


RESEARCH LETTER

Heart Failure Risk Associated With Severity of Modifiable Heart Failure Risk Factors: The ARIC Study

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There is an urgent need to improve heart failure (HF) prevention. Global cardiovascular health, as reflected by Life's Simple 7, is linked to incident HF.^{1,2} However, the extent to which HF incidence might be mitigated by simultaneously optimizing the modifiable HF risk factors of hypertension, diabetes, and obesity has not been rigorously quantified.

ARIC (Atherosclerosis Risk in Communities) study data have been made publicly available through the National Heart, Lung, and Blood Institute Biological Specimen and Data Repository Information Coordinating Center and can be accessed at (<https://biolincc.nhlbi.nih.gov/home/>). We performed a prospective analysis of 13 313 participants in the ARIC study (mean age, 57 years, 55% women, 24% Black) without prevalent HF at cohort Visit 2 (1990–1992). The ARIC protocol was approved by the Institutional Review Board associated with each field center and all participants provided informed consent. We examined the association of comprehensive risk factor control with incident HF through December, 31 2018. Incident HF was defined as hospitalization or death related to HF using *International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10)* codes (*ICD-9* code 428 or *ICD-10* code I50). The primary exposures were Visit 2 measures of body mass index (BMI), mean

systolic blood pressure (SBP), and hemoglobin A_{1c} (HbA_{1c}).

We categorized each risk factor as absent, controlled, mild-to-moderately uncontrolled, or severely uncontrolled. Levels of risk factor control were defined among individuals with hypertension and/or diabetes. Hypertension was defined as SBP ≥ 130 mm Hg, diastolic blood pressure ≥ 80 mm Hg, and/or self-reported use of anti-hypertensive medications. Diabetes was defined as a fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL, self-reported physician diagnosis of diabetes, self-reported use of diabetes medications, and/or HbA_{1c} $\geq 6.5\%$. Having all “controlled” risk factors was defined as SBP < 130 mm Hg for those with hypertension, HbA_{1c} $< 7\%$ for those with diabetes and BMI < 30 kg/m² (those with BMI < 18.5 kg/m² excluded). Severely uncontrolled risk factors were defined as BMI ≥ 35 kg/m², SBP ≥ 160 mm Hg, and HbA_{1c} $\geq 8\%$. Intermediate risk factor levels were considered mild-to-moderately controlled.

We categorized individuals as: absent risk factors, all controlled, 1 mild-to-moderately uncontrolled, 2 to 3 mild-to-moderately uncontrolled, 1 severely uncontrolled, or 2 to 3 severely uncontrolled. We constructed Kaplan–Meier cumulative survival curves (with proportional hazards assumption met) and

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used Poisson regression to estimate confounder-adjusted HF incidence rates at mean covariate levels for these subgroups of collective risk factor control. We used multivariable Cox regression to assess HF risks associated with different subtypes of 1 severely uncontrolled risk factor. We estimated the population attributable fraction of HF because of any uncontrolled risk factors using the equation $\text{Population Attributable Fraction} = \frac{(P \text{ population} \times (RR - 1))}{(P \text{ population} \times (RR - 1) + 1)}$, where RR is relative risk.

Within the study population, 36% had absent risk factors, 15% had all controlled risk factors, 32% had only mild-to-moderately uncontrolled risk factors, and 16% had ≥ 1 severely uncontrolled risk factor (Figure A). There were 2827 HF events over 26 years of follow-up. While those with absent risk factors had the lowest HF risk (Figure A), less collective risk factor control was associated with lower HF free survival, with a cumulative survival of 68% among those with all controlled risk factors versus 32% among those with 2 to 3 severely uncontrolled risk factors. Adjusted HF incidence rates (per thousand person-years) increased from 6.1 with absent risk factors, to 10.5 with all controlled risk factors, to 14.4 with 2 to 3 mild-to-moderately uncontrolled risk factors, to 35.1 with 2 to 3 severely uncontrolled risk factors (Figure B).

The HF risk associated with 1 severely uncontrolled risk factor (versus all controlled) was greatest for HbA1c $\geq 8\%$ (hazard ratio, 3.07; 95% CI, 2.57–3.66), versus ≈ 2 -fold increased HF risk for BMI $\geq 35 \text{ kg/m}^2$ and SBP $\geq 160 \text{ mm Hg}$. Overall, with all controlled risk factors as the reference, we estimated that 22% (95% CI, 15%–28%) of incident HF cases in the population were potentially attributable to uncontrolled risk factors.

While higher levels of weight, blood pressure and glycemia, considered individually, are each associated with greater HF risk,^{3–5} they often co-exist in real-world settings. This study examines simultaneous control of these risk factors, demonstrating that poorly controlled levels of multiple modifiable risk factors are linked to markedly increased HF risk.

