Exome sequencing in 63,700 patients in TIMI trials uncovers pathogenic cardiomyopathy variant carriers with high risk for heart failure and cardiovascular death

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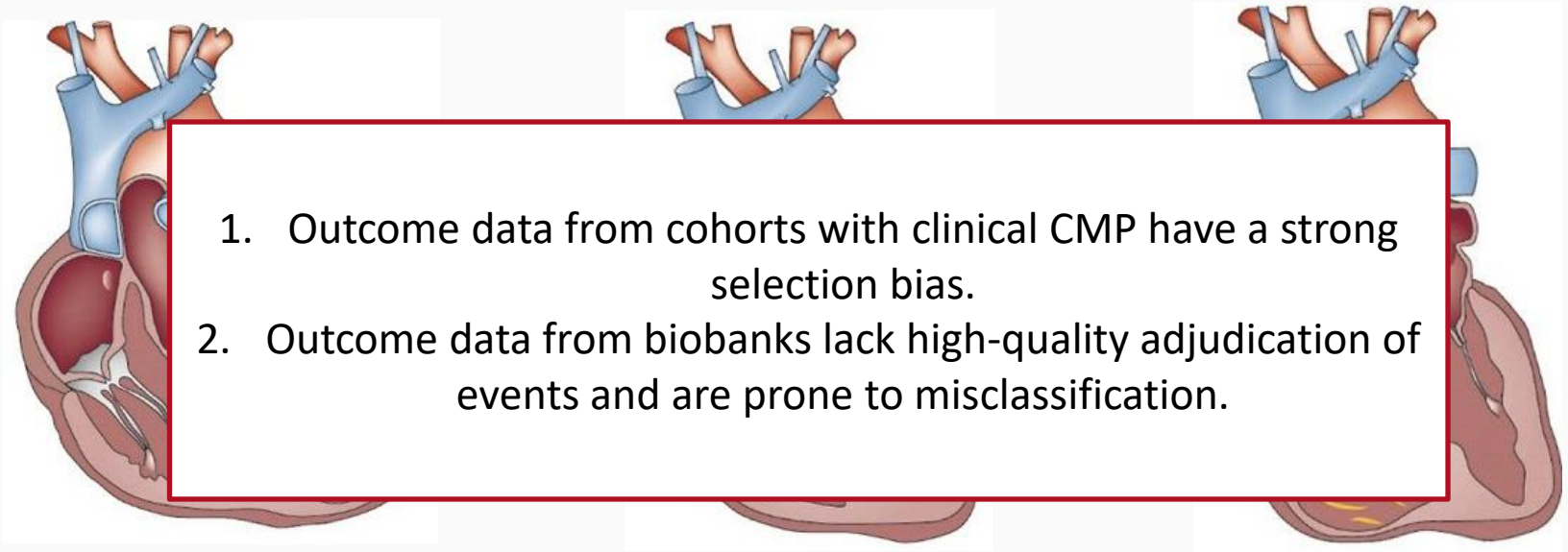
Genetic basis of cardiomyopathies

Dilated Cardiomyopathy (DCM)

Hypertrophic Cardiomyopathy (HCM)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)



1. Outcome data from cohorts with clinical CMP have a strong selection bias.
2. Outcome data from biobanks lack high-quality adjudication of events and are prone to misclassification.

TTN, BAG3, *DES*, *TNNT2*, *FLNC*, *PLN*, *LMNA*, *MYH7*, *RBM20*, *SCN5A*, *TNNC1*, *DSP*

MYH7, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *ACTN2*, *CSRP3*, *PLN*, *TTR*, *PRKAG2*

PKP2, *DSP*, *TMEM43*, *DSC2*, *DSG2*

Hershberger, R. et al. Nat Rev Cardiol 10, 531–547 (2013)

