# Predictors of Incident Heart Failure Hospitalizations Among Patients With Impaired Glucose Tolerance

## Insight From the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research Study

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***Background***—Impaired glucose tolerance and metabolic syndrome are associated with increased risk of heart failure (HF). However, predictors associated with the increased risk of incident HF have not been well characterized. We aimed to identify independent predictors of incident HF hospitalization among patients with impaired glucose tolerance.

***Methods and Results***—In Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), 9306 research participants with impaired glucose tolerance and ≥1 cardiovascular risk factors were randomized to valsartan versus placebo and nateglinide versus placebo in a 2×2 factorial manner, with a median follow-up of 6.5 years. Using a multivariable Cox proportional hazards model, we analyzed the relationships among baseline clinical factors and the outcome of incident HF hospitalization in patients without history of HF. Significant predictors were identified by forward selection. Increasing age, history of coronary heart disease, and atrial fibrillation or flutter were among several known independent predictors of incident HF hospitalization. Increased waist circumference (hazard ratio per 10 cm, 1.37; 95% confidence interval, 1.21–1.55; $P<0.001$) and increased urinary albumin–creatinine ratio ($P<0.001$) were identified as novel predictors. The predictive model for incident HF hospitalization showed good discrimination, with an optimism-corrected C-index of 0.79.

***Conclusions***—Among research participants with impaired glucose tolerance, there are several easily identifiable predictors of incident HF hospitalization, including traditional risk factors and novel indices of central adiposity and increased urinary albumin–creatinine ratio, which enable further risk stratification and help distinguish patients who could benefit from more aggressive risk factor management. **(*Circ Heart Fail*. 2013;6:203-210.)**

**Key Words:** central adiposity ■ heart failure ■ impaired glucose tolerance ■ microalbuminuria ■ predictive model



The overall burden of heart failure (HF) continues to increase because of aging population and increasing cardiovascular (CV) risk factors in low- and middle-income countries.[1,2] The prognosis of patients with established HF remains poor despite many partially effective treatments. To reduce death and disability, both early identification of populations at risk and prevention of HF are increasingly emphasized strategies in professional guidelines.[3] However, such strategies remain poorly developed and implemented.[4]

### Clinical Perspective on p 210

Diabetes mellitus is an important risk factor for HF, and the level of glycated hemoglobin (HbA1c) is associated with the magnitude of risk of incident HF and worse outcomes.[5,6] In addition, among patients without diabetes mellitus, high-to-normal HbA1c (≥5.5%–6%) is associated with increased rates of incident HF.[7] Other studies in selected populations have shown that impaired glucose tolerance

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(IGT) is independently associated with the risk of incident HF.[8] In addition to the well-established risk associated with comorbidities, such as coronary heart disease and hypertension, that are prevalent in this patient population, several other potential pathophysiological mechanisms underlie the association between IGT and HF. Insulin resistance in patients with IGT may contribute to impaired myocardial energy metabolism and increased free fatty acid utilization.[9,10] Accumulation of advanced glycation end products in the presence of dysglycemia and hyperinsulinemia may also lead to increased myocardial fibrosis and adverse ventricular remodeling.[11]

Because patients with IGT are at risk of developing diabetes mellitus and HF, this patient population may benefit from early identification and preventative measures. By identifying patients while they are in earlier disease stages, who are either at risk of developing clinical HF (American Heart Association/American College of Cardiology Stage A) or who have asymptomatic left ventricular dysfunction (American Heart Association/American College of Cardiology Stage B), potential treatment strategies can be developed. However, further risk stratification can refine the selection of patients to minimize unnecessary screening and to enable a more targeted prevention strategy. To address these issues, this analysis aimed to characterize the risk of incident HF hospitalization and associated predictors among patients with diagnosed IGT and CV disease or CV risk factors who were enrolled in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.

