Incident heart failure in outpatients with chronic coronary syndrome: results from the international prospective CLARIFY registry

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Abstract

Aim. The contemporary incidence of heart failure (HF) in patients with chronic coronary syndrome is unclear. We aimed to study the incidence and predictors of cardiovascular (CV) death, HF hospitalization or new-onset HF not requiring hospitalization, in patients included in the CLARIFY registry.

Methods and results. CLARIFY is a contemporary, international registry of ambulatory patients with chronic CAD, conducted in 45 countries. At baseline, data on demographics, ethnicity, CV risk factors, medical history, cardiac parameters and medication were collected. Patients were followed-up yearly up to 5 years. In this analysis we included 26769 patients with no HF history. At 5-year follow-up, 4393 patients (16.4%) reached the primary endpoint comprising CV death, HF hospitalization or new-onset HF. Only 16.7% of them (N = 732) required hospitalization for HF. All-cause death occurred in 6.6% of patients (61.4% were cardiovascular). Age over 70 years, left ventricular ejection fraction <50%, CCS class $\geq$2 angina, atrial fibrillation or paced rhythm on the ECG, body mass index <20, and a history of stroke, were the most robust predictors of the primary outcome. Age <50 years, Asian ethnicity, and percutaneous revascularization were negative predictors of the outcome.

Conclusion. A sizeable proportion of patients with chronic coronary syndrome develop HF, which only infrequently requires hospitalization. Early identification of patients with HF may lead to early treatment, and help to further decrease mortality and morbidity. This concept needs confirmation in future studies.

Keywords

chronic coronary syndrome; prognosis; heart failure; CLARIFY registry

Introduction

Coronary artery disease (CAD) remains the leading cause of death on the global level [1]. It is also one of the most important causes of heart failure (HF) [2, 3]. In patients with CAD, HF may be not only caused by acute myocardial tissue loss due to myocardial infarction (MI), but also by left ventricular remodelling or severe chronic ischaemia. In developed countries, 1-2% of the adult population suffer from HF, with much higher prevalence in the elderly [2]. Despite constant advances in management, mortality in HF remains high, and patients require frequent hospital admissions [4]. In the elderly, 5-year mortality after a first MI tends to decrease, while the rate of subsequent HF increases [4]. Hospitalization for HF represents a great public health and financial burden. Chronic coronary syndromes account for a high proportion of cardiac hospitalizations, with a growing number of HF admissions over time [5]. However, a large proportion of patients with newly diagnosed or worsening HF may not require hospitalization, either because of less severe symptoms, or a growing tendency to provide ambulatory treatment [6]. These patients are generally neglected in clinical studies, but their inclusion in the analyses appears to be of importance [6-8]. In any case, development of HF puts patients at high risk for mortality [9-12]. Although the incidence of HF events has been previously studied in patients with stable CAD and in those with a history of MI [6,11,13,14], within the entire spectrum of chronic coronary syndromes, HF outcomes remain relatively poorly explored, which is especially relevant in patients who do not require hospital admission [7,8]. In addition, previous data come mainly from clinical trials, as opposed to registries which provide data more representative of routine clinical practice.

In major registries involving patients with chronic CAD, between 7 and 28% were diagnosed with HF [15]. However, over the last decades, there has been a clear change in the characteristics of patients with CAD. Contemporary patients are older and more likely to have

a history of MI or coronary revascularization than before. The prevalence of HF, diabetes, chronic renal and pulmonary disease, and peripheral artery disease have increased [15]. Data on the incidence of HF in patients with chronic CAD are limited [10]. Therefore, we aimed to study the incidence of HF outcomes and their predictors in a contemporary population of patients with CCS included in the prospeCtive observational LongitudinAl RegIstry oF patients with stable coronarY artery disease (CLARIFY), a worldwide registry of over 30 000 ambulatory patients. CLARIFY is registered in the ISRCTN Registry of clinical trials (IRSCTN43070564).

Methods

Study design

Rationale, design, and baseline characteristics of the entire CLARIFY population have been previously published [16,17]. Briefly, 32703 ambulatory patients with chronic CAD were enrolled between November 2009 and June 2010 in 45 countries in Europe, Middle East, Asia, Africa, and North and South America. Patients had to fulfil at least one of the following criteria to be eligible for the study: myocardial infarction or coronary revascularization (coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)) >3 months before enrolment, coronary stenosis >50% on angiography, or angina with documented myocardial ischaemia. The main exclusion criteria were: hospitalization for cardiovascular (CV) disease within previous 3 months, planned revascularization, and any condition that might affect participation or the 5-year follow-up. Study sites were selected by national coordinators among cardiologists, internists and general practitioners, based in different urban, suburban and rural areas, in order to obtain a sample best representing the disease epidemiology. Participating physicians were asked to manage patients according to their usual practice. No specific diagnostic or therapeutic procedures were required. Each

physician was requested to enrol 10-15 consecutive ambulatory patients. Patients were followed-up annually for up to 5 years.

CLARIFY was conducted according to the principles specified in the Declaration of Helsinki. The research protocol was approved by the Ethics Committees and regulatory agencies according to national and local legal requirements. All participants gave written informed consent before study entry.

The present study is a post-hoc analysis of data from the CLARIFY registry. Patients with a history of hospitalization for heart failure and/or heart failure symptoms at baseline were excluded from the analysis.We did not exclude patients based on EF availability or value.

Data collection

Data were collected using standardized electronic case-report forms available in a local language, completed at baseline and at annual visits. In case of missed visits, telephone contacts with the patients or their representatives, or site visits by investigators were attempted. If no contact was possible, vital status was retrieved from country databases whenever legally permitted. All data were centrally verified for accuracy, consistency and completeness. To assure data quality, on-site audits of all the data were performed in five percent of randomly selected centres over the study period (1% per year). At baseline, data on demographic characteristics, ethnicity, risk factors, medical history, cardiac parameters, and current medication were collected. At each annual visit clinical outcomes were recorded.

