Cardiac Rehabilitation for Patients with Heart failure: Association With Readmission and Mortality Risk

Lau Caspar Thygesen[1]; Line Zinckernagel[1]; Hasnain Dalal[2,3]; Kenneth Egstrup[4]; Charlotte Glümer[5]; Morten Grønbæk[1]; Teresa Holmberg[1]; Lars Køber[6]; Karen la Cour[7]; Anne Nakano[8]; Claus Vinther Nielsen[9,10,11]; Kirstine Lærum Sibilitz[6]; Janne Schurmann Tolstrup[1]; Ann Dorthe Zwisler[12]; Rod S Taylor[1,13]

[1]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[2]University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, UK

[3]Primary care Research Group, University of Exeter Medical School, St Luke's Campus, Exeter, UK

[4]Department of Cardiovascular Research, Odense University Hospital, Svendborg, Denmark

[5]Center for Diabetes in The City of Copenhagen, Copenhagen, Denmark

[6]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[7]Department of Public Health, University of Southern Denmark, Odense, Denmark

[8]The Danish Clinical Registries (RKKP), Aarhus. Denmark

[9]Institute of Public Health, Aarhus University, Aarhus, Denmark

[10]DEFACTUM, Central Denmark Region, Aarhus, Denmark

[11]Regional Hospital West Jutland, Herning, Denmark

[12]REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital, and University of Southern Denmark, Nyborg, Denmark

[13]Institute of Health and Well Being, University of Glasgow, Glasgow, UK

Corresponding author:

Lau Caspar Thygesen

National Institute of Public Health

University of Southern Denmark

Studiestræde 6

DK-1455 København K

Denmark

E-mail: lct@sdu.dk

Phone: +4565507771

Word count (abstract): 250

Word count (main text excluding abstract): 3167

Abstract

Aims: To examine the temporal trends and factors associated with national CR referral and compare the risk of hospital readmission and mortality in those referred for CR versus no referral.

Methods and results: This cohort study includes all adult patients alive 120 days from incident HF identified by the Danish Heart Failure Register (n=33,257) between 2010 and 2018. Multivariable logistic regression models were used to assess the association between CR referral and patient factors and acute all-cause hospital readmission and mortality at 1-year following HF admission.

Overall, 46.7% of HF patients were referred to CR, increasing from 31.7% in 2010 to 52.2% in 2018. Several factors were associated with lower odds of CR referral: male sex (odds ratio (OR): 0.85; 95% CI, 0.80-0.89), older age, unemployment, retirement, living alone, non-Danish ethnic origin, low educational level, New York Heart Association (NYHA) class IV vs I. (OR: 0.75; 0.60-0.95), left ventricular ejection fraction (LVEF) >40% and comorbidity (stroke, chronic kidney disease, atrial fibrillation/flutter, and diabetes). Myocardial infarction, arthritis, coronary artery bypass grafting, percutaneous coronary intervention, valvular surgery, NYHA class II, and use of angiotensin-converting enzyme inhibitors were associated with higher odds of CR referral. CR referral was associated with lower risk of acute all-cause readmission (OR: 0.92; 0.87-0.97) and all-cause mortality (OR: 0.65; 0.58-0.72).

Conclusion: Although increased over time, only one in two HF patients in Denmark were referred to CR in 2018. Strategies are needed to reduce referral disparities, focusing on subgroups of patients to be at highest risk of non-referral.

Keywords: Heart failure, cardiac rehabilitation, secondary prevention, guideline adherence, registries.

Introduction

Heart failure (HF) is a major cause of morbidity, mortality and healthcare costs.[1, 2] It affects around 1 to 2 % of the adult population in developed countries,[1, 2] and accounts for 1 to 3% of the total healthcare expenditure in North America, Western Europe and Latin America.[3, 4] People with HF experience marked reductions in their exercise capacity which is associated with reduced quality of

life and adverse clinical outcomes.[5] The prognosis of HF is poor with high hospitalization and mortality rates.[1, 2] In the US, HF results in about 1.0 million hospitalizations annually.[6]

Meta-analyses of randomized controlled trials (RCT) have demonstrated that exercise-based cardiac rehabilitation (CR) improves health-related quality of life, reduces hospitalizations and is cost-effective.[7-12] The effect on mortality is, however, equivocal.[7, 13] Accordingly, the current guidelines from the American College of Cardiology, American Heart Association and the European Society of Cardiology recommend the provision of exercise-based CR (Class I, Level A evidence) for the management of HF.[1, 14]

Despite this evidence and strong guideline recommendation, CR referral remains suboptimal among patients with HF.[15-22] However, previous studies of CR referral and access are typically based on data sets from single or a small number of centers and therefore likely to be prone to bias and lack of external generalizability and statistical power. Therefore, we undertook a national register-based study including all HF patients admitted to a hospital in Denmark in 2010-2018 to: (1) examine the temporal trends and factors associated with CR referral; and (2) compare the risk of acute all-cause readmission and mortality in those referred for CR compared to those not referred.

Methods

Study design

This was a national register-based cohort study of all adult HF patients admitted to a hospital in Denmark in the period 2010-2018.

Setting

The Danish healthcare system is universal with the goal of equal access to healthcare for all 5.8 million inhabitants. The majority of healthcare services including CR is financed by general taxes.[23]

The Danish Health Authority released the first national guidelines on CR with exercise training in 1997,[24] and HF became an indication for CR in 2004.[25] According to national guidelines, patients should be referred from the hospital to CR either at the hospital or the municipalities, no later than at the time of discharge.[26]

Data sources

The Danish Heart Failure Registry (DHFR) is a nationwide register established in 2003 as a quality improvement initiative aimed at monitoring and improving quality of care for patients with specific severe diseases, including HF.[27] Reporting is mandatory for all hospital departments and outpatient cardiology clinics treating patients with HF. The register holds information on all adult patients (≥18 years old) with incident HF and provides information on referral to exercise-based CR and clinical factors. Less-severe cases may not be recorded in the DHFR if only treated in general practice.[27]

The Civil Registration System includes all Danish residents and provides person identification number to all residents[28], which is used by all public authorities and registers making linkage possible.

The Danish National Patient Register includes all inpatient hospital contacts since 1977 and also emergency room and outpatient contacts since 1995.[29] Each registration has information on primary and secondary diagnoses.

