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Methods

Analytical approaches to minimizing immeasurable time bias in cohort studies

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Abstract

Background: Immeasurable time bias exaggerates drug benefits in pharmacoepidemiological studies due to exposure misclassification arising from the inability to measure in-hospital medications in many health care databases.

Methods: To compare the ability of different methodological approaches to minimize immeasurable time bias, we conducted a cohort study of β-blocker use and all-cause mortality among patients with heart failure (HF), using a nationwide health care database which contains both in- and outpatient prescriptions. In our gold-standard analysis, we assessed exposure using a time-varying approach involving both in- and outpatient prescriptions. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality, with exposure to β-blockers defined as a time-varying variable. To estimate the magnitude of the immeasurable time bias, we repeated the analyses using outpatient prescriptions only and compared 10 approaches to minimize the bias, which are categorized as restriction, adjustment, assumption and weighting.

Results: The HR for β-blocker use versus non-use was 0.76 (95% CI: 0.71 to 0.80) in our gold-standard analysis. When exposure assessment was restricted to outpatient prescriptions only, β-blocker use was substantially more protective (HR 0.43, 95% CI: 0.40 to 0.46). Of the 10 approaches examined, adjusting for hospitalization as a time-varying variable successfully minimized the bias (HR 0.75, 95% CI: 0.68 to 0.82).

Conclusions: The immeasurable time bias can result in substantial bias in pharmacoepidemiological studies. Time-varying adjustment for hospitalization appears to reduce the immeasurable time bias in the absence of inpatient medication data.

Key words: Immeasurable time bias, pharmacoepidemiology, β-blockers, mortality, heart failure, observational study

Key Messages

- Immeasurable time bias, an information bias that occurs because of the lack of in-hospital medication information in many health care databases, exaggerates drug benefits in pharmacoepidemiological studies.
- Analytical approaches to minimize the immeasurable time bias were assessed in a cohort study of β-blocker use and all-cause mortality among heart failure patients.
- The gold-standard exposure was defined using drug data from both in- and outpatient settings. We repeated analyses using outpatient prescriptions only to estimate the magnitude of the immeasurable time bias.
- In the present, real-world example, the magnitude of immeasurable time bias was substantial. Our findings suggest that adjusting for hospitalization as a time-varying variable reduces immeasurable time bias when information on inpatient medication use is not available.

Introduction

Pharmacoepidemiological studies using large, population-based databases are a key component to the assessment of the real-world effectiveness of prescription drugs and the post-marketing surveillance of adverse drug effects. However, such databases typically lack information on inpatient medication use, which can result in immeasurable time bias.[1] This bias occurs when hospitalized patients, who are typically at a higher risk of adverse events, are incorrectly classified as unexposed due to the lack of in-hospital drug data, exaggerating the drug's benefits. The benefits of a drug are overestimated because hospitalizations are likely associated with an increased risk of death. These periods of hospitalization therefore result in differential exposure misclassification where patients exposed to the drug of interest and at higher risk of the event of interest are incorrectly classified as unexposed, decreasing the estimate rate in the exposed group and increasing the rate in the unexposed group, biasing the hazard ratio (HR) downward.[1] This bias typically results in spuriously protective associations, but may also mask increased risks.

Despite the potential consequences of immeasurable time bias, few studies have estimated its magnitude or examined approaches to minimize its impact, largely because health care databases that are frequently used for pharmacoepidemiological studies (e.g. the UK Clinical Practice Research Datalink,[2] US Medicaid/Medicare[3] and Canadian provincial health care databases[4,5]) do not capture in-hospital medication use. Nevertheless, one study using the General Sample of Beneficiaries of France demonstrated that assuming inpatients were either all exposed or unexposed influenced the estimated treatment effects.[6] Although they described the possible impact of immeasurable time bias, their data source did not capture inpatient prescription records, preventing the estimation of the 'true' measure of association (i.e. including these missing data). Moreover, unlike many health care databases, inpatient medication records are available in the database of South Korea owing to the fee-for-service reimbursement system, allowing for an accurate exposure ascertainment even when patients are hospitalized. A recent study examined the impact of the immeasurable time bias and three potential approaches to overcome it, using nested case-control studies.[7]

The objective of this study was 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), and to compare the ability of different methodological approaches to minimize this bias.

