Clinical Characteristics and Outcomes of Patients With Coronary Artery Disease and Angina

Analysis of the Irbesartan in Patients With Heart Failure and Preserved Systolic Function Trial

Athar A. Badar, MBChB; Ana Cristina Perez-Moreno, MD; Nathaniel M. Hawkins, MBChB, MD; Pardeep S. Jhund, MBChB, PhD; Alan P.T. Brunton, BSc (Hons); Inder S. Anand, MD, DPhil (Oxon); Robert S. McKelvie, MD, PhD; Michel Komajda, MD; Michael R. Zile, MD; Peter E. Carson, MD; Roy S. Gardner, MBChB, MD; Mark C. Petrie, MBChB, BSc; John J.V. McMurray, MBChB, MD

Background—The aim of our study was to investigate the relationship between coronary artery disease (CAD), angina, and clinical outcomes in patients with heart failure and preserved ejection fraction enrolled in the irbesartan in patients with heart failure and preserved systolic function (I-Preserve) trial.

Methods and Results—The mean follow-up period for the 4128 patients enrolled in I-Preserve was 49.5 months. Patients were divided into 4 mutually exclusive groups according to history of CAD and angina: patients with no history of CAD or angina (n=2008), patients with no history of CAD but a history of angina (n=649), patients with a history of CAD but no angina (n=468), and patients with a history of CAD and angina (n=1003); patients with no known CAD or angina were the reference group. After adjustment for other prognostic variables using Cox proportional-hazard models, patients with CAD but no angina were found to be at higher risk of all-cause mortality (hazard ratio [HR], 1.58 [1.22–2.04]; $P<0.01$) and sudden death (HR, 2.12 [1.33–3.39]; $P<0.01$), compared with patients with no CAD or angina. Patients with CAD and angina were also at higher risk of all-cause mortality (HR, 1.29 [1.05–1.59]; $P=0.02$) and sudden death (HR, 1.83 [1.24–2.69]; $P<0.01$) compared with the same reference group and had the highest risk of unstable angina or myocardial infarction (HR, 5.84 [3.43–9.95]; $P<0.01$).

Conclusions—Patients with heart failure and preserved ejection fraction and CAD are at higher risk of all-cause mortality and sudden death when compared with those without CAD.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

(*Circ Heart Fail*. 2015;8:717-724. DOI: 10.1161/CIRCHEARTFAILURE.114.002024.)

Key Words: angina pectoris ■ coronary artery disease ■ heart failure ■ human ■ irbesartan

The few studies to examine the relationship between coronary artery disease (CAD) and outcomes in patients with heart failure and preserved ejection fraction (HF-PEF) have produced conflicting results. CAD was associated with higher all-cause mortality in a single-center study from the United States, which included 376 patients with HF-PEF (255 with CAD).[1] In a retrospective analysis of the Coronary Artery Surgery Study (CASS) registry, among 284 patients with HF-PEF, the number of diseased coronary arteries was an independent predictor of survival (68 patients had no CAD).[2] However, these findings contradict those of a Framingham cohort analysis and a multicenter, prospective European study where in both there was no difference in mortality between HF-PEF patients with and without CAD.[3,4] Even less is known about the relationship between CAD and modes of cardiovascular mortality, such as sudden death, which to our knowledge has only been examined in a handful of previous studies.[4–6]

Clinical Perspective on p 724

Received December 23, 2014; accepted June 1, 2015.

From the BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (A.A.B., A.C.P.-M., P.S.J., A.P.T.B., R.S.G., M.C.P., J.J.V.M.); Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Glasgow, United Kingdom (A.A.B., R.S.G., M.C.P.); Division of Cardiology, University of British Columbia, Vancouver, Canada (N.M.H.); Veterans Affairs Medical Center and University of Minnesota, Minneapolis (I.S.A.); Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada (R.S.M.); Pitié-Salpêtrière Hospital, Paris, France (M.K.); Ralph H. Johnson Veterans Affairs Medical Center and Medical University of South Carolina, Charleston (M.R.Z.); and Georgetown University and Washington DC Veterans Affairs Medical Center (P.E.C.).

Guest Editor for this article was James Fang, MD.

Correspondence to John J.V. McMurray, MBChB, MD, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, United Kingdom. E-mail john.mcmurray@glasgow.ac.uk

The prognostic implications of symptomatic myocardial ischemia (ie, angina) in HF-PEF are also poorly defined. In some patients, myocardial ischemia occurs even in the absence of major epicardial CAD. This is especially likely in the presence of left ventricular hypertrophy, which is pathognomonic of the HF-PEF phenotype. Other factors such as coronary microvascular dysfunction may also precipitate angina and in 1 single-center analysis of consecutive patients with HF-PEF referred for angiography, the proportion of patients reporting angina symptoms was similar in those with and without epicardial CAD.[1,7] We, therefore, investigated the relationship between CAD, angina and a range of clinical outcomes in the irbesartan in patients with heart failure and preserved systolic function (I-Preserve) trial.[8]

Methods

The design, baseline characteristics, and results of I-Preserve are published.[8–10] Briefly, 4128 patients aged ≥60 years with a left ventricular ejection fraction (LVEF) ≥45%, current signs and symptoms of heart failure and corroborating evidence (relevant electrocardiographic, chest x-ray, or echocardiographic abnormalities) were randomized to 300 mg once daily of irbesartan or placebo. Patients in New York Heart Association (NYHA) functional classes II to IV were eligible but those in class II were required to have had a hospitalization for heart failure within the previous 6 months. Ethics committees at each participating institute approved the trial and all patients provided written informed consent. The mean follow-up was of 49.5 months. No significant treatment difference was seen in the primary composite outcome of death from any cause or hospitalization for a cardiovascular cause, or in any of the prespecified secondary end points.

