Coronary Angiography in worsening heart failure: Determinants, Findings, and Prognostic Implications

João Pedro Ferreira, MD, PhD[1,2]; Patrick Rossignol, MD, PhD[1]; Biniyam Demissei, MD, PhD[3]; Abhinav Sharma, MD[4,5]; Nicolas Girerd, MD, PhD[1]; Stefan D. Anker, MD, PhD[6]; John G. Cleland, MD, PhD[7]; Kenneth Dickstein, MD, PhD[8,9]; Gerasimos Filippatos, MD, PhD[10]; Hans L. Hillege, MD, PhD[3]; Chim C. Lang, MD[11]; Marco Metra, MD[12]; Leong L. Ng, MD[13]; Piotr Ponikowski, MD, PhD[14]; Nilesh J. Samani, MD, PhD[15]; Dirk J. van Veldhuisen, MD; PhD[3]; Aeilko H. Zwinderman, PhD[16]; Adriaan Voors, MD, PhD[3]; Faiez Zannad, MD, PhD[1]

Affiliations :

[1] INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Université de Lorraine, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France.

[2] Cardiovascular Research and Development Unit, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, Portugal.

[3] Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

[4] Duke Clinical Research Institute, Duke University, Durham, North Carolina.

[5] Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada.

[6] Department of Innovative Clinical Trials, University Medical Centre Göttingen (UMG), Robert-Koch-Straße, D-37075, Göttingen, Germany.

[7] Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit, Glasgow, UK.

[8] University of Bergen, Bergen, Norway.

[9] Stavanger University Hospital, Stavanger, Norway.

[10] National and Kopodistrian University of Athens, School of Medicine, Heart Failure Unit, Department of Cardiology, Athens University Hospital Attikon, Rimini 1, Athens 12462, Greece.

[11] Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.

[12] University of Brescia, Italy

[13] Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; Cardiovascular theme, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, LE3 9QP, United Kingdom

[14] Department of Cardiology, Centre for Heart Diseases, 4th Military Hospital, Wroclaw, Poland; Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland.

[15] Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, Glenfield Hospital, Groby Rd, Leicester, LE3 9QP, United Kingdom

[16] Academic Medical Center, Clinical Epidemiology Biostatistics and Bioinformatics, Amsterdam, Netherlands

Corresponding author:
Professor Faiez Zannad
Centre d'Investigation Clinique Inserm, CHU, Université de Lorraine.
Institut Lorrain du Coeur et des Vaisseaux
4, rue du Morvan, 54500 VANDOEUVRE-LES-NANCY
Mail to: f.zannad@chru-nancy.fr

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Abstract

Objectives: Coronary angiography is regularly performed in patients with worsening signs and/or symptoms of heart failure (HF). However, little is known on the determinants, findings, and associated clinical outcomes of coronary angiography performed in patients with worsening heart failure.

Methods: The BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) program enrolled 2516 patients with worsening symptoms and/or signs of HF, either hospitalized or in the out-patient setting. All patients were included in the present analysis.

Results: Of the 2516 patients included, 315 (12.5%) underwent coronary angiography within the 30 days after the onset of worsening symptoms and/or signs of heart failure. Subjects who underwent angiography were more often observed as inpatients, had more often an overt acute coronary syndrome, had higher troponin I levels, were younger, and had better renal function (all $p \leq 0.01$). Patients who underwent coronary angiography had a lower risk of the primary outcome of death and/or HF hospitalization (adjusted HR=0.71, 95%CI=0.57-0.89; p=0.003) and death (adjusted HR=0.59, 95%CI=0.43-0.80, p=0.001). Among the patients who underwent coronary angiography, those with a coronary stenosis (39%) had a worse prognosis than those without stenosis (adjusted HR for the primary outcome=1.71, 95%CI=1.10-2.64, p =0.016).

Conclusions: Coronary angiography was performed in <13% of patients with symptoms and/or signs of worsening heart failure. These patients were remarkably different from those that did not undergo coronary angiography and had a lower risk of subsequent events. The presence of coronary stenosis on coronary angiography was associated with a worse prognosis.

Key-words: Decompensated Heart Failure; Coronary Angiography; Acute Coronary Syndrome; Outcomes

Key Messages

What is already known about this subject?

Coronary angiography is regularly performed in patients with worsening signs and/or symptoms of heart failure (HF), however previous reports show that less than 10% of these patients undergo coronary angiography.

What does this study add?

In our study 12.5% of patients underwent coronary angiography within the 30 days after the onset of worsening symptoms and/or signs of heart failure. Subjects who underwent angiography were more likely to be in-patients, more likely to have an overt acute coronary syndrome, had higher troponin I levels, were younger, and had better renal function. Patients who underwent coronary angiography had a lower risk of death and/or HF hospitalization. Those with a coronary stenosis had a worse prognosis than those without stenosis.

How might this impact on clinical practice?

These observations help inform the debate regarding the utility of coronary angiography for the investigation of worsening HF and might stimulate further research specifically to address this question.

Introduction

Coronary angiography is the "reference standard" technique for the assessment of the presence and the extent/severity of coronary artery disease, and to define the most appropriate therapy[1]. Current heart failure guidelines state that coronary angiography is recommended for the determination of heart failure (HF) etiology, especially in patients who suffer from angina pectoris, those with a history of ventricular arrhythmia or aborted cardiac arrest, and in patients with intermediate to high pre-test probability of coronary artery disease, which includes a "positive" non-invasive stress test[2, 3].

In patients with worsening symptoms and/or signs of heart failure, coronary angiography may be infrequently performed, regardless of hospitalization or ambulatory status[4, 5]. However, little is known about the type of patients that undergo coronary angiography, whether significant coronary artery disease is found, and whether it has prognostic implications.

The aims of the present analysis are to assess: 1) related factors and characteristics of patients with worsening heart failure who undergo coronary angiography; 2) the findings of coronary angiography regarding the presence of coronary stenosis; 3) the prognostic value of coronary angiography and coronary stenosis.

