Sex-Specific Clinical Outcomes of the PACT-HF Randomized Trial

Van Spall, Harriette G.C.; DeFilippis, Ersilia M.; Lee, Shun Fu; Oz, Urun Erbas; Perez, Richard; Healey, Jeff S.; Allen, Larry A.; Voors, Adriaan A.; Ko, Dennis T.; Thabane, Lehana

Published in:
Circulation: Heart Failure

DOI:
10.1161/CIRCHEARTFAILURE.121.008548

Publication date:
2021

Circulation: Heart Failure

ORIGINAL ARTICLE

Sex-Specific Clinical Outcomes of the PACT-HF Randomized Trial

Harriette G.C. Van Spall, MD, MPH; Ersilia M. DeFilippis, MD; Shun Fu Lee, PhD; Urun Erbas Oz, PhD; Richard Perez, MSc; Jeff S. Healey, MD, MSc; Larry A. Allen, MD; Adriaan A. Voors, MD; Dennis T. Ko, MD, MSc; Lehana Thabane, PhD; Stuart J. Connolly, MD, MSc

BACKGROUND: Transitional care may have different effects in males and females hospitalized for heart failure. We assessed the sex-specific effects of a transitional care model on clinical outcomes following hospitalization for heart failure.

METHODS: In this stepped-wedge cluster randomized trial of adults hospitalized for heart failure in Ontario, Canada, 10 hospitals were randomized to a group of transitional care services or usual care. Outcomes in this exploratory analysis were composite all-cause readmission, emergency department visit, or death at 6 months; and composite all-cause readmission or emergency department visit at 6 months. Models were adjusted for stepped-wedge design and patient age.

RESULTS: Among 2494 adults, mean (SD) age was 77.7 (12.1) years, and 1258 (50.4%) were female. The first composite outcome occurred in 371 (66.3%) versus 433 (64.1%) males (hazard ratio [HR], 1.04 [95% CI, 0.86–1.26]; P=0.67) and in 326 (59.9%) versus 463 (64.8%) females (HR, 0.83 [95% CI, 0.69–1.01]; P=0.06) in the intervention and usual care groups, respectively (P=0.012 for sex interaction). The second composite outcome occurred in 357 (63.8%) versus 417 (61.7%) males (HR, 1.03 [95% CI, 0.85–1.24]; P=0.76) and 314 (57.7%) versus 450 (63.0%) females (HR, 0.81 [95% CI, 0.67–0.99]; P=0.037) in the intervention and usual care groups, respectively (P=0.024 for sex interaction). The sex differences were driven by a reduction in all-cause emergency department visits among females (HR, 0.66 [95% CI, 0.51–0.87]; P=0.003), but not males (HR, 1.10 [95% CI, 0.85–1.43]; P=0.46), receiving the intervention (P<0.001 for sex interaction).

CONCLUSIONS: A transitional care model offered a reduction in all-cause emergency department visits among females but not males following hospitalization for heart failure.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02112227.

Key Words: attention ■ comorbidity ■ heart failure ■ hospitalization ■ transitional care

Sex differences exist in almost every aspect of heart failure (HF).[1] While the lifetime risk of HF is similar between male and female patients, there are sex differences in etiology, comorbidities, treatment response, and outcomes in HF.[1–6] Relative to males with HF, females are older and more likely to have preserved ejection fraction, for which there are limited evidence-informed therapies; and less likely to have reduced ejection fraction, in which significant advances in therapies have been made.[5] In a registry of patients with HF with reduced ejection fraction, there was no between-sex difference in receiving or reaching target dose of guideline-directed medical therapies.[6] However, other registry and trial data have shown that females are less likely to be prescribed guideline-directed medications and receive implantable cardioverter-defibrillators than males.[4,7–9] Furthermore, there appear to be sex differences in medication adherence[10,11] and in the utilization of and response to health care services in HF.[12]

Correspondence to: Harriette G.C. Van Spall, MD, MPH, 20 Copeland Ave, David Braley Research Institute Bldg, Ste C3-117, Hamilton ON L8L 2X2, Canada. Email harriette.vanspall@phri.ca

This manuscript was sent to Ileana L. Piña, MD, MPH, Guest Editor, for review by expert referees, editorial decision, and final disposition.
The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.121.008548.
For Sources of Funding and Disclosures, see page 1167.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- In this sub-study of a cluster randomized trial, we found that a patient-centered transitional care model offered greater clinical benefit to females than males 6 following hospitalization for heart failure.
- Females receiving the intervention experienced a greater reduction in composite clinical end points at 6 months than males, with benefit driven primarily by a reduction in emergency department visits.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Supportive transitional care services should be offered to patients hospitalized for heart failure, with particular attention paid to females, to reduce emergency department visits
- The reasons for sex differences in response to health care services are unknown, and deserve further research

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin-receptor neprilysin inhibitor
ED	emergency department
HF	heart failure
HR	hazard ratio
PACT-HF	Patient-Centered Care Transitions in Heart Failure

The PACT-HF (Patient-Centered Care Transitions in HF) pragmatic stepped-wedge cluster randomized controlled trial implemented and tested the effectiveness of a hospital-to-home transitional care model across 10 hospitals in a publicly funded health care system in Ontario, Canada.[13–15] While the transition program had no significant effect on the co-primary composite clinical outcomes at 3 months and 30 days, the benefits of interventions included in the program may have accrued only after longer term follow-up.[13] Furthermore, the transitional care program may have had different effects in male and female patients. For example, informal caregivers in the home provide crucial roles in HF management, and prior studies have demonstrated that females are less likely to live with an informal caregiver.[16–19] Thus, females may be more likely to derive benefit from supportive transitional care services following hospitalization for HF.

In this exploratory analysis of the PACT-HF trial, we investigated sex differences in the effect of the transitional care model on the outcomes of composite all-cause readmission, emergency department (ED) visit, or death at 6 months; and composite all-cause readmission or ED visit at 6 months.

METHODS

The methods have been described previously.[13,14] The study was approved by all Institutional Research Ethics Boards with waiver of written consent as services were guided by research evidence.[20,21] Patients provided verbal informed consent for participation. The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted following review of the request by a committee at the Population Health Research Institute. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification.

Patients

We included patients hospitalized with a primary diagnosis of HF. We excluded patients who did not have a primary diagnosis of HF, did not consent to receiving the intervention, died during hospitalization, or were transferred to another hospital.[13,14] Diagnosis of HF was confirmed using the Boston criteria[22] as well as B-type natriuretic peptide or NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels.[13,14]

Randomization

Following a stepped-wedge cluster randomized design, 10 hospitals crossed over from usual care to intervention in a randomized sequence at monthly intervals.[13,14]

Intervention

A hospital nurse navigator provided HF self-care education to the patient and informal caregiver and a structured patient-centered discharge summary with action-plan to the patient and family physician. All patients were referred for ≤1 week follow-up with the family physician, and those with LACE (Length of Stay, Acuity, Comorbidities, ER Visits) index[23,24] ≥13 were referred for post-discharge nurse-led visits and Heart Function Clinic care. The nurse-led visits included weekly structured home and telephone visits for 4 to 6 weeks until patients were seen in the Heart Function Clinic. Heart Function Clinic visits were initiated and continued according to the clinicians' discretion. In the usual care group, transitional care occurred at the discretion of clinicians.

