

Original Article

Impact of the sustained control of cardiovascular risk factors on first episode heart failure: The relevant role of primary care

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KEY MESSAGE:

- Since most patients at high cardiovascular risk are attended in primary care, the role of general practitioners is crucial in preventing the development of heart failure.
- Control of cardiovascular risk factors has shown to be determinant to prevent a first heart failure hospitalization.

ABSTRACT

Background: The role of cardiovascular risk factor control in the development of heart failure (HF) has not yet been clearly established.

Objective: To determine the effect of cardiovascular risk factor control on the occurrence of a first episode of hospital admission for HF.

Methods: A case-control study using propensity score-matching was carried out to analyse the occurrence of first hospital admission for HF taking into account the degree of cardiovascular risk factor control over the previous 24 months. All patients admitted to the cardiology unit of the Hospital del Mar between 2008 and 2011 because of a first episode of HF were considered cases. Controls were selected from the population in the hospital catchment area who were using primary care services. Cardiovascular risk factor measurements in the primary healthcare electronic medical records prior to the first HF episode were analysed.

Results: After the matching process, 645 participants were analysed (129 HF cases and 516 controls). Patients suffering a first HF episode had modest increments in body mass index and blood pressure levels during the previous two years. Adjusted odds ratio for experiencing a first HF hospital admission episode according to systolic blood pressure levels and body mass index was (OR: 1.031, 95% CI: 1.001–1.04), and (OR: 1.09, 95% CI: 1.03–1.15), respectively.

Conclusion: Increased levels of body mass index and systolic blood pressure during the previous 24 months may determine a higher risk of having a first HF hospital admission episode.

Keywords: Heart failure, hospital admission, primary care, cardiovascular risk factors

INTRODUCTION

Worldwide, cardiovascular diseases are the greatest cause of mortality (1). In 2013, the American Heart Association reported that 28 million Americans suffered from cardiovascular diseases and, among these, five million had experienced heart failure (HF) (2). HF repre-

sents a growing problem due to general population aging and to the prolongation of patients' lives as a result of improvements in medical treatment and procedures (3). From a clinical point of view, it is noteworthy that most HF cases can be attributed to modifiable risk factors and, consequently, preventable (4).

The relationship between several cardiovascular risk factors (CVRF) such as hypertension, high blood cholesterol, diabetes, obesity, and smoking and HF incidence has been well-established (5–8). It has also been shown that minor reductions in the prevalence of some CVRF can decrease HF incidence (9). Nevertheless, prior to the publication of the 2009 ARIC Study there was insufficient evidence concerning the impact of CVRF control on HF incidence.

While adequate CVRF management has been reported to result in lower HF incidence, most studies have only measured them at the commencement of the cohort follow-up, without considering an intermediate analysis (10). In addition, the optimum high-risk cut-off remains to be determined.

Although several cohort studies have analysed the effect of CVRF in a long-term follow-up, little is known about the control of these factors prior to onset, particularly at the period close to the HF episode. This study aimed to determine the effect of good CVRF control on the occurrence of first episode HF hospitalization.

METHODS

Study design

A retrospective, observational study was carried out comparing two groups, one with and the other without HF. Information used in the analysis came from a database located at the Heart Failure Unit of the Hospital del Mar, which covers the catchment area of the study (to identify the cases), and the SIDIAP (system information for the development of research in primary care) for the controls. The SIDIAP is a clinical database of anonymized patient records containing information for almost six million people coming from 274 primary care practices in Catalonia.

Since a number of factors, such as variability in the quality of the primary healthcare record registration, could have influenced the effect of CVRF control on HF occurrence, we designed a case-control study using propensity score-matching methodology. This allowed us to assemble two balanced groups of patients sharing the same co-variable profile, with the exception of those of interest, in order to minimize the effect of potential bias (11) (Figure 1).