The Cause of Death Register provides information on underlying and contributing causes of death.[30]

Information on socio-economic factors was included from the Education Register[31] and the Employment Classification Module.[32]

Study population

The study population was based on DHFR. The dataset comprised of 36,361 adult patients admitted with an incident primary diagnosis of HF between 1/1-2010 and 31/12-2018 since we only had information from the Danish National Patient Register until 2018.

We linked this population with Civil Registration System and excluded those patients not in the register from 2009 to 2019 (n=49) or those not in the register in the year of the heart failure diagnosis (n=19). This resulted in a study population of 35,052. Since rehabilitation is implemented within 120 days after HF admission, we excluded those patients who died within 120 days from HF admission (n=1795), leaving a study population of 33,257 patients.

Variables

We identified exercise-based CR referral within 120 days from HF admission by combining information from DHFR (whether the patient was referred to or had started supervised physical training by physiotherapist) and the Danish National Patient Register (procedure codes related to physical training.)[33] Information on data sources and coding of all variables in eTable 1.

Information on demographics included sex, age, calendar-year and region.

Socio-economic factors included employment status, living alone, ethnic origin and educational level.

Clinical factors included admission type (in- or outpatient), New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), comorbidities (history of myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, and diabetes mellitus), surgical interventions (coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and valvular surgery) and use of drugs (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists/digoxin).

We included risk of acute all-cause readmission as an outcome and followed HF patients in the Danish National Patient Register for all acute admissions. We also evaluated cause-specific mortality with heart failure as the underlying cause of death based on The Cause of Death Register and overall mortality based on the Civil Registration System.

Statistical analyses

Descriptive statistics were reported as numbers, proportions, means and standard deviations. Differences were tested with chi2- and t-tests for categorical and continuous variables, respectable. The trend in CR referral over time was assessed using linear regression. The associations between CR referral and demographic, socio-economic, and clinical factors were evaluated using multivariable logistic regression models adjusted for all variables (sex, age, calendar-year, region, admission type, employment status, living alone, ethnic origin, educational level, NYHA class, LVEF, myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, diabetes mellitus, CABG, PCI, valvular surgery, and use of beta-blockers, ACE inhibitors, or aldosterone antagonists/digoxin) and Danish geographical regions. The main analyses were conducted among patients alive 120 days after first heart failure admission (n=33,257). As a sensitivity analysis, we also performed multivariable logistic regression modelling based on all HF patients (n=35,052).

The associations between CR referral and the risk of acute all-cause readmission and mortality (HF-specific and overall) were evaluated by multivariable logistic regression models. These analyses were conducted among patients alive 120 days after first HF admission and followed up for a year after admission. We included patients between 2010 and 2017 in the analyses of acute all-cause readmission and overall mortality (n=29,501) since outcome data was available until 2018, and patients between 2010 and 2016 for cause-specific mortality (n=25,921) since the Cause of Death Register was updated to 2017. We conducted both a model adjusted for sex and age and a model adjusted for all variables (as listed above). As a sensitivity analysis, we

performed the analyses of acute all-cause readmission and overall mortality stratified by NYHA classes and LVEF categories.

Logistic regression model results are reported as odds ratios (OR) with 95% confidence intervals (95% CI). All statistics performed using SAS version 9.4.

Ethics

The study was approved by the University of Southern Denmark (no. 10.553). According to Danish law, this study based on registers does not require formal ethical approval.

Results

CR referral levels and trend over time

The study population included 33,257 adult patients with an incident diagnosis of HF in the period 2010-2018 who survived at least 120 days after first HF-admittance (Fig. 1). Over this 9-year period 46.7% of patients with HF were referred for CR. CR referral increased from 37.7% in 2010 to 54.1% in 2017 and decrease slightly in 2018 (52.2%) (slope: 2.3%; P-trend <0.0001) (Fig. 2). This trend was similar across LVEF categories (i.e., 1.8-2.5% referral per year). However, patients with an LVEF 50+% and in some periods also patients with LVEF <25% and 41-49% appeared to be referred less than others.

Factors associated with CR referral

In the age-, sex- and region-adjusted analyses, the majority of patient demographic, socio-economic and clinical factors were associated with CR referral (Table 1).

In the all variable adjusted analyses, the following factors were associated with lower CR referral (see Table 2): male sex (OR: 0.85; 95% CI, 0.80-0.89), older age, unemployment (OR: 0.89; 0.80-0.99), retirement (OR: 0.79; 0.73-0.85), living alone (OR: 0.76; 0.72-0.80), non-Danish ethnic origin

(OR: 0.85; 0.77-0.94), low educational level (e.g. basic school vs. theoretical education, OR: 0.66; 0.61-0.70), NYHA class IV vs I (OR: 0.75; 0.60-0.95), LVEF>40% and comorbidity (stroke (0.90;0.83-0.97), chronic kidney disease (OR: 0.72 ;0.66-0.79), atrial fibrillation/flutter (OR: 0.84; 0.79-0.88), and diabetes (OR: 0.84; 0.79-0.90).

Myocardial infarction, arthritis, CABG, PCI, valvular surgery, NYHA class II, and use of ACE inhibitors were associated with higher CR referral (Table 2).

Admission type (inpatient vs. outpatient), use of beta-blockers and aldosterone antagonists/digoxin were not associated with CR referral (Table 2).

As a sensitivity analysis, we performed the same analyses based on all HF patients, i.e., not conditioning for survival at 120 days. These results showed almost same results as the main analysis (eTable 2).

Association between CR referral and acute all-cause readmission and mortality

CR referral was associated with a reduction in the risk of acute all-cause readmission with an adjusted OR of 0.92 (95% CI: 0.87-0.97) (Table 3). CR referral was also associated with lower odds of overall mortality (OR: 0.65; 0.58-0.72). Whilst similar association between CR referral and HF-specific mortality was seen, it was not statistically significant (OR: 0.66; 0.42-1.04).

As sensitivity analyses, we evaluated the risk of acute all-cause readmission and all-cause mortality stratified by NYHA classes and LVEF categories. These results showed similar results in all subgroups (see eTable 3).

