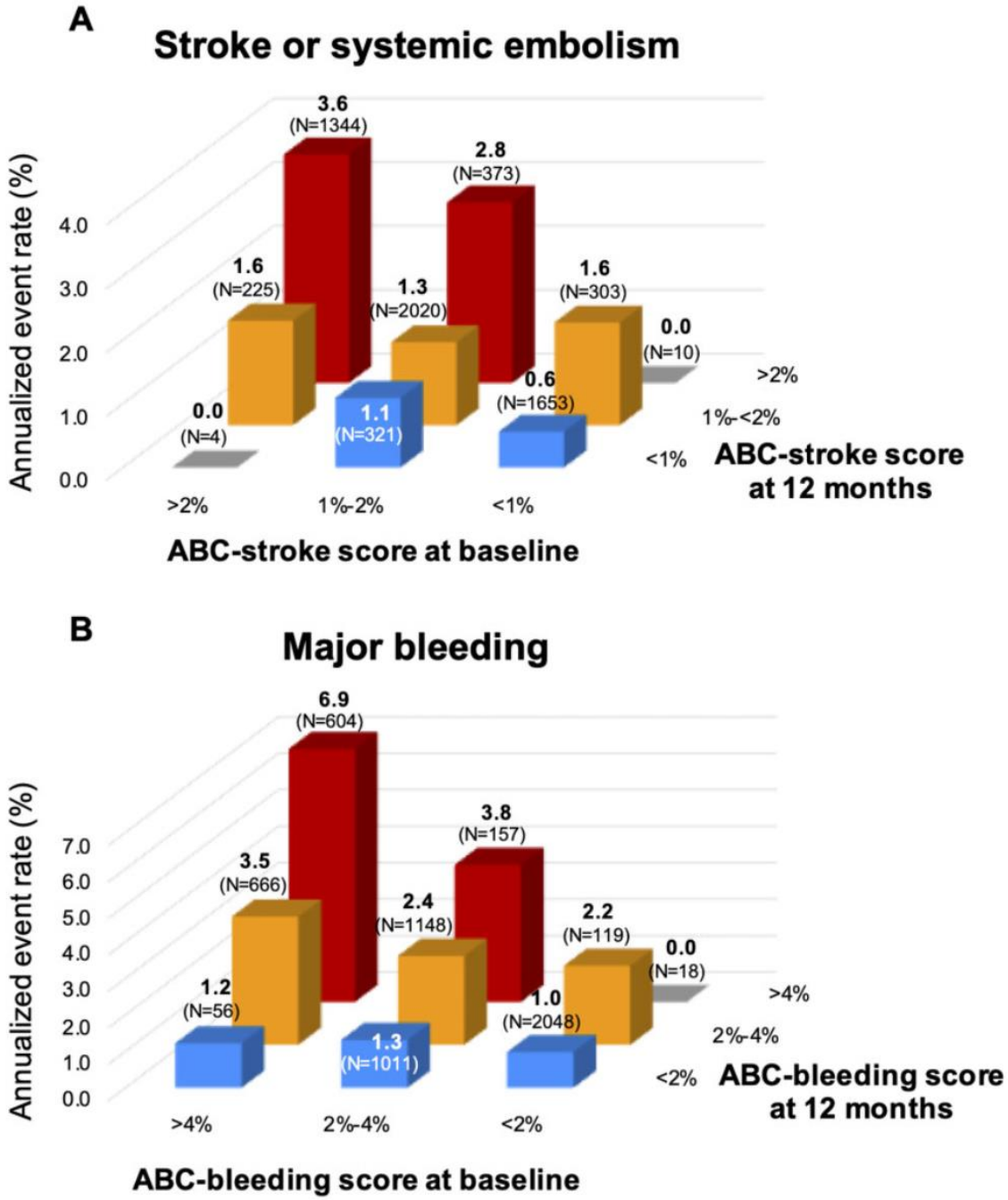
Annualized subsequent event rates stratified by age, biomarker, and clinical history score at baseline and 12 months for stroke or systemic embolism (A) and major bleeding (B). ABC, age, biomarker, and clinical history



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Serial assessment by the ABC-stroke and ABC-bleeding scores

- Reassessment of the ABC-stroke and ABC-bleeding risk scores at 12 months accurately reclassified a significant proportion of patients compared with their baseline risk (NRI 0.50; 95% CI 0.36–0.65; NRI 0.42; 95% CI 0.33–0.51, respectively.

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Limitations

- ENGAGE AF-TIMI 48 enrolled higher-risk patients with a larger burden of comorbid diseases compared with the clinical trial patients in which the ABC scores were derived → the performance of the ABC scores may be diminished in populations with a higher prevalence of non-AF comorbidities.
- All patients in the trial were anticoagulated and had at least two risk factors for stroke, application of findings in patients with AF who are not anticoagulated and those at low risk for stroke would require prospective investigation.
- Exclusion of the first 1 year of events→power was diminished in the landmark analyses performed starting at 12 months.
- Blood samples were available for the biomarker substudy only at baseline and 12 months → not assess prognostic performance at intermediate time periods (e.g. 3–6 months).
- Biomarkers or the ABC scores are not specific to cardioembolic events or bleeding in AF → the ABC score risk score may identify patients with overall poor prognosis.

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Conclusions

- In an analysis of patients with AF treated with anticoagulation from the ENGAGE AF-TIMI 48 trial, serial assessment of hsTnT, NT-proBNP, and GDF-15 revealed a substantial proportion of patients with AF had dynamic values.
- Greater increases in these three biomarkers measured over 1 year are associated with important clinical outcomes in anticoagulated patients with AF.

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