# Methods

## Study Population

The design and results of NAVIGATOR have been previously published.[12] In brief, NAVIGATOR was a prospective, double-blinded, randomized, 2×2 factorial clinical trial that enrolled 9306 research participants aged 50 years or older with IGT and prior CV diseases or risk factors. A complete version of the study protocol was published as online-only Data Supplement material with earlier articles.[12] IGT was defined as 2-hour postchallenge glucose after a 75 g oral glucose tolerance test ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L) at baseline and a fasting plasma glucose concentration of at least 95 mg/dL (5.3 mmol/L) but <126 mg/dL (7.0 mmol/L). Patients with a history of New York Heart Association class III–IV symptomatic HF were excluded from enrollment. Although patients with New York Heart Association class I–II HF were included in NAVIGATOR, these patients were excluded from this analysis. Patients were randomized to valsartan or placebo and, in addition, nateglinide or placebo. All research participants were required to follow a standardized lifestyle modification program. The primary outcomes of the main study were as follows: (1) development of diabetes mellitus; (2) a core CV composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization; and (3) an extended CV composite that included hospitalization for unstable angina and arterial revascularization in addition to the core composite outcome components. Analysis of the individual components of the core CV outcome was also prespecified. Randomized patients were followed for a median of 5 years for the incident diabetes mellitus end point and 6.5 years for vital status. All research participants enrolled in NAVIGATOR were included in this analysis.

## Definition of HF

Incident HF hospitalization was defined as development of >1 symptom and >1 sign of HF not present at screening and requiring hospital management. The NAVIGATOR study end point committee independently adjudicated these events in a blinded fashion based on predefined event definitions that included subjective symptoms of HF and objective physical signs, imaging findings, or elevated brain natriuretic peptide level (Appendix I in the online-only Data Supplement). Only events that required overnight hospital admission were included as end point events for this analysis.

## Definitions of Baseline Variables

Coronary heart disease included prior myocardial infarction, revascularization procedure, or symptomatic angina. Similarly, cerebrovascular disease consisted of prior stroke or transient ischemic attack. Peripheral artery disease included nontraumatic limb or foot amputation, peripheral revascularization procedure, or significant peripheral arterial stenosis (>50%) on angiography. Chronic obstructive pulmonary disease (COPD) included chronic bronchitis, emphysema, or COPD. Current cigarette smoking status was defined by self-reported history of smoking. Patients who had quit smoking <12 months before enrollment were considered as current smokers. Baseline ECGs were reported by investigators using a predefined classification with the following checkbox options on the case report form: (1) normal, (2) clinically insignificant abnormality, and (3) clinically significant abnormality.

## Statistical Analysis

Continuous baseline variables were summarized as means±SDs, except where otherwise noted. Between groups, comparisons were performed using *t* tests for normally distributed data or nonparametric tests (Wilcoxon rank-sum) otherwise. Categorical variables were summarized as counts and percentages and were compared using $\chi^2$ tests or the Fisher exact test.

### *Predictive Model Development*

A multivariable Cox proportional hazards model was developed for the outcome of incident HF hospitalization. For model selection, candidate variables included demographic features, baseline comorbidities, vital signs, anthropometric measurements, laboratory values, and investigator-reported baseline ECG results (Table 1). The number of candidate variables was limited to 25 to reduce the likelihood of overfitting, given the number of events relative to the number of candidate predictors being considered. These variables were statistically significant predictors identified by the Cox model and developed for all HF hospitalizations (including patients with history of congestive HF), which had a more extensive set of candidate variables (Appendix II in the online-only Data Supplement). This was not intended as a variable screening process, but given the importance of these variables in the overall population, there was strong rationale to include them in the incident HF hospitalization analysis. In addition, several other key variables (sex, race, baseline history of hypertension, cerebrovascular disease, renal dysfunction, current smoking at baseline, family history of diabetes mellitus, fasting glucose, oral glucose tolerance test result, heart rate, and low-density lipoprotein) were specifically identified by the authors based on clinical relevance and were included in the model selection process. Of note, waist circumference was the only obesity measure included as a candidate variable. Weight and body mass index (BMI) were not included, as they were not found to be significant independent predictors in the presence of waist circumference in the all HF hospitalization model (Appendix III in the online-only Data Supplement). Similarly, baseline HbA1c was not included as a candidate variable, as it was not found to be a significant predictor in the all HF hospitalization model. In addition, not all research participants were required to have a baseline HbA1c as part of inclusion. However, because of the clinical importance of both BMI and HbA1c, these variables were tested in the final incident HF hospitalization model to confirm nonsignificance. Restricted cubic splines were used to assess linearity of continuous variables. For variables that were found to be nonlinear, appropriate transformations, such as logarithmic transformation (urinary albumin–creatinine ratio [UACR]) or linear splines (systolic blood pressure [BP]), were applied. Variable selection for the final model was based on forward selection (variables were sequentially added to the developing model),