Methods

Patient population

BIOSTAT-CHF is a European project that enrolled 2516 HF patients from 69 centres in 11 European countries to determine profiles of patients with HF that do not respond to recommended therapies, despite anticipated up-titration. The design and first results of the study and patients have been described elsewhere[6]. In brief, patients were aged ≥18 years with symptoms of new-onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a BNP and/or NT-proBNP plasma levels >400 pg/ml or >2000pg/ml, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence based therapies (ACEi/ARBs and β-blockers) or were receiving <50% of the target doses of at least one of these drugs at the time of inclusion. Initiation or up-titration of ACEi/ARB and/or β-blocker therapy should have been anticipated by the treating physician. The first three months of treatment were considered to be the optimization phase after which a stabilization phase of 6 months was defined. During the optimization phase, initiation or up-titration of ACEi/ARB and/or β-blocker was performed according to the routine clinical practice of the treating physicians, who were encouraged to follow the ESC guidelines at the time of treatment[7, 8]. Patients with acute coronary syndrome or stroke could be included when the primary diagnosis for admission to hospital or outpatient clinic visit was heart failure[6]. The

recruitment period was 24 months, starting from December 2010. The last patient was included on December 15, 2012. Median follow-up was 21 months.

In this post-hoc analysis, we included all coronary angiographies performed within 30 days after the baseline visit, because coronary angiography could have been done as "programmed intervention" and, therefore, a time gap between the intervention and the baseline visit was expected. Coronary stenosis was defined as >50% luminal stenosis (**Supplemental Table 1**). Participating European countries were also divided in North and South for comparison, as follows: Northern Europe - Netherlands, Norway, Sweden, Germany, and UK; Southern Europe – France, Slovenia, Italy, Greece, Serbia, and Poland. A subanalysis by country was also performed.

Ethics Board approval was obtained and all participants signed written informed consent before entering the study.

Statistical analysis

In descriptive analyses, continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequencies and proportions (%). Population description and comparison of patients with coronary angiography vs. no coronary angiography performed (and coronary artery coronary stenosis vs. no stenosis) was performed using independent samples t-test for normally distributed continuous variables, Mann-Whitney test for continuous variables with a skewed distribution, and chi-square test for categorical variables. Normality assumptions were verified by visual inspection. No multiple imputation was performed.

To determine the factors associated with having coronary angiography performed (or not) and to having a coronary artery coronary stenosis (or not), we developed logistic regression models. These models used clinical and laboratory variables with a p-value <0.1 as entry criteria (from Table 1). Logistic regression assumptions were checked and multicollinearity excluded. Linear relationship between continuous independent variables and the logit transformation of the dependent variable was verified by plotting the means vs. the β estimates in quintiles (**Supplemental Figure 1**). If a linear relationship was not present, then the variable was dichotomized at the inflexion point. Then a stepwise backward selection process was applied and the final model presented.

Cox proportional hazard regression models were used to model long-term event rate both in univariable and multivariable analysis. Proportional hazard assumption was verified graphically using "log-log" plots. In the multivariable models, the covariates for adjustment were chosen from demographic (age and gender), clinical (previous HF hospitalization, use of beta-blockers and systolic blood pressure), and laboratory (NT-proBNP, blood urea nitrogen, hemoglobin, HDL-cholesterol, creatinine, sodium). All parameters were previously found to be independently associated with the outcomes in the BIOSTAT cohort and were used to build the

risk models derived from this cohort (URL: https://biostat-chf.shinyapps.io/calc/)[9].

The primary outcome was a composite of hospitalization for heart failure and all-cause death. The outcomes of HF hospitalization and death were also analyzed separately. For the outcome of HF hospitalization, a competing risk model (using death as competing risk) was used according to the method of Fine and Gray[10].

The adjudication of events (heart failure hospitalizations) were done by the treating physician.

All the analysis was performed using R® software (R Core Team, 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/). The competing risk models and proportional hazard assumption were performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

Characteristic of the study population

From the 2516 patients included in BIOSTAT-CHF, 12.5% (n=315) underwent coronary angiography.

Characteristics of patients with or without coronary angiography are presented in **Table 1**. Patients who underwent coronary angiography more often presented as inpatients, with an acute coronary syndrome (ACS), were younger, had higher heart rate, hemoglobin, estimated glomerular filtration rate (eGFR), alanine/aspartate aminotransferase (ALAT/ASAT) and troponin I levels. The troponin I threshold for coronary angiography performance was high: only patients in the highest troponin quintile (>36 pg/mL) were more likely to have a coronary angiogram performed. **Supplemental Figure 1**. Nonetheless, troponin I levels were linear and independently associated with worse prognosis in this population but added little prognostic information to the BIOSTAT risk models. **Supplemental Table 2** and **Supplemental Table 3**. Patients who underwent coronary angiography were also more often smokers and more frequently treated with ACEi/ARBs, had lower LVEF, urea, and potassium, were less often hospitalized in the year before baseline visit, had ischemic cardiomyopathy less often documented, had lower proportion of atrial fibrillation, previous stroke, device therapy, and previous coronary intervention ($p < 0.01$ for all). **Table 1**. Country subanalysis shows that the Netherlands and France had the higher proportion of patients undergoing coronary angiography. Of notice, the Netherlands contributed with more than 25% of all angiographies performed. **Supplemental Table 4**.

Independent predictors for performing coronary angiography are presented in **Table 2**. The strongest independent predictors of undergoing coronary angiography were an in-hospital visit (Odds Ratio, OR =11.6, 95% Confidence Interval, CI =4.6-28.8, $p < 0.0001$), overt acute

coronary syndrome (OR =3.1, 95%CI =1.9-5.0, p <0.0001), troponin I levels above 36 pg/mL (OR =1.6, 95%CI =1.1-2.3, p =0.011), a younger age (OR per each decade less = 1.4, 95%CI =1.2-1.6, p <0.0001), and better renal function (OR per 10 ml/min/1.73m^2 increase in eGFR =1.1, 95%CI =1.0-1.2, p =0.049). Patients with a cardiac device, those with previous HF hospitalization and those with previous coronary intervention were less likely to have coronary angiography performed. **Table 2**.

Coronary angiographic findings

A coronary stenosis (>50% luminal stenosis) was found in 38.7% (n=122) of the 315 patients who underwent coronary angiography. Characteristics of patients with and without a coronary stenosis are presented in the **Supplemental Table 1**. Patients with a coronary stenosis were older, more often male, smokers, and hypertensive, had higher proportion of pulmonary rales, HF of ischemic etiology more often documented, higher troponin I levels, and higher proportion of previous coronary intervention (p <0.01 for all).

