

Effect of contraindicated drugs for heart failure on hospitalization among seniors with heart failure

A nested case-control study

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Abstract

Little is known about the effect of nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones (TZDs), nifedipine and nondihydropyridine calcium channel blockers (CCBs) usage on the risk of all-cause hospitalization among seniors with heart failure (HF). We assessed the risk of all-cause hospitalization associated with exposure to each of these drug classes, in a population of seniors with HF.

Using the Quebec provincial databases, we conducted a nested case-control study in a population of individuals aged ≥ 65 with a first HF diagnosis between 2000 and 2009. Patients were considered users of a potentially inappropriate drug class if their date of hospital admission occurred in the interval between the date of the last drug claim and the end date of its days' supply. The risks of hospitalization were estimated using multivariate conditional logistic regression.

Of the 128,853 individuals included in the study population, 101,273 (78.6%) were hospitalized. When compared to nonusers, users of NSAIDs (adjusted odds ratio: 1.16; 95% confidence interval: 1.13–1.20), TZD (1.09; 1.04–1.14), and CCBs (1.03; 1.01–1.05) had an increased risk of all-cause hospitalization, but not the users of nifedipine (1.00; 0.97–1.03).

Seniors with HF exposed to a potentially inappropriate drug class are at increased risk of worse health outcomes. Treatment alternatives should be considered, as they are available.

Abbreviations: ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor antagonists, CCBs = calcium channel blockers, COX = cyclooxygenase, HF = heart failure, HFpEF = heart failure patients with preserved ejection fraction, ICD-9 = International Classification of Diseases, Ninth Revision, NSAIDs = nonsteroidal anti-inflammatory drugs, RAMQ = Quebec Health Insurance Board, TZDs = thiazolidinediones.

Keywords: heart failure, hospitalization, potentially inappropriate treatment, risk, seniors

1. Introduction

Heart failure (HF) is a major health issue, especially among seniors. In fact, annual incidence of HF after age 65 is around 10/

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1000 person-years.^[1] Clinical guidelines^[2–4] recommend that patients with HF be exposed to drugs that reduce mortality and the need for hospitalization (bisoprolol, carvedilol, or metoprolol and angiotensin converting enzyme inhibitors [ACEI] or angiotensin receptor antagonists [ARB]). However, patients should also not be exposed to drugs that can cause fluid retention or decrease cardiac function, that is, nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones (TZD) nifedipine and nondihydropyridine calcium channel blockers (CCBs).

Among HF patients aged ≥ 65 , almost 50% depicts ≥ 5 comorbidities,^[5,6] up to 21% are clinically frail^[7] and almost 45% take ≥ 9 drugs.^[8] Thus, elderly HF patients are at great risk of exposure to potentially inappropriate treatment while also being at risk of worse health outcomes if exposed.

The risk of adverse outcomes such as hospitalization due to contraindicated drug exposure is not well defined among HF patients, particularly seniors. Indeed, the adverse effects of exposure to nondihydropyridine CCBs on hospitalization in patients with HF come from studies in patients who had a myocardial infarction.^[9,10] Previous studies on the effects of potentially inappropriate drugs in patients with HF, took place either when the β -blockers and ACEI were not yet standard therapy for HF, with respect to exposure to nifedipine,^[11] or as a secondary objective, in the case of the effect of TZDs on hospitalizations.^[12] One study looked at the effect of exposure to NSAIDs on hospitalization and mortality among patients with HF.^[13] The authors observed that an exposure to NSAIDs was associated with an increased risk of hospitalization for HF or

myocardial infarction. However, the risk of hospitalization for any cause, among elderly patients with multiple comorbidities, was never assessed. To help clinicians to better weigh the risks associated with potentially inappropriate drugs in HF, we designed a study in a population of individuals aged ≥ 65 , to determine the effect of exposure to NSAIDs, TZDs, nifedipine or nondihydropyridine CCBs on all-cause hospitalization after the first HF diagnosis.

