UNDEREXPOSURE OF SENIORS TO HEART FAILURE DRUG THERAPY

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ABSTRACT

Background
Little is known about exposure to heart failure (HF) treatment among seniors with ischemic heart disease.

Objectives
In a population of seniors, we: 1) estimated the association between age and exposure to HF drug therapy at 6, 12, 36 and 60 month intervals after HF diagnosis, and 2) determined the influence of the passage of time on exposure to drug therapy.

Methods
Using the Quebec provincial administrative databases, we conducted a population-based inception cohort study that included all individuals aged ≥ 65 with a first HF diagnosis between 2000 and 2009 and an ischemic heart disease diagnosis in the year before HF diagnosis. We assessed exposure to HF drug therapy and to drug therapy at target doses at 6, 12, 36 and 60 month intervals after HF diagnosis. Adjusted prevalence ratios (aPR) between age at diagnosis and exposure to drug therapy and the influence of time (6-month periods) were assessed using multivariate modified Poisson regressions.

Results
Among the 86,428 seniors, those who were older were less likely to be exposed to both HF drug therapy and drug therapy at target doses at each time point, than were the younger ones (aged 65-69). The aPRs for exposure to drug therapy for the 90+ age group were 0.64, 0.64, 0.56 and 0.53 at the 6, 12, 36 and 60 month intervals, respectively. After HF diagnosis, exposure increased by a maximum of 8% per 6-month period.

Conclusion
Increasing age is associated with a decrease in exposure to drug therapy, with only slight improvement in exposure after HF diagnosis.

Key Words: *Heart failure, aging, evidence-based health care, drug therapy*

Heart failure (HF) is a major cause of hospitalization and mortality, particularly in seniors. HF is the main reason for hospitalization of individuals aged 65+.[1] Risk of dying is 3.6 times higher in individuals with HF than in the general population.[2] Ischemic heart disease (IHD) is the most frequent cause of HF. It is responsible for up to 46% of cases.[3] The presence of IHD among patients with HF is associated with increased risk of HF hospitalization[4] and mortality.[5]

Using treatments of well-established efficacy can reduce both morbidity and mortality in patients with HF. Evidence-based treatments are β-blockers (carvedilol, bisoprolol or metoprolol) combined with an angiotensin-

converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), or hydralazine used in association with isosorbide dinitrate. These drug combinations are now standard drug therapy for HF and are recommended by clinical guidelines[6], especially for HF patients with decreased left ventricular ejection fraction.[7] In addition, patients with both IHD and HF should be exposed to a β-blocker and an ACEi or ARB unless contra-indicated[7]. However, to benefit in clinical practice from the reduced morbidity and mortality associated with evidence-based drug treatments, patients must take the medications over a long period of time and at doses found efficacious in HF clinical trials.[6]

Although the majority of HF patients are seniors, little is known about exposure to HF drug therapy in this population and the effect of aging on exposure to HF drug therapy. However, this is an important clinical question since there is evidence associating older age among seniors with underuse of evidence-based drug treatments in many areas of cardiology.[8,9] On the other hand, association between aging and underuse of HF drugs remains unclear. Studies pertaining to the treatment of seniors with HF offer only partial answers, as they focused on exposure to a single drug[10-13], or did not consider drug doses[10-14], or limited the assessment period for exposure to drug treatment to less than one year.[10-14]

Moreover, it is not known whether exposure to HF drug therapy is optimized in seniors on the long term. Consequently, we performed a study aimed at describing drug therapy patterns for HF among newly diagnosed patients aged 65 years and older with an IHD diagnosis in the year prior to HF diagnosis. More specifically, our objectives were: 1) to gauge the association between age at diagnosis and exposure to HF drug therapy and exposure to drug therapy at target doses at 6, 12, 36 and 60 month intervals after diagnosis, and 2) to estimate, across age groups (65-69, 70-74, 75-79, 80-84, 85-89 and 90+ years), the influence of time passing on exposure to both HF drug therapy and drug therapy at target doses.

METHODS

Study Design and Data Source

We performed a population-based inception cohort study using the Quebec Provincial Health Insurance Board (RAMQ) databases (physician services, drug plan and hospitalization registries) and the *Institut de la statistique du Québec* (death registry). Together these databases include inpatient and outpatient information on patient demographics, hospital and physician services for all permanent residents of Quebec province. The RAMQ drug plan database contains information on 97% of individuals aged 65 years and older. It is known to be accurate for outpatient prescription drug claims.[15]