Blinding

Clinicians were un-blinded to treatment allocation. Patients were considered un-blinded although the study protocol and allocation was not shared with them.[13,14]

Measurement of Outcomes

Clinical outcomes, obtained from linkages to administrative databases, were composite all-cause readmission, ED visit (which did not result in hospitalization), or death at 6 months; and composite all-cause readmission or ED visit at 6 months. Outcomes were measured relative to the discharge date of the index HF hospitalization.[25] Treatment effect was estimated by making within- and between-hospital comparisons of

intervention versus usual care clusters at baseline and whenever a hospital crossed over from usual care to intervention.[13,14]

Pragmatic Design

The domains of this study—patient selection, delivery of intervention, data collection, and analysis[13,14]—were pragmatic,[26,27] designed to assess effectiveness rather than efficacy. Decision makers and patients were involved in the study design.

Statistical Analysis

Analysis was at the level of the patient, following the intention-to-treat principle. We used the Canadian Institute for Health Information database accessed at ICES to identify the cohort for analysis.[13] ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

In a stepped-wedge trial, usual care occurs early in the study period, while the intervention occurs later in the study period. To minimize research burden on trial participants and investigators, eligible intervention patients identified prospectively in hospital were matched to a usual care group that was selected from the administrative database that records hospitalizations. Since there are temporal and seasonal variations in hospital admissions, we selected usual care patients by applying propensity scores ≥0.4 to ensure that characteristics between the groups were balanced. The variables for the propensity score were age, sex, admission via the ED, length of stay >2 days, and presence of diabetes, chronic kidney disease, myocardial infarction, or atrial fibrillation. These data were linked using unique encoded identifiers and analyzed at ICES.

To summarize the data, we used means with SD or medians with interquartile ranges for continuous variables, and counts with percentages for categorical variables. For each sex, we computed the standardized mean difference between the intervention and usual care groups, with a value of 0.10 or less indicating negligible difference.

Regression models for all clinical outcomes were adjusted for the stepped-wedge design, with the intervention and steps (time) as fixed-effects and hospitals as random-effects. We analyzed clinical outcomes using shared frailty survival models nested within hospitals.[28] We plotted Kaplan-Meier curves for the composite outcomes. We described effects on survival using hazard ratio (HR) with 95% CI. All models were adjusted for age to account for baseline differences in age between males and females. We assessed for effect modification by sex and age using sex and age interaction terms, respectively. We set the criterion for statistical significance at α=0.05. We did not adjust the analyses for multiple testing since the analyses were exploratory.[29]

We conducted all analyses using SAS Version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

RESULTS

Hospitals

The 10 clusters were urban tertiary or quaternary care hospitals, with facilities and services as described previously.[14]

Patients

Patients were enrolled from February 1, 2015, to March 30, 2016. Among 2494 eligible patients included in the analysis, 1236 (49.6%) were male. The mean (SD) age was 75.4 (12.8) years among male and 80.0 (10.9) years among female patients. Relative to male patients, female patients were older, more commonly resided in long-term care facilities, had a poorer self-reported health status at baseline, and had a lower Charlson comorbidity index.[30] Within each sex group, the intervention and usual care groups were similar overall in baseline demographics, comorbidities, health care resource utilization, and estimated risk (standardized differences ≤0.10, Table 1).

Drug administrative data were available for patients who were 65 years and older (Table 2). Among the total of 2140 patients (1004 males and 1136 females) on whom data were available, there was no difference between the intervention and usual care groups in the proportion that filled new postdischarge prescriptions for angiotensin-converting enzyme inhibitors, mineralocorticoid antagonists, diuretics, and β-blockers at 30 days (for any of the 4 drugs: 93.1% versus 92.3%; *P*=0.62 for males and 92.5% versus 93.1%; *P*=0.70 for females). Because the study population included patients with both reduced and preserved ejection fraction, not all the patients would have met indications for these classes of medications. Among male patients, there was a greater proportion that filled postdischarge prescriptions for diuretics in the intervention versus usual care group (87.9% versus 82.9%; *P*=0.026), but this difference was not seen among female patients (85.9% versus 85.5%; *P*=0.84).

Intervention Fidelity

Fidelity measures for the entire intervention group have been previously reported.[14] Of 537 male and 506 female patients in the intervention group for whom information was available, 474 (88.5%) male and 442 (87.4%) female patients had a discharge summary faxed to their family physician within a day of discharge (Table I in the Data Supplement). Among the 1104 patients in the intervention group, 38.7% had a LACE index ≥13; 220 (41.0%) male and 196 (38.7%) female patients were scheduled to be seen in a Heart Function Clinic; and 192 (35.8%) male and 183 (36.2%) female patients received nurse-led home visits within a month of index discharge. There was no difference between males and females in the number of structured home visits (mean [SD] 2.67 [1.11] versus 2.60 [1.17], *P*=0.62 or telephone calls mean [SD] 3.84 [2.07] versus 3.60 [1.91], *P*=0.32) received during the postdischarge month. The possible uptake of the intervention in the usual care group was not audited, but personnel were clustered by site to mitigate contamination.

Table 1. Characteristics of Patients (N=2494) Enrolled in the PACT-HF Trial Stratified by Sex

	Males			Females		
	PACT-HF (N=560)	Usual care (N=676)	Standardized difference	PACT-HF (N=544)	Usual care (N=714)	Standardized difference
Demographics and quality of life						
Age, mean (SD)	75.12±13.41	75.63±12.26	0.04	80.50±10.65	79.44±11.22	0.10
Resides in long-term care	59 (10.5%)	82 (12.1%)	0.05	105 (19.3%)	140 (19.6%)	0.01
EQ visual acuity score, mean (SD)*	55.62±22.02	54.44±22.13	0.05	53.05±21.74	50.60±23.22	0.11
Comorbidities						
Hypertension uncomplicated, n (%)	386 (68.9)	469 (69.4)	0.01	401 (73.7)	533 (74.6)	0.02
Hypertension complicated, n (%)	31 (5.5)	44 (6.5)	0.04	26 (4.8)	38 (5.3)	0.02
Atrial fibrillation, n (%)	279 (49.8)	337 (49.9)	0.00	304 (55.9)	347 (48.6)	0.15
Diabetes with chronic complication, n (%)	268 (47.9)	354 (52.4)	0.09	256 (47.1)	350 (49.0)	0.04
Diabetes without chronic complication, n (%)	153 (27.3)	210 (31.3)	0.08	148 (27.2)	228 (31.9)	0.10
Chronic kidney disease, n (%)	145 (25.9)	161 (23.8)	0.05	97 (17.8)	155 (21.7)	0.10
Myocardial Infarction, n (%)	137 (24.5)	150 (22.2)	0.05	103 (18.9)	145 (20.3)	0.03
Chronic pulmonary disease, n (%)	112 (20.0)	163 (24.1)	0.10	123 (22.6)	171 (23.9)	0.03
Peripheral vascular disease, n (%)	61 (10.9)	80 (11.8)	0.03	46 (8.5)	55 (7.7)	0.03
Cerebrovascular disease, n (%)	52 (9.3)	64 (9.5)	0.01	49 (9.0)	65 (9.1)	0.00
Dementia, n (%)	43 (7.7)	51 (7.5)	0.01	55 (10.1)	72 (10.1)	0.00
Gastrointestinal bleeding, n (%)	27 (4.8)	45 (6.7)	0.08	52 (9.6)	52 (7.3)	0.08
Mild liver disease, n (%)	16 (2.9)	23 (3.4)	0.03	16 (2.9)	19 (2.7)	0.02
Cancer (any), n (%)	10 (1.8)	10 (1.5)	0.02	9 (1.7)	12 (1.7)	0.00
Resource utilization						
ED visits in prior 6 months, median [IQR]	2 [1–3]	2 [1–3]	0.02	2 [1–2]	2 [1–3]	0.12
Acute length of stay, median [IQR]	6 [4–9]	6 [4–9]	0.10	6 [4–10]	6 [4–10]	0.02
Resource intensity weight, mean (SD)†	1.50±1.35	1.44±0.77	0.06	1.40±1.15	1.43±0.85	0.03
Estimated risk						
LACE index, median [IQR]‡	12 [10–14]	12 [10–14]	0.11	12 [10–14]	12 [10–14]	0.08
Charlson comorbidity index, mean (SD)§	2.49±1.33	2.54±1.35	0.03	2.35±1.21	2.37±1.33	0.08

