Analytical approaches to minimizing immeasurable time bias in cohort studies

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Background

Large, population-based databases are typically lack information of inpatient medication use which is important for the “real-world effectiveness” assessment of prescription drugs.

It can result in immeasurable time bias.

Hospitalized patients, who are at higher risk of adverse events, are incorrectly classified as unexposed due to the lack of inpatient drug data.

Background

Decrease of the estimate rate of events in exposed group and Increase the rate in unexposed group will bias the hazard ratio(HR) downward.

Previous studies have estimated its magnitudes and examined approaches to minimize the impact. However, there are limitation for inpatients data sources.

Inpatient medication records are available in the database of South Korea due to fee-for-service reimbursement system, accurate exposure ascertainment is allowed.

Objectives of this paper

To describe the magnitude of the immeasurable time bias in a cohort design using a case study of the association between β-blocker use and mortality among patients with heart failure(HF)

To compare the ability of different methodological approaches to minimize this bias.

The case study in this cohort design

P: patients with HF

I: β-blocker used

C: no β-blocker used

O: mortality

Study design:

retrospective population-based cohort

Methods

Data sources:

South Korea's National Health Insurance Service-National Sample Cohort (NHIS-NSC) database between 2002-2013

Study population:

Patients with HF identified by ICD-10: I50, I13, I09.0, I11.0 between 1st Jan 2003 and 31st Dec 2013

Exclusion:

- Pts with β-blocker prescription in the year preceding HF diagnosis

- Previous diagnosed with HF

Methods

Exposure definition : current use of β-blocker

- Using time-varying approach
- Person-time of follow up as ‘exposed’, ‘unexposed’
- In gold standard: inpatient and out-patient

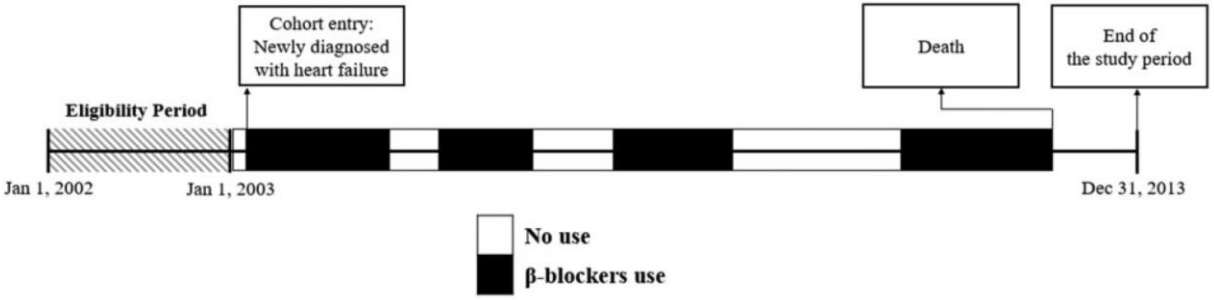


Figure 1. Exposure to β-blockers assessed using a time-varying approach by defining β-blocker prescribed periods as ‘exposed’ and periods with no prescription for β-blockers as ‘unexposed’. All subjects were followed until death or censoring due to the end of the study period (31 December 2013), whichever occurred first.

Methods

Outcome:

- Death from any cause after cohort entry and recorded in the NHIS-NSC database (recorded by physicians in hospitals or police stations)

Methods

How to set cohort

- Date start (index date): date of incident diagnosis of HF
- End date:
  - Date of death
  - Date of end of study (31 Dec 2013)

Potential confounders

Demographic information

- Age, sex, type of health insurance, income level

Comorbidities

- HT, DM, DLP, AF, CAD, CVD, PVD, coronary revascularization, MI , stroke, COPD, chronic liver disease, chronic lung disease

Comedications

- ACEI, ARBs, aldosterone antagonists, CCB, diuretics, nitrates, digoxin, inotropics, amiodarone, hydralazine, Aspirin, lipid lowering agents, antidiabetics, anti-thrombotic medications

  (set as binary variables; 1 if present, 0 if otherwise)

No. of medications(>4, =<4), No. of hospitalization(>2, <=2) in previous yr.