Discussion

Our study of CR referral among all adult patients in Denmark admitted with incident HF between 2010 and 2018 presents several noteworthy findings. First, there was an increasing trend in CR referral during the period, yet only one in two patients were referred to CR in 2018. Second, major

disparities in CR referral were observed across different demographic, socio-economic and clinical subgroups. Third, CR was associated with lower odds of acute all-cause readmission, HF-specific mortality (not statistically significant) and overall mortality. Our results underline the urgent need for improving levels of CR referral and reduce the disparities in CR access by targeting patient subgroups in high risk of not being referred such as patients with older age, living alone, low educational level, NYHA class IV, and several comorbidities.

CR referral levels

Exercise-based CR has been demonstrated to be an efficacious intervention for people with HF. The 2019 Cochrane review of 44 randomized controlled trials in 5,783 HF patients showed that participation in CR results in a reduction in all-cause hospitalization (relative risk 0.70, 95% CI: 0.60-0.83) and a clinically meaningful improvement in health-related quality of life (Minnesota Living with Heart Failure Questionnaire mean difference: -7.1, 95% CI -10.5 to -3.7).[7] In spite of this evidence and strong recommendation by current clinical guidelines,[1, 14, 26] our study shows that only one in two patients were referred in 2018. Considerably lower levels of CR referral have been reported in other country settings. For example, in the US and UK only 10-13% of HF patients are referred to CR.[18, 22] Moreover, the ExtraHF survey of 172 European cardiac centers across 41 European countries (78,514 HF patients), found that an exercise CR program was lacking in 40% of the centers with regional differences (23%-64%).[17] Lack of national and local guidelines and inadequate insurance coverage for HF patients were highlighted as explanations in these studies. The higher CR referral figures in Denmark, likely reflect universal healthcare coverage and two key national initiatives i.e. regular updates of the national guidelines on CR (2013 and 2018), that may have led to an increase in referral physicians awareness of the evidence base of CR, together with the implementation of the Danish Heart Failure Register from 2003, an initiative aimed at monitoring and improving the quality of care. Nevertheless, although there was a rising trend in the proportion of patients with HF being referred for CR, we demonstrated a persistent gap between the national guideline recommendation and clinical practice.

Factors associated with CR referral

The barriers to CR access and specifically referral among HF patients are potentially complex and may include organizational (e.g., automated referral systems), clinician level (e.g., lack of knowledge), and patient level factors.[34] Our study focuses on patient level factors.

Patient socio-economic factors including non-Danish ethnic origin, living alone, unemployment, retirement and lower educational level were independently associated with lower referral, demonstrating social inequality in CR referral. Similar disparities have been found in other cardiac groups,[35, 36] and our study confirms the results to be consistent in HF patients even in a country with universal healthcare coverage. Contrary to previous studies,[15, 18] male sex was associated with lower CR referral.

Myocardial infarction as well as CABG, PCI and valvular surgery were associated with higher CR referral. This was expected because they are more traditional indications for CR, and other studies have similarly demonstrated relatively higher CR among such cardiac groups.[15, 16, 18] In the Netherlands, 29% of patients with acute coronary syndrome and/or cardiac procedure participated in CR, compared to 3% of HF patients,[15] and in the EuroCaReD study 2,054 CR patients across 12 European countries found that only 4% were admitted to CR due to HF.[16] Patients with reduced ejection fraction (HFrEF, EF≤40%) were also more likely to be referred to CR in our study, although international and national guidelines recommend CR to HF patients, regardless of ejection fraction.[1, 14, 26, 37] There is increasing evidence that exercise training in HF patients with preserved ejection fraction (HFpEF) has positive effects on exercise capacity, and quality of life,[8, 11, 12, 14] but US Medicare coverage for CR to HF patients is for instance still restricted to HFrEF.[38] Patients with HFpEF may be increasingly important since it is the fastest growing form of HF.[14] Please note, that the proportion of patients with an EF>40% (HFpEF/HFmrEF) is 13% in our study population. This indicates that this patient group is not recorded in DHFR to the same extent as

HFrEF, since it has been estimated that about 50% of HF patients have HFpEF/HFmrEF.[1] This may be due to a weaker evidence base for pharmacological treatment of this patient group.[1]

Older patients, patients with comorbidity (stroke and chronic kidney disease, atrial fibrillation/flutter and diabetes), and severe HF symptoms were associated with lower CR referral, indicating that healthcare professionals may perceive this group to be less likely to benefit from CR. Other studies have also found that comorbidity is associated with lower referral and CR uptake.[15, 18] It has previously been suggested that physicians who incorporate evidence-based pharmacological treatment are more likely to refer patients to CR.[18] This was, nevertheless, only the case for one out of three cardiovascular medications in our study.

CR referral and acute all-cause readmission and all-cause mortality

We found that CR referral was associated with lower odds of acute all-cause readmissions, HF-related mortality (not statistically significant) and all-cause mortality. Whilst our findings are in accordance with previous observational analyses of improvements in admissions and survival with CR following acute coronary syndrome and post-revascularisation,[39-42] there have been few such analyses in HF. One study found in line with our results that CR participation is associated with an all-cause mortality risk reduction of 28% among HF patients,[43] and another study showed larger estimates with 42% lower odds of all-cause mortality and 26% lower odds of hospitalization.[44] In interpreting these results, it is important to consider the observational design and risk of bias. We uniquely utilize nationwide data and used multivariable analyses including many covariates, but still need to acknowledge especially the risk of confounding by indication. RCTs have similarly demonstrated that exercise-based CR reduces hospitalizations,[7] but have not been able to demonstrate lowered mortality in HF patients.[7, 13]

Clinical and health policy implications

Our findings underline the need for improving CR referral. Strategies to promote CR referral are needed to improve access to CR, and it is paramount to address the disparities in CR referral; not

least because the incidence of HF is higher and prognosis poorer in many of the subgroups associated with low CR referral.[2, 45] Moreover, the recent meta-analysis (ExTraMATCH II) showed that the benefits of CR are consistent across HF patient subgroups (age, sex, ethnicity, NYHA class, ischemic etiology, ejection fraction, and baseline exercise capacity).[8] Raising healthcare professionals' awareness about guideline recommendations, the benefits of CR in HF, and current disparities in referral may be effective, as well as implementation of automatic referral systems. A recent study has for instance showed that an opt-out CR referral pathway that automatically identify eligible patients and notify staff was associated with a significant increase in referrals.[46] Moreover, it is well-known that a large proportion of cardiac patients referred to CR do not participate.[47] Travelling time and cost to a rehabilitation center, dislike of group exercise, and inconvenient timings (e.g. within working hours) are all barriers to participation.[48] This calls for utilization of alternative methods of CR delivery such as home-based and virtual approaches.[49] Home-based CR has similar benefits to center-based CR in terms of HRQoL, all-cause readmissions, and cost.[50]

Limitations

Our nationwide study has several strengths also in comparison to previous analyses: high external validity, large sample size, no loss to follow-up, and access to a wide range of patient level factors potentially associated with CR referral.

