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Incident Heart Failure in Relation to Vascular Disease:

Insights from the Health, Aging, and Body Composition Study

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Abstract

Background—The contribution of heart failure (HF) unrelated to vascular disease to the overall HF burden in older adults is not well characterized.

Methods and Results—We assessed HF incidence and outcomes in 2895 participants of the Health ABC Study (age 74±3 years, 48.4% men, 41.4% black) in relation to vascular disease (coronary or peripheral or cerebrovascular disease) present either at baseline or developed prior to HF. During 11.4 years follow-up, 493 participants developed HF; 134 (27.2%) in participants without any prior vascular disease and 177 (36.8%) without coronary disease. Both baseline (hazard ratio [HR] 2.4, 95% confidence interval [CI] 1.9–2.8) and incident vascular disease (HR 4.3, 95%CI 3.6–5.2) were associated with HF. During a median follow-up of 2.1 years after HF

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onset, 67.5% participants died. Annual mortality after HF development was 21.3% in those with compared to 24.6% in those without vascular disease (HR 1.11, 95%CI 0.87–1.43; P=0.399). There were 658 all-cause (436.3/1000 person-year) and 523 HF related (346.4/1000 person-year) hospitalizations after HF development. There was no significant difference in hospitalizations between those with and without vascular disease (RR 1.04 95%CI: 0.86–1.24 for all-cause, and RR 0.84 95%CI 0.69–1.02 for HF hospitalization). HF with preserved ejection fraction was more common in participants without vascular disease (67.0% vs. 55.0%, P=0.040).

Conclusion—A significant proportion of HF in older adults develops without prior vascular disease. Outcomes for these patients are comparably poor to those with preceding vascular disease. These data suggest the need for more targeted HF prediction and prevention efforts.

Keywords

Heart failure; epidemiology; race; sex

Heart failure (HF) is an emerging pandemic that portends a poor prognosis with a 5-year mortality rate of approximately 50%.[1, 2] Epidemiological evidence, mostly from younger cohorts, ascribes the majority of HF burden to coronary artery disease (CAD).[3–10] This assertion, at least in part, underlies the current paradigm of cardiovascular disease (CVD) prediction and prevention efforts to focus exclusively on either CAD,[11] or vascular disease in general, including CAD, cerebrovascular, and peripheral vascular disease (PVD) combined.[12–15] At present there are no targeted interventions focused exclusively on HF prevention. If indeed the vast majority of incident HF was preceded by clinically manifest vascular disease, then targeted HF specific prevention efforts may not be necessary or cost-effective.

According to a recent American Heart Association policy statement, the proportional increase in HF over the next two decades will be more than any other major cardiovascular condition, which will translate into a 215% increase in direct medical costs of care by 2030.[16] In older adults, HF may develop due to age-related cardiac changes, or other comorbidities, that may or may not be related to at least manifest CAD.[17] Cardiovascular fibrotic changes and structural remodeling related to hypertension, diabetes, renal dysfunction, and obesity, may all cause HF in the absence of clinical CAD.[17, 18] Beyond increased prevalence of cardiometabolic risk factors, older adults demonstrate higher levels of low-grade inflammation,[19] endothelial dysfunction,[20] and higher prevalence of atrial fibrillation.[21] These age-related changes can contribute to development of manifest HF independent of intervening CAD.[22–24] The risk related to these risk factors may be lessened with generic prevention interventions e.g. lifestyle choices. More targeted efforts focused on interstitial matrix remodeling may provide alternate unexplored means to prevent HF in older adults. Such targeted interventions may not be warranted, however, if indeed most HF was truly preceded by CAD, in which case the current prevention focus on vascular disease should suffice.

There is a paucity of information on reliable population-based estimates of HF epidemiology in relation to vascular disease in older adults.[25–27] To address this issue, we studied the data on the participants of the Health Aging and Body Composition (Health ABC) Study.[28]

Methods

Study Population

The Health ABC Study enrolled 3075 well-functioning, community dwelling adults aged 70 to 79 years between April 1997 and June 1998. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated zip code areas surrounding Pittsburgh, PA and Memphis, TN. Exclusion criteria included difficulties with activities of daily living, obvious cognitive impairment, inability to communicate, anticipated move within 3 years, or participation in a trial involving lifestyle intervention. The institutional review boards at both study sites approved the protocol. Participants with known or missing HF status at baseline (N=140) and those with information missing on preceding vascular disease (N=40) were excluded from the analysis. The final cohort analyzed for this study included 2895 participants.

Study Outcomes

All participants were asked to report any hospitalizations and every 6 months were asked direct questions about interim events. Medical records for overnight hospitalizations were reviewed at each site. All first admissions with an overnight stay that was confirmed as related to HF were classified as incident HF. HF diagnosis was adjudicated based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study.[29] The criteria required at least HF diagnosis from a physician and treatment for HF.[30] In addition data on left ventricular ejection fraction during the index HF hospitalization was available in subset of HF cases. All deaths were reviewed by the Health ABC Study diagnosis and disease ascertainment committee and underlying causes of death were determined by central adjudication.

Study Definitions

Race was self-defined by the participant. Hypertension was defined as self-reported history of physician diagnosis accompanied by use of antihypertensive medications. Diabetes mellitus was considered present if the participant reported a history of diabetes mellitus or use of anti-hyperglycemic medication. Smoking was defined as current, past (≥100 lifetime cigarettes), or never. Left ventricular hypertrophy was diagnosed based on the following criteria; R amplitude >26 mm in either V5 or V6, or >20 mm in any of leads I, II, III, aVF, or >12 mm in lead aVL or R in V5 or V6 plus S amplitude in V1 >35 mm. Left ventricular ejection fraction (LVEF) was defined as preserved if ≥ 40%or reduced if <40.