2. Methods

2.1. Study design and data sources

We conducted a nested case-control study using the databases of the Quebec Health Insurance Board (RAMQ), the *Institut de la statistique du Québec* (death registry), and the Quebec Registry of Hospitalizations. These databases include information on patient demographics, vital status, in-hospital and outpatient medical diagnoses, and the medical services used by all permanent residents of Quebec province. The RAMQ drug plan database contains information on prescription drugs for Quebec residents not covered by a private drug insurance group plan, welfare recipients and all seniors, except those living in long-term care facilities.

2.2. Source population

To assemble our source population many steps were done. First, RAMQ identify all Quebec residents covered by the public health insurance plan, who had at least 1 registered HF diagnosis in the outpatient medical visits database or the hospitalizations' registry (ICD-9 code: 428; ICD-10 code: I50) from January 1, 2000, to December 31, 2009. From this group of people, RAMQ removed all those aged under 18 at their first HF diagnosis plus those not continuously eligible for Quebec's public drug insurance plan in the 365-day period before the first HF diagnosis and those who had a previous HF diagnosis during the same time period. The RAMQ provided all data registered in the databases until December 31, 2009, death or end of drug plan eligibility for each of them.

Second, we excluded all individuals who had only 1 HF diagnosis registered in the outpatient medical visits database.^[14] In cases of more than 1 HF diagnosis, the date of the first HF diagnosis became the HF diagnosis baseline date. Next, we excluded everyone < 65 years at HF diagnosis, all individuals who died on the same date as their HF diagnosis or who died during the hospital stay in which HF was diagnosed, and all individuals without follow-up. For individuals whose HF was diagnosed in hospital, the discharge date became the diagnosis date. We followed individuals until study end (31 December 2009), loss of eligibility for the public drug plan, or death.

2.3. Cases and controls selection

We created a set of cases by identifying all individuals hospitalized during the follow-up. A hospitalization was defined as a stay longer than 1 day in an acute care hospital. The first day of the first hospitalization constitutes the event date. For each case, we randomly paired 4 to 10 controls using incidence density sampling. Incidence density sampling assures that the observation period (i.e. the time period between HF diagnosis [included] and event date [excluded]) is identical for a given case and its controls.^[15] Controls and cases were matched according to age group, sex, calendar year at time of HF diagnosis, record of an ischemic heart disease, and record of a diabetes diagnosis in the

365 days prior the HF diagnosis. The event date for controls was the date when the matched case was hospitalized.

2.4. Independent variable: exposure to a potentially inappropriate drug

For each of the potentially inappropriate drug class examined (NSAIDs [COX-2 selective inhibitors: celecoxib and rofecoxib; nonselective NSAIDs: diclofenac, ibuprofen, naproxen, and other (diflunisal, indomethacin, ketoprofen, meloxicam, piroxicam, tenoxicam, and sulindac)], TZD [pioglitazone and rosiglitazone], nifedipine and nondihydropyridines CCB [verapamil and diltiazem]), we classified patients as user or nonuser. Among dihydropyridine CCBs, only nifedipine was considered as there is evidence of contra-indications in heart failure only for that drug.^[16] We searched for a claim for a contra-indicated drug class in the 365 days before HF diagnosis and between HF diagnosis and the event date. We selected the claim closest to the event date and then determined the exposure time period by adding 1.5 times the number of days' supply to this last claim date. If the event date occurred in the exposure time period, we deemed the patient as being a user. We repeated the process for each medication class.

2.5. Potentially confounding variables

We considered many variables as potential confounders. To determine each patient's frailty, we used an evaluation based on the accumulation of deficits model.^[17,18] According to this model, frailty results from the additive effect of deficits and not just the presence of certain types of deficits.^[17,18] We considered 47 deficits comprising 11 different anatomical systems.^[19] To determine the number of deficits each patient had, we searched the outpatient medical services database and the hospitalizations' registry for a diagnosis of any of the 47 selected deficits in the 365 days before HF diagnosis. To calculate the frailty index value, we divided the number of deficits found for a patient by the maximum number of possible deficits.