All CVRF measurements obtained in a primary care setting during the two years prior to the first HF hospital admission were analysed. Four controls were taken for every case. Time was divided as follows: 24 to 13 months prior to the first HF episode; from 12 months to the day of the first HF episode; and the whole period of 24 months prior to the HF episode.

Study population and inclusion criteria

Primary healthcare in this area is provided by 10 large centres with 168 general practitioners (GPs). All the

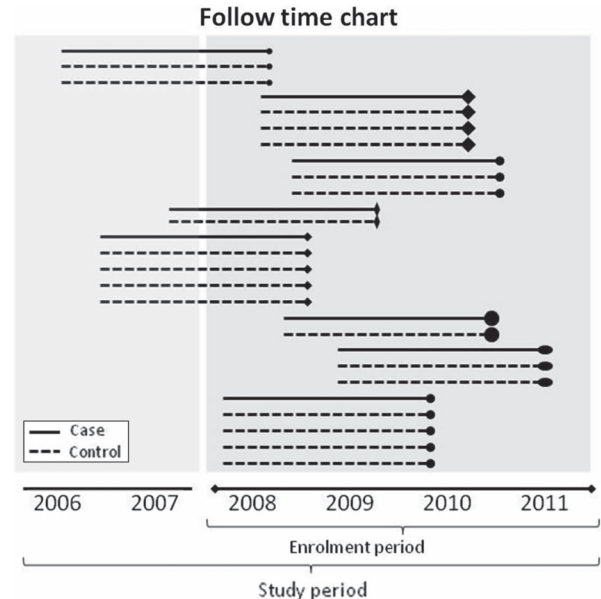


Figure 1. Follow-up chart showing the enrolment period of all participants according to inclusion date.

centres share the same information technology system for recording clinical information electronically. Hospital reports are also available from this system and can be consulted by GPs. Clinical and laboratory test data corresponding to the two years prior to study inclusion were drawn from the primary healthcare records of all participants.

Cases. All patients were admitted because of a first HF episode between 2008 and 2011 to a hospital covering a population of 176 659 inhabitants living in Barcelona (Spain). The diagnoses were retrieved from the hospital discharge reports, which included the International Classification of Diseases (ICD 9: 428).

Controls. Initially, the whole adult population > 30 years old residing in the catchment area was selected, who had consulted their GP in the study period, and who were free from HF on the date of inclusion (ICD 10: I50). ICD 10 was employed because it is the classification system used in primary healthcare records in Catalonia.

Matching process. Groups were paired by age, gender, CVRF, treatment for cardiovascular prevention, and the presence of coronary heart disease.

The process was carried out with the 'nearest neighbour (calliper = 0.2),' 'MatchIt' procedure, which improved the quality of matching (12,13). R Statistical package was used to analyse the results (14). Because of the high number of available controls, it was possible to achieve a very similar co-variable distribution in both groups. As a result, no more than one control for each case was needed to have statistical power to test the main hypothesis.

Variables

The day of the incident HF episode was proposed as the date of study inclusion for both cases and matched controls. Incident HF was defined as a first hospitalization that, on the discharge report, included ICD 9: 428 as a first diagnosis since ICD 9 is the classification system used by hospitals. For each matched potential control, information was collected according to the date of hospital admission of the respective case. This procedure allowed us to obtain the same period of analysis for cases and controls.

Variables used for the matching procedures. Cases and controls were paired for multiple variables that could influence the effect of CVRF on HF occurrence. In addition to socio-demographic variables (gender and age), the following were included in the matching process:

- Cardiovascular co-morbidity: hypertension (ICD 10: I10–I15), dyslipidaemia (ICD10: E78), coronary heart disease (ICD 10: I20–I25), stroke (ICD 10: I61, I63, I64), and diabetes mellitus (ICD 10: E10–E14).
- Drug therapy for CVRF: angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker, dosazoxine, statins, diuretics, calcium channel blockers, beta-blockers, aspirin, and glucose-lowering drugs.