Other than self-reported quality of life, all data were obtained from administrative databases. Baseline comorbidities were obtained using a 5-year retrospective review of databases. ED indicates emergency department; IQR, interquartile range; PACT-HF, Patient-Centered Care Transitions in Heart Failure; and RIW, resource intensity weights.

*EQ visual acuity score, measured by the EuroQoL visual scale, is a self-reported quality of life or health status measure ranging from 0 to 100, with higher scores reflecting better health status. This was measured on hospital admission.

†RIW provide an estimate of the cost of resources used in the care of a patient relative to the average hospitalized patient. The higher the RIW, the higher the resource utilization relative to the average inpatient.

‡LACE (Length of Stay, Acuity, Comorbidities, ER Visits) index is derived from length of stay, acuity of presentation, comorbidities, and ED visits in the preceding 6 months. It ranges from 1 to 19, with higher scores associated with a higher risk of readmission or death following hospitalization.

§Charlson comorbidity index is a method of predicting mortality and assessing disease burden based on comorbidities. The severity of comorbidity is categorized into three grades: mild (scores of 1–2); moderate (scores of 3–4); and severe (scores ≥5).

Outcomes

Time to First Composite All-Cause Readmission, ED Visit, or Death at 6 Months

Among 1236 male patients (560 in the intervention and 676 in the usual care group), there was no significant difference between the intervention and usual care group, respectively, in the first composite outcome of all-cause readmission, ED visit, or death at 6 months (incidence, 66.3% versus 64.1%; HR, 1.04 [95% CI, 0.86–1.26]; *P*=0.67; Figure 1).

Among 1258 female patients (544 in the intervention and 714 in the usual care group, there was no significant difference between the intervention and usual care group, respectively, in the first composite outcome of all-cause readmission, ED visit, or death at 6 months (incidence, 59.9% versus 64.8%; HR, 0.83 [95% CI, 0.69–1.01]; *P*=0.06). However, a significant difference in treatment effect was noted between males and females in 6-month composite all-cause readmission, ED visit, or death (*P* for sex interaction=0.012).

Composite All-Cause Readmission or ED Visit at 6 Months

Among male patients, there was no significant difference in the second composite outcome of all-cause readmission or ED visit at 6 months (incidence, 63.8% versus 61.7%; HR, 1.03 [95% CI, 0.85–1.24];

Table 2. Prescription Refills at 30 Days Stratified by Sex*

	Males age 65 and over			Females age 65 and over		
	PACT-HF (N=448)	Usual care (N=556)	*P* value	PACT-HF (N=496)	Usual care (N=640)	*P* value
Ace-inhibitors, n (%)†	158 (35.3%)	183 (32.9%)	0.43	153 (30.8%)	198 (30.9%)	0.97
Mineralocorticoid antagonists, n (%)	85 (19.0%)	117 (21.0%)	0.42	89 (17.9%)	100 (15.6%)	0.30
β-blockers, n (%)	269 (60.0%)	326 (58.6%)	0.65	321 (64.7%)	405 (63.3%)	0.62
Diuretics, n (%)	394 (87.9%)	461 (82.9%)	0.026	426 (85.9%)	547 (85.5%)	0.84
Any of the 4 drugs, n (%)	417 (93.1%)	513 (92.3%)	0.62	459 (92.5%)	596 (93.1%)	0.70

PACT-HF indicates Patient-Centered Care Transitions in Heart Failure.

*Data set limited to patients ≥65 years of age (2140 patients) and includes 1004 males (448 in PACT-HF and 556 in usual care) and 1136 females (496 in PACT-HF and 640 in usual care).

†As recruitment was completed before the publication of the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) and TRANSITION trials, no patients were discharged from the hospital on angiotensin-receptor neprilysin inhibitors.

P=0.76; Figure 2). Among females, there was a significant difference in composite all-cause readmission or ED visit at 6 months (incidence, 57.7% versus 63.0%; HR, 0.81 [95% CI, 0.67–0.99]; *P*=0.037). There was a significant sex interaction noted for composite readmission or ED visit (*P* for sex interaction=0.024; Figure 2).

Components of Composite Outcomes at 6 Months

At 6 months, there was no significant difference between male patients in the intervention and usual care group, respectively, in time to first all-cause readmission (incidence, 47.1% versus 50.6%; HR, 0.99 [95% CI, 0.81–1.21]; *P*=0.89), ED visit (incidence, 36.4% versus 31.4%; HR, 1.10 [95% CI, 0.85–1.43]; *P*=0.46), death (incidence, 17.7% versus 16.0%; HR, 1.13 [95% CI, 0.79–1.62]; *P*=0.50), and HF readmission (incidence, 19.8% versus 21.6%; HR, 1.09 [95% CI, 0.80–1.49]; *P*=0.60; Figure 3).

At 6 months, there was no significant difference between female patients in the intervention and usual care group, respectively, in time to first all-cause readmission (incidence, 47.6% versus 47.8%; HR, 1.02 [95% CI, 0.83–1.24]; *P*=0.88), death (incidence, 16.4% versus 15.0%; HR, 1.08 [95% CI, 0.74–1.56]; *P*=0.69), and HF readmission (incidence, 19.5% versus 24.9%; HR, 0.83 [95% CI, 0.61–1.12]; *P*=0.22). However, among females, there was a significant between-group difference in time to first all-cause ED visit at 6 months (150 events [27.6%] versus 204 [36.4%]; HR 0.66 [95% CI, 0.51–0.87]; *P*=0.003).

There was a significant sex interaction for time to first ED visit (*P* for sex interaction=0.0004; Figure 3).

There was no heterogeneity in treatment effect across age groups (*P* for age interaction >0.05 for all outcomes; Figure 3).

DISCUSSION

In this exploratory analysis of a pragmatic stepped-wedge cluster randomized trial, we found that a patient-centered transitional care model did not improve the composite end points of all-cause readmission, ED visits, or death; and composite all-cause readmission or ED visit at 6 months following hospitalization for HF. However, there was a sex-treatment interaction for both composite outcomes, with a beneficial treatment effect noted among female relative to male patients. This was driven by a significant reduction in ED visits in females—but not males—who received the intervention (Figure 4).

