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Novel Metabolic Risk Factors for Heart Failure

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OBJECTIVES Our objectives were to explore novel metabolic risk factors for development of heart failure (HF).

BACKGROUND In the past decade, considerable knowledge has been gained from limited samples regarding novel risk factors for HF, but the importance of these in the general population is largely unexplored.

METHODS In a community-based prospective study of 2,321 middle-aged men free from HF and valvular disease at baseline, variables reflecting glucose and lipid metabolism and variables involved in oxidative processes were compared with established risk factors for HF (prior myocardial infarction, hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, obesity, and serum cholesterol) using Cox proportional hazards analyses.

RESULTS During a median follow-up time of 29 years, 259 subjects developed HF. In a multivariable Cox proportional hazards backward stepwise model, a 1-SD increase of fasting proinsulin (hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.15 to 1.66) and apolipoprotein B/A-I-ratio (HR 1.27, 95% CI 1.09 to 1.48) increased the risk, whereas a 1-SD increase in serum beta-carotene (HR 0.79, 95% CI 0.66 to 0.94) decreased the risk of HF. These variables also remained significant when adjusting for acute myocardial infarction during follow-up.

CONCLUSIONS Novel variables reflecting insulin resistance and dyslipidemia, together with a low beta-carotene level, were found to predict HF independently of established risk factors. If confirmed, our observations could have large clinical implications, as they may offer new approaches in the prevention of HF. (J Am Coll Cardiol 2005;46:2054–60) © 2005 by the American College of Cardiology Foundation

Heart failure (HF), a major cause of morbidity and mortality, is reported to consume 1% to 2% of the total health care costs in industrialized countries (1). The age-adjusted mortality for HF patients is four to eight times to that of the general population (2), comparable to that of cancer diseases in the same age groups (3). Therefore, the identification of potentially modifiable risk factors for HF is of great importance.

The predominant causes of HF are hypertension and coronary heart disease (CHD). Other identified risk factors for HF include left ventricular (LV) hypertrophy, valvular heart disease, diabetes mellitus, cigarette smoking, obesity, and dyslipidemia (2,4–8). Population-based studies to date have shown different results concerning the relative importance of these risk factors. In the past decade, considerable knowledge has been gained regarding the pathophysiology of HF in the experimental setting, small clinical samples, and larger population-based studies. New mechanisms, such as insulin resistance (9,10), inflammation (11,12), and oxidative stress (13–15), have been investigated, but the importance of many of these mechanisms is largely unexplored in the general population. Epidemiologic studies investigating the importance of novel risk factors for HF are therefore highly motivated.

Our primary aim was to analyze established and novel risk factors for development of HF in a community-based sample of middle-aged men. As several of the risk factors identified for HF also are risk factors for CHD, a secondary aim was to analyze whether the risk factors predicted HF independently of an interim myocardial infarction (MI) during the follow-up.

METHODS

Study sample. The study is based on the Uppsala Longitudinal Study of Adult Men (ULSAM) cohort, a health investigation focusing at identifying metabolic risk factors for cardiovascular disease, to which all 50-year-old men living in Uppsala in 1970 to 1974 were invited. Of these, 82% (2,322 men) participated in the investigation (16). In addition to regular re-examinations, the data have been completed with annual updates on mortality and in-hospital morbidity using national registers. The ULSAM trial is described in detail on the Internet (17). One subject was excluded because of valvular disease at baseline; thus, 2,321 men were eligible for the investigation. All subjects gave written consent, and the ethics committee of Uppsala University approved the study.

Examinations at baseline. Examinations, performed when the subjects were 50 years old, included a medical examination, a questionnaire, blood sampling (after an overnight

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Abbreviations and Acronyms

BMI	= body mass index
CHD	= coronary heart disease
CI	= confidence interval
ECG-LVH	= electrocardiographic left ventricular hypertrophy
HDL	= high-density lipoprotein
HF	= heart failure
HOMA	= homeostasis model assessment
HR	= hazard ratio
ICD	= International Classification of Diseases
IVGTT	= intravenous glucose tolerance test
LDL	= low-density lipoprotein
LV	= left ventricular
MI	= myocardial infarction
ULSAM	= Uppsala Longitudinal Study of Adult Men

