Predictors of Heart Failure in Patients with Stable Coronary Artery Disease:

A PEACE Study

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ABSTRACT:

Background: Heart failure (HF) is a disease commonly associated with coronary artery disease (CAD). Most risk models for HF development have focused on acute myocardial infarction (MI) patients. The prevention of events with angiotensin-converting enzyme inhibition (PEACE) population enabled the development of a risk model to predict HF in patients with stable CAD and preserved ejection fraction.

Methods and Results: In the 8290 PEACE patients without pre-existing HF, new-onset HF hospitalizations and fatal HF were assessed over a median follow-up of 4.8 years. Covariates were evaluated and maintained in the Cox regression multivariable model using backward selection if p<0.05. A risk score was developed and converted to an integer-based scoring system. Among the PEACE population (age 64±8, female 18%, prior MI 55%), there were 268 cases of fatal and non-fatal HF. Twelve characteristics were associated with increased risk of HF along with several baseline medications, including older age, history of hypertension, and diabetes. Randomization to trandolapril independently reduced risk of HF. There was no interaction between trandolapril treatment and other risk factors for HF. The risk score (range 0-21) demonstrated excellent discriminatory power (c-statistic 0.80). Risk of HF ranged from 1.75% in patients with a risk score of 0 to 33% in patients with risk score≥16.

Conclusion: Among patients with stable CAD and preserved EF, traditional and newer factors were independently associated with increased risk of HF. Trandolopril decreased the risk of HF in these patients with preserved EF.

Key words: heart failure, coronary artery disease, ACE-inhibitors, predictors
INTRODUCTION:

The prevalence of coronary artery disease (CAD) is expected to increase over the next few decades given the increase in the prevalence of risk factors such as obesity and diabetes and the improved survival after the diagnosis(1, 2). These patients living with CAD are at higher risk for death and a range of additional cardiovascular outcomes, including recurrent myocardial infarction (MI), arrhythmia, stroke, and heart failure(3-6). The risk of experiencing these important cardiovascular events also varies considerably across the spectrum of CAD survivors. The development of heart failure (HF) is particularly serious since patients manifesting HF have a several fold increase in the risk of death when compared with other CAD patients and MI survivors(3, 7). Among a MI population with low left ventricular ejection fraction (LVEF), those who developed HF had increased mortality (8). Thus, efforts to prevent development of HF have major implications for individual patients as well as the health care and public health community given the economic and societal impact of the syndrome(9).

Many of the prediction models of HF development have focused on patients with hypertension(10, 11) and MI survivors in the acute and sub-acute phase(12, 13). A few investigators have characterized risk factors for HF in patients with higher-risk, stable CAD(14). Moreover, angiotensin-converting enzyme (ACE) inhibitors have been demonstrated to reduce mortality and morbidity in patients with HF, MI complicated by HF, and high-risk CAD(8, 15-17). Less is known about predictors associated with HF in lower-risk patients with CAD. A better understanding of the factors involved in the eventual development of HF among these lower risk patients may enable new strategies to prevent progression of disease, preserve quality of life, and improve overall survival.
The Prevention of Events with an ACE Inhibitor (PEACE) cohort of patients was a low-risk CAD population that was the focus of this study. The aims were a) to identify predictors of HF in a low-risk CAD population, b) to determine the impact of trandolapril on subsequent HF events, and c) to develop a risk score to predict HF.

METHODS:

The design and results of the PEACE trial have been previously published(18). Briefly, 8290 patients ≥50 years with documented CAD and documented left ventricular ejection fraction ≥40% were randomized to trandolapril or placebo and followed for a median of 4.8 years. The primary endpoint was cardiovascular death, non-fatal MI, or coronary revascularization. Patients with a serum creatinine >2.0 mg/dL or who had hospitalization for unstable angina within 2 months or revascularization within 3 months were excluded. In addition, patients with a condition that required the use of an ACE-inhibitor, including HF, were excluded.

Baseline characteristics were obtained by site investigators and staff and included medical history, prior MI and/or coronary revascularization, vital signs, and left ventricular ejection fraction. Serum creatinine was obtained at baseline. Glomerular filtration rate (GFR) was estimated using the 4-component Modification of Diet in renal Disease (MDRD) equation which includes serum creatinine, sex, age, and race(19). New HF was determined by the investigators and required hospitalization for the treatment of HF or was adjudicated as the primary cause of death by a clinical endpoints committee. In addition, all deaths were sub-classified and those deaths attributed to HF were noted. The primary outcome for this study focused on HF hospitalization or fatal HF.