Among the patients who underwent coronary angiography, those with HF of ischemic etiology (OR =33.4, 95%CI =16.4-68.0, p <0.0001) and with higher troponin I levels (OR per 1 *log* increase =1.3, 95%CI =1.0-1.7, p =0.026) were more likely to have a coronary stenosis. **Table 3**.

Prognostic implications of coronary angiography and presence of coronary stenosis

Patients who underwent coronary angiography had a better clinical outcome compared to those who did not undergo coronary angiography (adjusted Hazard Ratio, HR for the primary composite outcome of death and/or heart failure hospitalization =0.71, 95%CI =0.57-0.89, p =0.003 and HR =0.59, 95%CI =0.43-0.80, p =0.001 for the outcome of death). **Table 4**. Among the patients who underwent coronary angiography, those with a coronary stenosis had worse prognosis (adjusted HR for the primary composite outcome of death and/or heart failure hospitalization =1.71, 95%CI =1.10-2.64, p =0.016 and HR =2.09, 95%CI =1.10-3.96, p =0.024 for the outcome of death). **Table 4**.

A significant interaction between HF etiology (ischemic vs. other) and coronary angiography (yes vs. no) was found. Patients who underwent coronary angiography with non-ischemic HF had a greater reduction of the primary composite outcome (HR =0.55, 95%CI =0.40-0.76, p <0.001) than patients who underwent coronary angiography with ischemic heart failure (HR =1.00, 95%CI =0.74-1.37, p =0.98; p for interaction =0.007. **Figure 1** and **Figure 2**.

Discussion

The present study shows that ≈13% of patients with worsening HF underwent coronary angiography within 30 days of presentation for worsening symptoms and/or signs of HF. In

general, these patients had a better clinical profile and outcome than those who did not undergo coronary angiography. However, patients with a coronary stenosis on coronary angiography had a worse prognosis compared to those without a coronary stenosis.

In our study, the coronary angiography rate was higher than in previous reports where less than 10% of the patients with worsening HF underwent coronary angiography[5, 11]. Nonetheless, in patients with decompensated HF, coronary artery disease may be the primary HF etiology in more than 50% of the patients[12]. Hence, addressing coronary artery disease as a therapeutic target in worsening HF (even without overt ACS) may be associated with improved clinical outcome, and although a causal relation cannot be inferred, recurrent ischemic events are a major cause of subsequent HF decompensation and death[13].

In the present report, only 23% (n=54) of the subjects presenting with an overt ACS underwent coronary angiography within the worsening HF episode (±30 days). These data suggest that the large majority of the coronary angiographies were performed in patients with other primary causes for HF decompensation. Hence, in the present study physicians possibly decided to perform coronary angiography based on the suspicion that an underlying coronary artery disease was a major contributor for worsening HF signs and/or symptoms (also supported by particularly high troponin threshold for angiography performance). Troponin elevation is frequently observed in patients with decompensated HF, possibly reflecting myocardial injury and/or impaired myocardial perfusion, and has been associated with worse prognosis[14]. While doctors acknowledge troponin elevation as part of the decompensation episode, they may withhold coronary angiography unless very high troponin levels are found, because despite the myocardial injury, patients with decompensated HF may have a predominance of respiratory symptoms, high prevalence of diabetes, and use medications such as nitrates, beta-blockers, and ivabradine that may blunt "typical" angina *pectoris* symptoms[15, 16]. Hence, from a clinical standpoint it may be challenging to distinguish between a primary diagnosis of ACS with associated HF versus worsening HF with elevated troponin without "typical" symptoms of ischaemia. In selected cases, tests for myocardial viability and ischaemia and/or coronary angiography may help make therapeutic decisions.

A large country variability in the performance of coronary angiography was also found, notably more than 25% of the angiographies were performed in the Netherlands and more than 15% in France. These findings may reflect country variation in the accessibility to a catheterization laboratory.

Diagnostic procedures may influence treatment decisions (directly and/or indirectly) and consequently prognosis[17-19]. In this context, the performance of coronary angiography may provide information regarding the extent/severity of coronary artery disease and also provide an opportunity for direct intervention (e.g., coronary revascularization) that will likely have influence on the follow-up, treatment and prognosis of these patients[15, 20]. In the present study

performing coronary angiography was associated with improved outcomes, finding that is consistent with the OPTIMIZE-HF registry[11], however no causality can be established as this may reflect selection bias and better baseline patient profile. In a patient-population with coronary artery disease and HF with reduced ejection fraction performing coronary artery bypass grafting (CABG) led to improved outcomes compared to medical therapy alone[21]. Whether performing more coronary angiographies in patients with decompensated HF leads to outcome improvement needs to be prospectively evaluated in an adequately powered trial.

Older patients and those with worse renal function were less likely to have coronary angiography performed. It has been thoroughly documented that elderly patients and those with impaired renal function presenting with an ACS and/or acute HF undergo substantially less angiographic/revascularization procedures, despite deriving similar relative benefits of these interventions[11, 22, 23]. Remarkably, coronary angiography was not less likely to be performed in females, even though females in this study were older. Patients with cardiac devices, previous coronary interventions and HF hospitalization, and those observed as outpatients were less likely to undergo coronary angiography. These findings may be due to the assumption that the patients were already investigated for coronary disease at the timing of device implantation or that those presenting as outpatients may have less severe symptomatology and require less investigation. Nevertheless, these patients may be at higher risk for myocardial ischemia and stent restenosis[24].

We found an "interaction" between HF etiology (ischemic vs. other) and the prognostic value of coronary angiography. Performing a coronary angiography in patients with non-ischemic HF was associated with a better outcome than in patients with ischemic HF. This finding is possibly due to the differences found in critical stenosis rates, which were much higher in patients with ischemic HF (>80%) and were associated with worse prognosis. Patients who underwent coronary angiography and had coronary stenosis documented (≈39% in the present cohort) had worse prognosis compared to those without coronary stenosis. The presence of significant coronary lesions is associated with worse prognosis, as also documented in previous reports[25].

