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## **Coronary Angiography in patients with worsening heart failure: Determinants, Findings, and Prognostic Implications**

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

### **Affiliations :**

<sup>1</sup> INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Université de Lorraine, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France.

<sup>2</sup> Cardiovascular Research and Development Unit, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, Portugal.

<sup>3</sup> Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

<sup>4</sup> Duke Clinical Research Institute, Duke University, Durham, North Carolina.

<sup>5</sup> Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada.

<sup>6</sup> Department of Innovative Clinical Trials, University Medical Centre Göttingen (UMG), Robert-Koch-Straße, D-37075, Göttingen, Germany.

<sup>7</sup> Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit, Glasgow, UK.

<sup>8</sup> University of Bergen, Bergen, Norway.

<sup>9</sup> Stavanger University Hospital, Stavanger, Norway.

<sup>10</sup> National and Kapodistrian University of Athens, School of Medicine, Heart Failure Unit, Department of Cardiology, Athens University Hospital Attikon, Rimini 1, Athens 12462, Greece.

<sup>11</sup> Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.

<sup>12</sup> University of Brescia, Italy

<sup>13</sup> Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; Cardiovascular theme, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, LE3 9QP, United Kingdom

<sup>14</sup> Department of Cardiology, Centre for Heart Diseases, 4th Military Hospital, Wrocław, Poland; Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland.

<sup>15</sup> Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, Glenfield Hospital, Groby Rd, Leicester, LE3 9QP, United Kingdom

<sup>16</sup> 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**

*Introduction:* 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 HF.

*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 HF. Subjects who underwent angiography were younger, more often conducted on inpatients, had more often an overt acute coronary syndrome, had higher troponin I levels, were younger, and had better renal function (all  $p \leq 0.01$ ). Only 35% ( $n=54$ ) of patients with an ACS ( $n=155$ ) underwent coronary angiography. 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. Coronary angiography appears to be underutilized among patients who present with an ACS and HF. Strategies to optimize the use of coronary angiography among eligible patients may represent an opportunity to improve outcomes.

*Key-words:* Decompensated Heart Failure; Coronary Angiography; Myocardial Infarction; Outcomes

## **Introduction**

Coronary angiography is the “gold standard” technique for the assessment of the presence and the extension/severity of coronary artery disease, and to define the most appropriate therapy<sup>1</sup>. 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 and intermediate to high pre-test probability of coronary artery disease, which includes a “positive” non-invasive stress test<sup>2,3</sup>.

In patients with worsening symptoms and/or signs of HF, coronary angiography may be infrequently performed, regardless of hospitalization or ambulatory status<sup>4,5</sup>. 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) baseline characteristics of patients with worsening HF who undergo coronary angiography; 2) the prevalence of coronary stenosis among those undergoing coronary angiography; 3) the prognostic value of coronary angiography and coronary stenosis; and 4) assess whether HF etiology modifies the association between coronary angiography and outcomes.

## **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<sup>6</sup>. In brief, patients were aged  $\geq 18$  years with symptoms of new-onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of  $\leq 40\%$  or a BNP and/or NT-proBNP plasma levels  $>400$  pg/ml or  $>2000$  pg/ml, respectively. Patients needed to be treated with either oral or intravenous furosemide  $\geq 40$  mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence based therapies (ACEi/ARBs and  $\beta$ -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  $\beta$ -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  $\beta$ -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<sup>7,8</sup>. 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<sup>6</sup>. 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 the present 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.

### **Statistical analysis**

In descriptive analyses, continuous variables are expressed as mean  $\pm$  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 a 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  $\beta$  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. Cox models’ assumptions were verified. 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/>)<sup>9</sup>. 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.

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/>).

## 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, had an acute coronary syndrome (ACS) as the precipitating cause of HF, 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 ng/dL) were more likely to have a coronary angiogram performed. **Supplemental Figure 1**. Nonetheless, troponin I levels were linear and independently associated with increased risk of adverse outcomes in this population and added 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 cardiopathy 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, France and Germany had higher proportion of patients undergoing coronary angiography, with the Netherlands contributing to 25% of all angiographies performed. **Supplemental Table 4**.