Prevalent CAD was defined as: (1) history of surgical or percutaneous revascularization; or (2) electrocardiographic evidence of myocardial infarction; or (3) self-reported history of myocardial infarction or angina accompanied by use of antianginal medications. Incident CAD was defined as hospitalization for myocardial infarction or angina pectoris, or elective revascularization. Prevalent vascular disease was defined as prevalent: (1) CAD; (2) cerebrovascular disease (history of stroke, transient ischemic attack, or carotid endarterectomy); or (3) PVD (history of intermittent claudication or vascular bypass or angioplasty).[31, 32] Incident vascular disease was defined as incident (1) CAD; (2)

cerebrovascular disease (stroke, transient ischemic attack, or symptomatic carotid artery disease); (3) PVD; or (4) death due to cardiovascular causes.

Participants were classified as having “preceding CAD” if they had prevalent CAD at baseline or developed incident CAD that preceded or coincided with the onset of HF. Individuals were classified as having “preceding vascular disease” if they had prevalent CAD, cerebrovascular disease, or PVD at baseline or developed incident CAD, or cerebrovascular disease, or PVD that preceded or coincided with the onset of HF.

Risk Factors for Incident HF

We have previously reported independent predictors of incident HF in the Health ABC Study, including age, history of smoking, coronary heart disease, left ventricular hypertrophy, systolic blood pressure, heart rate, serum glucose, albumin, and creatinine levels.[14, 28, 33] The association of these risk factors with risk of HF was assessed in both those with and without prior vascular disease.

Statistical Analysis

The baseline characteristics were compared in individuals with and without incident HF. Individual participant characteristics were also compared in those who develop HF with and without preceding vascular disease. Continuous variables were compared using the t-test and categorical variables with the chi-square test. Cumulative event rates were obtained with the Kaplan-Meier method and compared with the log-rank statistic. Time-to-event analyses were conducted using Cox proportional hazard models. The proportional hazards assumption was evaluated by examining the Schoenfeld residuals. To assess the association of established risk factors as identified in the Health ABC HF Risk Score (age, history of smoking, coronary heart disease, left ventricular hypertrophy, systolic blood pressure, heart rate, serum glucose, albumin, and creatinine levels)[14, 27, 28, 33] with HF in participants with vs. without baseline vascular disease, multivariable hazard ratios (HR) adjusted for gender were calculated. All-cause and HF-related hospitalizations post-HF development were analyzed as count data over time at risk. Hospitalization rates and rate ratios (RR) with 95% confidence intervals (CI) were obtained by Poisson regression model for participants who developed HF with vs. without preceding vascular disease, adjusted for age and gender. In a secondary analysis, we examined post HF outcomes in a subset of participants with LVEF available at the time of incident HF, categorized as preserved (≥40%) or reduced (<40). All analyses were performed using Stata release 11 (Stata Corp LP, College Station, Texas).

Results

Baseline Participant Characteristics

The mean age of participants was 74±3 years; 48.4% were men, 41.4% were black and 27.7% had prevalent vascular disease. The baseline characteristics are presented in Table 1. Compared to participants who did not develop HF, those who did were older, had higher systolic blood pressure, heart rate, and body mass index, in both individuals with and without a preceding vascular disease. Higher prevalence of diabetes mellitus and fasting

glucose levels, and lower high-density lipoprotein cholesterol levels were observed in participants who developed HF with preceding vascular disease only.

Incident Heart Failure

After median follow-up of 11.4 (interquartile range [IQR] 7.0, 11.7) years, 493 participants (16.8%) developed HF (annual rate 18.1/1000 person-years, 95%CI 16.5, 19.7). Among those participants who developed HF, 211 (42.8%) had prevalent vascular disease, 72 (14.6%) developed incident vascular disease before HF onset, 64 (13.0%) developed HF simultaneously with a vascular event, and 7 (1.4%) had missing information on vascular disease, and were subsequently dropped from further analysis. Overall, 134 (27.2%) participants developed HF without preceding or concomitant vascular event (Figure 1a) and 177 (36.8%) without preceding CAD (Figure 1b).

Incidence of HF increased progressively across age groups, both for those with (P=0.03) and without a preceding vascular event (P<0.001), Figure 2. Gender and race related incident HF event rates stratified by preceding vascular disease are shown in Table 2 and Figure 3. Blacks were more likely to develop HF than whites with preceding vascular disease (stratified log-rank $\chi 2$ for race 4.21, P=0.04), but not without preceding vascular disease (stratified log-rank $\chi 2$ for race 2.48, P=0.11).

Heart Failure Risk Factors

All Health ABC HF Risk Model variables (age, albumin, creatinine, heart rate, fasting glucose, left ventricular hypertrophy, systolic blood pressure, and smoking) were independently associated with HF in those with and without preceding vascular disease at baseline, Table 3 Systolic blood pressure and heart rate were more strongly associated with HF in those without preceding vascular disease (interaction P<0.05) in blacks. Both baseline (HR 2.4, 95% CI 1.9, 2.8) and incident (HR 4.3, 95%CI 3.6, 5.2) vascular disease was associated with HF.

Outcomes after Heart Failure Development

Participants who remained free of HF had an annual mortality of 4.2% (95%CI 3.9, 4.5) and an all cause hospitalization rate of 23.9 admissions per 1000 person-years. During a median follow-up of 2.1 (IQR 0.4, 5.1) years after HF onset, 67.5% participants died. Annual mortality was 21.3% (18.8, 24.2) after HF development in those with preceding vascular disease and 24.6% (19.9, 30.4) in those without vascular disease (HR 1.11, 95%CI 0.87, 1.43; P=0.399). Figure 4 shows the overall survival by HF status and vascular disease. There were 658 all-cause admissions (436.3 admissions per 1000 person-year) after HF development. Of these, 495 (75.2%; 438.1 per 1000 person-years) occurred in those with preceding vascular disease and 153 (23.2%; 425.7 per 1000 person-years) in those without vascular disease (RR 1.04 95% CI: 0.86–1.24, P=0.696). There were 523 HF related hospitalizations (79.5%; 346.4 per 1000 person-year). Of these, 373 (71.3%; 330.3 per 1000 person-years) occurred in those with preceding vascular disease and 143 (27.3%; 396.3 per 1000 person-years) in those without vascular disease (RR 0.84 95% CI: 0.69, 1.02, P=0.087).