However, we recognize that our study has limitations. First, by focusing on CR referral we do not know how many of those referred attended CR. As it is not currently mandatory for municipalities (only for hospitals) to register information on CR participation, this information is not comprehensively available in Danish health registers. Second, our analysis may have underestimated the 'appropriate referral' proportion as it includes HF patients in the denominator who might have been deemed unsuitable for CR. The registration of referral to exercise-based CR is mandatory to all hospitals treating HF patients. In addition, thorough efforts are made to ensure data validity by conducting regular multidisciplinary audits which include evaluation of

completeness of patient registration against hospital discharge registers. Third, since this is an observational study, confounding cannot be ruled out, even though, we had access to extensive patient information to reduce the risk of confounding. Fourth, the results of this national study may not be generalizable to other international healthcare settings. Finally, although our analysis predates the onset of COVID-19 pandemic, global reductions in healthcare access over the last years, underscore the importance of our findings in informing future improvements in CR access.

Conclusions

Although CR referral for patients admitted with heart failure in Denmark has increased over time, our data from 2018 shows that only one in two HF patients are referred to CR. We identified important disparities in CR referral linked to particularly patient demographic, socio-economic, and clinical characteristics. CR referral is associated with lower odds in acute all-cause readmission and mortality. These findings underline the urgent need for strategies to promote CR referral to improve access to CR, especially in those patient groups at highest risk of not being referred.

Acknowledgements

Thank you to the staff of the hospital departments caring for patients with HF. Their continuous effort and contribution in the collection of data to the Danish Heart Failure Registry are making studies like this possible.

Funding

This work was supported by The Danish Heart Foundation [grant number: 20-R145-A9654-22157].

Conflict of interests

Dr. Zinckernagel reports grants from The Danish Heart Foundation, during the conduct of the study. Dr. Kober reports personal fees from speakers honorarium from Novo, Novartis,

AstraZeneca and Boehringer, outside the submitted work. Dr. Taylor reports grants from DK:REACH-HF, during the conduct of the study; grants from REACH-HFpEF trial, grants from SCOT:REACH-HF trial, outside the submitted work. All other Authors declare no conflict of interests.

Data availability

Data are linked administrative and research registers and can be accessed through affiliation with University of Southern Denmark. Other researchers can apply for the same data through Statistics Denmark and the Danish Clinical Registries.

Authors' contributions

LCT, KE, MG, KlC, AN, ADZ and RST designed and conceptualized the study. LCT analyzed the data in close collaboration with all authors. LCT, LZ and RST drafted the first version of the manuscript. All authors interpreted the data and contributed to the development of the manuscript including critical revision and drafting for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021 2021/08/28. DOI: 10.1093/eurheartj/ehab368.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021; 143: e254-e743. 2021/01/28. DOI: 10.1161/CIR.0000000000000950.
3. Metra M and Teerlink JR. Heart failure. *Lancet* 2017; 390: 1981-1995. 2017/05/04. DOI: 10.1016/S0140-6736(17)31071-1.
4. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail* 2014; 1: 4-25. 2014/09/01. DOI: 10.1002/ehf2.12005.
5. Working Group on Cardiac R, Exercice P and Working Group on Heart Failure of the European Society of C. Recommendations for exercise training in chronic heart failure patients. *Eur Heart J* 2001; 22: 125-135. 2001/02/13. DOI: 10.1053/euhj.2000.2440.
6. Murphy SP, Ibrahim NE and Januzzi JL, Jr. Heart Failure With Reduced Ejection Fraction: A Review. *JAMA* 2020; 324: 488-504. 2020/08/05. DOI: 10.1001/jama.2020.10262.

7. Taylor RS, Long L, Mordi IR, et al. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. *JACC Heart Fail* 2019; 7: 691-705. 2019/07/16. DOI: 10.1016/j.jchf.2019.04.023.
8. Taylor RS, Walker S, Smart NA, et al. Impact of Exercise Rehabilitation on Exercise Capacity and Quality-of-Life in Heart Failure: Individual Participant Meta-Analysis. *J Am Coll Cardiol* 2019; 73: 1430-1443. 2019/03/30. DOI: 10.1016/j.jacc.2018.12.072.
9. Shields GE, Wells A, Doherty P, et al. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart* 2018; 104: 1403-1410. 2018/04/15. DOI: 10.1136/heartjnl-2017-312809.
10. Fukuta H, Goto T, Wakami K, et al. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2016; 23: 78-85. 2014/12/19. DOI: 10.1177/2047487314564729.
11. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail* 2015; 8: 33-40. 2014/11/18. DOI: 10.1161/CIRCHEARTFAILURE.114.001615.
12. Fukuta H, Goto T, Wakami K, et al. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019; 24: 535-547. 2019/04/30. DOI: 10.1007/s10741-019-09774-5.
13. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; 301: 1439-1450. 2009/04/09. DOI: 10.1001/jama.2009.454.
14. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 62: e147-239. 2013/06/12. DOI: 10.1016/j.jacc.2013.05.019.
15. van Engen-Verheul M, de Vries H, Kemps H, et al. Cardiac rehabilitation uptake and its determinants in the Netherlands. *Eur J Prev Cardiol* 2013; 20: 349-356. 2012/02/22. DOI: 10.1177/2047487312439497.
16. Benzer W, Rauch B, Schmid JP, et al. Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. *Int J Cardiol* 2017; 228: 58-67. 2016/11/20. DOI: 10.1016/j.ijcard.2016.11.059.
17. Piepoli MF, Binno S, Coats AJS, et al. Regional differences in exercise training implementation in heart failure: findings from the Exercise Training in Heart Failure (ExTraHF) survey. *Eur J Heart Fail* 2019; 21: 1142-1148. 2019/07/26. DOI: 10.1002/ejhf.1538.
18. Golwala H, Pandey A, Ju C, et al. Temporal Trends and Factors Associated With Cardiac Rehabilitation Referral Among Patients Hospitalized With Heart Failure: Findings From Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol* 2015; 66: 917-926. 2015/08/22. DOI: 10.1016/j.jacc.2015.06.1089.
19. Sola M, Thompson AD, Coe AB, et al. Utilization of Cardiac Rehabilitation Among Cardiac Intensive Care Unit Survivors. *Am J Cardiol* 2019; 124: 1478-1483. 2019/09/11. DOI: 10.1016/j.amjcard.2019.07.039.
20. Dalal HM, Wingham J, Palmer J, et al. Why do so few patients with heart failure participate in cardiac rehabilitation? A cross-sectional survey from England, Wales and Northern Ireland. *Bmj Open* 2012; 2: e000787. 2012/03/29. DOI: 10.1136/bmjopen-2011-000787.
21. Buttery AK, Carr-White G, Martin FC, et al. Limited availability of cardiac rehabilitation for heart failure patients in the United Kingdom: findings from a national survey. *Eur J Prev Cardiol* 2014; 21: 928-940. 2013/03/21. DOI: 10.1177/2047487313482286.
22. National Institute for Cardiovascular Outcomes Research (NICOR). *National heart failure audit (NHFA) 2020 summary report (2018/19 data)*. 2019. Healthcare Quality Improvement Partnership (HQIP).
23. The Ministry of Health. *Healthcare in Denmark - An overview*. 2017. København K, Denmark.

