Effectiveness of clinical pathway in subjects with heart failure: A real-world study from Italian health claims

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ABSTRACT

Background: Several process-of-care indicators have been developed and implemented to improve the quality of heart failure (HF) patients care. The aim of this study is to assess the relationship between a set of recommendations for HF care with measurable clinical outcomes, also in terms of outcomes that could be avoided.
Methods: A retrospective cohort study was carried out on subjects with at least one hospitalization with a primary diagnosis of HF in 2007. Data were retrieved from healthcare utilization databases of Lombardy region (Italy). Exposure to selected recommendations (periodic control of echocardiogram and use of blockers of the renin-angiotensin system and beta-blockers) was recorded. All-cause mortality and hospitalization with primary diagnosis of HF were considered as outcomes. Multivariable Cox models and Poisson model were fitted to estimate the exposure-outcome association.
Results: Among 8207 cases of HF, those who adhered to none, one or all recommendations during the first year after diagnosis were 11%, 60% and 30%, respectively. Compared to patients who adhered to no recommendation, a significant mortality risk reduction of 24% (95% CI 17-31%) and 44% (36-52%) were observed for those who adhered to one and all recommendations, respectively. A significant reduction in the rate of re-hospitalizations in subjects adhered to at least one recommendation was also observed. A decreased trend in Population Attributable Fraction for death cases according to follow-up time was observed.
Conclusion: A strict control of patients with HF through regular clinical examinations must be considered as fundamental for the reduction of mortality and re-hospitalizations.

Key words: Heart failure; Healthcare Utilization database; Clinical pathway; Adherence; Population Attributable Fraction

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that affects more than 23 million people worldwide [1]. Its prevalence is between 1% and 3% in adult population of high-income countries, but it increases up to 30% among older people [2,3]. Because HF is the leading cause of hospitalizations in subjects aged over 65 years [4,5] and

it is associated with increased healthcare costs in Europe and a high burden of mortality and morbidity [6], HF is considered a major public health issue.

As recently done for other conditions such as diabetes [7], several standard, guideline-based, process-of-care performance measures have been developed and implemented in the last years, that provide a mechanism through which the quality of HF care can be measured and improved [8]. The selection of appropriate process measures for use in quality improvement, public profiling or financial incentives is quite important, with potential implications for patients' outcomes, the healthcare system and the administrative burden [9]. Studies have been conducted on inpatient HF performance measures, and some process-of-care measures were associated with post-discharge clinical outcomes [10–13]. Only a few studies examine the relationships between adherence to several current and emerging outpatient HF process measures and clinical outcomes [11,14–16]. However, to date, no studies explore the impact of outpatient recommendations' adherence profiles on clinical outcomes for these patients.

Given these gaps in the literature, we conducted a population-based cohort study in the Lombardy region of Italy to evaluate the association between the adherence to defined process-of-care indicators and selected outcomes for HF outpatient subjects. Moreover, the second aim of this study was to assess the impact of indicators' adherence profiles in terms of outcomes that could be avoided.

METHODS

Data sources

This study is based on computerized healthcare utilization databases from the Italian Lombardy Region, that covered almost 10 million beneficiaries of the Italian National Health Service (NHS). As reported in a previous study [17], the Regional information system of healthcare utilization databases collects a variety of information including: (i) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data, other than the dates in which the individual started (because he/she was born or immigrated) or stopped (because he/she died or emigrated) the condition of NHS beneficiary; (ii) a database on hospital discharge records including information about primary diagnosis, co-existing conditions and performed procedures (coded according to the ICD-9 CM classification system); (iii) a drug prescription database providing information on all community drugs reimbursed by the NHS (coded according to the Anatomical Therapeutic Chemical (ATC) classification system); (iv) a database on outpatient visits, including visits in specialist ambulatories, diagnostic imaging and diagnostic laboratories accredited from the NHS. A unique identification code was used and, in order to preserve privacy, identification codes were automatically converted into anonymous codes, and the inverse process was prevented by deletion of the conversion table.

Diagnostic and therapeutic codes used in the current study are reported in Supplementary material.

Cohort selection and follow-up

Beneficiaries of the NHS who in 2007 (index year) had aged 50 years or older and were resident in Lombardy Region formed target population. In order of allowing patients' characterization through their previous contacts with the NHS, cohort members were excluded if they were recorded as beneficiaries of the regional NHS after the year 2004.