Study Population

To compile the study population, we asked RAMQ to identify all adults covered by the public drug insurance plan with ≥1 diagnosis of HF in the medical services database or in the hospitalizations registry (ICD-9 codes: 428, ICD-10 codes: I50) between January 1, 2000 and December 31, 2009. RAMQ removed those not continuously covered by Quebec's public drug plan for the 365-day period before HF diagnosis and those who had a previous HF diagnosis during the same time period. From this database, we kept only patients aged 65+ who had a diagnosis of IHD in the year before HF diagnosis and with one recorded inpatient HF diagnosis or one physician billing (physician services registry) followed by a second record from either source within one year. This definition of HF has been shown to be valid when using administrative data.[16] The date of the first HF diagnosis registered in one of the two databases forms the date of HF diagnosis. Patients were assumed to have IHD if, in the year before the HF diagnosis, they had a diagnosis of angina or acute myocardial infarction, underwent revascularisation as a dilatation of one or more coronary artery, or coronary artery bypass graft surgery. We also assumed they had IHD if they had a claim for a nitrate drug as it was shown before to be 96% specific for a diagnosis of angina.[17]

Variables

Age at HF diagnosis

To account for the heterogeneity of aging, age was *a priori* classified into 5-year age groups.

HF drug therapy and drug therapy at target doses

Exposure to HF drug therapy and to drug therapy at target doses was assessed at 6, 12, 36 and 60 month intervals post-HF diagnosis among patients still alive and covered by the public drug plan. In order to account for reasons other than HF to be exposed to drugs part of the drug therapy of HF prior to HF diagnosis (e.g. ACEi for treatment of systemic hypertension), we also assessed whether patients were already exposed to such treatment at HF diagnosis. To determine exposure at each time point, we looked back in the database for the last claim for a β-blocker, ACEi, ARB, hydralazine and isosorbide dinitrate before each time point. We considered a patient exposed to one of those drugs at a time point if, according to the claim, the patient had obtained a sufficient number of days' supply to be covered at the date of this time point. Then, to take into account less than optimal adherence to treatment, we added 0.5 times the number of days' supply to the date of this last claim. Hospitalization days occurring during follow-up were excluded from the calculation. If at the time point, the patient was exposed to both a β-blocker and an ACEi/ARB, or to a β-blocker and hydralazine plus isosorbide dinitrate, the patient was classified as being exposed to HF drug therapy.

For patients exposed to HF drug therapy, we looked at each drug dose to determine whether these individuals were exposed to an evidence-based target dose (Table 1). To determine target doses we looked at the Canadian guidelines for HF treatment.[6] When no dose was specified in the guidelines, we looked for doses used in clinical trials that studied these drugs for the treatment of HF. In the absence of clinical trial doses data, we then used the dose recommended in the product monographs.[18] To determine at each time point whether patients were exposed to drug therapy at target doses, we calculated daily doses of β-blocker, ACEi, ARB, hydralazine and isosorbide dinitrate, where applicable. To be classified as exposed to drug therapy at target doses, the daily doses of all drugs in the drug therapy had to be equal to or more than target dose. When more than one β-blocker was used (for example, a drug switch) or when both an ACEi and an ARB were used, we considered only the dose of the drug for whom the dose was the closest to the target one.

TABLE 1 Daily minimum target doses for drugs included in the heart failure drug treatment

Drugs	Daily minimum target doses
Angiotensin converting enzyme inhibitors	
Captopril	75 mg[6]
Enalapril	20 mg[6]
Ramipril	10 mg[6]
Lisinopril	20 mg[6]
Cilazapril	1.5 mg[31]
Fosinopril	40 mg[32]
Perindopril	4 mg[18]
Quinapril	20 mg[33]
Trandolapril	4 mg[34]
β-blockers	
Carvedilol	50 mg[6]
Bisoprolol	10 mg[6]
Metoprolol	200 mg[6]
Angiotensin II receptor blockers	
Candesartan	32 mg[6]
Valsartan	320 mg[6]
Eprosartan	600 mg[18]
Irbesartan	300 mg[18]
Losartan	150 mg[35]
Telmisartan	10 mg[36]
Olmesartan	20 mg[18]
Vasodilatators	
Isosorbide dinitrate	120 mg[6]
Hydralazine	225 mg[6]

Potential Confounders

Because prescriber adherence to recommendations is known to increase over time, calendar year at diagnosis was considered a potential confounder. We also considered baseline factors known to influence prescription writing for seniors: sex, socio-economic status (no/partial/maximum guaranteed income supplement), specialty of the physician who made the HF diagnosis, and hospitalization at time of HF diagnosis. We adjusted for comorbidity level using as an index, the number of drugs from different classes of the Anatomical Therapeutic Chemical Classification used in the year before HF diagnosis and up to each time point. We also searched for each disease likely to constitute an indication for the prescription of drugs comprising the HF drug therapy (arterial hypertension, atrial fibrillation or flutter, cerebrovascular atherosclerotic disease, chronic kidney disease and diabetes). Additionally, we looked for contraindications and conditions requiring close treatment monitoring for the prescription of drugs comprising the HF drug therapy (acute renal failure, aortic stenosis, asthma, chronic obstructive pulmonary disease, conduction disorder without a pacemaker, hepatic failure, hyperkalemia, mitral stenosis, orthostatic hypotension and peripheral atherosclerotic disease). We also looked for the presence of diseases that might reduce life expectancy (dementia, non-skin neoplasia). We checked for a diagnosis for each of these conditions in the physician services or hospitalization registry during the year before HF diagnosis plus the interval up to each of the specific time points. We also ascertained the number of days of hospitalization and the number of medical consultations and specialty of physicians consulted during these same periods.