24. Zwisler AD, Traeden UI, Videbaek J, et al. Cardiac rehabilitation services in Denmark: still room for expansion. *Scand J Public Health* 2005; 33: 376-383.
25. The Danish Health Authority. *Guideline on Cardiac Rehabilitation at Hospitals [Vejledning om hjerterehabilitering på sygehuse]*. 2004.
26. The Danish Health Authority. *Anbefalinger for tværsektorielle forløb for mennesker med hjertesygdom [Guidelines on cross-sectional patient journeys for patients with heart disease]* 2018.
27. Schjodt I, Nakano A, Egstrup K, et al. The Danish Heart Failure Registry. *Clin Epidemiol* 2016; 8: 497-502. 2016/11/09. DOI: 10.2147/CLEP.S99504.
28. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39: 22-25. 2011/08/04. DOI: 10.1177/1403494810387965.
29. Lynge E, Sandegaard JL and Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; 39: 30-33. 2011/08/04. DOI: 10.1177/1403494811401482.
30. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011; 39: 26-29. DOI: 10.1177/1403494811399958.
31. Jensen VM and Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011; 39: 91-94. 2011/08/04. DOI: 10.1177/1403494810394715.
32. Petersson F, Baadsgaard M and Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011; 39: 95-98. 2011/08/04. DOI: 10.1177/1403494811408483.
33. The Danish Clinical Registries (RKKP) and the expert panel for The Heart Failure Registry. *Yearly report for the Danish Heart Failure Registry 2019 [Dansk Hjerterehabiliteringsdatabase (DHRD). Årsrapport 2019]*. 2020.
34. Ragupathi L, Stribling J, Yakunina Y, et al. Availability, Use, and Barriers to Cardiac Rehabilitation in LMIC. *Glob Heart* 2017; 12: 323-334 e310. 2017/03/18. DOI: 10.1016/j.gheart.2016.09.004.
35. Hansen TB, Berg SK, Sibilitz KL, et al. Availability of, referral to and participation in exercise-based cardiac rehabilitation after heart valve surgery: Results from the national CopenHeart survey. *Eur J Prev Cardiol* 2015; 22: 710-718. 2014/05/27. DOI: 10.1177/2047487314536364.
36. Li S, Fonarow GC, Mukamal K, et al. Sex and Racial Disparities in Cardiac Rehabilitation Referral at Hospital Discharge and Gaps in Long-Term Mortality. *J Am Heart Assoc* 2018; 7 2018/04/08. DOI: 10.1161/JAHA.117.008088.
37. The Danish Health Authority. *National klinisk retningslinje for hjerterehabilitering 2013 [National clinical guidelines on cardiac rehabilitation 2013]*. 2015.
38. United Healthcare Medicare Advantage. Cardiac Rehabilitation Programs for Chronic Heart Failure (NCD 20.10.1). 2021.
39. de Vries H, Kemps HM, van Engen-Verheul MM, et al. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *Eur Heart J* 2015; 36: 1519-1528. 2015/04/19. DOI: 10.1093/eurheartj/ehv111.
40. Patel DK, Duncan MS, Shah AS, et al. Association of Cardiac Rehabilitation With Decreased Hospitalization and Mortality Risk After Cardiac Valve Surgery. *JAMA Cardiol* 2019; 4: 1250-1259. 2019/10/24. DOI: 10.1001/jamacardio.2019.4032.
41. Beatty AL, Doll JA, Schopfer DW, et al. Cardiac Rehabilitation Participation and Mortality After Percutaneous Coronary Intervention: Insights From the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *J Am Heart Assoc* 2018; 7: e010010. 2018/10/30. DOI: 10.1161/JAHA.118.010010.
42. Ekblom O, Cider A, Hambraeus K, et al. Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women: results from the SWEDEHEART registry. *Eur J Prev Cardiol* 2021 2021/06/08. DOI: 10.1093/eurjpc/zwab083.

43. Eijsvogels TMH, Maessen MFH, Bakker EA, et al. Association of Cardiac Rehabilitation With All-Cause Mortality Among Patients With Cardiovascular Disease in the Netherlands. *JAMA Netw Open* 2020; 3: e2011686. 2020/07/28. DOI: 10.1001/jamanetworkopen.2020.11686.
44. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, et al. Cardiac rehabilitation and all-cause mortality in patients with heart failure: a retrospective cohort study. *Eur J Prev Cardiol* 2021 2021/08/02. DOI: 10.1093/eurjpc/zwab035.
45. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018; 391: 572-580. 2017/11/28. DOI: 10.1016/S0140-6736(17)32520-5.
46. Adusumalli S, Jolly E, Chokshi NP, et al. Referral Rates for Cardiac Rehabilitation Among Eligible Inpatients After Implementation of a Default Opt-Out Decision Pathway in the Electronic Medical Record. *JAMA Netw Open* 2021; 4: e2033472. 2021/01/15. DOI: 10.1001/jamanetworkopen.2020.33472.
47. Parashar S, Spertus JA, Tang F, et al. Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction. *Circulation* 2012; 126: 1587-1595. 2012/08/30. DOI: 10.1161/CIRCULATIONAHA.111.088799.
48. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *Int J Cardiol* 2016; 223: 436-443. 2016/08/25. DOI: 10.1016/j.ijcard.2016.08.120.
49. Dalal HM, Doherty P, McDonagh ST, et al. Virtual and in-person cardiac rehabilitation. *BMJ* 2021; 373: n1270. 2021/06/05. DOI: 10.1136/bmj.n1270.
50. Anderson L, Sharp GA, Norton RJ, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev* 2017; 6: CD007130. 2017/07/01. DOI: 10.1002/14651858.CD007130.pub4.