Statistical analysis
We computed descriptive statistics for all potential covariates. For each continuous variable, we tested for linearity in the log hazard using cubic splines. We then used the collinearity index to check for intercorrelations among the variables. All covariates were entered into a Cox proportional hazard model and the final model was chosen using a backward selection procedure. Of note, a forward selection procedure resulted in the same independent predictors of HF events. All two-way interactions with treatment were tested and a p-value of 0.01 was considered significant. We tested model fit using residual analysis and the proportional hazards assumptions using the log-log survival function. To validate the final Cox model, we used the methods of Assman, Cullen, and Schulte. We randomly divided the sample into five equal parts and generated models using every possible combination of four of the five sets. A c-score was computed to assess the model’s predictive ability. Hazard ratios with 95% confidence intervals are reported for the final model.

To develop a risk stratification algorithm, we assigned a point score to baseline characteristics that independently predicted CHF. A risk score was developed using the methods of Rassi et al. Each coefficient was divided by the smallest coefficient and rounded to the nearest integer. Kaplan-Meier survival curves were generated for each risk score. The scores were grouped into 3 categories of risk; low (<9 points), medium (10-14 points), and high (>15 points). We used the log-rank test to test for differences in survival between the groups.

Several supportive analyses were conducted. The variables that were determined to be predictive of HF in a stable MI cohort in Cholesterol and Recurrent Events (CARE) were compared with PEACE population using Cox Proportional Hazards Model. Patients
in the PEACE trial who suffered a MI post-randomization were evaluated to determine the proportion of patients who had a MI prior to HF event. The SAS analysis system version 9.1 was used for all analyses (SAS Institute, Inc., Cary, NC).

RESULTS:

The baseline characteristics of the PEACE population have been previously reported(18). Briefly, the mean age was 64±8 with 18% female and 31.0% having a body mass index >30 kg/m². The mean left ventricular ejection fraction was 58±9% with only 14.9% of patients having a LVEF between 40-50%, the lowest eligible range of left ventricular function. The mean estimated glomerular filtration rate was 78±19 ml/kg/min/1.73 m², and 16.4% of patients had Stage 3 chronic kidney disease based upon an eGFR<60 ml/kg/min/1.73 m². A history of hypertension was present in 45% of patients and 55% had a prior MI. A total of 412 patients (5%) had missing quantitative values of LVEF, but systolic function was reported by echocardiography as being qualitatively preserved, and 405 patients (5%) were missing cholesterol values. The remainder of the data required for the multivariable model was available in 99% of patients. Mean arterial pressure and serum creatinine were not in the multivariable model as they were highly correlated with systolic/diastolic blood pressure and eGFR respectively.

Fatal and Nonfatal Heart Failure Events

During a median follow-up of 4.8 years, there were 268 patients (3.3%) of 8211 PEACE patients who had a HF event which averages to 0.7%/year. The majority of patients with a HF event (n=239) were hospitalized and 29 patients (0.35%) died of HF without ever being hospitalized. After adjudication by a blinded endpoints committee,
patients who were felt to have died predominantly as a result of pump failure were
classified as “fatal HF”. Of these 268 patients, 47 (17.5%) had an acute MI between
randomization and the HF event, but the majority developed HF without an interim MI.
Baseline characteristics of patients are listed in Table 1.

Multivariable analyses identified increasing age, diabetes, prior revascularization,
hypertension, and current smoking as the most robust predictors of HF (Table 2).
Patients with a prior MI had a 43% increased risk of HF and patients with lower LVEF
(LVEF 41-50%) had a 41% increased risk. Higher body mass index and lower eGFR
were also associated with increased risk. Several baseline medications that were used at
the discretion of the treating physician were also associated with HF development,
including use of diuretic, digitalis, calcium channel blocker, or anti-arrhythmic drugs.
Use of lipid lowering medicines was associated with a lower risk of HF.

