Supplemental Online Content

Selvaraj S, Claggett BL, Quarta CC, et al. Age dependency of cardiovascular outcomes with the amyloidogenic *pV142I* transthyretin variant among Black individuals in the US. *JAMA Cardiol*. Published online May 22, 2023. doi:10.1001/jamacardio.2023.1525

This supplemental material has been provided by the authors to give readers additional information about their work.

eMETHODS

ARIC study design

ARIC is a prospective study in four United States communities comprised of 15,792 individuals, aged 45–64 years recruited between 1987 and 1989 (visit 1).[1] Participants were examined approximately every 3 years until 1998, with a second examination in 1990–1992, a third in 1993–1995, and a fourth in 1996–1998. Participants returned for visit 5 between 2011-2013 and for visit 6 between 2016-2017. The institutional review board at each participating site approved the study protocol, and informed consent was obtained in writing at each examination. For the present study, we examined self-reported Black participants (N=4,266), and excluded those with missing genotypic data (either due to lack of consent or inadequate quality) for *pV142I,* leaving 3,856 participants for analysis.[2]

Definition of comorbidities

Hypertension was defined by a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or currently taking antihypertensive medication. Blood pressure was reported after averaging two readings (taken from the last two of three readings). Diabetes was defined by a self-report of physician diagnosis of diabetes, fasting serum glucose of ≥126 mg/dl, a non-fasting glucose ≥200 mg/dl, or pharmacologic treatment for diabetes. Prevalent coronary heart disease at visit 1 was defined by electrocardiographic evidence of myocardial infarction or reported history of myocardial infarction or revascularization, while prevalent coronary heart disease at visit 6 additionally includes interim coronary heart disease events obtained through ARIC adjudication. Prevalent stroke at visit 1 was defined by patient self-report of physician informed diagnosis of stroke, while prevalent stroke at visit 6 additionally includes any interim stroke events obtained through ARIC adjudication. Prevalent HF at visit 1 was defined by use of medications for HF or satisfied Gothenburg criteria. Prevalent HF at visit 6 was defined by 1)

prior hospitalization (from 2005 onward but before V6 visit) classified as definite, probable, or chronic; 2) physician HF survey with HF onset date prior to V6 (from those with self-reported HF) in which the physician answers “yes” to "has this patient ever had HF or CM?"; or (3) hospitalization with an ICD code 428.x in first position (before 01/01/2005).

Laboratory testing

Laboratory testing presented here were derived from visits 1 and 6. Genotyping for the nonsynonymous *pV142I* TTR variant (rs76992529) was determined by genotyping with the Illumina HumanExome BeadChip, version 1.0. The methods of genotyping, allele calling, and quality control have been published previously.[3]

Event Ascertainment

Longitudinal outcomes of the study included HF hospitalization, atrial fibrillation, all-cause mortality, and a composite outcome of HF hospitalization or mortality. Incident HF events post Visit 1 were initially identified using ICD discharge codes and HF events were later adjudicated (beginning in 2005). Atrial fibrillation was defined by an electrocardiogram showing atrial fibrillation, hospital discharge coded as atrial fibrillation, or atrial fibrillation listed as a cause of death. Mortality data were obtained by trained abstractors who accrued information about all out-of-hospital deaths via death certificates, hospitalized patients, physician questionnaires, and next-of-kin interview. Events were ascertained during follow-up visits for the ARIC study as well as through annual calls to participants (semi-annual since 2012), ongoing surveillance of health department certificate files, and review of local hospital-discharge lists (with outcomes determined on the basis of *International Classification of Diseases* codes).

Follow-up is complete through December 31, 2019 for all outcomes. The methods utilized for quality control, detection, and adjudication of events have been previously presented.[4-6]