Clinical outcomes

For the purpose of the current analysis the primary outcome was defined as a composite of CV death, hospitalization for HF or new HF symptoms not requiring hospital admission (new-onset HF). The secondary outcome was a composite of CV death or HF hospitalization. We also analysed the incidence of all-cause death, the combination of HF

hospitalization and new-onset HF, and each component of the primary outcome. If new-onset HF and HF hospitalization were recorded on the same day, only the latter was taken into account.

CV death was defined as death within 28 days after MI or stroke, any sudden death including unobserved and unexpected death unless proven otherwise by autopsy, death ascribed to heart failure, ruptured aneurysm, pulmonary embolism, amputation (except for trauma and malignancy), following cardiac or vascular procedure/operation, or any death not classified as non-cardiovascular. Hospitalization for HF was diagnosed if caused by presence of signs and symptoms of HF. New-onset HF was defined as the presence of new signs and symptoms of HF confirmed by non-invasive or hemodynamic measurements, and not requiring hospital admission.

Statistical analysis

Baseline characteristics are presented for all patients and split by occurrence of the primary outcome. Continuous variables are described using mean ± standard deviation and compared between groups using t-tests, whilst counts and percentages are used to describe categorical variables which were compared between groups using Chi-Square tests for association. Kaplan-Meier curves were generated for both the primary and the secondary outcomes and are shown as incidence curves.

For the primary outcome, univariate Cox regression models were fitted using each of the baseline characteristics to evaluate their independent association with outcome, with hazard ratios and corresponding 95% confidence intervals reported. Multivariable Cox regression models were then fitted to further assess the associations. A stepwise procedure was used in which all selected baseline covariates were permitted entry into the starting model and then sequentially removed, and in turn considered for re-entry, based on the covariate p-value. A 5% significance level was set and the final model was obtained when no more

covariates met the removal or re-entry significance threshold. A multivariable Cox regression model was then fitted for the secondary outcome using the same covariates obtained from the final stepwise primary outcome model. Forest plots were generated displaying hazard ratios, 95% confidence intervals and p-values for the covariates from the final stepwise model for the primary outcome, and from the corresponding model for the secondary outcome.
Analysis was conducted in SAS Version 9.4 and R Version 3.3.3.

All statistical analyses were performed by the independent centre (Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK).

Results

Patient characteristics

In the whole CLARIFY registry population (N = 32703), 5-year follow-up was available in 32378 (99.0%) patients. A history of hospitalization for HF or current HF symptoms was present at baseline in 5607 (17.3%) patients. These patients were excluded. Finally, 26769 patients were included in the current analysis (Figure 1). Patient characteristics at baseline are presented in Table 1. Mean patients' age was 64.2±10.4 years, and 78.4% were male. Their ethnicity was differentiated, with around 60% of Caucasian, and 20% of Asian origin. Nearly 60% of patients were current or former smokers, pproximately 30% had diabetes, around 70% had hyperlipidaemia or hypertension, and more than 70% were obese or overweight. Almost 60% of patients had a history of MI and/or myocardial revascularization, and only a minority had CCS class ≥2 angina or documented chest pain with myocardial ischemia. Blood pressure and heart rate were relatively well controlled. Among those with available data (N=19397, 72.5%), atrial fibrillation was present in 2.6%, and paced rhythm in 1.3% of patients. Left ventricular ejection fraction measured by echocardiography (available in N=17654, 65.9%), was normal in 74.7%, mildly depressed (40-50%) in 20.6%, and severely depressed (<40%) in 4.7% of patients. Among patients who underwent coronary angiography (N=23721, 88.6%)

54% had multivessel coronary disease. The use of guideline recommended medical therapy was high. Antiplatelet treatment was prescribed in 95.7%, lipid-lowering drugs in 92.6%, and beta-blockers in 73.7% of registry participants.

Clinical outcomes

During follow-up, 4393 patients (16.4%) reached the primary outcome of CV death, hospitalization for HF or new HF symptoms not requiring hospital admission. There were substantial differences between those with and without the primary outcome (Table 1). Kaplan-Meier curves for the primary and secondary outcome are provided in Figure 2. The overall clinical outcomes are presented in Table 2. In addition, outcomes by sex and race are shown in Supplementary Tables 1 and 2. The combination of CV death and hospitalization for HF occurred in 6.4%, all-cause death in 6.6%, and CV death in 4.1% of patients (61.4% of all deaths). Among 3022 patients (11.3%) who presented with new-onset HF symptoms, HF hospitalization was subsequently necessary in 210, and CV death occurred in 196 (6.9 and 6.5% of this group, respectively). In 522 subjects (2.0%) HF hospitalization was the initial event, counted as a component of primary outcome. In addition, 210 subjects required HF hospitalization after the initial HF diagnosis. Eventually, out of the 4393 patients who reached the primary outcome 732 (16.7%, or 2.8% of the entire study population) underwent hospitalization for HF.

Factors predicting heart failure outcomes

Figure 3 shows predictors of the primary outcome. Age over 70 years, left ventricular ejection fraction <50%, CCS class $\geq$2 angina, atrial fibrillation or paced rhythm on the ECG, body mass index <20, and a history of stroke, were the most robust predictors of the primary outcome. Female sex, current or former smoking, hypertension, asthma/COPD, diabetes, obesity, peripheral artery disease, carotid disease, inadequate heart rate control, systolic blood pressure over 140 or under 120 mmHg, multiple vessel disease, previous MI and coronary

arteriography not done were also associated with increased risk of the primary outcome. At the same time, age <50 years, Asian ethnicity, and PCI, were associated with reduced risk of the outcome. Primary outcome according to the availability and value of baseline EF is shown in Supplementary Table 3.

Since subjects with coronary artery disease are at risk of recurrent coronary events, interim acute coronary events were additionally considered. In 154 patients we identified a myocardial infarction occurring since baseline up to the year of new HF onset. Adding this information to the previous results from the stepwise model for the primary outcome indicated that incident MI was significantly associated with the primary outcome ($p<0.0001$), in addition to MI as recorded from medical history, which also remained statistically significantly associated with the primary outcome.

