

Ischemic heart failure as a complication of incident acute myocardial infarction: timing and time trends – a national analysis including 78 814 Danish patients during 2000-2009

Running title: Trends in heart failure following acute myocardial infarction

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Abstract

Aim: Heart failure (HF) is a serious complication of acute myocardial infarction (AMI) leading to poor prognosis. We aimed at exploring time trends of HF and its impact on mortality among patients with an incident AMI.

Methods: We collected from the National Patient Danish Registry (NPDR) all patients hospitalized with an incident AMI during 2001-2009 and identified cases with in-hospital HF (presented on admission or developing HF during AMI hospitalization) or post-discharge HF (an hospitalization or outpatient visit following AMI discharge) and assessed in-hospital, 30-day and one-year mortality.

Results: Of 78 814 patients included in the study, 10 248 (13.0%) developed in-hospital HF. The odds of in-hospital HF declined 0.9% per year [odds ratio (OR)=0.991, 95% CI: 0.983–0.999]. In-hospital HF was associated with 13% (OR=1.13, 95% CI: 1.06–1.20) and 14% (OR=1.14, 95% CI: 1.07–1.20) higher in-hospital and 30-day mortality, respectively.

Of 61 637 patients discharged alive, without in-hospital HF, 5978 (9.7%) experienced post-discharge HF; 4116 (6.7%) were hospitalized and 1862 (3.0%) diagnosed at outpatient clinics. The risk of HF requiring hospitalization declined 5.5% per year [hazard ratio (HR)=0.945, 95% CI: 0.934–0.955] while the risk of HF diagnosed at outpatient clinics increased 13.4% per year (HR=1.134, 95% CI: 1.115–1.153). Post-discharge HF was associated with 239% (HR=3.39, 95% CI: 3.18–3.63) higher one-year mortality.

Conclusion: In-hospital and post-discharge HF requiring hospitalization decreased while post-discharge HF diagnosed at outpatient clinics increased among incident AMI patients during 2000-2009. The development of HF - especially after AMI discharge - indicate a poor prognosis.

Keywords: Heart failure; Time trends; Prognostic significance; Acute myocardial infarction; Denmark.

Introduction

Heart failure (HF) is a serious health condition affecting 38 million patients worldwide ¹. Its prevalence is increasing ² due to improved survival of cardiac patients and aging of the population.

Coronary heart disease (CHD) is the most common underlying condition for HF ^{3,4}. The risk of HF is influenced by many factors, including clinical presentation and anatomical extent of CHD, quality of acute coronary care, prior use of cardiac drugs in the primary and secondary prevention setting and burden of comorbidities. The complex interplay between these factors - each displaying individual trends - make it difficult the prediction of trends of HF over time in coronary patients. This, is reflected by the discrepant results of published studies, with some demonstrating increases ^{5,6} and others declines ⁷⁻¹⁰ in the risk of HF among coronary patients.

The negative effect of HF among AMI patients has mainly been studied in association with short-term mortality ¹¹⁻¹³. Few studies have extended the follow up beyond discharge. Of those, some did not distinguish between in-hospital or post-discharge HF ^{9,14} and others included a mixture of incident and prevalent AMI cases ¹⁵. A recent nationwide analysis from Norway focusing on the excess mortality associated with post-discharge HF, could only identify HF cases requiring hospitalization due to the lack of data from outpatient clinics ¹⁶.

Using data from the Danish National Patient Registry (DNPR) we aimed at i) exploring trends in the risk of HF (separately for in-hospital and post-discharge HF) as a complication of an incident AMI and ii) assessing the prognostic impact of HF on short and long-term mortality after an AMI, with additional focus on its potential changes over time.

Materials and methods

The DNPR has collected information on in-patients from all somatic (from 1977) and psychiatric (from 1995) hospitals as well as outpatient contacts (from 1995) in Denmark. Detailed information on the content, structure and quality of data in the registry is provided here ¹⁷. Shortly, data in the DNPR include patient's age, gender, admission and discharge dates, one primary and all secondary discharge diagnoses as well as information on medical diagnostic and treatment procedures.