Independent variables considered for analysing the effect of CVRF control on HF occurrence. Values for systolic and diastolic blood pressure, total cholesterol, LDL and HDL cholesterol, heart rate, creatinine, fasting blood glucose, triglycerides, glycosylated haemoglobin, and body mass index were also gathered from medical records. For the purpose of the analysis, measurements were summarized in three groups: the mean of all variable measurements taken the year prior to the inclusion date; the mean of all variable measurements taken in the period 24 to 13 months prior to inclusion; and, and the mean of the whole period (the two years) prior to the inclusion date.

In 2013, European guidelines set a goal to achieve blood pressure levels below 150–140/90 mmHg (15). Lipids were considered well controlled when LDL-cholesterol was lower than 115 mg/dl and glucose control when glycosylated haemoglobin was lower than 7% (16).

Statistical analysis

An initial, descriptive comparison between groups of all variables was performed to evaluate their balance after the matching process. Statistical significance was assessed by the chi-square test when the frequencies of comorbidity and demographic variables were compared among groups. The average determinations between one year and two years prior to the inclusion date were

compared by student's *t*-test. This analysis was conducted with complete cases (Tables 1 and 2).

Different logistic regression models (ENTER method) were developed to analyse the relationship among the values of previous determinations of risk factors and the occurrence of HF. Models were adjusted by variables that were statistically significant at bivariate analysis or were clinically associated with HF. In all models, the goodness of fit hypothesis was tested by the Hosmer–Lemeshow test.

Multiple imputation procedure was used to handle missing data in the multivariate analysis using Stata 12 (Stata Statistical Software: Release 12; StataCorp LP, College Station, TX). The estimates of the parameters for each imputed data set were combined using Rubin's rules. Estimates of the risk differences and odds ratios are reported with corresponding 95% confidence intervals and *P* values. In all tests, a level <0.05 was considered statistically significant.

Ethics

All Helsinki Declaration ethical criteria were respected. Since it was an observational study, participants underwent no interventions other than the usual clinical care. Information from clinical records was correctly anonymized before analysis in order to preserve participants' confidentiality. The study protocol was approved by the Primary Healthcare University Research Institute IDIAP-Jordi Gol.

RESULTS

From the potentially eligible 152 cases and 176 090 controls, 645 participants were finally selected (129 cases and 516 controls) after the matching process, which reduced the probability of a selection bias by 98% (Figure 2).

Table 1. Differences in cardiovascular comorbidity between individuals admitted to hospital because of a first heart failure episode and those without heart failure, after the matching process.

	Cases (heart failure) <i>n</i> = 129 <i>n</i> (%)	Controls (free from heart failure) <i>n</i> = 516 <i>n</i> (%)	<i>P</i> value
Comorbidity			
Smoker	20 (15.5)	58 (11.2)	0.184
Dyslipidaemia	57 (44.2)	230 (44.6)	0.937
Hypertension	87 (67.4)	363 (70.3)	0.52
Coronary heart disease	23 (17.8)	72 (14.0)	0.267
Diabetes	47 (36.4)	215 (41.7)	0.279
Stroke	11 (8.5)	47 (9.1)	0.836
Sex			
Male	68 (52.7)	268 (51.9)	0.875
Female	61 (47.3)	248 (48.1)	

SD, standard deviation.

Table 2. Differences in cardiovascular risk factor levels and their control between individuals admitted to hospital because of a first heart failure episode (cases) and those free from heart failure (controls), according to the time elapsed before the date of inclusion. (The inclusion date was determined by the hospital admission of the corresponding cases.).