Preserved vs. Reduced Ejection Fraction

Data on left ventricular ejection fraction during the index HF hospitalization was available in 381 (77.3%) participants. The ejection fraction median was 42%, IQR 30%–55%. Median ejection fraction was lower in those with than those without preceding vascular disease (40% vs. 50% respectively, P<0.030). Proportion of participants with reduced versus preserved left ventricular ejection fraction was 45.0% and 55.0% for those with preceding vascular disease and 33.0% vs. 67.0% for those without preceding vascular disease (P=0.040). Mortality and hospitalization risk was higher among participants with reduced ejection fraction versus preserved ejection fraction for participants with preceding vascular disease (HR 1.52, 95%CI 1.14, 2.02 for mortality, P=0.004; RR 1.18, 95% CI: 0.97, 1.43, P=0.092 for all-cause hospitalization; and RR 1.32, 95%CI: 1.06, 1.64, P=0.013 for HF hospitalization) and for those without preceding vascular disease (HR 1.13, 95%CI 0.68, 1.89 for mortality, P=0.637; RR 2.31, 95% CI 1.62, 3.28, P<0.001 for all cause hospitalization; and RR 2.36, 95%CI 1.64, 3.39, P<0.001 for HF hospitalization).

Discussion

In this study, consistent with previous reports, we found that vascular disease was an independent predictor of HF in older adults and that the majority of incident cases occurred among individuals with some form of vascular disease[34, 35]. However, over a quarter of HF cases were not preceded by a vascular event and one third of cases developed among participants without clinically manifest CAD. These proportions represent a relatively large segment of the at-risk HF population that would be overlooked by the current cardiovascular disease prediction and prevention strategies focusing either specifically on CAD or vascular disease in general.

As the proportion of older individuals in the population increases, the prevalence of HF is predicted to increase substantially.[36, 37] Older individuals are more likely than younger people to develop HF, especially HF with preserved ejection fraction (HFpEF), due to increasing prevalence of cardiometabolic risk factors with ageing and age-related cardiac structural and functional changes. Our data are consistent with this finding that participants without preceding vascular disease were particularly prone to HFpEF. Beyond increased prevalence of hypertension, diabetes, obesity, and renal dysfunction, all of which can lead to cardiomyopathic changes and exert direct negative effects on the myocardium without preceding CAD, older adults demonstrate higher levels of low-grade inflammation.[19] In cohort studies, inflammation has been demonstrated to contribute to development of HF,[22] potentially through altered response to stressors, enhanced extracellular matrix remodeling, direct effects on the myocardium, and functional vascular changes (increased vascular stiffness and endothelial dysfunction) even without overt vascular disease.[38] In addition, endothelial function worsens with ageing[20] and has been demonstrated to contribute to development of HF independently of traditional risk factors.[23, 39] Finally, the incidence and prevalence of atrial fibrillation is increasing with age[21] and this may further precipitate clinical HF in older adults with stiffer left ventricles.[24] Therefore, as the population ages, it is expected that the proportion of HF not associated with vascular disease will increase, which in turn will continue to increase the proportion of HFpEF in the general population.

These trends are confirmed by recent community based observational study and by registries, showing the increases in hospitalization of patients with HFpEF compared to HF with reduced ejection fraction (HFrEF).[40]

Participants who develop HF without preceding vascular disease are at similar risk for adverse outcomes as compared to those with vascular disease, underscoring the clinical importance of this entity. Participants who developed HF without preceding vascular disease had significantly higher readmission risk than age-matched older adults without HF, and this risk was comparable to those who developed HF with preceding vascular disease. This is consistent with previous reports indicating that patients with HFpEF, which is less likely to be related to previous vascular disease, have similar event rates compared to HFrEF patients. In agreement with previous data patients with HFpEF may be more likely to survive HF hospitalization than those with HFrEF, even though they have equally high rates of readmission.[41]

In our study, those participants developing HF without preceding vascular disease were more likely to be older, had higher systolic blood pressure, heart rate and body mass index. However, these characteristics were common among those with a history of vascular disease preceding development of HF as well. While those with a history of vascular disease preceding development of HF had a higher prevalence of diabetes, other risk factors, such as hypertension were similar between the two groups. This is also consistent with previous reports indicating that those with HFpEF are more likely to be older and have a history of hypertension.

There may be physiologic mechanisms specific to development of HF in older people unrelated to vascular disease. For example, more collagen is deposited in the ventricles with aging.[42, 43] This may be related to the aging process per se or could be secondary to common co-morbidities such as diabetes and hypertension.[44, 45] Future research is needed to determine the mechanisms relevant to HF development among the elderly beyond that which can be attributed to vascular disease. In addition targeted risk prediction models are needed for HF in the elderly or HF may be including in pan-cardiovascular risk prediction models, to aid in risk stratification for HF, especially among the elderly.

Our study has several limitations. The diagnosis of incident HF was based on HF hospitalization and therefore likely underestimated the true incidence. The Health ABC Study did not record data on atrial fibrillation and did not perform echocardiograms at baseline, and therefore no data on asymptomatic left ventricular dysfunction or atrial fibrillation in our cohort. However, since prediction and prevention strategies are targeted mostly to clinically manifest HF, this limitation does not minimize the importance of our results. The incidence of asymptomatic left ventricular dysfunction in previous community-based epidemiologic studies was very low.[46, 47] In addition, this is consistent with coronary disease risk prediction and prevention strategies, e.g. in such studies, patients do not routinely undergo left heart catheterization or carotid or peripheral angiography to rule out asymptomatic coronary artery or other vascular disease, and the focus is on clinically manifest vascular or coronary disease. Nevertheless future studies must address the

incidence of HF in relation to unrecognized CAD, which is an important clinical entity in the elderly and is associated with increased mortality.[48]

In conclusion, the present study underscores the importance of vascular disease in relation to risk of HF but also reaffirms the existence of an important yet largely ignored clinical entity of HF without preceding vascular disease. Integrating incident HF into cardiovascular disease risk prediction and prevention strategies should be considered. Targeted HF prevention strategies may be beneficial at the population level and need further study.