The positive predictive values (PPV) of first time AMI in the DNPR is >90%¹⁸ while the HF diagnosis has a somehow lower PPV (80%)^{18 19} but a very high specificity (99%)¹⁹. Cardiac procedures relevant to this study have a very high PPV (100% for coronary angiography and 98% for PCI and CABG)²⁰.

The Danish Civil Registration System was established in 1968 for administrative purposes ²¹. It assigns a unique Civil Personal Register number to all persons residing in Denmark, allowing individual-level linkages between different registers.

For these analyses, we identified all Danish residents ≥ 40 years, hospitalized with an incident AMI (ICD–10 codes, I21, I22) as the primary discharge diagnosis from 1 January 2000 to 31 December 2009. We excluded from the analyses patients a) with history of HF (ICD–10 codes, I11.0, I13.0, I13.2, I42.0, I42.2; I42.6; I42.7, I42.8; I42.9; I50.0; I50.1; I50.2; I50.3; I50.8 and I50.9) prior to incident AMI hospitalization, b) missing information on age and/or gender and c) unusually long hospital stays ($> 99^{\text{th}}$ percentile of the hospital stay distribution).

Clinically relevant complications during the incident of AMI included pulmonary edema (J81), cardiogenic shock (R57.0), second (I44.1) or third (I44.2) degree atrioventricular block (AV), ventricular fibrillation (I49.0) or mechanical complication (I23).

We followed patients up to one year from incident AMI discharge. New episodes of HF were classified based on their timing in relation to the incident AMI hospitalization into two mutually exclusive categories; HF presented on admission or developing during AMI hospitalization (in-hospital HF) and a new hospitalization or outpatient visit with a HF diagnosis following AMI discharge (post-discharge HF). In the analyses of post-discharge HF, we included only patients discharged without in-hospital HF from the incident AMI hospitalization.

The diagnosis of HF was based on ICD–10 codes suggestive for HF (I11.0, I13.0, I13.2, I42.0, I42.2; I42.6; I42.7, I42.8; I42.9; I50.0; I50.1; I50.2; I50.3; I50.8 and I50.9).

We estimated the excess mortality associated with HF by calculating the ratio of risk of dying between AMI patients with HF and those without HF. We estimated the impact of in-hospital HF on in-hospital and 30-day mortality and the impact of post-discharge HF on one-year mortality.

Data analyses

Categorical variables are presented as proportions and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR).

Trends of in-hospital HF were explored using logistic regression and results presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). To account for the potential competing effect of early deaths on in-hospital HF occurrence, we conducted additional analyses, including only patients who survived the first AMI hospitalization day.

Trends of post-discharge HF were explored using Cox regression models and results presented as hazard ratios (HRs) and corresponding 95% CIs. In addition to overall analyses, we stratified the analyses on the diagnostic settings of HF (hospitalization vs outpatient contacts).

The impact of in-hospital HF on early (in-hospital and 30-day) mortality was explored using logistic regression. The impact of post-discharge HF on one-year mortality was explored using Cox models with HF as a time-varying covariate.

Models were adjusted for age, sex and relevant comorbidities which a) predict HF^{3 22} [hypertension, (ICD–10 codes, I10–I15), diabetes mellitus (DM) (ICD–10 codes, E10–E14), renal failure (ICD–10 codes, N17–N19), chronic obstructive pulmonary disease (COPD) (ICD–10 codes, J40–J44, J47), valvular heart disease (ICD–10 codes, I05–I09; I34–I35) and atrial fibrillation (ICD–10 code, I48)] and b) showed different distribution among AMI patients across study years. These covariates were identified through discharge diagnoses (primary or secondary) from previous hospitalizations or outpatient visits within five years prior to, or during the incident AMI hospitalization.