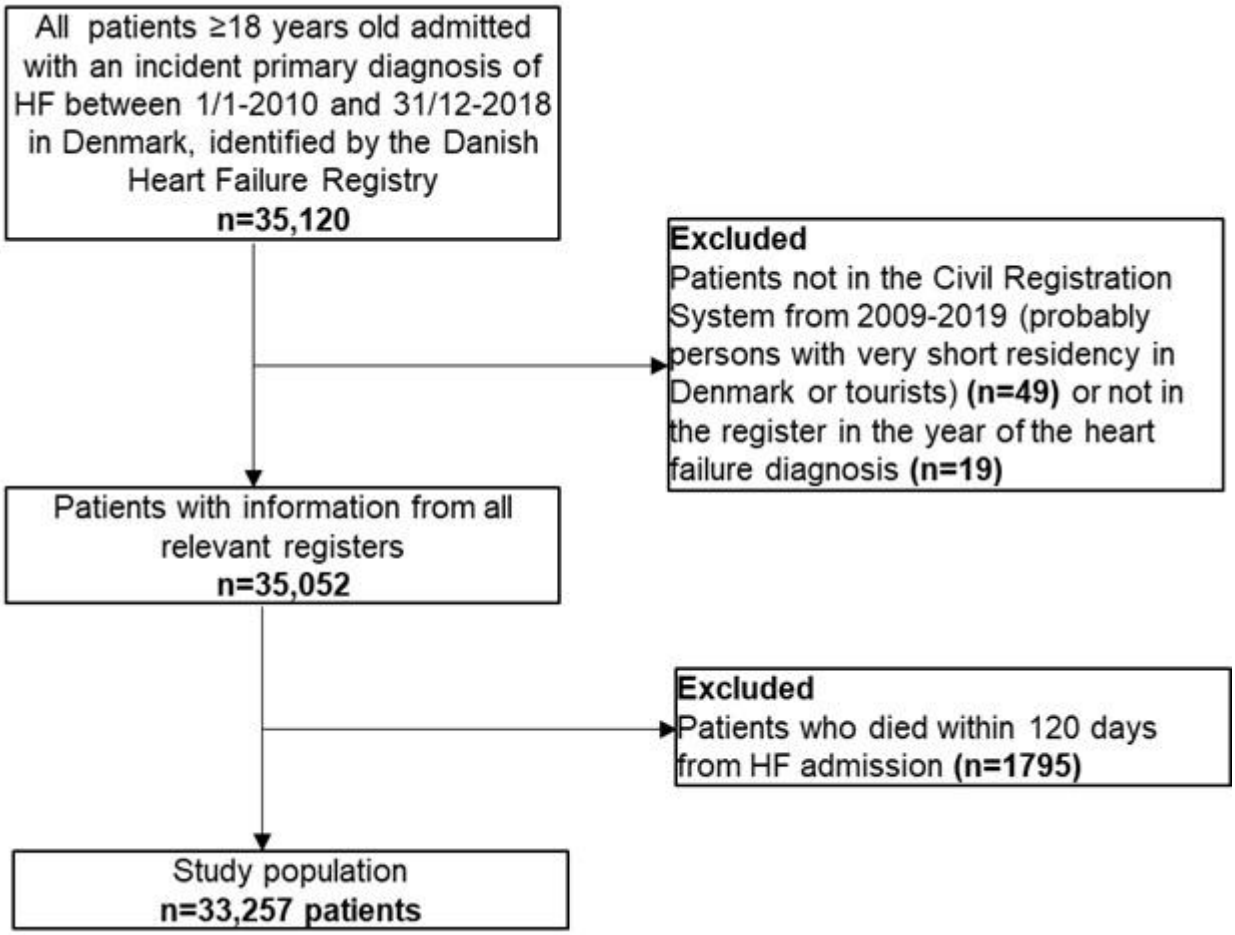

Fig. 1: Flowchart depicting the derivation of the study population

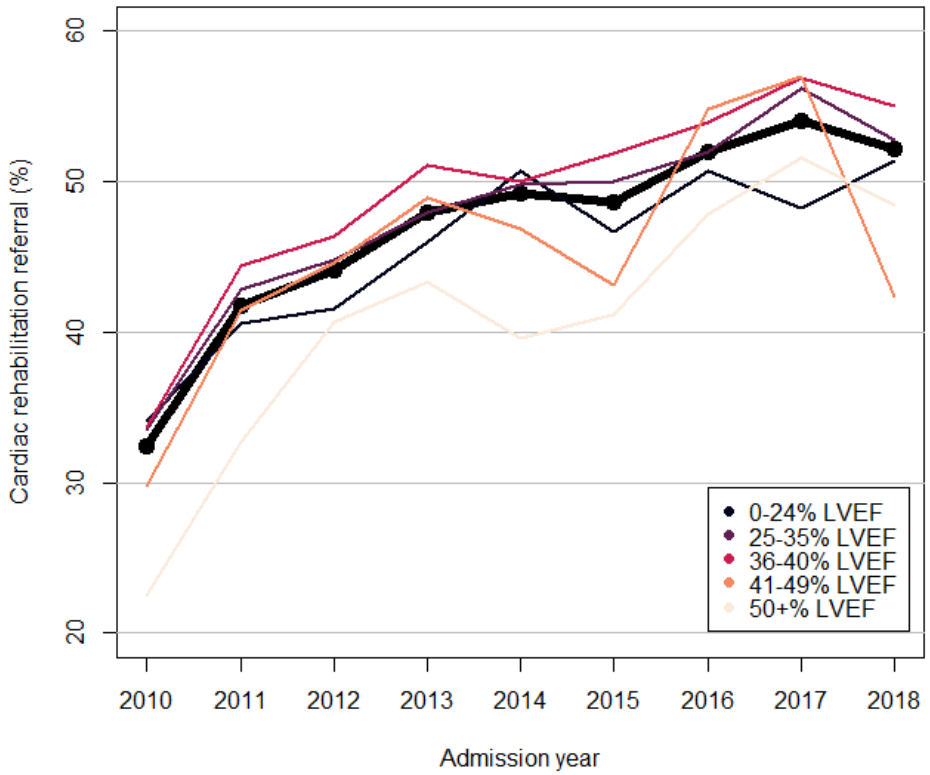

Fig. 2. Temporal trends in cardiac rehabilitation referral among patients with heart failure, across four LVEF categories. The bold black line is the temporal trend among all patients.

Abbreviations: LVEF, left ventricular ejection fraction.

Table 1. Comparison of patient characteristics between heart failure patients referred and not referred to cardiac rehabilitation (N=33,257).

		All patients N	Not referred N (%)	Referred N (%)	p-value
Total		33,257	17,733 (53.3)	15,524 (46.7)	
Demographics					
Sex	Male	22,754	11,895 (52.3)	10,859 (47.7)	<0.0001
	Female	10,503	5,838 (55.6)	4,665 (44.4)	
Age	Mean (SD)	68.9 (12.6)	71.1 (12.7)	66.5 (12.0)	<0.0001
	18-49 years	2,570	1,093 (42.5)	1,477 (57.5)	<0.0001
	50-59 years	4,719	2,048 (43.4)	2,671 (56.6)	
	60-69 years	8,577	4,066 (47.4)	4,511 (52.6)	
	70-79 years	10,288	5,472 (53.2)	4,816 (46.8)	
	80-89 years	6,295	4,382 (69.6)	1,913 (30.4)	
	90+ years	808	672 (83.2)	136 (16.8)	
Region	Capital region	8,441	5,247 (62.2)	3,194 (37.8)	<0.0001
	Zealand	7,775	4,023 (51.7)	3,752 (48.3)	
	South Denmark	7,973	4,054 (50.8)	3,919 (49.2)	
	Central Denmark	6,563	3,036 (46.3)	3,527 (53.7)	
	North Jutland	2,505	1,373 (54.8)	1,132 (45.2)	
Socio-economics					
Employment status	In employment or self-employed	7,794	3,202 (41.1)	4,592 (58.9)	<0.0001
	Unemployed or studying	1,809	848 (46.9)	961 (53.1)	
	Retired	23,654	13,683 (57.8)	9,971 (42.2)	
Living alone	No	19,130	9,311 (48.7)	9,819 (51.3)	<0.0001
	Yes	14,127	8,422 (59.6)	5,705 (40.4)	
Ethnic origin	Non-Danish	1,915	1,052 (54.9)	863 (45.1)	0.14
	Danish	31,342	16,681 (53.2)	14,661 (46.8)	
Educational level	Basic school	13,577	7,902 (58.2)	5,675 (41.8)	<0.0001
	Vocational education	12,439	6,232 (50.1)	6,207 (49.9)	
	Short or long theoretical education	5,972	2,747 (46.0)	3,225 (54.0)	