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References

1. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. The New England journal of medicine. 2002; 347:1397–1402. [PubMed: 12409541]
2. Schaufelberger M, Swedberg K, Köster M, Rosén M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. European heart journal. 2004; 25:300–307. [PubMed: 14984918]
3. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. The New England journal of medicine. 2005; 352:225–237. [PubMed: 15659722]
4. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. The New England journal of medicine. 1986; 314:1547–1552. [PubMed: 3520315]
5. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F 3rd, DeMets DL, White BG. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. The New England journal of medicine. 1998; 339:1810–1816. [PubMed: 9854116]
6. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation. 1998; 97:282–289. [PubMed: 9462531]
7. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, Sadowski Z, Golba KS, Prior DL, Rouleau JL, Bonow RO. Navigating the crossroads of coronary artery disease and heart failure. Circulation. 2006; 114:1202–1213. [PubMed: 16966596]
8. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. The New England journal of medicine. 1996; 334:1349–1355. [PubMed: 8614419]
9. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine. 1999; 341:709–717. [PubMed: 10471456]
10. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks

with heart failure. The New England journal of medicine. 2004; 351:2049–2057. [PubMed: 15533851]

11. Grundy SM. Primary prevention of coronary heart disease: integrating risk assessment with intervention. Circulation. 1999; 100:988–998. [PubMed: 10468531]
12. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart (British Cardiac Society). 2005; 91(Suppl 5):v1–52. [PubMed: 16365341]
13. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European journal of preventive cardiology. 2012; 19:585–667. [PubMed: 22763626]
14. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2010; 56:e50–103. [PubMed: 21144964]
15. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; 117:743–753. [PubMed: 18212285]
16. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PWF, Woo YJ. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011; 123:933–944. [PubMed: 21262990]
17. Biernacka A, Frangogiannis NG. Aging and Cardiac Fibrosis. Aging and disease. 2011; 2:158–173. [PubMed: 21837283]
18. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. Circulation. 2003; 107:346–354. [PubMed: 12538439]
19. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev. 2011; 10:319–29. [PubMed: 21145432]
20. Pierce GL, Larocca TJ. Reduced vascular tetrahydrobiopterin (BH4) and endothelial function with ageing: is it time for a chronic BH4 supplementation trial in middle-aged and older adults? J Physiol. 2008; 586:2673–4. [PubMed: 18388135]
21. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J. 2008; 156:57–64. [PubMed: 18585497]
22. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J, Health ABCSI. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. J Am Coll Cardiol. 2010; 55:2129–37. [PubMed: 20447537]
23. Matsuzawa Y, Sugiyama S, Sumida H, Sugamura K, Nozaki T, Ohba K, Matsubara J, Kurokawa H, Fujisue K, Konishi M, Akiyama E, Suzuki H, Nagayoshi Y, Yamamuro M, Sakamoto K, Iwashita S, Jinnouchi H, Taguri M, Morita S, Matsui K, Kimura K, Umemura S, Ogawa H. Peripheral endothelial function and cardiovascular events in high-risk patients. J Am Heart Assoc. 2013; 2:e000426. [PubMed: 24275629]
24. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna W, Seward JB, Iwasaka T, Tsang TS. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J. 2006; 27:936–41. [PubMed: 16399778]

25. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. European heart journal. 1997; 18:208–225. [PubMed: 9043837]
26. Hoes AW, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. European heart journal. 1998; 19(Suppl L):L2–9. [PubMed: 9821002]
27. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol. 2000; 35:1628–37. [PubMed: 10807470]
28. Kalogeropoulos A, Georgiopoulou V, Kritchevsky SB, Psaty BM, Smith NL, Newman AB, Rodondi N, Satterfield S, Bauer DC, Bibbins-Domingo K, Smith AL, Wilson PWF, Vasan RS, Harris TB, Butler J. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. Archives of internal medicine. 2009; 169:708–715. [PubMed: 19365001]
29. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. Annals of epidemiology. 1991; 1:263–276. [PubMed: 1669507]
30. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Archives of internal medicine. 2005; 165:2460–2466. [PubMed: 16314541]
31. Cesari M, Penninx BWJH, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Tracy RP, Rubin SM, Harris TB, Pahor M. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). The American journal of cardiology. 2003; 92:522–528. [PubMed: 12943870]
32. Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA: the journal of the American Medical Association. 2006; 295:2018–2026. [PubMed: 16670410]
33. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circ Heart Fail. 2008; 1:125–33. [PubMed: 19777072]
34. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. Journal of the American College of Cardiology. 2000; 35:1628–1637. [PubMed: 10807470]
35. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002; 106:3068–3072. [PubMed: 12473553]
36. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. 2006 National Hospital Discharge Survey. Natl Health Stat Report. 2008:1–20. [PubMed: 18841653]
37. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012; 125:e2–e220. [PubMed: 22179539]
38. Kalogeropoulos AP, Georgiopoulou VV, Butler J. From risk factors to structural heart disease: the role of inflammation. Heart Fail Clin. 2012; 8:113–23. [PubMed: 22108731]
39. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation. 2007; 115:2390–7. [PubMed: 17452608]
40. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012; 126:65–75. [PubMed: 22615345]

41. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007; 50:768–77. [PubMed: 17707182]

42. Barasch E, Gottdiener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ, Tracy RP. Association between elevated fibrosis markers and heart failure in the elderly: the cardiovascular health study. Circ Heart Fail. 2009; 2:303–10. [PubMed: 19808353]

43. Gazoti Debessa CR, Mesiano Maifrino LB, Rodrigues de Souza R. Age related changes of the collagen network of the human heart. Mech Ageing Dev. 2001; 122:1049–58. [PubMed: 11389923]

