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Sex-Specific Temporal Trends in Ambulatory Heart Failure Incidence, Mortality and Hospitalization in Ontario, Canada from 1994-2013

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Title: Sex-Specific Temporal Trends in Ambulatory Heart Failure Incidence, Mortality and Hospitalization in Ontario, Canada from 1994-2013

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ABSTRACT

Objectives: To examine the temporal trends in mortality and heart failure (HF) hospitalization in ambulatory patients following a new diagnosis of HF.

Design: Retrospective cohort study

Setting: Outpatient

Participants: Ontario residents who were diagnosed with HF in an outpatient setting between 1994-2013.

Primary and Secondary Outcome Measures: The primary outcome was all-cause mortality within one year of diagnosis and the secondary outcome was HF hospitalization within one year. Risks of mortality and hospitalization were calculated using the Kaplan-Meier method and the relative hazard of death was assessed using multivariable Cox proportional hazard models.

Results: A total of 352,329 patients were studied (50% female). During the study period, there was a greater decline in age standardized one-year mortality rates (AMR) in men (33%) than in women (19%). Specifically, female AMR at one-year was 104.4 (95% CI, 90.5-119.8) per 1000 in 1994 and 84.8 (75.2-95.3) in 2013, and male AMR at one-year was 123.0 (110.6-136.5) in 1994 and 83.0 (75.3-91.2) in 2013. Conversely, age standardized HF hospitalization rates declined in men (114.2 [101.0-128.5] per 1000 person-years in 1994 and 91.1 [82.3-100.7] in 2013) but remained unchanged in women (97.4 [83.3-113.3] in 1994 and 97.6 [86.0-110.3] in 2013).

Conclusion: Among patients with HF over a 20-year period, there was a greater improvement in the prognosis of men compared to women. Further research should focus on the determinants of this disparity and ways to reduce this gap in outcomes.

Strengths and Limitations:

- First and largest population-based study to examine temporal, sex-specific trends in heart failure (HF) outcomes in an ambulatory setting.
- The nature of our publicly funded healthcare system allowed for analysis of all patients diagnosed with HF in Ontario without selection bias.
- Information on ejection fraction was not available in the databases used.

Key Words: heart failure, mortality, hospitalization, women, epidemiology, prognosis

Introduction

Heart failure (HF) is a significant cause of morbidity and mortality for both women and men [1, 2]. Despite the current era of guideline directed medical therapy, HF continues to be a leading cause of admission to hospital. It is associated with a poor prognosis and contributes to 35% of cardiovascular mortality in women [3]. Despite this, HF remains poorly understood in women, and women continue to be underrepresented in HF clinical trials [4]. The underlying mechanism of HF is often different in women and men, with women suffering more often from HF of a hypertensive rather than ischemic etiology [5, 6]. Important trends in the incidence and outcomes of hospitalized HF patients have been recently published [7, 8]; these studies suggest that the incidence of HF has declined in many inpatient cohorts, however the prognosis of this disease remains poor. An in-depth understanding of the temporal trends in HF incidence and outcomes is also needed in the ambulatory setting, where the majority of HF cases are diagnosed and managed. Also, given the sex differences in co-morbidities and outcomes in HF, it is not known if these temporal changes are modified by sex. We therefore examined the sex differences in HF co-morbidities, incidence, mortality and hospitalization in a population-based ambulatory cohort from fiscal years 1994 to 2013.

Methods

Design and Study Population

We conducted a population-based, retrospective cohort study of Ontario residents who were diagnosed with HF in an outpatient setting over a 20-year period, using linked administrative databases. The Research Ethics Board of Sunnybrook Health Sciences, Toronto, Canada approved this study and waived the need for informed consent.

Included were adult patients ≥ 40 years of age, who were newly diagnosed with HF in an ambulatory setting between April 1, 1994 and March 31, 2014. We excluded non-Ontario residents, those who were ≥ 105 years of age on the date of HF diagnosis, those who were diagnosed with HF in an inpatient setting and in whom HF had developed as a post-admission complication. Ontario is Canada's most populous and ethnically diverse province with a public funded healthcare system that reimbursed all medically necessary physician and hospital services.

Patient and Public Involvement

Patients will be invited to participate in the dissemination of our findings.

Data Sources

Databases were linked deterministically using unique encoded identifiers. Ambulatory incident HF cases were identified using the ICES Congestive Heart Failure database, based on 2 outpatient billing claims for HF within one year. This algorithm was validated in primary care patient records and shown to have 85% sensitivity and 97% specificity in identifying HF events [9]. The Congestive Heart Failure database allowed us to study a validated cohort of HF patients with consistent entry criteria over time. Our analyses were conducted by linking the Congestive Heart Failure database with the Registered Persons Database, which contains demographic and vital statistics information, the Canadian Institute for Health Information Discharge Abstract Database, which contains data on all hospitalizations and co-morbidities, and Same Day Surgery database

for co-morbidities. Physician fee-for-service claims data was obtained from the Ontario Health Insurance Plan database. While lacking physiologic and laboratory measures, these databases have been validated for many outcomes, exposures, and co-morbidities [10-13].

Outcome

The primary outcome was all-cause mortality within one year of HF diagnosis. Mortality was ascertained by using the Registered Persons Database. Secondary outcome was HF hospitalization, which was ascertained using the Discharge Abstract Database.

Covariates

Demographic variables were obtained from the Registered Persons Database. We estimated socioeconomic status based on patients' neighborhood median income in the Canadian census, and determined rural versus urban residence using Statistics Canada definitions [14]. We identified hypertension [10], asthma [15], chronic obstructive pulmonary disease (COPD) [16] and diabetes mellitus [12] using validated algorithms. Other co-morbidities were identified using Discharge Abstract Database, Same Day Surgery and Ontario Health Insurance Plan databases based on International Classification of Diseases 10th Revision codes within five years of HF diagnosis, using previously described methods [17-29]. Frailty was identified using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, which is an instrument designed and validated for research of frailty-related outcomes and resource utilization using administrative data [25, 28, 30-34].

Statistical Analysis

Analyses were stratified by sex. Continuous variables were expressed as mean (standard deviation) and categorical variables as number (proportion). Mortality was assessed at one-year post HF diagnosis. Survival time was defined as the date of HF diagnosis until date of death or last follow up. Patients were censored when they lost possession of a valid Ontario health

insurance number for two consecutive eligibility quarters (i.e., have left the province of Ontario). Probability of death within given durations of follow-up were calculated using the Kaplan-Meier method, with the significance of the difference between sexes assessed using the log-rank test. We estimated the cumulative incidence of HF hospitalizations using cumulative incidence functions (CIF), which treated death as a competing risk. We constructed age standardized plots of HF incidence, one-year mortality and HF hospitalization in men and women over the 20-year period. These rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population.

To examine the temporal changes in co-morbidities, we divided the 20-year period into 4 temporal cohorts: those diagnosed with HF between April 1, 1994 – March 31, 1999 (the historical cohort), between April 1, 1999 – March 31, 2004, between April 1, 2004 – March 31, 2009 and between April 1, 2009 – March 31, 2014 (the modern cohort). The hazard of death in the historical cohort and the modern cohort were assessed using Cox proportional hazard models with and without multivariable adjustment. To justify sex-specific analyses, we also tested for the presence of any interaction between sex and each of the mortality risk factors in these two cohorts using multiplicative interaction terms. The measure of association was hazard ratios (HR) with 95% CI. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), with statistical significance defined by a two-sided P-value of < 0.05.

Results

Over a 20-year period in Ontario, a total of 352,329 patients were diagnosed with HF in an ambulatory setting (50% women). There were 91,583 incident HF cases in the historical cohort (52% women) and 90,707 in the modern cohort (47% women). In the modern cohort, women with HF were more likely to be older, more frail, of lower income status, have co-morbid conditions such as hypertension, hypothyroidism, anemia, dementia and depression, but were less likely to have myocardial infarction (MI), peripheral arterial disease, diabetes and alcohol abuse compared to men (Table 1). Compared to the historical cohort, modern HF patients were less likely to have peripheral and cerebral vascular disease, psychosis, paraplegia and venous thromboembolic disease; but more likely to be urban dwellers, have hypertension, atrial fibrillation, MI, valvular heart disease, pulmonary circulatory disorder, COPD/asthma, alcohol abuse, renal disease, and are increasingly frail.

Trends in HF Incidence

During the historical period (1994-1998), a total of 47,676 (0.36%) incident HF cases were identified in women and 43,907 (0.36%) in men. During the modern era (2009-2013), 42,746 (0.24%) incident cases were identified in women and 47,961 (0.29%) in men. Although the incidence of HF declined in both sexes over the 20-year period, it remained higher in men than in women (Figure 1). Age standardized incidence for women decreased from 369.0 (95% CI, 361.7-376.3) per 100,000 population in 1994 to 205.8 (201.4-210.3) in 2013. For men, HF incidence decreased from 480.6 (470.6-490.9) per 100,000 in 1994 to 312.8 (306.8-318.9) in 2013 (eTable 1).

Trends in Mortality

One-year mortality occurred in 8,319 (17.5%) women and 8,238 (18.8%) men during the historical period; it occurred in 7,156 (16.8%) women and 7,138 (14.9%) men during the modern

period (eTable 2). These survival patterns are reinforced by the Kaplan-Meier survival curves in Figure 3, as well as the stacked Kaplan-Meier curves in Figure 4 that demonstrate an improvement in male survival but little change in female survival over time. Age-standardized one-year mortality rates (AMR) also declined in both sexes but the magnitude of reduction was greater in men than in women. Men had higher AMR than women at most time points prior to 2009 (Figure 2). Specifically, the female AMR per 1000 was 104.4 (95% CI, 90.5-119.8) in 1994 and 84.8 (75.2-95.3) in 2013, representing a 19% reduction. Conversely, male AMR per 1000 was 123.0 (110.6-136.5) in 1994 and 83.0 (75.3-91.2) in 2013, representing a 33% reduction (eTable 3).

In the unadjusted analysis, female sex was protective against one-year mortality in the historical cohort (unadjusted HR 0.93, 95% CI 0.90-0.95) but was associated with a higher risk of mortality (unadjusted HR 1.14, 95% CI 1.10-1.18) in the modern cohort. Adjusted analysis demonstrated that the protective effect conferred by female sex had diminished over time (adjusted HR 0.85, 95% CI 0.82-0.88 in the historical and 0.97, 95% CI 0.93-1.00 in the modern cohort).

Table 2 lists the multivariable predictors of one-year mortality in the modern cohort. Compared to the historical cohort, the mortality risk associated with age > 75 years, liver disease, dementia and venous thromboembolism had increased while the risk associated with male sex, complicated hypertension, diabetes, renal disease and pulmonary circulatory disease had diminished. Of note, alcohol abuse and venous thromboembolism emerged as new mortality risk factors while urban residence and MI were no longer risk factors.

Sex-specific mortality risk factors have evolved over time. Table 3a and 3b illustrate the sex-specific HRs in the historical and modern cohorts, respectively. In the modern cohort, low income was associated with a higher risk of mortality in men but not in women. Conversely, MI

had a mild protective effect on men but not in women. In addition, women with peripheral arterial disease had a higher risk of death while men with COPD/asthma, dementia, primary and metastatic malignancies had a higher risk of mortality than women with similar co-morbidities. Compared to the historical cohort, most sex-specific risk factors have evolved over time, with the exception of COPD/asthma.

Trends in HF Hospitalization

HF hospitalizations occurred in 5,271 (13.4%) women and 5,169 (14.4%) men within one-year of HF diagnosis in the historical cohort. During the modern period, there were 5,420 (15.6%) HF hospitalizations in women and 5,503 (13.8%) hospitalizations in men. Age-standardized HF hospitalization rates declined in men but remained unchanged in women during the 20-year period (eFigure 1 and eTable 4). Specifically, male age-standardized HF hospitalization rates were 114.2 (95% CI, 101.0-128.5) per 1000 person-years in 1994 and 91.1 (82.3-100.7) in 2013. Female rates were 97.4 (83.3-113.3) in 1994 and 97.6 (86.0-110.3) in 2013.The temporal trends in the cumulative incidence of HF hospitalizations are illustrated in eFigure 2.

Discussion

This population-based study evaluated 352,329 individuals with a first-time diagnosis of HF from 1994-2013 in the ambulatory care setting. There are four main findings reported in this study: 1) HF mortality declined over time 2) The reduction in mortality is greater in men than in women. 3) Rates of hospitalization decreased for men but remained unchanged for women. 4) The incidence and significance of co-morbidities associated with HF have changed over time, and suggest that women continue to experience a greater burden of co-morbid disease when compared to men.

Trends in HF Incidence and Mortality

Population-based temporal trends in HF incidence and mortality have been previously reported across many cohorts, however many of these studies have been limited to patients hospitalized with a diagnosis of HF or have not provided detailed, sex-stratified analyses. Temporal trends in the incidence and survival of HF patients were first reported by the Framingham group over a 50 year period from 1950-1999 [35]. These authors reported that the incidence of HF had declined in women but not men, with improving survival in both sexes [35]. This pivotal study was followed by findings from a community-based cohort of 4537 patients from 1979-2000, which reported that although HF incidence remained unchanged for both sexes, mortality declined – with greater survival gains in men than women [36]. A recent study by our group demonstrated that amongst ambulatory Ontario residents from 2009-2013, the incidence of heart failure decreased more rapidly in men than women. At the same time, heart failure associated deaths and hospitalizations remain higher in women than men within a year of HF diagnosis [19]. The present study extends these findings by demonstrating a continued disproportionate decrease in HF mortality for men compared to women from 1994-2013. Our findings corroborate with our previous study of HF incidence and one-year mortality in rural and

urban Eastern Ontario from 1994-2013 [24]. They also corroborate the work of Tu and colleagues [7] who used similar administrative databases to report on the HF incidence and mortality of Ontario patients ≥ 20 years of age from 1997-2007. Tu evaluated both admitted and ambulatory HF patients and reported declines in HF incidence over this time period, a finding that was most evident in the older cohorts [7]. Sex stratified mortality rates were not reported in this study. A recent study from Denmark demonstrated a decrease in HF incidence over time only in cohorts >50 years of age, but an increase in HF incidence in younger patients. Although detailed sex-specific outcomes were not provided, sex-stratified models showed similar trends in incidence and mortality over time with men having a higher incidence overall [8].

The present study extends these observations by providing detailed sex-specific data on mortality trends over time. Our findings suggest that in Ontario, one-year mortality rates have decreased over the past 20 years. However, this mortality reduction was greatest for men, and observed to a lesser extent for women. This translates to the observation that women had better AMR than men in the first three temporal cohorts of this study (1994-2008); however in the most recent cohort (2009-2013) we observed mortality to be higher in women than men for the first time. The basis for this sex-based difference is unclear but may be explained in part by the observation that women are more likely than men to have a diagnosis of HFpEF, a disease for which there remains no evidence-based therapies which can improve survival, in contrast to the significant advances in medical therapy for HF with reduced ejection fraction (HFrEF) [37]. In addition, female HF patients have a higher co-morbidity burden than their male counterparts. Complex co-morbid conditions, coupled with atypical presentation of cardiac disease in women, may also have lead to delays in diagnosis and differences in management or response to medical therapy [38]. Further work is needed to determine whether the other sex-based differences in

management, response to treatment or underlying pathophysiology remain to explain these sex-based trends in HF mortality over time.

Trends in HF hospitalization

Rates of hospitalization for HF decreased only for men in this time period. This is consistent with recent reports of sex and race differences in hospitalization trends over a similar time period [19, 39]. It is possible that this sex-based difference may be due to death being a competing risk for hospitalization in men, such that men with HF may suffer earlier deaths whereas women with HF survive to an older age and are more likely to become hospitalized. Alternatively, it is possible that the rates of hospitalization in men and women reflect the underlying HF type, since men are more likely to have HFrEF (for which there are several treatments known to improve outcomes and decrease hospitalization) while women are more likely to have HFpEF (for which there are no substantial evidence-based therapies). Nonetheless, the observed sex differences may also be attributed to the greater co-morbidity burden in women, differences in social determinants of health, or genetic or physiologic differences that cannot be explained within the observational context of this study; all of these point to the need for further exploration to determine the adverse trends for mortality and hospitalization in women with a diagnosis of HF.

Trends in HF Co-morbidities

Sex-based differences in co-morbidities have been previously reported in hospitalized patients; women with HF are older and more likely than men to have co-morbid hypertension, renal failure, obesity, and depression. Men with HF are more often smokers, and tend to have more ischemic heart disease, COPD, and HFrEF [40]. Our study is the first to report on the relationship between sex and co-morbidity in ambulatory HF patients over time. Compared to our historical cohort, our most recent cohort of patients demonstrates an overall increase in important

co-morbidities such as frailty, diabetes, renal disease, MI, atrial fibrillation, COPD and hypertension. This has been observed in other population-based studies [8] and speaks to the increased complexity of the HF patient in the current era. The increased prevalence of these co-morbidities over time was seen in both women and men. Certain co-morbidities remained more common in women than in men in both the historical and recent cohorts; including depression, hypertension, advanced age, frailty, dementia and thyroid disease. Interestingly, frailty, chronic pulmonary disease, and metastatic cancer became more common in women than men in the recent cohort. Collectively these findings suggest that the co-morbidity of the HF patient is increasing over time, and that women continue to experience a greater co-morbidity burden than men. This observation may also explain in part the sex difference in mortality trends.

Important trends in the risk associated with these co-morbidities were also observed. Hypertension conferred a greater protective effect in the modern era. This may actually reflect the known adverse prognosis associated with low blood pressure in HF [41, 42]. In addition, the risk associated with diabetes, renal disease and pulmonary circulatory disease has decreased over time. In addition, MI was no longer a mortality risk factor in the recent cohort when compared to the historical cohort. These changes over time may be due to significant advances in the medical management of these co-morbidities, which have influenced overall survival.

