Insulin Resistance and Risk of Incident Heart Failure
Cardiovascular Health Study

Dipanjan Banerjee, MD, MS; Mary L. Biggs, PhD, MPH; Laina Mercer, MS; Kenneth Mukamal, MD; Robert Kaplan, PhD; Joshua Barzilay, MD; Lewis Kuller, MD, DrPH; Jorge R. Kizer, MD; Luc Djousse, MD, ScD; Russell Tracy, PhD; Susan Zieaman, MD, PhD; Donald Lloyd-Jones, MD, ScM; David Siscovick, MD, MPH; Mercedes Carnethon, PhD

Background—Patients with heart failure (HF) have higher fasting insulin levels and a higher prevalence of insulin resistance as compared with matched controls. Insulin resistance leads to structural abnormalities in the heart, such as increased left atrial size, left ventricular mass, and alterations in transmitral velocity that can precede the diagnosis of HF. It is not known whether insulin resistance precedes the development of HF or whether the relationship between insulin resistance and HF is present among adults with HF caused by nonischemic heart disease.

Methods and Results—We examined 4425 participants (60% women) from the Cardiovascular Health Study after excluding those with HF, myocardial infarction, or treated diabetes mellitus at baseline. We used Cox proportional hazards models to estimate the relative risk of incident HF associated with fasting insulin measured at study entry. There were 1216 cases of incident HF (1103 without antecedent myocardial infarction) during a median follow-up of 12 years (maximum, 19 years). Fasting insulin levels were positively associated with the risk of incident HF (hazard ratio, 1.10; 95% confidence interval, 1.05–1.15, per SD change) when adjusted for age, sex, race, field center, physical activity, smoking, alcohol intake, high-density lipoprotein-cholesterol, total cholesterol, systolic blood pressure, and waist circumference. The association between fasting insulin levels and incident HF was similar for HF without antecedent myocardial infarction (hazard ratio, 1.10; 95% confidence interval, 1.05–1.15). Measures of left atrial size, left ventricular mass, and peak A velocity at baseline were associated both with fasting insulin levels and with HF; however, additional statistical adjustment for these parameters did not completely attenuate the insulin-HF estimate (hazard ratio, 1.08; 95% confidence interval, 1.03–1.14 per 1-SD increase in fasting insulin).

Conclusions—Fasting insulin was positively associated with adverse echocardiographic features and risk of subsequent HF in Cardiovascular Health Study participants, including those without an antecedent myocardial infarction.


Key Words: epidemiology ■ heart failure ■ insulin

Adults with cardiomyopathy exhibit a higher prevalence of abnormal glucose tolerance and insulin resistance (IR) as compared with matched controls or patients with valvular heart disease.1,2 Although the direction of the association between IR and cardiomyopathy is unknown, some authors have proposed that IR predates cardiomyopathy.3–5 Patients with microvascular angina also exhibit IR, suggesting that IR is involved in the pathogenesis of subsequent cardiomyopathy.6

The seminal study investigating the association between IR and incident congestive heart failure (CHF) by Ingelsson7 followed elderly Scandinavian men for a median follow-up of 9 years after obtaining baseline risk factors for heart failure (HF), including IR. They found that IR by euglycemic clamp (the gold standard for measuring insulin sensitivity), 2-hour oral glucose tolerance test values, and fasting serum proinsulin levels were each associated with CHF incidence independent of established risk factors. However, their analysis did not distinguish between types of HF nor did they examine the role of echocardiographic parameters, brain natriuretic peptide (BNP) levels, or subclinical...
atherosclerosis on the association. An analysis of a subset of CHS participants by Kaplan et al.\(^8\) did not observe an association with incident CHF, but was focused on insulin-like growth factors and did not include all CHS participants.

In this investigation, we sought to determine the relationship between IR and incident heart failure in a prospective cohort of older adults who were free of diabetes mellitus. Secondary questions included determining whether associations were consistent among participants without an antecedent myocardial infarction (MI), persisted after adjustment for confounders and mediators and varied across different measures of IR.