The end points used for this analysis were measured at 6 months to assess longer-term outcomes of the intervention since the HF clinic visits were only initiated at the end of the home nurse visit period; the neutral clinical outcomes overall at 6 months were consistent with those at 30 days and 3 months.[14] Our assessment of outcomes at 6 months allowed for more events to accrue, and therefore, for greater statistical power to test for subgroup differences and treatment interactions than at 30 days or 3 months.

This pragmatic trial included elderly, multimorbid patients who lived in nursing homes, retirement residences, respite centers, and temporary housing. English language proficiency and literacy were not among the inclusion criteria. Relative to patients in contemporary HF RCTs,[31,32] patients were older and had a higher prevalence of comorbidities. These factors may have posed as barriers to receiving or deriving benefit from transitional care services. The transitional care services were titrated to risk, and nurse-led home visits and HF clinic care were only offered to 40% of patients, diluting the impact of the interventions. Furthermore, the risk prediction tool that was used to guide services was modest in risk discrimination, similar in performance to other tools used to prediction rehospitalization or death in HF; some high-risk patients would have been classified incorrectly and, therefore, deprived of the intervention.[33,34] Finally, hospitals may have improved baseline health care quality to qualify for financial incentives that were initiated by the province during the trial,[26] thereby producing a ceiling effect and minimizing benefit of the intervention.

Our finding of a sex interaction with transitional care services was unrelated to differences in age between females

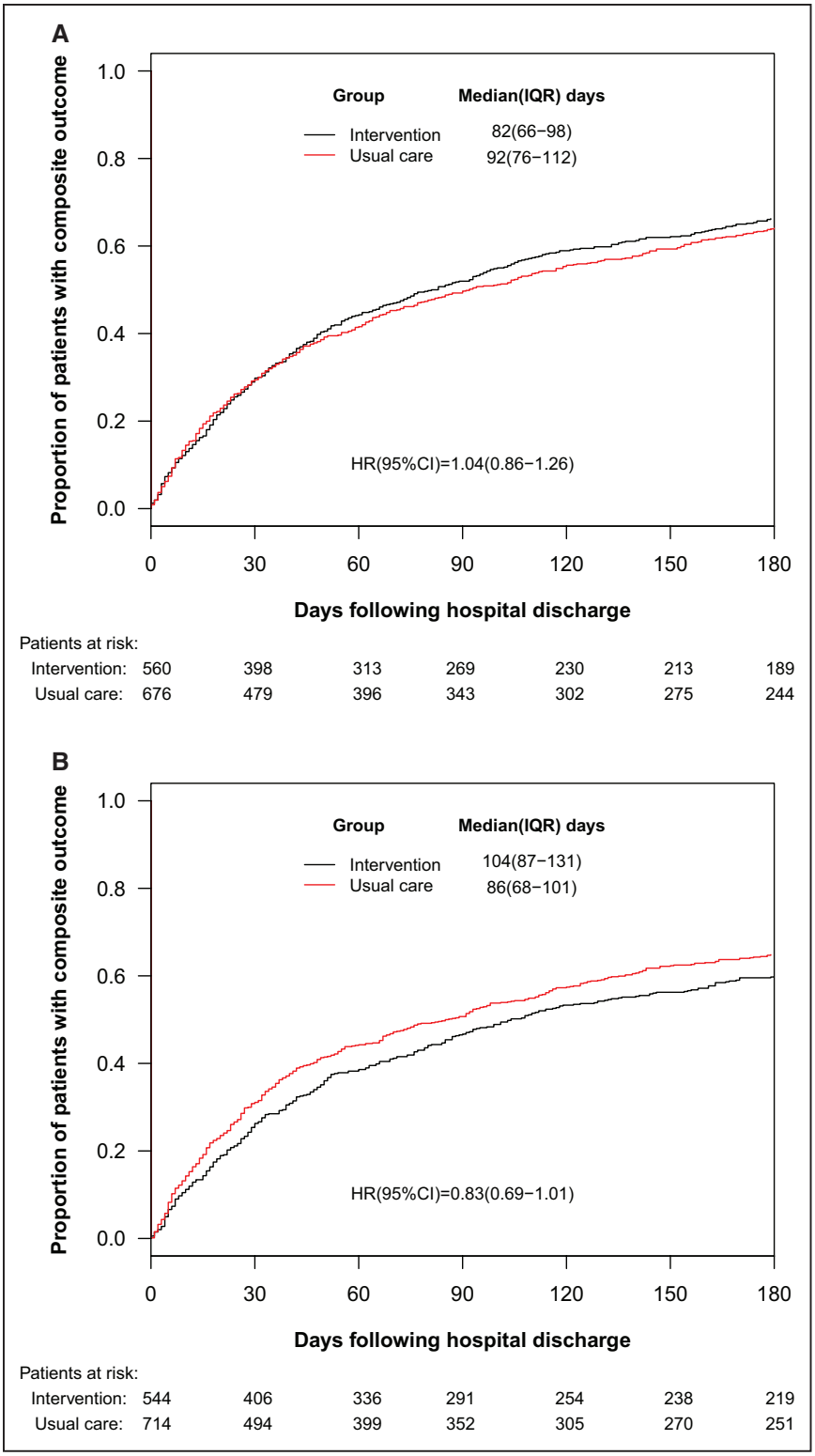

Figure 1. Effect of the transition care model on the composite outcome of all-cause readmission, emergency department visit, or death at 6 months.
Kaplan-Meier curves shown for male (**A**) and female (**B**) patients, adjusted for age. A significant sex-treatment interaction was observed (*P* for sex interaction=0.01). HR indicates hazard ratio; and IQR, interquartile range.

and males hospitalized for HF as all models were adjusted for age. Furthermore, the treatment effect was not modified by age. While females in the trial were older, more likely to reside in long-term care facilities, and had hypertension and dementia more commonly than males, there were no significant sex differences in the overall comorbidity burden or resource intensity use, as measured by the Charlson comorbidity and resource intensity weight, respectively. It should be noted that in each sex subgroup, baseline characteristics were balanced between the treatment and usual care group, important when treatment effect in each sex is being estimated. Our findings are consistent with sex differences in response to other health care services among patients with cardiovascular disease.[35]