**Table 1. Baseline Characteristics of Research Participants With or Without Incident Heart Failure Hospitalization**

| Baseline Characteristics | No HF Hospitalization (N=8851) | Incident HF Hospitalization (N=124) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, y* | 63.6±6.8 | 68.7±7.8 | <0.001 |
| Female* | 4523 (51.1) | 56 (45.2) | 0.189 |
| Race* | | | |
| White | 7331 (82.8) | 106 (85.5) | … |
| Black | 223 (2.5) | 4 (3.2) | … |
| Asian | 595 (6.7) | 5 (4.0) | … |
| Other | 702 (7.9) | 9 (7.3) | … |
| Anthropometric variables | | | |
| Weight, kg | 83.4±17.1 | 86.1±17.5 | 0.056 |
| Height, cm* | 165.3±9.9 | 164.9±9.5 | 0.612 |
| BMI, kg/m$^2$ | 30.4±5.4 | 31.7±6.1 | 0.022 |
| Waist circumference, cm* | 100.8±13.5 | 105.6±14.2 | <0.001 |
| Male | 103.6±12.4 | 107.3±13.2 | 0.002 |
| Female | 98.1±13.9 | 103.6±15.1 | 0.015 |
| Clinical features | | | |
| Systolic blood pressure, mm Hg* | 139.7±17.3 | 141.0±22.2 | 0.674 |
| Diastolic blood pressure, mm Hg | 82.6±10.1 | 80.9±13.6 | 0.027 |
| Heart rate, bpm | 70.2±10.6 | 68.4±11.1 | 0.092 |
| Medical history | | | |
| Hypertension* | 6840 (77.3) | 101 (81.5) | 0.270 |
| Left ventricular hypertrophy | 230 (2.6) | 4 (3.2) | <0.567 |
| Coronary heart disease* | 2304 (26.0) | 66 (53.2) | <0.001 |
| Current smoker* | 974 (11.0) | 10 (8.1) | 0.298 |
| Atrial fibrillation or flutter* | 261(2.9) | 19 (15.3) | <0.001 |
| Cerebrovascular disease* | 665 (7.5) | 15 (12.1) | 0.055 |
| Peripheral artery disease* | 277 (3.1) | 11 (8.9) | 0.002 |
| Renal dysfunction* | 67 (0.8) | 3 (2.4) | 0.072 |
| COPD/chronic bronchitis/emphysema* | 374 (4.2) | 17 (13.7) | <0.001 |
| Pulmonary embolism and DVT | 118 (1.3) | 5 (4.0) | 0.028 |
| Family history of premature CHD | 1467 (16.6) | 19 (15.3) | 0.710 |
| Family history of diabetes mellitus* | 3401 (38.4) | 35 (28.2) | 0.020 |
| Glycemic status | | | |
| Plasma glucose level, mmol/L | | | |
| Baseline fasting* | 6.1±0.5 | 6.1±0.4 | 0.506 |
| 2 h after glucose challenge* | 9.2±0.9 | 9.1±1.0 | 0.718 |
| Glycated hemoglobin, % | 5.8±0.4 | 5.9±0.5 | 0.004 |
| Baseline ECG interpretation* | | | <0.001 |
| Normal | 4439 (50.2) | 31 (25.0) | … |
| Clinically insignificant abnormality | 3147 (35.6) | 48 (38.7) | … |
| Clinically significant abnormality | 1265 (14.3) | 45 (36.3) | … |
| Baseline laboratory results | | | |
| Sodium, mmol/L | 142.4±2.5 | 142.4±2.7 | 0.944 |
| Potassium, mmol/L | 4.3±0.4 | 4.4±0.5 | 0.145 |
| Hemoglobin, g/L* | 146.8±12.6 | 143.9±13.4 | 0.030 |
| Platelets, ×10$^9$/L* | 257.8±63.7 | 243.4±66.3 | 0.016 |
| White blood cells, ×10$^9$/L* | 6.9±1.7 | 7.1±1.7 | 0.104 |
| eGFR, mL/min per 1.73m$^2$* | 80.9±18.0 | 73.1±18.3 | <0.001 |

(*Continued*)