Charlson Comorbidity index

Statistical analysis

Model for analysis:

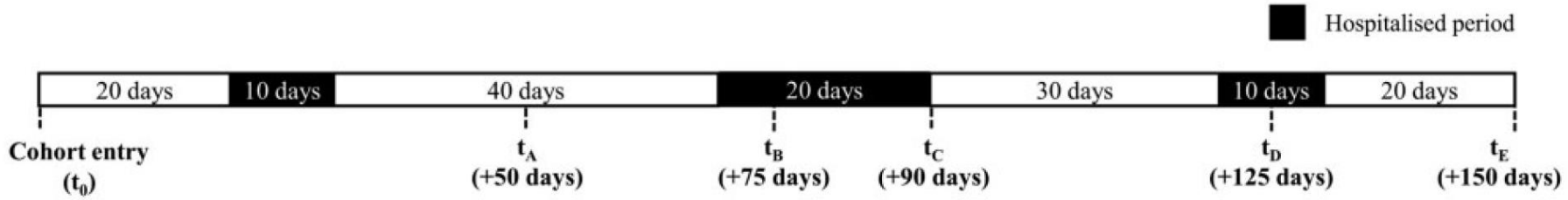
time-dependent Cox proportional hazards models to estimate adjusted HR with 95%CI of all cause-mortality between β-blocker use and no β-blocker use

Data analysis divided into 2 parts:

- Gold standard analysis: include drug data from both in- and outpatient settings
- Restricted analysis with outpatient only

Reduction of immeasurable time bias with 10 methodological approaches

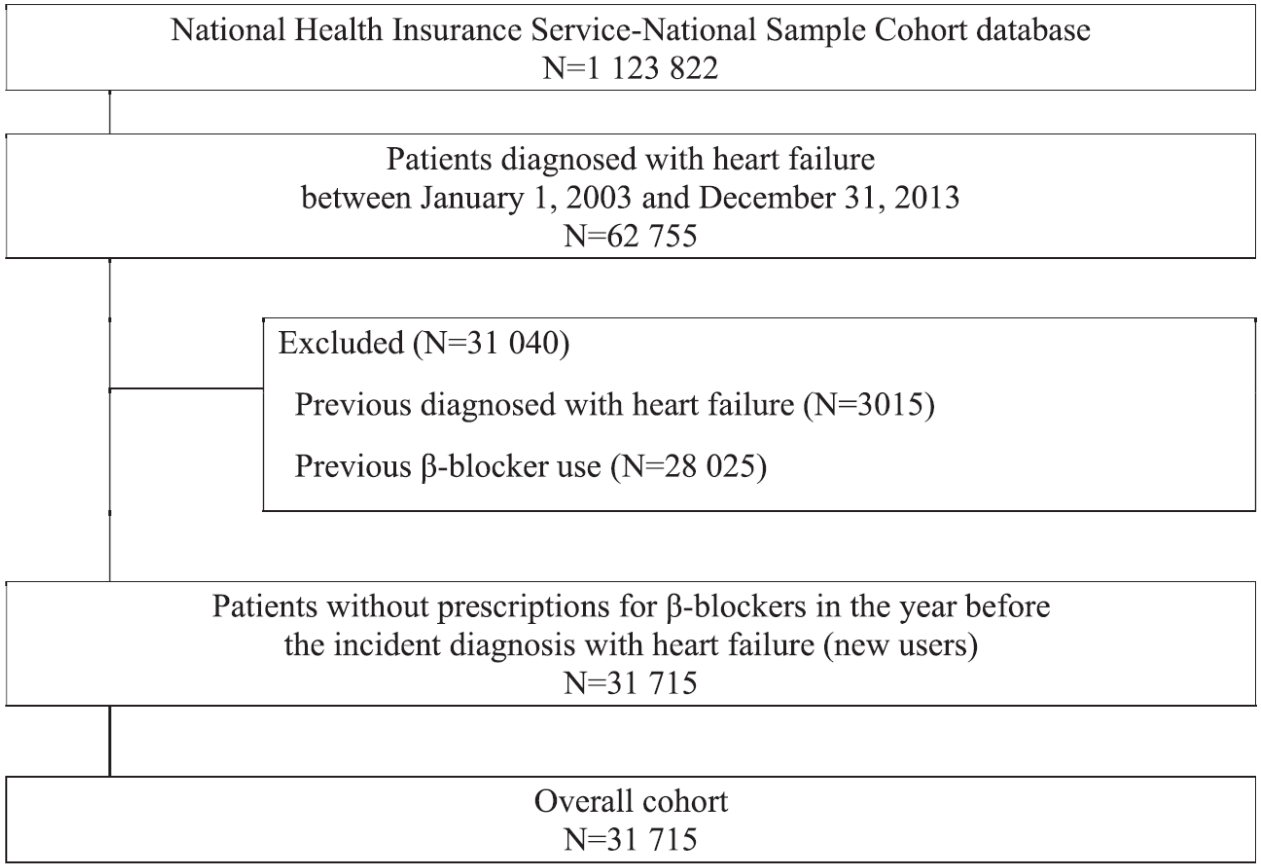
1. Restriction to individuals not hospitalized
2. Restriction to individuals with hospitalization <50%
3. Assuming 'exposed' while hospitalized
4. Adjusted for hospitalization during each pts' follow up as dichotomous time varying variable in multivariate Cox proportional hazards model
5. Adjusted for the number of hospitalization during follow-up
6. Adjusted for proportion of no. of hospitalization (divided by person-yrs)
7. Weighting by the number of hospitalization during follow-up
8. Weighting by proportion of no. of hospitalization (divided by person-yrs)
9., 10. Weighting by proportions of measurable and immeasurable time