Subjects belonging to the target population were included in the cohort whether they had at least one hospitalization with a primary diagnosis of HF with a date of discharge between 1st January and 31st December 2007 (prevalent subjects). In case of multiple hospitalizations, the first one during the index year will be consider as the index hospitalization. Subjects who died during the index hospitalization were excluded from the study. Furthermore, only incident cases, i.e., those who did not experience any hospital admission with diagnosis of HF and/or with the DRG code (Diagnosis-Related Group) of HF and shock in the last three years prior the index one [18], were included in the study cohort.

According to the user-only design [19,20], only HF patients with at least one prescription of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) or beta-blockers within 90 days from the index hospitalization discharge date were considered for the analysis. Therefore, the most recent prescription date between the first prescription of ACE inhibitors/ARB and the first prescription of beta-blockers was considered as the index date. Cohort members accumulated person-years of follow-up starting from the index date until the occurrence of one of the following events, whichever came first: the study outcomes (emergency hospital admission for HF and death), emigration, or end-point of follow-up, i.e., December 31, 2012.

Covariates

Baseline characteristics of cohort included gender, age, drug therapies and comorbidities. Drug therapies included antidiabetic drugs, antiplatelet, digitalis glycosides, organic nitrates, other blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for respiratory disease. Comorbidities were measured through previous hospitalizations for cancer, diabetes, ischaemic

heart, cerebrovascular, respiratory and kidney disease. In addition, the so-called Multisource Comorbidity Score (MCS), a new comorbidity index obtained from both inpatients' diagnostic information and outpatients' drug prescriptions, and recently validated using data from the here considered Italian regions [21], was considered.

Adherence to recommendations

Echocardiogram execution and drug dispensation of ACE inhibitors/ARB and beta-blockers during follow-up were identified. A patient was considered adherent to recommendations whether he/she was submitted to at least one echocardiogram [22] and had a *proportion of days covered* (PDC) by treatment (with ACE inhibitors/ARB and beta-blockers) ≥ 75% [23–25] in the first year after the index date.

Other than for each individual recommendation, a classification describing the adherence profile of each subject was developed and cohort members were classified in three groups: non-adherent to any recommendations (Score 0), adherent to at least one of the two drugs recommendations (Score 1) and adherent to at least one of the two drugs recommendations and to echocardiogram one (Score 2).

Outcome

Two outcomes were considered to take into account complications of HF potentially avoidable: (i) all-cause mortality; (ii) a new emergency hospitalization occurred with primary diagnosis of HF (ICD-9 CM codes used for capturing outcomes are reported in Supplementary material). Both outcomes were calculated through the whole follow-up.

Association between adherence profile and outcomes

To assess the impact of recommendation's adherence on defined outcomes, only patients with at least 365 days of follow-up were included in the final cohort. The analysis was performed in three steps.

In the first step, a propensity score (PS) matching design was used to ensure that patients classified according to their adherence with recommendations had similar baseline features [26]. Two strategies were used for calculating the PS. Conventional logit regression considering the dichotomous exposure to an individual recommendation as the outcome of interest was initially fitted. Logit regression was extended to the setting of three levels overall adherence index as the outcome of interest. In both the settings, the outcome was modelled as a function of specific covariates and balanced cohorts were then built by using 1:1 (adherence vs. no adherence) and 1:1:1 (increasing levels of overall adherence index) nearest neighbour matching algorithm [27].

Then, a Cox proportional hazard regression model was fitted for estimating the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to each recommendation taken individually, as well as to adherence group, and the risk of experiencing the outcomes. In particular, mortality risk was assessed starting from the second year after the index date until the end of follow-up period, while emergency re-hospitalization risk was calculated only during the second year of follow up.

In the second analysis, a Poisson model was also fitted to evaluate the impact of the adherence on the number of re-hospitalizations during the second year in terms of incidence rate ratio (IRR) and its 95% CI.

In the latter analysis, the Population Attributable Fraction (PAF) was used to assess the impact of process' adherence on outcomes in terms of cases that would not have occurred if all subjects were adherent to drug recommendations or to drug and echocardiogram recommendations (Score 1 and Score 2 group, respectively). A SAS macro was applied, following the approach proposed by Laaksonen et al [28] for PAF estimation in cohort studies. Both mortality and new emergency hospitalizations were used as outcome of interest in the whole follow-up.

For all hypotheses tested, p-value less than 0.05 was considered significant.

RESULTS

Adherence to recommendations and outcome

Baseline characteristics of the cohort of 9,178 subjects hospitalized for HF during 2007 are shown in Table 1. Among these subjects, those who had at least 365 days of follow-up were 8,207.