Variable	Last 12 months before the date of inclusion				<i>P</i> value	Between 24 and 13 months before the date of inclusion				<i>P</i> value
	Cases (heart failure episode) <i>n</i> = 129		Controls (free from heart failure) <i>n</i> = 516			Cases (heart failure episode) <i>n</i> = 129		Controls (free from heart failure) <i>n</i> = 516		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Body mass index	33.0	6.2	29.8	5.4	0.001	33.4	6.9	30.0	5.1	< 0.001
Heart rate	76.1	10.9	73.6	11.6	0.133	74.9	11.8	73.0	10.9	0.279
Systolic blood pressure	142.2	20.6	135.4	14.4	0.001	138.6	17.8	136.7	16.3	0.413
Diastolic blood pressure	76.2	10.0	73.0	8.9	0.009	75.9	8.0	74.6	9.2	0.331
Blood pressure uncontrolled (%) ^a	44.0%		34.0%		0.12	45.6%		42.9%		0.713
Glycosylated haemoglobin	7.3	1.6	6.9	1.3	0.173	7.3	2.1	6.5	1.2	0.011
Glycosylated haemoglobin ≥ 7 (%)	58.0%		36.5%		0.029	38.1%		24.7%		0.209
Fasting blood glucose	133.6	53.3	128.7	41.4	0.491	153.9	58.0	125.2	33.3	< 0.001
Total cholesterol	186.8	42.8	198.2	39.9	0.059	191.7	43.0	199.0	40.2	0.322
HDL cholesterol	46.5	10.5	52.7	14.0	0.004	47.0	12.5	53.8	14.3	0.016
LDL cholesterol	114.7	33.9	120.8	33.7	0.264	111.0	35.0	121.1	34.3	0.154
Lipids uncontrolled (%) LDL ≥ 115)	50.0%		52.7%		0.734	39.3%		54.6%		0.131
Triglycerides	145.2	71.8	128.2	58.6	0.072	197.8	150.8	126.9	61.7	< 0.001
Renal function (creatinine)	1.0	0.3	1.0	0.4	0.246	1.0	0.3	1.0	0.3	0.406

HDL, high density lipoprotein; LDL, low density lipoprotein.

^aSystolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg.

Population characteristics

The average age was 73.0 (SD: 11.8) years, and 47.9 % were women. Among cases, 49.6% had HF with preserved ejection fraction. The most frequent CVRF present in both groups was hypertension (69.8%), followed

by hypercholesterolaemia (44.5%), type 2 diabetes (40.6%), and smoking (12.1%). Since the two groups were paired for all these factors, differences between them after the matching process were not significant. Mean age was 71.9 (SD: 11.2) in the group of cases and 73.4 (SD: 11.9) in the control group ($P = 0.187$). Other variables are presented in Table 1.

With respect to the number of CVRF present at inclusion, 84.7% had at least one CVRF, and 57.5% had two or more. There were no differences between cases and controls with respect to the number of CVRF present at inclusion (P trend = 0.474).

Cardiovascular risk factors

Regarding the time elapsed before the first HF episode, body mass index was found to be significantly higher in both the previous one and two years (Table 2). Systolic blood pressure was higher during the whole period, particularly in the 12 months prior to the first HF episode. Blood pressure control (systolic blood pressure < 140 mmHg and/or diastolic blood pressure < 90 mmHg) was worse during the whole study period without reaching a statistical significance. Fasting blood glucose levels appeared to be related to HF occurrence. Total cholesterol and low-density lipoprotein cholesterol did not show statistical differences between cases and controls although high-density lipoprotein cholesterol levels were significantly lower in the former.