We checked claims for an echocardiograph or for a pacemaker installation in the 365 days before HF diagnosis. We also looked for any recorded diagnosis for chronic kidney disease, high blood pressure, atrial fibrillation, chronic obstructive pulmonary disease/asthma, stroke, and peripheral atherosclerotic disease in the same time period. We also explored medical services used in the 365-day period up to the day of HF diagnosis, examining both the number of days of hospitalization and the number of outpatient medical consultations ($<$ median or \geq median). If the HF diagnosis was made during a hospitalization, we excluded this period from the calculation. At the time of HF diagnosis, we checked for the specialty of the diagnosing physician and the number of days of hospitalization (or 0 days if the patient was not hospitalized at that time). During the observation period, we looked for: (1) installation of a pacemaker, (2) an internal cardiac defibrillator or cardiac resynchronization device, (3) presence of medical consultation with a cardiologist, general practitioner, or other medical consultations, and (4) exposure to other cardiovascular medications (amiodarone, class I antiarrhythmic, diuretics, spironolactone, digitalis, β -blocker, ACEI/ARBs, antiplatelets, warfarin, and nitrates).

2.6. Statistical analysis

Means, medians, and proportions described the characteristics of cases and controls. To assess the association between exposure to

potentially inappropriate treatment and hospitalization, we performed a multivariate conditional logistic regression that included variables of exposure at time of event date for each medication part of the potentially inappropriate treatment (nonusers being the reference) and all the potential confounding variables. Since NSAIDs, as a class, include a large number of medications with different mechanisms of action,^[13,20] we conducted another analysis to look at the effect of exposure to COX-2 selective inhibitors (celecoxib and rofecoxib), ibuprofen, diclofenac, and other NSAIDs on the risk of hospitalization. To test the sensitivity of the results to the length of the grace period used in defining users, we repeated the analysis using on one hand, no grace period, and on the other hand, a grace period equals to the number of days' medication supply. Analyses were done using S.A.S. version 9.3 (SAS Institute Inc., Cary, NC).

2.7. Ethical considerations

The Commission d'accès à l'information du Québec and the Research Ethics Committee of the CHU de Québec—Université Laval approved this study.

3. Results

RAMQ identified 291,033 people who had a first HF diagnosis in the medical services database or the hospitalizations' registry in our recruitment period, who were aged ≥ 18 and who were continuously eligible for Quebec's public drug insurance plan in the 365-day period before the first HF diagnosis. Among them, we excluded 21,402 people aged < 65 years, 124,023 who had only 1 outpatient HF diagnosis, 10,651 who died the same date their HF was diagnosed or died during the hospital stay in which HF was diagnosed and 6104 who had no follow-up. As a consequence, our source population comprised 128,853 individuals. Among them, 101,412 (78.7%) were hospitalized at least once during follow-up. The main cause of hospitalization for 16,070 patients (15.9%) was HF. For 22,267 (22.0%), it was cardiovascular causes other than HF and 63,075 (62.2%) patients were hospitalized for other causes. Median time between HF diagnosis and hospitalization was 105 days (16–422 days).

Table 1 shows the characteristics of cases and their controls. Mean length of exposure ranged from 2.5 months for NSAIDs to 8.7 months for nondihydropyridine CCBs. Users of NSAIDs, TZD, and nondihydropyridine CCBs had a statistically significant increased risk of hospitalization, whereas the risk among nifedipine users was not increased (Figs. 1 and 2). Also, among NSAIDs users, 53% were using COX-2 selective inhibitors, 17% diclofenac, 13% naproxen, 3% ibuprofen, and 14% other NSAIDs. Increased risk of all-cause hospitalization was similar among all type of NSAIDs, except for ibuprofen, which was associated with a nonstatistically significant increased risk in multivariate analysis (Fig. 1). Results were not sensitive to changes in the definition for users of drugs (data not shown).

4. Discussion

In this large population-based study of seniors with HF, we found an increased risk of hospitalization among those exposed to contraindicated NSAIDs, TZD, and nondihydropyridines CCBs.

Individuals exposed to NSAIDs had a 16% greater risk of hospitalization than those who were not exposed to these drugs.