Investigators recorded details of heart failure cause and medical history, including stable angina pectoris, by checking boxes on the trial case report form. For the purposes of this retrospective analysis, patients with a history of CAD were defined as those with a history of previous myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass grafting, or a primary ischemic cause as defined by investigators. Patients were divided into 4 mutually exclusive groups; those without a history of CAD or angina, patients without a history of CAD but with a history of angina, patients with a history of CAD but no angina and those with a history of CAD and angina.

Clinical Outcomes

The 3 other groups were compared with the reference group of patients without a history of CAD or angina for the following clinical outcomes: all-cause death, cardiovascular death, sudden death, death because of HF, HF death or HF hospitalization (the predefined composite HF end point in I-Preserve), HF hospitalization, fatal or nonfatal MI, and the composite of MI or unstable angina (UA). Sudden death was defined as an unexpected death in a previously stable patient. Patients with sudden death had to have human contact in the 24 hours preceding the event; those who had been out of contact for more prolonged periods were classified as unknown.[11]

Statistical Analysis

Baseline characteristics were described using percentages for categorical variables and mean with SDs for continuous variables. The 1-way ANOVA test was used to compare continuous variables except where data were not normally distributed where the Welch test was used. The χ^2 test was used to compare categorical variables.

The relationships between a history of CAD, angina, and outcomes were assessed using Kaplan–Meier cumulative event survival curves and Cox proportional-hazard regression analyses. In sensitivity analyses, we examined the impact of the competing risk of all-cause mortality on the cumulative incidence of HF hospitalizations and the competing risk of noncardiovascular death on cardiovascular death. In both analyses, no substantial differences were found between the competing risks approach and the Kaplan–Meier approach (data not shown). For consistency, Kaplan–Meier estimates are presented.[12,13] Published predictors of fatal and nonfatal outcomes in I-Preserve were used in the multivariable analyses.[11,14] The variables adjusted were N-terminal pro-brain natriuretic peptide (NT-proBNP; log) levels, age, recent HF hospitalization, diabetes mellitus, neutrophil count (log), ejection fraction, chronic obstructive pulmonary disease or asthma, glomerular filtration rate, disease-specific quality of life measured using the Minnesota living with HF questionnaire, and heart rate; the presence of left bundle branch block was also included in the analysis of sudden death. The Cox proportional-hazard survival analyses used a conventional 2-tailed $P<0.05$ as the statistical level of significance. All statistical analyses were performed using Stata version 13, Stata Corp, College Station, TX and IBM SPSS Statistics for Mac, version 22.0. Armonk, NY.

Results

Of 4128 patients in I-Preserve, 2657 (64% of the total) had no recorded history of CAD; 649 (24%) of these patients without CAD had a history of angina. Of the 1471 patients (36% of the total) with a history of CAD, 1003 (68%) had a history of angina.

Baseline Characteristics

Baseline characteristics stratified by history of angina and CAD are presented in Table 1.

Comparison of Patients With and Without a History of CAD

Patients with a history of CAD were more likely to be men (52% versus 33%), have a history of diabetes mellitus (32% versus 25%), a higher median NT-proBNP level (449 versus 282 pg/mL), and a slightly lower mean LVEF (58% versus 61%). They were less likely to have a history of hypertension (82% versus 92%) or atrial fibrillation (13% versus 18%). Patients with a history of CAD were more likely to be in NYHA functional class III or IV (82% versus 77%) than those without a history of CAD. However, their quality of life, as assessed by the Minnesota living with HF questionnaire, was similar (score of 42 versus 43). Patients with CAD were also more likely to be prescribed a statin (41% versus 23%) or antiplatelet agent (78% versus 48%) at baseline. There was no significant difference in diuretic use in patients with and without CAD (82% versus 83%).

Patients With No History of CAD: Angina Versus No Angina

Patients without a history of CAD but a history of angina were more likely to be women (70% versus 66%), have a history of hypertension (96% versus 91%), and have a lower median NT-proBNP level (241 versus 298 pg/mL) than patients with neither a history of CAD nor angina. They were less likely to have diabetes mellitus (22% versus 26%) or atrial fibrillation (12% versus 20%). Their quality of life, as assessed by the Minnesota living with HF questionnaire, was worse (score of 46 versus 41). The mean LVEF was similar in the 2 groups (60% versus 61%). Patients without a history of CAD but a history of angina were also more likely to be prescribed a diuretic (89% versus 82%) or antiplatelet agent (65% versus 42%) at baseline. The use of statins was similar in the 2 groups (23% versus 23%).