fast) with fasting and 60-min blood glucose and plasma insulin concentrations after an intravenous glucose tolerance test (IVGTT), supine blood pressure, pulse rate, and anthropometric measurements as previously described (16). The concentrations of intact and 32-33 split proinsulin were analyzed in 1995 to 1998 by a two-site immunometric assay technique (18). Because of a freezer failure, proinsulin-like molecules were determined in baseline plasma samples from 1,306 of the subjects. Homeostasis model assessment (HOMA) insulin resistance index was calculated using fasting plasma glucose and insulin concentrations by the formula: fasting insulin · fasting glucose/22.5 (19). The methods of lipid determinations have been extensively described (20). Apo(a) and ApoB were determined by a two-site immuno-radiometric assay and ApoA-I by a competitive radioimmunoassay. Alpha tocopherol and beta-carotene were simultaneously determined by high-performance liquid chromatography (21). The serum tocopherol concentrations as reported are corrected for the sum of serum cholesterol and serum triglycerides [tocopherol/(cholesterol+triglyceride)] (22). Uric acid in serum was measured by spectrophotometry.

The presence of hypertension at baseline was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or anti-hypertensive medication. The presence of diabetes at baseline was defined as fasting blood glucose ≥6.1 mmol/l and/or the use of oral hypoglycemic agents or insulin. Electrocardiographic left ventricular hypertrophy (ECG-LVH) was defined as high-amplitude R waves according to the revised Minnesota code (23), together with LV strain pattern (4). The presence of valvular disease (International Classification of Diseases [ICD]-8 codes 394-396 and 424, ICD-9 codes 394-397 and 424 or ICD-10 codes I05-I08 and I34-I37) and prior MI (ICD-8 code 410, ICD-9 code 410, or ICD-10 code I21) were assessed from the hospital discharge register. The diagnosis of acute MI was chosen as a proxy for CHD, as the precision of the MI diagnosis in the Swedish hospital discharge register is high (24,25). Furthermore, adjusting for or excluding interim MI is an established method for examining "non-ischemic" HF (26,27).

Follow-up and outcome parameter. The subjects had a median follow-up time of 28.8 years (range 0.04 to 31.7 years), contributing to 58,084 person-years at risk. A total of 321 men had a hospital discharge register diagnosis of HF between the entry to the ULSAM trial and the end of 2001. As a possible diagnosis of HF, we considered ICD HF codes 427.00, 427.10, 428.99 (ICD-8), 428 (ICD-9), I50 (ICD-10) and hypertensive heart disease with HF, I11.0 (ICD-10). The medical records from the relevant hospitalization were reviewed by two physicians (E.I. and L.L.), blinded to the baseline data, who classified the cases as definite, questionable, or miscoded. The classification relied on the definition proposed by the European Society of Cardiology (28), and the review process has been described extensively (29). After this validation, 259 cases of definite HF were included in the present study. A total of 840 subjects (36%) died during follow-up. None of the subjects were lost to follow-up.

Statistical methods. Data are given as percentages for categorical variables, means ± SD for normal distributed continuous variables or medians (interquartile range) for skewed variables. Logarithmic transformation was performed to achieve normal distribution for the skewed variables (IVGTT s-insulin 60 min, fasting insulin, fasting proinsulin, fasting split proinsulin, high-density lipoprotein [HDL] cholesterol, apo(a), serum triglycerides and beta-carotene). The residuals of all regression analyses were examined and found to be normally distributed. Persons who developed and did not develop HF during follow-up were compared at baseline with Kruskal-Wallis tests (skewed continuous variables), *t* tests (normal distributed continuous variables), or chi-square analyses (categorical variables). The prognostic values of a one-standard deviation increase in the continuous variables, or transfer from one level to another for the dichotomous variables, for HF incidence were investigated with Cox proportional hazards analyses. Proportionality of hazards was confirmed by visually examining Nelson-Aalen curves. Nonlinear relations were excluded by examining incidence rates in quartiles of the independent variables. We used four sets of models in a hierarchical fashion:

1. Unadjusted analyses.
2. Analyses adjusted for the following known risk factors: prior acute MI, hypertension, diabetes, ECG-LVH, smoking, body mass index (BMI), and serum cholesterol.
3. Novel variables significant in models 1 and 2 were then included in a multivariable Cox proportional hazards backward stepwise model together with the established risk factors in order to evaluate the independency between different novel variables. A level of $p < 0.05$ was used for exclusion.
4. As in model 3 with addition of interim MI.