Sex-based differences in the risks associated with certain co-morbidities were also observed. In the most recent cohort, MI had a mild protective effect in men but not in women. This may be due to a lower detection rate of ischemic heart disease in women due to atypical presentation [43], which leads to missed management and poorer outcomes. Ischemic heart disease is a leading cause of HF in both sexes. When diagnosed with

ischemic heart disease, women are less likely than men to undergo cardiac catheterization and revascularization; whether this is wholly attributed to the increased microvascular disease in women is not well understood [44]. In the most recent cohort, peripheral arterial disease was associated with a higher risk of mortality in women, while COPD, dementia and malignancy posed a greater risk of mortality in men. Whether these differences are clinically relevant, or help to explain the variability in mortality risk associated with HF, remains to be determined. There remains a significant knowledge gap on sex specific differences in epidemiology, pathophysiology, management and prognosis of co-morbidities related to HF [40]. Such knowledge could determine if HF management should be targeted to specific sex-based co-morbidities to improve outcomes and narrow the gap in mortality improvement between women and men.

Limitations and Strengths

Our study has several limitations. *Firstly*, cases of HF were identified in the ambulatory care setting based on the requirement of 2 claims for HF within one year. Although this method may have led to an underestimate of HF, it has been validated previously and shown to improve the specificity of our case selection [7, 9]. *Secondly*, information on ejection fraction was not available in the databases used, which precluded analyses in subtypes of HF based on ventricular function. *Thirdly*, the diagnostic criteria for HFpEF have become more specific over time; whether this may influence incidence and prognosis cannot be determined from this study. *Finally*, cohort studies are by nature subjected to residual confounding. Despite these limitations, our study is the first to address the epidemiology of HF in a validated cohort of *ambulatory* patients, and one of the first to report on detailed sex-based outcome and co-morbidity

differences within a large universal healthcare system, using the same entry criteria over a 20-year time period. The nature of our publicly funded healthcare system allowed for complete analysis of all Ontario HF patients, which minimized selection bias and greatly improved the generalizability of our findings.

Conclusions

Over a 20-year window, we found an overall reduction in all-cause mortality in the year following HF diagnosis. However, there was a much larger reduction of mortality in men than in women, and HF hospitalization rates have decreased for men but remained unchanged in women. Female HF patients continue to experience a greater burden of co-morbidities than male HF patients in the modern era. Further research should focus on the determinants of this disparity such as sex differences in medical and device management, to better characterize incidence and outcomes by HF type, and ways to reduce this gap in outcomes.

Authorship Contributions:

Conception: LYS, LMM

Design: LYS, LMM, JVT

Data acquisition and analysis: LYS, ABE

Interpretation of results: all

Drafting of manuscript: LYS, LMM

Critical revision: all

Agreement to be accountable for all aspects of the work: LYS

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Declaration of Interests: none

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A and Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-847.
2. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML and Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *Journal of the American College of Cardiology*. 2013;61:1510-7.
3. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.
4. Heiat A, Gross CP and Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med*. 2002;162:1682-8.
5. Scantlebury DC and Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol*. 2011;26:562-8.
6. Kenchaiah S and Vasan RS. Heart Failure in Women--Insights from the Framingham Heart Study. *Cardiovasc Drugs Ther*. 2015;29:377-90.
7. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE and Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ*. 2012;184:E765-73.
8. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, Gislason GH, Torp-Pedersen C and Andersson C. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. *Circulation*. 2017;135:1214-1223.
9. Schultz SE, Rothwell DM, Chen Z and Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33:160-6.
10. Tu K, Campbell NRC, Chen ZL, Cauch-Dudek KJ and McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Medicine*. 2007;1.
11. Juurlink D, Preya C, Croxford R, Chong A, Austin P, Tu J and Laupacis A. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. ICES Investigative Report*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2006.
12. Hux JE, Ivis F, Flintoft V and Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25.
13. Austin PC, Daly PA and Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144.
14. du Plessis V, Beshiri R, Bollman RD and Clemeson H. *Definitions of "rural". Agriculture and Rural Working Paper Series, No. 61*. Ottawa, ON: Statistics Canada; 2002.

15. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L and To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J*. 2009;16.
16. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L and To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. *COPD*. 2009;6.
17. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE and Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43.
18. Sun LY, Gershon AS, Ko DT, Thilen SR, Yun L, Beattie WS and Wijeysundera DN. Trends in Pulmonary Function Testing Before Noncardiothoracic Surgery. *JAMA Intern Med*. 2015;175:1410-2.
19. Sun L.Y. Tu JV, Coutinho T., Turek M., Rubens F., McDonnell L., Tulloch H., Mielniczuk L.M. Sex Differences in Heart Failure Outcomes in an Ambulatory, Population-Based Cohort. *CMAJ*. 2018;190:E848-E854.
20. Sun L.Y. Tu JV, Lee D.S., Beanlands R.S., Ruel M., Austin P.C., Bader Eddeen A., Liu P.P. Disability-Free Survival After Coronary Artery Bypass Grafting in Women and Men with Heart Failure. *BMJ Open Heart*. 2018;5:e000911.
21. Sun LY, Gaudino M, Chen RJ, Bader Eddeen A and Ruel M. Long-term Outcomes in Patients With Severely Reduced Left Ventricular Ejection Fraction Undergoing Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting. *JAMA cardiology*. 2020.
22. Sun LY, Kimmoun A, Takagi K, Liu PP, Bader Eddeen A and Mebazaa A. Ethnic differences in acute heart failure outcomes in Ontario. *Int J Cardiol*. 2019;291:177-182.
23. Sun LY, Tu JV, Eddeen AB and Liu PP. Prevalence and long-term survival after coronary artery bypass grafting in women and men with heart failure and preserved versus reduced ejection fraction. *Journal of the American Heart Association*. 2018;7:1-14.
24. Sun LY, Tu JV, Sherrard H, Rodger N, Coutinho T, Turek M, Chan E, Tulloch H, McDonnell L and Mielniczuk LM. Sex-Specific Trends in Incidence and Mortality for Urban and Rural Ambulatory Patients with Heart Failure in Eastern Ontario from 1994 to 2013. *Journal of Cardiac Failure*. 2018;24:568-574.
25. Tran DTT, Tu JV, Dupuis J-Y, Bader Eddeen A and Sun LY. Association of Frailty and Long-Term Survival in Patients Undergoing Coronary Artery Bypass Grafting. *Journal of the American Heart Association*. 2018;7.
26. Johnston AM, T. G; Lee, D. S.; Bader Eddeen, A.; Sun, L. Y. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. *Journal of the American Heart Association*. 2019;8:e013260.
27. Hayatsu Y, Ruel M, Bader Eddeen A and Sun L. Single Versus Multiple Arterial Revascularization in Patients With Reduced Renal Function: Long-term Outcome Comparisons in 23,406 CABG Patients From Ontario, Canada. *Ann Surg*. 2020.
28. Sun LY, Spence SD, Benton S, Beanlands RS, Austin PC, Bader Eddeen A and Lee DS. Age, Not Sex, Modifies the Effect of Frailty on Long-term Outcomes After Cardiac Surgery. *Ann Surg*. 2020.
29. Rubens FD, Wells GA, Coutinho T, Eddeen AB and Sun LY. Sex differences after coronary artery bypass grafting with a second arterial conduit. *The Journal of thoracic and cardiovascular surgery*. 2020.
30. Lieberman R AC, Weiner J. Development and evaluation of the Johns Hopkins University Risk Adjustment Models for Medicare+ Choice Plan Payment. 2003.

31. Sternberg SA, Bentur N, Abrams C, Spalter T, Karpati T, Lemberger J and Heymann AD. Identifying frail older people using predictive modeling. *Am J Manag Care*. 2012;18:e392-7.
32. The Johns Hopkins Adjusted Clinical Groups Technical Reference Guide, version 9.0. 2009.
33. Bronskill S CM, Costa A, et al. Aging in Ontario: An ICES Chartbook of Health Services Use by Older Adults - a Technical Report. 2010.
34. Bronskill S CX, Gruneir A, Ho M. Health system use by frail Ontario seniors: an in-depth examination of four vulnerable cohorts. 2011.
35. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM and Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397-402.
36. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP and Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344-50.
37. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134:e282-93.
38. Taylor AL. Heart failure in women. *Curr Heart Fail Rep*. 2015;12:187-95.
39. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH and Fonarow GC. National Differences in Trends for Heart Failure Hospitalizations by Sex and Race/Ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10.
40. Hopper I, Kotecha D, Chin KL, Mentz RJ and von Lueder TG. Comorbidities in Heart Failure: Are There Gender Differences? *Curr Heart Fail Rep*. 2016;13:1-12.
41. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, Mayet J and Francis DP. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart*. 2009;95:56-62.
42. Schmid FA, Schlager O, Keller P, Seifert B, Huang R, Frohlich GM, Luscher TF, Ruschitzka F and Enseleit F. Prognostic value of long-term blood pressure changes in patients with chronic heart failure. *Eur J Heart Fail*. 2017;19:837-842.
43. Jarvie JL and Foody JM. Recognizing and improving health care disparities in the prevention of cardiovascular disease in women. *Curr Cardiol Rep*. 2010;12:488-96.
44. McSweeney J, Pettey C, Lefler LL and Heo S. Disparities in heart failure and other cardiovascular diseases among women. *Women's health (London, England)*. 2012;8:473-85.

FIGURE LEGENDS

Figure 1. Sex-specific temporal trends in the incidence of heart failure in Ontario from April 1, 1994 to March 31, 2014.

Legend: Incidence rates were directly standardized by age and expressed per 100,000. The solid line represents incidence trends in women. The dotted line represents incidence trends in men.

Figure 2. Sex-specific temporal trends in mortality within one year of ambulatory heart failure diagnosis.

Legend: Mortality rates were directly standardized by age and expressed per 1000. The solid line represents mortality trends in women. The dotted line represents mortality trends in men.

Figure 3. Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis, in each of the 5-year cohorts.

Legend: The red line represents survival in men. The blue line represents survival in women.

Figure 4a. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in men.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

Figure 4b. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in women.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

Figure 1. Sex-specific temporal trends in the incidence of heart failure in Ontario from April 1, 1994 to March 31, 2014.

Legend: Incidence rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population and expressed per 100,000. The solid line represents incidence trends in women. The dotted line represents incidence trends in men.

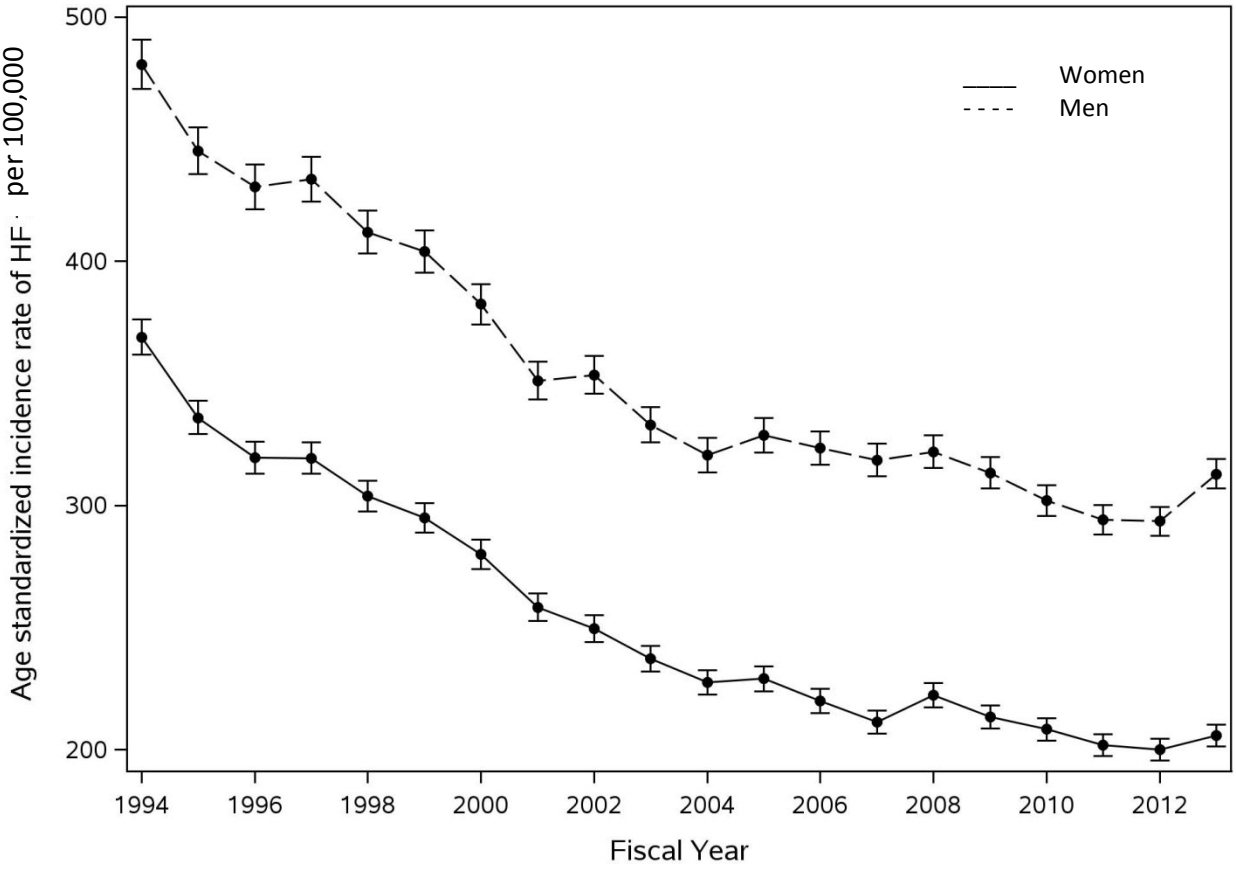


Figure 2. Sex-specific temporal trends in mortality within one year of ambulatory heart failure diagnosis.

Legend: Mortality rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population and expressed per 1000. The solid line represents mortality trends in women. The dotted line represents mortality trends in men.

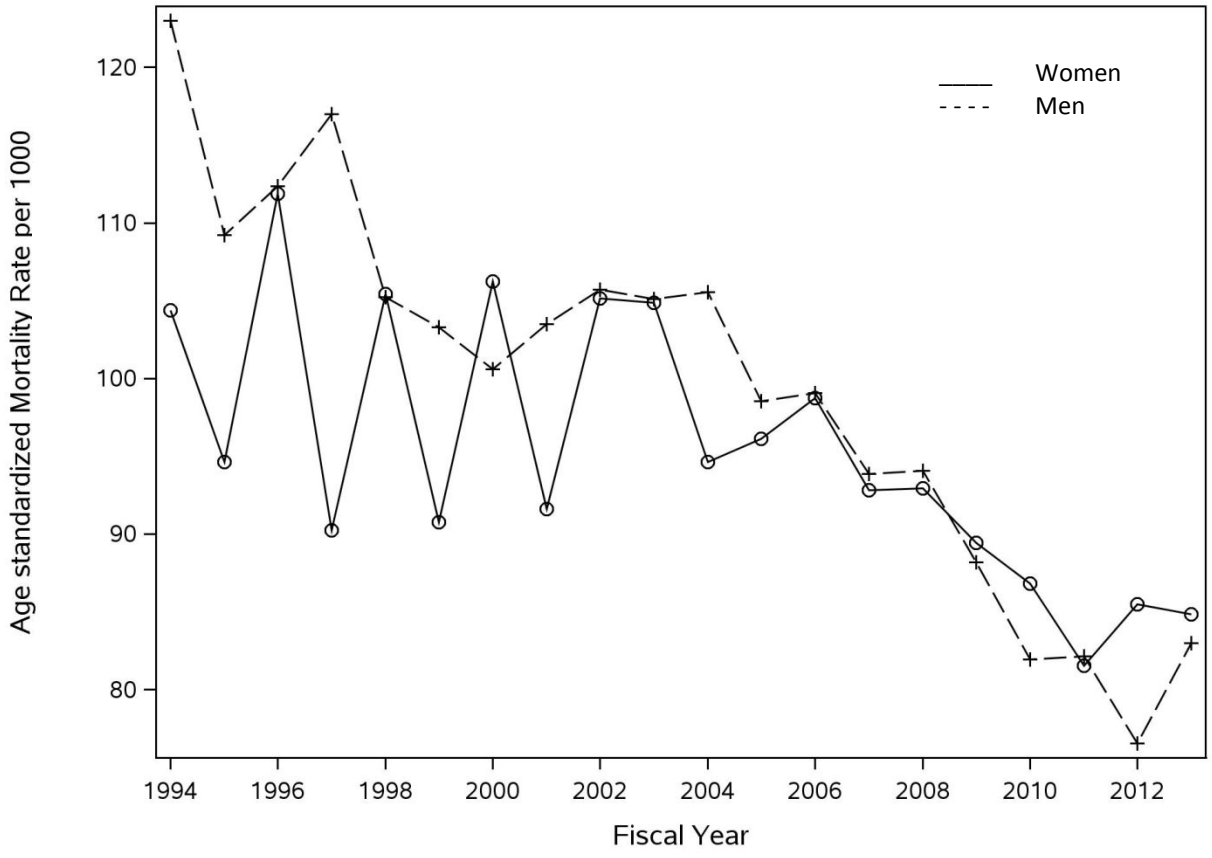
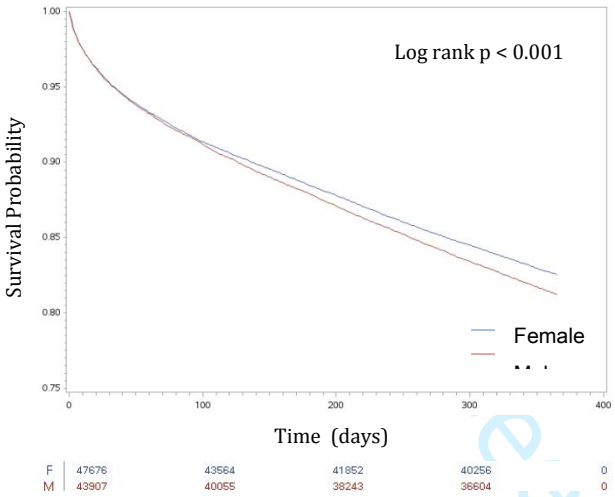


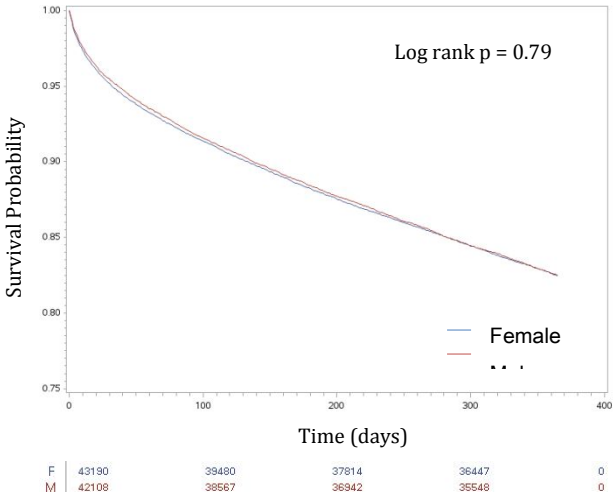
Figure 3. Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis, in each of the temporal cohorts.