Predictors of the secondary outcome including CV death and heart failure hospitalization are shown in Figure 4. Most predictors were identical, but in comparison to the primary outcome, Hispanic ethnicity appeared as a new positive and CABG as a negative independent predictor, and the association with sex, obesity, history of hypertension, blood pressure and carotid disease was no longer present.

In addition, predictors of the combined endpoint including new-onset HF and HF hospitalization are shown in Supplementary Figure 1. This endpoint is primarily driven by HF not requiring hospitalization, and does not include CV death, that might not have been HF-related. The determinants did not differ from those for the primary and secondary endpoints.

Discussion

Most studies in patients with stable CAD focus on outcomes directly related to atherothrombosis, such as CV death, myocardial infarction and stroke [2,8,10,18-21], but the presence of HF is recognized as an important prognostic factor [10-12]. However, data on HF incidence are generally limited to patients requiring hospitalization [6,11,13,14]. The key

novel aspect of the present analysis is the reported onset of HF not requiring hospitalization in the setting of real life practice.

In the present study of ambulatory patients with chronic CAD, free from HF at baseline, at 5-year follow up approximately one in six patients (16.4%) achieved the primary composite outcome including CV death, hospitalization for HF and new-onset HF. These 16.4% add to the 17.3% of patients with prior HF (whom we excluded from this analysis), indicating that approximately a third of patients with chronic CAD are affected by HF.

The secondary outcome was the more standard combination of CV death and HF hospitalization. It was reached by 6.4% of patients, indicating that most cases of incident HF would have been missed if only HF hospitalizations and CV deaths had been taken into consideration. Of note, the BIOSTAT-CHF study compared the outcome in inpatients versus outpatients with HF. Although inpatients were generally sicker, a substantial proportion of outpatients had similar or higher event rates compared to inpatients [84].

Importantly, while almost 14% of patients developed HF, only less than one fifth of them required hospitalization. Lamblin et al. [11] have recently analysed the incidence of hospitalization for heart failure in the CORONOR registry. During the 5-y follow-up 5.7% of patients were hospitalized for HF, around twice as many as in our study. This difference may reflect a less severe course of heart failure in our patients, the current trend to use out-of-hospital management strategies, or differences in patient selection. In any case, it indicates that the group of patients with new-onset HF with no need for hospitalization should not be neglected.

We identified a number of predictors of the primary outcome. Some, such as older age, decreased LVEF, atrial fibrillation, higher body mass index, diabetes, history of hypertension, angina, and multivessel CAD, have been previously shown to predict HF hospitalization in the CORONOR registry [11]. We previously described the detrimental effect of angina

symptoms on the outcome including CV death, MI or stroke in patients with chronic CAD [22]. Heart failure outcomes, however, were not analyzed. In agreement with our findings, in the REACH registry, patients with angina were at increased risk of HF [23].

The effect of revascularization on the incidence of HF remains ambiguous. Available data on the impact of different modes of coronary revascularization versus optimal medical treatment differ between randomized trials and observational data [24]. Contrary to previous reports [4,24], we found that previous PCI was associated with decreased HF incidence. Interestingly, in the REACH registry, PCI (but not CABG) was linked to a lower risk of CV death [25], although this may reflect selection of lower risk patients for PCI. However, heart failure outcomes were not included in their analysis. In addition to the factors that have previously been shown to have an impact on development of HF, we found that female sex, systolic blood pressure <120 mmHg, inadequate heart rate control, paced rhythm and any of the reversible CV risk factors are predictive of the primary outcome, while Asian ethnicity appears to show lower propensity for HF.

Our population is representative of contemporary patients with CCS and without heart failure at baseline, managed in an ambulatory setting in different geographical areas. In the present study, the rate of all-cause death at 5 years was lower than in CORONOR [26] and in CALIBER [10] studies (6.6% vs 16.2 and 20.6%, respectively). Similarly to our findings, in both CORONOR [18,26] and CALIBER [10] a substantial proportion of deaths were non-cardiovascular.

It should be noted that the definition of chronic CAD encompasses a wide spectrum of patients, and their outcomes are highly dependent on the clinical setting and entry criteria (hospitalized vs ambulatory patients, inclusion of patients with heart failure etc.). Trullas et al. [27] showed that in the registry setting, even in patients with similar clinical characteristics,

HF outcomes may significantly differ. Therefore, in the case of a complex and heterogeneous disease such as HF, the results of registries must be interpreted with caution.

Strengths and limitations of the study

Strengths. This paper is based on data from the large, contemporary, international CLARIFY registry, well reflecting real-world management of ambulatory patients with chronic CAD. In the current analysis we used a wide definition of HF, including patients with no need for hospitalization, but with the HF diagnosis confirmed by non-invasive or hemodynamic assessment. This group of patients is of increasing importance, because they represent an early stage of the disease, whose management may prevent future CV events. In addition, there is a growing trend to avoid hospitalization of patients with HF, and exclusion of this group might significantly distort the image of HF outcomes.

Limitations. Our study shares the limitations of observational analyses, with their potential intrinsic biases. In CLARIFY, every effort was made to collect accurate data, but only a limited number of centres were directly monitored throughout the study. Outcome events were investigator reported and did not undergo central adjudication. We were unable to differentiate between HF with reduced versus preserved EF. Since HF events were not adjudicated, some cases of HF hospitalization could have been due to acute coronary events. Confirmation of HF by non-invasive or haemodynamic measurements was specified in the protocol, but there was no requirement for the investigators to describe the imaging tool and the findings at the time of HF diagnosis. However, the close similarity between predictors of the primary and secondary outcome supports the concept that the diagnosis of new-onset HF without hospital admission was generally correct.

Conclusion

Data from this contemporary registry of ambulatory patients with chronic CAD indicate that during the 5-year follow-up a relatively large proportion of ambulatory patients

with chronic CAD and no known HF will develop heart failure, which only infrequently requires hospitalization. Patients with left ventricular ejection fraction <50%, CCS class ≥2 angina, atrial fibrillation or paced rhythm on the ECG, body mass index <20, and a history of stroke, were at the highest risk of reaching the primary outcome). Early identification of patients with HF may lead to early treatment institution, and potentially help to further decrease mortality and morbidity in ambulatory patients with chronic CAD. This concept needs confirmation in future studies.