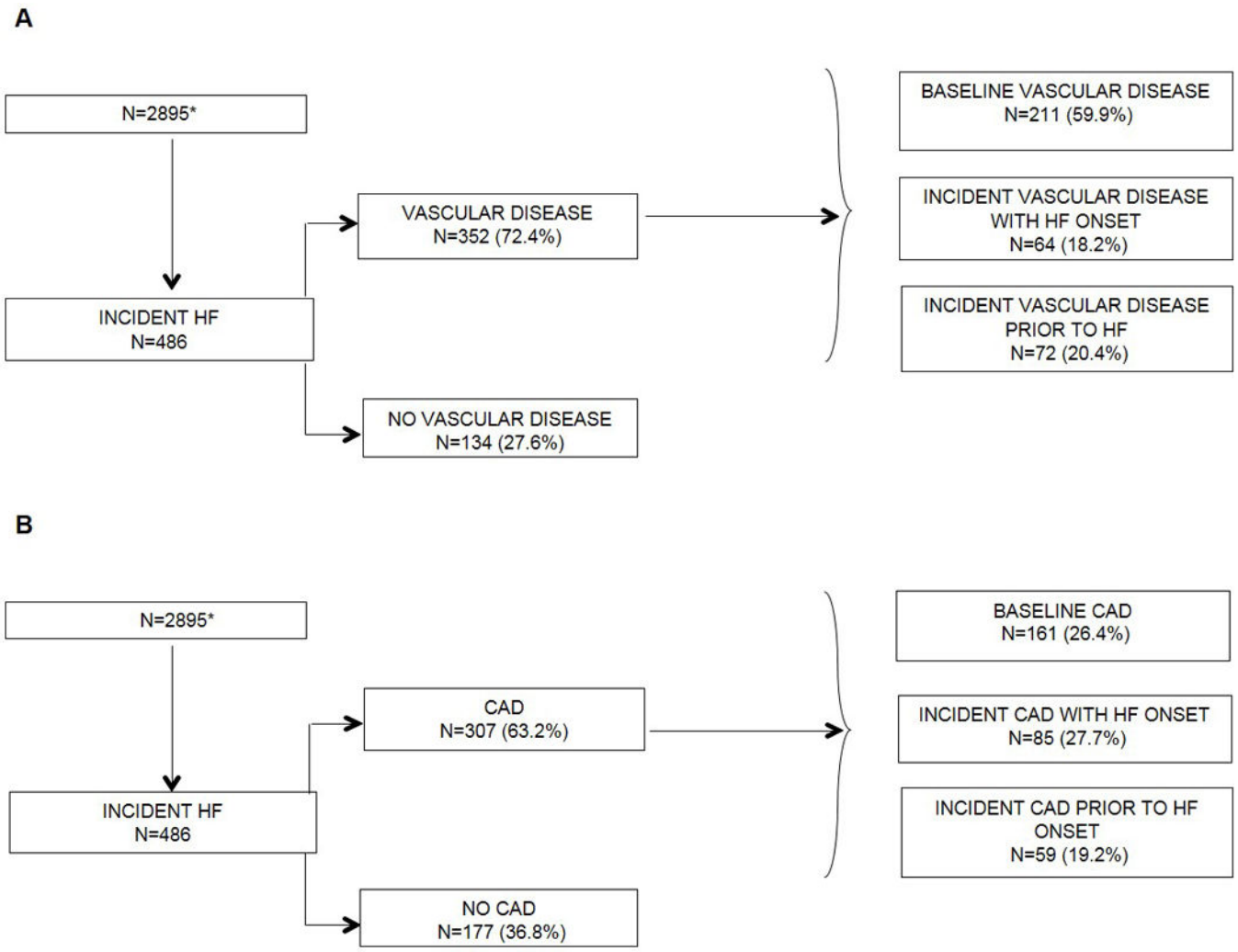
44. Falcao-Pires I, Hamdani N, Borbely A, Gavina C, Schalkwijk CG, van der Velden J, van Heerebeek L, Stienen GJ, Niessen HW, Leite-Moreira AF, Paulus WJ. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation. 2011; 124:1151–9. [PubMed: 21844073]

45. Plaksej R, Kosmala W, Frantz S, Herrmann S, Niemann M, Stork S, Wachter R, Angermann CE, Ertl G, Bijnens B, Weidemann F. Relation of circulating markers of fibrosis and progression of left and right ventricular dysfunction in hypertensive patients with heart failure. J Hypertens. 2009; 27:2483–91. [PubMed: 19887955]

46. Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of "asymptomatic" left ventricular systolic dysfunction: implications for screening. Ann Intern Med. 2003; 138:907–16. [PubMed: 12779301]

47. Betti I, Castelli G, Barchielli A, Beligni C, Boscherini V, De Luca L, Messeri G, Gheorghiade M, Maisel A, Zuppiroli A. The role of N-terminal PRO-brain natriuretic peptide and echocardiography for screening asymptomatic left ventricular dysfunction in a population at high risk for heart failure. The PROBE-HF study. J Card Fail. 2009; 15:377–84. [PubMed: 19477397]

48. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, Dyke CK, Thorgeirsson G, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Arai AE. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA: the journal of the American Medical Association. 2012; 308:890–6. [PubMed: 22948699]



* Individuals with missing prior vascular disease status or HF at baseline were excluded (N=180)

Vascular disease (VD): includes Coronary heart disease, cerebrovascular disease and peripheral vascular disease.

Figure 1.