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An analysis of the interaction terms between interim MI and significant variables in model 4 was performed. All the above analyses were repeated in a subsample without subjects with prior MI at baseline or MI during follow-up. Because fasting insulin, proinsulin, and split proinsulin were analyzed in only 55% of the cohort, we excluded these variables in secondary analyses of models 3 and 4 in order to produce a larger sample. Two-tailed 95% confidence intervals and p values were given, with $p < 0.05$ regarded as significant. Statistical software package STATA 8.2 (Stata Corp., College Station, Texas) was used.

RESULTS

The incidence rate for HF during the follow-up period was 4.5/1,000 person-years at risk. Table 1 shows the clinical characteristics at baseline of subjects with and without incident HF during follow-up.

In unadjusted Cox proportional hazards analyses, established risk factors for HF, as well as several novel variables, were significant predictors of HF incidence (Table 2, middle column). When adjusting for established risk factors for HF (prior acute MI, hypertension, diabetes, ECG-LVH, smoking, BMI, and serum cholesterol), fasting intact proinsulin, fasting 32-33 split proinsulin, HOMA-insulin resistance, HDL cholesterol, apolipoprotein B/A-I-ratio, and beta-carotene remained significant predictors of HF (Table 2, right column).

These variables were included in a multivariable Cox proportional hazards backward stepwise model together with the established risk factors. In this analysis, fasting proinsulin, apolipoprotein B/A-I-ratio, beta-carotene (protective), hypertension, BMI, and ECG-LVH were independent predictors of HF (Table 3). When we adjusted for the incidence of acute MI during follow-up, all these six variables remained independent predictors of HF (Fig. 1A). Cumulative incidence plots for values above and below the median value of the first three of these variables are presented in Figure 2. Evidence of MI during the follow-up was present in 409 of the subjects in the total cohort and in 98 of the 259 HF cases (38%). In an unadjusted Cox proportional hazards analysis, an interim MI was a significant predictor of HF (hazard ratio [HR] 3.50, 95% confidence interval [CI] 2.72 to 4.50, $p < 0.001$).

As there was a significant interaction between ECG-LVH and interim MI, and a borderline significant interaction between hypertension and interim MI, we performed a

Table 1. Baseline Clinical Characteristics of the Total Cohort and Groups of Persons Who Remained Free From or Developed Heart Failure During Follow-Up

	Total Cohort (n = 2,321)	Did Not Develop HF (n = 2,062)	Developed HF (n = 259)
Glucometabolic variables			
IVGTT b-glucose 60 min (mmol/l)	11.3 ± 3.2	11.2 ± 3.1	11.7 ± 3.7
IVGTT s-insulin 60 min (μU/ml)	24.3 (15.7–36.0)	24.1 (15.7–35.4)	25.7 (15.5–42.2)
Fasting insulin (pmol/l)	41 (28–62)	40 (28–61)	49 (33–75)‡
Fasting proinsulin (pmol/l)	2.3 (1.4–3.7)	2.2 (1.4–3.6)	3.1 (1.7–4.8)‡
Fasting split proinsulin (pmol/l)	5.7 (3.7–8.8)	5.6 (3.7–8.7)	6.8 (4.6–11.0)‡
HOMA-insulin resistance	3.0 ± 2.0	2.8 ± 1.8	3.9 ± 3.3‡
Lipometabolic variables			
HDL cholesterol (mmol/l)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.2 (1.1–1.5)†
LDL cholesterol (mmol/l)	5.3 ± 1.3	5.3 ± 1.2	5.5 ± 1.4†
Apo(a) (U/l)	119 (49–320)	115 (48–317)	138 (64–421)
Apolipoprotein B/A-I-ratio	0.89 ± 0.26	0.88 ± 0.26	0.97 ± 0.28‡
S-triglycerides (mmol/l)	1.7 (1.3–2.2)	1.6 (1.3–2.2)	1.8 (1.4–2.5)‡
Oxidative stress variables			
Alpha tocopherol (mg/l)	1.50 ± 0.26	1.50 ± 0.26	1.50 ± 0.26
Beta-carotene (μg/l)	135 (91–200)	137 (93–202)	118 (79–184)†
S-uric acid (mg/100 ml)	4.3 ± 1.0	4.3 ± 1.0	4.5 ± 1.1*
Established risk factors for HF			
Prior acute myocardial infarction	7 (0.3)	5 (0.2)	2 (0.8)
Hypertension prevalence	990 (43)	833 (40)	157 (61)‡
Diabetes prevalence	132 (6)	109 (5)	23 (9)*
ECG-LVH	40 (1.7)	26 (1.3)	14 (5.4)‡
Current cigarette smoking	1184 (51)	1039 (50)	145 (56)
BMI (kg/m^2)	25.0 ± 3.2	24.9 ± 3.1	26.4 ± 3.5‡
S-cholesterol (mmol/l)	6.9 ± 1.3	6.9 ± 1.3	7.1 ± 1.4*