Aims and Methods

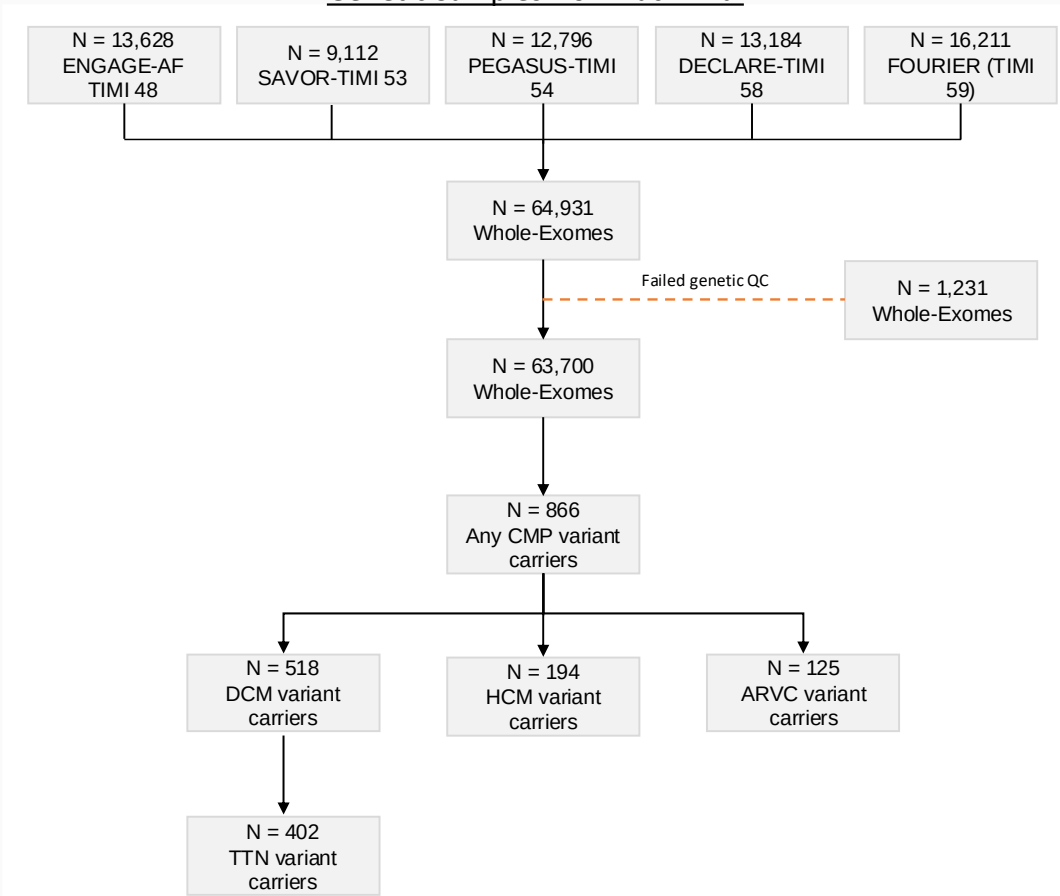
- What is the prevalence of CMP variants in patients from 5 TIMI cardiovascular outcome trials
- Do variant carriers have worse outcomes compared with non-carriers in cardiovascular outcome trials?

- Protein-truncating variants predicted to be ‘likely pathogenic’ or ‘pathogenic’ classification (PLP) in ClinVar database
- Genes with strong evidence for CMP and its subtypes DCM, HCM, or ARVC
- Logistic regression and Cox propotional hazard models adjusted for age, sex, trial and PC 1-10
- Outcomes: Hospitalization for HF, Atrial fibrillation, CV death, all-cause death

Study flow chart

Trial Populations

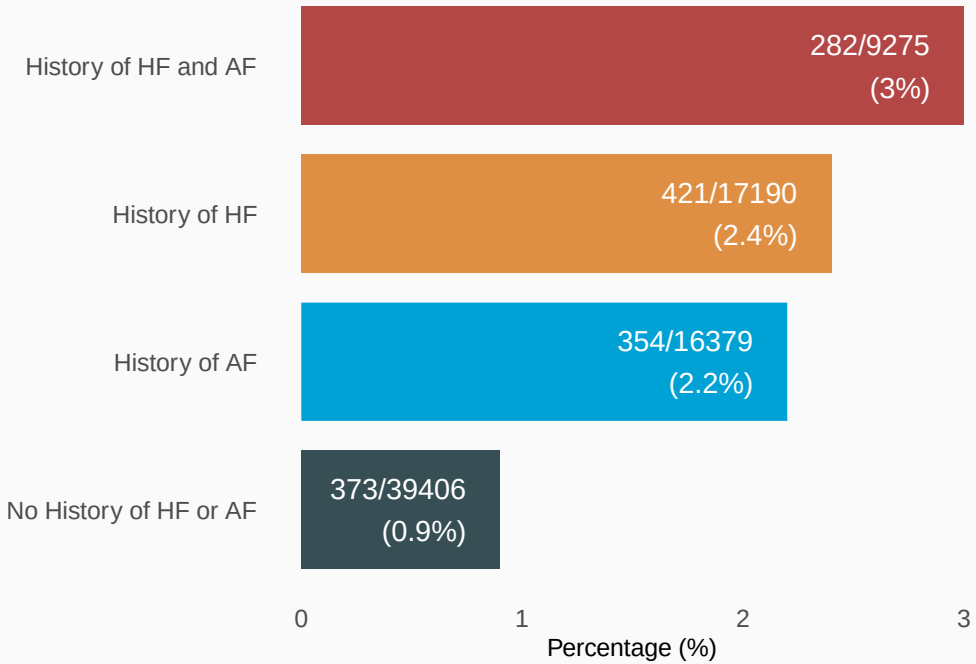
- **ENGAGE AF-TIMI 48:** Atrial Fibrillation
- **SAVOR-TIMI 53:** DM with or at risk for ASCVD
- **PEGASUS-TIMI 54:** Prior MI
- **DECLARE-TIMI 58:** DM with or at risk for ASCVD
- **FOURIER (TIMI 59):** ASCVD