Randomization to trandolapril significantly reduced the risk of HF compared with
placebo after adjusting for all other predictors of HF (HR 0.73, 95% CI 0.57-0.93,
p=0.01). There were no significant interactions between trandolapril and each variable in
the final model. The same variables were identified using forward selection as well as
backward selection. Cross-validation resulted in several variables that changed
significance levels in one or more validity data sets. This included the presence of
angina, LVEF stratification (40-50% vs. ≥50%), non-randomized use of calcium channel
blockers, and history of MI. A multivariable model developed with an endpoint of “HF
or all-cause mortality resulted in similar predictors.

Risk Score
For the purpose of risk score development, continuous variables were categorized (i.e., eGFR, age, and BMI). There was no difference in the Cox regression model when using these 3 variables as either categorized or continuous (Table 3). Patients with eGFR≤60 were at higher risk of HF (HR 1.67, 95% CI 1.3-2.2, p<0.001) as well as those with a BMI≥35 (HR 2.09, 95% CI 1.5-3.0). As expected, risk increased linearly with age. The risk score assigned to each variable ranged from 1 to 4 based upon the estimate size (Table 3). The risk score, calculated by the sum of scores for each patient, ranged from 0 to 21 and almost half of the patients in PEACE had a score ranging from 4 through 7. The low risk of HF events in PEACE is reflected in the distribution of events stratified by the risk score (Figure 1). Patients were stratified into 3 groups based upon the risk score (low risk<9, intermediate risk 9-14, and high risk >14). Figure 2 illustrates the HF event rates in the 3 different groups with a 5-year event rate of <2% in the group with the lowest risk, 10% risk in the group with the intermediate risk and over 30% in the highest risk group. The c-statistic of the final model with the best fit was 0.79 suggesting excellent discriminatory ability. The full model with all variable entered was not significantly different with a c-statistic of 0.80.

The model used to predict HF in CARE, a population of stable, MI survivors a mean of 10 months beyond their acute MI without antecedent HF, was evaluated in PEACE. This model in CARE was derived from the 4 strongest predictors of HF in this population based upon the multivariable model(14). Patients were grouped into low risk, intermediate risk, and high risk in CARE based upon age, LVEF, hypertension, and diabetes (Table 4). Only 2 patients (0.3%) in the low risk group developed HF compared with 3.4% and 10.8% respectively in the intermediate and high risk, albeit with wide
confidence intervals in the higher risk group. This validates the very low risk of HF events in patients with normal LVEF and no history of hypertension or diabetes in stable CAD as well as uncomplicated MI. The overall risk increased in the 3 groups of patients regardless of use of the CARE risk model or the PEACE risk model.

DISCUSSION:

In a low risk, stable CAD population with documented preserved LVEF who are well-treated with contemporary therapy, most will not develop HF over a 5 year period. Among this relatively low-risk population, several risk factors emerged among those who developed HF, including older age, diabetes, prior revascularization, and stroke. A few factors did not remain statistically significant during cross-validation procedures, and should be interpreted cautiously. LVEF did not remain in the model likely given the prerequisite normal or near normal LVEF to be randomized in PEACE. Use of lipid-lowering agents was associated with a lower likelihood of HF events. Despite this finding, most patients did not suffer from a clinically apparent MI prior to the HF event although microvascular ischemia or injury could not be excluded. Randomization to an ACE-inhibitor significantly reduced the risk of HF development even among this low risk group in which relatively few patients had a HF event. The lack of effect of ACE-inhibitor on mortality is likely related to the relatively small proportion of patients who developed HF. Finally, non-randomized medication use is likely a reflection of disease burden, which may contribute to their predictive ability. Analysis without these medicines did not significantly change the model.

Prevention of HF is an important goal of therapy for patients with a variety of conditions such as hypertension, diabetes, and survivors of MI and these patients have
been well-characterized in multiple prediction models(14, 25, 26). Most prediction models in CAD patients have focused on those patients with higher risk features such as low ejection fraction or vascular complications. In HOPE, in addition to HF hospitalization and fatal HF, the authors included HF requiring open-label ACE-inhibitor and symptoms and signs consistent with HF as a part of the HF endpoint(27). This higher risk population had an event rate of 10.2% over 4.5 years using the definition that included less severe HF not requiring hospitalization and/or requiring open label ACE-inhibitor. PEACE analysis confirmed several predictors of HF that were identified in the HOPE population, including older age, higher body mass index, prior CABG, diabetes, stroke, and lack of lipid lowering therapy. Approximately 80% of the HOPE patients had CAD and less patients were treated with beta-blockers, lipid-lowering agents, and anti-platelet therapy(28). In addition, impaired renal function was also associated with increased risk of HF in PEACE. Lower GFR has previously been shown to be predictive of adverse events in patients with myocardial infarction(29) and chronic HF(30, 31) and has identified patients who may be more likely to benefit from medical interventions(32). Among women with CAD, only a GFR<40 cc/min/m² was predictive of subsequent HF(33). This increasingly recognized risk factor may be associated with HF development due to left ventricular remodeling and worsening anemia. Additional predictors identified in PEACE include presence of angina, current smoking, and history of MI.