Table 1. Baseline Characteristics of Patients Stratified by Severity of History of Angina Pectoris and CAD

Variable	No CAD No Angina (n=2008)	No CAD Angina (n=649)	CAD No Angina (n=468)	CAD Angina (n=1003)	*P* Value
Age, y	71.8±7.1	71.0±6.7	72.6±7.0	71.3±6.8	<0.01
Women, n (%)	1330 (66)	455 (70)	214 (46)	492 (49)	<0.01
White, n (%)	1835 (91)	634 (98)	435 (93)	955 (95)	<0.01
NYHA III/IV, n (%)	1563 (78)	492 (76)	385 (82)	817 (81)	<0.01
Minnesota living with HF score	41.2 (21.0)	45.6 (18.5)	41.1 (21.9)	44.5 (20.9)	<0.01
LVEF, %	60.6±9.5	60.1±8.5	58.6±9.4	57.0±8.1	<0.01
Systolic BP, mm Hg	137±15	137±13.	135±16	135±15	<0.01
Heart rate, beats per minute	71.9±10.8	71.3±9.5	70.9±10.6	70.8±10.1	0.02
BMI, kg/m^2	30.0±5.6	29.4±4.8	29.3±5.1	29.2±4.9	<0.01
Medical history					
MI, n (%)	0 (0)	0 (0)	308 (66)	661 (66)	<0.01
PCI or CABG, n (%)	0 (0)	0 (0)	200 (43)	348 (35)	<0.01
Hypertension, n (%)	1823 (91)	622 (96)	380 (81)	825 (82)	<0.01
Diabetes mellitus, n (%)	520 (26)	145 (22)	179 (38)	290 (29)	<0.01
AF at baseline, n (%)	401 (20)	81 (12)	70 (15)	118 (12)	<0.01
Stroke or TIA, n (%)	178 (9)	56 (9)	61 (13)	104 (10)	0.03
Pacemaker, n (%)	122 (6)	35 (5)	37 (8)	58 (6)	0.33
ICD, n (%)	3 (0)	1 (0)	3 (1)	5 (0)	0.15
Laboratory measurements					
Anemia at baseline, n (%)	239 (13)	60 (9)	72 (16)	143 (15)	<0.01
Estimated GFR	72.5±23.1	72.8±19.8	70.4±21.3	73.4±23.3	0.13
Median NT-proBNP concentrations, pg/mL*	298 (119–942)	241 (102–773)	455 (196–1196)	455 (188–1043)	<0.01
Medication					
Diuretic, n (%)	1639 (82)	576 (89)	357 (76)	846 (84)	<0.01
ACE inhibitor, n (%)	438 (22)	167 (26)	139 (30)	289 (29)	<0.01
β-blocker, n (%)	1016 (51)	434 (67)	296 (63)	681 (68)	<0.01
CCB, n (%)	857 (43)	282 (44)	143 (31)	355 (36)	<0.01
Long-acting Nitrate, n (%)	186 (9)	245 (38)	135 (29)	542 (54)	<0.01
Antiplatelet, n (%)	843 (42)	422 (65)	344 (74)	807 (81)	<0.01
Statin, n (%)	459 (23)	150 (23)	229 (49)	372 (37)	<0.01

Qualitative variables percentages and systolic BP reported as integers. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*NT-proBNP concentrations expressed as medians with first and third quartile values contained within parenthesis.

Patients With a History of CAD: Angina Versus No Angina

Patients with a history of CAD and angina were more likely to be women (49% versus 46%) and had a slightly lower mean LVEF (57% versus 59%), worse quality of life score (45 versus 41), and less frequent previous coronary revascularization (35% versus 43%) than patients with CAD but no angina. They were also less likely to have a history of diabetes mellitus (29% versus 38%) or atrial fibrillation (12% versus 15%); however, the proportion of patients with a history of hypertension (82% versus 81%) was similar in the 2 groups. The proportion of patients in NYHA functional class III or IV (81% versus 82%) and the median NT-proBNP level (455 versus 455 pg/mL) was also similar in the 2 groups. Patients with CAD and angina were more likely to be prescribed a diuretic (84% versus 76%) or antiplatelet agent (81% versus 74%) but less likely to be prescribed a statin at baseline (37% versus 49%).

Clinical Outcomes

Mortality

In I-Preserve, cardiovascular death accounted for 70% of all deaths. Sudden death accounted for 38% of all cardiovascular deaths (n=231); approximately double the number of patients with death because of HF (20% of all cardiovascular deaths, n=125).

In patients without a history of CAD, those with and without angina had a similar risk of death from any cause, cardiovascular death and sudden death (Tables 2 and 3; Figure 1).

Patients with a history of angina had a lower risk of death because of HF that was nominally statistically significant in the unadjusted analysis but not after adjustment for other prognostic variables in a multivariable analysis: hazard ratio (HR), 0.54, 0.24 to 1.21; *P*=0.14.

Patients with a history of CAD (with or without angina) were at higher risk of death from any cause compared with those without a history of CAD or angina in both adjusted and unadjusted analyses (Tables 2 and 3; Figure 1).

Patients with a history of CAD and angina were at higher risk of death from any cause (HR, 1.29 [1.05–1.59]; *P*=0.02), cardiovascular death (HR, 1.46 [1.14–1.86]; *P*<0.01), and sudden death (HR, 1.83 [1.24–2.69]; *P*<0.01), compared with those without a history of CAD or angina (Tables 2 and 3; Figure 1).

Patients with a history of CAD but no angina had the highest risk of death from any cause (HR, 1.58 [1.22–2.04]; *P*<0.01), cardiovascular causes (HR, 1.50 [1.10–2.06]; *P*=0.01), as well as the highest risk of sudden death (HR, 2.12 [1.33–3.39]; *P*<0.01). They were not, however, at higher risk of death because of HF (HR, 0.66 [0.29–1.49]; *P*=0.32; Tables 2 and 3; Figure 1).