Data described as medians (interquartile range) for all skewed variables (IVGTT s-insulin 60 min, fasting insulin, fasting proinsulin, fasting split proinsulin, HDL cholesterol, apo(a), s-triglycerides and beta-carotene) and as mean values ± SD for the other continuous variables. Data for categorical variables are shown as a number of cases, with percentages in brackets. Persons who developed and did not develop HF during follow-up were compared at baseline with Kruskal-Wallis tests (skewed continuous variables), *t* tests (normal distributed continuous variables), or chi-square analyses (categorical variables). *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.

BMI = body mass index; ECG-LVH = electrocardiographic left ventricular hypertrophy; HDL = high-density lipoprotein; HF = heart failure; HOMA = homeostasis model assessment; IVGTT = intravenous glucose tolerance test; LDL = low-density lipoprotein.

Table 2. Heart Failure Morbidity in Relation to Established and Novel Risk Factors in the Total Sample (n = 2,321)

	Unadjusted Values	Adjusted for Established Risk Factors
	Hazard Ratio for HF Corresponding to a 1-SD Increase (95% CI)	Hazard Ratio for HF Corresponding to a 1-SD Increase (95% CI)
Glucometabolic variables		
IVGTT b-glucose 60 min (mmol/l)	1.22 (1.06–1.41)†	0.98 (0.84–1.14)
IVGTT s-insulin 60 min (μU/ml)	1.21 (1.05–1.41)†	0.96 (0.84–1.10)
Fasting insulin (pmol/l)	1.45 (1.25–1.69)‡	1.14 (0.95–1.37)
Fasting proinsulin (pmol/l)	1.65 (1.41–1.92)‡	1.38 (1.15–1.64)‡
Fasting split proinsulin (pmol/l)	1.60 (1.37–1.86)‡	1.28 (1.07–1.54)†
HOMA-insulin resistance	1.57 (1.37–1.79)‡	1.16 (1.00–1.35)*
Lipometabolic variables		
HDL cholesterol (mmol/l)	0.80 (0.70–0.92)‡	0.86 (0.74–0.99)*
LDL cholesterol (mmol/l)	1.23 (1.09–1.39)‡	1.57 (0.89–2.80)
Apo(a) (U/l)	1.14 (0.99–1.31)	
Apolipoprotein B/A-I-ratio	1.42 (1.26–1.61)‡	1.31 (1.11–1.54)‡
S-triglycerides (mmol/l)	1.37 (1.23–1.54)‡	1.07 (0.93–1.22)
Oxidative stress variables		
Alpha tocopherol (mg/l)	0.95 (0.83–1.08)	
Beta-carotene (μg/l)	0.75 (0.66–0.86)‡	0.86 (0.74–0.99)*
S-uric acid (mg/100 ml)	1.17 (1.04–1.32)*	1.02 (0.90–1.16)
Established risk factors for HF		
Prior acute myocardial infarction	4.51 (1.12–18.14)*	3.37 (0.83–13.63)
Hypertension prevalence	2.45 (1.91–3.14)‡	1.93 (1.48–2.52)‡
Diabetes prevalence	1.91 (1.24–2.92)†	1.61 (1.05–2.48)*
ECG-LVH	5.69 (3.31–9.77)‡	4.43 (2.55–7.69)‡
Current cigarette smoking	1.48 (1.16–1.89)†	1.76 (1.37–2.26)‡
BMI (kg/m^2)	1.60 (1.44–1.79)‡	1.47 (1.31–1.65)‡
S-cholesterol (mmol/l)	1.20 (1.07–1.35)†	1.12 (0.99–1.26)

Presented as unadjusted data and adjusted for established risk factors (only for variables significant in unadjusted analysis). Cox proportional hazards ratios are given for a 1-SD increase in raw or logarithmically transformed variables, except for the dichotomous variables where the hazard ratios reflect a transfer from normal to abnormal. Data are hazard ratios (95% confidence intervals), crude or adjusted for established risk factors (prior acute myocardial infarction, hypertension, diabetes, ECG-LVH, smoking, BMI, and serum cholesterol). The values shown for established risk factors in the right column are acquired from a multivariable model incorporating only these variables. p values <0.05 were considered significant. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.