Risk scores have been commonly developed in the prediction of a variety of outcomes in patients with cardiovascular disease. The clinical utility has been relatively low for a variety of factors, including the cumbersome use in medical decision making.
This risk score employs an integer-based scoring system, which could facilitate its clinical applicability. Although it has excellent discriminatory characteristics, the very low event rate in this low risk population attenuates the overall impact of the score. Patients with intermediate and high risk scores are at much greater risk of HF development. However, the majority of patients had a score < 9 and was at low risk. Improving the ability to stratify these lowest risk patients may impact a larger population with CAD. The addition of biomarkers may increase the precision of prediction models using clinical characteristics. Brain natriuretic peptide (BNP) and pro-BNP have been predictive of HF events in PEACE and increased the c-statistic from 0.82 using several baseline characteristics and CRP to 0.84 with BNP added and 0.85 with pro-BNP added to the model(34). In the Heart and Soul study, pro-BNP was an independent predictor of new-onset HF in patients with stable CAD, but the number of clinical characteristics adjusted in the multivariable model was limited by the small number of events(33). Other possible biomarkers include anemia, C-reactive protein, and cystatin C(35). Most of the publications regarding predictors of HF in low risk CAD populations have focused on biomarkers or in patients with imaging evidence of ischemia(36).

The use of ACE-inhibitors has been established as clearly beneficial in a variety of patient populations, including those with chronic HF across the spectrum of disease severity, myocardial infarction patients with low LVEF and/or signs of HF, diabetes mellitus with proteinuria, and complicated CAD patients with high risk features. The current guidelines recommend ACE-inhibitors as a Class IIa indication for patients with CAD and normal to mildly reduced LVEF(37). In HOPE and EUROPA, ACE-inhibition decreased CV risk and mortality(17, 38).
In a lower risk population in PEACE with documented preserved LVEF, randomization to trandolapril reduced HF development, but not the primary endpoint or mortality. This efficacy was seen after adjusting for factors associated with HF development. Based upon other studies, HF development was associated with a 4 to 9 fold increased mortality, and prevention of this complication of CAD may attenuate this mortality (14, 27). Longer follow-up in patients at less risk of mortality may enable realization of benefit of ACE-inhibition. Also, HF management costs an estimated 29 billion dollars annually in the United States alone and prevention of HF development in patients with CAD would decrease the economic burden of CV disease. Patients who develop HF have a distinctly different life trajectory with decreased survival, increased anxiety and depression, and worse quality of life. Finally, a meta-analysis of HOPE, EUROPA, and PEACE demonstrated consistent reduction in CV events and HF (39).

There are several limitations to this study. First, several predictors in the final model were non-randomized medications and we cannot adjust for the underlying rationale for their use by the treating physician. However, this may improve the significance of the other variables as it may further adjust for disease severity. We did not include the milder forms of HF, such as those patients who did not require HF hospitalization. This group has worse subsequent mortality, albeit not as high as those requiring hospitalization (40). In HOPE, these patients who required open label ACE-inhibitor or had symptoms consistent with HF were included in the final model, and our study confirms the value of ACE-inhibition even when focused on the more severe HF events. Also, there were a small percentage of patients who developed HF in this very low risk population. The absolute number of patients with HF events, however, enabled
the development of a robust multivariable model. We do not have LVEF assessment at
the time of the HF event and cannot subclassify into low vs. preserved LVEF. However,
the quality of life and symptom burden of these patients are similar irrespective of
LVEF(41). Despite these limitations, this study expands our understanding of predictors
of HF among a low risk CAD population and demonstrated the independent effect of
ACE-inhibition in reducing this risk.