In addition to their anti-inflammatory effects, NSAIDs are known to increase gastrointestinal bleeding risk,^[21] increase risk of cardiovascular event,^[22,23] and increase risk of developing HF. However, only Gislason et al^[13] evaluated the risks of hospitalization associated with the use of NSAIDs among patients suffering from HF. In their cohort of patients aged ≥ 30 , the risks of hospitalizations for HF and acute myocardial infarction ranged from 1.16 to 1.40 and 1.30 to 1.52, respectively. These risks of hospitalization are comparable to the risk of all-cause hospitalization observed in our cohort. Also, in accordance with our data, they found increased risk to be consistent among all NSAIDs. This result suggests that patients with HF who need an NSAID should be switched to an alternative treatment. For example, patients suffering from osteoarthritis can benefit from physiotherapy^[24] and when a pharmacological treatment is needed, the American Geriatric Society recommends using opioids among seniors instead of NSAIDs, given the increased risk of adverse effects from this class of molecules.^[25]

Secondly, we found an increased risk of hospitalization among patients exposed to TZD. Since studies among patients with diabetes have reported evidence of early plasma volume expansion after TZD initiation (8 to 12 weeks),^[26,27] it is likely that patients with HF also display signs of early stage volume overload and must be hospitalized. Some studies have looked at the risk of developing HF among patients with diabetes.^[28,29] Only Masoudi et al^[12] looked at the risk of exposure to TZD among patients with diabetes with HF. They observed a nonstatistically significant increase in HF and all-cause mortality among patients exposed to a TZD after a hospitalization for HF. Since hospitalization was a secondary outcome, they may have lacked the power to detect any significant increase in the risk of hospitalization.

Next, we found no statistically significant increase in the risk of all-cause hospitalization among individuals exposed to nifedipine. Nifedipine reduces systemic vascular resistance and has a neurohumoral effect and a negative inotropic and chronotropic effect.^[16,30] Nifedipine, contrary to NSAID and TZD, may be beneficial to HF patients with preserved ejection fraction (HFpEF). In fact, guidelines recommend that blood pressure has to be treated optimally among patients with HFpEF to help relax the ventricle.^[31] Since our population included both HF individuals with decreased and preserved left ventricular ejection fraction, it is possible that the benefit of exposure to nifedipine among HFpEF masked the risk of exposure among those individuals with decreased left ventricular ejection fraction.

Finally, exposure to nondihydropyridine CCBs was associated with an increased risk of hospitalization. Although small in magnitude, this increased risk could be of clinical importance. As nondihydropyridine CCBs have negative chronotropic and inotropic activity, it might explain their effect on increased risk of hospitalization. A study looking at the effect of CCBs after myocardial infarction^[9] found that patients with signs/symptoms of HF who were exposed to CCBs were at increased risk of a cardiovascular event. In addition, since patients exposed to nondihydropyridine CCBs may not have been properly exposed to β -blockers due to the increased risk of severe bradycardia, patients exposed to nondihydropyridine CCBs are at increased risk of adverse outcomes since they cannot benefit from the complete protection conferred by β -blockers.

This study has strengths and limitations that should be considered when interpreting our results. One of the limitations is