Legend: The red line represents survival in men. The blue line represents survival in women.

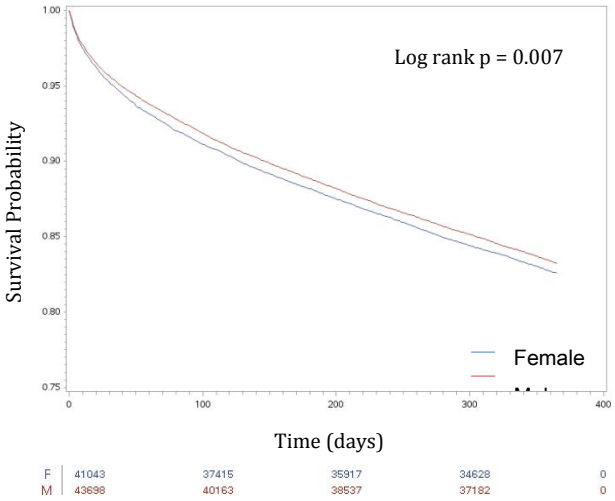
April 1, 1994 – March 31,1999:



April 1, 1999 – March 31, 2004:



April 1, 2004 – March 31, 2009:



April 1, 2009 – March 31, 2014:

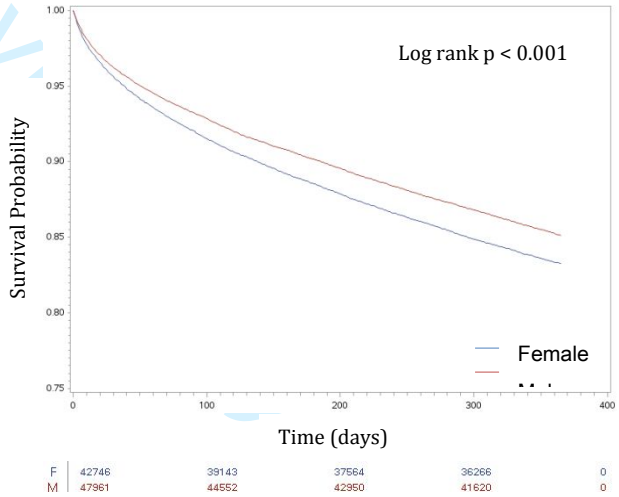


Figure 4a. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in men.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

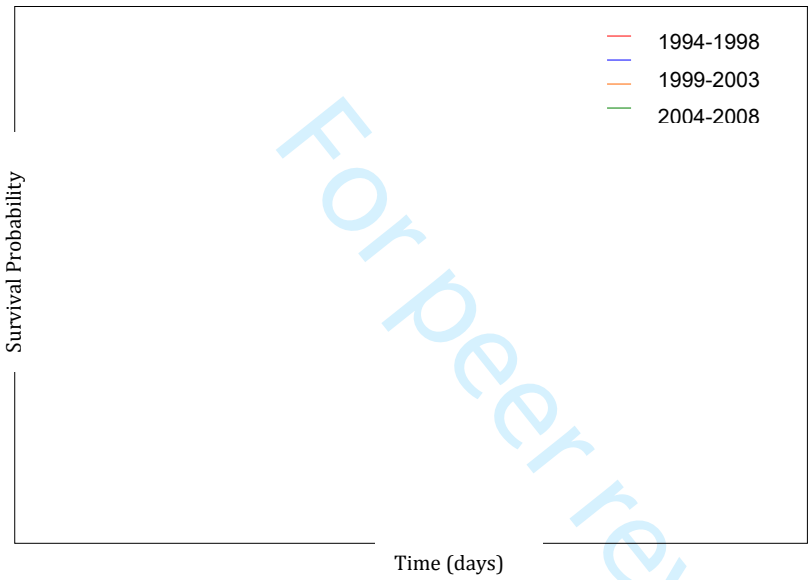


Figure 4b. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in women.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

Table 1. Tempor

1 Table 1. Temporal trends in characteristics of men and women with incident heart failure over time.

Variable	Historic Cohort (1994-1998)			1999 – 2003			2004-2009			Modern Cohort (2009-2013)		
	Women N=47,676	Men N=43,907	P-Value	Women N=43,190	Men N=42,108	P-Value	Women N=41,0423	Men N=43,698	P-Value	Women N=42,746	Men N=47,961	P-Value
Socio-Demographics												
Age (Mean ± SD)	76.3 ± 11.2	72.0 ± 11.3	<.001	76.2 ± 11.8	71.9 ± 11.8	<.001	76.0 ± 12.3	71.6 ± 12.4	<.001	75.8 ± 12.9	71.5 ± 12.8	<.001
Rurality	8,256 (17.3)	8,518 (19.4)	<.001	6,781 (15.7)	6,996 (16.6)	<.001	5,602 (13.6)	6,667 (15.3)	<.001	5,358 (12.5)	6,788 (14.2)	<.001
Income Quintile												
1 (Lowest)	11,651 (24.4)	9,297 (21.2)	<.001	10,121 (23.4)	8,529 (20.3)	<.001	9,661 (23.5)	9,096 (20.8)	<.001	9,613 (22.5)	9,541 (19.9)	<.001
2	10,377 (21.8)	9,418 (21.4)		9,814 (22.7)	9,319 (22.1)		9,070 (22.1)	9,317 (21.3)		9,243 (21.6)	9,833 (20.5)	
3	9,506 (19.9)	8,983 (20.5)		8,571 (19.8)	8,683 (20.6)		7,891 (19.2)	8,576 (19.6)		8,325 (19.5)	9,444 (19.7)	
4	8,208 (17.2)	8,024 (18.3)		7,403 (17.1)	7,770 (18.5)		7,274 (17.7)	8,308 (19.0)		8,017 (18.8)	9,775 (20.4)	
5 (Highest)	7,698 (16.1)	7,956 (18.1)		7,168 (16.6)	7,690 (18.3)		6,976 (17.0)	8,233 (18.8)		7,388 (17.3)	9,188 (19.2)	
Comorbidities												
Uncomplicated HTN	31,751 (66.6)	26,068 (59.4)	<.001	31,381 (72.7)	27,909 (66.3)	<.001	31,336 (76.3)	30,730 (70.3)	<.001	32,809 (76.8)	34,103 (71.1)	<.001

Complicated HTN	2,507 (5.3)	2,006 (4.6)	<.001	2,178 (5.0)	1,921 (4.6)	<.001	3,254 (7.9)	3,551 (8.1)	0.29	32,809 (76.8)	6,516 (13.6)	0.15
Atrial Fibrillation	4,660 (9.8)	4,769 (10.9)	<.001	5,034 (11.7)	5,313 (12.6)	<.001	5,180 (12.6)	5,956 (13.6)	<.001	5,669 (13.3)	6,919 (14.4)	0.035
Myocardial Infarction	2,954 (6.2)	4,697 (10.7)	<.001	3,629 (8.4)	5,937 (14.1)	<.001	4,323 (10.5)	8,030 (18.4)	<.001	5,957 (13.9)	9,617 (20.1)	<.001
Valvular Disease	1,835 (3.8)	1,864 (4.2)	0.002	1,981 (4.6)	2,087 (5.0)	0.002	1,759 (4.3)	2,163 (4.9)	<.001	5,051 (11.8)	2,841 (5.9)	<.001
PVD	3,136 (6.6)	3,994 (9.1)	<.001	2,928 (6.8)	3,684 (8.7)	<.001	1,584 (3.9)	2,405 (5.5)	<.001	2,099 (4.9)	2,257 (4.7)	<.001
CVD	4,429 (9.3)	4,401 (10.0)	<.001	3,841 (8.9)	3,834 (9.1)	<.001	2,808 (6.8)	3,003 (6.9)	0.86	1,272 (3.0)	2,713 (5.7)	0.18
PCD	296 (0.6)	286 (0.7)	0.561	491 (1.1)	362 (0.9)	0.56	807 (2.0)	588 (1.3)	<.001	2,506 (5.9)	882 (1.8)	<.001
COPD/Asthma	13,091 (27.5)	14,352 (32.7)	<.001	14,557 (33.7)	14,988 (35.6)	<.001	15,209 (37.1)	15,996 (36.6)	0.17	1,113 (2.6)	17,164 (35.8)	<.001
Alcohol Abuse	128 (0.3)	398 (0.9)	<.001	187 (0.4)	562 (1.3)	<.001	313 (0.8)	965 (2.2)	<.001	16,261 (38.0)	1,123 (2.3)	<.001
Renal Disease	1,127 (2.4)	1,527 (3.5)	<.001	1,410 (3.3)	1,935 (4.6)	<.001	1,849 (4.5)	2,588 (5.9)	<.001	337 (0.8)	2,865 (6.0)	<.001
Diabetes	9,600 (20.1)	10,462 (23.8)	<.001	10,359 (24.0)	12,182 (28.9)	<.001	12,204 (29.7)	15,243 (34.9)	<.001	1,954 (4.6)	18,721 (39.0)	<.001
Hypothyroidism	2,155 (4.5)	541 (1.2)	<.001	2,212 (5.1)	597 (1.4)	<.001	1,421 (3.5)	428 (1.0)	<.001	14,751 (34.5)	479 (1.0)	<.001

Liver Disease	559 (1.2)	772 (1.8)	<.001	541 (1.3)	800 (1.9)	<.001	540 (1.3)	775 (1.8)	<.001	1,300 (3.0)	895 (1.9)	<.001
Dementia	1,935 (4.1)	1,188 (2.7)	<.001	2,007 (4.6)	1,258 (3.0)	<.001	1,816 (4.4)	1,121 (2.6)	<.001	579 (1.4)	1,194 (2.5)	<.001
Depression	1,788 (3.8)	911 (2.1)	<.001	1,617 (3.7)	872 (2.1)	<.001	1,364 (3.3)	859 (2.0)	<.001	1,791 (4.2)	756 (1.6)	<.001
Psychosis	1,932 (4.1)	1,134 (2.6)	<.001	1,695 (3.9)	1,106 (2.6)	<.001	486 (1.2)	350 (0.8)	<.001	1,213 (2.8)	171 (0.4)	<.001
Primary Tumor	3,055 (6.4)	4,363 (9.9)	<.001	3,026 (7.0)	4,045 (9.6)	<.001	2,947 (7.2)	4,060 (9.3)	<.001	223 (0.5)	4,419 (9.2)	<.001
Metastatic Malignancy	869 (1.8)	804 (1.8)	0.924	925 (2.1)	775 (1.8)	0.92	850 (2.1)	723 (1.7)	<.001	3,376 (7.9)	840 (1.8)	<.001
Paraplegia	840 (1.8)	899 (2.0)	0.002	854 (2.0)	903 (2.1)	0.002	521 (1.3)	572 (1.3)	0.61	1,000 (2.3)	475 (1.0)	0.71
VTE	1,161 (2.4)	1,017 (2.3)	0.238	945 (2.2)	714 (1.7)	0.24	557 (1.4)	505 (1.2)	0.008	434 (1.0)	512 (1.1)	0.83
Frailty	4,302 (9.0)	2,700 (6.1)	<.001	5,598 (13.0)	4,364 (10.4)	<.001	10,163 (24.8)	7,175 (16.4)	<.001	450 (1.1)	8,409 (17.5)	<.001

1 Values are expressed number (%) unless otherwise indicated. SD, standard deviation; HTN, hypertension; IHD, ischemic heart disease; PAD, peripheral arterial

2 disease; CVD, cerebrovascular disease; PCD, pulmonary circulatory disease; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism

Table 2. Evolution of multivariable risk factors of one-year mortality over time. Risk factors that have changed in magnitude between the historical (1994-1998) and modern (2009-2013) times are indicated in bold.

	Adjusted HR (95% CI)			
Variable	**1994-1998**	**1999-2003**	**2004-2008**	**2009-2013**
Age Category				
40-64 years	Reference	Reference	Reference	Reference
65-74 years	1.56 (1.47-1.65)	1.64 (1.53-1.74)	1.66 (1.56-1.77)	1.54 (1.44-1.64)
75-84 years	**2.26 (2.14-2.39)**	2.36 (2.23-2.5)	2.48 (2.34-2.63)	**2.58 (2.43-2.73)**
> 85 years	**3.68 (3.48-3.90)**	4.25 (4.00-4.51)	4.57 (4.31-4.85)	**4.89 (4.62-5.18)**
Female	**0.85 (0.82-0.88)**	0.89 (0.86-0.92)	0.91 (0.88-0.94)	**0.97 (0.93-1.00)**
Rural	**0.94 (0.90-0.98)**	1.00 (0.96-1.05)	0.99 (0.95-1.04)	**1.01 (0.96-1.06)**
Income Quintile				
1 (Low)	1.06 (1.01-1.11)	1.08 (1.03-1.14)	1.12 (1.06-1.18)	1.08 (1.02-1.14)
2	1.03 (0.98-1.08)	1.04 (0.99-1.09)	1.04 (0.99-1.10)	1.04 (0.98-1.09)
3	1.06 (1.01-1.11)	1.03 (0.98-1.09)	1.04 (0.98-1.10)	0.99 (0.94-1.04)
4	1.02 (0.97-1.08)	0.99 (0.94-1.05)	1.08 (1.03-1.14)	1.01 (0.95-1.06)
5 (High)	Reference	Reference	Reference	Reference
Benign Hypertension	0.76 (0.74-0.79)	0.74 (0.72-0.77)	0.73 (0.70-0.76)	0.78 (0.75-0.81)
Complicated Hypertension	**0.93 (0.86-1.00)**	0.95 (0.88-1.02)	0.87 (0.82-0.93)	**0.77 (0.73-0.81)**
Atrial Fibrillation	**0.89 (0.85-0.94)**	0.92 (0.88-0.96)	0.96 (0.92-1.01)	**0.99 (0.95-1.04)**
Myocardial Infarction	**1.12 (1.06-1.18)**	0.99 (0.94-1.05)	1.02 (0.97-1.06)	**0.98 (0.94-1.03)**
Valvular Disease	**1.00 (0.92-1.08)**	0.98 (0.91-1.06)	0.97 (0.90-1.05)	**0.93 (0.86-1.00)**
Peripheral Arterial Disease	1.22 (1.16-1.29)	1.2 (1.14-1.27)	1.28 (1.20-1.37)	1.34 (1.24-1.44)
Cerebrovascular Disease	1.29 (1.23-1.35)	1.25 (1.19-1.32)	1.23 (1.16-1.30)	1.20 (1.13-1.28)
Pulmonary Circulatory Disease	**1.67 (1.43-1.96)**	1.73 (1.52-1.97)	1.54 (1.38-1.71)	**1.24 (1.12-1.37)**
COPD/Asthma	1.15 (1.12-1.19)	1.18 (1.14-1.22)	1.21 (1.17-1.25)	1.17 (1.13-1.21)
Alcohol Abuse	**1.16 (0.97-1.38)**	1.34 (1.16-1.55)	1.51 (1.34-1.70)	**1.62 (1.45-1.82)**
Renal Disease	**2.04 (1.90-2.18)**	1.86 (1.74-1.98)	1.73 (1.63-1.84)	**1.67 (1.58-1.77)**

Diabetes	**1.25 (1.21-1.30)**	1.19 (1.15-1.24)	1.13 (1.09-1.17)	**1.13 (1.10-1.17)**
Hypothyroidism	0.99 (0.91-1.07)	1.01 (0.93-1.09)	1.03 (0.93-1.13)	1.06 (0.96-1.17)
Liver Disease	**1.90 (1.72-2.10)**	1.86 (1.68-2.06)	1.99 (1.79-2.21)	**2.34 (2.12-2.59)**
Dementia	**1.74 (1.63-1.85)**	1.97 (1.86-2.09)	2.03 (1.91-2.16)	**1.96 (1.84-2.09)**
Depression	1.15 (1.07-1.25)	1.18 (1.09-1.28)	1.19 (1.09-1.30)	1.16 (1.06-1.28)
Psychosis	1.29 (1.20-1.38)	1.36 (1.26-1.46)	1.14 (0.99-1.31)	1.43 (1.17-1.76)
Primary Tumor	1.56 (1.49-1.64)	1.69 (1.60-1.77)	1.61 (1.53-1.70)	1.64 (1.56-1.73)
Metastatic Malignancy	3.47 (3.22-3.74)	3.59 (3.33-3.87)	3.14 (2.90-3.41)	3.42 (3.17-3.70)
Paraplegia	1.36 (1.24-1.50)	1.33 (1.21-1.46)	1.52 (1.35-1.70)	1.53 (1.35-1.75)
Venous Thromboemoblism	**1.07 (0.98-1.17)**	1.18 (1.07-1.30)	1.16 (1.03-1.31)	**1.40 (1.24-1.58)**

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

Table 3a. Sex-specific risk factors of one-year mortality in the historical cohort (1994-1998).