CONCLUSIONS:

This analysis demonstrates that several traditional and easily available factors are
associated with a greater risk of HF development, even among a low-risk CAD
population. ACE-inhibition reduces the risk of HF among this low risk population
irrespective of these factors. As the prevalence of CAD continues to increase, more
aggressive secondary prevention efforts and newer therapies can target those patients
among this low risk group who may derive the greatest benefit from more aggressive
interventions and the risk score may be used to stratify patients for future clinical trials.

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http://www.bsc.gwu.edu/peace/.

Conflict of Interest Disclosures
Dr Lewis has received research grants from Novartis, and has received research grants
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Knoll Pharmaceuticals and Abbott Laboratories. Dr Gersh has served on scientific advisory boards for AstraZeneca, Abbott Laboratories, Bristol-Myers Squibb, Boston Scientific, and Novartis. Dr. Hsia is currently employed by and owns stock in AstraZeneca. Dr. Rouleau served as a consultant for Novartis, received research funds from Scios, and has received honoraria and has served as a consultant for Bristol Myers Squibb. Dr Pfeffer has received research grant support from Amgen, Baxter, Bristol-Myers Squibb, Celladon, Novartis, and Sanofi-Aventis; has served on scientific advisory boards for Amgen, AstraZeneca, Biogen, BMS, CV Therapeutics, Genentech, Medtronic, Merck, Novartis, Sanofi; and is the coinventor on patent held by Brigham and Women’s Hospital for the use of inhibitors of the renin-angiotensin system in survivors of MI. Dr Braunwald has received research grant support from AstraZeneca, Johnson & Johnson, Beckman Coulter, Bristol Myers Squibb, CV Therapeutics, Eli Lilly, Genentech, Integrated Therapeutics Group, Merck, Novartis, Pfizer, Roche Diagnostics, Sanofi Aventis, Schering Plough Research Institute, Daiichi Sankyo, and Eisai Medical Research; honoraria from Eli Lilly, Merck, Schering-Plough, and Sanofi Aventis; he has served as a consultant or is on the advisory board for Bayer, CV Therapeutics, Daiichi Sankyo, Merck, Momenta, Pfizer, Schering-Plough, Sanofi Aventis, Cytokinetics, Genzyme, and GlaxoSmithKline. Dr. Maggioni has received research support from AstraZeneca, Novartis, Takeda, and Pfizer and has been a consultant for Novartis. Drs. Solomon, Zabalgoitia, Clemenza, Cuddy, and Huynh have nothing to disclose.
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Dr. Judith Hsia is now an employee of AstraZeneca and is no longer at George Washington University.
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congestion and/or left ventricular dysfunction: a VALIANT study. *Eur Heart J* 2008; 29:748-756.


**LEGEND:**

**Figure 1.** Distribution of risk score. The score ranges from 0 to 21 with higher score representing a higher risk for heart failure development. Red represents patients who did not develop heart failure and green represents the patients who had an event.

**Figure 2a.** Discriminatory Characteristics of Risk Score on fatal and non-fatal heart failure when patients are grouped into 3 categories: low, medium, and high risk.

**Figure 2b.** Kaplan-Meier curve of heart failure events in patients stratified into the 3 risk categories: low risk (black line), intermediate risk (blue line), and high risk (green line). This illustrates the early separation of risk in the patients.
Table 1. Baseline characteristics of PEACE patients

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Mean ± standard deviation</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.9± 8.2</td>
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</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.4± 4.7</td>
<td></td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/m²)</td>
<td>77.6±19.4</td>
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<tr>
<td>History of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4553 (55.0)</td>
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<tr>
<td>Coronary artery bypass graft surgery</td>
<td>3234 (39.0)</td>
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<tr>
<td>Diabetes</td>
<td>1386 (16.7)</td>
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<tr>
<td>Hypertension</td>
<td>3765 (45.4)</td>
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<tr>
<td>Angina (Canadian Classification System)</td>
<td></td>
<td></td>
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<tr>
<td>No symptoms of angina</td>
<td>5985 (72.2)</td>
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<tr>
<td>Class I</td>
<td>1494 (18.0)</td>
<td></td>
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<tr>
<td>Class II</td>
<td>708 (8.5)</td>
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<tr>
<td>Class III</td>
<td>73 (0.9)</td>
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<tr>
<td>Class IV</td>
<td>27 (0.3)</td>
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<tr>
<td>Stroke or transient ischemic attack</td>
<td>554 ( 6.7)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1177 (14.2)</td>
<td></td>
</tr>
<tr>
<td>LVEF 41-50%</td>
<td>1236 (14.9)</td>
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</tr>
<tr>
<td>Non-randomized medicines</td>
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<tr>
<td>Calcium Channel Blocker</td>
<td>2938 (35.5)</td>
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<tr>
<td>Lipid lowering med use</td>
<td>5802 (70.0)</td>
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<tr>
<td>Any diuretic</td>
<td>1075 (13.0)</td>
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<tr>
<td>Digitalis use</td>
<td>291 ( 3.5)</td>
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</tr>
<tr>
<td>Anti-arrhythmic med use</td>
<td>176 ( 2.1)</td>
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Table 2. Multivariable Cox regression model showing the relationship between clinical characteristics, randomized and non-randomized medicines and heart failure