**Table 1. Continued**

| Baseline Characteristics | No HF Hospitalization (N=8851) | Incident HF Hospitalization (N=124) | *P* Value |
|---|---|---|---|
| UACR, mg/mmol† | 0.8 (0.5–1.7) | 1.3 (0.6–4.5) | <0.001 |
| Log UACR* | 0.1±1.1 | 0.7±1.4 | <0.001 |
| HDL cholesterol, mmol/L | 1.3±0.3 | 1.3±0.3 | 0.240 |
| LDL cholesterol, mmol/L* | 3.3±0.9 | 3.2±1.0 | 0.185 |
| Triglycerides, mmol/L | 1.9±1.1 | 1.9±1.1 | 0.209 |
| Medications at randomization‡ | | | |
| Any antihypertensive | 6393 (72.2) | 109 (87.9) | <0.001 |
| ACE inhibitors | 501 (5.7) | 21 (16.9) | <0.001 |
| Angiotensin receptor blocker | 30 (0.3) | 0 (0) | 1.000 |
| α-Blocker | 545 (6.2) | 13 (10.5) | 0.048 |
| β-Blocker | 3392 (38.3) | 66 (53.2) | 0.001 |
| Calcium channel blocker | 2870 (32.4) | 54 (43.5) | 0.009 |
| Diuretics | 2697 (30.5) | 51 (41.1) | 0.011 |
| Lipid-lowering drug | 3394 (38.3) | 54 (43.5) | 0.237 |
| Aspirin | 3183 (36.0) | 56 (45.2) | 0.034 |

Continuous variables are presented as means±SDs. Categorical variables are presented as actual frequencies (n) and percentages (%).

ACE indicates angiotensin-converting enzyme; BMI, body mass index; bpm, beats per minute; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; IQR, interquartile range; LDL, low-density lipoprotein; and UACR, urinary albumin–creatinine ratio.

*Variables included as candidate variables for the incident heart failure hospitalization predictive model.

†Urinary albumin–creatinine ratio summarized as median with IQR.

‡Medications at randomization were not included in the multivariable models as candidate variables.

with the α level set at 0.05. Multilevel categorical variables such as race (eg, black, white, Asian, and other) and ECG findings were tested as a group.

The discrimination ability of the models was assessed with C-statistics, which were corrected for optimism induced by assessing the model in the derivation dataset. The optimism correction was achieved by bootstrapping the incident HF hospitalization dataset and repeating the model selection from among 25 covariates, in 100 bootstrap samples.[13] A plot of observed and predicted event rates was developed to visualize the calibration of the predictive model.

## Results

Among the 9306 research participants enrolled in the NAVIGATOR study, 331 patients with history of HF at baseline were excluded, resulting in a cohort of 8975 research participants for this analysis. During the median follow-up of 6.5 years (interquartile range, 6.0–6.9), 124 patients experienced an incident HF hospitalization (event rate of 2.3 per 1000 patient-years).

### Patient Characteristics

The baseline characteristics of patients with and without incident HF hospitalization differed significantly (Table 1). Patients with HF hospitalization were older, had a larger waist circumference (for both males and females), and were more likely to have coronary heart disease, atrial fibrillation or flutter, peripheral artery disease, or COPD. The majority of patients, with or without incident HF hospitalization, had a history of hypertension (81.5% and 77.3%, respectively). At baseline, patients with subsequent incident HF hospitalization were also more likely to have a clinically significant ECG abnormality reported by investigators. The baseline estimated glomerular filtration rate was lower among patients with incident HF hospitalization than among those without; however, the majority of research participants had preserved renal function. At randomization, patients with subsequent incident HF hospitalization were more likely to have been prescribed an antihypertensive agent, angiotensin-converting enzyme inhibitor, β-blocker, or diuretic.

### Predictors of Incident HF Hospitalization

The strongest predictors of incident HF hospitalization were older age and central adiposity indicated by an increase in waist circumference (Table 2). Every 10 cm increase in waist circumference was associated with a 37% increased risk of HF hospitalization. In addition, taller height was associated with better prognosis.

Baseline history of coronary heart disease, atrial fibrillation or flutter, and COPD were associated with increased risk of incident HF hospitalization. A clinically significant abnormal ECG (compared with a normal ECG at baseline) was associated with a 1.8× increased risk of incident HF hospitalization. In the presence of COPD, cigarette smoking was not found to be an independent predictor of incident HF hospitalization.