During the first year after diagnosis, HF subjects had similar and high adherence to recommendation related to drug assumption (69.9% and 67.3% for ACEi/ARB and beta-blockers assumption, respectively) but a low adherence to echocardiogram, being only 31.9% of them submitted to this exam (Table 2). It is noteworthy that about 60% of newly taken in care HF subjects adhered to at least one drug recommendation. In calculating the total adherence score, 260 subjects were not included in any of the defined groups, therefore they were not considered in the subsequent analysis.

During follow-up, cohort members accumulated 40,028 person-years of observation and experienced 3,242 deaths (incidence rate, 80.9 cases every 1,000 PY) and 2,768 new emergency admissions with a primary diagnosis of HF (incidence rate, 83.9 cases every 1,000 PY).

Association between adherence and outcomes

Forrest plots for the adherence-outcome relationship

are shown in Figure 1 and Figure 2. Adherence to recommendations related to drugs assumption is associated with a significant mortality risk reduction (23% (95% CI, 16% to 30%) and 32% (26% to 38%) for ACEi/ARB and beta-blockers assumption, respectively), but no association is observed with emergency re-hospitalization risk. Adherence to echocardiogram recommendation seemed to be not related with both outcomes (Figure 1). Compared to subjects who were non-adherent to any recommendation, a significant mortality risk reduction of 24% (17% to 31%) and 44% (36% to 52%) were observed for those who adhered to at least one drugs' recommendation (Score 1 group) and to at least one drug and echocardiogram recommendations (Score 2

TABLE 1. Baseline characteristics of patients in the whole study cohort as well as according to the clinical profile. Lombardy Region, Italy (2007)

	Clinical profile			Combined (N = 9,178)
	Good (N = 3,067)	Intermediate (N = 3,305)	Poor (N = 2,806)	
Male gender	1,684 (54.9)	1,769 (53.5)	1,624 (57.9)	5,077 (55.3)
Age (years)				
50-59	457 (14.9)	217 (6.6)	136 (4.85)	810 (8.8)
60-69	783 (25.5)	629 (19.0)	554 (19.74)	1,966 (21.4)
70-79	1,091 (35.6)	1,333 (40.3)	1,240 (44.1)	3,664 (39.9)
80-89	664 (21.6)	1,003 (30.4)	788 (28.08)	2,455 (25.8)
≥90	72 (2.4)	123 (3.7)	88 (3.1)	283 (3.1)
Medications †				
Antidiabetic	364 (11.9)	847 (25.6)	1,153 (41.1)	2,364 (25.8)
Antiplatelet	1,046 (34.1)	2,612 (79.0)	2,403 (85.6)	6,061 (66.0)
Digitalis glycosides	54 (1.8)	700 (21.2)	550 (19.6)	1,304 (14.2)
Organic nitrates	126 (4.1)	1,211 (36.6)	1,273 (45.4)	2,610 (28.4)
Antiarrhythmics	170 (5.5)	632 (19.1)	668 (23.8)	1,470 (16.0)
Other Blood-pressure lowering agents	1,197 (39.0)	2,598 (78.6)	2,376 (84.7)	6,171 (67.2)
Lipid lowering agents	537 (17.5)	1,248 (37.8)	1,320 (47.0)	3,105 (33.8)
Antidepressants	218 (7.1)	346 (10.5)	477 (17.0)	1,041 (11.3)
NSAIDs	989 (32.2)	1,335 (40.4)	1,194 (42.6)	3,518 (38.3)
Anti-gout drugs	95 (3.1)	472 (14.3)	909 (32.4)	1,476 (16.1)
Drugs for respiratory disease	265 (8.6)	582 (17.6)	798 (28.4)	1,645 (17.9)
Comorbidities #				
Cancer	71 (2.3)	106 (3.2)	625 (22.3)	802 (8.7)
Diabetes	79 (2.6)	317 (9.6)	883 (31.5)	1,279 (13.9)
Ischemic heart disease	159 (5.2)	692 (20.9)	1,221 (43.5)	2,072 (22.6)
Cerebrovascular disease	32 (1.0)	150 (4.5)	656 (23.4)	838 (9.1)
Respiratory disease	112 (3.6)	309 (9.4)	772 (27.5)	1,193 (13.0)
Kidney disease	4 (0.1)	34 (1.0)	494 (17.6)	532 (5.8)