<table>
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<tr>
<th>Baseline Characteristic</th>
<th>HR</th>
<th>(95% Confidence Interval)</th>
<th>p-val</th>
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<tr>
<td>Age (per 1 year increase)</td>
<td>1.06</td>
<td>(1.05-1.08)</td>
<td>&lt;0.001</td>
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<td>Body Mass Index (per 1 kg/m² increase)</td>
<td>1.03</td>
<td>(1.01-1.06)</td>
<td>0.02</td>
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<tr>
<td>History of:</td>
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<td></td>
<td></td>
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<tr>
<td>Myocardial Infarction</td>
<td>1.43</td>
<td>(1.11-1.84)</td>
<td>0.006</td>
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<td>Coronary artery bypass graft surgery</td>
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<td>(1.23-2.03)</td>
<td>&lt;0.001</td>
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<td>Diabetes</td>
<td>2.16</td>
<td>(1.67-2.79)</td>
<td>&lt;0.001</td>
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<td>Hypertension</td>
<td>1.63</td>
<td>(1.25-2.12)</td>
<td>&lt;0.001</td>
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<td>Angina (Canadian Classification System)</td>
<td>1.42</td>
<td>(1.10-1.83)</td>
<td>0.007</td>
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<td>Stroke or transient ischemic attack</td>
<td>1.74</td>
<td>(1.24-2.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.06</td>
<td>(1.47-2.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerular filtration rate (per 1 ml/min/m²)</td>
<td>0.99</td>
<td>(0.98-1.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF 41-50% (vs ≥ 50%)</td>
<td>1.41</td>
<td>(1.05-1.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-randomized medicines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>1.39</td>
<td>(1.09-1.78)</td>
<td>0.009</td>
</tr>
<tr>
<td>Lipid lowering med use</td>
<td>0.62</td>
<td>(0.48-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any diuretic</td>
<td>1.78</td>
<td>(1.36-2.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digitalis use</td>
<td>2.88</td>
<td>(2.03-4.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-arrhythmic med use</td>
<td>2.36</td>
<td>(1.47-3.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Randomization to trandolapril</td>
<td>0.73</td>
<td>(0.57-0.93)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All potential variables with significance <0.05 were eligible for the final model. All variables were tested in separate Cox regression models with treatment. A backwards selection procedure was used to eliminate variables at the 0.05 level of significance. The same variables remained when approached with a forward selection model. The proportional hazards assumption was tested and confirmed for all final covariates.
Table 3. Multivariable Cox regression model and integer-based risk score assignment to quantify the predictors of heart failure