Table 1**Characteristics of the study population.**

	Hospitalization (all causes)			
	Cases (hospitalized) (N = 101,273)		Controls (not hospitalized) (N = 1,011,218)	
	N	%	N	%
At time of HF diagnosis				
Age, mean/SD	78.7	7.4	78.7	7.3
65–69	12,524	12.4	125,072	12.4
70–74	18,982	18.7	189,662	18.8
75–79	23,716	23.4	236,937	23.4
80–84	22,659	22.4	226,201	22.4
85+	23,392	23.1	233,346	23.1
Sex*				
Male	46,711	46.1	466,219	46.1
Female	54,562	53.9	544,999	53.9
Calendar year*				
2000	18,042	17.8	180,009	17.8
2001	15,115	14.9	150,829	14.9
2002	11,968	11.8	119,447	11.8
2003	10,621	10.5	106,018	10.5
2004	9932	9.8	99,193	9.8
2005	8882	8.8	88,737	8.8
2006	8131	8.0	81,244	8.0
2007	7481	7.4	74,778	7.4
2008	6635	6.6	66,333	6.6
2009	4466	4.4	44,630	4.4
Specialty of the doctor who made the HF diagnosis				
Cardiologist	35,856	35.4	362,739	35.9
Internal medicine	13,907	13.7	135,458	13.4
General practitioner	44,762	44.2	442,470	43.8
Other	6748	6.7	70,551	7.0
Number of hospitalization days at time of HF diagnosis mean, SD	4.6	10.8	4.8	11.1
In the year before HF diagnosis				
Medical conditions				
Diabetes*	30,547	30.2	304,219	30.1
Ischemic heart disease*	60,338	59.6	602,788	59.6
Chronic kidney disease	19,160	18.9	168,410	16.7
Chronic obstructive pulmonary disease /asthma	31,554	31.2	283,711	28.1
High blood pressure	58,366	57.6	586,425	58.0
Atrial fibrillation	28,096	27.7	278,434	27.5
Stroke	13,281	13.1	126,581	12.5
Peripheral atherosclerotic disease	14,887	14.7	135,351	13.4
Frailty, mean, SD	0.08	0.06	0.08	0.05
Medical services use				
Number of days of hospitalization, median, IQR			–	
≤ 0, median	55,168	54.5	585,037	57.9
> 0, median	46,105	45.5	426,181	42.2
Number of medical consultations, median, SD	–		–	
≤ 10, median	51,347	50.7	547,716	54.2
> 10, median	49,926	49.3	463,502	45.8
Cardiac echography performed	33,898	33.5	346,361	34.3
Presence of a pacemaker	6846	6.8	68,579	6.8
During observation period				
Medical services use				
Pacemaker	4886	4.8	47,136	4.7
Implantable cardioverter-defibrillator	446	0.4	4106	0.4
Cardiologist visit	38,496	38.0	305,552	30.2
General practitioner visit	75,046	74.1	443,093	43.8
Internal medicine visit	21,519	21.3	125,785	12.4
Drug exposure				
Amiodarone	5844	5.8	53,656	5.3
Diuretics	59,836	59.1	604,977	59.8
Spirolactone	6297	6.2	58,699	5.8
Digitalis	16,017	15.8	157,549	15.6
B-blocker	40,795	40.3	438,884	43.4
Class I antiarrhythmic	970	1.0	9000	0.9
ACEi/ARB	51,506	50.9	554,887	54.9
Antiplatelet	47,041	46.5	493,932	48.9
Warfarin	23,470	23.2	233,186	23.1
Nitrates	35,030	34.6	332,734	32.9

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor antagonist, HF = heart failure, IQR = interquartile range, SD = standard deviation.

* Variables used for matching cases and controls.