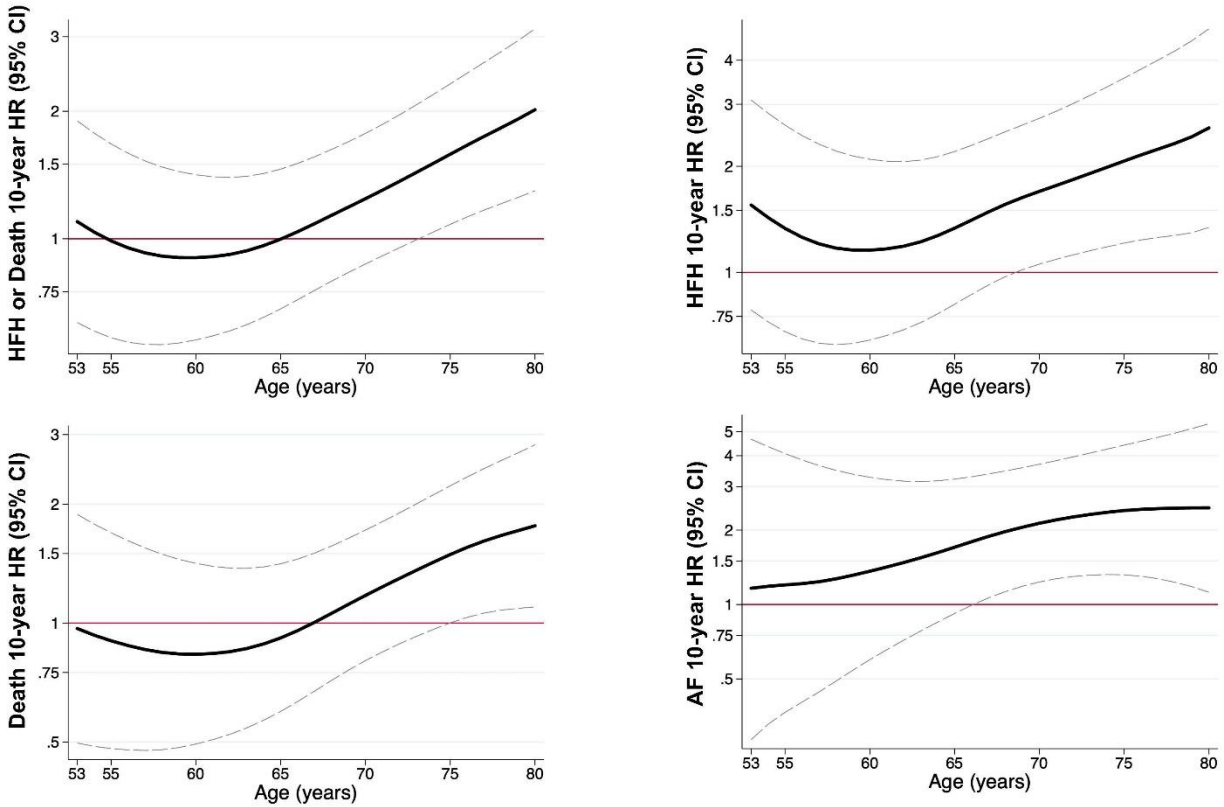
eTable. Percent of Participants Experiencing an Adverse Event at 5 and 10 Years by Carrier Status, Landmarked at 80 Years of Age

	Percent Carriers Experiencing Event (95% CI)	Percent Noncarriers Experiencing Event (95% CI)	Risk Difference Between Carriers and Noncarriers (95% CI)
Combined endpoint of HF hospitalization or death			
• **5-year risk**	45 (29, 63)	25 (22, 28)	20 (2, 47), p=0.03
• **10-year risk**	73 (50, 92)	50 (46, 53)	24 (1, 47), p=0.04
HF hospitalization			
• **5-year risk**	24 (12, 46)	11 (9, 13)	13 (-3, 30), p=0.11
• **10-year risk**	51 (25, 84)	24 (21, 28)	27 (-6, 60), p=0.11
Death			
• **5-year risk**	38 (25, 56)	23 (21, 26)	15 (-1, 31), p=0.06
• **10-year risk**	57 (37, 78)	47 (43, 50)	10 (-12, 32), p=0.38
Atrial fibrillation			
• **5-year risk**	22 (9, 46)	10 (8, 12)	12 (-6, 30), p=0.20
• **10-year risk**	33 (14, 64)	25 (21, 31)	7 (-19, 33), p=0.58

CI, confidence interval.