Definitions	Values used weighting or adjustment				
	t_A	t_B	t_C	t_D	t_E
Hospitalisation as a dichotomous variable	0	1	1	1	0
The number of hospitalisations	1	2	2	3	3
The number of hospitalisations divided by person-years	$\frac{1}{50/365} = 7.3$	$\frac{2}{75/365} = 9.73$	$\frac{2}{90/365} = 8.11$	$\frac{3}{125/365} = 8.76$	$\frac{3}{150/365} = 7.3$
The proportion of measurable time	$\frac{40}{50} = 0.8$	$\frac{60}{75} = 0.80$	$\frac{60}{90} = 0.66$	$\frac{90}{125} = 0.72$	$\frac{110}{150} = 0.73$
The proportion of immeasurable time	$\frac{10}{50} = 0.2$	$\frac{15}{75} = 0.20$	$\frac{30}{90} = 0.33$	$\frac{35}{125} = 0.28$	$\frac{40}{150} = 0.27$

Figure 2. Visual example showing methodological approaches used to calculate values by hospitalization, measurable time, and immeasurable time.
[a]Weight or adjustment values were calculated in a time-varying manner for every day of follow-up.

Result



' chart of patients included and excluded from National Health Insurance Service-National Sample Cohort database.

Characteristics

Table 1. Baseline characteristics of the overall study population and among users and non-users of β-blocker at cohort entry

Variable	Entire cohort ($n = 31\,715$)	β-blocker[a] ($n = 7982$)	No β-blocker[a] ($n = 23\,823$)	aSD
Age group				0.157
<34	2794 (8.8)	474 (6.0)	2320 (9.7)	
35-54	7149 (22.5)	1724 (21.8)	5425 (22.8)	
55-64	6654 (21.0)	1609 (20.4)	5045 (21.2)	
65-84	13 364 (42.1)	3594 (45.5)	9770 (41.0)	
85≤	1754 (5.5)	491 (6.2)	1263 (5.3)	
Sex (*n*, %)				0.024
Female	17 499 (55.2)	4426 (56.1)	13 073 (54.9)	
Year of cohort entry				0.144
2003	5075 (16.0)	1025 (13.0)	4050 (17.0)	
2004	3264 (10.3)	871 (11.0)	2393 (10.0)	
2005	3003 (9.5)	814 (10.3)	2189 (9.2)	
2006	2398 (7.6)	574 (7.3)	1824 (7.7)	
2007	2453 (7.7)	565 (7.2)	1888 (7.9)	
2008	2755 (8.7)	752 (9.5)	2003 (8.4)	
2009	2373 (7.5)	653 (8.3)	1720 (7.2)	
2010	2197 (6.9)	527 (6.7)	1670 (7.0)	
2011	2992 (9.4)	846 (10.7)	2146 (9.0)	
2012	2606 (8.2)	609 (7.7)	1997 (8.4)	
2013	2599 (8.2)	656 (8.3)	1943 (8.2)	