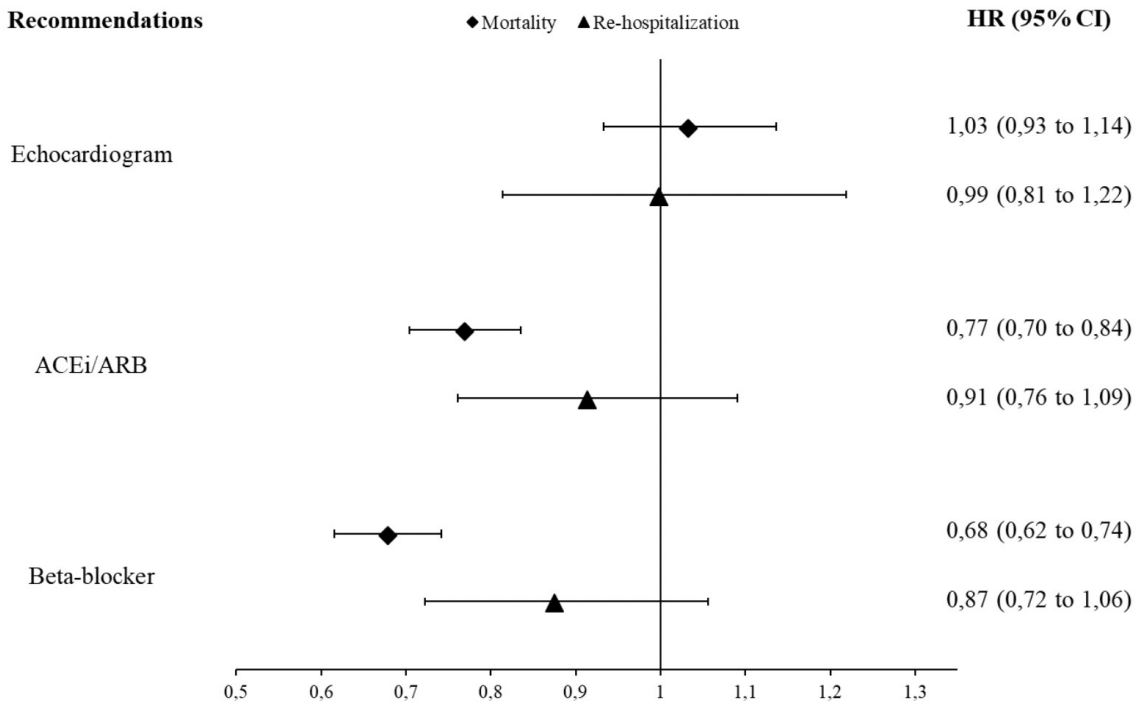
Abbreviations: MCS, Multisource Comorbidity Score; NSAID, Non-steroidal anti-inflammatory drugs
† According to drug dispensed in the 3 years before 2007
 # According to hospital admissions in the 3 years before 2007
Clinical profile was assessed by means of the Multisource Comorbidity Score (MCS). Three groups of the clinical profile were defined as follows: good (MCS = 1), intermediate (MCS=2) and poor (3≤MCS≤5)

TABLE 2. Cohort subjects with at least 365 days of follow-up who, during the first year after index date, adhered to selected recommendations. Lombardy Region, Italy (2007)

	Cases (8,207)	
	N	%
Echocardiogram	2,618	31.9
ACEi/ARB assumption†	5,739	69.9
Beta-blockers assumption#	5,521	67.3
Total adherence score		
Score 0	843	10.6
Score 1	4,746	59.7
Score 2	2,358	29.7

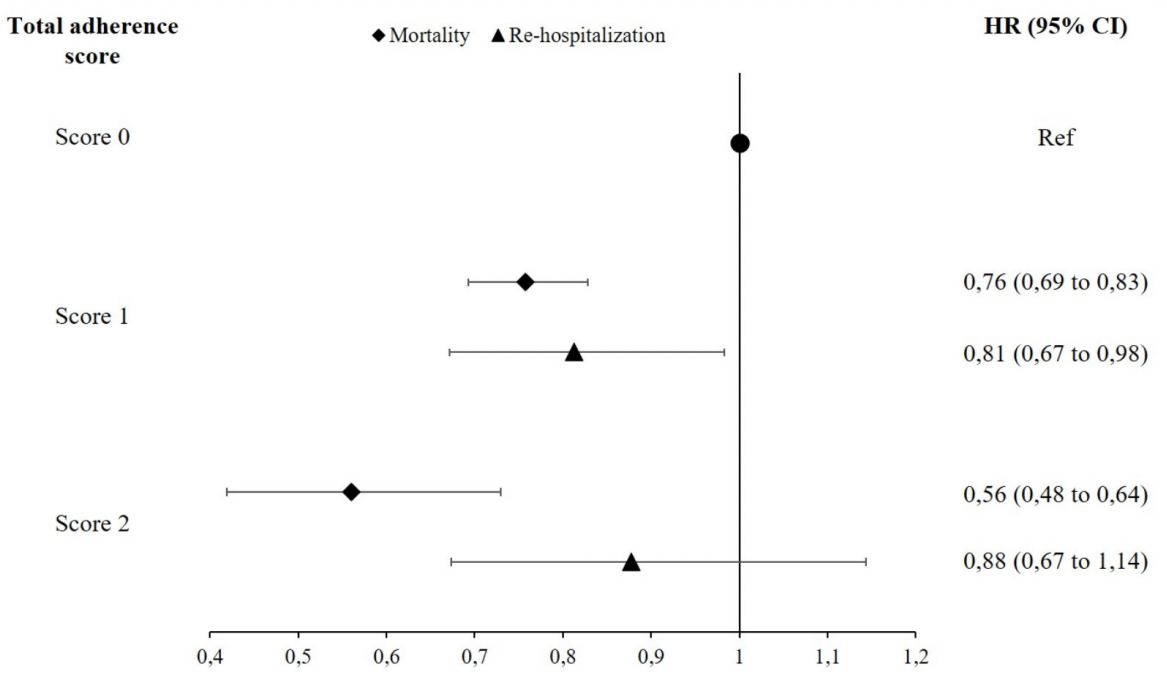
Subjects non-adherents to any recommendations belong to Score 0 group, those adherents to at least one of the two drugs' recommendations belong to Score 1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score 2.
Abbreviations: ACEi, Angiotensin Converting Enzyme inhibitors; ARB, Angiotensin Receptor Blockers
† Considered among subjects who received a prescription of ACEi/ARB within 3 months from the index date
 # Considered among subjects who received a prescription of beta-blockers within 3 months from the index date