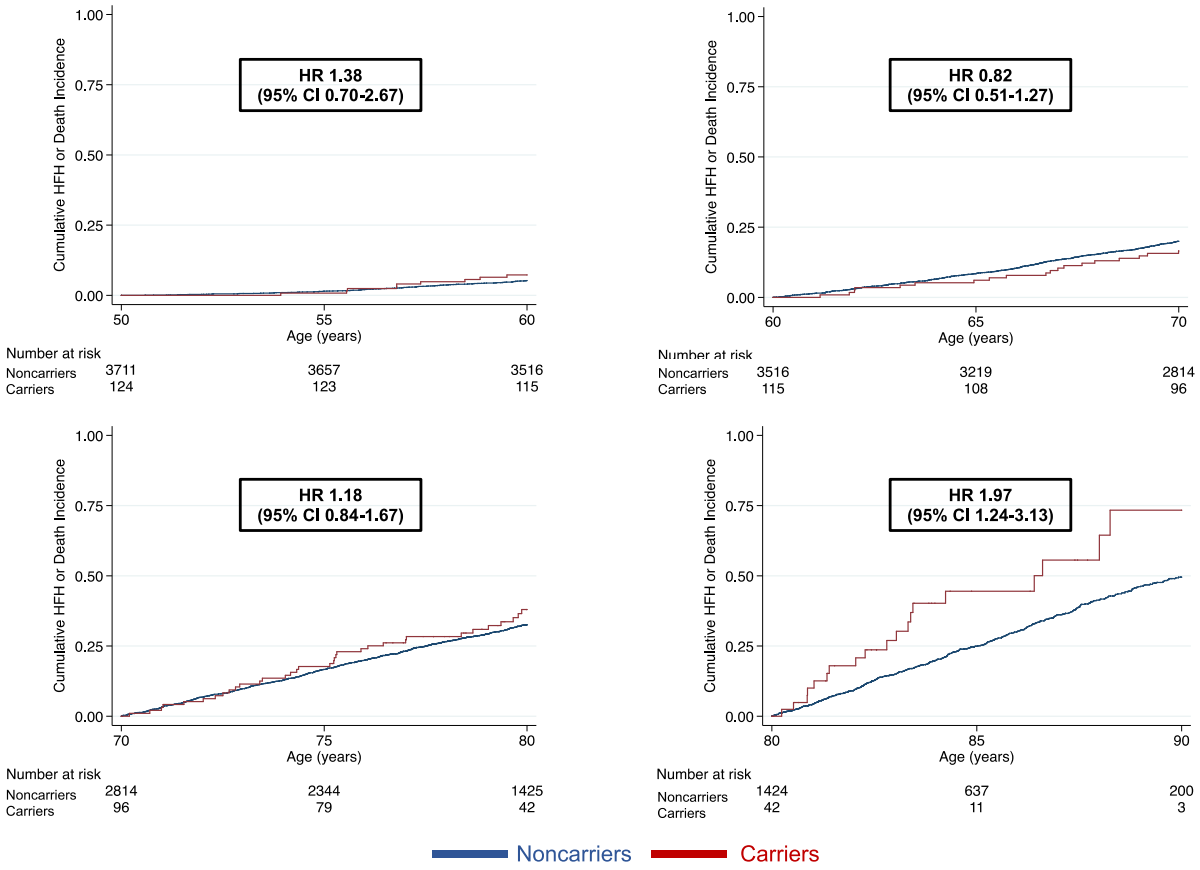
eFigure 1. pV142I Hazard Ratio for Adverse Cardiovascular Events by Age.

Caption: 10-year hazard ratios and 95% CIs are estimated at each age for carriers versus non-carriers between 53-80 for HFH or death, HF, death, and AF. Analyses are adjusted for sex and the first 5 principal components of ancestry. AF, atrial fibrillation; HFH, heart failure hospitalization; HR, hazard ratio; CI, confidence interval.