Incident heart failure events stratified by vascular disease

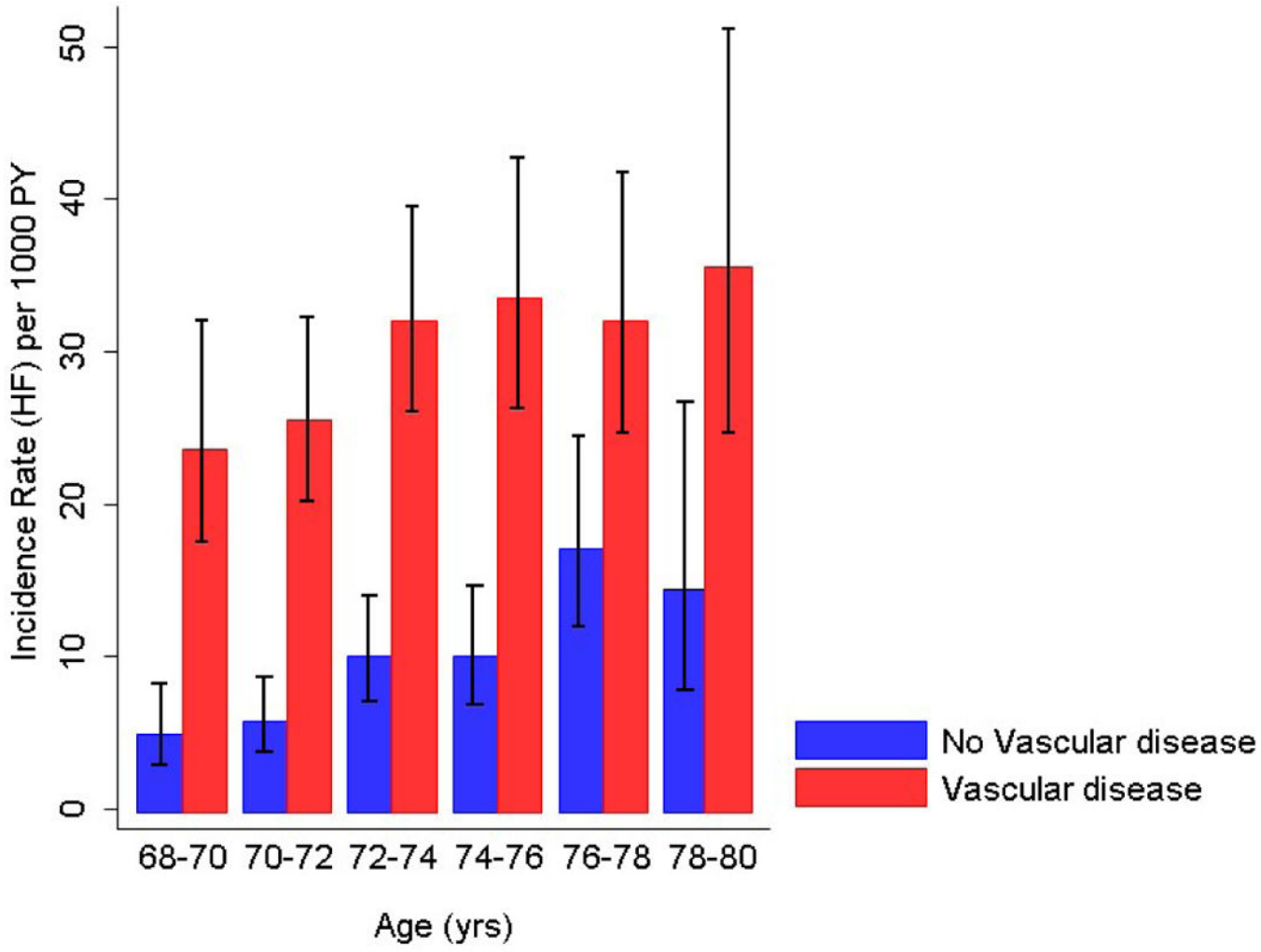


Figure 2. Heart failure rates per 1000 person-years
Error bars represent 95% confidence intervals.

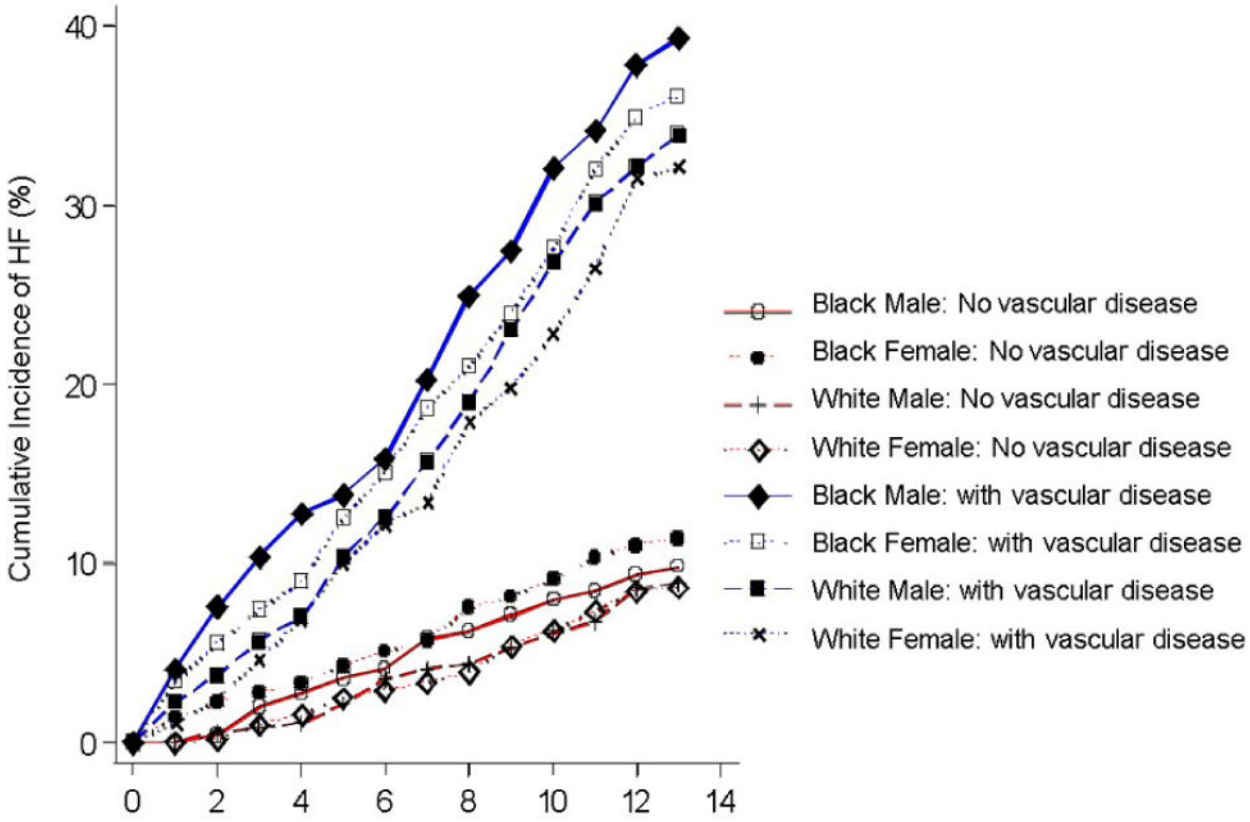


Figure 3. Incident heart failure by race, gender, and vascular disease status

Individuals with vascular disease were more likely to develop HF (stratified log-rank χ^2 for vascular disease 165.69, P<0.0001). Blacks participants with prior vascular disease were more likely to develop HF (stratified log-rank χ^2 for sex 0.41, P=0.523; for race 4.21, P=.04) but not in those without vascular disease (stratified log-rank χ^2 for sex 0.23, P=.63; for race 2.48, P=.11).