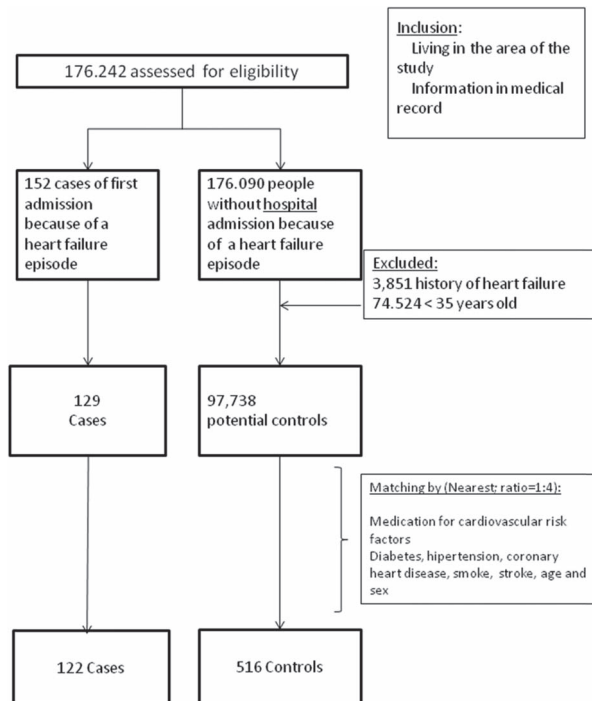


Figure 2. Flow chart showing the participants' selection process.

When analysing all blood pressure measurements taken during the whole period of the study, it was found that 11.0% (mean 2.03) and 6.0% (mean 1.2) of the total ($P = 0.001$) were badly controlled in cases and controls, respectively. No differences were found between cases and controls regarding the percentage of well-controlled glycosylated haemoglobin and LDL measurements.

Multivariable analysis, after adjusting for potential confounding factors, showed that the probability of having an HF episode when systolic blood pressure was greater during the year immediately before diagnosis (OR: 1.03 95% CI: 1.01–1.04) (Table 3).

DISCUSSION

Main findings

In this study was found that even moderately increased levels of body mass index and systolic blood pressure determined a higher risk of having a first HF episode. This risk was especially significant in the case of systolic blood pressure where the possibility of experiencing an HF was 1.3 times higher for every 5 mmHg increment during the year prior to the first HF hospitalization episode. Although fasting blood glucose tended to be high in all HF patients, when diabetic patients were considered separately glycosylated haemoglobin did not affect the risk. Regarding lipid profile, only high-density lipoproteins were related to HF occurrence.

Hypertension

Hypertension is the principal risk factor involved in HF occurrence (17). Aggressive lowering of blood pressure has been reported to play a key role in reducing the risk

of cardiovascular diseases and help prevent HF development (18). However, the extent to which these levels must be lowered to achieve maximum benefit remains controversial (15). A community based cohort study found a continuous positive association between systolic blood pressure and HF risk in the elderly for levels as low as 115 mmHg (19). Nevertheless, a recent meta-analysis did not observe any benefits in reaching blood pressure levels below 150/80 mmHg (20). Regarding the elderly, two Japanese studies reported that reductions of systolic blood pressure under 142 mmHg did not add any benefit to cardiovascular risk (21,22).

The results are in accordance with those recommending a more exhaustive blood pressure control (19).

Body mass index

In concurrence with other studies, a greater proportion of HF in both subjects with a higher body mass index and individuals with worse fasting blood glucose levels was observed (23–25). However, and in contrast to some other studies, we did not find a higher frequency of HF in diabetic patients with poorly controlled glycosylated haemoglobin, which may have been due to our small sample size (26).

With respect to cholesterol and in agreement with a review published by Kannel in 2000, no relationship was observed between total cholesterol and a higher occurrence of HF (3).

Strengths and limitations

The cases included in the study, had a validated HF diagnosis based on discharge reports. More than 170 000 potential controls (all living in the area and complying with the inclusion criteria) were initially retrieved from

Table 3. Crude and adjusted odds ratio for the first heart failure hospital admission episode according to previous clinical determinations. ORs have been calculated according to the variation for each unit of the corresponding variables.