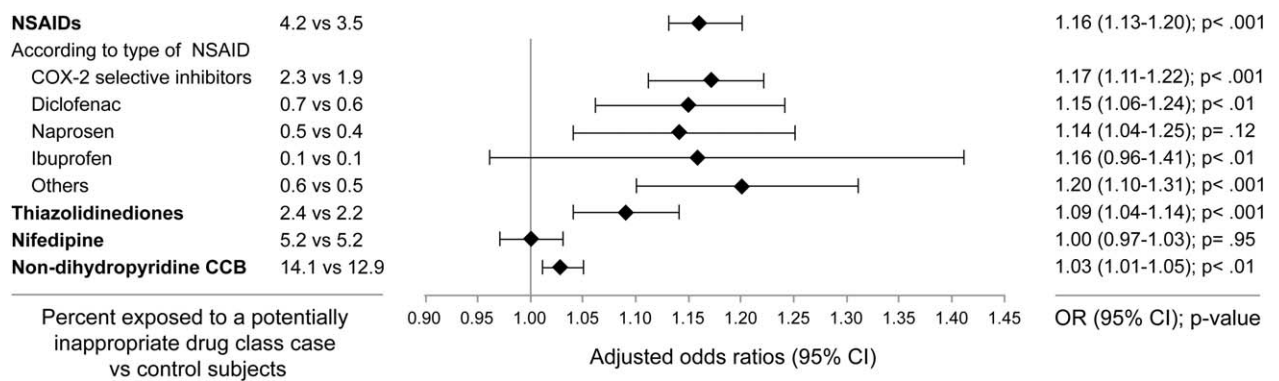


Figure 1. Adjusted associations between current exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones, nifedipine and nondihydropyridines calcium channels blockers (CCB), and all-cause hospitalization. CCB = calcium channels blockers, NSAIDs = nonsteroidal anti-inflammatory drugs.

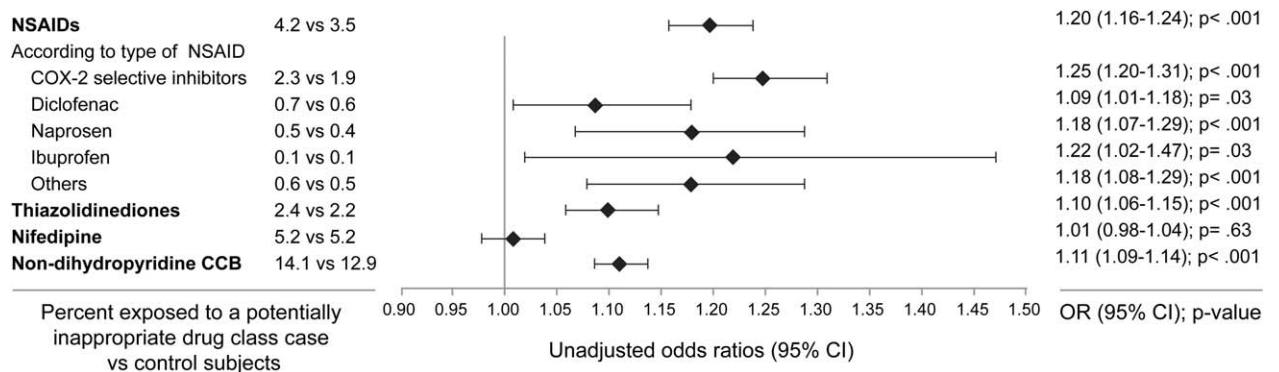


Figure 2. Crude associations between current exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones, nifedipine and nondihydropyridines calcium channels blockers (CCB), and all-cause hospitalization. CCB = calcium channels blockers, NSAIDs = nonsteroidal anti-inflammatory drugs.

that we may have classified some patients as unexposed when they were, in fact, exposed to over-the-counter NSAIDs. We have no information about exposure to those over-the-counter drugs. However, only ibuprofen in small dosages is available over-the-counter in the province of Quebec. This misclassification is likely to be nondifferential and so would result in an underestimation of the risk of hospitalization observed in our study. A further limitation is that, since clinical guidelines^[31] indicate that these drugs are to be used with caution in patients with HF and therefore physicians are aware of the risks for patients in being exposed to these drugs, it is likely that a higher proportion of patients with less severe disease and considered at low risk of hospitalization are being exposed than others.^[32] Another limitation also came from our data source. Since the database does not include echocardiographic data, it is impossible to distinguish between HF patients with decreased and preserved left ventricular ejection fraction. Since nifedipine and non-dihydropyridine CCBs might be of benefit to HFpEF,^[2] the risk of exposure among patients with decreased ejection fraction may have been underestimated.

The study's greatest strength is that it includes all elderly Quebecers with a first HF diagnosis during the study period. These individuals typify "real-world" patients with HF. In addition to this feature, we could access extensive information about medication use.

5. Conclusion

Many seniors with HF have multiple comorbidities and are exposed to numerous medications, some of which being potentially harmful. Clinicians should care about their patient's quality of life. One way to maximize their quality of life is to keep them out of the hospital. We observed that using NSAIDs, TZD and nondihydropyridine CCBs might increase the risk of all-cause hospitalization among HF seniors. Since alternatives do exist for each of these drug classes, potentially inappropriate treatment should not be used.

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