	Missing	1,269	852 (67.1)	417 (32.9)	
Clinical factors					
Admission type	Inpatient	12,278	7,238 (59.0)	5,040 (41.0)	<0.0001
	Outpatient	20,979	10,495 (50.0)	10,484 (50.0)	
NYHA	Class I	4,873	2,473 (50.7)	2,400 (49.3)	<0.0001
	Class II	19,364	9,505 (49.1)	9,859 (50.9)	
	Class III	6,710	3,950 (58.9)	2,760 (41.1)	
	Class IV	401	278 (69.3)	123 (30.7)	
	Not classified/missing	1,909	1,527 (80.0)	382 (20.0)	
LVEF (%)	0-24	7,764	4,198 (54.1)	3,566 (45.9)	<0.0001
	25-35	14,284	7,438 (52.1)	6,846 (47.9)	
	36-40	6,584	3,317 (50.4)	3,267 (49.6)	
	41-49	2,046	1,141 (55.8)	905 (44.2)	
	50+	2,221	1,339 (60.3)	882 (39.7)	
	Missing	358	300 (83.8)	58 (16.2)	
Comorbidities	Myocardial infarction	11,740	5,376 (45.8)	6,364 (54.2)	<0.0001
	Hypertension	14,456	7,949 (55.0)	6,507 (45.0)	<0.0001
	Chronic obstructive lung disease	5,152	2,965 (57.6)	2,187 (42.4)	<0.0001
	Stroke	3,484	2,060 (59.1)	1,424 (40.9)	<0.0001

	Arthritis	9,384	5,011 (53.4)	4,373 (46.6)	0.86
	Chronic kidney disease	2,495	1,582 (63.4)	9,13 (36.6)	<0.0001
	Atrial fibrillation/flutter	11,425	6,762 (59.2)	4,663 (40.8)	<0.0001
	Diabetes mellitus	6,012	3,470 (57.7)	2,542 (42.3)	<0.0001
Cardiac procedures	Coronary artery bypass grafting	2,966	1,382 (46.6)	1,584 (53.4)	<0.0001
	Percutaneous coronary intervention	7,764	3,049 (39.3)	4,715 (60.7)	<0.0001
	Valvular surgery	1,246	573 (46.0)	673 (54.0)	<0.0001
Cardiovascular medication	Beta-blockers	16,643	8,531 (51.3)	8,112 (48.7)	<0.0001
	ACE inhibitors	18,155	9,126 (50.3)	9,029 (49.7)	<0.0001
	Aldosterone antagonists/digoxin	3,602	1,837 (51.0)	1,765 (49.0)	0.003

Abbreviations: SD, standard deviation; NYHA, New York Heart Association class; LVEF, left ventricular ejection fraction; ACE inhibitors, angiotensin-converting enzyme inhibitors.

Table 2. Association between patient level factors and cardiac rehabilitation referral within 120 days of incident heart failure admission (N=33,257).