### Methods

#### Study Participants

The CHS is a prospective population-based cohort study of 5888 Medicare-eligible adults, aged ≥65 years, in 4 US communities. Two cohorts were recruited. In the original cohort, 5201 eligible men and women were enrolled during 1989–1990. In the second recruitment during 1992–1993, designed to increase the number of black participants, 687 predominantly black men and women were enrolled. Clinic examinations were performed at study baseline and at annual visits through 1998–1999, and again in 2005–2006. Participants were contacted by telephone annually between exams, and twice per year during 2000–2004 and 2007 till present when no clinic examinations occurred. Data collection included fasting blood specimens, resting ECGs, physical examinations (including height, weight, and blood pressure), and questionnaires comprising medical history, use of prescription medications, and health-related behaviors. Each center’s institutional review board approved the study and all participants gave informed written consent. A description of the design, sampling, and recruitment in the CHS has been published previously.\(^9\)

After excluding participants with prevalent HF (n=275), prior MI (451), treated diabetes mellitus at baseline (n=375), missing fasting glucose (n=259), and missing insulin measures (n=103), 4425 participants were available for analysis.

#### Ascertainment of CHF and MI

All incident CHF events, MIs, as well as other vascular events, hospitalizations, and deaths, were identified through semiannual participant contacts, notification by participants and proxies, and review of Medicare hospitalization records. Potential incident events were investigated by review of medical records, and final classification was assigned by the CHS Events Subcommittee using standardized criteria. Details of the adjudication processes have been published previously.\(^10\)

Confirmation of CHF required, in addition to a physician diagnosis, supporting evidence consisting of ≥2 of the following: (1) documentation of symptoms, including shortness of breath, fatigue, orthopnea,
and paroxysmal nocturnal dyspnea, plus physical signs (edema, rales, tachycardia, a gallop, or a displaced left ventricular [LV] apical impulse); or (2) supportive clinical findings, such as cardiomegaly and pulmonary edema on chest X-ray, evidence of a dilated left ventricle, and global or segmental wall-motion abnormalities with decreased LV systolic function either by echocardiography or by contrast ventriculography; or (3) medical therapy for CHF, defined as diuretics plus either digitalis or a vasodilator (angiotensin-converting enzyme inhibitors, hydralazine, or long-acting nitrates).

At baseline, self-report of a history of physician-diagnosed MI was confirmed by ECG evidence of a previous MI defined as the presence of major Q waves or the combination of minor q waves and ST-T wave changes. When ECG results did not match the participant’s report of history of MI, medical records and physician questionnaires were reviewed to validate the reported history. Incident MI was defined as electrocardiographic evidence of MI (Q waves on electrocardiogram), elevated serum markers of myocardial damage, and segmental wall-motion abnormalities on echocardiography or by contrast ventriculography.

**Laboratory Methods**

Fasting blood specimens from each visit were stored at a central laboratory (CHS Central Laboratory, University of Vermont, Burlington, VT). Fasting insulin, glucose, lipids, and other laboratory parameters were measured at the central laboratory as previously described. Oral glucose tolerance testing performed in the original cohort at baseline entailed ingestion of 75 g of glucose after fasting, with glucose and insulin levels measured at baseline and 2 hours after ingestion.

**Covariates**

Diabetes mellitus was defined as use of antihyperglycemic medication or a fasting glucose level >126 mg/dL. Postload glucose was not used to define diabetes mellitus because it was not available at the baseline examination for the supplemental cohort of black participants. Measures of IR apart from fasting insulin levels included homeostasis model assessment (HOMA)-IR, calculated as (fasting plasma insulin (μIU/mL)×fasting plasma glucose (mmol/L)/22.5), the Gutt index (75 000+(fasting glucose–2-hour glucose)/0.19×body weight/120×log ([fasting insulin+2-hour insulin]/2)+([fasting glucose+2-hour glucose]/2), and triglyceride/high-density lipoprotein (HDL) ratio. Carotid intima thickness was determined by carotid ultrasonography. Echocardiographic examinations were performed at baseline in the original CHS cohort, recorded on super-VHS (video home system) tape using a standard protocol, and all studies were sent to a reading center.