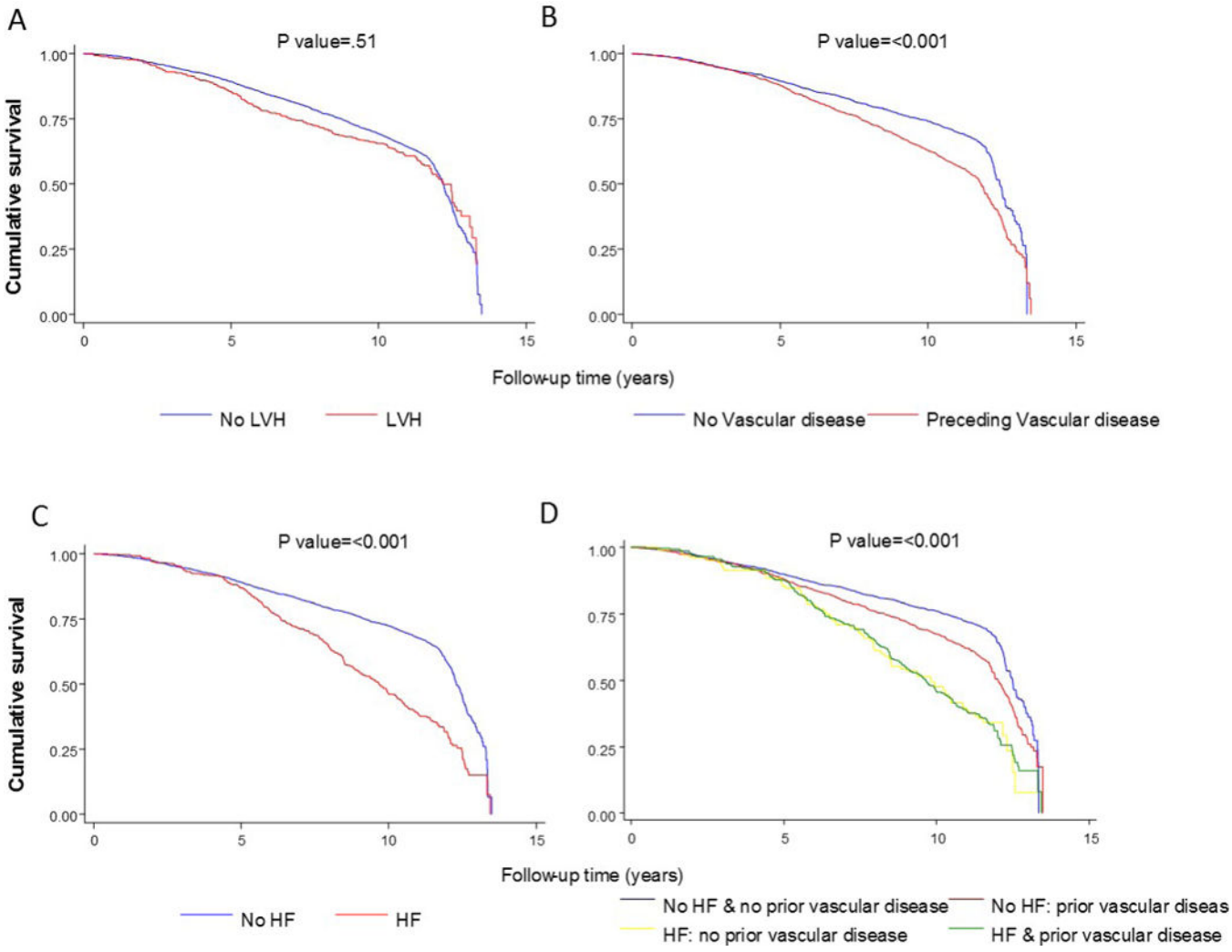


Figure 4. Cumulative survival by HF status, vascular disease status and history of LVH

A: LVH status at baseline did not affect overall survival (stratified log-rank χ^2 for LVH 0.05, P=0.828) **B:** Individuals with HF overall had shorter survival than those without HF (stratified log-rank χ^2 for vascular disease 108.13, P<0.0001). **C** Individuals with prior vascular disease had shorter survival than those without prior vascular disease (stratified log-rank χ^2 for prior vascular disease 40.67, P=<0.001). **D** In individuals with HF both with and without prior vascular disease had a lower cumulative survival than those with no HF and prior vascular disease or those without HF and vascular disease (stratified log-rank χ^2 152.18, P=<0.001).