HF Outcomes

In patients without a history of CAD, those with and without angina had a similar risk of heart failure outcomes (Tables 2 and 3; Figure 2). Patients with a history of angina had a lower risk of HF hospitalization that was nominally statistically significant in the unadjusted analysis but not after adjustment for other prognostic variables in a multivariable analysis (HR, 0.94 [0.70–1.25]; *P*=0.67).

Patients with a history of CAD (with or without angina) were at moderately higher risk of both HF hospitalization and the composite end point of HF death or HF hospitalization when compared with patients without a history of CAD or angina. However, following multivariable adjustment only the composite end point of HF death or HF hospitalization in patients with CAD and angina remained significant (HR, 1.26 [1.03–1.54]; *P*=0.02; Tables 2 and 3; Figure 2).

Coronary Outcomes

Coronary events occurred infrequently in I-Preserve. Only 5% of the overall study sample were hospitalized for UA or MI during follow-up.

In patients without a history of CAD, those with angina had a higher risk of the composite outcome of UA or MI compared with patients without CAD or angina. This relationship was strengthened after multivariable adjustment (HR, 2.20 [1.10–4.37]; *P*=0.03). The risk of fatal or nonfatal MI was not increased in patients with a history of angina, even after multivariable adjustment (HR, 1.51 [0.66–3.43]; *P*=0.33; Tables 2 and 3; Figure 2).

Patients with a history of CAD but no history of angina and patients with a history of CAD and angina both had a higher adjusted risk of UA or MI when compared with patients with no history of CAD or angina ([HR, 4.44 {2.31–8.54}; *P*<0.01] and [HR, 5.84 {3.43–9.95}; *P*<0.01], respectively). A similar finding was seen in relation to fatal or nonfatal MI after multivariable analysis ([HR, 2.75 {1.26–5.97}; *P*=0.01] and [HR, 5.14 {2.90–9.13}; *P*<0.01], respectively; Tables 2 and 3; Figure 2).

Discussion

In our analysis of the 4128 patients with HF-PEF randomized in I-Preserve, angina was present in 68% of patients with CAD and 24% of those with no history of CAD. Patients with a history of CAD were at higher risk of death from any cause, which was driven by a higher rate of sudden death in particular.

The relatively high frequency of angina pectoris in patients without a history of CAD is consistent with an earlier single-center study of 376 patients hospitalized with HF-PEF in the United States.[1] In that study, after discharge, all participants underwent angiography within 12 months and a similar

Table 2. Clinical Outcomes According to History of Angina Pectoris and Coronary Disease (Univariate Analysis)

	No CAD No Angina (n=2008)	No CAD Angina (n=649)	CAD No Angina (n=468)	CAD Angina (n=1003)	No CAD/Angina vs No CAD/No Angina		CAD/No Angina vs No CAD/No Angina		CAD/Angina vs No CAD/No Angina	
Group Comparison	No. (event rate)	No. (event rate)	No. (event rate)	No. (event rate)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mortality outcomes										
All-cause death	379 (46.0)	110 (39.5)	153 (86.2)	239 (59.7)	0.85 (0.69–1.05)	0.14	1.90 (1.57–2.29)	<0.01	1.30 (1.10–1.52)	<0.01
CV death	243 (29.5)	83 (29.8)	104 (58.6)	183 (45.7)	1.00 (0.78–1.29)	0.97	2.00 (1.59–2.52)	<0.01	1.55 (1.28–1.88)	<0.01
Sudden death	83 (10.1)	31 (11.1)	43 (24.2)	74 (18.5)	1.10 (0.73–1.66)	0.66	2.42 (1.67–3.49)	<0.01	1.83 (1.34–2.50)	<0.01
Deaths because of HF	61 (7.4)	10 (3.6)	18 (10.1)	36 (9.0)	0.48 (0.25–0.95)	0.03	1.38 (0.81–2.33)	0.24	1.22 (0.81–1.84)	0.35
HF outcomes										
HF death/HFH	390 (51.5)	106 (41.1)	126 (77.8)	244 (67.7)	0.81 (0.65–1.00)	0.05	1.49 (1.22–1.82)	<0.01	1.31 (1.12–1.54)	<0.01
HFH	312 (41.2)	81 (31.4)	88 (54.3)	180 (49.9)	0.78 (0.61–0.99)	0.04	1.29 (1.02–1.64)	0.03	1.21 (1.00–1.45)	0.05
Coronary outcomes										
Fatal/nonfatal MI	33 (4.0)	14 (5.1)	25 (14.3)	77 (19.8)	1.26 (0.68–2.36)	0.46	3.52 (2.09–5.92)	<0.01	4.89 (3.25–7.35)	<0.01
UA/MI	41 (5.0)	20 (7.3)	33 (19.1)	100 (26.0)	1.46 (0.86–2.49)	0.17	3.75 (2.37–5.93)	<0.01	5.16 (3.59–7.43)	<0.01

Event rates expressed as per 1000 patient-years. CAD indicates coronary artery disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, HF hospitalization; HR, hazard ratio; MI, myocardial infarction; and UA, unstable angina.