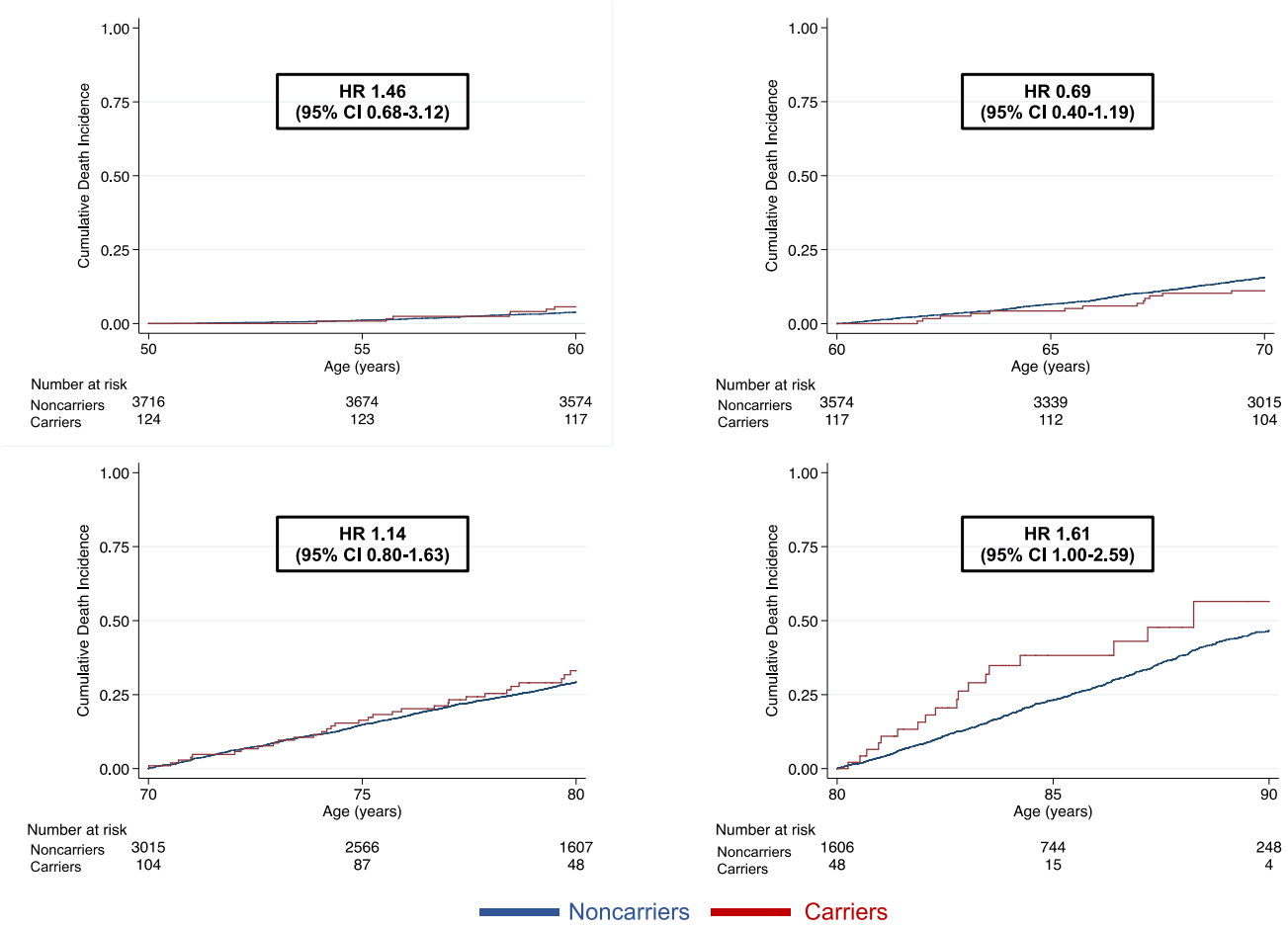
eFigure 2. *pV142I* Hazard Ratio for Heart Failure Hospitalization or Death by Decade.

Caption: Cumulative incidence curves for HFH or death by decade are shown. Analyses are adjusted for sex and the first 5 principal components of ancestry. HFH, heart failure hospitalization, HR, hazard ratio; CI, confidence interval.