Variable	Women HR (95% CI)	Men HR (95% CI)	Multiplicative Interaction P-Value*
Age Category			
40-64 years	Reference	Reference	0.004
65-74 years	1.45 (1.32-1.59)	1.63 (1.51-1.75)	
75-84 years	2.06 (1.89-2.24)	2.42 (2.25-2.60)	
> 85 years	3.53 (3.24-3.85)	3.70 (3.41-4.00)	
Benign Hypertension	0.70 (0.67-0.73)	0.82 (0.79-0.86)	<0.001
Myocardial Infarction	1.26 (1.16-1.36)	1.02 (0.95-1.10)	<0.001
COPD/Asthma	1.10 (1.05-1.16)	1.20 (1.15-1.25)	0.01
Renal Disease	2.26 (2.04-2.50)	1.90 (1.74-2.07)	0.01
Diabetes	1.31 (1.25-1.38)	1.20 (1.14-1.26)	0.01

HR, hazard ratio; CI, confidence interval; COPD; chronic obstructive pulmonary disease

* Multiplicative interaction terms were formed by multiplying sex by each of the covariates in the multivariable Cox proportional hazard model for one-year mortality. Only significant interaction terms (i.e., ones demonstrating sex-specific risk factors) were reported in this table.

Table 3b. Sex-specific risk factors of one-year mortality in the modern cohort (2009-2013).

Variable	Women HR (95% CI)	Men HR (95% CI)	Multiplicative Interaction P-Value *
Income Quintile			
1 (Low)	1.02 (0.94-1.09)	1.15 (1.06-1.23)	0.001
2	0.97 (0.90-1.05)	1.10 (1.02-1.18)	
3	0.99 (0.92-1.07)	0.98 (0.91-1.06)	
4	1.01 (0.93-1.09)	1.01 (0.93-1.08)	
5 (High)	Reference	Reference	
Myocardial Infarction	1.05 (0.98-1.12)	0.94 (0.89-1.00)	0.02
Peripheral Arterial Disease	1.48 (1.32-1.66)	1.25 (1.14-1.37)	0.02
COPD/Asthma	1.12 (1.07-1.17)	1.23 (1.17-1.29)	0.005
Dementia	1.87 (1.72-2.02)	2.10 (1.92-2.30)	0.05
Primary Tumor	1.44 (1.34-1.56)	1.79 (1.68-1.91)	<0.001
Metastatic Malignancy	3.05 (2.75-3.38)	3.85 (3.49-4.26)	<0.001

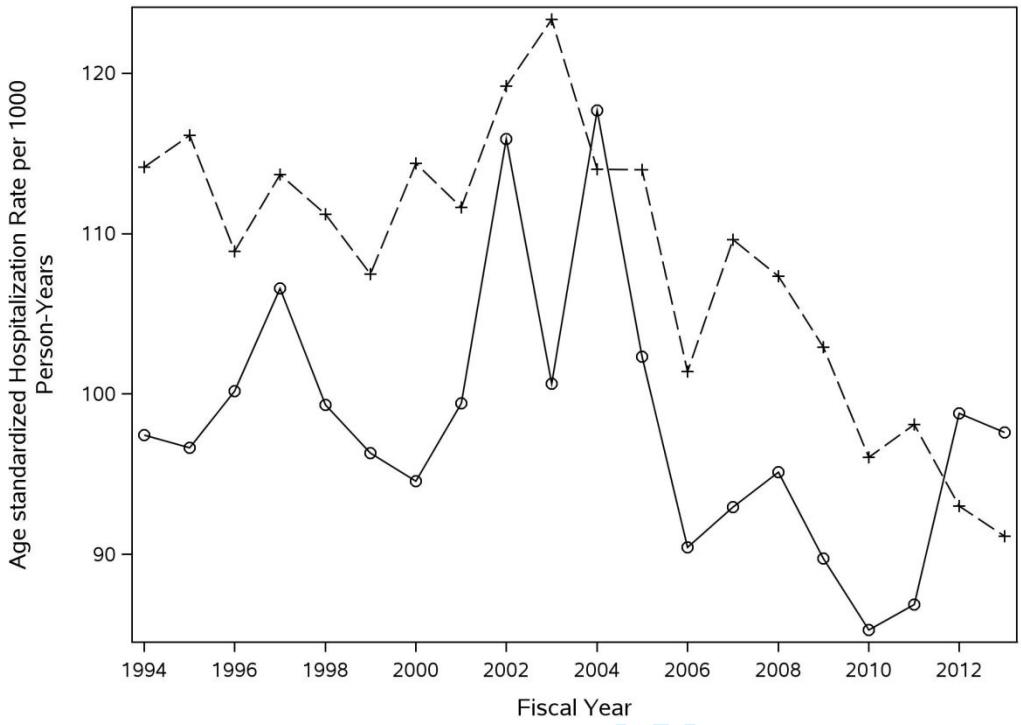
HR, hazard ratio; CI, confidence interval; COPD; chronic obstructive pulmonary disease

* Multiplicative interaction terms were formed by multiplying sex by each of the covariates in the multivariable Cox proportional hazard model for one-year mortality. Only significant interaction terms (i.e., ones demonstrating sex-specific risk factors) were reported in this table.

ed in this table.

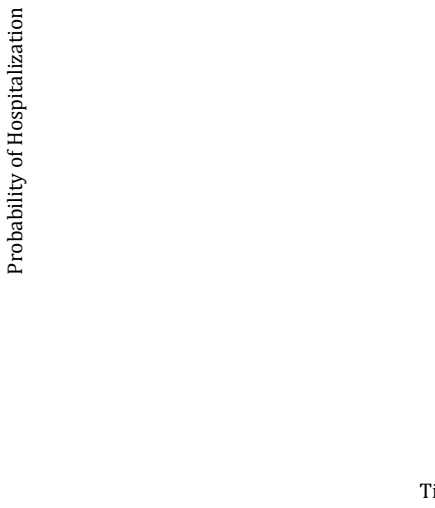
SUPPLEMENTAL MATERIAL

eFigure 1. Sex-specific temporal trends in heart failure hospitalizations within one year of ambulatory heart failure diagnosis. Hospitalization rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population and expressed per 1000 person-years.
Legend: The solid line represents trends in women. The dotted line represents trends in men.



eFigure 2a. Stacked cumulative incidence curves representing temporal trends of heart failure hospitalization within one year of diagnosis in men.
Legend: The red line represents cumulative incidence of hospitalization in the historical cohort (1994-1998). The blue line represents hospitalizations in the 1999-2003 cohort. The orange line represents hospitalizations in the 2004-2008 cohort. The green line (which is nearly superimposed on the blue line) represents hospitalizations in the modern cohort (2009-2013).

eFigure 2a. Stacked cumulative incidence curves representing temporal trends of heart failure hospitalization within one year of diagnosis in women.
Legend: The red line represents cumulative incidence of hospitalization in the historical cohort (1994-1993). The blue line represents hospitalizations in the 1999-2003 cohort. The orange line represents hospitalizations in the 2004-2008 cohort. The green line represents hospitalizations in the modern cohort (2009-2013).



eTable 1. Crude and age standardized incidence rates of ambulatory heart failure per 100,000 population.

				Incidence Rate		95% CI	
Year	Sex	HF Cases	Denominator	Crude	Standardized	Lower	Upper
1994	Female	10123	2544992	397.76	368.95	361.74	376.27
	Male	8998	2290949	392.76	480.63	470.55	490.88
1995	Female	9502	2615417	363.31	335.99	329.21	342.88
	Male	8622	2359605	365.40	445.26	435.73	454.95
1996	Female	9312	2686591	346.61	319.55	313.03	326.18
	Male	8621	2430438	354.71	430.39	421.20	439.74
1997	Female	9518	2753376	345.68	319.39	312.93	325.94
	Male	8939	2497920	357.86	433.52	424.43	442.76
1998	Female	9221	2815590	327.50	303.76	297.52	310.10
	Male	8727	2560459	340.84	411.86	403.12	420.74
1999	Female	9158	2880244	317.96	294.91	288.82	301.09
	Male	8810	2624357	335.70	403.94	395.42	412.61
2000	Female	8921	2948815	302.53	279.98	274.11	285.94
	Male	8548	2693918	317.31	382.41	374.22	390.74
2001	Female	8466	3018031	280.51	258.26	252.69	263.91
	Male	8132	2763947	294.22	351.15	343.46	358.98
2002	Female	8403	3088112	272.11	249.62	244.21	255.11
	Male	8441	2835687	297.67	353.43	345.83	361.16
2003	Female	8242	3159200	260.89	237.25	232.05	242.53
	Male	8177	2908486	281.14	333.06	325.78	340.45
2004	Female	8082	3226254	250.51	227.56	222.51	232.70
	Male	8101	2976603	272.16	320.70	313.67	327.86
2005	Female	8283	3286052	252.07	229.05	224.02	234.17
	Male	8588	3037995	282.69	328.77	321.77	335.87
2006	Female	8107	3340543	242.69	220.03	215.14	225.01
	Male	8774	3091317	283.83	323.41	316.60	330.32
2007	Female	7993	3388916	235.86	211.27	206.53	216.09
	Male	8929	3136755	284.66	318.62	311.98	325.36
2008	Female	8578	3437633	249.53	222.31	217.49	227.21
	Male	9306	3182320	292.43	322.03	315.46	328.71
2009	Female	8433	3486229	241.89	213.46	208.78	218.22
	Male	9312	3225967	288.66	313.38	306.98	319.87
2010	Female	8366	3534061	236.72	208.36	203.77	213.03
	Male	9262	3269161	283.31	301.92	295.75	308.19
2011	Female	8424	3578607	235.40	201.79	197.35	206.31
	Male	9292	3308050	280.89	294.17	288.17	300.26
2012	Female	8526	3618133	235.65	199.93	195.55	204.39
	Male	9585	3341596	286.84	293.47	287.58	299.45
2013	Female	8997	3653530	246.25	205.83	201.43	210.30
	Male	10510	3369203	311.94	312.82	306.82	318.90

HF, heart failure; CI, confidence interval

eTable 2. Temporal trends of one-year mortality rates in men and women with incident heart failure.

Time Cohort	Sex	Number of Deaths	Number of Incident HF Cases	Crude Rate (%)	Age-Standardized Rate (%, 95% CI)
April 1994-March 1999	F	8319	47676	17.5	10.1 (9.5-10.8)
	M	8238	43907	18.8	11.4 (10.8-11.9)
April 1999-March 2004	F	7572	43190	17.5	9.9 (9.3-10.6)
	M	7365	42108	17.5	10.4 (9.9-10.8)
April 2004-March 2009	F	7148	41043	17.4	9.5 (9.0-10.1)
	M	7322	43698	16.8	9.8 (9.4-10.2)
April 2009-March 2014	F	7156	42746	16.8	8.6 (8.1-9.0)
	M	7138	47961	14.9	8.2 (7.9-8.6)

HF, heart failure; CI, confidence interval

eTable 3. Crude and age-standardized one-year mortality rates following ambulatory heart failure diagnosis. Rates are expressed per 1000 population.

				Mortality Rate		95% CI	
Year	**Sex**	**Deaths**	**Incident HF Cases**	**Crude**	**Standardized**	**Lower**	**Upper**
1994	Female	1733	10123	171.19	104.40	90.54	119.78
	Male	1710	8998	190.04	123.00	110.57	136.45
1995	Female	1629	9502	171.44	94.64	82.33	108.27
	Male	1578	8622	183.02	109.23	97.89	121.53
1996	Female	1679	9312	180.30	111.88	95.19	130.64
	Male	1643	8621	190.58	112.37	101.72	123.83
1997	Female	1674	9518	175.88	90.24	78.73	102.95
	Male	1741	8939	194.76	116.99	105.34	129.56
1998	Female	1604	9221	173.95	105.45	92.82	119.32
	Male	1566	8727	179.44	105.22	94.57	116.74
1999	Female	1527	9158	166.74	90.75	78.76	104.04
	Male	1522	8810	172.76	103.32	93.50	113.88
2000	Female	1556	8921	174.42	106.23	92.32	121.65
	Male	1489	8548	174.19	100.59	90.80	111.15
2001	Female	1473	8466	173.99	91.60	79.23	105.34
	Male	1364	8132	167.73	103.48	92.72	115.15
2002	Female	1504	8403	178.98	105.15	91.98	119.68
	Male	1511	8441	179.01	105.70	96.26	115.82
2003	Female	1512	8242	183.45	104.88	90.32	121.12
	Male	1479	8177	180.87	105.10	94.47	116.60
2004	Female	1468	8082	181.64	94.64	82.57	107.97
	Male	1486	8101	183.43	105.57	95.67	116.22
2005	Female	1445	8283	174.45	96.12	83.52	110.08
	Male	1454	8588	169.31	98.53	88.69	109.16
2006	Female	1395	8107	172.07	98.75	86.46	112.30
	Male	1459	8774	166.29	99.06	89.97	108.82
2007	Female	1384	7993	173.15	92.81	81.59	105.15
	Male	1475	8929	165.19	93.86	85.68	102.61
2008	Female	1456	8578	169.74	92.93	82.04	104.86
	Male	1448	9306	155.60	94.08	85.56	103.21
2009	Female	1464	8433	173.60	89.43	79.65	100.09
	Male	1461	9312	156.89	88.17	80.01	96.95
2010	Female	1373	8366	164.12	86.81	76.58	98.03
	Male	1396	9262	150.72	81.93	74.92	89.43
2011	Female	1418	8424	168.33	81.54	71.43	92.68
	Male	1381	9292	148.62	82.13	74.91	89.87
2012	Female	1404	8526	164.67	85.48	75.84	96.01
	Male	1377	9585	143.66	76.53	69.60	83.97
2013	Female	1497	8997	166.39	84.84	75.24	95.32
	Male	1523	10510	144.91	82.99	75.34	91.22

CI, confidence interval

eTable 4. Crude and age standardized one-year heart failure hospitalization rates in patients who were diagnosed with heart failure in an ambulatory setting between 1994-2013. Rate is expressed per 1000 person years.

		Heart Failure		Hospitalization Rate		95% CI	
Year	Sex	Hospitalizations	Denominator	Crude	Standardized	Lower	Upper
1994	Female	1105	8417.52	131.27	97.43	83.29	113.28
	Male	1108	7325.60	151.25	114.15	101.01	128.52
1995	Female	1067	7860.78	135.74	96.64	83.94	110.71
	Male	1001	7065.84	141.67	116.14	100.74	133.23
1996	Female	1065	7632.79	139.53	100.19	85.97	116.09
	Male	1015	7022.96	144.53	108.91	96.08	122.98
1997	Female	1028	7859.13	130.80	106.59	90.03	125.30
	Male	1082	7232.55	149.60	113.69	100.95	127.59
1998	Female	1006	7603.66	132.30	99.32	85.96	114.16
	Male	963	7180.72	134.11	111.22	97.10	126.82
1999	Female	983	7607.15	129.22	96.32	82.75	111.47
	Male	936	7305.04	128.13	107.48	95.17	120.95
2000	Female	917	7402.64	123.87	94.57	80.28	110.67
	Male	994	7033.00	141.33	114.37	101.66	128.24
2001	Female	903	6997.61	129.04	99.40	84.75	115.86
	Male	901	6711.51	134.25	111.64	97.95	126.71
2002	Female	937	6838.58	137.02	115.90	100.22	133.33
	Male	1007	6854.11	146.92	119.20	106.86	132.57
2003	Female	994	6645.28	149.58	100.66	86.86	116.02
	Male	1016	6629.94	153.24	123.36	110.31	137.54
2004	Female	1002	6508.80	153.95	117.67	101.49	135.69
	Male	993	6504.80	152.66	114.02	102.01	127.06
2005	Female	962	6775.02	141.99	102.34	88.21	118.09
	Male	1026	7052.13	145.49	113.98	101.59	127.48
2006	Female	982	6565.14	149.58	90.43	78.78	103.32
	Male	989	7237.69	136.65	101.40	90.93	112.73
2007	Female	987	6493.03	152.01	92.95	81.45	105.61
	Male	1069	7307.83	146.28	109.62	98.84	121.25
2008	Female	1046	6963.90	150.20	95.11	83.30	108.13
	Male	1097	7646.02	143.47	107.36	97.12	118.38
2009	Female	1021	6841.22	149.24	89.74	79.39	101.06
	Male	1085	7697.71	140.95	102.92	92.38	114.34
2010	Female	1042	6799.72	153.24	85.28	75.41	96.08
	Male	1078	7694.92	140.09	96.05	86.94	105.86
2011	Female	1061	6842.81	155.05	86.86	76.87	97.78
	Male	1038	7754.49	133.86	98.10	87.99	109.06
2012	Female	1137	6895.19	164.90	98.80	87.24	111.46
	Male	1097	8017.47	136.83	93.00	84.28	102.37
2013	Female	1159	7269.34	159.44	97.59	86.03	110.27
	Male	1205	8772.03	137.37	91.14	82.26	100.71

CI, confidence interval

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	8-10

		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Sex-Specific Temporal Trends in Ambulatory Heart Failure Incidence, Mortality and Hospitalization in Ontario, Canada from 1994-2013 – a Population-Based Cohort Study

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Title: Sex-Specific Temporal Trends in Ambulatory Heart Failure Incidence, Mortality and Hospitalization in Ontario, Canada from 1994-2013 – a Population-Based Cohort Study

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ABSTRACT

Objectives: To examine the temporal trends in mortality and heart failure (HF) hospitalization in ambulatory patients following a new diagnosis of HF.

Design: Retrospective cohort study

Setting: Outpatient

Participants: Ontario residents who were diagnosed with HF in an outpatient setting between 1994-2013.

Primary and Secondary Outcome Measures: The primary outcome was all-cause mortality within one year of diagnosis and the secondary outcome was HF hospitalization within one year. Risks of mortality and hospitalization were calculated using the Kaplan-Meier method and the relative hazard of death was assessed using multivariable Cox proportional hazard models.

Results: A total of 352,329 patients were studied (50% female). During the study period, there was a greater decline in age standardized one-year mortality rates (AMR) in men (33%) than in women (19%). Specifically, female AMR at one-year was 10.4% (95% CI, 9.1-12.0) in 1994 and 8.5% (7.5-9.5) in 2013, and male AMR at one-year was 12.3% (11.1-13.7) in 1994 and 8.3% (7.5-9.1) in 2013. Conversely, age standardized HF hospitalization rates declined in men (11.4% [10.1-12.9] in 1994 and 9.1% [8.2-10.1] in 2013) but remained unchanged in women (9.7% [8.3-11.3] in 1994 and 9.8% [8.6-11.0] in 2013).

Conclusion: Among patients with HF over a 20-year period, there was a greater improvement in the prognosis of men compared to women. Further research should focus on the determinants of this disparity and ways to reduce this gap in outcomes.