Systolic BP was found to be a nonlinear continuous variable when the restricted cubic spline was examined. Based on the spline, systolic BP was truncated at 130 mm Hg and a marginal protective effect was associated with every 1 mm Hg increase in systolic BP up to 130 mm Hg. Systolic BP levels above 130 mm Hg were not significantly associated with HF hospitalization in this multivariable regression model. In the presence of systolic BP as a continuous variable, baseline

**Table 2. Multivariable Cox Proportional Hazards Model Showing Independent Baseline Predictors of Incident Heart Failure Hospitalizations Among Patients With Impaired Glucose Tolerance**

| Baseline Characteristics | HR (95% CI) | $\chi^2$ Statistics | *P* Value |
|---|---|---|---|
| Age (per 10 y increase) | 2.27 (1.77–2.93) | 41.24 | <0.001 |
| Waist circumference (per 10 cm increase) | 1.37 (1.21–1.55) | 24.72 | <0.001 |
| History of coronary heart disease | 2.42 (1.67–3.51) | 21.97 | <0.001 |
| Baseline clinically significant abnormal ECG (vs normal) | 2.81 (1.73–4.55) | 17.58 | <0.001 |
| History of atrial fibrillation or flutter | 2.64 (1.56–4.47) | 13.14 | <0.001 |
| Log of urinary albumin–creatinine ratio | 1.25 (1.10–1.41) | 12.51 | <0.001 |
| History of COPD/emphysema/chronic bronchitis | 2.46 (1.46–4.13) | 11.50 | <0.001 |
| Systolic BP up to 130 mm Hg* (per unit increase) | 0.97 (0.94–0.99) | 7.21 | 0.007 |
| Hemoglobin (per 10 g/L decrease) | 1.17 (1.01–1.35) | 4.41 | 0.036 |
| Height (per 10 cm increase) | 0.82 (0.67–0.99) | 4.17 | 0.041 |
| Baseline clinically insignificant abnormal ECG (vs normal) | 1.58 (1.00–2.50) | 3.79 | 0.051 |

Optimism-corrected C-statistic for this model was 0.79.
BP indicates blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.
*Selected due to nonlinearity of systolic blood pressure as a continuous variable.

history of hypertension was not independently associated with increased risk of incident HF hospitalization.

Albuminuria, expressed as log of UACR, was also found to be an independent predictor of HF hospitalization. Of note, the median UACR is well below the range for microalbuminuria (>3.5 mg/mmol). Baseline estimated glomerular filtration rate or history of renal dysfunction was not independently associated with incident HF hospitalization.

When added to the final model (Table 2) sequentially, neither BMI nor HbA1c were shown to be significant (*P*=0.373 and *P*=0.398, respectively).

## Model Performance

The Cox regression model showed good discriminatory ability, with an optimism-corrected C-index of 0.79. In addition, the predicted probability of incident HF hospitalization was very similar to the observed probabilities. The Figure shows the calibration plot for the incident HF hospitalization Cox model with probability risks divided into quintiles.

## Discussion

In this well-characterized cohort of patients with IGT, the overall event rate of incident HF hospitalization during the trial follow-up period was 2.3 per 1000 patient-years. In addition to previously well-recognized determinants for the development of HF, this study also identified several novel predictive factors, such as increased waist circumference, taller body height, and increased UACR.

Obesity is an emerging risk factor for HF. Several epidemiological studies have established an incremental relation between obesity, as measured by BMI, and the incidence of HF across several communities.[14–16] In addition, other anthropometric measures of central obesity, such as waist circumference, have been shown to be independently associated with the risk of HF in several studies.[17–20] The Atherosclerosis Risk in Communities study showed that BMI, waist circumference, and waist-to-hip ratio were all independently associated with increased risk of incident HF hospitalization or death.[20] However, most studies, with the