Clinical and Research Implications

The present results show that coronary angiography was performed in <13% of patients with worsening HF. These subjects were younger and with a more favorable overall clinical profile. Therefore, these data should be taken as merely descriptive and no causality should be inferred from these observations. From a research standpoint, a trial comparing "usual care" versus an arm with a low threshold for coronary angiography could provide more definitive answers on the diagnostic and prognostic abilities of this intervention.

Limitations

Several limitations should be noticed in this study. First, this is a post-hoc analysis of a prospective non-randomized observational study, therefore all limitations inherent to such analysis are applied herein, including the inability to infer causality. Additionally, it is likely that unmeasured variables may have accounted for the different outcomes observed. Second, the present study focused on changes in medication and determinants of medication up-titration (and not to address coronary angiography performance). Therefore, we unfortunately have no reliable and consistent information regarding the clinical consequences of the findings during coronary angiography. However, these data may reflect "real-world" practices as no guidance was provided with regard to coronary interventions. Third, it is also impossible to account for the effect of indication biases that may have determined who underwent angiography as well as treatment biases that may have influenced who received pharmacological therapies for coronary artery disease and HF. Fourth, results from stress testing and/or coronary intervention outcomes (e.g., stent placement, coronary artery bypass grafting referral) are not available in the dataset. Fifth, the participating hospitals in the BIOSTAT-CHF differed in structure (from tertiary university hospitals to small non-academic structures) and likely in the access to a catheterization laboratory, hence these findings cannot be generalized to all hospitals and HF patients. However, further adjustment for the type of centre did not change the strength of the associations. Sixth, we can only hypothesize on the reasons that led clinicians to perform a coronary angiogram since this information is also not available. Lastly, the data from the BIOSTAT-CHF come from European centres only and may not be representative of HF patients in other world regions.

Conclusions

Coronary angiography was performed in <13% of patients with symptoms and/or signs of worsening heart failure, particularly those presenting as inpatients, with an acute coronary syndrome, with better renal function and younger age. Performing a coronary angiogram was associated with improved outcomes but this observation possibly reflects a selection bias. These observations help inform the debate regarding the utility of coronary angiography for the investigation of worsening HF and might stimulate further research specifically to address this question.

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Bibliography

1. Levine, G. N.; Bates, E. R.; Blankenship, J. C.; Bailey, S. R.; Bittl, J. A.; Cercek, B.; Chambers, C. E.; Ellis, S. G.; Guyton, R. A.; Hollenberg, S. M.; Khot, U. N.; Lange, R. A.; Mauri, L.; Mehran, R.; Moussa, I. D.; Mukherjee, D.; Ting, H. H.; O'Gara, P. T.; Kushner, F. G.; Ascheim, D. D.; Brindis, R. G.; Casey, D. E., Jr.; Chung, M. K.; de Lemos, J. A.; Diercks, D. B.; Fang, J. C.; Franklin, B. A.; Granger, C. B.; Krumholz, H. M.; Linderbaum, J. A.; Morrow, D. A.; Newby, L. K.; Ornato, J. P.; Ou, N.; Radford, M. J.; Tamis-Holland, J. E.; Tommaso, C. L.; Tracy, C. M.; Woo, Y. J.; Zhao, D. X., 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* **2016,** *133* (11), 1135-47.
2. Ponikowski, P.; Voors, A. A.; Anker, S. D.; Bueno, H.; Cleland, J. G.; Coats, A. J.; Falk, V.; Gonzalez-Juanatey, J. R.; Harjola, V. P.; Jankowska, E. A.; Jessup, M.; Linde, C.; Nihoyannopoulos, P.; Parissis, J. T.; Pieske, B.; Riley, J. P.; Rosano, G. M.; Ruilope, L. M.; Ruschitzka, F.; Rutten, F. H.; van der Meer, P., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* **2016**.
3. Yancy, C. W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D. E., Jr.; Colvin, M. M.; Drazner, M. H.; Filippatos, G.; Fonarow, G. C.; Givertz, M. M.; Hollenberg, S. M.; Lindenfeld, J.; Masoudi, F. A.; McBride, P. E.; Peterson, P. N.; Stevenson, L. W.; Westlake, C., 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College