FIGURE 1.



Forest plots of hazard ratios (HR) for the association between first-year adherence to selected recommendations and the risk of death and emergency hospital re-admission for HF.
Adherence to recommendations is considered during the first-year period after index date, mortality risk is considered during the whole follow-up period while the re-hospitalization risk is calculated in the second year after the index hospitalization. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Subjects were matched using propensity score method according to baseline covariates.
Abbreviations: HR, hazard ratio; ACEi, Angiotensin Converting Enzyme inhibitors; ARB, angiotensin receptor blockers.

FIGURE 2.



Forest plots of hazard ratios (HR) for the association between total adherence score and the risk of death and emergency hospital re-admission for HF Adherence to recommendations is considered during the first-year period after index date, mortality risk is considered during the whole follow-up period while the re-hospitalization risk is calculated in the second year after the index hospitalization. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Subjects were matched using propensity score method according to baseline covariates. Subjects non-adherents to any recommendations belong to Score 0 group, those adherents to at least one of the two drugs' recommendations belong to Score 1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score 2.
Abbreviations: HR, hazard ratio; CI, confidence interval.

group), respectively (Figure 2). A decreased risk of emergency re-hospitalization is also observed in subjects who adhered to at least one drug recommendation (Score 1 group), while the adherence to at least one drug and echocardiogram recommendations (Score 2 group) is not associated with a significant risk reduction.

In Figure 3 results from Poisson model are shown. There is a significant reduction in IRR for emergency re-hospitalizations of 22% (7% to 34%) in subjects adhered to at least one drug recommendation (Score 1 group), but no association is shown in subjects belonging to Score 2 group.

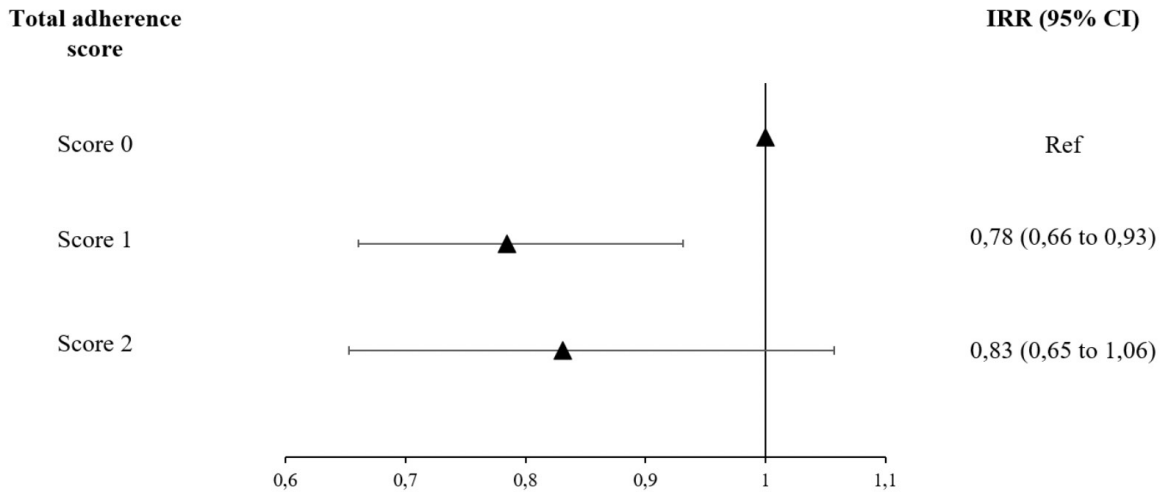
Figure 4 shows the impact of being adherent to recommendations on deaths and of emergency re-hospitalization for HF, using the PAF estimate. About 2 deaths and emergency re-hospitalizations cases out of 100 could be avoided if all no-adherent subjects were adherent to at least one drug recommendation (Score 1 group). Whether all no-adherent subjects were adherent to at least one drug and echocardiogram recommendations (Score 2 group), a mean of 6 and 5 (out of 100) deaths and emergency re-hospitalizations cases, respectively, could be prevented.