Strengths and Limitations:

- First and largest population-based study to examine temporal, sex-specific trends in heart failure (HF) outcomes in an ambulatory setting.
- The nature of our publicly funded healthcare system allowed for analysis of all patients diagnosed with HF in Ontario without selection bias.
- Information on ejection fraction was not available in the databases used.

Key Words: heart failure, mortality, hospitalization, women, epidemiology, prognosis

No Data Availability Statement: The dataset from this study is held securely in coded form at ICES (formerly the Institute for Clinical Evaluative Sciences).

Introduction

Heart failure (HF) is a significant cause of morbidity and mortality for both women and men [1, 2]. Despite the current era of guideline directed medical therapy, HF continues to be a leading cause of admission to hospital. It is associated with a poor prognosis and contributes to 35% of cardiovascular mortality in women [3]. Despite this, HF remains poorly understood in women, and women continue to be underrepresented in HF clinical trials [4]. The underlying mechanism of HF is often different in women and men, with women suffering more often from HF of a hypertensive rather than ischemic etiology [5, 6]. Important trends in the incidence and outcomes of hospitalized HF patients have been recently published [7, 8]; these studies suggest that the incidence of HF has declined in many inpatient cohorts, however the prognosis of this disease remains poor. An in-depth understanding of the temporal trends in HF incidence and outcomes is also needed in the ambulatory setting, where the majority of HF cases are diagnosed and managed. Also, given the sex differences in co-morbidities and outcomes in HF, it is not known if these temporal changes are modified by sex. We therefore examined the sex differences in HF co-morbidities, incidence, mortality and hospitalization in a population-based ambulatory cohort from fiscal years 1994 to 2013.

Methods

Design and Study Population

We conducted a population-based, retrospective cohort study of Ontario residents who were diagnosed with HF in an outpatient setting over a 20-year period, using linked administrative databases. The Research Ethics Board of Sunnybrook Health Sciences, Toronto, Canada approved this study and waived the need for informed consent.

Included were adult patients ≥ 40 years of age, who were newly diagnosed with HF in an ambulatory setting between April 1, 1994 and March 31, 2014. We excluded non-Ontario residents, those who were ≥ 105 years of age on the date of HF diagnosis, those who were diagnosed with HF in an inpatient setting and in whom HF had developed as a post-admission complication. Ontario is Canada's most populous and ethnically diverse province with a public funded healthcare system that reimburses all medically necessary physician and hospital services.

Patient and Public Involvement

Patients and the public were not involved in the design and conception of this study. However, the results will be publicly disseminated.

Data Sources

Databases were linked deterministically using unique encoded identifiers. Ambulatory incident HF cases were identified using the ICES Congestive Heart Failure database, based on two outpatient billing claims for HF within one year. This algorithm was validated in primary care patient records and shown to have 85% sensitivity and 97% specificity in identifying HF events [9]. The Congestive Heart Failure database allowed us to study a validated cohort of HF patients with consistent entry criteria over time. Our analyses were conducted by linking the Congestive Heart Failure database with the Registered Persons Database, which contains demographic and vital statistics information, the Canadian Institute for Health Information

Discharge Abstract Database, which contains data on all hospitalizations and co-morbidities, and Same Day Surgery database for co-morbidities. Physician fee-for-service claims data was obtained from the Ontario Health Insurance Plan database. While lacking physiologic and laboratory measures, these databases have been validated for many outcomes, exposures, and co-morbidities [10-13].

Outcome

The primary outcome was all-cause mortality within one year of HF diagnosis. Mortality was ascertained by using the Registered Persons Database. Secondary outcome was HF hospitalization within one year of HF diagnosis, which was ascertained using the Discharge Abstract Database.

Covariates

Demographic variables were obtained from the Registered Persons Database. We estimated socioeconomic status based on patients' neighborhood median income in the Canadian census, and determined rural versus urban residence using Statistics Canada definitions [14]. We identified hypertension [10], asthma [15], chronic obstructive pulmonary disease (COPD) [16] and diabetes mellitus [12] using validated algorithms applied on patient encounters within five years of HF diagnosis. Other co-morbidities were identified using Discharge Abstract Database, Same Day Surgery and Ontario Health Insurance Plan databases based on International Classification of Diseases 10th Revision codes within five years of HF diagnosis, using previously described methods [17-29]. Frailty was identified using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, which is an instrument designed and validated for research of frailty-related outcomes and resource utilization using administrative data [25, 28, 30-34].

Statistical Analysis

Analyses were stratified by sex. Continuous variables were expressed as mean (standard deviation) and categorical variables as number (proportion). Mortality was assessed at one-year post HF diagnosis. Survival time was defined as the date of HF diagnosis until date of death or last follow up. Patients were censored when they lost possession of a valid Ontario health insurance number for two consecutive eligibility quarters (i.e., have left the province of Ontario). Probability of death within given durations of follow-up were calculated using the Kaplan-Meier method, with the significance of the difference between sexes assessed using the log-rank test. We estimated the cumulative incidence of HF hospitalizations using cumulative incidence functions (CIF), which treated death as a competing risk. We constructed age standardized plots of HF incidence, one-year mortality and HF hospitalization in men and women over the 20-year period. These rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population.

We used linear regression with fiscal year as the independent variable to assess for temporal changes in HF incidence and outcomes in women and men across the 20-year period. To examine the temporal changes in co-morbidities, we divided the 20-year period into 4 temporal cohorts: those diagnosed with HF between April 1, 1994 – March 31, 1999 (the historical cohort), between April 1, 1999 – March 31, 2004, between April 1, 2004 – March 31, 2009 and between April 1, 2009 – March 31, 2014 (the modern cohort). The hazard of death in the historical cohort and the modern cohort were assessed using Cox proportional hazard models with and without multivariable adjustment. To justify sex-specific analyses, we also tested for the presence of any interaction between sex and each of the mortality risk factors in these two cohorts using multiplicative interaction terms. The measure of association was hazard ratios (HR) with 95% CI. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), with statistical significance defined by a two-sided P-value of < 0.05.

Results

Over a 20-year period in Ontario, a total of 352,329 patients were diagnosed with HF in an ambulatory setting (50% women). There were 91,583 incident HF cases in the historical cohort (52% women) and 90,707 in the modern cohort (47% women). Throughout the study period, women with HF were more likely to be older, more frail, of lower income status, have co-morbid conditions such as hypertension, hypothyroidism, anemia, dementia and depression, but were less likely to have myocardial infarction (MI), peripheral arterial disease, diabetes and alcohol abuse compared to men (Table 1). Compared to the historical cohort, modern HF patients were less likely to have peripheral and cerebral vascular disease, psychosis, paraplegia and venous thromboembolic disease; but more likely to be urban dwellers, have hypertension, atrial fibrillation, MI, valvular heart disease, pulmonary circulatory disorder, COPD/asthma, alcohol abuse, renal disease, and are increasingly frail.

Trends in HF Incidence

During the historical period (1994-1998), a total of 47,676 (0.36%) incident HF cases were identified in women and 43,907 (0.36%) in men. During the modern era (2009-2013), 42,746 (0.24%) incident cases were identified in women and 47,961 (0.29%) in men. Although the incidence of HF declined in both sexes over the 20-year period (linear regression slope, -0.031; $p<0.0001$ in women and -0.025; $p<0.0001$ in men), it remained higher in men than in women (Figure 1). Age standardized incidence for women decreased from 369.0 (95% CI, 361.7-376.3) per 100,000 population in 1994 to 205.8 (201.4-210.3) in 2013. For men, HF incidence decreased from 480.6 (470.6-490.9) per 100,000 in 1994 to 312.8 (306.8-318.9) in 2013 (eTable 1).

Trends in Mortality

One-year mortality occurred in 8,319 (17.5%) women and 8,238 (18.8%) men during the historical period; it occurred in 7,156 (16.8%) women and 7,138 (14.9%) men during the modern period (eTable 2). These survival patterns are reinforced by the Kaplan-Meier survival curves in Figure 2, as well as the stacked Kaplan-Meier curves in Figure 3 that demonstrate an improvement in male survival (linear regression slope, -0.020; p<0.0001) but relatively little change in female survival over time (linear regression slope, -0.010; p=0.001). Age-standardized one-year mortality rates (AMR) also declined in both sexes but the magnitude of reduction was greater in men than in women. Men had higher AMR than women at most time points prior to 2009 (Figure 4). Specifically, the female AMR was 10.4% (95% CI, 9.1-12.0) in 1994 and 8.5% (7.5-9.5) in 2013, representing a 19% reduction. Conversely, male AMR was 12.3% (11.1-13.7) in 1994 and 8.3% (7.5-9.1) in 2013, representing a 33% reduction (eTable 3).

In the unadjusted analysis, female sex was protective against one-year mortality in the historical cohort (unadjusted HR 0.93, 95% CI 0.90-0.95) but was associated with a higher risk of mortality (unadjusted HR 1.14, 95% CI 1.10-1.18) in the modern cohort. Adjusted analysis demonstrated that the protective effect conferred by female sex had diminished over time (adjusted HR 0.85, 95% CI 0.82-0.88 in the historical and 0.97, 95% CI 0.93-1.00 in the modern cohort).

Table 2 lists the multivariable predictors of one-year mortality in the modern cohort. Compared to the historical cohort, the mortality risk associated with age > 75 years, liver disease, dementia and venous thromboembolism had increased while the risk associated with male sex, complicated hypertension, diabetes, renal disease and pulmonary circulatory disease had diminished. Of note, alcohol abuse and venous thromboembolism emerged as new mortality risk factors while urban residence and MI were no longer risk factors.

Sex-specific mortality risk factors have evolved over time. Table 3a and 3b illustrate the sex-specific HRs in the historical and modern cohorts, respectively. In the modern cohort, low income was associated with a higher risk of mortality in men but not in women. Conversely, MI had a mild protective effect on men but not in women. In addition, women with peripheral arterial disease had a higher risk of death while men with COPD/asthma, dementia, primary and metastatic malignancies had a higher risk of mortality than women with similar co-morbidities. Compared to the historical cohort, most sex-specific risk factors have evolved over time, with the exception of COPD/asthma.

Trends in HF Hospitalization

HF hospitalizations occurred in 5,271 (13.4%) women and 5,169 (14.4%) men within one-year of HF diagnosis in the historical cohort. During the modern period, there were 5,420 (15.6%) HF hospitalizations in women and 5,503 (13.8%) hospitalizations in men. Age-standardized HF hospitalization rates declined in men (linear regression slope, -0.010; p=0.0002) but remained unchanged in women (linear regression slope, -0.005; p=0.11) during the 20-year period (eFigure 1 and eTable 4). Specifically, male age-standardized HF hospitalization rates were 11.4% (95% CI, 10.1-12.9) in 1994 and 9.1% (8.2-10.1) in 2013. Female rates were 9.7% (8.3-11.3) in 1994 and 9.8% (8.6-11.0) in 2013.The temporal trends in the cumulative incidence of HF hospitalizations are illustrated in eFigure 2.

Discussion

This population-based study evaluated 352,329 individuals with a first-time diagnosis of HF from 1994-2013 in the ambulatory care setting. There are four main findings reported in this study: 1) HF mortality declined over time 2) The reduction in mortality is greater in men than in women. 3) Rates of hospitalization decreased for men but remained unchanged for women. 4) The incidence and significance of co-morbidities associated with HF have changed over time, and suggest that women continue to experience a greater burden of co-morbid disease when compared to men.

Trends in HF Incidence and Mortality

Population-based temporal trends in HF incidence and mortality have been previously reported across many cohorts, however many of these studies have been limited to patients hospitalized with a diagnosis of HF or have not provided detailed, sex-stratified analyses. Temporal trends in the incidence and survival of HF patients were first reported by the Framingham group over a 50 year period from 1950-1999 [35]. These authors reported that the incidence of HF had declined in women but not men, with improving survival in both sexes [35]. This pivotal study was followed by findings from a community-based cohort of 4537 patients from 1979-2000, which reported that although HF incidence remained unchanged for both sexes, mortality declined – with greater survival gains in men than women [36]. A recent study by our group demonstrated that amongst ambulatory Ontario residents from 2009-2013, the incidence of heart failure decreased more rapidly in men than women. At the same time, heart failure associated deaths and hospitalizations remain higher in women than men within a year of HF diagnosis [19]. The present study extends these findings by demonstrating a continued disproportionate decrease in HF mortality for men compared to women from 1994-2013. Our findings corroborate with our previous study of HF incidence and one-year mortality in rural and

urban Eastern Ontario from 1994-2013 [24]. They also corroborate the work of Tu and colleagues [7] who used similar administrative databases to report on the HF incidence and mortality of Ontario patients ≥ 20 years of age from 1997-2007. Tu evaluated both admitted and ambulatory HF patients and reported declines in HF incidence over this time period, a finding that was most evident in the older cohorts [7]. Sex stratified mortality rates were not reported in this study. A recent study from Denmark demonstrated a decrease in HF incidence over time only in cohorts >50 years of age, but an increase in HF incidence in younger patients. Although detailed sex-specific outcomes were not provided, sex-stratified models showed similar trends in incidence and mortality over time with men having a higher incidence overall [8].

The present study extends these observations by providing detailed sex-specific data on mortality trends over time. Our findings suggest that in Ontario, one-year mortality rates have decreased over the past 20 years. However, this mortality reduction was greatest for men, and observed to a lesser extent for women. This translates to the observation that women had better AMR than men in the first three temporal cohorts of this study (1994-2008); however in the most recent cohort (2009-2013) we observed mortality to be higher in women than men for the first time. The basis for this sex-based difference is unclear but may be explained in part by the observation that women are more likely than men to have a diagnosis of HFpEF, a disease for which there remains no evidence-based therapies which can improve survival, in contrast to the significant advances in medical therapy for HF with reduced ejection fraction (HFrEF) [37]. In addition, female HF patients have a higher co-morbidity burden than their male counterparts. Complex co-morbid conditions, coupled with atypical presentation of cardiac disease in women, may also have lead to delays in diagnosis and differences in management or response to medical therapy [38]. Further work is needed to determine whether the other sex-based differences in

management, response to treatment or underlying pathophysiology remain to explain these sex-based trends in HF mortality over time.

Trends in HF hospitalization

Rates of hospitalization for HF decreased only for men in this time period. This is consistent with recent reports of sex and race differences in hospitalization trends over a similar time period [19, 39]. It is possible that this sex-based difference may be due to death being a competing risk for hospitalization in men, such that men with HF may suffer earlier deaths whereas women with HF survive to an older age and are more likely to become hospitalized. Alternatively, it is possible that the rates of hospitalization in men and women reflect the underlying HF type, since men are more likely to have HFrEF (for which there are several treatments known to improve outcomes and decrease hospitalization) while women are more likely to have HFpEF (for which there are no substantial evidence-based therapies). Nonetheless, the observed sex differences may also be attributed to the greater co-morbidity burden in women, differences in social determinants of health, or genetic or physiologic differences that cannot be explained within the observational context of this study; all of these point to the need for further exploration to determine the adverse trends for mortality and hospitalization in women with a diagnosis of HF.

Trends in HF Co-morbidities

Sex-based differences in co-morbidities have been previously reported in hospitalized patients; women with HF are older and more likely than men to have co-morbid hypertension, renal failure, obesity, and depression. Men with HF are more often smokers, and tend to have more ischemic heart disease, COPD, and HFrEF [40]. Our study is the first to report on the relationship between sex and co-morbidity in ambulatory HF patients over time. Compared to our historical cohort, our most recent cohort of patients demonstrates an overall increase in important

co-morbidities such as frailty, diabetes, renal disease, MI, atrial fibrillation, COPD and hypertension. This has been observed in other population-based studies [8] and speaks to the increased complexity of the HF patient in the current era. The increased prevalence of these co-morbidities over time was seen in both women and men. Certain co-morbidities remained more common in women than in men in both the historical and recent cohorts; including depression, hypertension, advanced age, frailty, dementia and thyroid disease. Interestingly, frailty, chronic pulmonary disease, and metastatic cancer became more common in women than men in the recent cohort. Collectively these findings suggest that the co-morbidity of the HF patient is increasing over time, and that women continue to experience a greater co-morbidity burden than men. This observation may also explain in part the sex difference in mortality trends.

Important trends in the risk associated with these co-morbidities were also observed. Hypertension conferred a greater protective effect in the modern era. This may actually reflect the known adverse prognosis associated with low blood pressure in HF [41, 42]. In addition, the risk associated with diabetes, renal disease and pulmonary circulatory disease has decreased over time. In addition, MI was no longer a mortality risk factor in the recent cohort when compared to the historical cohort. These changes over time may be due to significant advances in the medical management of these co-morbidities, which have influenced overall survival.

Sex-based differences in the risks associated with certain co-morbidities were also observed. In the most recent cohort, MI had a mild protective effect in men but not in women. This may be due to a lower detection rate of ischemic heart disease in women due to atypical presentation [43], which leads to missed management and poorer outcomes. Ischemic heart disease is a leading cause of HF in both sexes. When diagnosed with

ischemic heart disease, women are less likely than men to undergo cardiac catheterization and revascularization; whether this is wholly attributed to the increased microvascular disease in women is not well understood [44]. In the most recent cohort, peripheral arterial disease was associated with a higher risk of mortality in women, while COPD, dementia and malignancy posed a greater risk of mortality in men. Whether these differences are clinically relevant, or help to explain the variability in mortality risk associated with HF, remains to be determined. There remains a significant knowledge gap on sex specific differences in epidemiology, pathophysiology, management and prognosis of co-morbidities related to HF [40]. Such knowledge could determine if HF management should be targeted to specific sex-based co-morbidities to improve outcomes and narrow the gap in mortality improvement between women and men.