Table 3. Clinical Outcomes According to History of Angina Pectoris and CAD (Multivariable Analysis)

	No CAD/Angina vs No CAD/No Angina		CAD/No Angina vs No CAD/No Angina		CAD/Angina vs No CAD/No Angina	
Group Comparison	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mortality outcomes						
All-cause death*	0.95 (0.73–1.25)	0.72	1.58 (1.22–2.04)	<0.01	1.29 (1.05–1.59)	0.02
CV death*	1.11 (0.82–1.52)	0.50	1.50 (1.10–2.06)	0.01	1.46 (1.14–1.86)	<0.01
Sudden death†	1.08 (0.64–1.85)	0.77	2.12 (1.33–3.39)	<0.01	1.83 (1.24–2.69)	<0.01
Deaths because of HF*	0.54 (0.24–1.21)	0.14	0.66 (0.29–1.49)	0.32	1.08 (0.64–1.83)	0.78
Heart failure outcomes*						
HF death/HFH	0.93 (0.72–1.20)	0.56	1.19 (0.91–1.55)	0.20	1.26 (1.03–1.54)	0.02
HFH	0.94 (0.70–1.25)	0.67	1.03 (0.75–1.40)	0.87	1.12 (0.89–1.41)	0.35
Coronary outcomes*						
Fatal/nonfatal MI	1.51 (0.66–3.43)	0.33	2.75 (1.26–5.97)	0.01	5.14 (2.90–9.13)	<0.01
MI/UA	2.20 (1.10–4.37)	0.03	4.44 (2.31–8.54)	<0.01	5.84 (3.43–9.95)	<0.01

CAD indicates coronary artery disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, HF hospitalization; HR, hazard ratio; MI, myocardial infarction; NT-proBNP, N-terminal probrain natriuretic peptide; and UA, unstable angina.

*Adjusted for were NT-proBNP (log) concentration, age, recent HFH, diabetes mellitus, neutrophil count (log), ejection fraction, chronic obstructive pulmonary disease or asthma, glomerular filtration rate, quality of life score, and heart rate.

†Adjusted for were NT-proBNP (log) concentration, age, recent HFH, diabetes mellitus, neutrophil count (log), ejection fraction, chronic obstructive pulmonary disease or asthma, glomerular filtration rate, quality of life score, heart rate, and left bundle branch block on ECG.

prevalence of angina was noted irrespective of whether significant epicardial CAD was detected. Factors such as left ventricular hypertrophy and coronary microvasculature dysfunction may contribute to angina symptoms in patients without epicardial CAD.[7,15] An alternative explanation is that in our study at least some of these patients simply had undiagnosed CAD;