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Conflict of Interest

Dr. Parma reports personal fees from Servier, outside the submitted work.

Mr Jasilek has nothing to disclose.

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Dr. Ferrari reports grants and personal fees from SERVIER INTERNATIONAL, personal fees from MERCK SERONO, grants and personal fees from NOVARTIS, personal fees from LUPIN, personal fees from CIPLA, personal fees from PFIZER, personal fees from SPASPA, personal fees from DOC GENERICI, personal fees from ALPHA SIGMA, personal fees from BAYER, personal fees from BOEHRINGER INGELHEIM, outside the submitted work.

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Dr. Tendera reports personal fees from Servier, during the conduct of the study; personal fees from Bayer, personal fees from Cadila Pharmaceuticals, personal fees from Janssen-Cilag, personal fees from Kowa, personal fees from PERFUSE Group, personal fees from Servier, personal fees from UCB Pharmaceuticals, outside the submitted work.

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Figure legends

Figure 1. Patient flow

Figure 2. Kaplan-Meier curves for the primary and secondary outcome

Figure 3. Multivariable predictors of the primary outcome (CV death, hospitalization for heart failure or new heart failure symptoms)

Figure 4. Multivariable predictors of the secondary outcome (CV death or hospitalization for heart failure)

Supplementary Figure 1. Multivariable predictors of the combined outcome including new heart failure symptoms and hospitalization for heart failure

Tables

Table 1. Patient characteristics at baseline

Parameter (number of patients with data available)	**Total N = 26769**	**Primary outcome N = 4393**	**No primary outcome N = 22376**	**P value Primary outcome vs no primary outcome**
Demographic characteristics				
Age, years (N = 26 763); mean (SD)	64.2 (10.4)	66.8 (10.7)	63.7 (10.3)	<0.0001
Male sex (N = 26 767); N (%)	20976 (78.4)	3 297 (75.1)	17679 (79.0)	<0.0001
Ethnicity (N = 26769); N (%)				<0.0001
Caucasian	16452 (61.5)	3173 (72.2)	13279 (59.3)	
Asian	5524 (20.6)	651 (14.8)	4873 (21.8)	
Hispanic	1434 (5.4)	223 (5.1)	1211 (5.4)	
Black/African	283 (1.1)	43 (1.0)	240 (1.1)	
Unknown	3076 (11.5)	303 (6.9)	2773 (12.4)	
Cardiovascular risk factors; N (%)				
Dyslipidaemia (N = 26767)	19924 (74.4)	3331 (75.8)	16593 (74.2)	0.0209
Hypertension (N = 26767)	18521 (69.2)	3388 (77.1)	15133 (67.6)	<0.0001
Diabetes (N = 26767)	7694 (28.7)	1525 (34.7)	6169 (27.6)	<0.0001
Medical history; N (%)				
Myocardial infarction (N =	15316 (57.2)	2707 (61.6)	12609 (56.4)	<0.0001

26769)				
Myocardial revascularization (N = 26769)				<0.0001
CABG or PCI	21011 (78.5)	3195 (72.7)	17916 (79.6)	
Both CABG and PCI	1777 (6.6)	357 (8.1)	1420 (6.3)	
PCI only	14860 (55.5)	1986 (45.2)	12874 (57.5)	
CABG only	4374 (16.3)	852 (19.4)	3522 (15.7)	
PAD (N = 26767)	2369 (8.9)	592 (13.5)	1777 (7.9)	<0.0001
Carotid disease (N = 26769)	1842 (6.9)	432 (9.8)	1410 (6.3)	<0.0001
Stroke (N = 26768)	945 (3.5)	265 (6.0)	680 (3.0)	<0.0001
Asthma/COPD (N = 26769)	1801 (6.7)	429 (9.8)	1372 (6.1)	<0.0001
Symptomatic status (N = 26768)				
Angina CCS class ≥II	2567 (9.6)	749 (17.0)	1818 (8.1)	<0.0001
Cardiac parameters; N (%)				
Heart rate, bpm (N + 26747)				<0.0001
<60	4681 (17.5)	674 (15.3)	4007 (17.9)	
60-80	19452 (72.7)	3218 (73.3)	16234 (72.6)	
>80	2614 (9.8)	499 (11.4)	2115 (9.5)	
Systolic BP, mmHg (N = 26749)				<0.0001
<120	4910 (18.4)	784 (17.9)	4126 (18.5)	
120-140	16600 (62.1)	2619 (59.6)	13981 (62.5)	
>140	5239 (19.6)	989 (22.5)	4250 (19.0)	
Diastolic BP, mmHg (N =				<0.0001

26749)				
<70	4137 (15.5)	771 (17.6)	3366 (15.1)	
70-90	21294 (79.6)	3378 (76.9)	17916 (80.1)	
>90	1318 (4.9)	243 (5.5)	1075 (4.8)	
Heart rhythm (ECG) (N = 26769)				<0.0001
Sinus	18623 (69.6)	3030 (69.0)	15593 (69.7)	
Atrial fibrillation	514 (1.9)	170 (3.9)	344 (1.5)	
Paced	260 (1.0)	104 (2.4)	156 (0.7)	
Not available	7372 (27.5)	1089 (24.8)	6283 (28.1)	
LV ejection fraction; % (N = 26769)				<0.0001
>50	13190 (49.3)	1913 (43.5)	11277 (50.4)	
40-50	3640 (13.6)	879 (20.0)	2761 (12.3)	
<40	824 (3.1)	290 (6.6)	534 (2.4)	
Not available	9115 (34.1)	1311 (29.8)	7804 (34.9)	
Number of arteries with >50% stenosis on angiography (N = 26741)				<0.0001
0	851 (3.2)	137 (3.1)	714 (3.2)	
1	10061 (37.6)	1339 (30.5)	8722 (39.0)	
2-3	12809 (47.9)	2229 (50.8)	10580 (47.3)	
Angiography not done	3020 (11.3)	685 (15.6)	2335 (10.4)	