Methods

This study was approved by the institutional review board of Sungkyunkwan University (SKKU-IRB-2017–03-012), which waived the informed consent, as only de-identified data were used in this study.

Data source

We used South Korea's National Health Insurance Service-National Sample Cohort (NHIS-NSC) database between 2002 and 2013. The National Health Insurance (NHI) programme was initiated in Korea in 1977 and achieved universal coverage of the entire population in 1989. All Koreans are covered by the NHI system, and the database therefore contains all information on health care use and prescribed medications for approximately 50 million Koreans, including both in-hospital and outpatient prescriptions. The NHIS-NSC database is a 2.2% sample of the total Korean population (approximately 1 million

individuals) which was created using systematic stratified random sampling, with proportional allocation within each stratum based on each individual's total annual health expenditures from 2002 through 2013.[8]

The NHIS-NSC database includes a unique, anonymized code representing each individual, and available data include age, sex, diagnostic codes, visit dates for hospitalizations and ambulatory care, and drug prescription information. Prescription information includes generic name of the drug, prescription date, and duration from both in- and outpatient settings, owing to the fee-for-service reimbursement system of Korea.[8] Diagnosis codes are coded according to the International Classification of Disease, 10th Revision (ICD-10) codes. The NHIS-NSC database also contains death records, obtained from linkage to the national vital statistics of South Korea. Death information, including cause of death, is coded using ICD-10 codes.

Study population

We conducted a retrospective population-based cohort study of patients with incident HF (ICD-10: I50, I13, I09.0, I11.0) between 1 January 2003 and 31 December 2013. A previous validation study comparing diagnosis codes from health insurance claims data with those of electronic medical records found an overall positive predictive value of 82.3%.[9] In the present study, all patients had a minimum of 1 year of database history before their incident HF diagnosis to allow for the exclusion of prevalent HF, to assess new use of β-blockers and to assess comorbidities and comedications. To avoid biases associated with the inclusion of prevalent users,[10] we excluded patients with β-blocker prescriptions in the year preceding the diagnosis of HF. Cohort entry was defined as the date of the incident diagnosis of HF. Patients were followed until our outcome of interest (all-cause mortality), or censoring due to the end of study period (31 December 2013), whichever occurred first.

Exposure definition

Our exposure of interest was current use of β-blockers, which we assessed using a time-varying approach (Figure 1). Using this approach, each person-day of follow-up was classified as 'exposed' or 'unexposed' to β-blockers, and patients could contribute person-time to both exposure categories. Person-days for which a prescription for a β-blocker overlapped were considered exposed; no grace period was used. All remaining person-days of follow-up were considered unexposed to β-blockers. In the gold-standard analysis, we measured exposure using both in- and outpatient prescription data, and only outpatient prescription data were used in the analyses estimating the magnitude of the immeasurable time bias.

Outcome

Our study outcome was death from any cause after cohort entry and recorded in the NHIS-NSC database, which is linked with Korea's national vital statistics. In Korea, deaths are recorded by physicians in hospitals or police stations and transmitted to 'Statistics Korea'. A previous validation study reported 92% agreement between the recorded cause of death (defined using ICD codes) from the National Statistics database and those of hospital medical records.[11] The date of death was defined as the event date.

Potential confounders

We assessed potential confounders in the 1 year before cohort entry. Demographic information (age, sex, type of health insurance and income level) was assessed upon cohort entry. Comorbidities (hypertension, diabetes,