Baseline characteristics

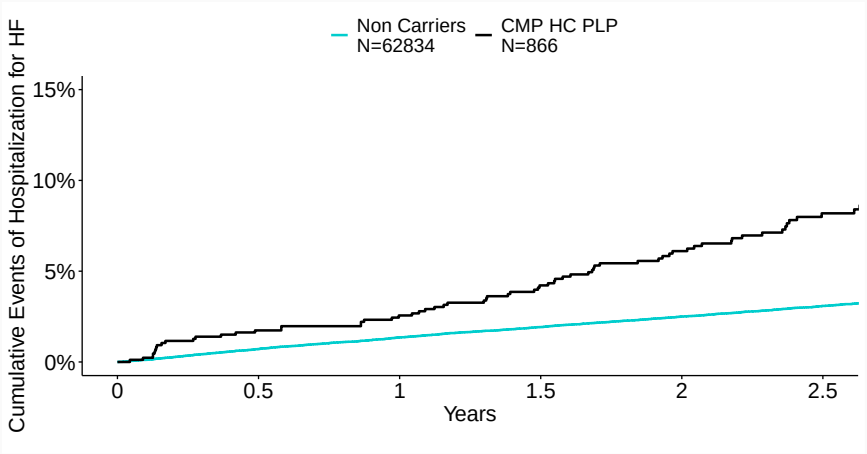
Trait	CMP variant carriers (N=866)	No CMP variant (N=62,834)	P Value
Age	65.5 ± 9.3	65.5 ± 8.9	0.72
Male Sex	68	69	0.54
ASCVD, %	66	74	<0.0001
History of Hypertension, %	85	85	0.89
History of CHF, %	41	26	<0.0001
History of Diabetes, %	50	56	0.001
History of AF, %	49	27	<0.0001
Ethnicity, %	Asian 5 Black 5 Other 4 White 86	Asian 6 Black 3 Other 4 White 88	0.006

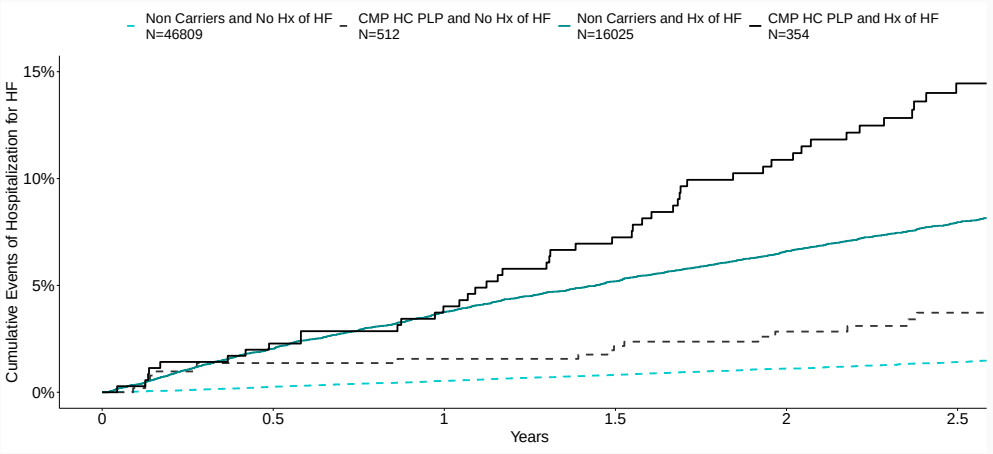
Genetic yield (positive CMP variant screening) based on baseline conditions