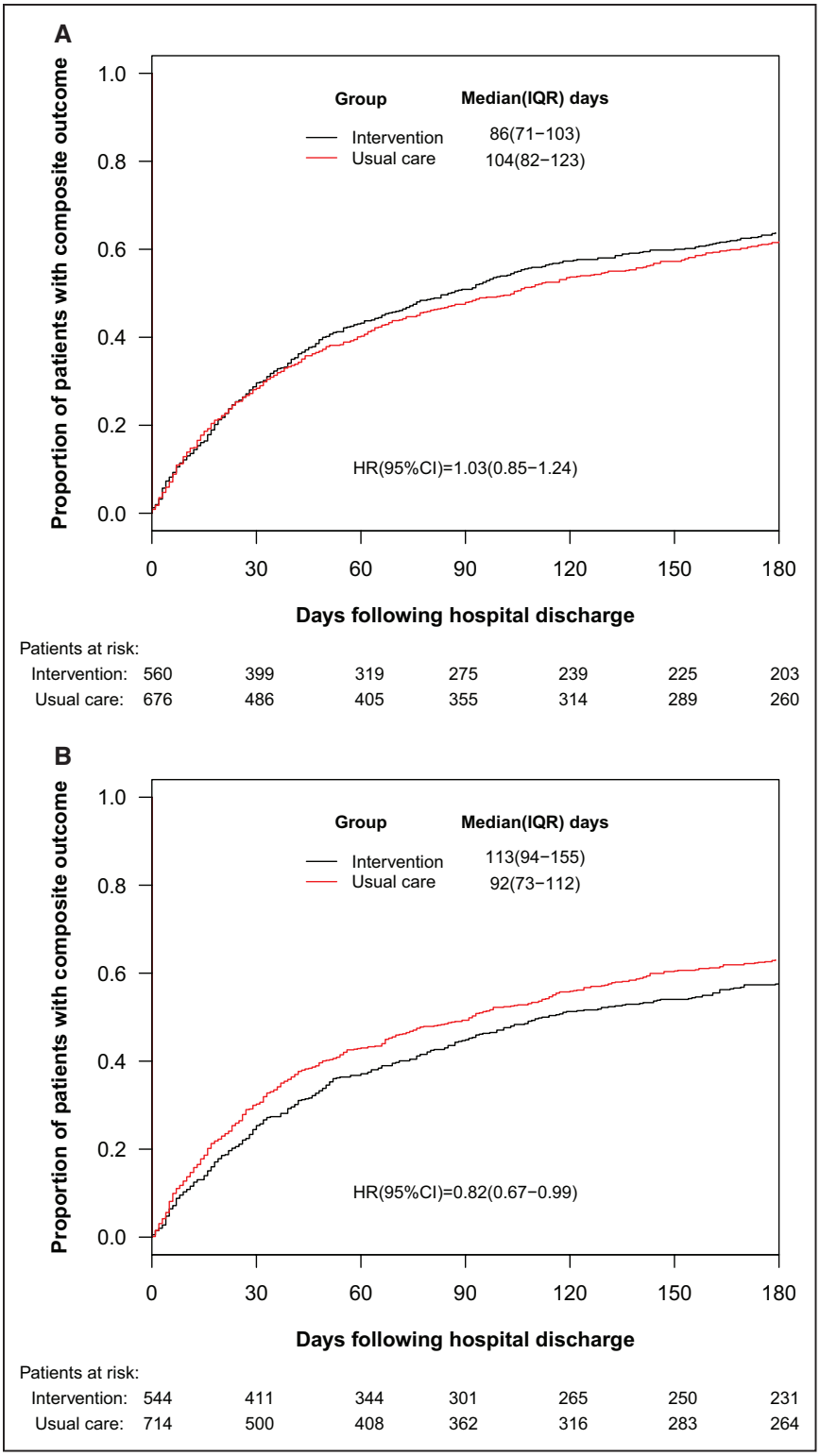

Figure 2. Effect of the transitional care model on the composite outcome of all-cause readmission or emergency department visit at 6 months.
Kaplan-Meier curves shown for male (**A**) and female (**B**) patients, adjusted for age. There was a significant sex-treatment interaction (*P* for sex interaction=0.02). HR indicates hazard ratio; and IQR, interquartile range.

The enhanced benefit in female patients and reduction in all-cause ED visits may be explained by differences in social support, although we did not measure caregiver support in this trial. Patients with HF often rely on caregiver involvement for self-management, including symptom recognition, monitoring of vitals and weights, dietary interventions, administration of medications, and navigation of the health care system,[15,36] and there is a gender gap in caregiving.[17–19] Women serve as informal caregivers more frequently than men, incurring secondary stressors including relational and financial problems.[37] The female patients in this study were 5 years older than the males, and unlike the males, may not have had a spouse or informal caregiver in their home to support them. In one study of patients

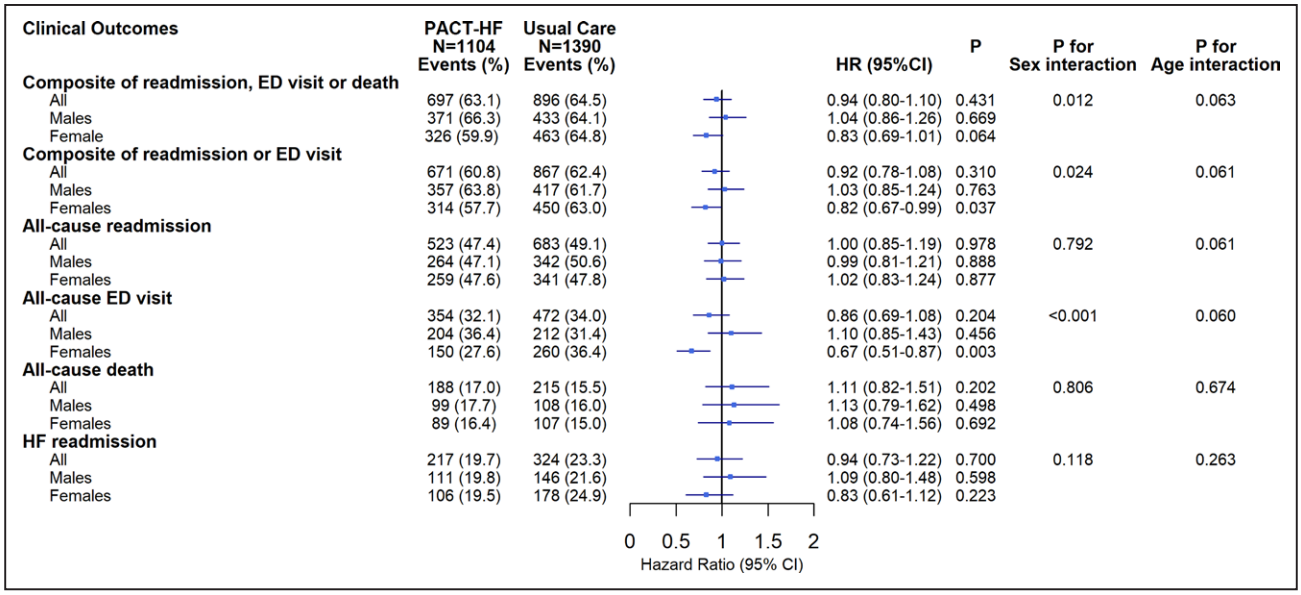

Figure 3. Forest plot of clinical outcomes in intervention and usual care groups by sex.
All models adjusted for age. ED indicates emergency department; HF, heart failure; HR, hazard ratio; and PACT-HF, Patient-Centered Care Transitions in Heart Failure.

with advanced HF being evaluated for left ventricular assist device therapy and heart transplantation, females were less likely to have a spouse as primary support compared with males[38] and were more likely to have supports who did not reside with them or had competing responsibilities. For these reasons, the supplemental support and structured home nursing visits provided by the transitional care program may have had a more significant impact in female than male patients who may have already had caregivers to complement these services. The comprehensive transitional care model may have allowed for improved management of cardiovascular as well as noncardiovascular conditions, leading to the reduction in ED visits.