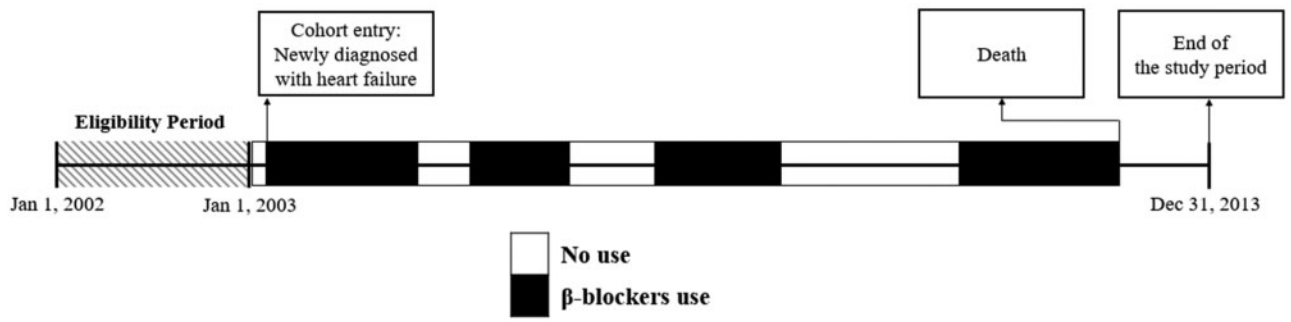


Figure 1. Exposure to β-blockers assessed using a time-varying approach by defining β-blocker prescribed periods as 'exposed' and periods with no prescription for β-blockers as 'unexposed'. All subjects were followed until death or censoring due to the end of the study period (31 December 2013), whichever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

hyperlipidaemia, atrial fibrillation, coronary artery disease, cerebrovascular disease, peripheral vascular disease, coronary revascularization, myocardial infarction, stroke, chronic obstructive pulmonary disease, chronic liver disease and chronic lung disease) and comedications [angiotensin converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARBs), aldosterone antagonists, calcium-channel blockers, diuretics, nitrates, digoxin, inotropics, amiodarone, hydralazine, aspirin, lipid-lowering agents, antidiabetic medications and anti-thrombotic medications] were assessed as binary variables in the year before cohort entry (1 if present, 0 otherwise). Furthermore, we estimated each patient's Charlson Comorbidity Index (CCI) score, based on a previous algorithm.[12] We also included the number of prescriptions (classified as >4 or ≤4) and number of hospitalizations (classified as >2 or ≤2) in the 1 year preceding cohort entry, as proxies for overall health.

Statistical analyses

We described demographic and clinical characteristics of the entire cohort and stratified by β-blocker use and non-use at cohort entry. We estimated the absolute standardized difference (aSD) to compare baseline characteristics between β-blocker users and non-users, where a value of aSD greater than 0.1 between groups was considered important.[13]

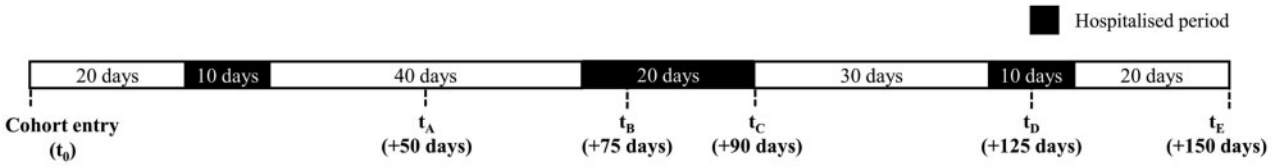
Time-dependent Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause death associated with current use of β-blockers versus no current use of β-blockers. Follow-up started at cohort entry (date of HF incident diagnosis) and ended at either death or end of study (31 December 2013), whichever occurred first. The duration of follow-up was the underlying time axis of the Cox model. Exposure to β-blockers was treated as a time-dependent binomial variable, with each person-day of follow-up classified as exposed or unexposed to β-blockers. Exposures to β-blockers was estimated by adding the number of days' supply to the date of the prescription; in the primary analysis, no grace period was used. Three models were created. The first model was unadjusted for any potential confounders. The second was adjusted for age and sex only. The third was adjusted for all potential confounders (described above). We estimated the 'gold-standard' HR by including drug data from both in- and outpatient settings, to allow exposure assessment. All other HRs were estimated using outpatient prescription data only.

To estimate the magnitude of the immeasurable time bias, we then repeated our 'gold-standard' analysis with exposure restricted to outpatient prescriptions only; we refer to this as our 'biased' estimate. We then examined 10 methodological approaches to reduce the immeasurable time bias, by comparing the estimated treatment effects obtained using these approaches with those of our gold-standard and biased analyses. First, we restricted inclusion to individuals not hospitalized during follow-up, in a time-varying manner. Second, we restricted inclusion to subjects hospitalized <50% of the observation period in a time-varying manner. Third, we assumed that patients were exposed while hospitalized. Fourth, in the multivariate Cox proportional hazards models, we adjusted for the presence of hospitalization during each patient's follow-up as a dichotomous time-varying variable. Fifth and sixth, we adjusted using a time-varying approach for the number of hospitalizations that occurred during the follow-up or by the proportion of these events (divided by person-years), respectively. Seventh and eighth, we applied weighting by these values, respectively. Ninth and tenth, each patient was weighted by the proportions of measurable and immeasurable time. Measurable time was defined by the number of observed days in an outpatient setting, and conversely, immeasurable time was defined by the number of observed hospitalized days. Each observation period was weighted by the proportions of cumulative measurable or immeasurable time divided by person-time, using the information from cohort entry to each point in time. All weights were estimated using a time-varying approach (visual representation of the approaches is shown in Figure 2).