Statistical Analysis

Socio-demographic variables, use of medical services and comorbidities were described using frequency distributions and summary statistics.

To estimate the association between age at HF diagnosis (independent variable) and our two dependent variables (HF drug therapy and drug therapy at target doses), we computed adjusted prevalence ratios and 95% confidence intervals by using a multivariable generalized linear model with a log link and a Poisson working model.[19]

Model-robust variances were obtained with sandwich estimators to account for the larger variance of Poisson variables compared with binomial variables.[20] The effect of passing time on exposure to HF drug therapy was estimated using generalized estimating equations, which took correlations over time into account. Any age group too small for the analysis was combined with the adjacent younger age group. On two occasions, at the 36 and 60 month time points, the 90+ age group was merged with the 85-89 years old for analysis of the association between age and exposure to drug therapy at target doses. A p-value < 0.05 was considered statistically significant. Analyses were carried out with SAS, version 9.3 (SAS Institute Inc., Cary, NC).

Ethical Considerations

To ensure anonymity, RAMQ assigned each individual a unique encrypted number. The Research Ethics Committee of the *Centre hospitalier affilié universitaire de Québec* approved this study.

RESULTS

A total of 86,428 patients formed our cohort (Figure 1). Table 2 shows baseline characteristics. In Table 3 we present the healthcare services used and the comorbidities experienced by patients during the year before HF diagnosis and up to each time point.

Figure 2 displays the prevalence at each time point for patients exposed to HF drug therapy and drug therapy at target doses. Exposure to HF drug therapy varies from a low 13.9% at baseline in the 90+ age group, to a high 41.5% at both 36 and 60 month post-HF diagnosis in the 65-69 age group. When target doses were considered, the highest prevalence (5.0%) was observed at 36 and 60 month in patients aged 65-69. Within the oldest age group (85+), this proportion never exceeded 1.4%. Influence of time passing on exposure to HF drug therapy and drug therapy at target doses varied little across age groups. On average for each 6-month interval post-HF

diagnosis, the maximum increase in adjusted prevalence ratios was 8% (Table 4).

At each time point, older patients were less likely than the youngest ones (65-69) to be exposed to HF drug therapy and to drug therapy at target doses, as demonstrated by the decrease in adjusted prevalence ratios with increase in age shown in Figure 3 and Table 5 (p-value of trend <0.001 at each time point). In the oldest age group (90+ years), the adjusted prevalence ratios observed were never higher than 0.65 and 0.28 for exposure to HF drug therapy and to drug therapy at target doses, respectively.