A decreased trend in PAF for death cases according to follow-up time (intervals of 365 days) is reported in Figure 5, starting from the second year after the index date. This trend started from about 12 and 4 cases of death that could be prevented in the first year until about 2 and 1 cases in the last year of follow-up, whether all subjects in Score 0 group were in both Score 2 and Score 1 groups, respectively.

DISCUSSION

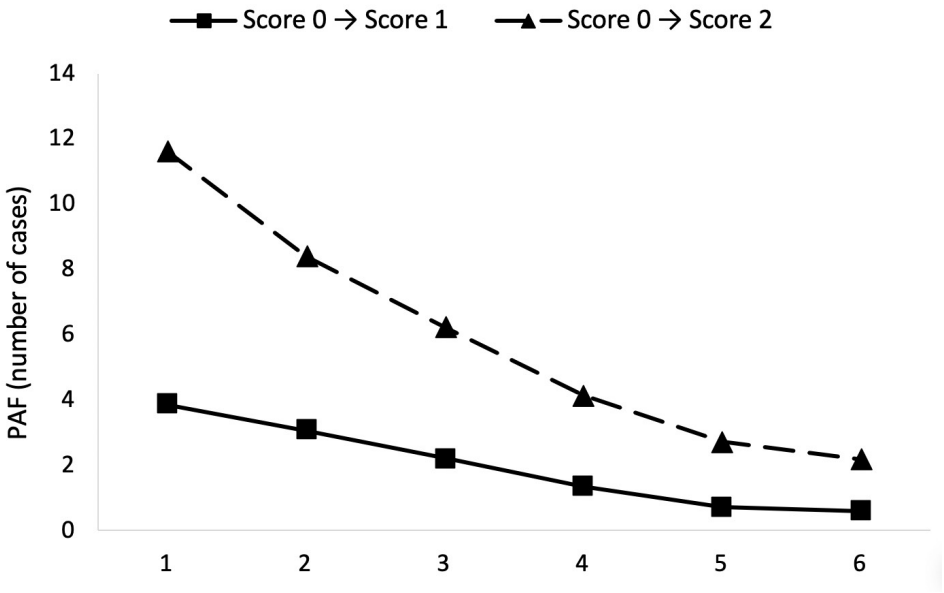
This study shows that the adherence to one or more recommendation can lead to a decreased risk of clinical outcomes in HF subjects. A non-adherence profile to recommendations could be considered as the non-adherence to a specific clinical pathway and, therefore, could represent a risk factor for developing the outcome. Results from this study show the impact of the adherence to specific recommendations on the outcome in terms of PAF, that represent the proportion of cases that could be prevented by eliminating the risk factor (a non-adherent behavior). We considered the adherence to the specific recommendations both taken individually and categorized in a total score of adherence. For the creation of score's classes, we taken in consideration two main aspects. The first is about subjects who, after a hospitalization for HF, were only subjected to echocardiographic examination

FIGURE 3.