of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* **2016**.
4. Cleland, J. G.; Swedberg, K.; Follath, F.; Komajda, M.; Cohen-Solal, A.; Aguilar, J. C.; Dietz, R.; Gavazzi, A.; Hobbs, R.; Korewicki, J.; Madeira, H. C.; Moiseyev, V. S.; Preda, I.; van Gilst, W. H.; Widimsky, J.; Freemantle, N.; Eastaugh, J.; Mason, J., The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* **2003,** *24* (5), 442-63.
5. Kurtz, C. E.; Gerber, Y.; Weston, S. A.; Redfield, M. M.; Jacobsen, S. J.; Roger, V. L., Use of ejection fraction tests and coronary angiography in patients with heart failure. *Mayo Clin Proc* **2006,** *81* (7), 906-13.
6. Voors, A. A.; Anker, S. D.; Cleland, J. G.; Dickstein, K.; Filippatos, G.; van der Harst, P.; Hillege, H. L.; Lang, C. C.; Ter Maaten, J. M.; Ng, L.; Ponikowski, P.; Samani, N. J.; van Veldhuisen, D. J.; Zannad, F.; Zwinderman, A. H.; Metra, M., A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* **2016,** *18* (6), 716-26.
7. McMurray, J. J.; Adamopoulos, S.; Anker, S. D.; Auricchio, A.; Bohm, M.; Dickstein, K.; Falk, V.; Filippatos, G.; Fonseca, C.; Gomez-Sanchez, M. A.; Jaarsma, T.; Kober, L.; Lip, G. Y.; Maggioni, A. P.; Parkhomenko, A.; Pieske, B. M.; Popescu, B. A.; Ronnevik, P. K.; Rutten, F. H.; Schwitter, J.; Seferovic, P.; Stepinska, J.; Trindade, P. T.; Voors, A. A.; Zannad, F.; Zeiher, A.; Bax, J. J.; Baumgartner, H.; Ceconi, C.; Dean, V.; Deaton, C.; Fagard, R.; Funck-Brentano, C.; Hasdai, D.; Hoes, A.; Kirchhof, P.; Knuuti, J.; Kolh, P.; McDonagh, T.; Moulin, C.; Reiner, Z.; Sechtem, U.; Sirnes, P. A.; Tendera, M.; Torbicki, A.; Vahanian, A.; Windecker, S.; Bonet, L. A.; Avraamides, P.; Ben Lamin, H. A.; Brignole, M.; Coca, A.; Cowburn, P.; Dargie, H.; Elliott, P.; Flachskampf, F. A.; Guida, G. F.; Hardman, S.; Iung, B.; Merkely, B.; Mueller, C.; Nanas, J. N.; Nielsen, O. W.; Orn, S.; Parissis, J. T.; Ponikowski, P., ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. In *Eur J Heart Fail*, Netherlands, 2012; Vol. 14, pp 803-69.
8. Dickstein, K.; Cohen-Solal, A.; Filippatos, G.; McMurray, J. J.; Ponikowski, P.; Poole-Wilson, P. A.; Stromberg, A.; van Veldhuisen, D. J.; Atar, D.; Hoes, A. W.; Keren, A.; Mebazaa, A.; Nieminen, M.; Priori, S. G.; Swedberg, K., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* **2008,** *29* (19), 2388-442.
9. Voors, A. A.; Ouwerkerk, W.; Zannad, F.; van Veldhuisen, D. J.; Samani, N. J.; Ponikowski, P.; Ng, L. L.; Metra, M.; Ter Maaten, J. M.; Lang, C. C.; Hillege, H. L.; van der Harst, P.; Filippatos, G.; Dickstein, K.; Cleland, J. G.; Anker, S. D.; Zwinderman, A. H., Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *Eur J Heart Fail* **2017**.
10. JP, F.; RJ, G., A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* **1999,** *94 :496–509.* .
11. Flaherty, J. D.; Rossi, J. S.; Fonarow, G. C.; Nunez, E.; Stough, W. G.; Abraham, W. T.; Albert, N. M.; Greenberg, B. H.; O'Connor, C. M.; Yancy, C. W.; Young, J. B.; Davidson, C. J.; Gheorghiade, M., Influence of coronary angiography on the utilization of therapies in patients with acute heart failure syndromes: findings from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* **2009,** *157* (6), 1018-25.
12. Fox, K. F.; Cowie, M. R.; Wood, D. A.; Coats, A. J.; Gibbs, J. S.; Underwood, S. R.; Turner, R. M.; Poole-Wilson, P. A.; Davies, S. W.; Sutton, G. C., Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* **2001,** *22* (3), 228-36.

13. Orn, S.; Cleland, J. G.; Romo, M.; Kjekshus, J.; Dickstein, K., Recurrent infarction causes the most deaths following myocardial infarction with left ventricular dysfunction. *Am J Med* **2005,** *118* (7), 752-8.
14. Felker, G. M.; Hasselblad, V.; Tang, W. H.; Hernandez, A. F.; Armstrong, P. W.; Fonarow, G. C.; Voors, A. A.; Metra, M.; McMurray, J. J.; Butler, J.; Heizer, G. M.; Dickstein, K.; Massie, B. M.; Atar, D.; Troughton, R. W.; Anker, S. D.; Califf, R. M.; Starling, R. C.; O'Connor, C. M., Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. In *Eur J Heart Fail*, Netherlands, 2012; Vol. 14, pp 1257-64.
15. Flaherty, J. D.; Bax, J. J.; De Luca, L.; Rossi, J. S.; Davidson, C. J.; Filippatos, G.; Liu, P. P.; Konstam, M. A.; Greenberg, B.; Mehra, M. R.; Breithardt, G.; Pang, P. S.; Young, J. B.; Fonarow, G. C.; Bonow, R. O.; Gheorghiade, M., Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. *J Am Coll Cardiol* **2009,** *53* (3), 254-63.
16. Lettman, N. A.; Sites, F. D.; Shofer, F. S.; Hollander, J. E., Congestive heart failure patients with chest pain: incidence and predictors of acute coronary syndrome. *Acad Emerg Med* **2002,** *9* (9), 903-9.
17. Logeart, D.; Thabut, G.; Jourdain, P.; Chavelas, C.; Beyne, P.; Beauvais, F.; Bouvier, E.; Solal, A. C., Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol* **2004,** *43* (4), 635-41.
18. Jourdain, P.; Jondeau, G.; Funck, F.; Gueffet, P.; Le Helloco, A.; Donal, E.; Aupetit, J. F.; Aumont, M. C.; Galinier, M.; Eicher, J. C.; Cohen-Solal, A.; Juilliere, Y., Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* **2007,** *49* (16), 1733-9.
19. Taylor, A. J.; Bindeman, J.; Feuerstein, I.; Le, T.; Bauer, K.; Byrd, C.; Wu, H.; O'Malley, P. G., Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. *J Am Coll Cardiol* **2008,** *51* (14), 1337-41.
20. Tavazzi, L.; Maggioni, A. P.; Lucci, D.; Cacciatore, G.; Ansalone, G.; Oliva, F.; Porcu, M., Nationwide survey on acute heart failure in cardiology ward services in Italy. In *Eur Heart J*, England, 2006; Vol. 27, pp 1207-15.
21. Velazquez, E. J.; Lee, K. L.; Jones, R. H.; Al-Khalidi, H. R.; Hill, J. A.; Panza, J. A.; Michler, R. E.; Bonow, R. O.; Doenst, T.; Petrie, M. C.; Oh, J. K.; She, L.; Moore, V. L.; Desvigne-Nickens, P.; Sopko, G.; Rouleau, J. L., Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med* **2016,** *374* (16), 1511-20.
22. Devlin, G.; Gore, J. M.; Elliott, J.; Wijesinghe, N.; Eagle, K. A.; Avezum, A.; Huang, W.; Brieger, D., Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. *Eur Heart J* **2008,** *29* (10), 1275-82.
23. Bach, R. G.; Cannon, C. P.; Weintraub, W. S.; DiBattiste, P. M.; Demopoulos, L. A.; Anderson, H. V.; DeLucca, P. T.; Mahoney, E. M.; Murphy, S. A.; Braunwald, E., The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med* **2004,** *141* (3), 186-95.
24. Yilmaz, S.; Akboga, M. K.; Aras, D.; Topaloglu, S., Evaluation of the Predictive Value of CHA2DS2-VASc Score for In-Stent Restenosis. *Angiology* **2017**, 3319717700746.
25. Harris, P. J.; Behar, V. S.; Conley, M. J.; Harrell, F. E., Jr.; Lee, K. L.; Peter, R. H.; Kong, Y.; Rosati, R. A., The prognostic significance of 50% coronary stenosis in medically treated patients with coronary artery disease. *Circulation* **1980,** *62* (2), 240-8.