We conducted four sensitivity analyses. First, we restricted inclusion to patients hospitalized for HF at cohort entry and repeated our main analyses. Second, to account for the biological half-life of β-blockers, we extended exposure to the β-blockers by assigning a grace period of 3 and 7 days, respectively, at the end of exposure. Third, to verify whether consistent results were obtained with other examples, we repeated the analyses with two other exposures, namely ACEi or ARBs, which are frequently prescribed among patients with HF. Last, to address potential misclassification of HF diagnosis, we conducted several sensitivity analyses as follows: (i) restricting our study cohort to patients hospitalized for HF as their primary or secondary diagnosis; (ii) restricting our study cohort to patients who were diagnosed with HF as their primary diagnosis twice within a month; and (iii) restricting our study cohort to patients who were diagnosed with heart failure as their primary diagnosis three times within a month.

Results

From 1 123 822 persons in the NHIS-NSC database, we included 59 740 patients diagnosed with incident HF



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.

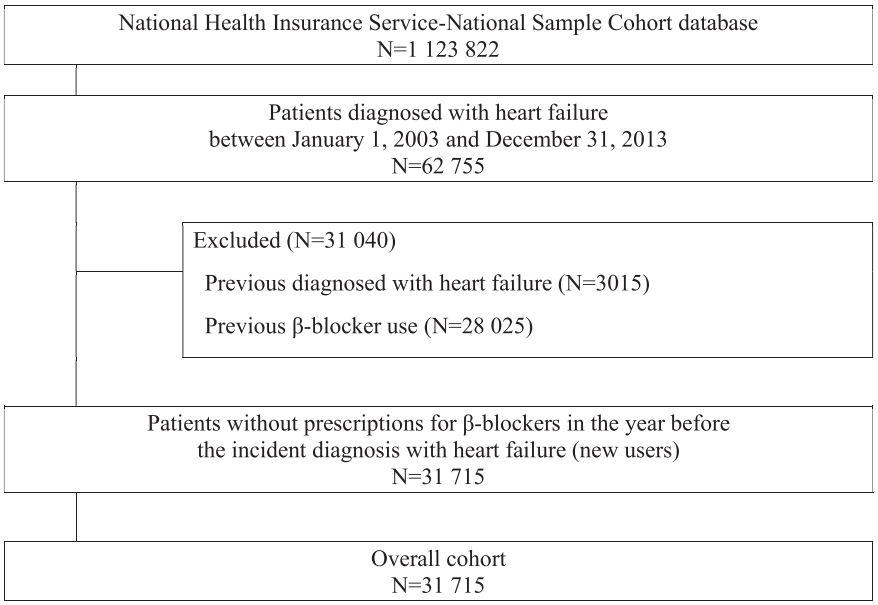


Figure 3. Flow chart of patients included and excluded from National Health Insurance Service-National Sample Cohort database.

between 1 January 2003 and 31 December 2013. After excluding individuals with a prescription for β-blockers in the year before cohort entry, our overall cohort included 31 715 patients (Figure 3). Table 1 shows the demographic characteristics of the cohort overall and by β-blocker use at cohort entry. Imbalances between β-blocker users and non-users at cohort entry were present in age, health insurance type, income level and various comorbidities and comedications.