We found no significant differences in services delivered to male versus female patients, with similar proportions of each group referred for family physician follow-up, nurse home visits, and HF clinic visits. The number of home visits in the month following hospital discharge was similar in male and female patients. These findings differ from observational data that demonstrate gaps in referral of females to HF services.[39] A prior study from Ontario demonstrated that only a minority (35.5%) of patients referred to HF clinics were female.[40] Similarly, a prospective cohort study of patients with HF seen at 8 emergency rooms in Quebec found that males were significantly more likely than females to be referred (odds ratio, 2.04 [95% CI, 1.12–3.74]).[41] In the PACT-HF trial, rates of HF clinic referral were similar among male and female patients, indicating a relative increase in HF care for females. These points of interaction with

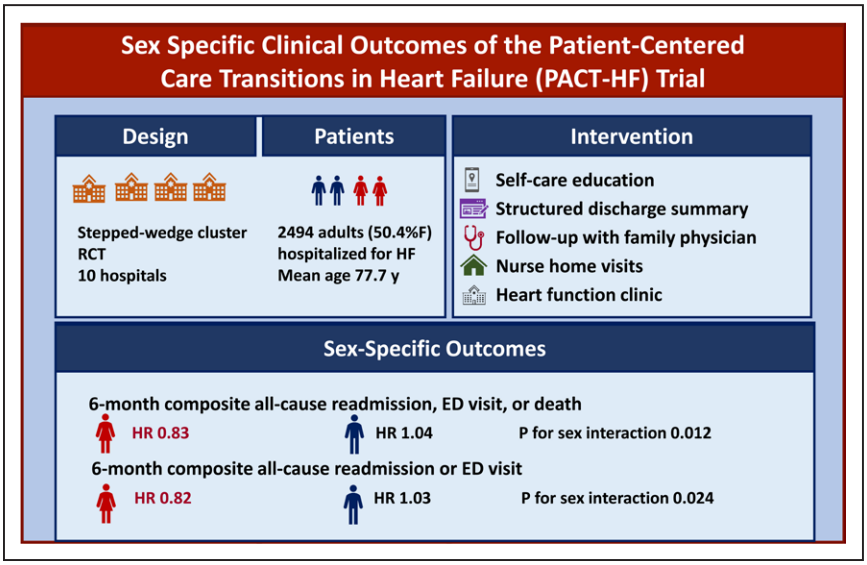

Figure 4. Sex-specific outcomes in the PACT-HF trial.
ED indicates emergency department; HF, heart failure; HR, hazard ratio; PACT-HF, Patient-Centered Care Transitions in Heart Failure; and RCT, randomized controlled trial.

the ambulatory health care system may explain the decreased ED utilization among females, but not males, in the intervention versus usual care group.

There were no sex differences in utilization of guideline-directed medical therapies (angiotensin-converting enzyme inhibitors, mineralocorticoid antagonists, and β-blockers) based on drug administrative data available for patients 65 years of age or older. Health Canada approved ARNI (angiotensin-receptor neprilysin inhibitor) use in ambulatory patients with HF with reduced ejection fraction in the final months of recruitment in PACT-HF, and trials that demonstrated safety of ARNI in patients hospitalized for HF were published after the trial ended.[42,43] Thus, none of the patients in this trial were discharged on ARNI. While we could not assess appropriateness of therapy, these findings suggest that females were no less likely than males to be prescribed HF treatments after discharge. This is in contrast to observational studies that have shown that females are less likely to receive HF therapies than males, and it is possible that the intervention helped close some of the sex-related treatment disparities. Indeed, multi-faceted interventions such as those tested in the PACT-HF trial have been shown to increase clinician uptake of guideline recommendations in HF.[9,44,45] Whether prescription of therapies correlated with adherence to them, however, is unclear.[10]

There are several strengths of this study. Inclusion criteria were broad and pragmatic, and patients were older and with a higher prevalence of comorbidities than those of contemporary HF clinical trials,[30,31] allowing for results to be generalizable to HF patients hospitalized in everyday clinical settings. We engaged patients, clinicians, and decision makers in the design and planning of this trial, ensuring that the study question was relevant, the research protocol was patient-centered, and the intervention was delivered using publicly funded personnel. We included outcomes that were important to patients and to the health care system. Notably, 50% of trial participants were females, which is higher than most HF trials[46] and allowed for analysis of sex-disaggregated data. We were likely able to successfully enroll females due to our pragmatic trial design which had broad eligibility criteria and minimal research burden on patients[46–50]; we obtained clinical outcomes via linkages of patient records with existing administrative databases and patient-reported outcomes via the telephone rather than in-person visits.[13–15]

Limitations

This study has several limitations. We used resources and personnel across urban settings in single-payer health care system, and results may have differed in rural settings and multi-payer health care systems. Left ventricular ejection fraction and laboratory values were not recorded in the administrative databases from which data on the patients were obtained. While we audited process-of-care indicators, we could not account for the quality of services or patients' adherence to discharge recommendations. We did not collect data on health care literacy or caregiver support. We restricted outcomes to those prespecified in the trial and did not have access to the causes of ED visits and how these differed by sex. The exploratory nature of this analysis and multiple end points leave open the possibility of type I error. While steps were taken to avoid contamination of usual care practices with the intervention, uptake of the intervention during the usual phase cannot be excluded.

Conclusions

Among patients hospitalized with HF in Ontario, Canada, implementation of a patient-centered transitional care model compared with usual care did not improve a composite of clinical outcomes at 6 months overall. However, there were significant sex differences in treatment response, with a large reduction in ED visits evident in females, but not males, who received the intervention. More research is needed to explain these differences and to assess how transitional care services can be tailored to improve clinical outcomes among the highest risk patients with HF.

ARTICLE INFORMATION

Received March 7, 2021; accepted August 24, 2021.

Affiliations

Department of Medicine (H.G.C.V., J.S.H.) and Department of Health Research Methods, Evidence, and Impact (H.G.C.V., S.F.L., J.S.H., L.T., S.J.C.), McMasterUniversity, Hamilton, Ontario, Canada. Population Health Research Institute, Hamilton, Ontario, Canada (H.G.C.V., S.F.L., J.S.H., S.J.C.). Columbia University Irving Medical Center, New York, NY (E.M.D.). Institute for Clinical Evaluative Sciences, Ontario, Canada (U.E.O., R.P., D.T.K.). University of Colorado School of Medicine, Aurora (L.A.A.). University Medical Center Groningen, the Netherlands (A.A.V.). Department of Medicine, University of Toronto, Ontario, Canada (D.T.K.).

Sources of Funding

This study was funded by peer-reviewed grants held by Dr Van Spall from Canadian Institutes of Health Research (No. 135917) and Ontario Ministry of Health and Long Term Care (MOHLTC) Health System Research Fund (No. 6686), as well as in-kind support from the participating hospitals and Community Care Access Centers. Dr Van Spall received research salary support from the MOHLTC, the Hamilton Health Sciences Early Career Award, and the Women as One Escalator Award during the study duration. The opinions, results, and conclusions reported in this article, and selection of journal for submission, are those of the authors and are independent from the funding sources.