CI = confidence interval; other abbreviations as in Table 1.

secondary analysis in a subsample, excluding persons with MI before baseline or during follow-up. In a multivariable Cox proportional hazards analysis in this subgroup using the six independently significant predictors of HF defined in the total cohort, the point estimates remained essentially the same except for ECG-LVH, but with somewhat wider CIs (Fig. 1B).

In secondary analyses, excluding the insulin-like molecule variables, we obtained essentially the same results as in the previous analyses that included these variables. However, when fasting proinsulin was removed from the multivariable model, HOMA-insulin resistance and smoking were included as significant predictors of HF in the final model (HR 1.29, 95% CI 1.09 to 1.53, p = 0.004 for a 1-SD increase and HR 1.55, 95% CI 1.10 to 2.18, p = 0.012 for smokers vs. nonsmokers).

DISCUSSION

Principal findings. In this community-based cohort study of middle-aged men with a median follow-up time of 29 years, we identified novel variables reflecting insulin resistance, an increased apolipoprotein B/A-I ratio and a low antioxidant level (beta-carotene) to be risk factors for HF, independent of MI and other established risk factors for HF.

Previous established risk factors. Previous studies have shown that the predominant causes of HF are hypertension and CHD, and this was confirmed in the present study. In our sample, 61% of the subjects who developed HF were hypertensive at baseline and 38% of the cases had a history of MI. This corresponds to the observations of other community-based studies (30). The risk for HF associated with hypertension is further captured in the ECG-LVH variable as previously described (4). Along with hypertension, LV hypertrophy, and MI, all the previous established risk factors for HF (2,4–8) were significant predictors of HF also in the ULSAM trial.

Markers of impaired glucose regulation. We observed that markers of impaired insulin secretion and insulin resistance were independently associated with an increased risk for HF. Several previous longitudinal studies have

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Table 3. Multivariable Cox Proportional Hazards Backward Stepwise Model, Examining the Independency of Novel and Established Risk Factors to HF Incidence in the Total Sample (n = 2,321)

	Hazard Ratio for HF Corresponding to a 1-SD Increase (95% CI)
Fasting proinsulin (pmol/l)	1.38 (1.15–1.66)†
Apolipoprotein B/A-I-ratio	1.27 (1.09–1.48)*
Beta-carotene (μg/l)	0.79 (0.66–0.94)*
Hypertension prevalence	1.70 (1.21–2.39)*
BMI (kg/m^2)	1.24 (1.06–1.46)*
ECG-LVH	3.38 (1.55–7.34)*

Cox proportional hazards ratios are given for a 1-SD increase in raw or logarithmically transformed variables, except for hypertension prevalence and electrocardiographic left ventricular hypertrophy, which are dichotomous variables where the hazard ratio reflects a transfer from normal to abnormal. Data are hazard ratios (95% confidence intervals). p values <0.05 were considered significant. Variables entered into the model are those significant in Table 2, right column. *p < 0.01, †p < 0.001.

CI = confidence interval. Other abbreviations as in Table 1.

shown an association between diabetes and HF (5,7,31,32). In the present study, proinsulin—and in the secondary analysis excluding proinsulin, HOMA-insulin resistance—rather than diabetes prevalence were included in the multivariable models, implying that these measures of glucose metabolism carry important risk information beyond the diabetes diagnosis. This may indicate that the risk for HF already increases in the subclinical phase of impaired glucose metabolism, better reflected in altered proinsulin and HOMA-insulin resistance values than in the diagnosis of diabetes. Proinsulin has been shown to be an independent long-term predictor of CHD (33,34). It is possible that some of the individuals had asymptomatic LV dysfunction at entry and that the insulin resistance was a consequence, not a possible