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>HR</th>
<th>(95% Confidence Interval)</th>
<th>p-value</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (vs Trandolapril)</td>
<td>0.32050</td>
<td>0.12382</td>
<td>1.38</td>
<td>(1.08-1.76)</td>
<td>0.010</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years (vs &lt; 65 years)</td>
<td>0.63557</td>
<td>0.15059</td>
<td>1.89</td>
<td>(1.41-2.54)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥75 years (vs &lt; 65 years)</td>
<td>1.14653</td>
<td>0.18174</td>
<td>3.15</td>
<td>(2.20-4.49)</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>Body Mass Index ≥35 kg/m² (vs. &lt;35)</td>
<td>0.73804</td>
<td>0.17998</td>
<td>2.09</td>
<td>(1.47-2.98)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>History of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.32584</td>
<td>0.12921</td>
<td>1.39</td>
<td>(1.08-1.78)</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>0.45676</td>
<td>0.12675</td>
<td>1.58</td>
<td>(1.23-2.02)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.74401</td>
<td>0.13207</td>
<td>2.10</td>
<td>(1.62-2.73)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.48222</td>
<td>0.13422</td>
<td>1.62</td>
<td>(1.25-2.11)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Angina*</td>
<td>0.33413</td>
<td>0.12866</td>
<td>1.40</td>
<td>(1.09-1.80)</td>
<td>0.009</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>0.60139</td>
<td>0.17234</td>
<td>1.82</td>
<td>(1.30-2.56)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.62075</td>
<td>0.16915</td>
<td>1.86</td>
<td>(1.34-2.59)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>eGFR* &lt; 60 ml/min/m² (vs. ≥60)</td>
<td>0.51334</td>
<td>0.13603</td>
<td>1.67</td>
<td>(1.28-2.18)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>LVEF* 41-50% (vs ≥ 50%)</td>
<td>0.33985</td>
<td>0.15298</td>
<td>1.40</td>
<td>(1.04-1.90)</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Non-randomized medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>0.34209</td>
<td>0.12627</td>
<td>1.41</td>
<td>(1.10-1.80)</td>
<td>0.007</td>
<td>1</td>
</tr>
<tr>
<td>* Not on lipid lowering medicine</td>
<td>0.52024</td>
<td>0.12487</td>
<td>1.68</td>
<td>(1.32-2.15)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Any diuretic</td>
<td>0.58426</td>
<td>0.14006</td>
<td>1.79</td>
<td>(1.36-2.36)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Digitalis use</td>
<td>1.07953</td>
<td>0.18122</td>
<td>2.94</td>
<td>(2.06-4.20)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>Anti-arrhythmic med use</td>
<td>0.93039</td>
<td>0.24283</td>
<td>2.54</td>
<td>(1.58-4.08)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
</tbody>
</table>

* LVEF-Left ventricular ejection fraction, eGFR-estimated glomerular filtration rate using MDRD equation, HR – Hazard ratio. Angina was measured using the Canadian Classification System. Risk score calculated by using dividing each coefficient by the smallest coefficient and rounding to the nearest integer.
Table 4. Validation of CARE risk model using the PEACE Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>N with outcome (%)</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using CARE risk model*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>2 (0.3)</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk (vs Low Risk)</td>
<td>258 (3.4)</td>
<td>&lt;0.001</td>
<td>10.0</td>
<td>2.5 40.3</td>
</tr>
<tr>
<td>High risk (vs Low Risk)</td>
<td>8 (10.8)</td>
<td>&lt;0.001</td>
<td>35.8</td>
<td>7.6 168.6</td>
</tr>
<tr>
<td>Using PEACE risk model†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>83 (1.4)</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk (vs Low Risk)</td>
<td>145 (7.2)</td>
<td>&lt;.0001</td>
<td>5.6</td>
<td>4.3 7.3</td>
</tr>
<tr>
<td>High risk (vs Low Risk)</td>
<td>40 (27.6)</td>
<td>&lt;.0001</td>
<td>24.9</td>
<td>17.1 36.3</td>
</tr>
</tbody>
</table>

* Low risk was defined as a patient younger than 55 with LVEF>50% and did not have diabetes or hypertension. High risk was defined as patients older than 60 years with LVEF<50% and both diabetes and hypertension. All other patients were intermediate risk.
† Low risk was defined as a PEACE HF Risk score <9, intermediate patients had a risk score of 9-14 and high risk patients had a risk score>14.
Figure 1

**Patients who developed heart failure are noted in green**
Figure 2a

C-statistic – 0.80

Risk Score Group

- <9
  - N=6048
- 9-14
  - N=1399
- >14
  - N=145
Figure 2b

n=268 (3.3%)
Predictors of Heart Failure in Patients with Stable Coronary Artery Disease: A PEACE Study
Eldrin F. Lewis, Scott D. Solomon, Kathleen A. Jablonski, Madeline Rice, Francesco Clemenza, Judith Hsia, Aldo P. Maggioni, Miguel Zabalgoitia, Thao Huynh, Thomas E. Cuddy, Bernard J. Gersh, Jean-Lucien Rouleau, Eugene Braunwald and Marc A. Pfeffer

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