		Odds Ratio (95% CI)[a]	Odds Ratio (95% CI)[b]	P-value[c]
Demographics				
Sex	Male	1.00 (0.95-1.05)	0.85 (0.80-0.89)	<0.0001
	Female	1.00 (ref)	1.00 (ref)	
Age	18-49 years	1.54 (1.41-1.68)	1.35 (1.21-1.51)	<0.0001
	50-59 years	1.48 (1.38-1.59)	1.26 (1.15-1.38)	
	60-69 years	1.26 (1.19-1.34)	1.16 (1.09-1.23)	
	70-79 years	1.00 (ref)	1.00 (ref)	
	80-89 years	0.50 (0.46-0.53)	0.55 (0.51-0.59)	
	90+ years	0.23 (0.19-0.28)	0.34 (0.28-0.41)	
Region	Capital region	1.00 (ref)	1.00 (ref)	<0.0001
	Zealand	1.53 (1.43-1.63)	1.40 (1.31-1.50)	
	South Denmark	1.60 (1.50-1.70)	1.47 (1.38-1.58)	
	Central Denmark	1.95 (1.82-2.08)	1.90 (1.77-2.04)	
	North Jutland	1.38 (1.25-1.51)	1.44 (1.30-1.59)	
Socio-economics				
Employment status	In employment or self-employed	1.00 (ref)	1.00 (ref)	<0.0001
	Unemployed or studying	0.77 (0.70-0.86)	0.89 (0.80-0.99)	
	Retired	0.69 (0.64-0.74)	0.79 (0.73-0.85)	
Living alone	No	1.00 (ref)	1.00 (ref)	<0.0001
	Yes	0.70 (0.67-0.73)	0.76 (0.72-0.80)	
Ethnic origin	Danish	1.00 (ref)	1.00 (ref)	0.002
	Non-Danish	0.82 (0.74-0.90)	0.85 (0.77-0.94)	
Educational level	Basic school	0.67 (0.62-0.71)	0.66 (0.61-0.70)	<0.0001
	Vocational education	0.83 (0.78-0.89)	0.79 (0.74-0.85)	
	Short or long theoretical education	1.00 (ref)	1.00 (ref)	
Clinical factors				
Admission type	Inpatient	0.74 (0.71-0.78)	0.99 (0.94-1.05)	0.82
	Outpatient	1.00 (ref)	1.00 (ref)	

NYHA	Class I	1.00 (ref)	1.00 (ref)	<0.0001
	Class II	1.18 (1.11-1.26)	1.26 (1.17-1.34)	
	Class III	0.87 (0.80-0.94)	1.03 (0.94-1.11)	
	Class IV	0.57 (0.46-0.71)	0.75 (0.60-0.95)	
	Not classified/ missing	0.33 (0.29-0.37)	0.48 (0.42-0.55)	
LVEF	0-24	0.88 (0.83-0.93)	1.01 (0.95-1.08)	<0.0001
	25-35	1.00 (ref)	1.00 (ref)	
	36-40	1.05 (0.99-1.11)	0.96 (0.91-1.03)	
	41-49	0.84 (0.77-0.93)	0.88 (0.80-0.97)	
	50+	0.72 (0.66-0.79)	0.73 (0.66-0.81)	
Comorbidities	Myocardial infarction	1.66 (1.59-1.74)	1.22 (1.15-1.30)	<0.0001
	Hypertension	0.96 (0.92-1.01)	0.97 (0.92-1.02)	0.26
	Chronic obstructive lung disease	0.86 (0.81-0.92)	0.95 (0.89-1.01)	0.10
	Stroke	0.84 (0.78-0.91)	0.90 (0.83-0.97)	0.008
	Arthritis	1.10 (1.05-1.16)	1.11 (1.06-1.17)	<0.0001
	Chronic kidney disease	0.68 (0.63-0.74)	0.72 (0.66-0.79)	<0.0001
	Atrial fibrillation/flutter	0.78 (0.75-0.82)	0.84 (0.79-0.88)	<0.0001
	Diabetes mellitus	0.79 (0.75-0.84)	0.84 (0.79-0.90)	<0.0001
Cardiac procedures	Coronary artery bypass grafting	1.41 (1.31-1.53)	1.33 (1.22-1.45)	<0.0001
	Percutaneous coronary intervention	2.04 (1.93-2.15)	1.73 (1.62-1.86)	<0.0001
	Valvular surgery	1.46 (1.30-1.64)	1.49 (1.32-1.69)	<0.0001
Cardiovascular medication	Beta-blockers	1.19 (1.14-1.25)	0.98 (0.92-1.03)	0.37
	ACE inhibitors	1.30 (1.24-1.36)	1.13 (1.08-1.20)	<0.0001
	Aldosterone antagonists/digoxin	1.09 (1.02-1.17)	1.02 (0.95-1.10)	0.58

Abbreviations: NYHA, New York Heart Association class; LVEF, left ventricular ejection fraction.
[a]Adjusted for age, sex, and calendar-year
[b]Adjusted for age, sex, calendar-year, and other covariates
[c]P-value from type-3 test in model 2

Table 3. Association between cardiac rehabilitation (CR) referral and risk of acute all-cause readmission and mortality.

	#patients	Cases (%)	OR (95% CI)[a]	OR (95% CI)[b]
Acute all-cause readmission (n=29,501)				
No CR referral	15,938	5,265 (33.0)	1.00 (ref)	1.00 (ref)
CR referral	13,563	3,669 (27.1)	0.83 (0.79-0.87)	0.92 (0.87-0.97)
Heart Failure specific mortality (n=25,921)				
No CR referral	14,294	103 (0.7)	1.00 (ref)	1.00 (ref)
CR referral	11,627	26 (0.2)	0.48 (0.31-0.75)	0.66 (0.42-1.04)
All-cause mortality (29,501)				
No CR referral	15,938	1,279 (8.0)	1.00 (ref)	1.00 (ref)
CR referral	13,563	479 (3.5)	0.54 (0.49-0.61)	0.65 (0.58-0.72)

[a]Logistic regression model adjusted for sex and age.
[b]Logistic regression model adjusted for sex, age, calendar-year, region, employment status, living alone, ethnic origin, educational level, admission type, NYHA class, LVEF (%), myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, diabetes mellitus, CABG, PCI, valvular surgery, and use of beta-blockers, ACE inhibitors or aldosterone antagonists/digoxin.