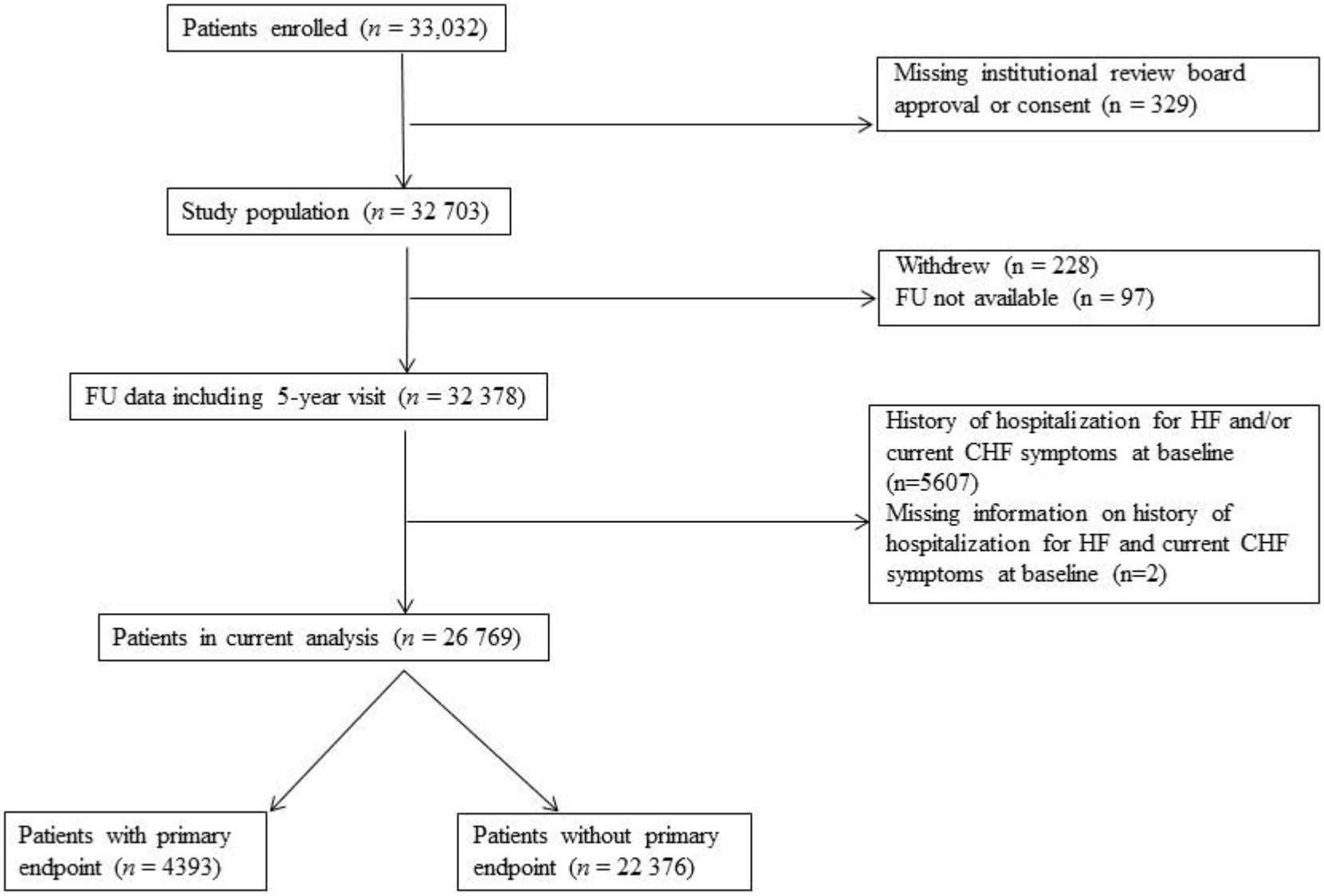
Abbreviations: BP – blood pressure; bpm – beats per minute; CABG – coronary artery bypass grafting; CCS – Canadian Cardiovascular Society; COPD – chronic obstructive pulmonary

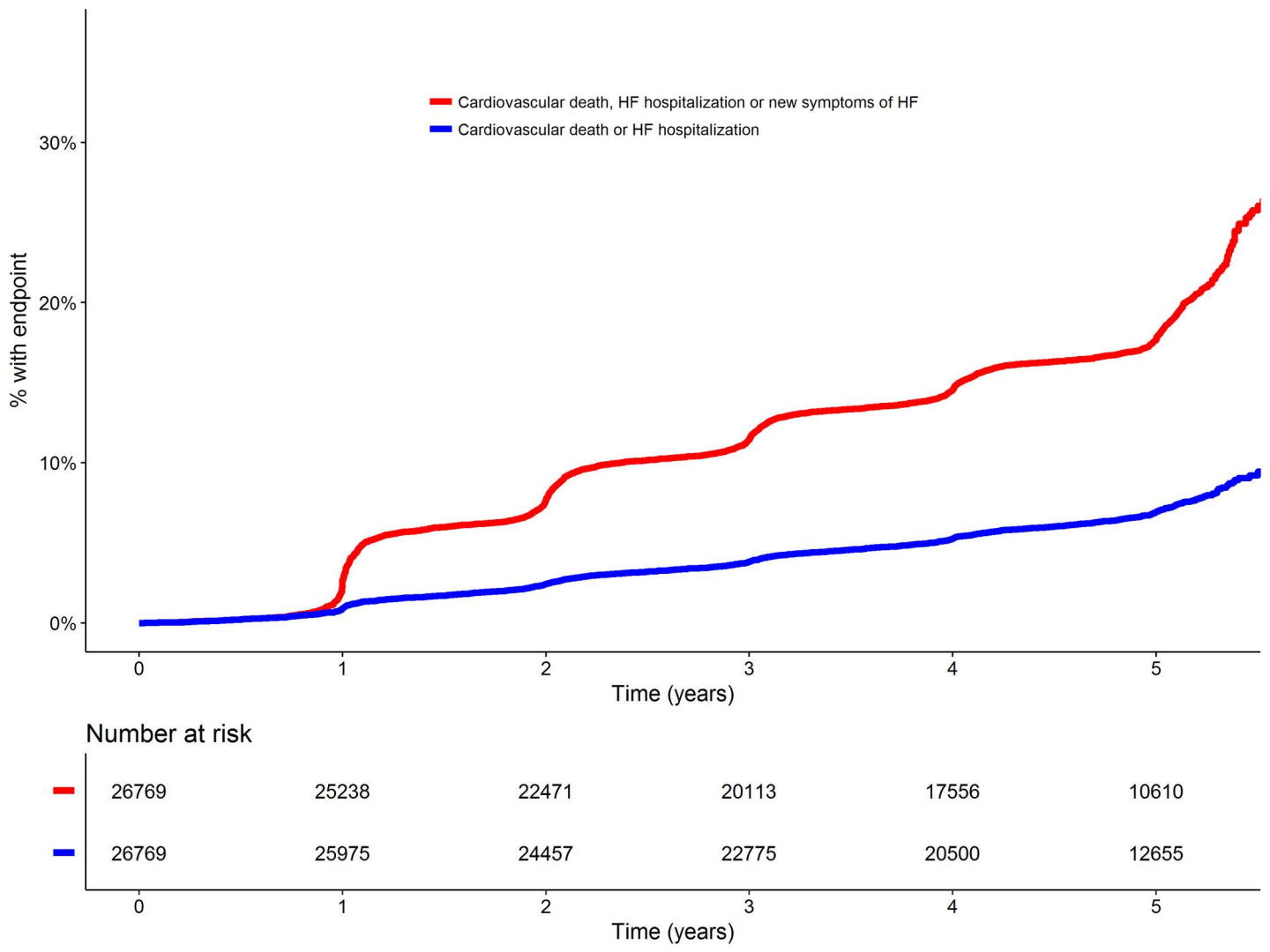
disease; LV – left ventricle; PAD – peripheral artery disease; PCI – percutaneous coronary intervention.