Table 2 shows the estimated HRs and 95% CIs for all-cause mortality associated with current β-blocker use versus non-use among patients with HF. In our gold-standard analysis that included both in- and outpatient medication use, the HR for β-blocker use versus non-use was 0.76 (95% CI: 0.71 to 0.80). In contrast, when exposure assessment was restricted to outpatient medication use only, the HR for all-cause mortality for β-blocker use versus non-use was 0.43 (95% CI: 0.40 to 0.46). A total of 137 patients died in hospital, and 4179 died within 30 days of their last hospital discharge. More detailed information regarding the occurrence of hospitalization in the study cohort is available in Supplementary Tables S2 and S3, available as Supplementary data at *IJE* online. Of the 10 approaches to minimize immeasurable time bias examined,

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)	
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
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

(Continued)

Table 1. Continued

Variable	Entire cohort ($n = 31\,715$)	β-blocker[a] ($n = 7982$)	No β-blocker[a] ($n = 23\,823$)	aSD
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
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)	

ACE, angiotensin converting enzyme; ARB, angiotensin-receptor blockers; aSD, absolute standardised differences; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a]β-blocker users and non-users at cohort entry.

[b]Income level was classified into 11 groups ranging from 0th quintile to 10th quintile, according to the type of health insurance; 0th quintile corresponds to the most deprived and 10th quintile is the most affluent, which means that higher number indicates higher income.

adjusting for hospitalization as a time-varying variable was the approach that successfully minimized the bias (HR: 0.75, 95% CI: 0.68 to 0.82, Table 2 and Figure 4).

Similar results were obtained across sensitivity analyses (Figure 5, Supplementary Tables S4–S11, available as Supplementary data at *IJE* online).

Discussion

Our study described the magnitude of the immeasurable time bias and compared potential methods to minimize it, in a cohort design using a case study of β-blocker use and the risk of all-cause mortality among patients with HF. We found that the magnitude of the bias was substantial in our real-world example, with the gold-standard analysis that considered both in-hospital and outpatient medication use resulting in an HR of 0.76 (95% CI: 0.71 to 0.80) and the analysis of outpatient drug data only producing an HR of 0.43 (95% CI: 0.40 to 0.46). We then applied 10 different methodological approaches, including those previously suggested as potential methods to minimize the immeasurable time bias.[1,6,14,15] Only one approach, that of adjusting for hospitalization as a dichotomous time-varying variable, was successful in fully overcoming the bias (HR 0.75, 95% CI: 0.68 to 0.82).

Although the exclusion of hospitalized patients, by definition, removed the immeasurable time bias (since there were no longer periods that were immeasurable), it also appears to have introduced selection bias that was of similar magnitude, with the excluded patients at a higher risk of death than those who remained in the cohort. This is because, as hospitalized patients are generally regarded to have more severe disease than those who are not hospitalized, the proportion of excluded patients is likely to be differential between β-blocker users and non-users. Given that immeasurable time bias has direct relationships with hospitalization, we applied novel methods of adjustment and weighting on the presence of hospitalization or its frequency as a time-varying variable. to attempt to minimize immeasurable time bias (while avoiding the selection bias caused by exclusion based on hospitalization). Although previous nested case-control studies adjusted for hospitalization[1,7,16] and cohort studies adjusted for the duration of hospitalization,[17,18] none successfully repaired the immeasurable time bias. Nevertheless, by adjusting for the continuously changing hospitalization status throughout the follow-up period, our method of adjusting for time-varying

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.