Results

Study population and excluding criteria

Information on selecting procedures, study population and outcomes is provided in Figure 1. Of 86 055 eligible patients, 1224 patients lacked information on age and gender, 5206 patients had history of HF and 811 patients had long AMI hospital stays. At the end, 78 814 patients were included in the analyses.

Baseline characteristics of study participants

Patients' age declined while the prevalence of comorbidities increased over the study period. The proportion of patients with AMI complications was generally low and did not show a clear trend while utilization of invasive coronary procedures increased substantially over time (Table 1). The length of AMI hospitalization shortened over time in both men and women (both age-adjusted $P_{\text{trend}} < 0.001$) (Supplemental material, Table S1).

Time trends in heart failure

Overall, 13.0% of AMI patients developed in-hospital HF (Table 2). Adjusted analyses revealed a relatively small decline in the odds of in-hospital HF (0.9% per year; $P_{\text{trend}} < 0.001$) (Figure 2). Restricting the analyses to 76 874 patients surviving the first hospitalization day, yielded very similar results to those of the main analyses (a decline of 1.0% per year; $P_{\text{trend}} < 0.001$).

Of patients discharged alive, without in-hospital HF, another 9.7% developed post-discharge HF (Table 2). The adjusted risk of overall post-discharge HF did not change significantly during the study period (Supplemental material, Figure S1). When analyzed separately, the risk of HF requiring hospitalization declined 5.5% per year while the risk of HF diagnosed in outpatient settings increased 13.4% per year (both $P_{\text{trend}} < 0.001$) (Figure 3).

HF cases requiring hospitalizations outnumbered those diagnosed at outpatient clinics. Over time, the diagnostic settings of post-discharge HF shifted from hospitals to outpatient clinics (Supplemental material, Table S2). To illustrate, the proportion of post-discharge HF cases required hospitalization dropped from 82.0% in 2000-2001 to 53.3% in 2008-2009.

The baseline characteristics of patients with post-discharge HF according to diagnostic setting are given in the Supplemental material (Table S3). Hospitalized cases were older, more often women, had a higher burden of comorbidities and received less often invasive coronary procedures compared to patients diagnosed with HF at outpatient clinics. We observed a shorter time from AMI discharge to HF diagnosis for outpatient contacts compared to those requiring hospitalization. (Supplemental material, Table S3).

Prognostic impact of heart failure

Overall, 10.7% of patients did not survive the incident AMI hospitalization. Among patients discharged without in-hospital HF, 9.6% died within one year from AMI discharge (Table 2).

Among AMI patients without in-hospital HF, 10.1% died at the hospital. The corresponding proportion among those with in-hospital HF was 14.8% (Table 3).

In-hospital HF was associated with 1.13 times higher odds (OR=1.13, 95% CI: 1.06–1.20) of dying at the hospital and 1.14 time higher odds (OR=1.14, 95% CI: 1.07–1.20) of dying within 30 days of AMI hospitalization (Table 3).

Post-discharge HF was associated with 3.39 times higher HF (HR=3.39, 95% CI: 3.18–3.63) one-year mortality (Table 4).

Over the study period, the excessive mortality associated with HF changed significantly (in-hospital mortality: $P_{\text{interaction}}=0.001$; 30-day mortality: $P_{\text{interaction}}=0.003$ and one-year mortality: $P_{\text{interaction}}=0.008$) but these changes did not display a clear increasing or decreasing trend (Tables 3 and 4).

Discussion

Among patients hospitalized with an incident AMI in Denmark during 2000-2009, the risk of in-hospital HF slightly declined while the overall risk of post-discharge HF did not change over time. The proportion of HF cases requiring hospitalization decreased and the proportion of HF cases diagnosed in outpatient clinics increased. HF, especially following AMI discharge remained an important source of excessive mortality.

Trends in the risk of heart failure

In line with our findings, the risk of in-hospital HF declined among AMI patients in Sweden (from 46% in 1996 to 26.6% in 2008) ¹⁰ and in Western Australia (from 21.7% in 1996-1998 to 12.1% in 2005-2007) ⁸. In Norway, the risk of in-hospital HF increased by 20% from 2001 to 2009 ²³.