Table 1. Characteristics of the BIOSTAT population by Coronary Angiography Realization

	N	Global Population (n=2516)	No Coronary Angiography (n=2201)	Coronary Angiography Performed (n=315)	P-value
Age, years	2516	68.4 ± 12.0	69.1 ± 11.9	63.7 ± 11.6	<0.0001
Male gender, n (%)	2516	1846 (73.4 %)	1621 (73.6 %)	225 (71.4 %)	0.40
BMI, kg/m²	2478	27.9 ± 5.5	27.8 ± 5.4	28.2 ± 6.1	0.29
Heart rate, bpm	2497	82.3 ± 21.4	81.6 ± 21.3	87.4 ± 21.4	<0.0001
SBP, mmHg	2511	124.7 ± 21.9	124.6 ± 21.6	125.3 ± 23.8	0.63
DBP, mmHg	2511	74.9 ± 13.4	74.7 ± 13.0	76.1 ± 15.8	0.079
Pulmonary rales, n (%)	2445	1291 (52.8 %)	1101 (51.5 %)	190 (61.5 %)	0.001
Peripheral edema, n (%)	2099	1256 (59.8 %)	1106 (59.9 %)	150 (59.3 %)	0.85
Elevated JVP, n (%)	1753	554 (31.6 %)	479 (31.2 %)	75 (34.4 %)	0.34
NYHA class III/IV, n (%)	2446	1522 (62.2 %)	1324 (61.8 %)	198 (65.1 %)	0.26
Orthopnea, n (%)	2511	879 (35.0 %)	745 (33.9 %)	134 (42.5 %)	0.003
LVEF, %	2243	31.0 ± 10.6	31.4 ± 10.7	28.7 ± 9.7	<0.0001
Northern Europe, n (%)	2516	1200 (47.7%)	1035 (47.0 %)	165 (52.4 %)	0.075
Inpatient visit, n (%)	2516	1694 (67.3 %)	1389 (63.1 %)	305 (96.8 %)	<0.0001
Heart failure hospitalization within the last year, n (%)	2516	794 (31.6 %)	751 (34.1 %)	43 (13.7 %)	<0.0001
HF etiology: Ischemic, n (%)	2516	1103 (43.8 %)	988 (44.9 %)	115 (36.5 %)	0.005
HF etiology: Hypertensive, n (%)		254 (10.1 %)	225 (10.2 %)	29 (9.2 %)	
HF etiology: Valvular, n (%)		190 (7.6 %)	169 (7.7 %)	21 (6.7 %)	
HF etiology: Other/mixed, n (%)		969 (38.5 %)	819 (37.2 %)	150 (47.6 %)	
Precipitating factors, n (%)					
Acute coronary syndrome, n (%)	1703	155 (9.1 %)	101 (6.9 %)	54 (23.1 %)	<0.0001
Non-compliance, n (%)	1702	304 (17.9 %)	274 (18.7 %)	30 (12.9 %)	0.032
Atrial Fibrillation, n (%)	1703	770 (45.2 %)	691 (47.0 %)	79 (33.8 %)	0.0002
Infection, n (%)	1703	224 (13.2 %)	199 (13.5 %)	25 (10.7 %)	0.23
Uncontrolled hypertension, n (%)	1703	244 (14.3 %)	198 (13.5 %)	46 (19.7 %)	0.012
Renal dysfunction, n (%)	1703	439 (25.8 %)	403 (27.4 %)	36 (15.4 %)	<0.0001
Other/mixed, n (%)	1703	287 (16.9 %)	228 (15.5 %)	59 (25.2 %)	0.0002
Coronary stenosis, n (%)	312	122 (39.1%)	0	122 (39.1 %)	NA
Hemoglobin, g/dL	2293	13.2 ± 1.9	13.1 ± 1.9	13.5 ± 1.9	0.0009
eGFR, ml/min/1.73m²	2516	62.4 ± 23.2	61.5 ± 23.3	69.4 ± 21.7	<0.0001
Urea, mmol/L	2083	11.4 (7.6 - 18.2)	11.8 (7.8 - 18.6)	8.9 (6.5 - 15.0)	<0.0001
Sodium, mmol/L	2327	139.1 ± 4.0	139.1 ± 4.1	139.2 ± 3.7	0.92
Potassium, mmol/L	2324	4.3 ± 0.6	4.3 ± 0.6	4.2 ± 0.6	0.001
Albumin, g/L	2361	32.4 ± 8.8	32.4 ± 8.9	32.2 ± 7.9	0.75
Glucose, mmol/L	1894	7.2 ± 3.1	7.1 ± 3.1	7.3 ± 2.8	0.31
ALAT, UI/L	1804	25.0 (17.0 - 38.0)	24.0 (16.0 - 36.0)	32.0 (21.0 - 48.5)	<0.0001
ASAT, UI/L	1598	25.0 (19.0 - 35.0)	25.0 (19.0 - 34.0)	29.0 (21.0 - 41.0)	<0.0001
Gamma-GT, UI/L	1151	55.0 (28.0 - 108.2)	55.0 (28.0 - 108.0)	56.0 (28.0 - 114.0)	0.055
Total bilirubin, µmol/L	1381	14.0 (10.0 - 21.0)	15.0 (10.0 - 21.0)	11.6 (8.7 - 17.0)	0.43
HDL, mmol/L	1166	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.32
LDL, mmol/L	1103	2.6 ± 1.1	2.5 ± 1.0	2.8 ± 1.1	0.007