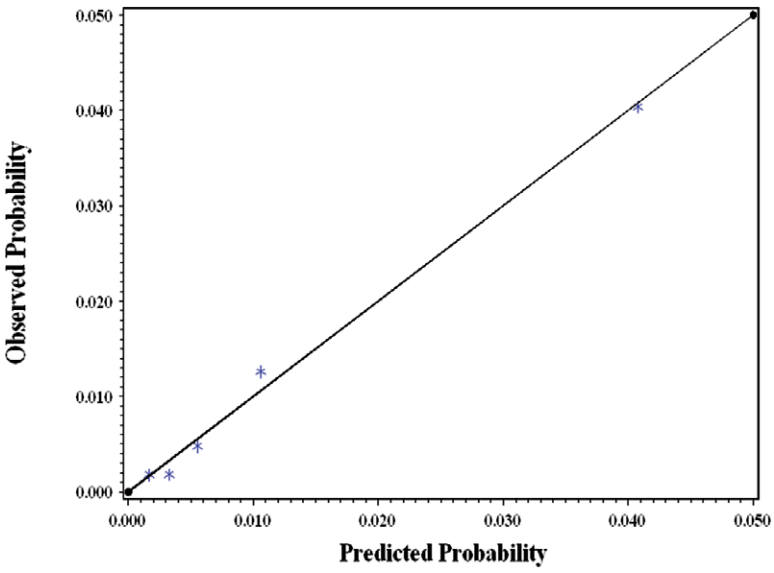


**Figure.** Calibration plot showing observed vs predicted probability of incident heart failure hospitalization at 5-year follow-up. The predicted probability estimates represent mean predicted probability from the Cox proportional hazards regression model, and observed probability estimates of the trial population were derived from Kaplan–Meier estimates. Predicted probability was divided into quintiles to represent each risk category.

exception of 1 study of elderly patients (aged 70–79),[19] did not take into account the glycemic status of patients, which is an important confounder in the context of metabolic syndromes and incident HF. The strength of our study is that increased waist circumference was shown to be a significant predictor of incident HF hospitalization, independent of a wide range of CV comorbidities, 2-hour oral glucose tolerance test results, and fasting glucose levels. These findings may support recent evidence suggesting that increased levels of adipokines secreted by visceral fat, such as resistin, are associated with increased risk of HF.[9,21,22] Nonetheless, further study is needed to clarify whether excess visceral adiposity is indeed a contributor to the development of HF in patients with dysglycemia. In addition, the inverse relation between body height and the risk of HF hospitalization, when interpreted in conjunction with waist circumference, further strengthens the focus of central adiposity's importance as a predictive factor.

Albuminuria, measured by UACR, has been found to be an independent predictor of adverse prognosis in patients with chronic HF.[23] Our study's finding that albuminuria is an independent predictor of incident HF hospitalization extends the observation that increased urinary albumin excretion is in some way connected with the pathophysiology of HF. In a study of 10 975 patients without HF at baseline, Blecker et al[24] found a linear relationship between UACR and the risk of incident HF after adjusting for multiple established risk factors and possible confounders. The linear relationships remained significant across the range of UACRs, starting from a detectable but within normal range of albuminuria to levels consistent with macroalbuminuria. This UACR–HF relationship was independent of the estimated glomerular filtration rate. Our observation in a cohort with IGT is consistent with previous population-based studies. Several possible mechanisms explaining the association have been postulated: albuminuria is most likely a marker of (1) activation of the renin-angiotensin aldosterone system,[25] (2) impaired vascular endothelial function with consequent increased renal vasculature permeability,[26] and (3) association with left ventricular hypertrophy.[27]

A history of hypertension at baseline and systolic BP above 130 mm Hg were not found to be independent predictors of incident HF hospitalization in our study. Several factors contributed to this observation. First, hypertension was highly prevalent in the overall study population: the prevalence of hypertension at baseline was >75% in those with and without subsequent HF hospitalization. This makes hypertension at baseline a poor discriminator for the selected end point. Second, continuous effort was made in NAVIGATOR to adhere to evidence-based recommendations for BP control, with a noticeable improvement in the overall mean systolic BP from a baseline of 140 mm Hg to 134 mm Hg (median systolic BP, 133 mm Hg) after 5 years of follow-up.[12] Systolic BP at baseline as a continuous variable was found to have a nonlinear relationship with HF hospitalization. Higher systolic BP up to 130 mm Hg was associated with a better outcome, perhaps due to confounding by the possibility that patients with subclinical left ventricular dysfunction and low BP (due to reduced cardiac output) are more likely to have poorer prognoses and higher risks of hospitalization.

Whereas not all risk factors are modifiable, earlier identification of patients at risk for HF may allow closer surveillance and additional therapeutic interventions to prevent worsening HF requiring hospitalization. Recognizing that IGT is associated with an increased risk of HF and other CV diseases, further screening of patients with central obesity and other risk factors identified in our analyses may be warranted if these findings are strengthened and validated in independent analyses. Multiple studies have found that IGT and diabetes mellitus itself are often missed in practice, both in patients with and without extant vascular disease. The independent predictors identified in this analysis will help clinicians to further stratify a patient within this population for the risk of incident HF.