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Table 1

Baseline Participant Characteristics

	Entire Cohort (N=2895)				Incident Heart Failure Cohort (N=486)		
Characteristic	**Overall N=2895**	**Heart Failure N=486**	**No Heart Failure N=2409**	**P**	**Vascular Disease N=352**	**No Vascular Disease N=134**	**P**
Age (years)	73.6(2.9)	74.2(2.9)	73.5(2.9)	<0.001	74.1(2.9)	74.5(2.9)	0.159
Male (%)	1393(48.4%)	253(51.7%)	1140(47.3%)	0.057	199(56.1%)	54(40.7%)	0.001
White (%)	1705(59.4%)	272(56.1%)	1433(59.4%)	0.15	199(56.1%)	73(55.0%)	0.683
Smoking Status (%)							
Never	1280(44.0%)	189(38.5%)	1091(45.1%)	0.028	127(36.3%)	62(46.2%)	0.093
Current	1307(45.1%)	236(48.4%)	1071(44.0%)	.	181(51.7%)	55(40.7%)	.
Past	304(11.0%)	60(12.1%)	244(9.9%)	.	43(12.1%)	17(13.2%)	.
Alcohol (%)							
Never	1435(49.5%)	261(53.9%)	1174(48.4%)	0.203	180(50.6%)	81(61.6%)	0.214
Occasional	612(20.9%)	92(18.7%)	520(22.0%)	.	71(19.8%)	21(15.4%)	.
1–7 drinks/week	621(22.0%)	94(19.8%)	527(22.0%)	.	74(20.9%)	20(15.4%)	.
>8 drinks/week	215(7.7%)	37(7.7%)	178(7.7%)	.	27(7.7%)	10(7.7%)	.
Diabetes (%)	426(14.3%)	105(22.0%)	321(13.2%)	<0.001	86(24.2%)	19(14.3%)	0.014
Hypertension (%)	1443(49.5%)	302(61.6%)	1141(47.3%)	<0.001	222(62.7%)	80(59.4%)	0.554
Left Ventricular Hypertrophy (%)	344(12.1%)	80(16.5%)	264(11.0%)	0.001	55(15.4%)	25(18.7%)	0.421
History of Atrial Fibrillation	38(1.1%)	17(3.3%)	21(1.1%)	<0.001	13(3.3%)	4(3.3%)	0.704
Body Mass Index (kg/m2)	27.3(4.8)	28.1(4.8)	27.1(4.7)	<0.001	28.1(4.6)	28.1(5.2)	0.974
Systolic blood pressure (mmHg)	136.0(21.0)	141.3(23.0)	134.9(20.4)	<0.001	140.1(23.0)	144.5(22.6)	0.06
Heart rate (beats/min)	65.3(11.1)	66.9(12.0)	65.0(10.8)	0.001	66.7(11.9)	67.4(12.3)	0.577
Fasting glucose (mg/dl)*	94.0(87.0,105.0)	96.0(89.0,113.0)	94.0(87.0,104.0)	<0.001	98.0(89.0,122.0)	94.0(88.0,105.0)	0.001
Albumin (g/dl)	4.0(0.3)	4.0(0.3)	4.0(0.3)	0.06	4.0(0.3)	3.9(0.3)	0.398
Creatinine (mg/dl)*	1.0(0.9,1.2)	1.0(0.9,1.2)	1.0(0.9,1.1)	0.001	1.0(0.9,1.2)	1.0(0.8,1.1)	0.01
Total cholesterol (mg/dl)	203.2(38.3)	201.5(38.1)	203.5(38.3)	0.291	200.5(174.0,226.5)	201.5(173.5,228.5)	0.837
Low density lipoprotein (mg/dl)	121.9(34.6)	121.5(33.5)	122.0(34.8)	0.814	122.6(33.3)	118.9(34.1)	0.287
High density lipoprotein (mg/dl)	54.3(17.1)	51.9(16.6)	54.7(17.1)	0.001	50.1(16.2)	56.7(17.0)	<0.001
Triglycerides (mg/dl)*	118.0(88.0,163.0)	119.0(88.0,166.0)	117.0(88.0,162.0)	0.38	129.5(90.5,173.0)	108.0(82.5,151.0)	0.009

* Value expressed as median (interquartile range) are due to highly skewed distributions and compared with the Mann-Whitney test

** Information on prior vascular event was missing for 40 participants

Table 2

Heart Failure Incidence

	Overall			Vascular Disease**			No Vascular Disease**		
	Heart Failure NN	**Cohort**	**Incidence(95% CI)**	**Heart Failure**	**Cohort**	**Incidence(95% CI)**	**Heart Failure**	**Cohort**	**Incidence(95% CI)**
Overall	493	2935	18.1 (16.6–19.8)	352	1357	29.7 (26.8–33.0)	134	1538	8.9 (7.5–10.6)
Race									
White	273	1720	16.5 (14.6–18.6)	199	797	27.5 (23.9–31.6)	73	908	8 (6.3–10.0)
Black	220	1215	20.6 (18.0–23.5)	153	560	33.3 (28.4–38.9)	61	630	10.4 (8.1–13.4)
Sex									
Male	256	1407	20.5 (18.1–23.1)	199	756	30.6 (26.6–35.2)	54	637	9.2 (7.1–12.0)
Female	237	1528	16.1 (14.1–18.2)	153	601	28.6 (24.4–33.5)	80	901	8.7 (7.0–10.9)

** Information on vascular disease was missing for 40 participants

Incidence rate calculated as per 1000 person-years

CI = confidence interval

The rates of incident HF significantly differed by race P<0.01; sex, P<0.01 and by vascular disease status, P<0.001 in all subjects.

Table 3

Heart Failure Risk Factors

	Overall		Vascular Disease		No Vascular Disease		
Risk Factor	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**P interaction**
Systolic blood pressure mmHg	1.3 (1.2–1.4)	<0.001	1.2 (1.1–1.3)	0.001	1.5 (1.3–1.8)	<0.001	0.004
Glucose mg/dl	1.2 (1.1–1.3)	<0.001	1.2 (1.1–1.3)	<0.001	1.0 (0.8–1.3)	0.756	0.180
Left Ventricular Hypertrophy	1.9 (1.4–2.5)	<0.001	1.4 (1.0–1.8)	0.032	1.8 (1.2–2.8)	0.010	0.295
Current Smoking	1.3 (1.1–1.6)	0.007	1.2 (0.9–1.5)	0.151	1.3 (0.9–1.8)	0.243	0.959
GFR ml/min/1.73m^2	0.9 (0.8–0.9)	0.001	0.8 (0.7–0.9)	0.001	1.0 (0.8–1.2)	0.963	0.150
Albumin g/dl	0.9 (0.8–1.0)	0.040	0.9 (0.8–1.0)	0.294	0.9 (0.7–1.0)	0.071	0.242
Heart Rate per minute	1.2 (1.1–1.3)	<0.001	1.2 (1.1–1.3)	0.001	1.3 (1.1–1.5)	0.004	0.529

* Note: RR (95% CI) for continuous variable are presented per 1SD higher levels of the variable

The effect estimates are adjusted for age, gender and race

BP=blood pressure, GFR= (estimated) glomerular filtration rate, HR=hazard ratio for incident heart failure, CI=confidence interval

** Information on prior vascular event was missing for 40 participants