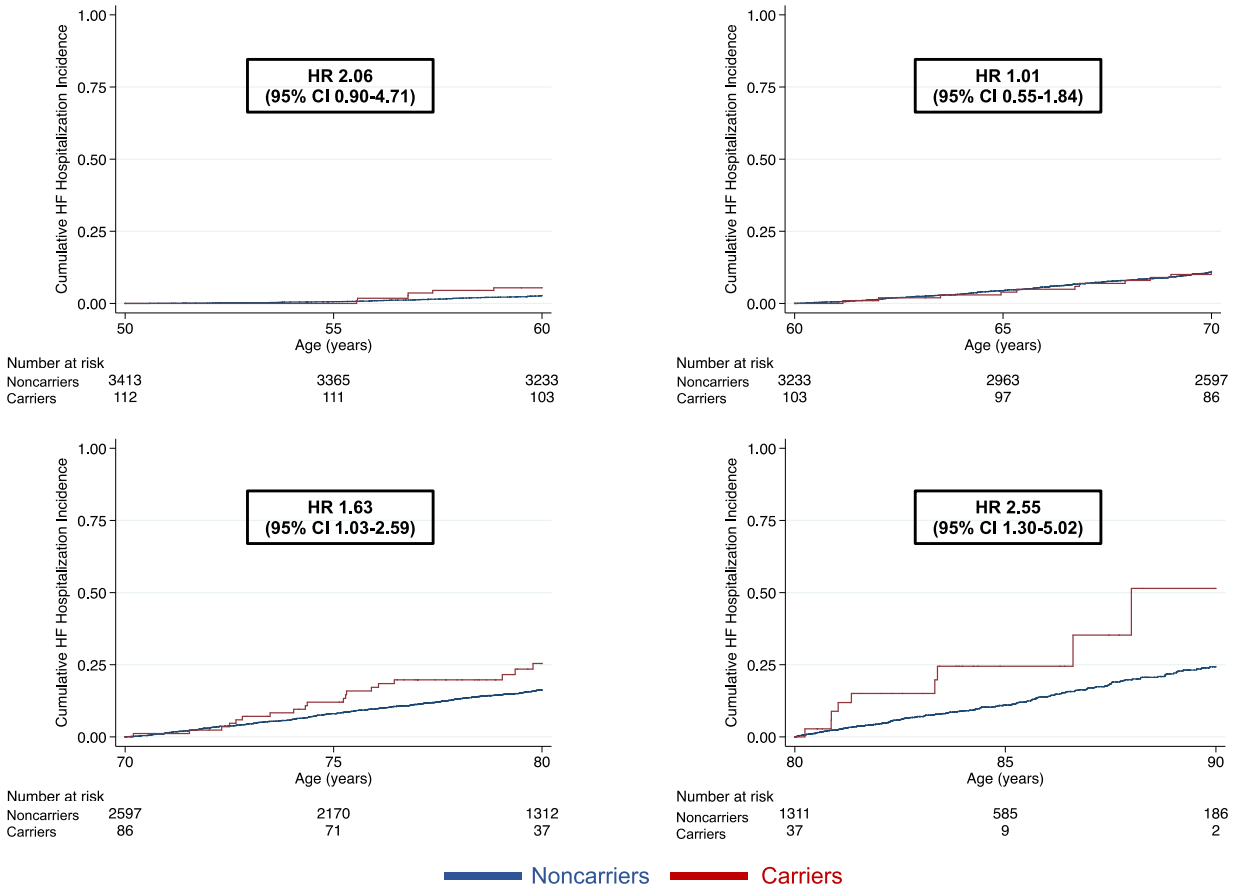
eFigure 3. *pV142I* Hazard Ratio for Death by Decade.

Caption: Cumulative incidence curves for death by decade are shown. Analyses are adjusted for sex and the first 5 principal components of ancestry. HR, hazard ratio; CI, confidence interval.



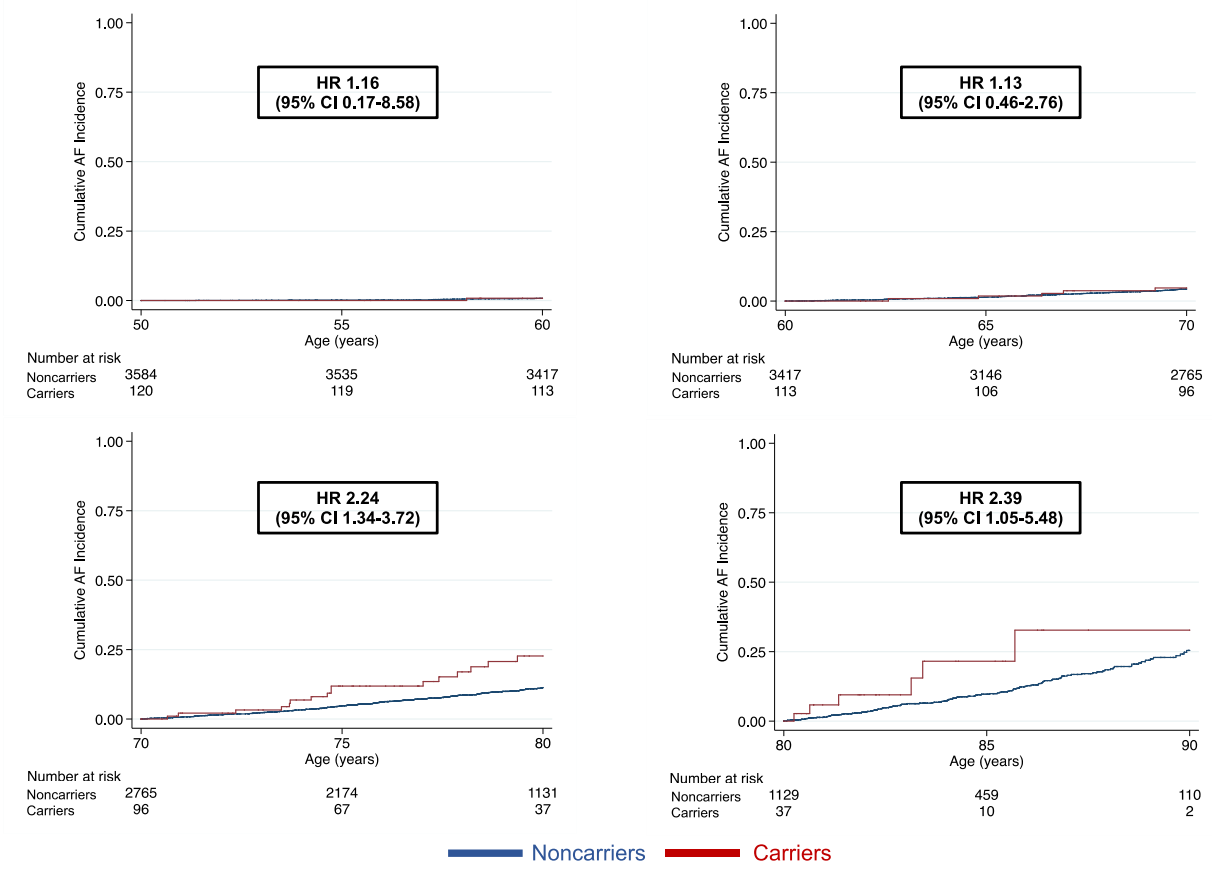
eFigure 4. *pV142I* Hazard Ratio for HF Hospitalization by Decade.