Post-discharge HF rates declined by 14.6% in USA (1998-2010) ¹⁵ and 6.3% per year in Norway (2001-2009) ²³. In Italy, one-year risk of HF following an incident AMI remained stable during 2001-2011 ²⁴. The only study conducted previously in Denmark reported a decline of 23% in risk of HF within 90 days from incident AMI discharge (1997-2010) ⁹.

Beside differences in the length of follow up, other methodological issues may account for differences in results between our study and that published by Gjesing et al. ⁹. We defined incident episodes of HF as new hospitalizations or outpatients contacts while in the previous study, Gjesing et al. ⁹ combined a discharge diagnosis of HF with use of loop diuretics.

Many factors can influence the risk of HF among AMI patients. The use of PCI within 30 days of hospitalization increased substantially during 1999-2008 in Denmark ⁹. Over the same period, there was a significant increase in the use of cardiac drugs, including beta-blockers, statins, inhibitors of the renin-angiotensin system and antiplatelet agents among AMI patients ⁹ as well as in the general population ²⁵. The increase in the utilization of these drugs contribute in the reduction of HF risk through at least two mechanisms. First, use of cardiac

therapy prior to an AMI has shown to reduce the severity of AMI expression ²⁶, thus reducing the risk of early HF. Second, in patients with AMI, increases in the use of evidence-based therapy have the potential to reduce the risk of adverse events, including ischemic recurrences and post-discharge HF. Further contribution in HF risk reduction may have been provided by declines in the prevalence of smoking, hypertension and hypercholesterolemia ²⁷.

Of note, the risk of post-discharge HF requiring hospitalization and that of post-discharge HF diagnosed at outpatient clinics went in opposite directions. The proportion of outpatient contacts within all HF cases varied widely; from 13.2% in Minnesota ²⁸ to 50% in Canada ²⁹. In our study, the outpatient contacts accounted for 31.1% of all post-discharge HF cases. We did not observe differences between groups with regard to AMI severity but patients who later experienced a HF episode requiring hospitalization had a greater burden of comorbidities at baseline compared to those diagnosed with HF in outpatient clinics. It is plausible that the presence of these comorbidities has an influence on the decision to hospitalize patients as hospitals offer a more convenient setting for diagnosing and/or treating comorbidities. The opposite trends in post-discharge HF requiring hospitalization and those diagnosed at outpatient clinics may have several explanations. The increase over time in the proportion of outpatient contacts corresponded with an increase in the number of outpatient heart failure clinics affiliated to Danish hospitals. An increased use of echocardiographic imaging and surveillance of HF over time in a period in which there has been great improvement in treatment of heart failure may have led to diagnosing HF at an early stage, preventing thus the need for hospitalization. The shorter time from AMI discharge to HF diagnosis among outpatient contacts compared to hospitalized cases in our study supports this hypothesis. Other possible explanation involve financial and availability constrains that hospital are increasingly facing over time.

Excess mortality associated with HF

Our study confirms previous findings of an excess early mortality associated with in-hospital HF among various subsets of acute coronary patients³⁰⁻³². The excess one-year mortality associated with post-discharge HF in our study was similar to that observed among acute coronary syndrome patients in Canada during 2002-2008²⁹ and Norway during 2001-2009¹⁶. Despite overall improvement in survival following an AMI in Denmark³³, HF remains a source of excessive mortality. The HF correlates with the extension of CHD and was associated in our study with higher incidence of pulmonary edema, cardiogenic shock and AV blocks. Patients with HF had also a greater burden of comorbidities and received less often invasive coronary procedures compared to those without HF (data not shown). This finding is in line with previous publications^{31,34}. However, due to the observational nature of our study and lack of data for in-hospital HF, we cannot establish a temporal relationship between myocardial revascularization and in-hospital HF. It seems plausible that certain comorbidities may represent contraindication to invasive interventions. Further, the rates of success of revascularization procedures are lower among patients with, compared to those without in-hospital HF³⁵.