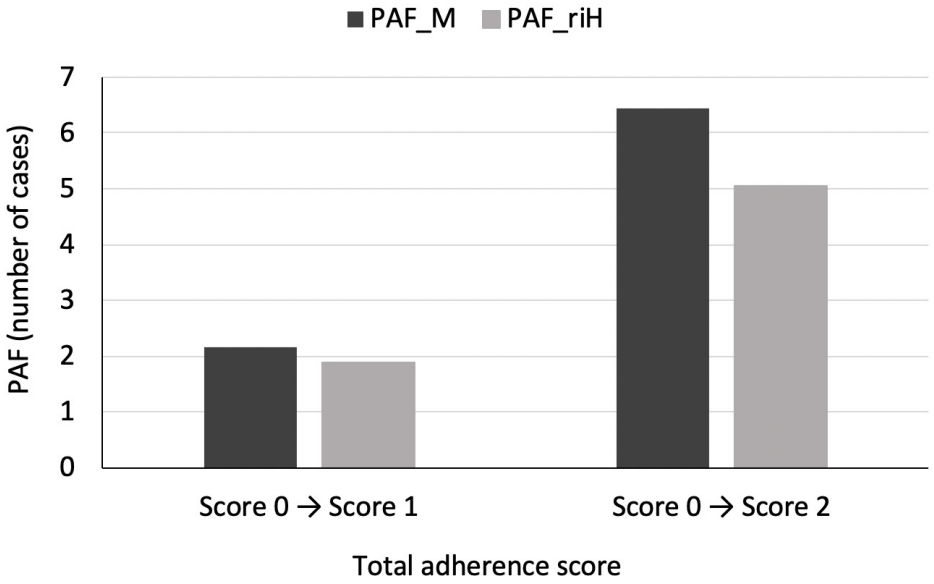
Forest plots of incidence rate ratios (IRR) for the association between the adherence profile and the number of emergency re-hospitalizations for HF Adherence to recommendations is considered during the first-year period after index date and the number of emergency re-hospitalizations for HF is calculated in the second year after the index date. IRR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Poisson model. Subjects were matched using propensity score method according to baseline covariates. Subjects non-adherents to any recommendations belong to Score 0 group, those adherents to at least one of the two drugs' recommendations belong to Score 1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score 2.
Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

FIGURE 5.



PAF trend for death according to follow-up time
PAF represents the number of outcome cases (deaths) that could be prevented if all subjects in Score 0 group (non-adherents to any recommendation) would be in Score 1 group (adherents to at least one of the two drugs' recommendations) or Score 2 group (adherents to at least one of the two drugs' and to echocardiogram recommendations). Adherence to recommendations is considered during the first-year period after index date, PAF is considered during the whole follow-up period, starting from the second year after the index hospitalization. PAF estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 1).
Abbreviations: PAF, population attributable fraction.

FIGURE 4.



PAF for deaths (PAF_M) and for emergency re-hospitalizations (PAF_riH)
PAF represents the number of outcome cases (deaths or emergency re-hospitalizations) that could be prevented if all subjects in Score 0 group (non-adherents to any recommendation) would be in Score 1 group (adherents to at least one of the two drugs' recommendations) or Score 2 group (adherents to at least one of the two drugs' and to echocardiogram recommendations). Adherence to recommendations is considered during the first-year period after index date, PAF for death is considered during the whole follow-up period while the PAF for emergency re-hospitalization is calculated in the second year after the index hospitalization. PAF estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 1).
Abbreviations: PAF, population attributable fraction; PAF_M, population attributable fraction for death; PAF_riH, population attributable fraction for emergency re-hospitalization.

and did not use drugs during the first year of follow-up. These subjects were excluded from our analysis (and do not fall into any of the score categories) because it is difficult to clinically justify such a behavior, and they are certainly different patients compared to all other cohort members. The second aspect concerned the recommendation about drug assumption. As indicated by clinical guidelines, not all subjects should undergo double hypotensive therapy (ACEi/ARB and beta-blockers) [8]. Therefore, in the construction of the score we took this issue into consideration, indicating that the condition was satisfied if subjects took at least one of the two recommended drugs.

However, this study shows a lower adherence rate of outpatient subjects with HF to drugs' assumption recommendations then that reported from other studies. In fact, about 70% and 67% of Lombard subjects with HF were adherent to ACE inhibitors/ARB therapy and to beta-blockers, respectively. Fonarow et al [11], reported an adherence rate of about 80% and 86% for ACE inhibitors/ARB and beta-blockers, respectively, while a study of Wu et al [15] showed an adherence rate of 88.8% for ACE inhibitors/ARB. However, both studies measured the adherence to ACE inhibitors/ARB indicator among only subjects with left ventricular ejection fraction (LVEF) lower than 40%, whereas we did not apply any exclusion criterion on LVEF.

Moreover, in our study, the adherence measured using both the three singles indicators (echocardiogram, ACE inhibitors/ARB and beta-blockers therapy) and the adherence score calculated in the first year after index date is related to a low mortality risk in HF subjects with a follow-up of at least 365 days. In particular, adherence to ACE inhibitors/ARB therapy shows a decreased mortality risk comparable with that reported by Wu et al [15]. Fonarow et al [11], also found that adherence to both ACE inhibitors/ARB and beta-blockers was associated with a low mortality risk of 49% and 55%, respectively. In his study, Wu consider the documentation about left ventricular function as a process-of-care indicator for outpatient care, as recommended by clinical guidelines [8]. In our study, we can consider the indicator of echocardiogram execution as a proxy of left ventricular assessment, because during an echocardiogram this particular assessment is always conducted, even if we do not know any result of this procedure. However, we found no association between the adherence to echocardiogram indicator and the mortality risk, as reported also by Wu et al [15].