Total cholesterol, mmol/L	1407	4.3 ± 1.3	4.2 ± 1.3	4.5 ± 1.3	0.037
Triglycerides, mmol/L	1309	1.5 ± 1.0	1.5 ± 1.1	1.4 ± 1.0	0.74
*Log*NT-pro BNP, ng/L	2174	3.0 ± 1.4	3.1 ± 1.4	2.9 ± 1.2	0.10
Troponin I, pg/mL	2352	12.8 (6.8 - 27.9)	12.3 (6.7 - 25.6)	19.1 (8.1 - 36.0)	<0.0001
Hypertension, n (%)	2516	1569 (62.4 %)	1381 (62.7 %)	188 (59.7 %)	0.29
Atrial Fibrillation, n (%)	2516	1143 (45.4 %)	1044 (47.4 %)	99 (31.4 %)	<0.0001
Diabetes mellitus, n (%)	2516	819 (32.6 %)	717 (32.6 %)	102 (32.4 %)	0.94
Never smoked, n (%)	2513	940 (37.4 %)	838 (38.1 %)	102 (32.5 %)	<0.0001
Past smoker, n (%)		1220 (48.5 %)	1083 (49.2 %)	137 (43.6 %)	
Current smoker, n (%)		353 (14.0 %)	278 (12.6 %)	75 (23.9 %)	
COPD, n (%)	2516	436 (17.3 %)	385 (17.5 %)	51 (16.2 %)	0.57
Stroke, n (%)	2516	233 (9.3 %)	217 (9.9 %)	16 (5.1 %)	0.006
Peripheral Artery Disease, n (%)	2516	273 (10.9 %)	245 (11.1 %)	28 (8.9 %)	0.23
Device therapy, n (%)	2516	618 (24.6 %)	591 (26.9 %)	27 (8.6 %)	<0.0001
PCI or CABG, n (%)	2516	842 (33.5 %)	774 (35.2 %)	68 (21.6 %)	<0.0001
Loop diuretic, n (%)	2516	2504 (99.5 %)	2193 (99.6 %)	311 (98.7 %)	0.081
ACEi/ARB, n (%)	2516	1820 (72.3 %)	1574 (71.5 %)	246 (78.1 %)	0.015
Beta-blocker, n (%)	2516	2093 (83.2 %)	1829 (83.1 %)	264 (83.8 %)	0.75
MRA, n (%)	2516	1339 (53.2 %)	1178 (53.5 %)	161 (51.1 %)	0.42
Digoxin, n (%)	2516	491 (19.5 %)	441 (20.0 %)	50 (15.9 %)	0.081
Death or heart failure hospitalization, n (%)	2516	1017 (40.4 %)	932 (42.3 %)	85 (27.0 %)	<0.0001
Death, n (%)	2516	657 (26.1 %)	612 (27.8 %)	45 (14.3 %)	<0.0001
Heart failure hospitalization n (%)	2516	609 (24.2 %)	559 (25.4 %)	50 (15.9 %)	0.0002

Legend: MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association; H, hospitalization; HF, heart failure; eGFR, estimated glomerular filtration rate; ALAT/ASAT, alanine and aspartate aminotransferase levels; NT-pro BNP, n-terminal pro brain natriuretic peptide; COPD, chronic pulmonary obstructive disease; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.
European regions were divided in Southern countries (Greece, Italy, Serbia, Slovenia, and France) vs. Northern countries (Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom).

Table 2. Logistic regression for the odds of performing a coronary angiography

Variable	Odds Ratio (95%CI) for Coronary Angiography Realization	P-value
Inpatient visit (yes)	11.554 (4.636-28.794)	<0.0001
Acute coronary syndrome (yes)	3.117 (1.939-5.009)	<0.0001
Troponin I (>36 pg/mL)	1.603 (1.115-2.305)	0.011
Age (per each decade less)	1.389 (1.202-1.605)	<0.0001
eGFR (per 10 ml/min/1.73m^2 increase)	1.085 (1.000-1.177)	0.049
Device Therapy (yes)	0.430 (0.254-0.727)	0.002
Heart failure hospitalization within the last year (yes)	0.577 (0.371-0.897)	0.014
Previous PCI or CABG (yes)	0.614 (0.413-0.912)	0.016

Legend: CI, confidence interval; eGFR, estimated glomerular filtration rate; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting.

Table 3. Logistic regression for the odds of having a coronary artery stenosis

Variable	Odds Ratio (95%CI) for Coronary Critical Stenosis	P-value
Ischemic Heart Failure (yes)	33.426 (16.439-67.967)	<0.0001
Troponin I (per 1 Log increase)	1.309 (1.032-1.661)	0.026

Legend: CI, confidence interval.

Table 4. Prognostic assessment of coronary angiography and presence of critical stenosis

Outcome	**Coronary angiography: unadjusted HR (95%CI)**	**P-value**	**Coronary angiography: adjusted* HR (95%CI)**	**P-value**
Death or HHF	0.568 (0.455-0.709)	<0.0001	0.714 (0.571-0.893) **	0.003
HHF	0.587 (0.437-0.787)	<0.0001	0.730 (0.541-0.984)	0.039
Death	0.460 (0.340-0.623)	<0.0001	0.586 (0.433-0.795) **	0.001
Outcome	**Coronary stenosis: unadjusted HR (95%CI)**	**P-value**	**Coronary stenosis: adjusted* HR (95%CI)**	**P-value**
Death or HHF	1.940 (1.261-2.985)	0.003	1.705 (1.103-2.635)	0.016
HHF	1.463 (0.836-2.560)	0.182	1.358 (0.771-2.390)	0.289
Death	2.716 (1.473-5.009)	0.001	2.089 (1.103-3.957)	0.024

Legend: HR, hazard ratio; 95%CI, 95% confidence interval; HHF, hospitalization for heart failure.