Variable	Entire cohort ($n = 31\,715$)	β-blocker[a] ($n = 7982$)	No β-blocker[a] ($n = 23\,823$)	aSD
Type of health insurance (n, %)				0.150
Health insurance	11 767 (37.1)	2826 (35.8)	8941 (37.5)	
Medical Aid	17 628 (55.6)	4244 (53.8)	13 384 (56.2)	
Veterans	2320 (7.3)	822 (10.4)	1498 (6.3)	
Income level[b] (n, %)				0.118
Q0-Q2	6910 (21.8)	2000 (25.3)	4910 (20.6)	
Q3-Q5	6663 (21.0)	1610 (20.4)	5053 (21.2)	
Q6-Q8	8895 (28.0)	2174 (27.5)	6721 (28.2)	
Q9-Q10	9247 (29.2)	2108 (26.7)	7139 (30.0)	
Comorbidities (n, %)				
Hypertension	13 069 (41.2)	2510 (31.8)	10 559 (44.3)	0.260
Diabetes	7514 (23.7)	1516 (19.2)	5998 (25.2)	0.144
Hyperlipidaemia	7583 (23.9)	1492 (18.9)	6091 (25.6)	0.161
Atrial fibrillation	949 (3.0)	187 (2.4)	762 (3.2)	0.050
Coronary artery disease	4543 (14.3)	905 (11.5)	3638 (15.3)	0.112
Cerebrovascular disease	3210 (10.1)	654 (8.3)	2556 (10.7)	0.083
Peripheral vascular disease	3303 (10.4)	690 (8.7)	2613 (11.0)	0.075
Coronary revascularization	389 (1.2)	88 (1.1)	301 (1.3)	0.014
Myocardial infarction	722 (2.3)	148 (1.9)	574 (2.4)	0.037
Stroke	2123 (6.7)	433 (5.5)	1690 (7.1)	0.066
COPD	6784 (21.4)	1581 (20.0)	5203 (21.8)	0.044
Chronic liver disease	3878 (12.2)	812 (10.3)	3066 (12.9)	0.081
Chronic lung disease	4982 (15.7)	1202 (15.2)	3780 (15.9)	0.018

Variable	Entire cohort ($n = 31\,715$)	β-blocker[a] ($n = 7982$)	No β-blocker[a] ($n = 23\,823$)	aSD
Comedications (n, %)				
ACE inhibitors	2628 (8.3)	401 (5.1)	2227 (9.3)	0.165
ARBs	5086 (16.0)	903 (11.4)	4183 (17.6)	0.174
Aldosterone antagonists	1364 (4.3)	145 (1.8)	1219 (5.1)	0.180
Calcium channel blockers	7597 (24.0)	1591 (20.2)	6006 (25.2)	0.121
Diuretics	3713 (11.7)	516 (6.5)	3197 (13.4)	0.231
Nitrates	1418 (4.5)	300 (3.8)	1118 (4.7)	0.044
Digoxin	1293 (4.1)	119 (1.5)	1174 (4.9)	0.195
Amiodarone	147 (0.5)	27 (0.3)	120 (0.5)	0.025
Aspirin	6308 (19.9)	1131 (14.3)	5177 (21.7)	0.193
Lipid-lowering agents	4126 (13.0)	755 (9.6)	3371 (14.2)	0.142
Antidiabetic medication	386 (1.2)	85 (1.1)	301 (1.3)	0.017

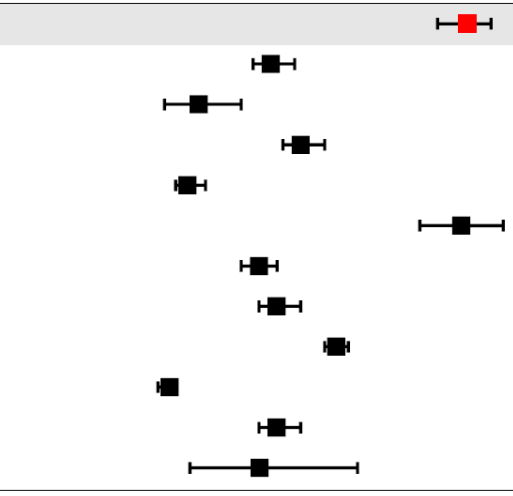
Variable	Entire cohort ($n = 31\,715$)	β-blocker[a] ($n = 7982$)	No β-blocker[a] ($n = 23\,823$)	aSD
Number of prescription drugs in previous year				0.251
>4	23 112 (72.9)	5075 (64.3)	18 037 (75.7)	
≤4	8603 (27.1)	2907 (36.4)	5786 (24.3)	
Number of hospitalizations in previous year				0.098
>2	1487 (4.7)	251 (3.2)	1236 (5.2)	
≤2	30 228 (95.3)	7731 (96.9)	22 587 (94.8)	
CCI (*n*, %)				
(Median, IQR)	(1, 0-3)	(1, 0-2)	(1, 0-3)	0.260
0	10 779 (34.0)	3333 (42.2)	7446 (31.3)	
1	7466 (23.5)	1851 (23.5)	5615 (23.6)	
2	5119 (16.1)	1130 (14.3)	3989 (16.7)	
3	3273 (10.3)	651 (8.2)	2622 (11.0)	
>3	5078 (16.0)	927 (11.7)	4151 (17.4)	