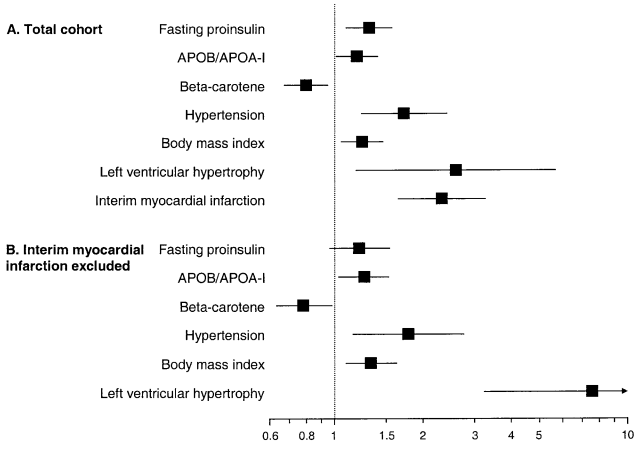

Figure 1. Boxes are point estimates of multivariable Cox proportional hazards ratios (lines indicate 95% confidence intervals) for a one-standard deviation increase of the continuous variables (fasting proinsulin, apolipoprotein B/A-I ratio [APOB/APOA-I], beta-carotene, and body mass index) and for occurrence versus non-occurrence of dichotomous variables (hypertension, electrocardiographic left ventricular hypertrophy, and interim myocardial infarction) as predictors of heart failure incidence in middle-aged men free from heart failure and valvular disease at baseline. **(A)** Variables that remained independently significant in Table 3, with the addition of interim myocardial infarction. **(B)** Subsample of subjects free from myocardial infarction at baseline and during follow-up.

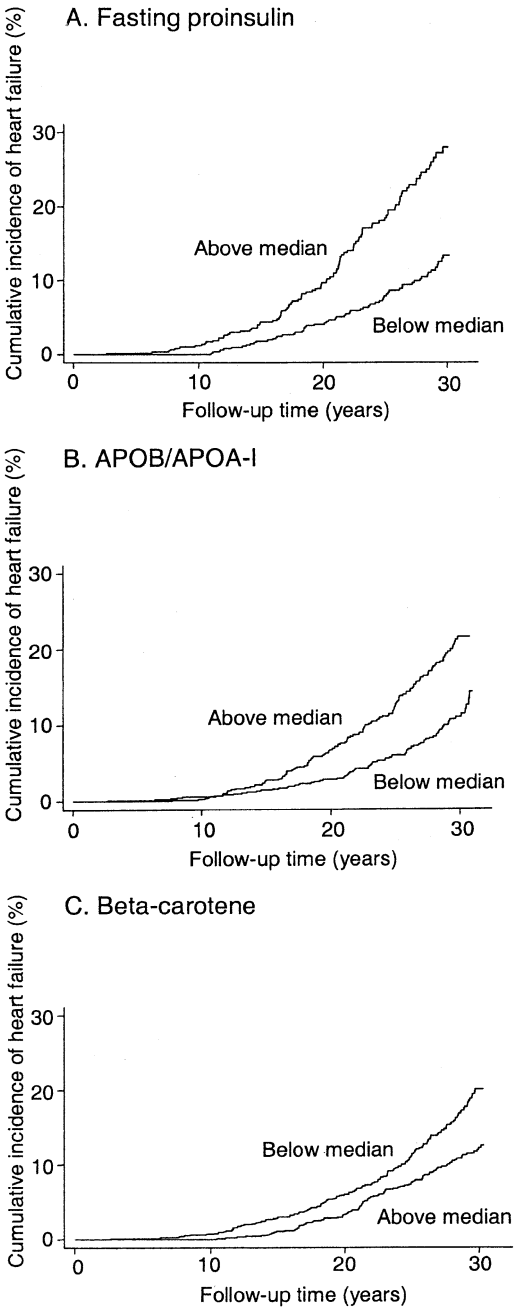

Figure 2. Nelson-Aalen plots of cumulative incidence of heart failure in the cohort, free from heart failure and valvular disease at baseline, by two groups (above vs. below median) of fasting proinsulin **(A)**, apolipoprotein B/A-I ratio (APOB/APOA-I) **(B)**, and beta-carotene **(C)**.

cause, of HF, which has been proposed earlier (35). On the other hand, there is some evidence of a direct atherogenic action of the proinsulin molecule, through coronary microcirculatory changes leading to ischemic injury. Clinical trials with proinsulin in diabetic patients were prematurely terminated owing to an increase in MIs in subjects treated with proinsulin (36). However, in the ULSAM cohort, increased proinsulin levels have previously been observed to precede LV systolic dysfunction (37) independently of other cardiovascular diseases, such as MI. Thus, non-atherogenic effects

of the proinsulin molecule or insulin resistance with direct myocardial effects may also be of importance for development of HF (38,39).