Caption: Cumulative incidence curves for HF hospitalization by decade are shown. Analyses are adjusted for sex and the first 5 principal components of ancestry. HF, heart failure; HR, hazard ratio; CI, confidence interval.



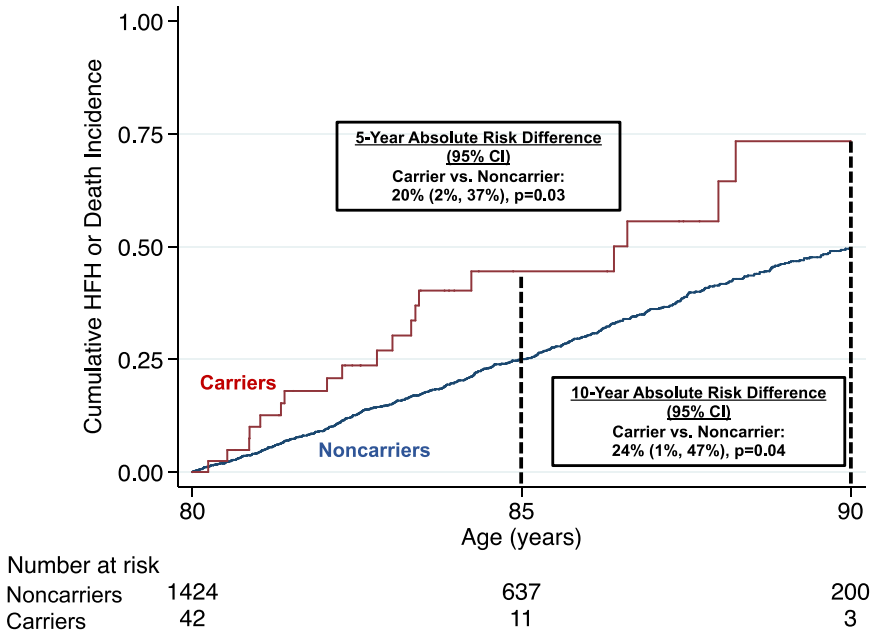
eFigure 5. *pV142I* Hazard Ratio for Atrial Fibrillation by Decade.

Caption: Cumulative incidence curves for AF by decade are shown. Analyses are adjusted for sex and the first 5 principal components of ancestry. AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval.



eFigure 6. Cumulative Heart Failure Hospitalization or Death Among Participants at least 80 Years Old.

Caption: Among participants surviving to 80 years, carriers had a significantly increased risk for the composite outcome of HFH or death. The 5-year and 10-year estimates for this outcome are delineated by carrier status. HFH, heart failure hospitalization; HR, hazard ratio; CI, confidence interval.



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