Acknowledgments

The study was coordinated by the Population Health Research Institute (PHRI) of Hamilton Health Sciences Corporation and McMaster University. The PHRI was responsible for the overall conduct of the study. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The data set from this study is held securely in coded form at ICES. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information. The analyses, results, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Dr Oz and R. Perez

had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication or veto the publication. The authors have no conflicts of interest relevant to this publication. The authors acknowledge the role of the local principal investigators; these include Peter R. Mitoff, MD; Manish Maingi, MD; Michael C. Tjandrawidjaja, MD; Michael Heffernan, MD, PhD; Mohammad I. Zia, MD; Liane Porepa, MD; and Mohamed Panju, MSc, MD. We are indebted to Daniel Ball, MA (Halton Healthcare), Elizabeth Banting, RN (Southlake Regional Health Centre), Maria De Leon, RN (Mississauga Halton Community Care Access Centre), Nancy Elford, MN (Michael Garron Hospital), Jeanine Harrison, MN (Southlake Regional Health Centre), Elena Holt, MHSc (St. Joseph's Health Centre), Quazi Ibrahim, MSc (PHRI), Gail Johnson, MSC (Guelph General Hospital), Colleen Lackey, RN (Ontario Telemedicine Network), Bill Liu, MSc (PHRI), Roberta Napoleoni, DipBA (PHRI), Tracy Renton, BNc (Trillium Health Partners), Donna Richardson, BScN (Trillium Health Partners), Teresa Smith, MBA (Hamilton Health Sciences), Nazneen Solkar, BPhm (PHRI), Anne Stephens, MEd (Toronto Central Local Health Integration Network), and Shannon Tyrrell, MHM (Trillium Health Partners) for their roles in the trial. PHRI employees received salary support for their roles through the study's grant funds. The roles of employees from other institutions were funded by in-kind institutional support.

Disclosures

Dr Van Spall reports grant funding from the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, and Ontario Ministry of Health and Long Term Care. Dr Connolly reports grants and personal fees from Bayer, Bristol Myers Squibb Pfizer, Portola, Daiichi Sankyo, and Medtronic. Dr Allen reports grant funding from American Heart Association, National Institutes of Health, and Patient-Centered Outcomes Research Institute and consulting fees from Abbott, ACI Clinical, Amgen, Boston Scientific, Cytokinetics, and Novartis. Dr Healey reports research grants and speaking fees from Medtronic, Boston Scientific, Abbott, Novartis, Myokardia, ARCA Biopharm, and Bristol Myers Squibb/Pfizer and consulting for Bayer and Boston Scientific. Dr Voors reports consultancy fees and research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, Novo Nordisk, and Roche Diagnostics. The other authors report no conflicts.

Supplemental Materials

Table I

REFERENCES

1. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859–3868c. doi: 10.1093/eurheartj/ehz835
2. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068–3072. doi: 10.1161/01.cir.0000039105.49749.6f
3. Gracia Gutiérrez A, Poblador-Plou B, Prados-Torres A, Ruiz Laiglesia FJ, Gimeno-Miguel A. Sex differences in comorbidity, therapy, and health services' use of heart failure in Spain: evidence from real-world data. *Int J Environ Res Public Health*. 2020;17:E2136. doi: 10.3390/ijerph17062136
4. Norberg H, Pranic V, Bergdahl E, Lindmark K. Differences in medical treatment and clinical characteristics between men and women with heart failure - a single-centre multivariable analysis. *Eur J Clin Pharmacol*. 2020;76:539–546. doi: 10.1007/s00228-019-02782-2
5. Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. *Cells*. 2020;9:E242. doi: 10.3390/cells9010242
6. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, Hillege H, Samani NJ, Zannad F, Dickstein K, et al; ASIAN-HF investigators. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet*. 2019;394:1254–1263. doi: 10.1016/S0140-6736(19)31792-1
7. Lenzen MJ, Rosengren A, Scholte op Reimer WJ, Follath F, Boersma E, Simoons ML, Cleland JG, Komajda M. Management of patients with heart failure in clinical practice: differences between men and women. *Heart*. 2008;94:e10. doi: 10.1136/hrt.2006.099523.
8. Opasich C, De Feo S, Ambrosio GA, Bellis P, Di Lenarda A, Di Tano G, Fico D, Gonzini L, Lavecchia R, Tomasi C, et al; TEMISTOCLE Investigators. The 'real' woman with heart failure. Impact of sex on current in-hospital management of heart failure by cardiologists and internists. *Eur J Heart Fail*. 2004;6:769–779. doi: 10.1016/j.ejheart.2003.11.021.
9. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72:351–366. doi: 10.1016/j.jacc.2018.04.070
10. Kayibanda JF, Girouard C, Grégoire JP, Demers E, Moisan J. Adherence to the evidence-based heart failure drug treatment: are there sex-specific differences among new users? *Res Social Adm Pharm*. 2018;14:915–920. doi: 10.1016/j.sapharm.2017.10.010
11. Granger BB, Ekman I, Granger CB, Ostergren J, Olofsson B, Michelson E, McMurray JJ, Yusuf S, Pfeffer MA, Swedberg K. Adherence to medication according to sex and age in the CHARM programme. *Eur J Heart Fail*. 2009;11:1092–1098. doi: 10.1093/eurjhf/hfp142
12. Van Spall HGC, Hill AD, Fu L, Ross HJ, Fowler RA. Temporal trends and sex differences in intensity of healthcare at the end of life in adults with heart failure. *J Am Heart Assoc*. 2021;10:e018495. doi: 10.1161/JAHA.120.018495
13. Van Spall HGC, Lee SF, Xie F, Ko DT, Thabane L, Ibrahim Q, Mitoff PR, Heffernan M, Maingi M, Tjandrawidjaja MC, et al. Knowledge to action: rationale and design of the Patient-Centered Care Transitions in Heart Failure (PACT-HF) stepped wedge cluster randomized trial. *Am Heart J*. 2018;199:75–82. doi: 10.1016/j.ahj.2017.12.013
14. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, Maingi M, Tjandrawidjaja MC, Heffernan M, Zia MI, et al. Effect of Patient-Centered Transitional Care Services on clinical outcomes in patients hospitalized for heart failure: The PACT-HF Randomized Clinical Trial. *JAMA*. 2019;321:753–761. doi: 10.1001/jama.2019.0710
15. Blumer V, Gayowsky A, Xie F, Greene SJ, Graham MM, Ezekowitz JA, Perez R, Ko DT, Thabane L, Zannad F, et al. Effect of patient-centered transitional care services on patient-reported outcomes in heart failure: sex-specific analysis of the PACT-HF randomized controlled trial. *Eur J Heart Fail*. 2021;23:1488–1498. doi: 10.1002/ejhf.2312
16. Kitko L, McIlvennan CK, Bidwell JT, Dionne-Odom JN, Dunlay SM, Lewis LM, Meadows G, Sattler ELP, Schulz R, Strömberg A; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Family caregiving for individuals with heart failure: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e864–e878. doi: 10.1161/CIR.0000000000000768
17. Marks NF, Lambert JD, Choi H. Transitions to caregiving, gender, and psychological well-being: A Prospective U.S. National Study. *J Marr Fam*. 2002;64:657–667. doi: 10.1111/j.1741-3737.2002.00657.x
18. Yee JL, Schulz R. Gender differences in psychiatric morbidity among family caregivers: a review and analysis. *Gerontologist*. 2000;40:147–164. doi: 10.1093/geront/40.2.147
19. Penning MJ, Wu Z. Caregiver stress and mental health: impact of caregiving relationship and gender. *Gerontologist*. 2016;56:1102–1113. doi: 10.1093/geront/gnv038
20. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail*. 2017;19:1427–1443. doi: 10.1002/ejhf.765
21. Feltner C, Jones CD, Cené CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, Arvanitis M, Lohr KN, Middleton JC, Jonas DE. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med*. 2014;160:774–784. doi: 10.7326/M14-0083
22. Marantz PR, Tobin JN, Wassertheil-Smoller S, Steingart RM, Wexler JP, Budner N, Lense L, Wachspress J. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. *Circulation*. 1988;77:607–612. doi: 10.1161/01.cir.77.3.607
23. van Walraven C, Dhalla IA, Bell C, Etchells E, Stiell IG, Zarnke K, Austin PC, Forster AJ. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. *CMAJ*. 2010;182:551–557. doi: 10.1503/cmaj.091117
24. Yazdan-Ashoori P, Lee SF, Ibrahim Q, Van Spall HG. Utility of the LACE index at the bedside in predicting 30-day readmission or death in