Those with absent risk factors had the lowest HF risk, underscoring that primordial prevention is most desirable.² However, as most of this ambulatory population had ≥ 1 modifiable risk factor, focusing on risk factor optimization for HF prevention is relevant for most of the population. With $>15\%$ of participants having at least 1 severely uncontrolled modifiable risk factor, addressing poorly controlled risk factors should be a particular focus.

This study had several limitations. It was observational, with the likelihood of residual confounding. We did not account for likely changes in risk factor levels over time that could influence the observed

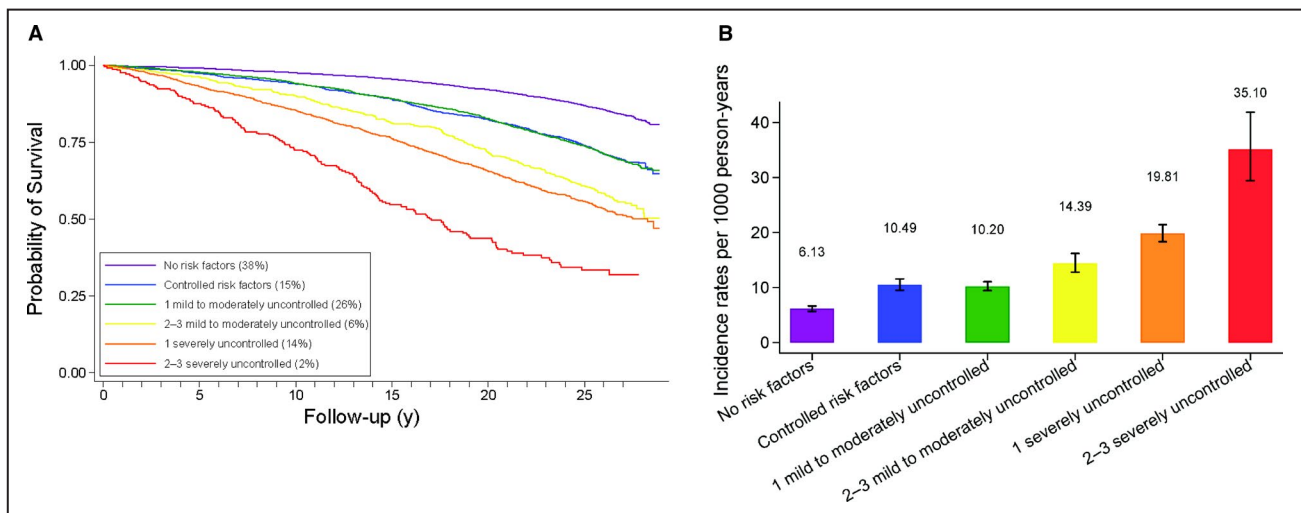


Figure. Absolute risks of heart failure associated with the levels of control and number of modifiable risk factors.

A, Kaplan–Meier curve for grouped categorization of modifiable risk factors. Probability of remaining free of heart failure based on categorizations of control of the 3 major modifiable risk factors (hypertension, diabetes, and obesity): No risk factors defined as no hypertension, no diabetes, and body mass index (BMI) $<30 \text{ kg/m}^2$; controlled risk factors defined as hypertension with systolic blood pressure $<130 \text{ mm Hg}$ and/or diabetes with hemoglobin A1c $<7\%$, and BMI $<30 \text{ kg/m}^2$; mild-to-moderately uncontrolled risk factors (any of the following): hypertension with systolic blood pressure 130 to $<160 \text{ mm Hg}$; diabetes with hemoglobin A1c 7% to 8%; BMI 30 to 35 kg/m^2 ; severely uncontrolled risk factors (any of the following): hypertension with systolic blood pressure $\geq 160 \text{ mm Hg}$; diabetes with hemoglobin A1c $\geq 8\%$; and BMI $\geq 35 \text{ kg/m}^2$. Those with BMI $<18.5 \text{ kg/m}^2$ ($n=122$) were excluded from this analysis. Each subgroup name is followed by prevalence in the study population in parentheses. **B**, Adjusted heart failure incidence rates for grouped categorization of modifiable risk factors. Adjusted incidence rates presented per 1000 person-years for different categorizations of control of 3 major modifiable risk factors (hypertension, diabetes, and obesity). Incidence rates calculated at mean levels of sex, race, occupation, education, smoking status, alcohol intake, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol, and estimated glomerular filtration rate in the study population.

associations. Also, we could not assess whether risk factor control was differentially associated with HF with reduced versus preserved ejection fraction.

In conclusion, the presence of multiple uncontrolled risk factors was linked to markedly increased HF risk. Almost a quarter of HF cases in the population were attributable to uncontrolled glycemia, blood pressure, and/or obesity. These results suggest that simultaneous risk factor optimization should be an important component of strategies to mitigate HF risk.

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