Although accounting for the minority of all HF cases, post-discharge HF in the context of CHD conveys a far greater excess mortality compared to that of in-hospital HF. Therefore, focused efforts on identification of factors associated with post-discharge HF would help reducing the mortality in this subset of AMI patients.

Strength and limitations

Our study included all individuals with an incident AMI in Denmark, without age, gender or geographical restrictions, maximizing thus the generalizability of our findings. The study period followed the introduction of troponin in AMI diagnostic criteria in Denmark (around year 2000); therefore, our results are minimally, if at all, influenced by changes in the AMI's

diagnostic criteria. We excluded with high probability previous episodes of AMI and HF using a fairly long retrospective search of five years³⁶, avoiding the mixture of incident with prevalent AMI. Our study is the first to include in the analyses and separately analyze trends in the risk of HF diagnosed as outpatient contacts.

Our study carries some limitations inherent to the nature of data sources. **No information on some relevant lifestyle factors such as smoking, obesity, physical activity and lipid profile was available.** No information on echocardiographic evaluation of ventricular function and/or number of vessels involved and degree of stenosis was available either. A distinction between ST-elevation MI (STEMI) and non ST-elevation MI (NSTEMI) based on the ICD-10 coding system was not possible. However, previous analyses have revealed that the excess mortality associated with HF among AMI patients did not differ by HF type (3.5 times higher for HF with reduced ejection fraction versus 3.1 times higher for HF with preserved ejection fraction; $P_{\text{heterogeneity}}=0.31$)¹⁴. Other studies conducting stratified analyses for STEMI and NSTEMI have shown that the magnitude and time trends of HF complicating the two AMI types are similar^{10 37 38}.

Lastly, many factors such as the study period, methodological differences in defining the study population and/or ascertaining the outcome, as well as the quality of register data can potentially influence the findings, however we are not able to quantify such influence.

Conclusions: In patients hospitalized with an incident AMI during 2000-2009, we observed a modest decline over time in the risk of in-hospital HF while the risk of post-discharge HF did not change. **When complicating AMI, HF conveys an increased risk of death, more pronounced for cases of HF developing after the AMI discharge.**

Declaration of conflicting interest:

The authors declare that there are no conflicts of interest.

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Figure legends

Figure 1

Flow chart of study participants

Figure 2

Changes in the adjusted odds of in-hospital heart failure among patients hospitalized with an incident acute myocardial infarction in Denmark during 2000-2009

Figure 3

Changes in the adjusted risk of post-discharge heart failure requiring hospitalization (a) or diagnosed at outpatient clinics (b) among patients hospitalized with an incident acute myocardial infarction in Denmark during 2000-2009

Table 1. Baseline characteristics of patients hospitalized with an incident acute myocardial infarction in Denmark during 2000–2009, overall and by study period

Characteristics of patients	All (n= 78 814)	2000-2001 (n=16 117)	2002-2003 (n=17 167)	2004-2005 (n=16 174)	2006-2007 (n=14 893)	2008-2009 (n=14 463)
Male gender, %	63.9	63.1	63.4	63.7	64.3	65.2
Age (years), mean (SD)	69.3 (12.8)	69.5 (12.5)	69.6 (12.7)	69.5 (12.9)	69.0 (13.0)	69.1 (13.1)
Previous history of CHD, %	9.9	9.3	10.4	10.1	10.0	9.5
Comorbidities, %						
Diabetes mellitus	13.3	12.4	13.3	13.6	13.7	13.8
Hypertension	26.2	15.4	22.5	27.7	32.7	34.3
Renal failure	2.9	2.1	2.5	3.0	3.4	3.6
Chronic obstructive pulmonary disease	8.4	7.8	8.6	8.5	8.4	8.6
Valvular heart disease	4.5	3.1	4.2	4.9	5.0	5.6
Atrial fibrillation	10.2	9.0	10.0	10.5	10.3	11.3
Complications of AMI, %						
Ventricular fibrillation	0.5	0.4	0.6	0.5	0.6	0.6
Pulmonary oedema	0.7	0.7	0.8	0.7	0.7	0.4
Cardiogenic shock	0.6	0.6	0.6	0.7	0.7	0.6
Atrioventricular block (2 nd or 3 ^d degree)	0.9	0.9	0.9	0.8	0.9	0.8
Mechanical complications	0.3	0.4	0.3	0.3	0.3	0.2
Invasive coronary procedures, %						
Coronary angiography	52.4	24.1	46.3	57.7	65.3	72.1
Percutaneous coronary intervention	36.6	14.6	31.2	41.7	47.7	50.7
Coronary artery bypass graft	4.5	3.9	5.0	4.5	4.5	4.4
Any revascularization	41.7	22.0	37.1	46.0	51.4	54.4