Table 2. Crude and adjusted hazard ratio estimates of mortality associated with β-blocker use versus non-use among patients with heart failure, obtained using time-varying exposure: 1 January 2003 to 31 December 2013

10 different methodological approaches	No. of events		Person-years		Incidence rate[a]		Hazard ratio (95% confidence interval)					
	β-blocker	Non-use	β-blocker	Non-use	β-blocker	Non-use	Crude		Adjusted for age, sex		Adjusted for all covariates[b]	
Gold standard[c]	1312	5469	37 260.9	123 447.0	35.2	44.3	0.79	(0.74 to 0.83)	0.72	(0.68 to 0.77)	0.76	(0.71 to 0.80)
Outpatient prescriptions	706	6075	35 421.9	125 286.0	19.9	48.5	0.42	(0.39 to 0.46)	0.40	(0.37 to 0.44)	0.43	(0.40 to 0.46)
Restricted to non-hospitalized patients	103	753	17 152.2	48 587.7	6.0	15.5	0.36	(0.29 to 0.44)	0.31	(0.26 to 0.39)	0.31	(0.25 to 0.38)
Restricted to those hospitalized for <50% of observation period	695	4872	35 379.6	123 143.4	19.6	39.6	0.50	(0.46 to 0.54)	0.46	(0.43 to 0.50)	0.48	(0.44 to 0.52)
All periods of hospitalizations considered as exposed	752	6029	39 882.4	120 825.5	18.9	49.9	0.37	(0.34 to 0.40)	0.32	(0.29 to 0.34)	0.29	(0.26 to 0.32)
Adjusted for hospitalization as a dichotomous time-varying variable	706	6075	35 421.9	125 286.0	19.9	48.5	0.93	(0.85 to 1.02)	0.77	(0.71 to 0.85)	0.75	(0.68 to 0.82)
Adjusted for the number of hospitalizations	706	6075	35 421.9	125 286.0	19.9	48.5	0.40	(0.37 to 0.43)	0.39	(0.36 to 0.42)	0.41	(0.38 to 0.44)
Adjusted for the number of hospitalizations divided by person-years	706	6075	35 421.9	125 286.0	19.9	48.5	0.44	(0.41 to 0.48)	0.42	(0.39 to 0.45)	0.44	(0.41 to 0.48)
Weighted by the number of hospitalizations	706	6075	35 421.9	125 286.0	19.9	48.5	0.55	(0.53 to 0.58)	0.52	(0.50 to 0.55)	0.54	(0.52 to 0.56)
Weighted by the number of hospitalizations divided by person-years	706	6075	35 421.9	125 286.0	19.9	48.5	0.22	(0.20 to 0.23)	0.23	(0.22 to 0.25)	0.26	(0.24 to 0.27)
Weighted by proportion of measurable time	706	6075	35 421.9	125 286.0	19.9	48.5	0.45	(0.42 to 0.49)	0.42	(0.39 to 0.46)	0.44	(0.42 to 0.48)
Weighted by proportion of immeasurable time	706	6075	35 421.9	125 286.0	19.9	48.5	0.37	(0.26 to 0.51)	0.40	(0.29 to 0.56)	0.41	(0.29 to 0.58)

[a]Per 1000 person-years.
[b]Adjusted for age, sex, comorbidities, comedication, Charlson Comorbidity Index, number of prescriptions (>4) and number of hospitalizations (2) in the year preceding the date of heart failure.
[c]Gold standard includes all outpatient and inpatient medication data.