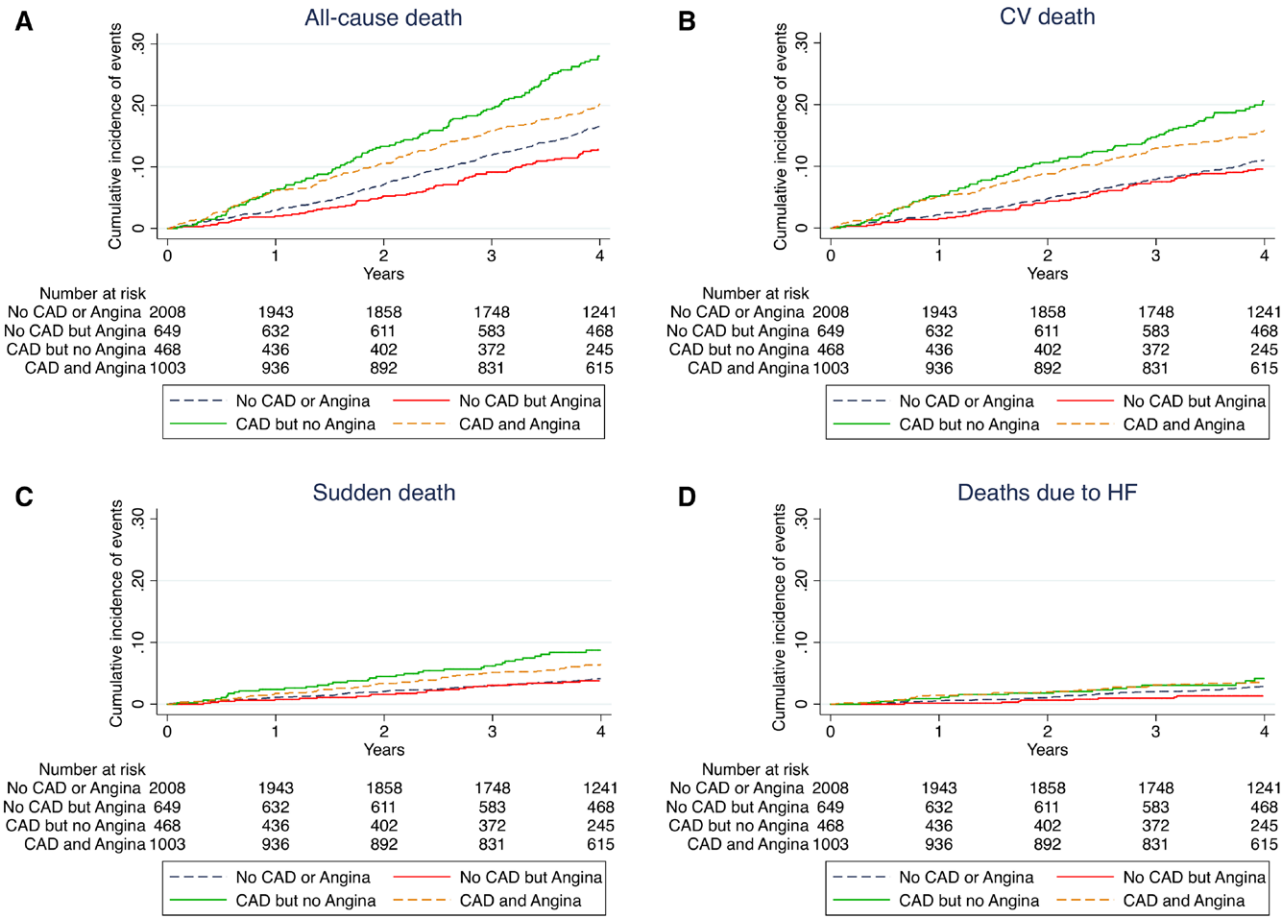

Figure 1. Kaplan–Meier curves illustrating relationship between history of angina, coronary artery disease (CAD), and outcomes. **A**, All-cause death, (**B**) cardiovascular (CV) death, (**C**) sudden death, and (**D**) deaths because of heart failure (HF).

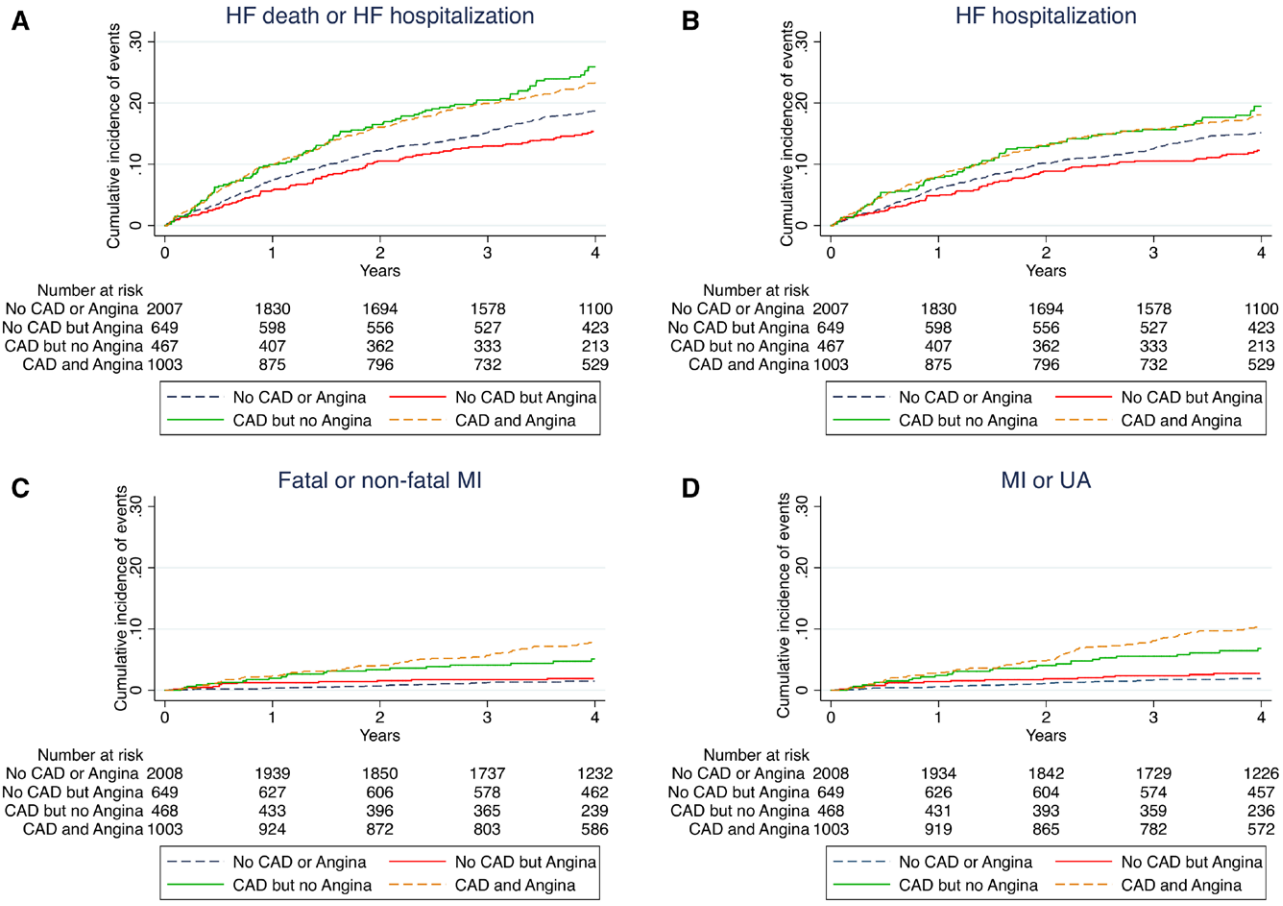

Figure 2. Kaplan–Meier curves illustrating relationship between history of angina, coronary artery disease (CAD) and outcomes. **A**, Heart failure (HF) death/HF hospitalization, (**B**) HF hospitalization, (**C**) fatal or nonfatal myocardial infarction (MI), and (**D**) MI or unstable angina (UA).

we do not know what proportion had coronary angiography but 3% did experience an acute MI or an episode of UA after randomization. Another consideration is that undiagnosed CAD, rather than HF-PEF per se, could have been the cause of symptoms in a proportion of patients enrolled in I-Preserve, given that the diagnosis of HF-PEF is difficult. Although most patients with no history of CAD but with a history of angina were in NYHA functional class III or IV (and these patients also had significantly reduced quality of life as measured by the Minnesota questionnaire), they also had the lowest baseline NT-proBNP level with levels that were entirely normal in over a quarter of patients.