FIG. 1 Selection of the study population

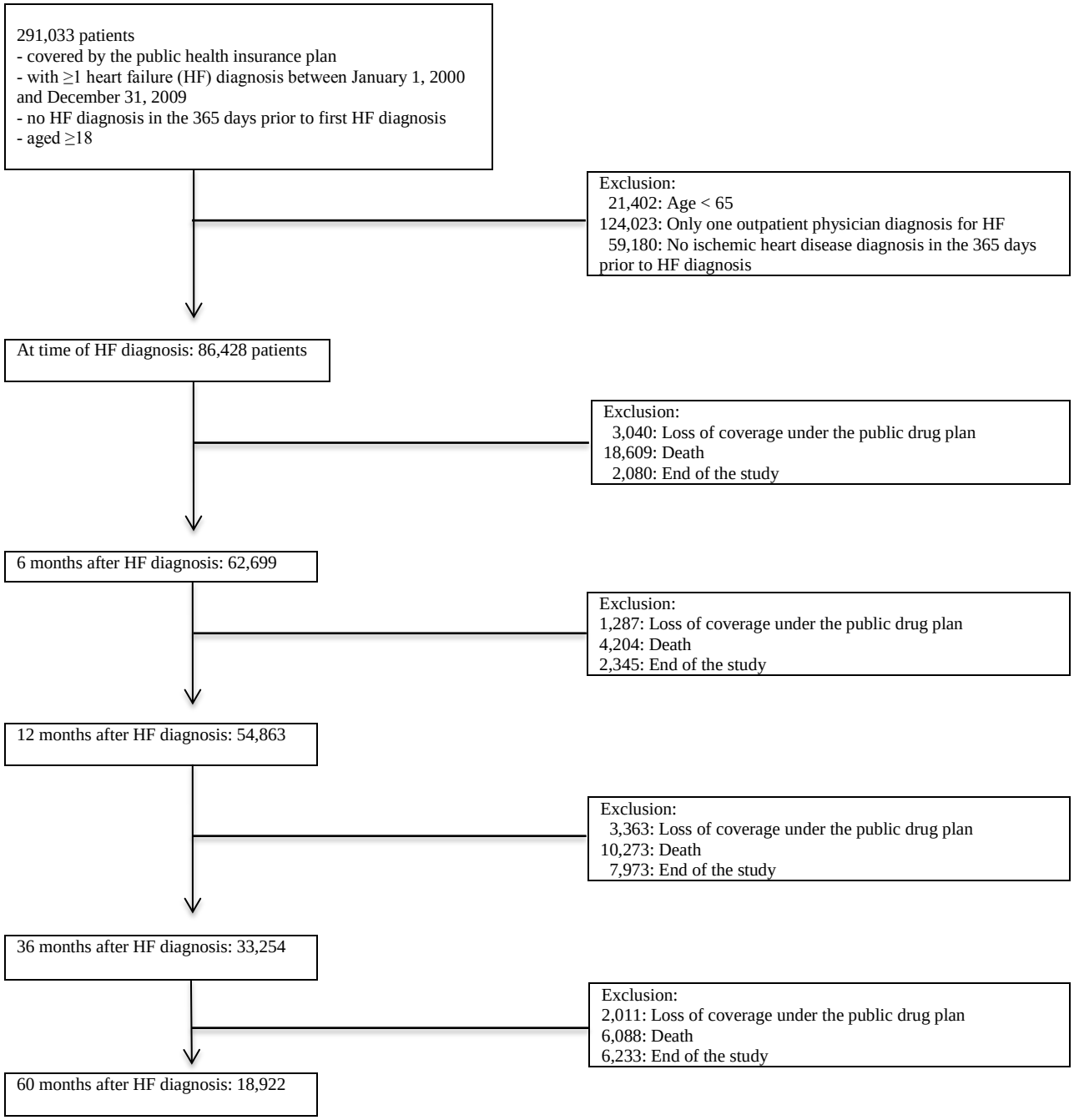

FIG. 2 Proportion of seniors exposed to evidence based heart failure (HF) drug therapy and to drug therapy at target doses at HF diagnosis and 6, 12, 36 and 60 months after HF diagnosis according to age.