Incident Heart Failure Hospitalization

Mean follow-up of ~2.5 years





Overall cohort

HR 1.89, 95%-CI 1.49-2.39, P<0.0001

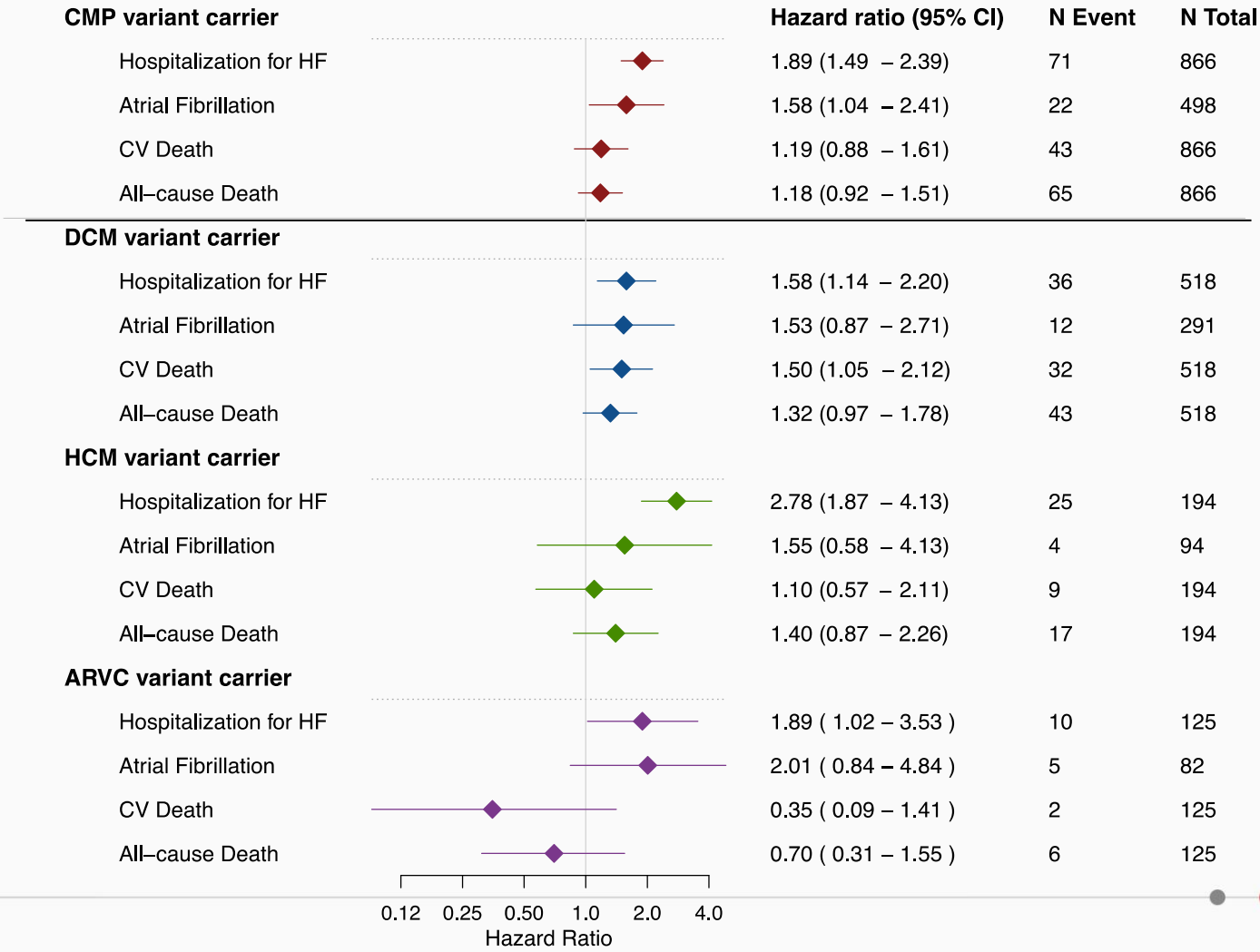
With history of CHF

HR 1.48, 95%-CI 1.12-1.95, P=0.006

Without a history of CHF

HR 2.06, 95%-CI 1.30-3.25, P=0.002

Incident events by CMP group



Conclusions

- **In over 63,000 people we observed 866 (1.3%) CMP variant carriers.**
- **Compared to those without HF or AF, the genetic yield was three-fold higher when a history of both HF and AF was present.**
- **CMP variant carriers had a higher rate for incident HHF (~1.9 fold), incident AF (~1.6 fold) and in particular DCM variant carriers a ~1.5 fold higher rate of cardiovascular death.**

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- PEGASUS-TIMI 54: AstraZeneca
- DECLARE-TIMI 58: AstraZeneca
- FOURIER (TIMI 59): Amgen