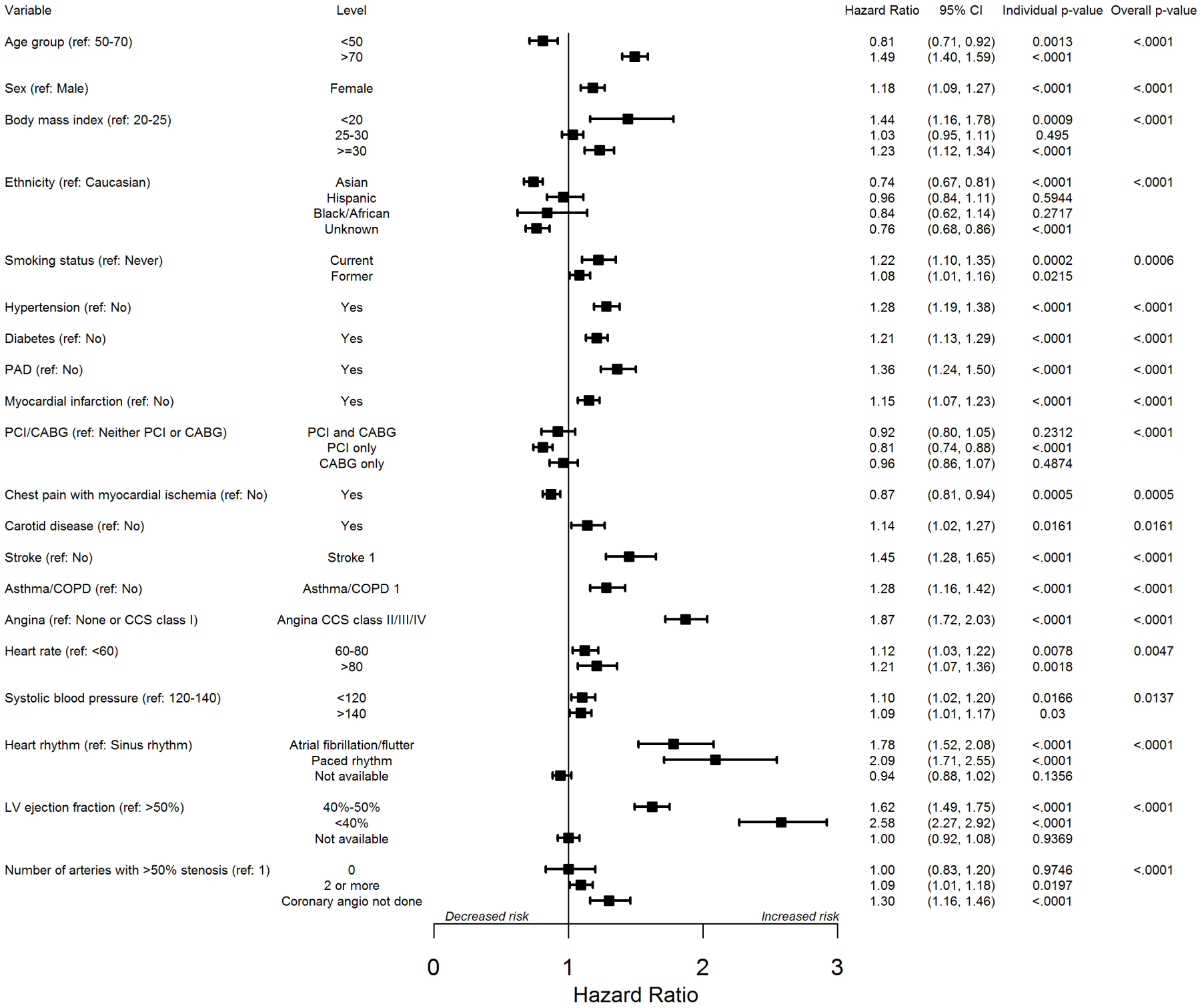
Table 2. Clinical outcomes

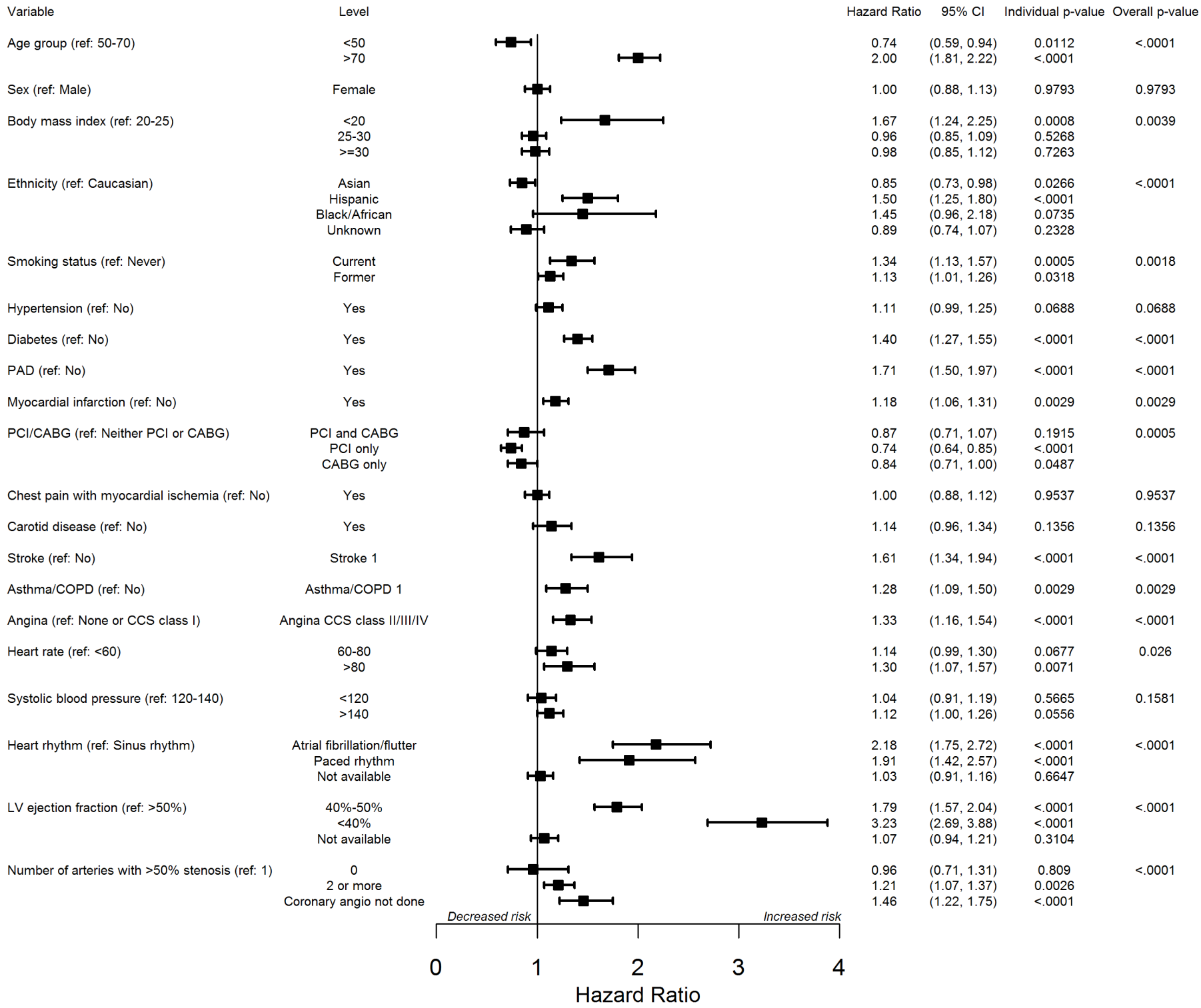
Outcome	All subjects (N = 26769)	
	N (%)	Incidence rate per 1000 PY
CV death, hospitalization for HF, or new HF symptoms	4393 (16.4)	41.1
CV death or hospitalization for HF	1712 (6.4)	14.6
Hospitalization for HF or new HF symptoms	3544 (13.7)	33.6
All-cause death	1776 (6.6)	14.9
CV death	1090 (4.1)	9.2
Hospitalization for HF	732 (2.8)	6.3
New-onset HF symptoms^	3022 (11.6)	28.6

CV – cardiovascular; HF – heart failure; PY – patient-years; ^ - patients in whom new HF symptoms and hospitalization for HF were reported on the same day are reported as HF hospitalization only.


Patients enrolled (n = 33,032)
Missing institutional review board approval or consent (n = 329)
Study population (n = 32 703)
Withdrew (n = 228)
FU not available (n = 97)
FU data including 5-year visit (n = 32 378)
History of hospitalization for HF and/or current CHF symptoms at baseline (n=5607)
Missing information on history of hospitalization for HF and current CHF symptoms at baseline (n=2)
Patients in current analysis (n = 26 769)
Patients with primary endpoint (n = 4393)
Patients without primary endpoint (n = 22 376)


Cardiovascular death, HF hospitalization or new symptoms of HF
Cardiovascular death or HF hospitalization
30%
20%
10%
0%
% with endpoint
0
1
2
3
4
5
Time (years)
Number at risk
26769
25238
22471
20113
17556
10610
26769
25975
24457
22775
20500
12655
0
1
2
3
4
5
Time (years)