Independent predictors for performing a 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 ACS (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<sup>2</sup> 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 a 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 **Supplementary 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 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 HF hospitalization =0.71, 95%CI =0.57-0.89, p =0.003; for the outcome of death HR =0.59, 95%CI =0.43-0.80, p =0.001). **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). **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**.

~~Patients that underwent coronary angiography also had their ACEi/ARBs more frequently up-titrated. **Supplemental Table 2**.~~

### **Discussion**

Using data from the BIOSTAT-HF project, we evaluated the characteristics and outcomes of patients who underwent coronary angiography after HF decompensation. The following are the major findings of our analysis: 1) 13% of patients with worsening HF underwent a coronary angiography within 30 days after the onset of worsening symptoms and/or signs of HF; 2) These patients had a better clinical profile and had reduced risk of outcome compared to those who did not undergo coronary angiography; 3) Patients with a coronary stenosis on coronary angiography had a worse prognosis compared to those without a

coronary stenosis; 4) among patients with a coronary stenosis, 20% of patients had a previous diagnosis of non-ischemic HF.

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<sup>5, 10</sup>. Nonetheless, in patients with decompensated HF, coronary artery disease may be the primary HF etiology in more than 50% of the patients<sup>11</sup>. Although a causal relation cannot be inferred, recurrent ischemic events are a major cause of subsequent HF decompensation and death<sup>12</sup> among patients with an ACS. Hence, evaluating for coronary artery disease as among patients with worsening HF (even without overt ACS) may be associated with improved clinical outcome. In the present report, only 23% (n=54) of the subjects presenting with an overt ACS (n=155) underwent coronary angiography within the worsening HF episode ( $\pm$ 30 days). These data suggest that the large majority of the coronary angiographies were performed in patients with other primary causes for HF decompensation. Our data suggests that physicians have a high threshold to consider coronary angiography, even among patients with an ACS. 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<sup>13</sup>. Our data extends on these findings as physicians appear to use a higher threshold of troponin elevation to conduct a 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<sup>14, 15</sup>.

Diagnostic procedures may influence treatment decisions (directly and/or indirectly) and consequently prognosis<sup>16-18</sup>. In this context, the performance of a 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<sup>14, 19</sup>. In the present study performing a coronary angiography was associated with improved outcomes, finding that is consistent with the OPTIMIZE-HF registry<sup>10</sup>, however no causality can be established as this may reflect only selection bias and better baseline patient profile.

Older patients and those with worse renal function were less likely to have a 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<sup>10, 20, 21</sup>. 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<sup>22</sup>.

We found an “interaction” between HF etiology (ischemic vs. other) and the prognostic value of coronary angiography. Our data suggested that among patients with a coronary stenosis, 20% had non-ischemic HF. Performing a coronary angiography in patients without previously known ischemic etiology was associated with a better outcome than in patients with documented HF of ischemic etiology, possibly because it may allow the assessment and treatment of coronary artery disease that would otherwise pass untreated<sup>23</sup>.

Patients who underwent coronary angiography and had coronary stenosis documented ( $\approx 39\%$  in the present cohort) had worse prognosis compared to those without coronary stenosis. The presence of significant coronary lesions is associated with increased risk of subsequent outcomes, as also documented in previous reports<sup>24</sup>.

### **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. Coronary angiography appears to be underutilized, even among patients presenting with an ACS as the cause for HF decompensation. Furthermore, patients with other reasons for HF decompensation are frequently undergoing coronary angiography, suggesting inconsistency in care among patients admitted with HF. Future trials comparing “usual care” versus strategies to optimize the use of coronary angiography among eligible patients 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 secondary 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 contributed for the different outcomes observed. Second, this study was not designed to address coronary angiography performance, 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 selection biases that may have determined who underwent angiography as well as treatment biases that may have influenced whom received pharmacological therapies for coronary artery disease and HF. Fourth, results from stress testing and coronary intervention outcomes (e.g., stent placement,

coronary artery bypass grafting referral) are not available. 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. Coronary angiography appears to be underutilized in patients presenting with an ACS as a cause for HF decompensation. Performing a coronary angiogram was associated with improved outcomes but this observation may reflect selection bias. Future studies to evaluate strategies to optimize the use of coronary angiography among eligible patients are warranted and may represent an opportunity to improve outcomes.

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