**Statistical Methods**

We categorized participants by quartiles of fasting insulin and generated Kaplan–Meier curves to describe the association between insulin concentrations and time to incident CHF. Time at risk was calculated as the interval in days from the date of the baseline visit to the earliest of date of incident CHF, death, or end of event follow-up (June, November 2008).
The study sample comprised 4425 participants. The major-

The initial multivariable model included the following covariates considered to be potential confounders: age, sex, race (black versus nonblack), field center, physical activity, smoking (never, former, and current), alcohol intake (never, former, <1 day/wk, 1 to <7 day/wk, and ≥7 day/wk), HDL-C, total cholesterol, systolic blood pressure, and waist circumference. To assess the role of possible mediators of the relationship between fasting insulin and incident CHF, we fit additional sequential models containing variables added separately to the baseline model, including carotid intima media thickness, presence/absence of a major ECG abnormality, and N-terminal (NT)-pro-BNP.

Among participants enrolled in 1989–1990 who had echocardiography measures available at baseline (n=3952), we investigated carotid intima media thickness, waist circumference, and LV mass and lower HDL levels as compared with participants without HF. Participants whose HF was not preceded by MI exhibited lower LV mass, carotid intima media thickness, and NT-BNP levels and higher alcohol use than those without antecedent, but were otherwise very similar (Table 2). Similar results were noted when participants with prior MI were included in the baseline cohort.

The Figure displays the unadjusted, positive relationship between quartile of fasting insulin and incident heart failure. When adjusted for baseline characteristics (age, sex, race, field center, physical activity, smoking, alcohol intake, HDL-C, total cholesterol, systolic blood pressure, and waist circumference), there remained a significant relationship between fasting insulin levels and incident HF (Table 3). No meaningful difference in the association between fasting insulin and CHF was noted for participants whose CHF was not preceded by MI.

Adjustment for possible mediators of the relationship between fasting insulin (major ECG abnormality and carotid intima media thickness) did not substantially alter the relationship between fasting insulin and incident HF (Table 3). Fasting insulin was positively associated with LA size, LV mass, and peak A velocity at baseline; however, additional statistical adjustment for these parameters among participants who had echocardiographic measures available modestly attenuated the insulin-HF estimate (model 1: hazard ratio [HR], 1.10; 95% confidence interval [CI], 1.05–1.15; model 1+LA size, LV mass, peak E velocity, and peak A velocity: HR, 1.08; 95% CI, 1.03–1.14 per 1-SD increase in fasting insulin). Adjustment for NT-BNP levels in participants who had this measure available did not attenuate the insulin-HF estimate (model 1: hazard ratio [HR], 1.09; 95% CI, 1.04–1.15; model 1+NT-BNP levels: HR, 1.09; 95% CI, 1.04–1.15 per 1-SD increase in fasting insulin). Additional exclusion of individuals with a fasting glucose of ≥126 mg/dL at baseline, or adjustment for prevalent and incident diabetes mellitus (defined as fasting glucose ≥126 mg/dL or use of diabetes
Incident Heart Failure by Quartile* of Fasting Insulin (Quartile 1=Referent Group) Among Cardiovascular Health Study Participants With All Measures (n=3792)

Table 4. Hazard Ratios and 95% Confidence Intervals of Incident Heart Failure by Different Measures of Insulin Resistance Among Cardiovascular Health Study Participants With All Measures (n=3792)