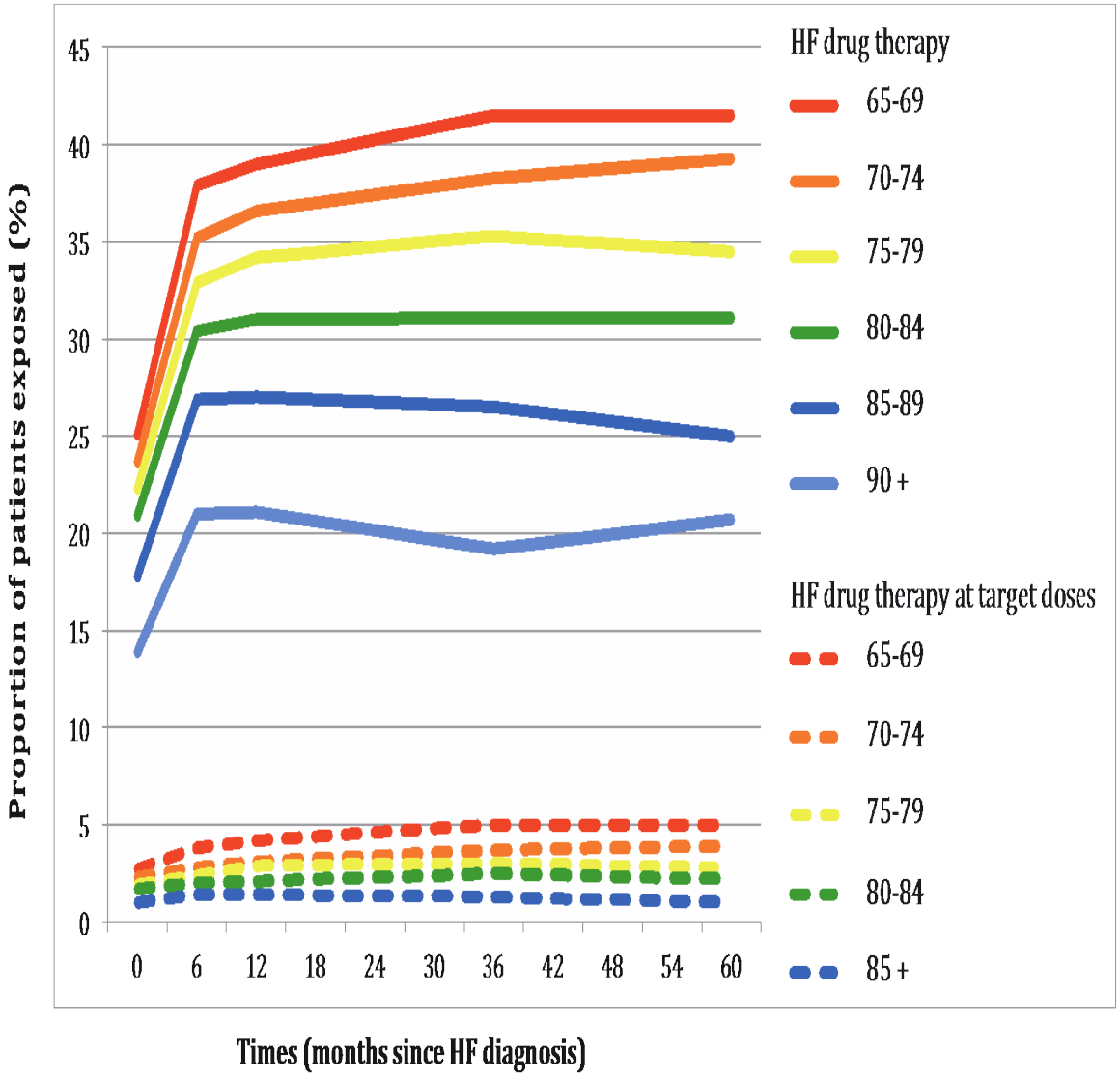

TABLE 2 Baseline characteristics of the 86,428 patients aged 65+ years newly diagnosed for heart failure and with history of ischemic heart disease

Characteristics	N	%
Age mean (standard deviation)	79.4	(7.7)
Age		
65-69 years	10,591	12.3
70-74 years	15,987	18.5
75-79 years	20,030	23.2
80-84 years	19,184	22.2
85-89 years	13,460	15.6
≥ 90 years	7,176	8.3
Sex		
Male	42,397	49.1
Female	44,031	50.9
Socio-economic status		
No Guaranteed Income Supplement (GIS)	35,264	40.8
Partial GIS	43,612	50.5
Welfare or maximum GIS	7,552	8.7
Calendar year at heart failure diagnosis		
2000	14,156	16.4
2001	12,064	14.0
2002	9,699	11.2
2003	8,568	9.9
2004	8,281	9.6
2005	7,380	8.5
2006	6,851	7.9
2007	6,748	7.8
2008	6,694	7.8
2009	5,987	6.9
Hospitalization at time of heart failure diagnosis		
Yes	64,246	74.3
No	22,182	25.7
Specialty of the physician who diagnosed heart failure		
Cardiologist	37,510	43.4
Internist	12,499	14.5
General practitioner	30,779	35.6
Geriatrician	564	0.7
Other	5,076	5.9

TABLE 3 Use of health services and observed comorbidities during the 365-day period before the initial heart failure diagnosis (baseline) plus the interval up to each of the particular time points (at 6, 12, 36, and 60 months post-heart failure diagnosis)

TIME POINTS

	Baseline		6th month		12th month		36th month		60th month	
Characteristics	(N=86,428)		(N= 62,699)		(N= 54,863)		(N= 33,254)		(N= 18,922)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Health services										
No of days of hospitalization (median (25-75 percentile))	8	(1-19)	15	(6-26)	17	(7-30)	23	(10-41)	28	(12-58)
Medical consultations (median (25-75 percentile))	12	(6-21)	22	(13-29)	27	(16-36)	45	(27-60)	62	(38-97)
Seen by:										
Cardiologist	41,147	47.6	41,115	65.6	37,828	69.0	25,160	75.7	15,167	80.2
Internist	22,166	25.7	22,430	35.8	21,436	39.1	15,756	47.4	10,026	53.0
Geriatrician	1,254	1.5	1,321	2.1	1,345	2.5	1,032	3.1	669	3.5
General practitioner	74,356	86.0	57,795	92.2	51,477	93.8	32,146	96.7	18,550	98.0
No of drugs used from different ATC classes (excluding cardiovascular drug) (mean (SD))	5.9	3.3	7.8	3.5	8.4	3.6	10.3	4.2	11.4	4.5
Comorbidities										
Acute renal failure	4,375	5.1	9,949	15.9	9,472	17.3	6,767	20.4	4,215	22.3
Aortic stenosis	4,694	5.4	6,961	11.1	6,475	11.8	4,652	14.0	2,942	15.6
Hypertension	41,361	47.9	46,458	74.1	42,628	77.7	28,187	84.8	16,737	88.5
Asthma	5,994	6.9	7,059	11.3	7,053	12.9	5,662	17.0	3,863	20.4
Atrial fibrillation	19,444	22.5	23,839	38.0	21,886	39.9	14,493	43.6	8,756	46.3
CVD	11,043	12.8	12,332	19.7	11,963	21.8	9,212	27.7	6,046	32.0
CKD	12,164	14.1	18,136	28.9	16,922	30.8	11,609	34.9	7,123	37.6
COPD	19,295	22.3	21,584	34.4	20,558	37.5	15,164	45.6	9,492	50.2
Conduction disorder without a pacemaker	2,221	2.6	4,616	7.4	4,605	8.4	3,678	11.1	2,359	12.5
Dementia	3,997	4.6	4,172	6.7	3,884	7.1	2,721	8.2	1,763	9.3
Diabetes	27,579	31.9	23,475	37.4	21,176	38.6	13,939	41.9	8,359	44.2
Hepatic failure	820	1.0	1,113	1.8	1,043	1.9	744	2.2	454	2.4
Hyperkalemia	839	1.0	1,788	2.9	1,777	3.2	1,419	4.3	920	4.9
Mitral stenosis	755	0.9	1,075	1.7	1,083	2.0	893	2.7	593	3.1
Non-skin neoplasia	15,735	18.2	12,812	20.4	12,029	21.9	8,941	26.9	5,903	31.2
Orthostatic hypotension	1,131	1.3	1,993	3.2	2,082	3.8	1,787	5.4	1,278	6.8
PAD	11,851	13.7	15,650	25.0	14,973	27.3	11,033	33.2	6,898	36.5