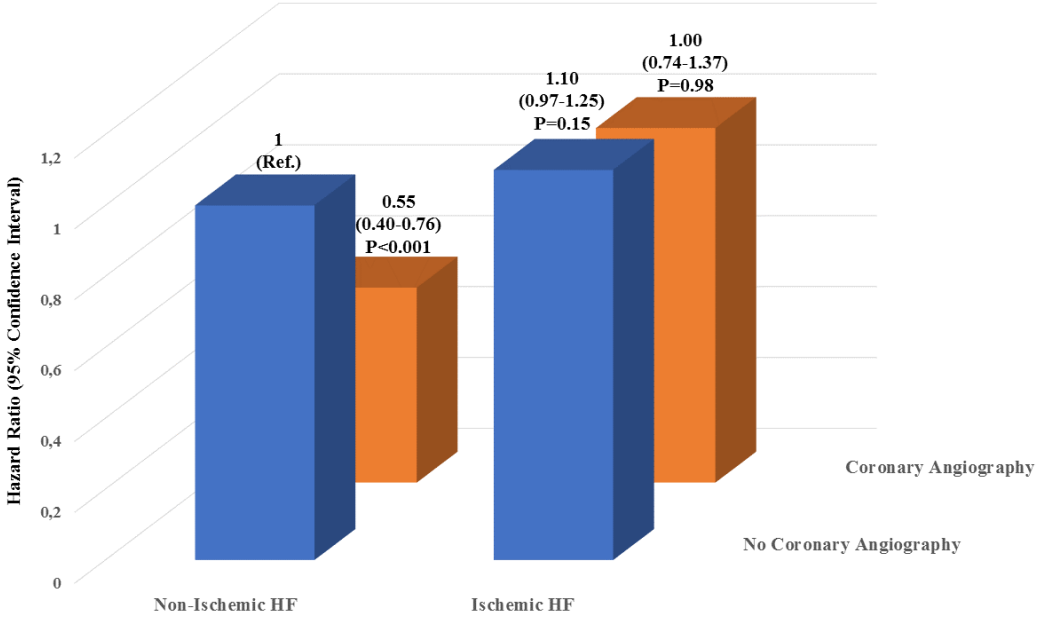
*model adjusted on age, gender, NT-pro BNP, hemoglobin, urea, HDL-cholesterol, serum sodium, serum creatinine, systolic blood pressure, use of beta-blockers, presence of peripheral edema, and hospitalization for heart failure in the year before inclusion – the BIOSTAT risk calculator (https://biostat-chf.shinyapps.io/calc/).

P for interaction HF etiology*Coronary Angiography =0.007 for the primary outcome of death or HHF; P =0.004 for death; and non-significant for HHF, P =0.326.

**HR (95%CI) results for Coronary Angiography adjusted on the above models plus Heart Failure Etiology (ischemic vs. other) plus the interaction between Heart Failure Etiology and Coronary Angiography: Death or HHF =0.553 (0.402-0.761), p <0.0001; Death =0.378 (0.235-0.609), p <0.0001.

Further adjustment on the type of centre: 1) university hospital, 2) large non-academic centre, and 3) small centre, provided overlapping results to those presented in the table.

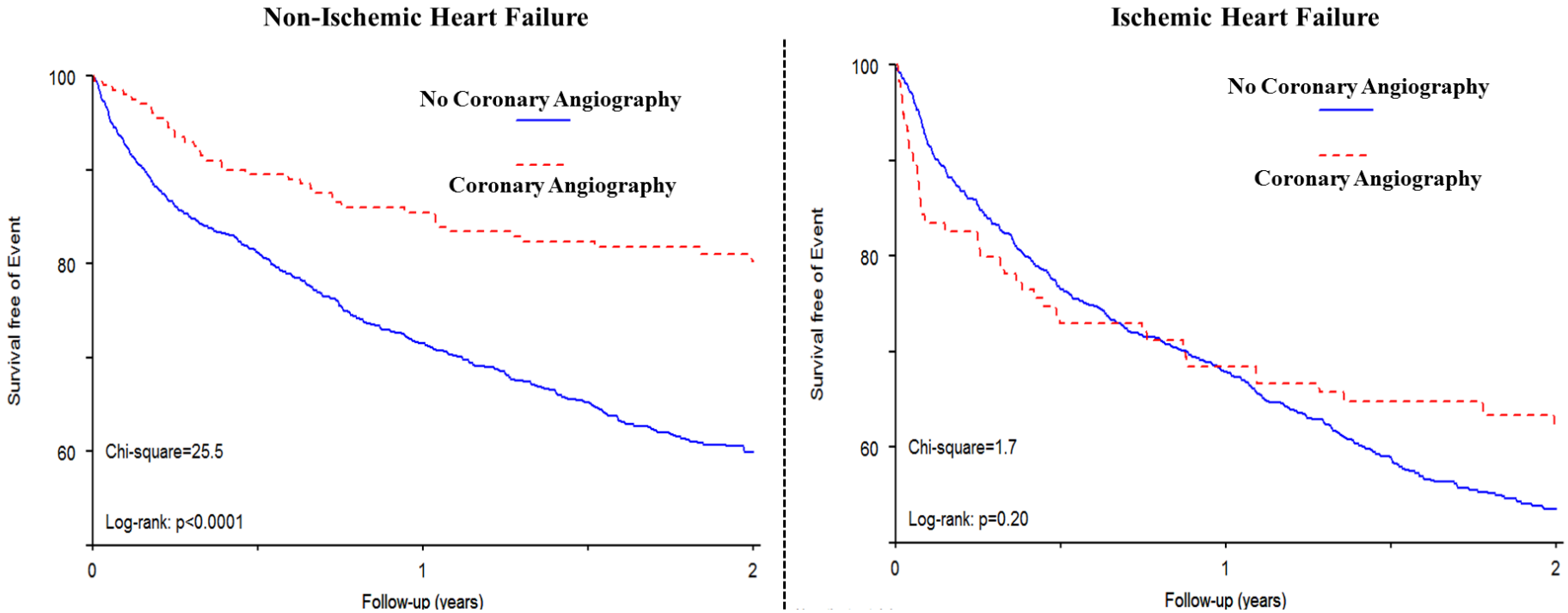
Figure 1. Interplay between Heart Failure Etiology and Prognostic Value of Coronary Angiography for the Primary Outcome of Heart Failure Hospitalization or Death*



*model adjusted on age, gender, NT-pro BNP, hemoglobin, urea, HDL-cholesterol, serum sodium, serum creatinine, systolic blood pressure, use of beta-blockers, presence of peripheral edema, and hospitalization for heart failure in the year before inclusion – the BIOSTAT risk calculator (https://biostat-chf.shinyapps.io/calc/).

HF, heart failure. P for interaction between HF etiology and Coronary Angiography =0.007.

Figure 2. Kaplan-Meier survival curves for Coronary Angiography performance according to Heart Failure etiology status



Legend: CA, coronary angiography; HF, heart failure.