<table>
<thead>
<tr>
<th>Fasting Insulin*</th>
<th>Gutt Index†</th>
<th>HOMA-IR‡</th>
<th>Triglyceride/HDL ratio§</th>
<th>2-h Glucose¶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.96 (0.82–1.14)</td>
<td>0.97 (0.82–1.15)</td>
<td>1.04 (0.87–1.24)</td>
<td>1.06 (0.86–1.31)</td>
</tr>
<tr>
<td>Q3</td>
<td>1.13 (0.96–1.33)</td>
<td>1.10 (0.92–1.31)</td>
<td>1.07 (0.89–1.29)</td>
<td>1.16 (0.91–1.47)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.18 (0.98–1.42)</td>
<td>1.17 (0.97–1.42)</td>
<td>1.27 (1.04–1.55)</td>
<td>1.15 (0.87–1.52)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.10 (1.05–1.15)</td>
<td>1.10 (1.05–1.15)</td>
<td>1.09 (1.05–1.15)</td>
<td>1.04 (0.97–1.13)</td>
</tr>
<tr>
<td><strong>Model 2††</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.94 (0.80–1.11)</td>
<td>0.95 (0.80–1.13)</td>
<td>1.09 (0.84–1.40)</td>
<td>1.16 (0.91–1.47)</td>
</tr>
<tr>
<td>Q3</td>
<td>1.11 (0.94–1.31)</td>
<td>1.09 (0.91–1.29)</td>
<td>1.27 (1.04–1.55)</td>
<td>1.15 (0.87–1.52)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.15 (0.96–1.38)</td>
<td>1.15 (0.95–1.39)</td>
<td>1.27 (1.04–1.55)</td>
<td>1.15 (0.87–1.52)</td>
</tr>
<tr>
<td>Per SD</td>
<td>1.09 (1.04–1.14)</td>
<td>1.09 (1.04–1.14)</td>
<td>1.09 (1.05–1.15)</td>
<td>1.04 (0.97–1.13)</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein.
*Insulin quartile ranges: <9, >9 to 12, >12 to 17, and >17; insulin SD: 9.86.
†Gutt index quartile ranges: >73.8, >55.9 to 73.8, >41.4 to 55.9, and ≤41.4; Gutt index SD: 24.9 (per SD is for decrease).
‡Homeostasis model assessment (HOMA)-IR quartile ranges: ≤2.2, >2.2 to 3.0, >3.0 to 4.3, and >4.3; HOMA-IR SD: 3.8.
§Triglyceride/HDL ratio quartile ranges: ≤1.5, >1.5 to 2.3, >2.3 to 3.5, and >3.5; triglyceride/HDL ratio SD: 2.4.
¶2-h glucose quartile ranges: ≤108, >108 to 134, >134 to 169, and >169; 2-h glucose SD: 56.4.
#Adjusted for age, sex, black (vs nonblack), field center, physical activity, smoking, alcohol intake, HDL-cholesterol, total cholesterol, systolic blood pressure, and waist circumference.
**Per SD increase except for Gutt index which is per SD decrease.
††Adjusted for covariates in model 1, carotid intima media thickness, and presence of major ECG abnormality.
measures of IR. Hyperglycemia, which develops when insulin levels are no longer sufficient to control serum glucose levels, may confer additional risk of HF beyond IR. Thus, hyperglycemic patients with IR may benefit the most from risk factor modification. By contrast, triglyceride/HDL ratio was less strongly associated with incident HF, which is consistent with available data suggesting that this surrogate measure of IR is not as sensitive as fasting insulin levels in defining IR.

There is strong evidence to suggest that the biological effects of higher fasting insulin levels/IR could lead to the development or worsening of HF. During periods of myocardial stress (ie, in advanced stages of HF), the heart switches to a fetal gene program, leading to a relative increase in the use of glucose as a fuel rather than free fatty acids. In the setting of IR, however, this switch is ineffective because glucose use is impaired, and the heart enters an energy starved state; thus, IR could initiate or exacerbate HF. IR may also contribute to the development of HF because of the direct effects of higher fasting insulin levels on the myocardium and its vasculature, including chronic adrenergic stimulation, cellular apoptosis, and endothelial dysfunction, as well as indirect effects, such as impairment of myocardial energy metabolism, hypertension, and dyslipidemia. Further evidence of the link between IR and HF lies in the association with IR and structural abnormalities that predispose to diastolic HF (increased LV mass and LV hypertrophy).