ATC, anatomical therapeutic chemical classification system; CKD, chronic kidney disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; IQ, interquartile range; PAD, peripheral atherosclerotic disease; SD, standard deviation.

TABLE 4 Influence of the passage of time (by 6-month intervals after heart failure diagnosis) on prevalence ratios of exposure to heart failure drug therapy and drug therapy at target doses over the 60 month-period following heart failure diagnosis, according to age

Age Group	Heart failure drug therapy			Heart failure drug therapy at target doses		
	uPR	aPR	95% CI	uPR	aPR	95% CI
65-69	1.04	1.05	(1.05-1.06)	1.05	1.07	(1.05-1.09)
70-74	1.04	1.06	(1.05-1.06)	1.05	1.07	(1.06-1.09)
75-79	1.04	1.06	(1.05-1.06)	1.04	1.06	(1.04-1.08)
80-84	1.03	1.06	(1.05-1.06)	1.04	1.07	(1.05-1.10)
85-89	1.03	1.06	(1.05-1.07)	1.04	1.06	(1.03-1.10)
90+[*]	1.05	1.08	(1.06-1.09)			

uPR, unadjusted prevalence ratio; aPR, adjusted prevalence ratio. *When the number of individuals aged 90+ was too small to carry out the analysis, patients were merged with the 85-89 age group. Adjusted for variables at baseline: sex, socio-economic status, calendar year at heart failure (HF) diagnosis, hospitalization at time of HF diagnosis, specialty of the physician who made the HF diagnosis. We also adjusted for variables measured in the period between 365 days before HF diagnosis and the date of measurement: number of days of hospitalization, number of medical consultations, specialty of the physician seen, number of different medications from different classes of the ATC classification and comorbidities (acute renal failure, aortic stenosis, arterial hypertension, asthma, atrial fibrillation or flutter, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, conduction disorder without a pacemaker, dementia, diabetes, hepatic failure, hyperkalemia, mitral stenosis, non-skin neoplasia, orthostatic hypotension and peripheral atherosclerotic disease)

TABLE 5 Prevalence ratios of exposure to heart failure drug therapy and to drug therapy at target doses, according to age