Baseline Characteristics

Patients with CAD (with or without a history of angina) had more advanced heart failure as evidenced by the higher frequency of NYHA class III or IV symptoms, slightly lower mean LVEF and higher median NT-proBNP level. However, disease-specific quality of life measured with the Minnesota living with HF questionnaire was not significantly different from those without CAD. Conversely, a history of angina pectoris was associated with worse quality of life, irrespective of CAD history. This finding suggests that treating angina in patients with HF-PEF has the potential to improve heart failure–related quality of life.

Relationship Between CAD, Angina, and Mortality

The association between CAD and all-cause mortality has been extensively investigated in HF-REF but not HF-PEF. CAD was an independent predictor of higher all-cause mortality in the aforementioned single-center study of 376 patients hospitalized with HF-PEF (adjusted HR, 1.71 [1.03–2.98]; *P*=0.04) and in the 284 patients with HF-PEF in the CASS registry.[1,2] In the CASS registry, HF-PEF patients with absent, moderate, or triple-vessel CAD had respective 6-year survival rates of 92%, 83%, and 68% (*P*=0.0001).[2] However, patients with HF-PEF in a cohort from the Framingham Heart Study (n=220) did not demonstrate a difference in survival related to the presence of CAD and this lack of association was also seen in a prospective multicenter study of 320 patients hospitalized with HF-PEF in France (adjusted HR, 0.93 [0.69–1.26]; *P*=0.65).[3,4] The reasons behind these conflicting results are not clear but small sample sizes, heterogeneous patient cohorts, and differences in the variables used to adjust survival may all contribute. In this study, patients with CAD, irrespective of angina, had higher risk of death than those without CAD or angina, even after extensive adjustment for other prognostic variables, including NT-proBNP.

The more important finding in I-Preserve was that the higher mortality in patients with CAD was because of a much higher (double) risk of sudden death. Although the highest

risk occurred in patients with a history of CAD but no angina (HR, 2.12 [1.33–3.39]; $P<0.01$), the HR was not significantly different to that in patients with CAD and angina (HR, 1.83 [1.24–2.69]; $P<0.01$). Presumably, therefore, by causing myocardial ischemia (or infarction), underlying CAD led to higher mortality rates in HF-PEF by precipitating lethal ventricular arrhythmias, although other causes of sudden death can occur (eg, a large MI, stroke, or rupture of an abdominal aortic aneurysm).

Two smaller, multicenter, retrospective analyses of patients discharged from hospital with a diagnosis of HF-PEF (n=320 and n=787, respectively) also showed that CAD was associated with a higher risk of sudden death.[4,5]

Although HF-PEF patients with CAD are at increased risk of sudden death, the absolute rate is low (≈2% per year) and the potential role of implantable cardioverter defibrillator therapy unclear, especially as coronary revascularization might also ameliorate this risk (see below). One planned study of implantable loop recorders in patients with HF-PEF designed to examine the frequency of significant ventricular arrhythmias will not fully address this question as patients with significant CAD or a recent MI will be excluded (http://clinicaltrials.gov/ct2/show/NCT01989299).

The Relationship Between CAD, Angina, and UA/MI

Patients with CAD and angina had the highest risk of UA/MI (HR, 5.84 [3.43–9.95]; $P<0.01$) when compared with those with no history of CAD or angina. However, the HR in the former group was not significantly different from that in patients with CAD but no history of angina (HR, 4.44 [2.31–8.54]; $P<0.01$). The strength of the association in the CAD and angina group was likely attenuated by our inability to differentiate patients with past and current angina. In a recent analysis of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program, patients with CAD and current angina were almost 3 times as likely to experience UA/MI end point (adjusted HR, 2.75 [1.88–4.01]; $P<0.01$) compared with patients with CAD but no history of angina.[16] However, in CHARM there was no significant association between past angina and UA/MI.

Clearly, both I-Preserve and CHARM-Preserved suggest new studies are needed to establish whether specific medical therapies or coronary revascularization have a role to play in reducing adverse events in patients with HF-PEF and CAD, whether or not they have angina. Two relatively small retrospective analyses assessing the role of coronary revascularization in these patients have produced conflicting results. A single-center study of 376 patients hospitalized with HF-PEF found complete revascularization was an independent predictor of lower all-cause mortality.[1] However, no such association was evident in the CASS registry although that study was conducted >20 years ago and it is not clear whether advances in medical therapy and coronary revascularization contributed to these conflicting findings.[2]

Our study has many limitations. This was a retrospective analysis that only included patients aged ≥60 years and excluded patients with additional comorbidities, such as resistant hypertension, significant renal dysfunction, and anemia.[8,9] Therefore, our findings may not be representative of a real-life cohort and cannot be generalized to all patients with HF-PEF, particularly younger patients. The history of angina was dependent on investigator-reported history. Also, patients in I-Preserve did not undergo routine angiography and it is possible that patients with CAD may have been misclassified (or vice versa); several studies have demonstrated the limitations of noninvasive assessment in accurately establishing HF cause.[17,18]

In summary, patients with CAD and HF-PEF have evidence of more advanced HF, whereas patients with angina and HF-PEF experience poorer quality of life, irrespective of the underlying cause. The risk of sudden death is significantly higher in patients with CAD and our findings suggest that specific interventions such as coronary revascularization or implantable cardioverter defibrillator therapy could improve outcomes in HF-PEF, although this hypothesis needs to be tested in prospective randomized trials.