Another unexpected observation was that NT-BNP levels were inversely associated with fasting insulin levels. Typically, patients with HF exhibit higher levels of NT-BNP than those without HF, and we might have expected a positive association between fasting insulin and NT-BNP levels. However, NT-BNP levels are lower in obese individuals as compared with normal weight individuals, so this finding may simply reflect the fact that higher fasting insulin levels are found in more obese individuals.

Strengths of our investigation include the use of a large, well-established cohort study with extended follow-up, a significant number of events, standardized, protocol-driven adjudication of events and measured parameters (ie, echocardiography), and the prospective study design. Limitations include an imperfect designation of ischemic versus nonischemic HF because the gold standard for defining ischemic cardiomyopathy requires the use of coronary angiography, which was not part of the study data. Although we subdivided our cohort by the presence or absence of previous MI, this may not be sufficient to differentiate patients with ischemic type HF and those with nonischemic HF.

Insulin resistance, whether measured by fasting insulin levels or triglyceride/HDL ratio, can be detected before the development of clinical HF and structural abnormalities of the heart. Although there are no large-scale clinical trials of therapy targeting IR in individuals at risk for HF, there are multiple treatment modalities that can improve or delay the progression of IR, including weight loss through dietary modification and exercise, and insulin sensitization via medications. HF is a prevalent condition and constitutes a large portion of healthcare expenditures. Targeted measures to treat IR in patients with other risk factors for HF could lead to the prevention of significant cardiovascular morbidity and a reduction in associated healthcare costs.

Acknowledgements
A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

Sources of Funding
This work was supported by contract numbers HHSN268201200036C, N01-HC-85239, and N01-HC-85079 through N01-HC-85086, N01-HC-85150, N01-HC-85222, N01-HC-85150, N01-HC-85153, and grants HL080295 and RO1HL094555 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through AG-023629, AG-15928, AG-20098, AG-027058, and grant 1R01AG031890 from the National Institute on Aging.

Disclosures
None.

References
Coronary artery disease are necessary to mitigate this risk. Insulin resistance as a risk factor for the development of heart failure, and suggest that measures beyond targeting pathways could be involved. Our investigation revealed a definite relationship between insulin resistance and incident heart failure is mediated entirely by coronary artery disease, or whether other pathways could be involved. Our investigation revealed a definite relationship between insulin resistance and incident heart failure is mediated entirely by coronary artery disease, or whether other pathways could be involved.

Clinical Perspective

The relationship between insulin resistance and incident heart failure is not well established. Neither is it clear whether the relationship between insulin resistance and heart failure is mediated entirely by coronary artery disease, or whether other pathways could be involved. Our investigation revealed a definite relationship between insulin resistance and incident heart failure, a relationship that held even in subjects without antecedent myocardial infarction. Insulin resistance also correlated with structural abnormalities of the heart as detected by echocardiography. These findings add to a growing literature implicating insulin resistance as a risk factor for the development of heart failure, and suggest that measures beyond targeting coronary artery disease are necessary to mitigate this risk.
Insulin Resistance and Risk of Incident Heart Failure: Cardiovascular Health Study
Dipanjan Banerjee, Mary L. Biggs, Laina Mercer, Kenneth Mukamal, Robert Kaplan, Joshua Barzilay, Lewis Kuller, Jorge R. Kizer, Luc Djousse, Russell Tracy, Susan Zieman, Donald Lloyd-Jones, David Siscovick and Mercedes Carnethon

_Circ Heart Fail._ 2013;6:364-370; originally published online April 10, 2013;
doi: 10.1161/CIRCHEARTFAILURE.112.000022
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/6/3/364

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the _Permissions and Rights Question and Answer_ document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/