### Limitations

There are several limitations to this study. First, incident HF hospitalization was defined by a lack of clinical history of existing HF at baseline, without objective screening tests, potentially creating a prevalence-incidence bias. Second, we were unable to differentiate between HF with (1) reduced or (2) preserved ejection fraction. Furthermore, only HF events requiring hospitalization were included in this analysis; patients with HF treated as outpatients were not captured. Third, we evaluated associations with 25 covariates in a sample with only 124 incident HF events. This corresponds to ≈5 events per variable. Given the low ratio of events to candidate variables, there is reason to expect some bias in the estimated hazard ratios and a possibility of overfitting. To address this, we do not emphasize the interpretation of marginally significant variables, and we have evaluated discrimination using optimism-corrected C-indices. We acknowledge that replication of our findings in another similar cohort or external validation of our predictive model may be required to ensure generalizability. Finally, the patient population consists of clinical trial participants and may not be representative of the general population. Patients in either randomization arm were treated aggressively in terms of their CV risk factors, and all patients were required to complete a structured lifestyle modification program. Results from the primary analysis of the NAVIGATOR study indicated that there was significant reduction in BP and body weight throughout the trial.[12] Despite these limitations, this study comprised a large population with clearly defined IGT. In these patients who were at risk of other adverse CV outcomes, we were able to identify independent and novel risk factors for HF.

## Conclusions

In summary, among research participants with IGT and CV risk factors, we identified established and novel independent predictors of incident HF hospitalization. In particular, our findings show the importance of central adiposity and even normal levels of UACR as predictors of incidence HF. These easily identifiable risk factors will allow primary care providers to further risk stratify patients with IGT, thereby identifying those who may benefit from risk factor modification, and potentially detecting HF earlier. These findings will also

allow researchers to identify patients who are most at risk and pursue them for future research to understand the mechanisms involved in the progression of IGT and insulin resistance to incident HF, to develop novel therapeutics and treatment strategies.

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Califf: Research grant and consultant/advisory board: Novartis.

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## CLINICAL PERSPECTIVE

Impaired glucose tolerance (IGT) is an important facet of metabolic syndrome, and is associated with increased risk of cardiovascular disease, including heart failure (HF). Although current evidence does not support routine oral glucose tolerance testing to diagnose IGT, targeted screening should be considered in patients presenting with the phenotype suggestive of IGT and cardiometabolic risk. The aim of this study was to identify independent predictors of incident HF hospitalization among research participants with IGT and cardiovascular risk factors or disease (excluding HF). IGT was diagnosed using oral glucose tolerance test. We identified several independent predictors of incident HF hospitalization that will help clinicians to further risk stratify patients with IGT. These include known predictors, such as history of coronary heart disease, atrial fibrillation, chronic obstructive pulmonary disease, and older age. We also identified more novel markers, such as greater waist circumference and higher urine albumin-to-creatinine ratio. Most of these factors are readily available to clinicians during routine assessment. Given the adverse prognosis associated with HF, early diagnosis and possible prevention are important among patients at risk. Furthermore, as HF shares many common risk factors with other cardiovascular outcomes and chronic kidney disease, these predictors will also help clinicians identify individuals who may obtain multiple benefits from intensive lifestyle modification and risk factor management.

# Predictors of Incident Heart Failure Hospitalizations Among Patients With Impaired Glucose Tolerance: Insight From the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research Study

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**Wong et al: Heart Failure in Impaired Glucose Tolerance**

## Supplemental Material

**APPENDIX 1. Endpoint definition for congestive heart failure requiring hospitalization**

| |
|---|
| Development of signs and symptoms of CHF not present at screening and requiring hospital management, or previously documented CHF that worsens requiring hospital management. |
| **CHF is clinically manifested by 1 or more of the following:** |
| • Dyspnea on exertion in the absence of new pulmonary disease<br>• Paroxysmal nocturnal dyspnea (shortness of breath that awakens the patient from sleep)<br>• Orthopnea |
| **AND 1 or more of the following criteria:** |
| • Pulmonary rales >1/3 of the way up the lung fields present after coughing in the absence of chronic lung disease or respiratory infection<br>• Pulmonary edema on chest X-ray in absence of high suspicion for non-cardiac origin<br>• New use of oral/IV diuretics, IV inotropes, IV vasodilators, or adjustment of previous diuretic dose<br>• Oxygen desaturation (<90%) with no evidence of acute or chronic lung disease<br>• Jugular venous distention<br>• Bilateral pedal edema<br>• Cardiomegaly (cardiothoracic ratio ≥0.55)<br>• Left ventricular ejection fraction ≤0.40 (new or presumably new)<br>• Left ventricular fractional shortening <0.25<br>• S3 gallop on auscultation<br>• Elevated BNP level |

BNP indicates brain natriuretic peptide; CHF, congestive heart failure; IV, intravenous.