10 different analytical approaches			Adjusted HR (95% CI) [a]
Gold standard [b]	0.76	(0.71 to 0.80)	
Outpatient prescriptions	0.43	(0.40 to 0.47)	
1) Restricted to non-hospitalised patients	0.31	(0.25 to 0.38)	
2) Restricted to those hospitalised for < 50% of observation period	0.48	(0.45 to 0.52)	
3) Periods of hospitalisations considered as exposed	0.29	(0.27 to 0.32)	
4) Adjusted for hospitalisation as a dichotomous time-varying	0.75	(0.68 to 0.82)	
5) Adjusted for the number of hospitalisations	0.41	(0.38 to 0.44)	
6) Adjusted for the number of hospitalisations divided by person-years	0.44	(0.41 to 0.48)	
7) Weighted by the number of hospitalisations	0.54	(0.52 to 0.56)	
8) Weighted by the number of hospitalisations divided by person-years	0.26	(0.24 to 0.27)	
9) Weighted by proportion of measurable time	0.44	(0.41 to 0.48)	
10) Weighted by proportion of measurable time	0.41	(0.29 to 0.58)	



Abbreviations: CI, confidence interval; HR, hazard ratio

[a] Adjusted for age, sex, comorbidities, co-medication, Charlson comorbidity index, number of prescriptions (> 4) and number of hospitalisations (> 2) in the year prior to the date of heart failure.

[b] Gold standard includes all outpatient and inpatient medication data.

Figure 4. Forest plot summarizing the estimated hazard ratios from the gold-standard analysis and 10 different approaches examined to minimize immeasurable time bias.

Discussion

The magnitude of the bias in the real-world example

- The gold-standard analysis: both in-hospital and outpatient

  HR of 0.76(95%CI: 0.71-0.80)

- The analysis of outpatient drug data only

  HR of 0.43(95%CI: 0.40-0.46)

Adjusting for hospitalization as a dichotomous time-varying variable can overcome the bias.

HR of 0.75(95%CI: 0.68-0.82)

Discussion

Exclusion of hospitalized patients(removing the immeasurable time bias) can lead to selection bias by excluding those with higher risk of death and not produce result that consistent with gold standard analysis.

Supplementary Table S12. Number of patients who excluded in methods of restriction to either non-hospitalised or those hospitalised for < 50% of observation period.

Methodological approaches restriction hospitalised patients	Number of patients in overall cohort	Total		Death		Reached end of study period	
		n	%	n	%	n	%
Restriction to non-hospitalised							
Main analysis	31 715	20 736	(65.38)	5923	(18.68)	14 813	(46.71)
Sensitivity analyses							
Re-analysis with angiotensin converting enzyme inhibitor	53 778	34 772	(64.66)	9535	(17.73)	25 237	(46.93)
Re-analysis with angiotensin-receptor blocker	52 076	34 221	(65.71)	9486	(18.22)	24 735	(47.50)
Restriction to those hospitalised for < 50% of observation period							
Main analysis	31 715	1831	(5.77)	1312	(4.14)	519	(1.64)
Sensitivity analyses							
Re-analysis with angiotensin converting enzyme inhibitor	53 778	3197	(5.94)	2211	(4.11)	986	(1.83)
Re-analysis with angiotensin-receptor blocker	52 076	4160	(7.99)	3245	(6.23)	915	(1.76)
Patients hospitalised with heart failure at cohort entry	9243	1480	(16.01)	1122	(12.14)	358	(3.87)

Discussion

Immeasurable time bias has direct relationships with hospitalization, novel methods of adjustment and weighting on the presence of hospitalization or its frequency as time-varying variable was applied.

Difference in study design, exposure definitions and lengths of follow-up used for weights in previous nested case-control study may cause unability to overcome the bias in this study.

Limitation

Its generalizability to other study is unclear.

Misclassification of HF may have resulted in the inclusion of patients without HF, who are likely to have a better prognosis than those with HF.

Residual confounding from unmeasured confounder may be present.

Conclusion

The immeasurable time bias caused by the lack of availability of in-hospital drug information can result in substantial bias and exaggeration of the benefits of prescription drugs.

The findings suggest that the time-varying adjustment for hospitalization may reduce immeasurable time bias in the absence of inpatient medication data in cohort studies.