Variable
Level
Hazard Ratio
95% CI
Individual p-value
Overall p-value
Age group (ref: 50-70)
<50
0.81
(0.71, 0.92)
0.0013
<.0001
>70
1.49
(1.40, 1.59)
<.0001
Sex (ref: Male)
Female
1.18
(1.09, 1.27)
<.0001
<.0001
Body mass index (ref: 20-25)
<20
1.44
(1.16, 1.78)
0.0009
<.0001
25-30
1.03
(0.95, 1.11)
0.495
>=30
1.23
(1.12, 1.34)
<.0001
Ethnicity (ref: Caucasian)
Asian
0.74
(0.67, 0.81)
<.0001
<.0001
Hispanic
0.96
(0.84, 1.11)
0.5944
Black/African
0.84
(0.62, 1.14)
0.2717
Unknown
0.76
(0.68, 0.86)
<.0001
Smoking status (ref: Never)
Current
1.22
(1.10, 1.35)
0.0002
0.0006
Former
1.08
(1.01, 1.16)
0.0215
Hypertension (ref: No)
Yes
1.28
(1.19, 1.38)
<.0001
<.0001
Diabetes (ref: No)
Yes
1.21
(1.13, 1.29)
<.0001
<.0001
PAD (ref: No)
Yes
1.36
(1.24, 1.50)
<.0001
<.0001
Myocardial infarction (ref: No)
Yes
1.15
(1.07, 1.23)
<.0001
<.0001
PCI/CABG (ref: Neither PCI or CABG)
PCI and CABG
0.92
(0.80, 1.05)
0.2312
<.0001
PCI only
0.81
(0.74, 0.88)
<.0001
CABG only
0.96
(0.86, 1.07)
0.4874
Chest pain with myocardial ischemia (ref: No)
Yes
0.87
(0.81, 0.94)
0.0005
0.0005
Carotid disease (ref: No)
Yes
1.14
(1.02, 1.27)
0.0161
0.0161
Stroke (ref: No)
Stroke 1
1.45
(1.28, 1.65)
<.0001
<.0001
Asthma/COPD (ref: No)
Asthma/COPD 1
1.28
(1.16, 1.42)
<.0001
<.0001
Angina (ref: None or CCS class I)
Angina CCS class II/III/IV
1.87
(1.72, 2.03)
<.0001
<.0001
Heart rate (ref: <60)
60-80
1.12
(1.03, 1.22)
0.0078
0.0047
>80
1.21
(1.07, 1.36)
0.0018
Systolic blood pressure (ref: 120-140)
<120
1.10
(1.02, 1.20)
0.0166
0.0137
>140
1.09
(1.01, 1.17)
0.03
Heart rhythm (ref: Sinus rhythm)
Atrial fibrillation/flutter
1.78
(1.52, 2.08)
<.0001
<.0001
Paced rhythm
2.09
(1.71, 2.55)
<.0001
Not available
0.94
(0.88, 1.02)
0.1356
LV ejection fraction (ref: >50%)
40%-50%
1.62
(1.49, 1.75)
<.0001
<.0001
<40%
2.58
(2.27, 2.92)
<.0001
Not available
1.00
(0.92, 1.08)
0.9369
Number of arteries with >50% stenosis (ref: 1)
0
1.00
(0.83, 1.20)
0.9746
<.0001
2 or more
1.09
(1.01, 1.18)
0.0197
Coronary angio not done
1.30
(1.16, 1.46)
<.0001
Decreased risk
Increased risk
0
1
2
3
Hazard Ratio


Variable
Level
Hazard Ratio
95% CI
Individual p-value
Overall p-value
Age group (ref: 50-70)
<50
0.74
(0.59, 0.94)
0.0112
<.0001
>70
2.00
(1.81, 2.22)
<.0001
Sex (ref: Male)
Female
1.00
(0.88, 1.13)
0.9793
0.9793
Body mass index (ref: 20-25)
<20
1.67
(1.24, 2.25)
0.0008
0.0039
25-30
0.96
(0.85, 1.09)
0.5268
>=30
0.98
(0.85, 1.12)
0.7263
Ethnicity (ref: Caucasian)
Asian
0.85
(0.73, 0.98)
0.0266
<.0001
Hispanic
1.50
(1.25, 1.80)
<.0001
Black/African
1.45
(0.96, 2.18)
0.0735
Unknown
0.89
(0.74, 1.07)
0.2328
Smoking status (ref: Never)
Current
1.34
(1.13, 1.57)
0.0005
0.0018
Former
1.13
(1.01, 1.26)
0.0318
Hypertension (ref: No)
Yes
1.11
(0.99, 1.25)
0.0688
0.0688
Diabetes (ref: No)
Yes
1.40
(1.27, 1.55)
<.0001
<.0001
PAD (ref: No)
Yes
1.71
(1.50, 1.97)
<.0001
<.0001
Myocardial infarction (ref: No)
Yes
1.18
(1.06, 1.31)
0.0029
0.0029
PCI/CABG (ref: Neither PCI or CABG)
PCI and CABG
0.87
(0.71, 1.07)
0.1915
0.0005
PCI only
0.74
(0.64, 0.85)
<.0001
CABG only
0.84
(0.71, 1.00)
0.0487
Chest pain with myocardial ischemia (ref: No)
Yes
1.00
(0.88, 1.12)
0.9537
0.9537
Carotid disease (ref: No)
Yes
1.14
(0.96, 1.34)
0.1356
0.1356
Stroke (ref: No)
Stroke 1
1.61
(1.34, 1.94)
<.0001
<.0001
Asthma/COPD (ref: No)
Asthma/COPD 1
1.28
(1.09, 1.50)
0.0029
0.0029
Angina (ref: None or CCS class I)
Angina CCS class II/III/IV
1.33
(1.16, 1.54)
<.0001
<.0001
Heart rate (ref: <60)
60-80
1.14
(0.99, 1.30)
0.0677
0.026
>80
1.30
(1.07, 1.57)
0.0071
Systolic blood pressure (ref: 120-140)
<120
1.04
(0.91, 1.19)
0.5665
0.1581
>140
1.12
(1.00, 1.26)
0.0556
Heart rhythm (ref: Sinus rhythm)
Atrial fibrillation/flutter
2.18
(1.75, 2.72)
<.0001
<.0001
Paced rhythm
1.91
(1.42, 2.57)
<.0001
Not available
1.03
(0.91, 1.16)
0.6647
LV ejection fraction (ref: >50%)
40%-50%
1.79
(1.57, 2.04)
<.0001
<.0001
<40%
3.23
(2.69, 3.88)
<.0001
Not available
1.07
(0.94, 1.21)
0.3104
Number of arteries with >50% stenosis (ref: 1)
0
0.96
(0.71, 1.31)
0.809
<.0001
2 or more
1.21
(1.07, 1.37)
0.0026
Coronary angio not done
1.46
(1.22, 1.75)
<.0001
Decreased risk
Increased risk
0
1
2
3
4
Hazard Ratio