Pathogenic cardiomyopathy-associated gene variants inform prognosis in atrial fibrillation

results from exome sequencing in 17000 individuals from the TIMI trials

Sean J Jurgens, Giorgio E.M. Melloni, Shinwan Kany, Joel T. Ramo, Frederick Kamanu, David D. Berg, Marc P. Bonaca, Robert P. Giugliano, Benjamin M. Scirica, Stephen D. Wiviott, Deepak L. Bhatt, Philippe Gabriel Steg, Itamar Raz, James P. Pirruccello, Eugene Braunwald, Marc S. Sabatine, Nicholas A. Marston, Patrick T. Ellinor, Christian T. Ruff

Background

- Atrial fibrillation (AF)
  - **high morbidity** and **mortality**
  - **little personalized** medicine
- **Rare genetic variants** contribute to AF
  - notably, for **cardiomyopathy (CMP)**
- AHA/ACC guidelines for AF
  - 2B for genetic testing in early-onset
- **Clinical implication of rare variant in AF?**

Methods

- Data from **5 large clinical trials** from TIMI
  - ENGAGE-AF, PEGASUS, DECLARE, SAVOR, FOURIER
  - all with **exome sequencing (WES)**
- Curation (**likely**) **pathogenic** variants for CMP
  - Loss-of-function and ClinVar variants
  - phenotype-specific, including DCM, HCM, ARVC
- Assoc for **heart failure (HF), stroke, CVD mortality**
  - Logistic regression for baseline diseases
  - Cox regression for incident events
  - Adj. for sex, age, trial, and ancestry PCs

Baseline characteristics

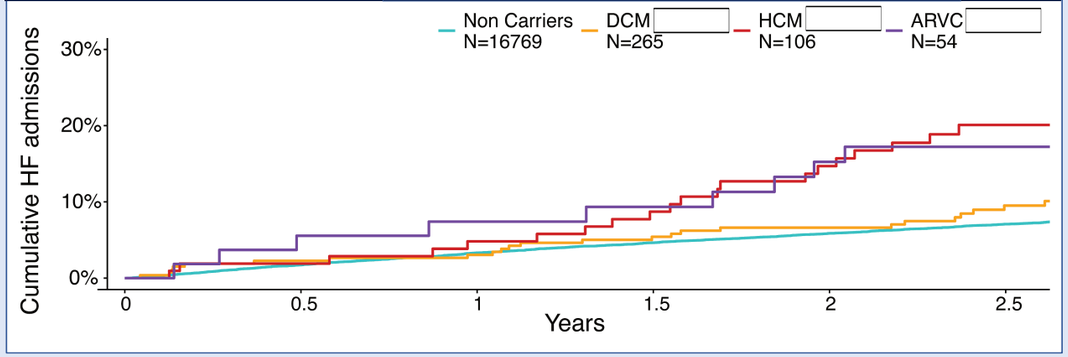
- **N=17 190 with baseline AF and WES**
- **N=421 CMP variant carriers**
  - 67±10 yrs, 65% male
- N=16 769 non-carriers
  - 70±9 yrs, 64% male

History of HF:	9 275	(54%)
HF admissions during FU:	1 365	(7.9%)
History of ischemic stroke:	2 991	(17.4%)
Ischemic stroke during FU:	599	(3.5%)
CVD death during FU:	1 147	(6.7%)

Results

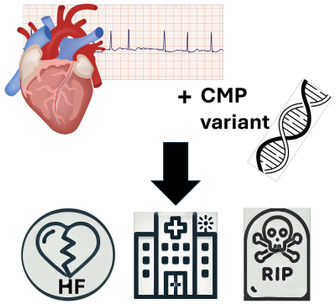
- Association between CMP variants and HF:
  - **elevated baseline HF** (OR 1.66, *P*<0.0001)
  - **elevated HF admissions** (HR 1.75, *P*<0.0001)
- between CMP variants and ischemic stroke:
  - not elevated at baseline (OR 0.99, *P*=0.96)
  - not elevated during FU (HR 0.95, *P*=0.84)
- between CMP variants and CVD death:
  - **elevated CVD death** (HR 1.46, *P*=0.02)
  - notable for DCM variants (HR 1.77, *P*=0.003)

Incident HF admissions by variant group



Conclusions

- CMP-associated variants in AF:
  - ↑ **HF and HF admissions**
  - ↑ **CVD mortality**
  - no effect on ischemic stroke
- Based on well-phenotyped trial data
- Support **prognostic implication** for rare variants
- Support select **genetic testing in AF**



Funding / Disclosures

- Parts of this study were sponsored by AstraZeneca

- **Email: sjurgens@broadinstitute.org**
- **Twitter/X: @JurgensSean**
- **LinkedIn: Sean Joseph Jurgens**