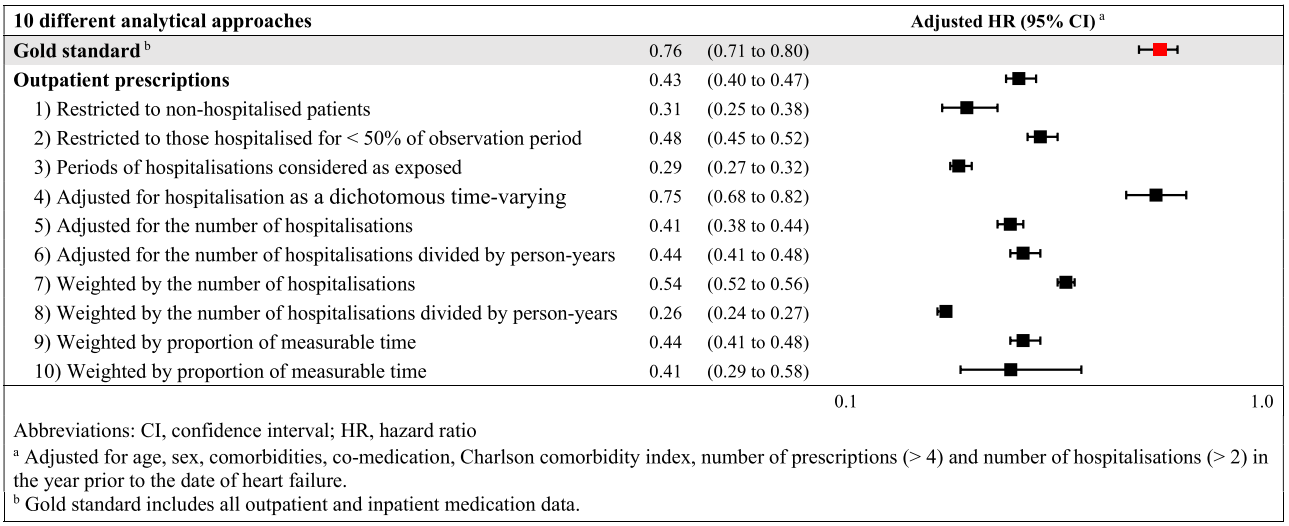


Figure 4. Forest plot summarizing the estimated hazard ratios from the gold-standard analysis and 10 different approaches examined to minimize immeasurable time bias.

hospitalization resulted in treatment effects that were consistent with those of the gold standard, overcoming the immeasurable time bias.

Considerable efforts have been made to reduce the immeasurable time bias in cohort studies.[6,14,15,19,20] A simulation cohort study, using the French claims database, assessed the direction of the immeasurable time bias by estimating the change in HRs under two scenarios of exposure status during hospitalization (considering in-hospital drug use as exposed or unexposed). When in-hospital medication use was considered unexposed, all-cause mortality was not associated with benzodiazepines (HR 0.85, 95% CI: 0.76 to 1.10), but an increased risk was observed when hospitalized patients were assumed to be exposed (HR 2.93, 95% CI: 2.46 to 3.48).[6] However, this assumption-based study did not reveal the true magnitude of the bias, as gold-standard estimates were unknown. To our knowledge, no study had succeeded in identifying an analytical approach to minimize the bias. One study suggested three potential approaches to minimize the immeasurable time bias in a nested case-control design, of which two applied weighting methods.[7] However, due to differences in study design, exposure definitions and lengths of follow-up used for weights between the nested case-control and cohort designs, this similar approach of weighting which involved measurable time was unable to overcome the immeasurable time bias in the cohort design.

Several pharmacoepidemiological studies have excluded hospitalized patients to reduce the immeasurable time bias. An Italian cohort study assessing the preventive effect of adherence to antidepressants and reduced mortality did not account for the follow-up time of any hospitalization events or the 10 days after hospital discharge; the study found a significant mortality reduction (HR 0.91, 95%CI: 0.86 to 0.97).[14] Another cohort study, conducted using Pennsylvania's pharmaceutical claims data, excluded all patients having 50% or more days of hospitalization during the eligibility ascertainment period, and found a protective effect of adherence to bisphosphonates and fracture risk reduction (HR:0.53, 95% CI: 0.38 to 0.74).[15]

Although exclusion has been previously examined as a potential solution to immeasurable time bias, doing so involves looking into the future to determine who is hospitalized, and thus could introduce immortal time bias. Rather than exclusion based on hospitalizations, it would have been more appropriate to censor on hospitalizations, as the person-time between cohort entry and hospitalization is not affected by the bias. In the present study, 20 736 patients (65.4% of the entire cohort) were excluded due to hospitalization (Supplementary Table S12, available as Supplementary data at *IJE* online). Whereas this approach reduced the immeasurable time bias, it likely introduced important selection bias; by excluding subjects based on the presence of hospitalization (i.e. those who are at elevated risk of mortality), selection into the study was differential. Importantly, in our case, this criterion excluded the majority of subjects from the cohort and did not produce results that were consistent with those of the gold-standard analysis.