**APPENDIX 2. Candidate variables included in the all HF hospitalization model**

| **Demographics** |
|---|
| Age, y |
| Female sex |
| Race |
| Region (Europe, North America, Latin America, Asia, Other) |
| **Anthropometric variables** |
| Weight, kg |
| Height, cm |
| BMI, kg/m$^2$ |
| Waist circumference, cm |
| **Clinical features** |
| Systolic blood pressure, mm Hg |
| Diastolic blood pressure, mm Hg |
| Heart rate, bpm |
| **Medical history** |
| Congestive HF |
| Hypertension |
| Left ventricular hypertrophy |
| Coronary heart disease |
| Current smoker |
| Atrial fibrillation or flutter |
| Cerebrovascular disease |
| Peripheral vascular disease |

| **Medical history (continued)** |
|---|
| Renal dysfunction |
| COPD/chronic bronchitis/emphysema |
| Pulmonary embolism and/or DVT |
| Family history of premature CHD |
| Family history of diabetes |
| **Glycemic status** |
| Baseline fasting glucose level, mmol/L |
| 2-hour after glucose challenge, mmol/L |
| Glycated hemoglobin (HbA1c), % |
| **Baseline ECG interpretation** |
| Clinically insignificant abnormality (vs. normal) |
| Clinically significant abnormality (vs. normal) |
| **Baseline laboratory results** |
| Sodium, mmol/L |
| Potassium, mmol/L |
| Hemoglobin, g/L |
| Platelets, x10$^9$/L |
| White blood cells, x10$^9$/L |
| eGFR, mL/min/1.73m$^2$ |
| Log urinary albumin:creatinine ratio |
| HDL cholesterol, mmol/L |
| LDL cholesterol, mmol/L |
| Triglycerides, mmol/L |

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; DVT, deep vein thrombosis; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein

**APPENDIX 3. Multivariable Cox proportional hazards model showing independent baseline predictors of all heart failure hospitalizations among patients with impaired glucose tolerance**

| Baseline Characteristics | HR (95% CI) | $\chi^2$ Statistics | *P* value |
|---|---|---|---|
| History of congestive HF | 4.41 (3.10–6.26) | 68.61 | <0.001 |
| History of atrial fibrillation or flutter | 2.98 (2.05–4.33) | 32.51 | <0.001 |
| History of coronary heart disease | 2.23 (1.60–3.11) | 22.64 | <0.001 |
| Waist circumference (per 10 cm increase) | 1.28 (1.16–1.42) | 22.37 | <0.001 |
| Baseline clinically significant abnormal ECG (vs. normal) | 2.73 (1.77–4.22) | 20.46 | <0.001 |
| Age (per 10 year increase) | 1.62 (1.31–2.00) | 19.96 | <0.001 |
| History of COPD/emphysema/chronic bronchitis | 2.11 (1.43–3.13) | 13.89 | <0.001 |
| Systolic BP up to 130 mm Hg* (per unit increase) | 0.97 (0.95–0.99) | 13.21 | <0.001 |
| Hemoglobin (per 10g/L decrease) | 1.23 (1.10–1.38) | 12.32 | <0.001 |
| Log of urinary albumin:creatinine ratio | 1.17 (1.05–1.30) | 8.71 | 0.003 |
| Platelets (per 10 unit increase) | 0.97 (0.94–0.99) | 6.99 | 0.008 |
| eGFR (per 10 unit decrease) | 1.11 (1.02–1.21) | 6.24 | 0.013 |
| Height (per 10 cm increase) | 0.81 (0.69–0.96) | 5.85 | 0.016 |
| History of PAD | 1.82 (1.09–3.06) | 5.17 | 0.023 |
| Baseline clinically insignificant abnormal ECG (vs. normal) | 1.62 (1.06–2.46) | 5.00 | 0.025 |
| White blood cells (per 10 unit increase) | 1.10 (1.01–1.20) | 4.43 | 0.035 |

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as actual frequency (n) and percentage (%).
Overall C-statistic for this model was 0.864.
*Selected due to nonlinearity of systolic blood pressure as a continuous variable.
BP indicates blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; PAD, peripheral artery disease.