	Heart failure drug therapy					Heart failure drug therapy at target doses				
	Prevalence (%)	uPR	aPR	95% CI	p-value of trend	Prevalence (%)	uPR	aPR	95% CI	p-value of trend
Baseline	**(N=86,428)**									
65-69	18.9	1.00	1.00	(Ref)		2.3	1.00	1.00	(Ref)	
70-74	18.3	0.97	0.98	(0.94-1.02)		1.9	0.82	0.83	(0.73-0.94)	
75-79	17.2	0.91	0.92	(0.89-0.96)		1.7	0.76	0.74	(0.65-0.84)	
80-84	16.2	0.86	0.88	(0.85-0.91)		1.4	0.62	0.61	(0.53-0.69)	
85-89	13.7	0.73	0.78	(0.75-0.82)		0.9	0.41	0.42	(0.36-0.50)	
90+	10.2	0.54	0.62	(0.59-0.66)	<0.001	0.4	0.19	0.20	(0.15-0.27)	<0.001
6 month	**(N=62,699)**									
65-69	32.6	1.00	1.00	(Ref)		3.3	1.00	1.00	(Ref)	
70-74	30.6	0.94	0.97	(0.94-0.99)		2.6	0.77	0.78	(0.69-0.88)	
75-79	28.1	0.86	0.91	(0.89-0.94)		2.3	0.68	0.69	(0.61-0.77)	
80-84	25.6	0.78	0.86	(0.83-0.89)		1.7	0.51	0.52	(0.46-0.60)	
85-89	22.4	0.68	0.78	(0.76-0.81)		1.3	0.39	0.41	(0.34-0.49)	
90+	17.0	0.52	0.64	(0.60-0.67)	<0.001	0.7	0.21	0.24	(0.18-0.32)	<0.001
12 month	**(N=54,863)**									
65-69	33.8	1.00	1.00	(Ref)		3.8	1.00	1.00	(Ref)	
70-74	31.8	0.94	0.97	(0.94-0.99)		2.9	0.77	0.78	(0.69-0.88)	
75-79	29.3	0.87	0.92	(0.89-0.95)		2.7	0.71	0.71	(0.63-0.80)	
80-84	26.2	0.77	0.85	(0.82-0.88)		1.9	0.49	0.50	(0.44-0.58)	
85-89	22.8	0.67	0.77	(0.74-0.80)		1.3	0.35	0.37	(0.31-0.44)	
90+	17.5	0.52	0.63	(0.59-0.67)	<0.001	0.6	0.16	0.18	(0.13-0.26)	<0.001
36 month	**(N=33,254)**									
65-69	36.9	1.00	1.00	(Ref)		4.7	1.00	1.00	(Ref)	
70-74	33.9	0.92	0.94	(0.91-0.97)		3.4	0.73	0.74	(0.65-0.84)	
75-79	30.9	0.84	0.89	(0.85-0.92)		2.7	0.58	0.60	(0.52-0.69)	
80-84	26.7	0.72	0.80	(0.76-0.83)		2.1	0.45	0.47	(0.40-0.55)	
85-89	22.6	0.61	0.70	(0.67-0.74)		1.0	0.22	0.25	(0.19-0.31)	
90+[a]	16.6	0.45	0.56	(0.50-0.61)	<0.001					<0.001
60 month	**(N=18,922)**									
65-69	37.0	1.00	1.00	(Ref)		4.8	1.00	1.00	(Ref)	
70-74	35.0	0.95	0.96	(0.92-1.00)		3.8	0.78	0.78	(0.66-0.91)	
75-79	30.6	0.83	0.87	(0.83-0.91)		2.8	0.58	0.58	(0.49-0.70)	
80-84	26.9	0.73	0.80	(0.75-0.84)		1.9	0.40	0.40	(0.32-0.51)	
85-89	21.6	0.58	0.68	(0.62-0.73)		0.8	0.17	0.19	(0.12-0.28)	
90+[*]	15.8	0.43	0.53	(0.44-0.63)	<0.001					<0.001

aPR, adjusted prevalence ratio; uPR, unadjusted prevalence ratio.*When the number of individuals aged ≥90 was too small to carry out the analysis, patients were merged with the 85-89 age group. Adjusted for variables at baseline: sex, socio-economic status, calendar year at heart failure (HF) diagnosis, hospitalization at time of HF diagnosis, specialty of the physician who made the HF diagnosis. We also adjusted for variables measured in the period between 365 days before 1st HF diagnosis and the date of measurement: number of days of hospitalization, medical consultation, specialty of the physician seen, number of different medications from different classes of the Anatomic Therapeutic Chemical classification and comorbidities (acute renal failure, aortic stenosis, arterial hypertension, asthma, atrial fibrillation or flutter, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, conduction disorder without a pacemaker, dementia, diabetes, hepatic failure, hyperkalemia, mitral stenosis, non-skin neoplasia, orthostatic hypotension and peripheral atherosclerotic disease).

DISCUSSION

Two main findings emerged from this study: prevalence of exposure to HF drug therapy is low across all age groups among seniors and even lower when target doses were considered. Plus, as seniors with HF age, they are less likely to be exposed to HF drug therapy.

This study is the first one to look at exposure to HF drug therapy for a long period of time. Some studies[12-14] have noted underexposure of HF patients to drugs that are part of the HF drug therapy. However, we observed a greater extent of underexposure than previously reported. For example, in 2001-2002, Cox et al[12] looked at seniors' exposure to HF drugs in the 30-day period following hospital discharge. The proportion of patients exposed to a β-blocker, an ACEi and an ARB was 32%, 54% and 7%, respectively.[12] DiMartino et al[13] observed that between 2000 and 2004, 35% and 43% of seniors with HF, were exposed at least once to a β-blocker and an ACEi, respectively, over one year. Compared to these two studies, the smaller proportion of exposed patients in our study is probably a result of our examining exposure to a combination of at least two drugs (the HF drug therapy) rather than single drugs taken separately. Conversely, Kim et al[14], in a study looking at exposure to a treatment consisting of an ACEi/ARB combined with a β-blocker in a population of seniors hospitalized for HF, observed that 21.7% had been exposed to the combination at least once after hospitalization. Unlike our study where exposure was assessed at different intervals of time post-HF diagnosis, Kim et al looked at exposure at no particular time interval. Moreover in their study, there was no attempt to study the effect of age on exposure to the drug combination. Finally, in our study, we found that 95% of the patients were not exposed to target doses. This finding suggests that physicians might assume that their older patients will not tolerate target doses, despite the fact that recommended doses for elderly patients are the same as for younger patients. Moreover, some studies[21,22] have shown that patients aged 70 and over can very well tolerate drugs part of the HF drug therapy and therefore benefit, just like younger patients, of increased dose. [23-25]