Limitations and Strengths

Our study has several limitations. *Firstly*, cases of HF were identified in the ambulatory care setting based on the requirement of 2 claims for HF within one year. Although this method may have led to an underestimate of HF, it has been validated previously and shown to improve the specificity of our case selection [7, 9]. *Secondly*, our algorithm for ascertainment of HF is validated in patients who are 40 years of age and older, thus limiting the generalizability of our findings. *Thirdly*, information on ejection fraction was not available in the databases used, which precluded analyses in subtypes of HF based on ventricular function. *Fourthly*, the diagnostic criteria for HFpEF have become more specific over time; whether this may influence incidence and prognosis cannot be determined from this study. *Finally*, cohort studies are by nature subjected to residual confounding. Despite these limitations, our study is the first to address the

epidemiology of HF in a validated cohort of *ambulatory* patients, and one of the first to report on detailed sex-based outcome and co-morbidity differences within a large universal healthcare system, using the same entry criteria over a 20-year time period. The nature of our publicly funded healthcare system allowed for complete analysis of all Ontario HF patients, which minimized selection bias and greatly improved the generalizability of our findings.

Conclusions

Over a 20-year window, we found an overall reduction in all-cause mortality in the year following HF diagnosis. However, there was a much larger reduction of mortality in men than in women, and HF hospitalization rates have decreased for men but remained unchanged in women. Specifically, mortality and hospitalization rates were higher in men than women at the start of the study period and were similar between sexes towards the end of this period. Female HF patients continue to experience a greater burden of co-morbidities than male HF patients in the modern era. Further research should focus on the determinants of this disparity such as sex differences in medical and device management, to better characterize incidence and outcomes by HF type, and ways to reduce this gap in outcomes.

Authorship Contributions:

Conception: LYS, LMM

Design: LYS, LMM, JVT

Data acquisition and analysis: LYS, ABE

Interpretation of results: LYS, LMM, PPL, RB, SC, RD, TC, DSL, PCA, ABE, JVT

Drafting of manuscript: LYS, LMM

Critical revision: LYS, LMM, PPL, RB, SC, RD, TC, DSL, PCA, ABE, JVT

Agreement to be accountable for all aspects of the work: LYS

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opinions and statements expressed in the manuscript are those of the authors, and do not necessarily reflect those of the above agencies.

Declaration of Interests: none

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A and Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-847.

2. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML and Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *Journal of the American College of Cardiology*. 2013;61:1510-7.

3. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.

4. Norberg H. Clinical trial enrolment favours men: Fewer women meet eligibility criteria for trials of heart failure medication is discussed by Helena Norberg from Sweden. *European Heart Journal*, 2019;40:1104–1105,5.

5. Scantlebury DC and Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol*. 2011;26:562-8.

6. Kenchaiah S and Vasan RS. Heart Failure in Women--Insights from the Framingham Heart Study. *Cardiovasc Drugs Ther*. 2015;29:377-90.

7. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE and Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ*. 2012;184:E765-73.

8. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, Gislason GH, Torp-Pedersen C and Andersson C. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. *Circulation*. 2017;135:1214-1223.

9. Schultz SE, Rothwell DM, Chen Z and Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33:160-6.

10. Tu K, Campbell NRC, Chen ZL, Cauch-Dudek KJ and McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Medicine*. 2007;1.

11. Juurlink D, Preya C, Croxford R, Chong A, Austin P, Tu J and Laupacis A. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. ICES Investigative Report*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2006.

12. Hux JE, Ivis F, Flintoft V and Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25.

13. Austin PC, Daly PA and Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144.

14. du Plessis V, Beshiri R, Bollman RD and Clemeson H. *Definitions of "rural". Agriculture and Rural Working Paper Series, No. 61*. Ottawa, ON: Statistics Canada; 2002.
15. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L and To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J*. 2009;16.
16. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L and To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. *COPD*. 2009;6.
17. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE and Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43.
18. Sun LY, Gershon AS, Ko DT, Thilen SR, Yun L, Beattie WS and Wijeysundera DN. Trends in Pulmonary Function Testing Before Noncardiothoracic Surgery. *JAMA Intern Med*. 2015;175:1410-2.
19. Sun L.Y. Tu JV, Coutinho T., Turek M., Rubens F., McDonnell L., Tulloch H., Mielniczuk L.M. Sex Differences in Heart Failure Outcomes in an Ambulatory, Population-Based Cohort. *CMAJ*. 2018;190:E848-E854.
20. Sun L.Y. Tu JV, Lee D.S., Beanlands R.S., Ruel M., Austin P.C., Bader Eddeen A., Liu P.P. Disability-Free Survival After Coronary Artery Bypass Grafting in Women and Men with Heart Failure. *BMJ Open Heart*. 2018;5:e000911.
21. Sun LY, Gaudino M, Chen RJ, Bader Eddeen A and Ruel M. Long-term Outcomes in Patients With Severely Reduced Left Ventricular Ejection Fraction Undergoing Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting. *JAMA cardiology*. 2020.
22. Sun LY, Kimmoun A, Takagi K, Liu PP, Bader Eddeen A and Mebazaa A. Ethnic differences in acute heart failure outcomes in Ontario. *Int J Cardiol*. 2019;291:177-182.
23. Sun LY, Tu JV, Eddeen AB and Liu PP. Prevalence and long-term survival after coronary artery bypass grafting in women and men with heart failure and preserved versus reduced ejection fraction. *Journal of the American Heart Association*. 2018;7:1-14.
24. Sun LY, Tu JV, Sherrard H, Rodger N, Coutinho T, Turek M, Chan E, Tulloch H, McDonnell L and Mielniczuk LM. Sex-Specific Trends in Incidence and Mortality for Urban and Rural Ambulatory Patients with Heart Failure in Eastern Ontario from 1994 to 2013. *Journal of Cardiac Failure*. 2018;24:568-574.
25. Tran DTT, Tu JV, Dupuis J-Y, Bader Eddeen A and Sun LY. Association of Frailty and Long-Term Survival in Patients Undergoing Coronary Artery Bypass Grafting. *Journal of the American Heart Association*. 2018;7.
26. Johnston AM, T. G; Lee, D. S.; Bader Eddeen, A.; Sun, L. Y. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. *Journal of the American Heart Association*. 2019;8:e013260.
27. Hayatsu Y, Ruel M, Bader Eddeen A and Sun L. Single Versus Multiple Arterial Revascularization in Patients With Reduced Renal Function: Long-term Outcome Comparisons in 23,406 CABG Patients From Ontario, Canada. *Ann Surg*. 2020.
28. Sun LY, Spence SD, Benton S, Beanlands RS, Austin PC, Bader Eddeen A and Lee DS. Age, Not Sex, Modifies the Effect of Frailty on Long-term Outcomes After Cardiac Surgery. *Ann Surg*. 2020.
29. Rubens FD, Wells GA, Coutinho T, Eddeen AB and Sun LY. Sex differences after coronary artery bypass grafting with a second arterial conduit. *The Journal of thoracic and cardiovascular surgery*. 2020.

30. Lieberman R AC, Weiner J. Development and evaluation of the Johns Hopkins University Risk Adjustment Models for Medicare+ Choice Plan Payment. 2003.
31. Sternberg SA, Bentur N, Abrams C, Spalter T, Karpati T, Lemberger J and Heymann AD. Identifying frail older people using predictive modeling. *Am J Manag Care*. 2012;18:e392-7.
32. The Johns Hopkins Adjusted Clinical Groups Technical Reference Guide, version 9.0. 2009.
33. Bronskill S CM, Costa A, et al. Aging in Ontario: An ICES Chartbook of Health Services Use by Older Adults - a Technical Report. 2010.
34. Bronskill S CX, Gruneir A, Ho M. Health system use by frail Ontario seniors: an in-depth examination of four vulnerable cohorts. 2011.
35. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM and Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397-402.
36. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP and Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344-50.
37. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134:e282-93.
38. Taylor AL. Heart failure in women. *Curr Heart Fail Rep*. 2015;12:187-95.
39. Ziaeian B, Kominski GF, Ong MK, Mays VM, Brook RH and Fonarow GC. National Differences in Trends for Heart Failure Hospitalizations by Sex and Race/Ethnicity. *Circ Cardiovasc Qual Outcomes*. 2017;10.
40. Hopper I, Kotecha D, Chin KL, Mentz RJ and von Lueder TG. Comorbidities in Heart Failure: Are There Gender Differences? *Curr Heart Fail Rep*. 2016;13:1-12.
41. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, Mayet J and Francis DP. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart*. 2009;95:56-62.
42. Schmid FA, Schlager O, Keller P, Seifert B, Huang R, Frohlich GM, Luscher TF, Ruschitzka F and Enseleit F. Prognostic value of long-term blood pressure changes in patients with chronic heart failure. *Eur J Heart Fail*. 2017;19:837-842.
43. Jarvie JL and Foody JM. Recognizing and improving health care disparities in the prevention of cardiovascular disease in women. *Curr Cardiol Rep*. 2010;12:488-96.
44. McSweeney J, Pettey C, Lefler LL and Heo S. Disparities in heart failure and other cardiovascular diseases among women. *Women's health (London, England)*. 2012;8:473-85.

FIGURE LEGENDS

Figure 1. Sex-specific temporal trends in the incidence of heart failure in Ontario from April 1, 1994 to March 31, 2014.

Legend: Incidence rates were directly standardized by age and expressed per 100,000. The solid line represents incidence trends in women. The dotted line represents incidence trends in men.

Figure 2a. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in men.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

Figure 2b. Stacked Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis in women.

Legend: The red line represents survival in the historical cohort (1994-1998). The blue line represents survival in the 1999-2003 cohort. The orange line represents survival in the 2004-2008 cohort. The green line represents survival in the modern cohort (2009-2013).

Figure 3. Sex-specific temporal trends in mortality within one year of ambulatory heart failure diagnosis.

Legend: Mortality rates were directly standardized by age and expressed per 1000. The solid line represents mortality trends in women. The dotted line represents mortality trends in men.

Figure 4. Kaplan-Meier curves representing temporal trends in one-year survival after heart failure diagnosis, in each of the 5-year cohorts.

Legend: The red line represents survival in men. The blue line represents survival in women.

1 Table 1. Temporal trends in characteristics of men and women with incident heart failure over time.

Variable	Historic Cohort (1994-1998)			1999 – 2003			2004-2009			Modern Cohort (2009-2013)		
	Women N=47,676	Men N=43,907	P-Value	Women N=43,190	Men N=42,108	P-Value	Women N=41,043	Men N=43,698	P-Value	Women N=42,746	Men N=47,961	P-Value
Socio-Demographics												
Age (Mean ± SD)	76.3 ± 11.2	72.0 ± 11.3	<.001	76.2 ± 11.8	71.9 ± 11.8	<.001	76.0 ± 12.3	71.6 ± 12.4	<.001	75.8 ± 12.9	71.5 ± 12.8	<.001
Rurality	8,256 (17.3)	8,518 (19.4)	<.001	6,781 (15.7)	6,996 (16.6)	<.001	5,602 (13.6)	6,667 (15.3)	<.001	5,358 (12.5)	6,788 (14.2)	<.001
Income Quintile												
1 (Lowest)	11,651 (24.4)	9,297 (21.2)	<.001	10,121 (23.4)	8,529 (20.3)	<.001	9,661 (23.5)	9,096 (20.8)	<.001	9,613 (22.5)	9,541 (19.9)	<.001
2	10,377 (21.8)	9,418 (21.4)		9,814 (22.7)	9,319 (22.1)		9,070 (22.1)	9,317 (21.3)		9,243 (21.6)	9,833 (20.5)	
3	9,506 (19.9)	8,983 (20.5)		8,571 (19.8)	8,683 (20.6)		7,891 (19.2)	8,576 (19.6)		8,325 (19.5)	9,444 (19.7)	
4	8,208 (17.2)	8,024 (18.3)		7,403 (17.1)	7,770 (18.5)		7,274 (17.7)	8,308 (19.0)		8,017 (18.8)	9,775 (20.4)	
5 (Highest)	7,698 (16.1)	7,956 (18.1)		7,168 (16.6)	7,690 (18.3)		6,976 (17.0)	8,233 (18.8)		7,388 (17.3)	9,188 (19.2)	
Comorbidities												
Uncomplicated HTN	31,751 (66.6)	26,068 (59.4)	<.001	31,381 (72.7)	27,909 (66.3)	<.001	31,336 (76.3)	30,730 (70.3)	<.001	32,809 (76.8)	34,103(71.1)	<.001

Complicated HTN	2,507 (5.3)	2,006 (4.6)	<.001	2,178 (5.0)	1,921 (4.6)	<.001	3,254 (7.9)	3,551 (8.1)	0.29	5,669 (13.3)	6,516 (13.6)	0.15
Atrial Fibrillation	4,660 (9.8)	4,769 (10.9)	<.001	5,034 (11.7)	5,313 (12.6)	<.001	5,180 (12.6)	5,956 (13.6)	<.001	5,957 (13.9)	6,919 (14.4)	0.035
Myocardial Infarction	2,954 (6.2)	4,697 (10.7)	<.001	3,629 (8.4)	5,937 (14.1)	<.001	4,323 (10.5)	8,030 (18.4)	<.001	5,051 (11.8)	9,617 (20.1)	<.001
Valvular Disease	1,835 (3.8)	1,864 (4.2)	0.002	1,981 (4.6)	2,087 (5.0)	0.002	1,759 (4.3)	2,163 (4.9)	<.001	2,099 (4.9)	2,841 (5.9)	<.001
PAD	3,136 (6.6)	3,994 (9.1)	<.001	2,928 (6.8)	3,684 (8.7)	<.001	1,584 (3.9)	2,405 (5.5)	<.001	1,272 (3.0)	2,257 (4.7)	<.001
CVD	4,429 (9.3)	4,401 (10.0)	<.001	3,841 (8.9)	3,834 (9.1)	<.001	2,808 (6.8)	3,003 (6.9)	0.86	2,506 (5.9)	2,713 (5.7)	0.18
PCD	296 (0.6)	286 (0.7)	0.561	491 (1.1)	362 (0.9)	0.56	807 (2.0)	588 (1.3)	<.001	1,113 (2.6)	882 (1.8)	<.001
COPD/Asthma	13,091 (27.5)	14,352 (32.7)	<.001	14,557 (33.7)	14,988 (35.6)	<.001	15,209 (37.1)	15,996 (36.6)	0.17	16,261 (38.0)	17,164 (35.8)	<.001
Alcohol Abuse	128 (0.3)	398 (0.9)	<.001	187 (0.4)	562 (1.3)	<.001	313 (0.8)	965 (2.2)	<.001	337 (0.8)	1,123 (2.3)	<.001
Renal Disease	1,127 (2.4)	1,527 (3.5)	<.001	1,410 (3.3)	1,935 (4.6)	<.001	1,849 (4.5)	2,588 (5.9)	<.001	1,954 (4.6)	2,865 (6.0)	<.001
Diabetes	9,600 (20.1)	10,462 (23.8)	<.001	10,359 (24.0)	12,182 (28.9)	<.001	12,204 (29.7)	15,243 (34.9)	<.001	14,751 (34.5)	18,721 (39.0)	<.001
Hypothyroidism	2,155 (4.5)	541 (1.2)	<.001	2,212 (5.1)	597 (1.4)	<.001	1,421 (3.5)	428 (1.0)	<.001	1,300 (3.0)	479 (1.0)	<.001

Liver Disease	559 (1.2)	772 (1.8)	<.001	541 (1.3)	800 (1.9)	<.001	540 (1.3)	775 (1.8)	<.001	579 (1.4)	895 (1.9)	<.001
Anemia	2,569 (5.4)	1,403 (3.2)	<.001	4,734 (11.0)	3,204 (7.6)	<.001	4,629 (11.3)	3,382 (7.7)	<.001	5,182 (12.1)	3,929 (8.2)	<.001
Dementia	1,935 (4.1)	1,188 (2.7)	<.001	2,007 (4.6)	1,258 (3.0)	<.001	1,816 (4.4)	1,121 (2.6)	<.001	1,791 (4.2)	1,194 (2.5)	<.001
Depression	1,788 (3.8)	911 (2.1)	<.001	1,617 (3.7)	872 (2.1)	<.001	1,364 (3.3)	859 (2.0)	<.001	1,213 (2.8)	756 (1.6)	<.001
Psychosis	1,932 (4.1)	1,134 (2.6)	<.001	1,695 (3.9)	1,106 (2.6)	<.001	486 (1.2)	350 (0.8)	<.001	223 (0.5)	171 (0.4)	<.001
Primary Tumor	3,055 (6.4)	4,363 (9.9)	<.001	3,026 (7.0)	4,045 (9.6)	<.001	2,947 (7.2)	4,060 (9.3)	<.001	3,376 (7.9)	4,419 (9.2)	<.001
Metastatic Malignancy	869 (1.8)	804 (1.8)	0.924	925 (2.1)	775 (1.8)	0.92	850 (2.1)	723 (1.7)	<.001	1,000 (2.3)	840 (1.8)	<.001
Paraplegia	840 (1.8)	899 (2.0)	0.002	854 (2.0)	903 (2.1)	0.002	521 (1.3)	572 (1.3)	0.61	434 (1.0)	475 (1.0)	0.71
VTE	1,161 (2.4)	1,017 (2.3)	0.238	945 (2.2)	714 (1.7)	0.24	557 (1.4)	505 (1.2)	0.008	450 (1.1)	512 (1.1)	0.83
Frailty	4,302 (9.0)	2,700 (6.1)	<.001	5,598 (13.0)	4,364 (10.4)	<.001	10,163 (24.8)	7,175 (16.4)	<.001	11,223 (26.3)	8,409 (17.5)	<.001

1 Values are expressed number (%) unless otherwise indicated. SD, standard deviation; HTN, hypertension; IHD, ischemic heart disease; PAD, peripheral arterial

2 disease; CVD, cerebrovascular disease; PCD, pulmonary circulatory disease; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism

Table 2. Evolution of multivariable risk factors of one-year mortality over time. Risk factors that have changed in magnitude between the historical (1994-1998) and modern (2009-2013) times are indicated in bold.