In our study, we explored the emergency re-hospitalization for HF as the second outcome of interest. In particular, we considered this outcome as an acute event that can occur early after the follow-up beginning, mostly in subjects that have a non-adherent profile to recommendations.

For this reason, as we calculated the adherence to recommendations in the first year after the index date, this outcome was assessed only in the second year of follow-up. Under this condition, we found that the adherence to drugs' recommendations (at least one between ACEi/ARB or beta-blockers assumption) was positively associated with a risk reduction of being re-hospitalized for HF. At the same time, for subjects with the adherence profile just mentioned, we found also a significant reduction in the number of emergency-re-hospitalization.

Furthermore, to quantitively evaluate the contribution of the adherence to recommendations to the outcomes, we estimated the PAF. Recently, this measure has been used in order to assess the impact of prescriptive inappropriateness on drug adverse outcomes at the population level [29]. To date, it has been one of the most applied measures for estimating the association between cardiovascular risk factors and clinical outcomes, allowing policy makers to anticipate the potential impact of preventive strategies targeting certain risk factors [30–33]. Nevertheless, there are no studies that measure the impact of following a specific clinical pathway on clinical outcomes, in particular in outpatient subjects.

From our study, we can observe that the PAF for mortality is higher in the first years of follow-up considered, and tent to decrease with time. This means that there is a higher risk of experiencing an outcome in the first years after an acute event, that can be kept under control by assuming a specific drug therapy. In fact, we observed that if non-adherent subjects become adherents to drugs' recommendations (at least one between ACEi/ARB or beta-blockers assumption), this change can lead to a higher number of avoidable cases. This number is even greater if subjects were adherent to both drugs' and echocardiogram recommendations. At the same time, this result can be interpreted as a survival curve, where subjects that had a longer free-outcome survival are those that more difficultly will experience the outcome itself. However, data from our analysis show that the adherence in the first year is sub-optimal and thus it is necessary to support patients on their clinical path, in order to make them aware of the importance of care to be followed.

This study has several limitations that should be taken into account for correctly interpreting our results. First, because of privacy regulations, hospital records were not available for scrutiny, which means that diagnosis of HF could not be checked. Second, information about health service outpatient facilities supplied by private organizations are not available from our databases. For example, we can suspect that a portion of echocardiograms, the indicator to which less patients were adherent, is performed in private clinics. Third, it should be remembered that the recommendation about ACEi/ARB assumption is indicated for subjects with reduced LVEF [8]. In the present study, a stratification of subjects according to LVEF was not carried out as this data, as well as other clinical information (e.g., blood pressure, serum cholesterol), was not available. Finally, validity of our estimates is based on the assumption that drugs dispensed by pharmacies correspond to drug consumption, which may not be the case [34]. It should be mentioned that this type of bias necessarily leads to an underestimation of attributable fractions.

CONCLUSIONS

This study is among the first ones that demonstrate a significant association between the adherence to HF process measure, calculated with ACEi/ARB, beta-blockers and echocardiogram, and the overall survival and the emergency re-hospitalization for HF. In particular, this is the first study that explore the impact of this adherence in terms of PAF, i.e., the proportion of outcomes that could be prevented if all HF subjects were to some extent adherent to clinical recommendations. Further evidence is thus needed to confirm the protective role of adherence to recommendations among HF subjects.

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SUPPLEMENTARY MATERIAL

ICD-9 codes

DESCRIPTION	ICD9-CM CODES
Case identification and outcome	
Heart failure	428.*, 402.01, 402.11 and 402.91
Covariates	
Cancer	140-239.*
Diabetes	250.*
Ischemic heart disease	410-414.*
Cerebrovascular disease	430-438.*
Respiratory disease	460-519.*
Kidney disease	584-586.*

ATC codes

Drugs	ATC codes
ACE inhibitors/ARB	C09
Beta-blockers	C07
Antidiabetic agents	A10
Antiplatelet	B01A
Digitalis glycosides	C01AA
Organic nitrates	C01DA
Antiarrhythmics	C01B
Other blood-pressure lowering agents	C02, C03, C08
Lipid lowering agents	C10
Antidepressants	N06A
NSAIDs	M01A
Anti-gout drugs	M04
Drugs for respiratory disease	R03