CHD: coronary heart disease

AMI: acute myocardial infarction

Table 2. The proportion of study population developing heart failure or dying during the follow up in Denmark during 2000-2009

Study outcomes	Age categories			
	All ages (n=78 814)	40-59 years (n=19 385)	60-79 years (n=39 754)	80+ years (n=19 675)
In-hospital outcomes, n (%)				
In-hospital heart failure	10 248 (13.0)	1203 (6.2)	5214 (13.1)	3831 (19.5)
In-hospital deaths	8449 (10.7)	578 (3.0)	3671 (9.2)	4200 (21.3)
Post-discharge outcomes*, n (%)	(n= 61 637)	(n=17 674)	(n=31 547)	(n=12 416)
Post-discharge heart failure	5978 (9.7)	975 (5.5)	3215 (10.2)	1788 (14.4)
Hospitalizations	4116 (6.7)	512 (2.9)	2127 (6.7)	1477 (11.9)
Outpatient contacts	1862 (3.0)	463 (2.6)	1088 (3.5)	311 (2.5)
Post-discharge deaths	5925 (9.6)	341 (1.9)	2398 (7.6)	3186 (25.7)

* Patients discharged from the incident acute myocardial infarction hospitalization without in-hospital heart failure.

Table 3. The adjusted* excess **early (in-hospital and 30-day) mortality** associated with in-hospital heart failure among patients hospitalized with an incident acute myocardial infarction in Denmark, 2000-2009

Study period	In-hospital heart failure		Odds ratio (95% CI)	P _{interaction} **
	No	Yes		
In-hospital mortality				
2000-2009	68 566/6929 (10.1)	10 248/1520 (14.8)	1.13 (1.06-1.20)	0.001
2000-2001	14 052/1775 (12.6)	2065/318 (15.4)	0.88 (0.77-1.01)	
2002-2003	14 879/1584 (10.7)	2288/362 (15.8)	1.11 (0.97-1.27)	
2004-2005	14 050/1352 (9.6)	2124/347 (16.3)	1.32 (1.15-1.51)	
2006-2007	13 058/1241 (9.5)	1835/261 (14.2)	1.16 (1.00-1.35)	
2008-2009	12 527/977 (7.8)	1936/232 (12.0)	1.24 (1.06-1.46)	
30-day mortality				
2000-2009	68 566/7837 (11.4)	10 248/1733 (16.9)	1.14 (1.07-1.20)	0.003
2000-2001	14 052/1957 (13.9)	2065/364 (17.6)	0.92 (0.81-1.04)	
2002-2003	14 879/1780 (12.0)	2288/422 (18.4)	1.17 (1.03-1.33)	
2004-2005	14 050/1561 (11.1)	2124/391 (18.4)	1.28 (1.12-1.46)	
2006-2007	13 058/1394 (10.7)	1835/279 (15.2)	1.08 (0.93-1.26)	
2008-2009	12 527/1145 (9.1)	1936/277 (14.3)	1.26 (1.08-1.46)	

* Adjusted for age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, valvular heart disease, renal failure and atrial fibrillation.