The association we observed between increasing age and underexposure to evidence-based treatment is in keeping with what others report. Komajda et al noted a decrease in exposure to a β-blocker/ACEi combination as age increases.[10] They observed that the proportion of seniors exposed to both a β-blocker and an ACEi at any time post-HF diagnosis was 13.6% for octogenarians, whereas it was 27% for younger patients (mean: 69 years old). When target doses of each single drug were considered, the proportion of octogenarians exposed was also lower than that of younger seniors, both for ACEi (13% vs. 26%) and β-blocker (5% vs. 11%). However, Komadja et al did not take into account other patient characteristics with potential to influence exposure to drug treatment, such as co-morbidities and contraindications to drugs forming part of the evidence-based drug treatment. On the other hand, in our study, we adjusted for the many factors (comorbidities, socio-demographic factors, health care services used) that could have accounted for a lesser probability of exposure in the oldest age group and we observed an inverse association between increasing age and the likelihood of being exposed to HF drug therapy.

We found that the likelihood of being exposed to the HF drug therapy and to drug therapy at target doses improves slightly with time post-HF diagnosis. Although small in magnitude, this improvement could be of clinical importance. It shows that if, within the first 6 months post-diagnosis, patients have not been exposed to the HF drug therapy or to the drug therapy at target doses, they are not very likely to be exposed later on. Exposure to HF drug has never been assessed over as long a time period as in our study; although, some studies have looked at exposure to individual HF drugs for periods up to 2 years[26,27]. Smith et al[26] measured exposure to a β-blocker before and after HF diagnosis in a population aged 65+. They noted a small increase in the proportion of patients exposed to a β-blocker post-HF diagnosis (23% before vs. 28% post-HF diagnosis) but, age had no influence on exposure

to a β-blocker. Patel et al[27] did not observe improvement in β-blocker doses towards the target dose over a 2-year follow-up period as mean doses were not statistically different than the doses used at initial hospital discharge.

Our study has some limitations inherent in the use of administrative databases. We assumed patients were exposed to drugs they obtained. Consequently, we may have overestimated the proportion of patients exposed. On the other hand, we may have underestimated the proportion of patients appropriately exposed to the evidence-based HF treatment as non-exposure of some patients to the HF drug therapy, for reasons such as HF patients with preserved left ventricular ejection fraction (HFpEF) or a contraindication for at least one of the drug part of the HF drug therapy, may have been appropriate. Since administrative databases do not capture the requisite clinical data, assessing such situations was not possible. Therefore, we were unable to disentangle patients with HFpEF from those with decreased left ventricle ejection fraction. As randomized control trials currently show no evidence that HFpEF benefit from the HF drug therapy, some patients might be appropriately not exposed to the HF drug therapy. Prevalence of HFpEF is estimated to vary between 34%[28] and 55%[29] in population aged 65+, the prevalence increasing with age. Although all patients in our study had both HF and IHD and therefore should have been exposed to a β-blocker and an ACEi or ARB, we cannot rule out the fact that HFpEF may have confounded the association we observed between aging and non-exposure to the evidence-based HF drug treatment. Also, in our study all patients had a prior diagnosis of IHD. Since IHD is an indication for exposure to a β-blocker (if HF is present) and to an ACEi/ARB[7], we may assume that these patients are more likely to be exposed to HF drug therapy than those with HF but without IHD. Thus, the presence of HFpEF cannot fully explain the inverse association we observed between exposure to treatment and age. Finally, for a patient to be considered exposed to the evidence-based drug treatment at target doses, all drugs had to be used at the minimum target doses. This rather stringent criterion may explain the very low prevalence of patients treated at target doses we observed.

This study is the first in which exposure to HF drug therapy in an elderly population is assessed over such a long period of time and taking into account drug doses. Since 97% of the Quebec population aged 65 years and older is covered by RAMQ's drug plan[30], this study is population-based and highly generalizable. Using administrative data allowed us to look at a large population in current clinical practice at specific time points. It also enabled us to look at evidence-based treatments rather than individual drugs only. It was also possible to classify patients within 5-year categories thereby allowing the assessment of age as a gradient.

The low exposure of senior HF patients to drug therapy and the very low exposure to HF therapy at target doses should alert practitioners involved in the care of seniors with HF. As age alone is no contraindication for exposure to HF drug therapy, these findings might help clinicians to improve their clinical practice. Further research is needed to better understand why according to our findings, some patients appear to be denied treatment on the basis of older age alone.

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