Variable	OR adjusted	95% CI	P value	OR crude	95% CI	P value
Time: 12 months before failure episode						
Body mass index (kg/m ²)	1.06	(0.99–1.13)	0.072	1.09	(1.03–1.15)	0.005
Heart rate (beat/min)	1.02	(1.00–1.05)	0.074	1.02	(1.00–1.05)	0.055
Systolic blood pressure (mm/Hg)	1.03	(1.01–1.04)	0.006	1.03	(1.01–1.04)	<0.001
Diastolic blood pressure (mm/Hg)	1.02	(0.98–1.05)	0.351	1.04	(1.01–1.07)	0.002
HDL cholesterol (mg/dl)	0.95	(0.92–0.98)	0.005	0.95	(0.92–0.98)	0.001
LDL cholesterol (mg/dl)	1.00	(0.99–1.01)	0.469	0.99	(0.99–1.00)	0.226
Time: between 24 and 13 months before heart failure episode						
Body mass index (kg/m ²)	1.08	(1.01–1.15)	0.022	1.09	(1.04–1.16)	0.001
Heart rate (beat/min)	1.02	(0.99–1.05)	0.159	1.02	(1.00–1.05)	0.086
Systolic blood pressure (mm/Hg)	1.01	(0.99–1.03)	0.274	1.01	(0.99–1.03)	0.263
Diastolic blood pressure (mm/Hg)	1.00	(0.97–1.04)	0.798	1.02	(1.00–1.05)	0.1
HDL cholesterol (mg/dl)	0.97	(0.94–1.00)	0.064	0.97	(0.94–1.00)	0.028
LDL cholesterol (mg/dl)	1.00	(0.99–1.01)	0.578	0.99	(0.99–1.00)	0.280

OR adjusted, odds ratio adjusted by logistic model by presented variables; OR crude, odds ratio without adjustment; 95% CI, 95% confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein

primary healthcare records, which signified a completely external validation of our population. A considerable number of the controls were originally from other European, African, Asian, and Latin American countries. Thus, the population was sufficiently heterogeneous to ensure external validity to many areas with similar population characteristics.

Propensity score methodology allowed us almost to eliminate the potential bias between cases and controls and to introduce a high number of co-variables into the matching process.

Unlike other studies, data from primary healthcare records were used. GPs have a privileged role in the care of a population at high cardiovascular risk and with varying chronic conditions (27,28) because of the possibility of carrying out a long-term follow-up of these patients. The asymptomatic left ventricular systolic dysfunction has been recently reported in approximately one out of every 20 at-risk medical inpatients with at least one HF risk factor (29).

Although HF still has a poor prognosis, the widespread use of evidence-based treatment has improved outcomes (30). Since a substantial number of patients with HF have preserved left ventricular ejection fraction, and that this condition is particularly frequent in older, female, obese, and hypertensive patients, we should be especially careful in treating these subjects and applying preventive measures, which have been proven effective (31).

Since this was an observational retrospective analysis, there could have been some variability in registration and quality of CVRF measurements. Laboratory tests in clinical practice are, however, well standardized and, in this study, centralized in two laboratories. Blood pressure measure procedure has a clear protocol in the primary care setting and it is usually taken with periodically calibrated automatic devices.

We have only employed data from the two years prior to the first HF episode, which means that the long-term effect of CVRF cannot be evaluated.

The lengthy period of analysis (2006–2011) could also have influenced variability in the quality of available data (during this period administrative changes were carried out to improve the register of information in the medical records). The issue was resolved by matching the data from each case with a control at the same period.

Anti-hypertensive medication was included in the matching process to minimize its effect on both CVRF control and the probability of having an HF. Nevertheless, we cannot be sure whether subjects taking more anti-hypertensive drugs had a worse prognosis, in spite of reaching lower blood pressure levels, due to the harmful effects of these medications. The issue could be raised as a future research question.

Implications for clinical practice

These results should encourage GPs to fill the preventive gap that occurs with many patients due to their not displaying a high-risk profile. The results indicate the relevance of sustained, well-controlled CVRF. Moreover, we would like to stress that the continuity and longitudinality of care provided by primary healthcare professionals are crucial in order to prevent a first episode of HF in a population at risk.

Conclusion

Increased levels of body mass index and systolic blood pressure during the previous 24 months may determine a higher risk of having a first HF hospitalization episode.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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