Apolipoproteins. Several studies have proposed apolipoproteins as a more specific alternative to low-density lipoprotein (LDL) cholesterol as a risk marker for cardiovascular diseases (40–42). A recent study showed that the APOB/APOA-I ratio was a powerful independent risk marker of fatal MI after adjustment for age, total cholesterol, and triglycerides (43). The reason for this may be that the APOB/APOA-I ratio also includes information on other atherogenic lipoproteins, such as the APOB containing very low-density lipoprotein, rich in triglycerides, as well as APOA-I-containing HDL. As such, the ratio gives comprehensive information on the classic risk of LDL cholesterol as well as on other important components of the metabolic syndrome. How this ratio directly affects cardiac performance independently of MI is not known, but recent studies have shown apolipoproteins to be closely linked to endothelial function, a determinant of cardiac afterload (44). As an increased afterload would influence both LV systolic and diastolic function, effects in the vasculature rather than a direct action on the heart might be the mechanism whereby the APOB/APOA-I ratio increases the risk for HF.

Antioxidants. There is emerging evidence that oxidative stress and inflammation are involved in the pathophysiology of HF. Some prior smaller case-control studies have pointed out a relationship between antioxidant levels and the severity of HF (13,15). It is possible that antioxidants, such as beta-carotene, lower the levels of free radicals, which are important mediators of oxidative stress and inflammation. However, it is still to be investigated if beta-carotene is an inverse marker of inflammation or possibly itself has anti-inflammatory effects. Our results might indicate that inflammation could be an important part in the development of HF, as indicated in previous studies, which have found a relationship between various inflammatory markers and HF (11,12,45). A recent cross-sectional case-control study has also found that inflammatory markers and a marker of oxidative stress were significantly correlated in HF subjects (14). Furthermore, a previous report from the ULSAM cohort showed that serum levels of beta-carotene predicted LV diastolic function after 20 years of follow-up (46). However, no previous longitudinal studies have shown that low serum levels of antioxidants, such as beta-carotene, predict a higher risk of developing HF, independent of established risk factors. Exactly what beta-carotene measures is uncertain. In addition to being a possible marker of oxidative stress, it might also reflect nutritional intake. The serum level of beta-carotene might be considered a marker for a high vegetable intake, reflecting a healthy lifestyle, which in turn could decrease the risk of HF regardless of the possible antioxidative effect of beta-carotene itself.

Subsamples in our study. In the subsample without subjects with a prior MI at baseline or MI during follow-up, we observed essentially the same point estimates for the hazard ratios as in the total sample. However, the confidence intervals were slightly wider, probably a result of reduced power in this subsample. Thus, further studies are needed to establish the role of these novel risk factors for non-ischemic HF.

We also performed secondary analyses with the exclusion of fasting proinsulin in order to use the total sample. The results in these secondary analyses were essentially the same, which implies that there was no bias introduced by the limited number of observations with insulin variables included.

Strengths and limitations. The strengths of this study include the large population, the long follow-up period, and the detailed metabolic characterization of the cohort. Furthermore, all HF cases were validated, limiting the inclusion of false positive cases. There are some limitations to this study. As we examined only men of the same age with a similar ethnic background, this study has an unknown generalizability to women or other age and ethnic groups. Furthermore, because this study was initiated in the 1970s and the HF diagnosis was based on a review of medical records, it was not possible to differ between systolic and diastolic HF because echocardiography was not available at the time of diagnosis for many of the cases. Thus, in our material it is not possible to examine whether the risk factors are different in systolic and diastolic HF, which might be possible. Another limitation of the study is that we used the presence of an interim MI during follow-up as a proxy for CHD. Even if this method is an established method for examining "non-ischemic" HF (26,27), it would be better to assess non-ischemic HF in a more specific way, e.g., by examining all subjects with coronary angiography. However, this is not a feasible option in a large, population-based epidemiologic study. Furthermore, we believe that the presence of a symptomatic MI is a good proxy for CHD because it includes the most advanced cases of CHD.

Conclusions. In conclusion, novel variables reflecting insulin resistance and dyslipidemia, together with a low beta-carotene level, were found to predict HF independently of established risk factors, including interim MI, in this community-based longitudinal study of middle-aged men. If confirmed, our observations could have large clinical implications because they may offer new approaches in the prevention of HF.

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