	Adjusted HR (95% CI)			
Variable	**1994-1998**	**1999-2003**	**2004-2008**	**2009-2013**
Age Category				
40-64 years	Reference	Reference	Reference	Reference
65-74 years	1.56 (1.47-1.65)	1.64 (1.53-1.74)	1.66 (1.56-1.77)	1.54 (1.44-1.64)
75-84 years	**2.26 (2.14-2.39)**	2.36 (2.23-2.5)	2.48 (2.34-2.63)	**2.58 (2.43-2.73)**
> 85 years	**3.68 (3.48-3.90)**	4.25 (4.00-4.51)	4.57 (4.31-4.85)	**4.89 (4.62-5.18)**
Female	**0.85 (0.82-0.88)**	0.89 (0.86-0.92)	0.91 (0.88-0.94)	**0.97 (0.93-1.00)**
Rural	**0.94 (0.90-0.98)**	1.00 (0.96-1.05)	0.99 (0.95-1.04)	**1.01 (0.96-1.06)**
Income Quintile				
1 (Low)	1.06 (1.01-1.11)	1.08 (1.03-1.14)	1.12 (1.06-1.18)	1.08 (1.02-1.14)
2	1.03 (0.98-1.08)	1.04 (0.99-1.09)	1.04 (0.99-1.10)	1.04 (0.98-1.09)
3	1.06 (1.01-1.11)	1.03 (0.98-1.09)	1.04 (0.98-1.10)	0.99 (0.94-1.04)
4	1.02 (0.97-1.08)	0.99 (0.94-1.05)	1.08 (1.03-1.14)	1.01 (0.95-1.06)
5 (High)	Reference	Reference	Reference	Reference
Benign Hypertension	0.76 (0.74-0.79)	0.74 (0.72-0.77)	0.73 (0.70-0.76)	0.78 (0.75-0.81)
Complicated Hypertension	**0.93 (0.86-1.00)**	0.95 (0.88-1.02)	0.87 (0.82-0.93)	**0.77 (0.73-0.81)**
Atrial Fibrillation	**0.89 (0.85-0.94)**	0.92 (0.88-0.96)	0.96 (0.92-1.01)	**0.99 (0.95-1.04)**
Myocardial Infarction	**1.12 (1.06-1.18)**	0.99 (0.94-1.05)	1.02 (0.97-1.06)	**0.98 (0.94-1.03)**
Valvular Disease	**1.00 (0.92-1.08)**	0.98 (0.91-1.06)	0.97 (0.90-1.05)	**0.93 (0.86-1.00)**
Peripheral Arterial Disease	1.22 (1.16-1.29)	1.2 (1.14-1.27)	1.28 (1.20-1.37)	1.34 (1.24-1.44)
Cerebrovascular Disease	1.29 (1.23-1.35)	1.25 (1.19-1.32)	1.23 (1.16-1.30)	1.20 (1.13-1.28)
Pulmonary Circulatory Disease	**1.67 (1.43-1.96)**	1.73 (1.52-1.97)	1.54 (1.38-1.71)	**1.24 (1.12-1.37)**
COPD/Asthma	1.15 (1.12-1.19)	1.18 (1.14-1.22)	1.21 (1.17-1.25)	1.17 (1.13-1.21)
Alcohol Abuse	**1.16 (0.97-1.38)**	1.34 (1.16-1.55)	1.51 (1.34-1.70)	**1.62 (1.45-1.82)**
Renal Disease	**2.04 (1.90-2.18)**	1.86 (1.74-1.98)	1.73 (1.63-1.84)	**1.67 (1.58-1.77)**

Diabetes	**1.25 (1.21-1.30)**	1.19 (1.15-1.24)	1.13 (1.09-1.17)	**1.13 (1.10-1.17)**
Hypothyroidism	0.99 (0.91-1.07)	1.01 (0.93-1.09)	1.03 (0.93-1.13)	1.06 (0.96-1.17)
Liver Disease	**1.90 (1.72-2.10)**	1.86 (1.68-2.06)	1.99 (1.79-2.21)	**2.34 (2.12-2.59)**
Dementia	**1.74 (1.63-1.85)**	1.97 (1.86-2.09)	2.03 (1.91-2.16)	**1.96 (1.84-2.09)**
Depression	1.15 (1.07-1.25)	1.18 (1.09-1.28)	1.19 (1.09-1.30)	1.16 (1.06-1.28)
Psychosis	1.29 (1.20-1.38)	1.36 (1.26-1.46)	1.14 (0.99-1.31)	1.43 (1.17-1.76)
Primary Tumor	1.56 (1.49-1.64)	1.69 (1.60-1.77)	1.61 (1.53-1.70)	1.64 (1.56-1.73)
Metastatic Malignancy	3.47 (3.22-3.74)	3.59 (3.33-3.87)	3.14 (2.90-3.41)	3.42 (3.17-3.70)
Paraplegia	1.36 (1.24-1.50)	1.33 (1.21-1.46)	1.52 (1.35-1.70)	1.53 (1.35-1.75)
Venous Thromboemoblism	**1.07 (0.98-1.17)**	1.18 (1.07-1.30)	1.16 (1.03-1.31)	**1.40 (1.24-1.58)**

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

Table 3a. Sex-specific risk factors of one-year mortality in the historical cohort (1994-1998).

Variable	Women HR (95% CI)	Men HR (95% CI)	Multiplicative Interaction P-Value*
Age Category			
40-64 years	Reference	Reference	0.004
65-74 years	1.45 (1.32-1.59)	1.63 (1.51-1.75)	
75-84 years	2.06 (1.89-2.24)	2.42 (2.25-2.60)	
> 85 years	3.53 (3.24-3.85)	3.70 (3.41-4.00)	
Benign Hypertension	0.70 (0.67-0.73)	0.82 (0.79-0.86)	<0.001
Myocardial Infarction	1.26 (1.16-1.36)	1.02 (0.95-1.10)	<0.001
COPD/Asthma	1.10 (1.05-1.16)	1.20 (1.15-1.25)	0.01
Renal Disease	2.26 (2.04-2.50)	1.90 (1.74-2.07)	0.01
Diabetes	1.31 (1.25-1.38)	1.20 (1.14-1.26)	0.01

HR, hazard ratio; CI, confidence interval; COPD; chronic obstructive pulmonary disease

* Multiplicative interaction terms were formed by multiplying sex by each of the covariates in the multivariable Cox proportional hazard model for one-year mortality. Only significant interaction terms (i.e., ones demonstrating sex-specific risk factors) were reported in this table.

Table 3b. Sex-specific risk factors of one-year mortality in the modern cohort (2009-2013).

Variable	Women HR (95% CI)	Men HR (95% CI)	Multiplicative Interaction P-Value *
Income Quintile			
1 (Low)	1.02 (0.94-1.09)	1.15 (1.06-1.23)	0.001
2	0.97 (0.90-1.05)	1.10 (1.02-1.18)	
3	0.99 (0.92-1.07)	0.98 (0.91-1.06)	
4	1.01 (0.93-1.09)	1.01 (0.93-1.08)	
5 (High)	Reference	Reference	
Myocardial Infarction	1.05 (0.98-1.12)	0.94 (0.89-1.00)	0.02
Peripheral Arterial Disease	1.48 (1.32-1.66)	1.25 (1.14-1.37)	0.02
COPD/Asthma	1.12 (1.07-1.17)	1.23 (1.17-1.29)	0.005
Dementia	1.87 (1.72-2.02)	2.10 (1.92-2.30)	0.05
Primary Tumor	1.44 (1.34-1.56)	1.79 (1.68-1.91)	<0.001
Metastatic Malignancy	3.05 (2.75-3.38)	3.85 (3.49-4.26)	<0.001

HR, hazard ratio; CI, confidence interval; COPD; chronic obstructive pulmonary disease

* Multiplicative interaction terms were formed by multiplying sex by each of the covariates in the multivariable Cox proportional hazard model for one-year mortality. Only significant interaction terms (i.e., ones demonstrating sex-specific risk factors) were reported in this table.

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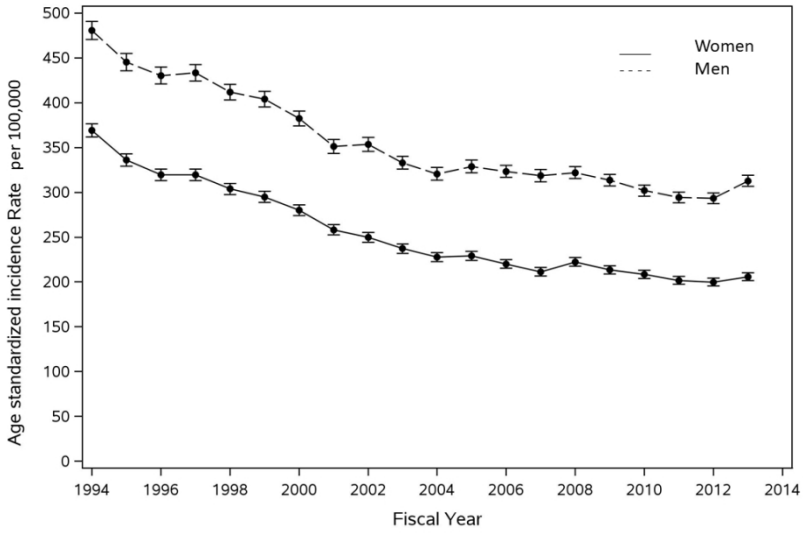
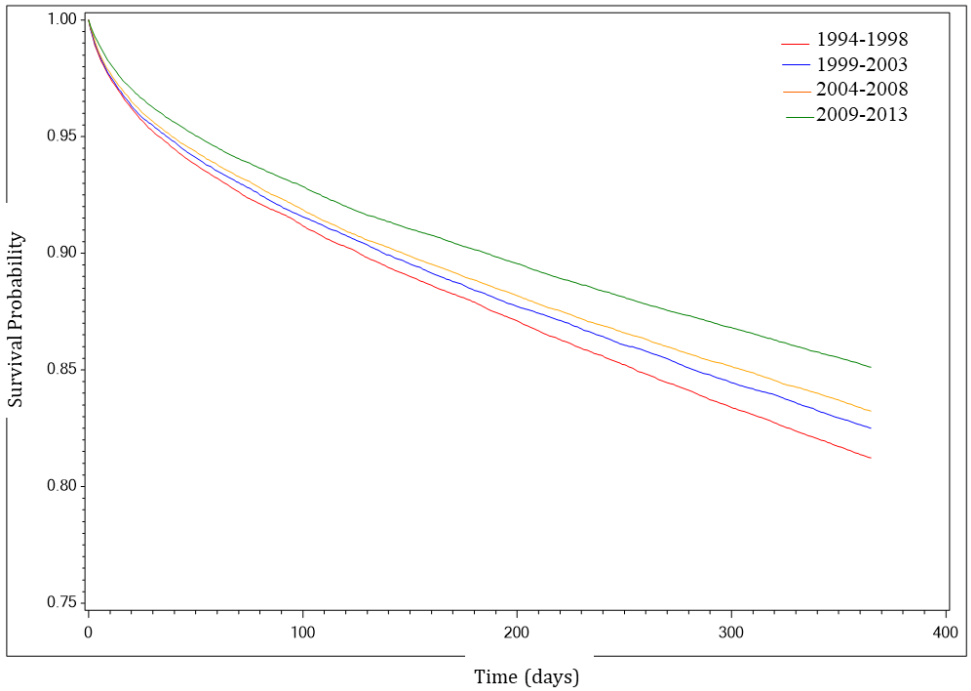


Figure 1. Sex-specific temporal trends in the incidence of heart failure in Ontario from April 1, 1994 to March 31, 2014.
Legend: Incidence rates were directly standardized by age and expressed per 100,000. The solid line represents incidence trends in women. The dotted line represents incidence trends in men.

338x190mm (96 x 96 DPI)

Figure 2a:



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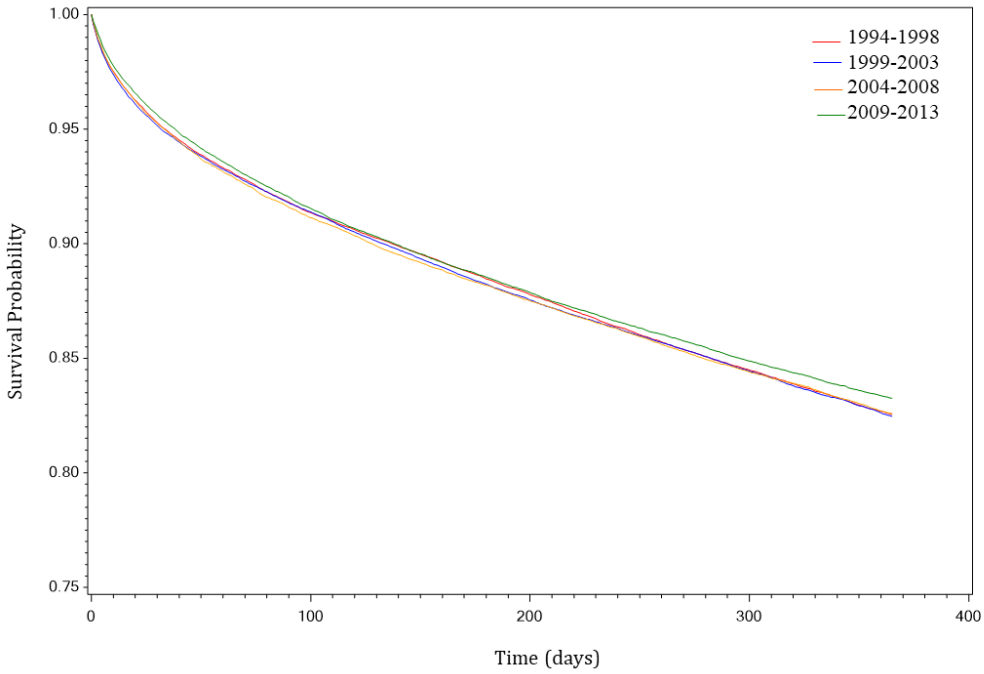

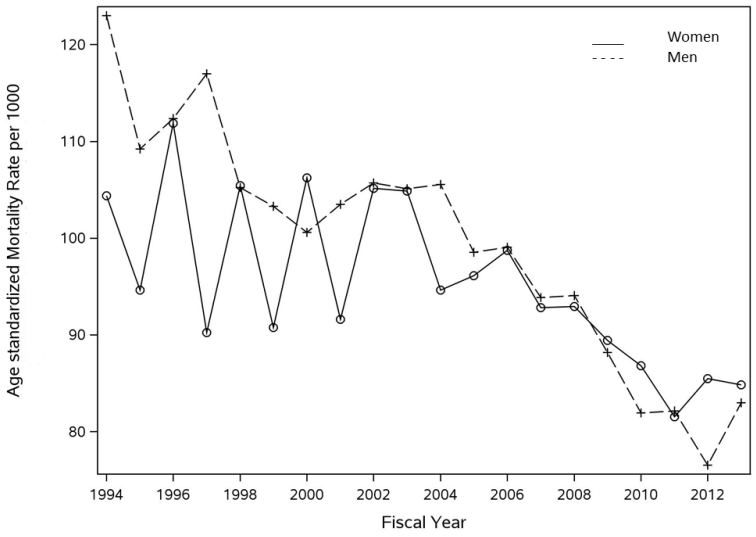

Figure 3. Sex-specific temporal trends in mortality within one year of ambulatory heart failure diagnosis.
Legend: Mortality rates were directly standardized by age and expressed per 1000. The solid line represents mortality trends in women. The dotted line represents mortality trends in men.

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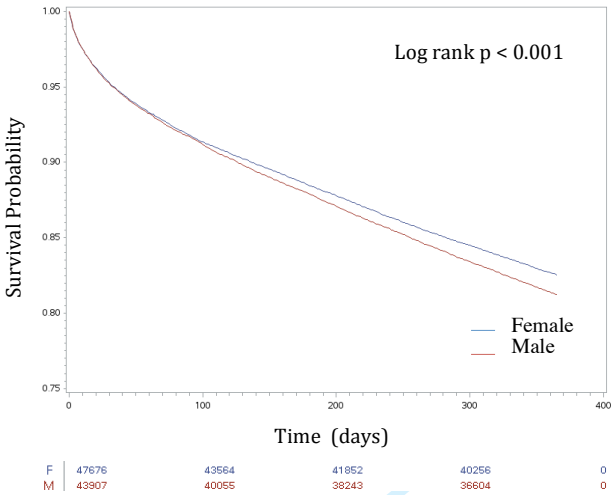

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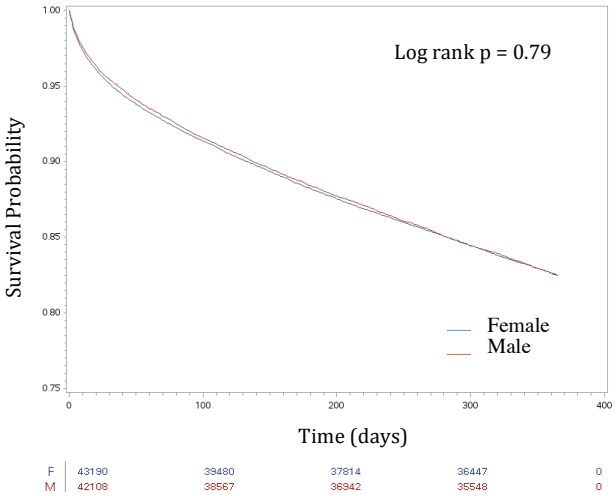

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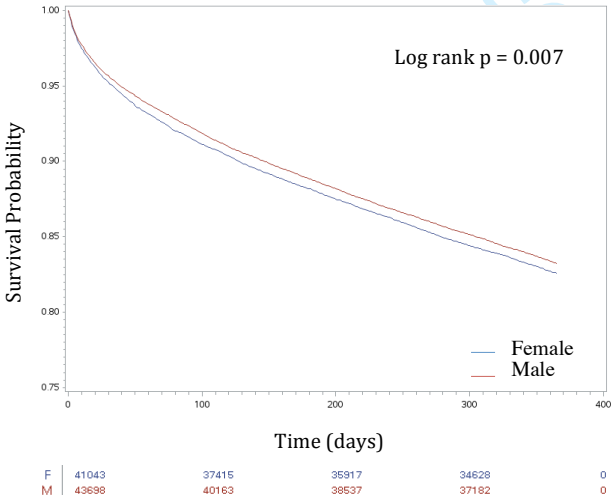