Disclosures

None.

References

1. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63(25 pt A):2817–2827. doi: 10.1016/j.jacc.2014.03.034.
2. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. *J Am Coll Cardiol*. 1991;18:377–382.
3. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the National Heart, Lung, and Blood Institute. *Circulation*. 2009;119:3070–3077. doi: 10.1161/CIRCULATIONAHA.108.815944.
4. Rusinaru D, Houpe D, Szymanski C, Lévy F, Maréchaux S, Tribouilloy C. Coronary artery disease and 10-year outcome after hospital admission for heart failure with preserved and with reduced ejection fraction. *Eur J Heart Fail*. 2014;16:967–976. doi: 10.1002/ejhf.142.
5. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. *J Card Fail*. 2012;18:749–754. doi: 10.1016/j.cardfail.2012.08.357.
6. Al-Khatib SM, Shaw LK, O'Connor C, Kong M, Califf RM. Incidence and predictors of sudden cardiac death in patients with diastolic heart failure. *J Cardiovasc Electrophysiol*. 2007;18:1231–1235. doi: 10.1111/j.1540-8167.2007.00957.x.
7. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol*. 2015;12:48–62. doi: 10.1038/nrcardio.2014.160.
8. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467. doi: 10.1056/NEJMoa0805450.
9. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G; I-PRESERVE Investigators. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. *J Card Fail*. 2005;11:576–585. doi: 10.1016/j.cardfail.2005.06.432.
10. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, Staiger C, Donovan JM, Massie BM. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail*. 2008;10:149–156. doi: 10.1016/j.ejheart.2007.12.010.
11. Adabag S, Rector TS, Anand IS, McMurray JJ, Zile M, Komajda M, McKelvie RS, Massie B, Carson PE. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2014;16:1175–1182. doi: 10.1002/ejhf.172.

12. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
13. Gray B. Subdistribution analysis of competing risks. The cmprsk library (v 2.2–6). 2013. http://cran.r-project.org. Accessed April 22, 2015.
14. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, Zile MR, Demets D, Massie BM. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4:27–35. doi: 10.1161/CIRCHEARTFAILURE.109.932996.
15. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263–271. doi: 10.1016/j.jacc.2013.02.092.
16. Badar AA, Perez-Moreno AC, Hawkins NM, Brunton AP, Jhund PS, Wong CM, Solomon SD, Granger CB, Yusuf S, Pfeffer MA, Swedberg K, Gardner RS, Petrie MC, McMurray JJ. Clinical characteristics and outcomes of patients with angina and heart failure in the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) Programme. *Eur J Heart Fail*. 2015;17:196–204. doi: 10.1002/ejhf.221.
17. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J*. 1999;20:421–428.
18. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, Turner RM, Poole-Wilson PA, Davies SW, Sutton GC. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J*. 2001;22:228–236. doi: 10.1053/euhj.2000.2289.

CLINICAL PERSPECTIVE

The few previous studies to investigate the relationship between coronary artery disease (CAD) and all-cause mortality in patients with heart failure and preserved ejection fraction (HF-PEF) have produced conflicting results. This may be a reflection of small sample sizes, heterogeneous patient cohorts, and differences in the variables used to adjust survival. In this analysis of >4000 patients in the irbesartan in heart failure with preserved systolic function (I-Preserve) trial, patients with a history of CAD had a higher risk of death compared with those without CAD or angina. The higher mortality overall in patients with CAD was because of a much higher (double) risk of sudden death. We also found a surprisingly high prevalence of angina in patients without a history of CAD. This finding is consistent with a smaller single-center analysis of consecutive patients with HF-PEF referred for angiography where the proportion of patients reporting angina was similar in those with and without epicardial CAD. It suggests that additional factors such as left ventricular hypertrophy and coronary microvasculature dysfunction may contribute to the symptom of angina in patients with HF-PEF. Patients with angina experienced worse quality of life, irrespective of CAD history. Our findings suggest that treating angina in patients with HF-PEF has the potential to improve heart failure–related quality of life. Similarly, specific interventions such as coronary revascularization might improve outcomes in patients with CAD and HF-PEF, although this hypothesis needs to be tested in prospective randomized trials.

Clinical Characteristics and Outcomes of Patients With Coronary Artery Disease and Angina: Analysis of the Irbesartan in Patients With Heart Failure and Preserved Systolic Function Trial

Athar A. Badar, Ana Cristina Perez-Moreno, Nathaniel M. Hawkins, Pardeep S. Jhund, Alan P.T. Brunton, Inder S. Anand, Robert S. McKelvie, Michel Komajda, Michael R. Zile, Peter E. Carson, Roy S. Gardner, Mark C. Petrie and John J.V. McMurray

Circ Heart Fail. 2015;8:717-724; originally published online June 11, 2015;
doi: 10.1161/CIRCHEARTFAILURE.114.002024
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297