patients hospitalized with heart failure. *Am Heart J*. 2016;179:51–58. doi: 10.1016/j.ahj.2016.06.007
25. Graumlich JF, Novotny NL, Aldag JC. Brief scale measuring patient preparedness for hospital discharge to home: Psychometric properties. *J Hosp Med*. 2008;3:446–454. doi: 10.1002/jhm.316
26. Ministry of Health and Long-Term Care. *Quality-Based Procedures: Clinical Handbook for Heart Failure (Acute and Postacute)* [Internet]. Health Quality Ontario; 2015. http://www.hqontario.ca/Portals/0/Documents/evidence/clinical-handbooks/heart-failure-02042015-en.pdf. Accessed January 19, 2021
27. WHO Regional Office for Europe. *Integrated Care Models: An Overview* [Internet]. World Health Organization; 2016. http://www.euro.who.int/__data/assets/pdf_file/0005/322475/Integrated-care-models-overview.pdf. Accessed January 19, 2021
28. Balan TA, Putter H. A tutorial on frailty models. *Stat Methods Med Res*. 2020;29:3424–3454. doi: 10.1177/0962280220921889
29. Li G, Taljaard M, Van den Heuvel ER, Levine MAH, Cook DJ, Wells GA, Devereaux PJ, Thabane L. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. 2017;46:746-755. doi: 10.1093/ije/dyw320
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383. doi: 10.1016/0021-9681(87)90171-8
31. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
32. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
33. Averbuch T, Lee SF, Mamas MA, Oz UE, Perez R, Connolly SJ, Ko DT, Van Spall HGC. Derivation and validation of a two-variable index to predict 30-day outcomes following heart failure hospitalization. *ESC Heart Fail*. 2021;8:2690–2697. doi: 10.1002/ehf2.13324
34. Van Spall HG, Averbuch T, Lee SF, Oz UE, Mamas MA, Januzzi JL, Ko DT. The LENT index predicts 30 day outcomes following hospitalization for heart failure. *ESC Heart Fail*. 2021;8:518–526. doi: 10.1002/ehf2.13109
35. Shah RM, Hirji SA, Jolissaint JS, Lander HL, Shah PB, Pelletier MP, Sobieszczyk PS, Berry NC, Shook DC, Nyman CB, et al. Comparison of sex-based differences in home or nonhome discharge utilization of rehabilitative services and outcomes following transcatheter aortic valve implantation in the United States. *Am J Cardiol*. 2019;123:1983–1991. doi: 10.1016/j.amjcard.2019.03.008
36. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, Gurvitz MZ, Havranek EP, Lee CS, Lindenfeld J, et al; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation*. 2009;120:1141–1163. doi: 10.1161/CIRCULATIONAHA.109.192628
37. Swinkels J, Tilburg TV, Verbakel E, Broese van Groenou M. Explaining the gender gap in the caregiving burden of partner caregivers. *J Gerontol B Psychol Sci Soc Sci*. 2019;74:309–317. doi: 10.1093/geronb/gbx036
38. Steinberg RS, Nayak A, Dong T, Morris AA. Primary caregiver relationships for advanced heart failure therapy differ based on sex and race and predict eligibility. *J Cardiac Fail*. 2020;26:S10. doi: 10.1016/j.cardfail.2020.09.035
39. Sullivan K, Doumouras BS, Santema BT, Walsh MN, Douglas PS, Voors AA, Van Spall H. Sex-based differences in heart failure: pathophysiology, risk factors, management, and outcomes. *Can J Cardiol*. 2021;37:560-571. doi: 10.1016/j.cjca.2020.12.025
40. Abrahamyan L, Sahakyan Y, Wijeysundera HC, Krahn M, Rac VE. Gender differences in utilization of specialized heart failure clinics. *J Womens Health (Larchmt)*. 2018;27:623–629. doi: 10.1089/jwh.2017.6461
41. Feldman DE, Huynh T, Des Lauriers J, Giannetti N, Frenette M, Grondin F, Michel C, Sheppard R, Montigny M, Lepage S, et al. Gender and other disparities in referral to specialized heart failure clinics following emergency department visits. *J Womens Health (Larchmt)*. 2013;22:526–531. doi: 10.1089/jwh.2012.4107
42. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E; PIONEER-HF Investigators. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548. doi: 10.1056/NEJMoa1812851
43. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, Fonseca C, Goncalvesova E, Cavusoglu Y, Fernandez A, et al; TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019;21:998–1007. doi: 10.1002/ejhf.1498
44. Shanbhag D, Graham ID, Harlos K, Haynes RB, Gabizon I, Connolly SJ, Van Spall HGC. Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure: a systematic review. *BMJ Open*. 2018;8:e017765. doi: 10.1136/bmjopen-2017-017765
45. Van Spall HG, Shanbhag D, Gabizon I, Ibrahim Q, Graham ID, Harlos K, Haynes RB, Connolly SJ. Effectiveness of implementation strategies in improving physician adherence to guideline recommendations in heart failure: a systematic review protocol. *BMJ Open*. 2016;6:e009364. doi: 10.1136/bmjopen-2015-009364
46. Wei S, Le N, Zhu JW, Breathett K, Greene SJ, Mamas MA, Zannad F, Van Spall HGC. Factors associated with racial and ethnic diversity among Heart Failure trial participants: a systematic bibliometric review. *Circ Heart Fail*. In press. 10.1161/CIRCHEARTFAILURE.121.008685
47. Whitelaw S, Sullivan K, Eliya Y, Alruwayeh M, Thabane L, Yancy CW, Mehran R, Mamas MA, Van Spall HGC. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. *Eur J Heart Fail*. 2021;23:15–24. doi: 10.1002/ejhf.2034
48. Whitelaw S, Thabane L, Mamas MA, Reza N, Breathett K, Douglas PS, Van Spall HGC. Characteristics of heart failure trials associated with underrepresentation of women as lead authors. *J Am Coll Cardiol*. 2020;76:1919–1930. doi: 10.1016/j.jacc.2020.08.062
49. Michos ED, Van Spall HGC. Increasing representation and diversity in cardiovascular clinical trial populations. *Nat Rev Cardiol*. 2021;18:537–538. doi: 10.1038/s41569-021-00583-8
50. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA*. 2007;297:1233–1240. doi: 10.1001/jama.297.11.1233