** Between in-hospital heart failure and year of the incident acute myocardial infarction.

Table 4. The adjusted* excess **one-year mortality** associated with post-discharge heart failure among patients hospitalized with an incident acute myocardial infarction in Denmark, 2000-2009

Study period	Post-discharge heart failure		Hazard ratio (95% CI)	P _{interaction} **
	No	Yes		
2000-2009	55 659/4731 (8.5)	5978/1194 (20.0)	3.39 (3.18-3.63)	0.008
2000-2001	11 113/994 (8.9)	1164/273 (23.5)	4.31 (3.75-4.96)	
2002-2003	12 028/1057 (8.8)	1267/255 (20.1)	3.11 (2.69-3.60)	
2004-2005	11 457/945 (8.3)	1241/251 (20.2)	3.50 (3.02-4.05)	
2006-2007	10 692/867 (8.1)	1125/199 (17.7)	3.05 (2.60-3.59)	
2008-2009	10 369/868 (8.4)	1181/216 (18.3)	3.11 (2.67-3.63)	

* Adjusted for age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, valvular heart disease, renal failure and atrial fibrillation.

** Interaction between in-hospital heart failure and year of the incident acute myocardial infarction.

Figure 1

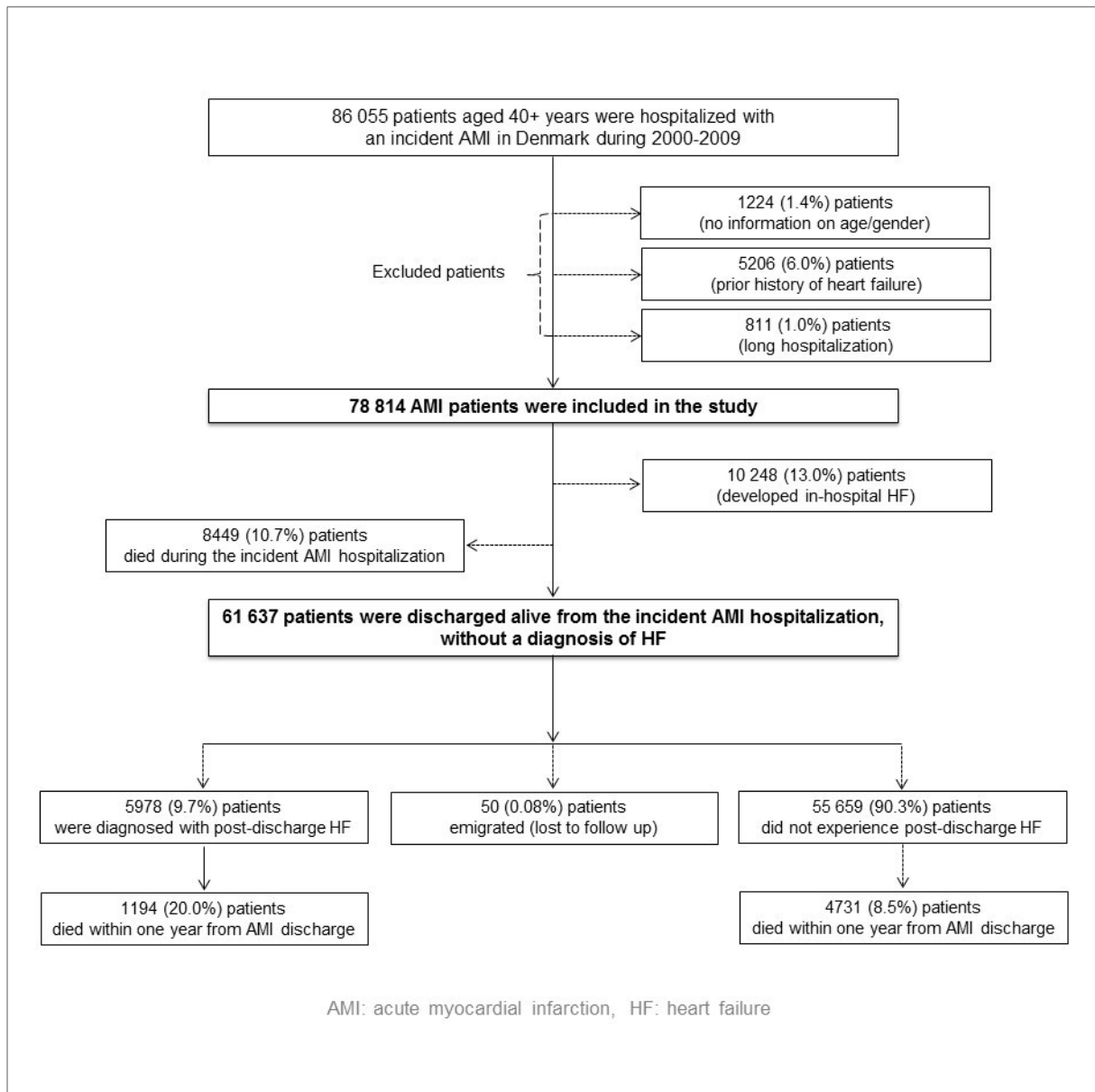


Figure 2

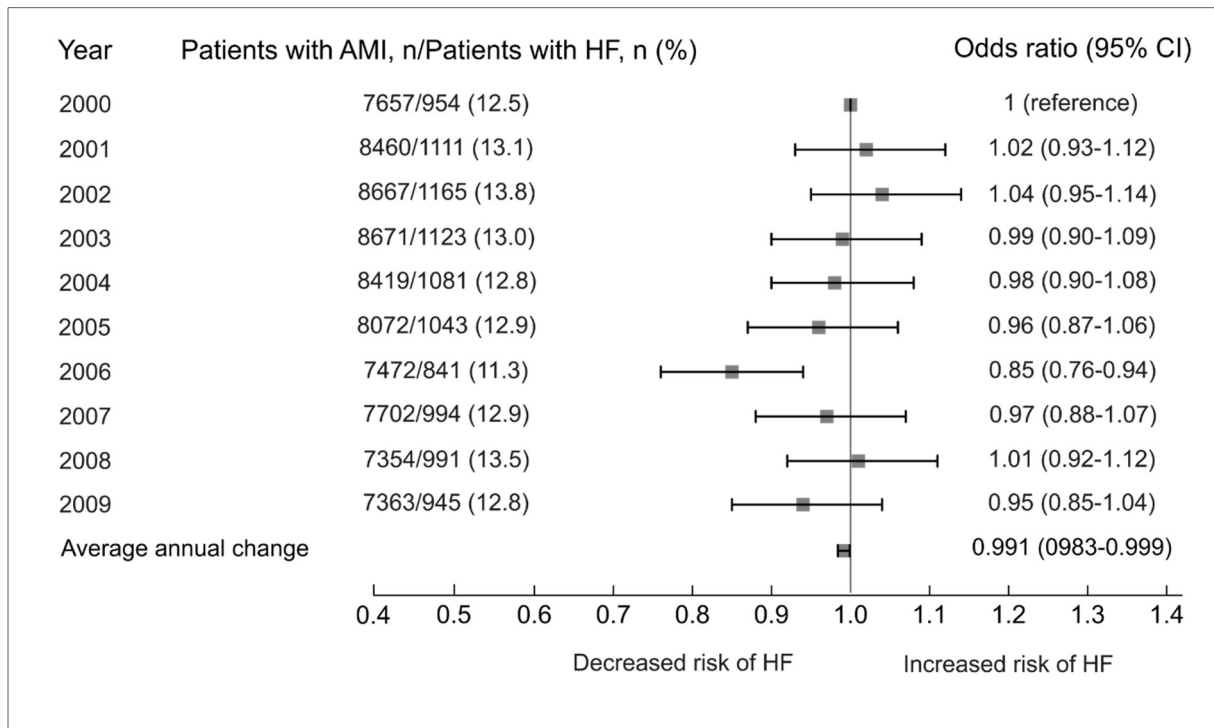


Figure 3