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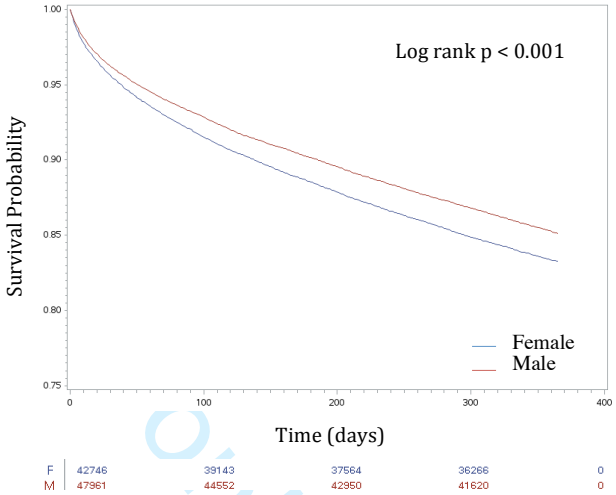
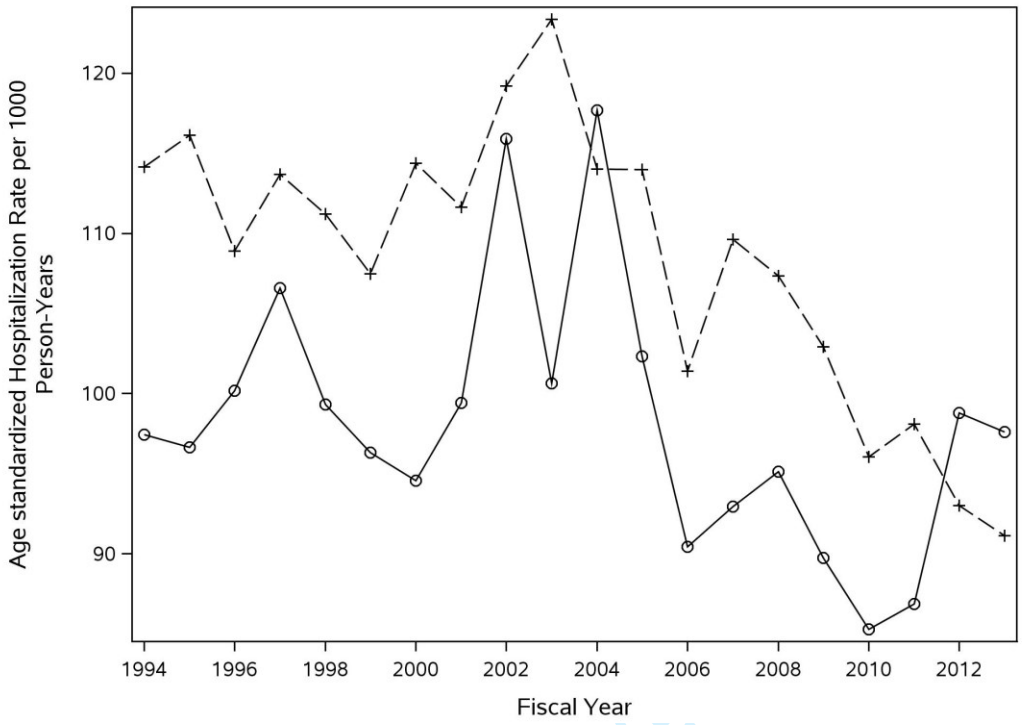
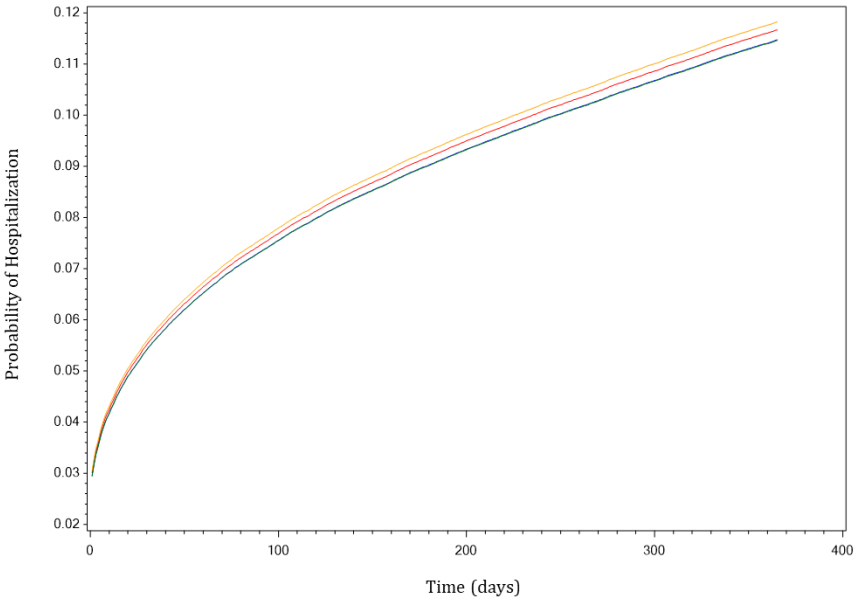


SUPPLEMENTAL MATERIAL

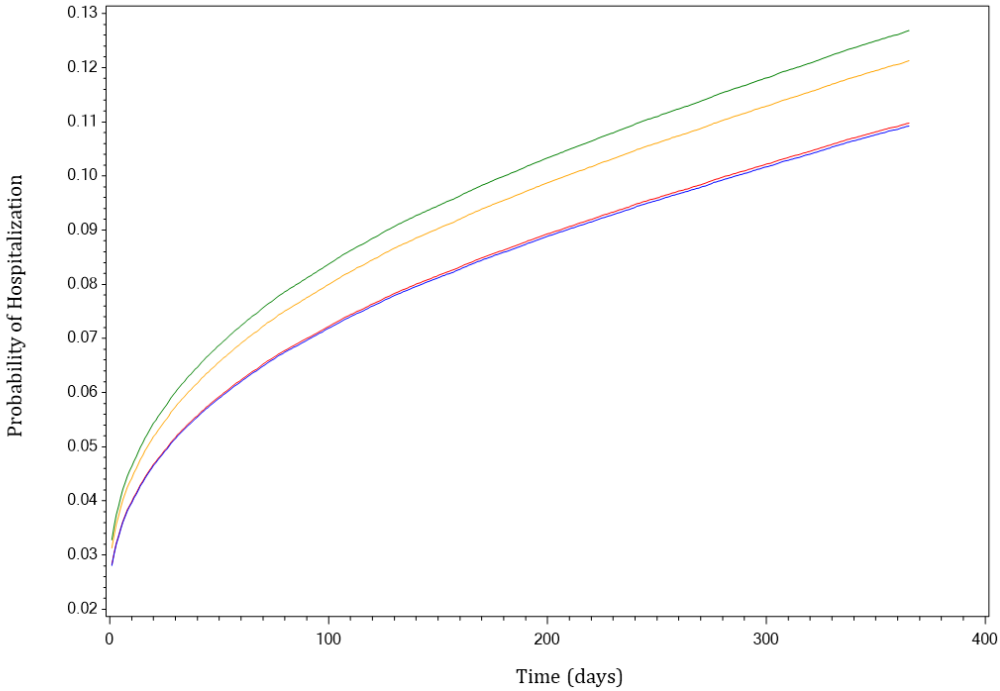
eFigure 1. Sex-specific temporal trends in heart failure hospitalizations within one year of ambulatory heart failure diagnosis. Hospitalization rates were directly standardized by age using the 1991 Canadian population aged ≥ 40 years as the reference population and expressed per 1000 person-years.
Legend: The solid line represents trends in women. The dotted line represents trends in men.



eFigure 2a. Stacked cumulative incidence curves representing temporal trends of heart failure hospitalization within one year of diagnosis in men.
Legend: The red line represents cumulative incidence of hospitalization in the historical cohort (1994-1998). The blue line represents hospitalizations in the 1999-2003 cohort. The orange line represents hospitalizations in the 2004-2008 cohort. The green line (which is nearly superimposed on the blue line) represents hospitalizations in the modern cohort (2009-2013).



eFigure 2b. Stacked cumulative incidence curves representing temporal trends of heart failure hospitalization within one year of diagnosis in women.
Legend: The red line represents cumulative incidence of hospitalization in the historical cohort (1994-1993). The blue line represents hospitalizations in the 1999-2003 cohort. The orange line represents hospitalizations in the 2004-2008 cohort. The green line represents hospitalizations in the modern cohort (2009-2013).



eTable 1. Crude and age standardized incidence rates of ambulatory heart failure per 100,000 population.

				Incidence Rate		95% CI	
Year	Sex	HF Cases	Denominator	Crude	Standardized	Lower	Upper
1994	Female	10123	2544992	397.76	368.95	361.74	376.27
	Male	8998	2290949	392.76	480.63	470.55	490.88
1995	Female	9502	2615417	363.31	335.99	329.21	342.88
	Male	8622	2359605	365.40	445.26	435.73	454.95
1996	Female	9312	2686591	346.61	319.55	313.03	326.18
	Male	8621	2430438	354.71	430.39	421.20	439.74
1997	Female	9518	2753376	345.68	319.39	312.93	325.94
	Male	8939	2497920	357.86	433.52	424.43	442.76
1998	Female	9221	2815590	327.50	303.76	297.52	310.10
	Male	8727	2560459	340.84	411.86	403.12	420.74
1999	Female	9158	2880244	317.96	294.91	288.82	301.09
	Male	8810	2624357	335.70	403.94	395.42	412.61
2000	Female	8921	2948815	302.53	279.98	274.11	285.94
	Male	8548	2693918	317.31	382.41	374.22	390.74
2001	Female	8466	3018031	280.51	258.26	252.69	263.91
	Male	8132	2763947	294.22	351.15	343.46	358.98
2002	Female	8403	3088112	272.11	249.62	244.21	255.11
	Male	8441	2835687	297.67	353.43	345.83	361.16
2003	Female	8242	3159200	260.89	237.25	232.05	242.53
	Male	8177	2908486	281.14	333.06	325.78	340.45
2004	Female	8082	3226254	250.51	227.56	222.51	232.70
	Male	8101	2976603	272.16	320.70	313.67	327.86
2005	Female	8283	3286052	252.07	229.05	224.02	234.17
	Male	8588	3037995	282.69	328.77	321.77	335.87
2006	Female	8107	3340543	242.69	220.03	215.14	225.01
	Male	8774	3091317	283.83	323.41	316.60	330.32
2007	Female	7993	3388916	235.86	211.27	206.53	216.09
	Male	8929	3136755	284.66	318.62	311.98	325.36
2008	Female	8578	3437633	249.53	222.31	217.49	227.21
	Male	9306	3182320	292.43	322.03	315.46	328.71
2009	Female	8433	3486229	241.89	213.46	208.78	218.22
	Male	9312	3225967	288.66	313.38	306.98	319.87
2010	Female	8366	3534061	236.72	208.36	203.77	213.03
	Male	9262	3269161	283.31	301.92	295.75	308.19
2011	Female	8424	3578607	235.40	201.79	197.35	206.31
	Male	9292	3308050	280.89	294.17	288.17	300.26
2012	Female	8526	3618133	235.65	199.93	195.55	204.39
	Male	9585	3341596	286.84	293.47	287.58	299.45
2013	Female	8997	3653530	246.25	205.83	201.43	210.30
	Male	10510	3369203	311.94	312.82	306.82	318.90

HF, heart failure; CI, confidence interval

eTable 2. Temporal trends of one-year mortality rates in men and women with incident heart failure.

Time Cohort	Sex	Number of Deaths	Number of Incident HF Cases	Crude Rate (%)	Age-Standardized Rate (%, 95% CI)
April 1994-March 1999	F	8319	47676	17.5	10.1 (9.5-10.8)
	M	8238	43907	18.8	11.4 (10.8-11.9)
April 1999-March 2004	F	7572	43190	17.5	9.9 (9.3-10.6)
	M	7365	42108	17.5	10.4 (9.9-10.8)
April 2004-March 2009	F	7148	41043	17.4	9.5 (9.0-10.1)
	M	7322	43698	16.8	9.8 (9.4-10.2)
April 2009-March 2014	F	7156	42746	16.8	8.6 (8.1-9.0)
	M	7138	47961	14.9	8.2 (7.9-8.6)

HF, heart failure; CI, confidence interval

eTable 3. Crude and age-standardized one-year mortality rates following ambulatory heart failure diagnosis. Rates are expressed per 1000 population.

				Mortality Rate		95% CI	
Year	**Sex**	**Deaths**	**Incident HF Cases**	**Crude**	**Standardized**	**Lower**	**Upper**
1994	Female	1733	10123	171.19	104.40	90.54	119.78
	Male	1710	8998	190.04	123.00	110.57	136.45
1995	Female	1629	9502	171.44	94.64	82.33	108.27
	Male	1578	8622	183.02	109.23	97.89	121.53
1996	Female	1679	9312	180.30	111.88	95.19	130.64
	Male	1643	8621	190.58	112.37	101.72	123.83
1997	Female	1674	9518	175.88	90.24	78.73	102.95
	Male	1741	8939	194.76	116.99	105.34	129.56
1998	Female	1604	9221	173.95	105.45	92.82	119.32
	Male	1566	8727	179.44	105.22	94.57	116.74
1999	Female	1527	9158	166.74	90.75	78.76	104.04
	Male	1522	8810	172.76	103.32	93.50	113.88
2000	Female	1556	8921	174.42	106.23	92.32	121.65
	Male	1489	8548	174.19	100.59	90.80	111.15
2001	Female	1473	8466	173.99	91.60	79.23	105.34
	Male	1364	8132	167.73	103.48	92.72	115.15
2002	Female	1504	8403	178.98	105.15	91.98	119.68
	Male	1511	8441	179.01	105.70	96.26	115.82
2003	Female	1512	8242	183.45	104.88	90.32	121.12
	Male	1479	8177	180.87	105.10	94.47	116.60
2004	Female	1468	8082	181.64	94.64	82.57	107.97
	Male	1486	8101	183.43	105.57	95.67	116.22
2005	Female	1445	8283	174.45	96.12	83.52	110.08
	Male	1454	8588	169.31	98.53	88.69	109.16
2006	Female	1395	8107	172.07	98.75	86.46	112.30
	Male	1459	8774	166.29	99.06	89.97	108.82
2007	Female	1384	7993	173.15	92.81	81.59	105.15
	Male	1475	8929	165.19	93.86	85.68	102.61
2008	Female	1456	8578	169.74	92.93	82.04	104.86
	Male	1448	9306	155.60	94.08	85.56	103.21
2009	Female	1464	8433	173.60	89.43	79.65	100.09
	Male	1461	9312	156.89	88.17	80.01	96.95
2010	Female	1373	8366	164.12	86.81	76.58	98.03
	Male	1396	9262	150.72	81.93	74.92	89.43
2011	Female	1418	8424	168.33	81.54	71.43	92.68
	Male	1381	9292	148.62	82.13	74.91	89.87
2012	Female	1404	8526	164.67	85.48	75.84	96.01
	Male	1377	9585	143.66	76.53	69.60	83.97
2013	Female	1497	8997	166.39	84.84	75.24	95.32
	Male	1523	10510	144.91	82.99	75.34	91.22

CI, confidence interval

eTable 4. Crude and age standardized one-year heart failure hospitalization rates in patients who were diagnosed with heart failure in an ambulatory setting between 1994-2013. Rate is expressed per 1000 person years.

		Heart Failure		Hospitalization Rate		95% CI	
Year	Sex	Hospitalizations	Denominator	Crude	Standardized	Lower	Upper
1994	Female	1105	8417.52	131.27	97.43	83.29	113.28
	Male	1108	7325.60	151.25	114.15	101.01	128.52
1995	Female	1067	7860.78	135.74	96.64	83.94	110.71
	Male	1001	7065.84	141.67	116.14	100.74	133.23
1996	Female	1065	7632.79	139.53	100.19	85.97	116.09
	Male	1015	7022.96	144.53	108.91	96.08	122.98
1997	Female	1028	7859.13	130.80	106.59	90.03	125.30
	Male	1082	7232.55	149.60	113.69	100.95	127.59
1998	Female	1006	7603.66	132.30	99.32	85.96	114.16
	Male	963	7180.72	134.11	111.22	97.10	126.82
1999	Female	983	7607.15	129.22	96.32	82.75	111.47
	Male	936	7305.04	128.13	107.48	95.17	120.95
2000	Female	917	7402.64	123.87	94.57	80.28	110.67
	Male	994	7033.00	141.33	114.37	101.66	128.24
2001	Female	903	6997.61	129.04	99.40	84.75	115.86
	Male	901	6711.51	134.25	111.64	97.95	126.71
2002	Female	937	6838.58	137.02	115.90	100.22	133.33
	Male	1007	6854.11	146.92	119.20	106.86	132.57
2003	Female	994	6645.28	149.58	100.66	86.86	116.02
	Male	1016	6629.94	153.24	123.36	110.31	137.54
2004	Female	1002	6508.80	153.95	117.67	101.49	135.69
	Male	993	6504.80	152.66	114.02	102.01	127.06
2005	Female	962	6775.02	141.99	102.34	88.21	118.09
	Male	1026	7052.13	145.49	113.98	101.59	127.48
2006	Female	982	6565.14	149.58	90.43	78.78	103.32
	Male	989	7237.69	136.65	101.40	90.93	112.73
2007	Female	987	6493.03	152.01	92.95	81.45	105.61
	Male	1069	7307.83	146.28	109.62	98.84	121.25
2008	Female	1046	6963.90	150.20	95.11	83.30	108.13
	Male	1097	7646.02	143.47	107.36	97.12	118.38
2009	Female	1021	6841.22	149.24	89.74	79.39	101.06
	Male	1085	7697.71	140.95	102.92	92.38	114.34
2010	Female	1042	6799.72	153.24	85.28	75.41	96.08
	Male	1078	7694.92	140.09	96.05	86.94	105.86
2011	Female	1061	6842.81	155.05	86.86	76.87	97.78
	Male	1038	7754.49	133.86	98.10	87.99	109.06
2012	Female	1137	6895.19	164.90	98.80	87.24	111.46
	Male	1097	8017.47	136.83	93.00	84.28	102.37
2013	Female	1159	7269.34	159.44	97.59	86.03	110.27
	Male	1205	8772.03	137.37	91.14	82.26	100.71

CI, confidence interval

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	8-10

		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 1 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.