Previous studies have examined the association between β-blocker use and all-cause mortality among patients with HF. In a study using a regional Canadian claims database, β-blocker users in a study population of patients with more than one hospitalization for HF had substantial reductions in all-cause mortality (HR 0.72, 95% CI: 0.65 to 0.80) and mortality due to HF (HR 0.65, 95% CI: 0.47 to 0.90).[21]

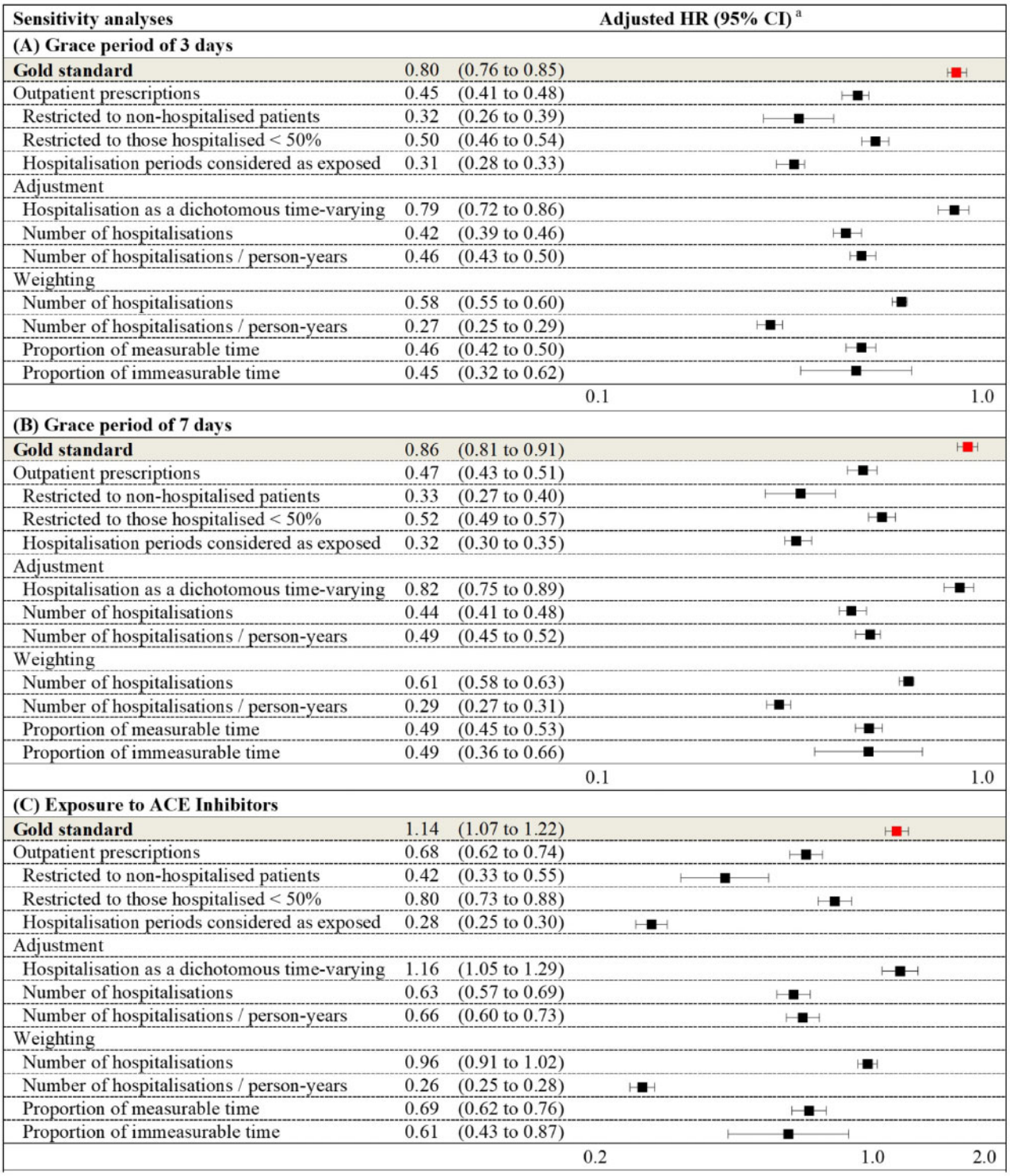
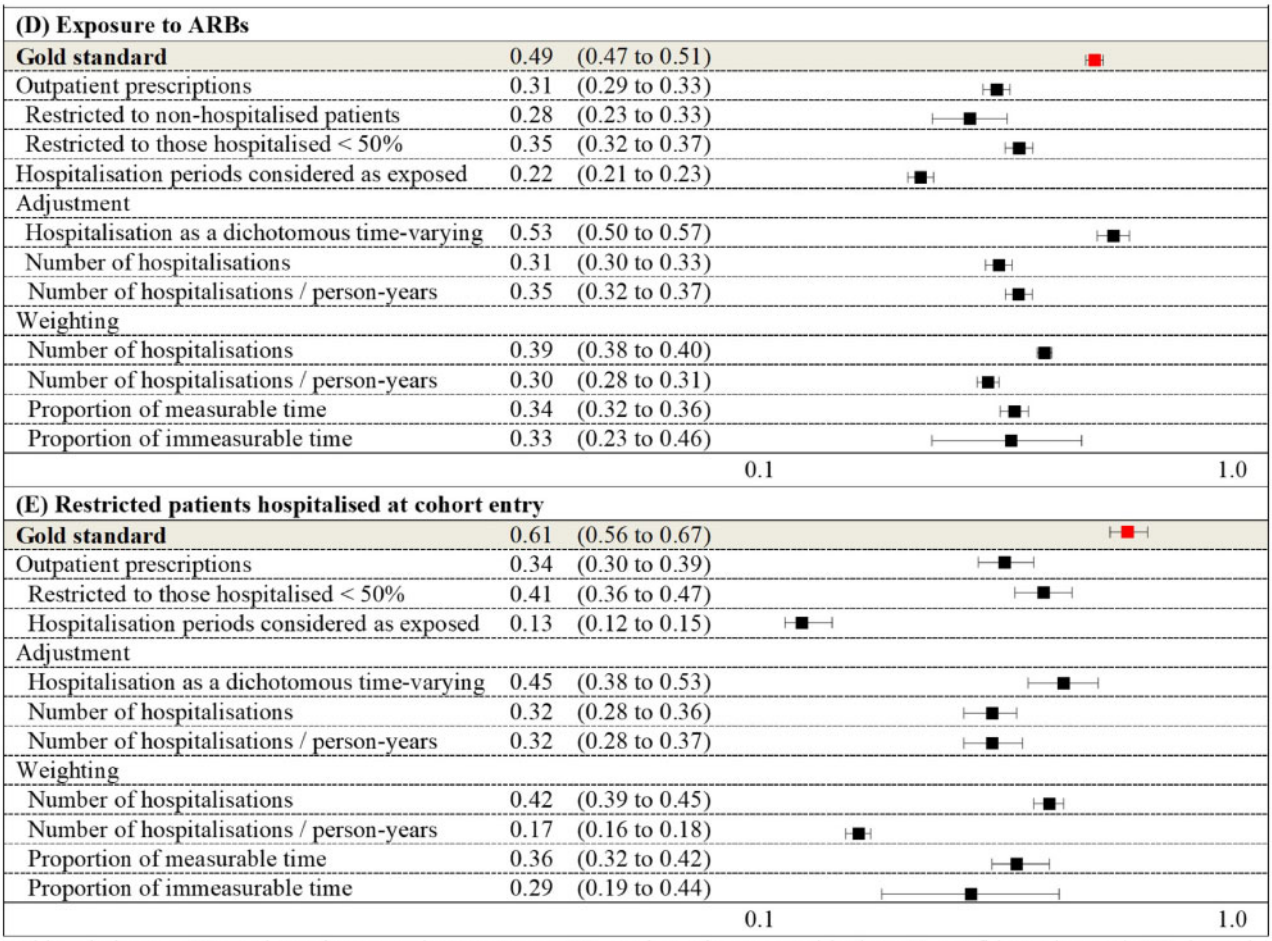


Figure 5. Forest plot summarizing the sensitivity analyses that included a grace period, assessed additional exposures and restricted patients hospitalized at cohort entry.



Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; 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.

Figure 5. Continued.

As potential exposure misclassification during hospitalization is possible due to the lack of in-hospital medication use, patients may have been incorrectly classified as unexposed, thereby exaggerating treatment effects.

Our study has several strengths. First, to our knowledge, this is the first cohort study to have estimated the magnitude of immeasurable time bias. Although previous studies have attempted to assess the magnitude of the immeasurable time bias, the lack of inpatient prescription data prevented the estimation of treatment effects based on in- and outpatient prescription data.[6] Second, we produced generalizable results by using a representative and nationwide NHIS-NSC database. Third, we applied rigorous statistical methods to minimize confounding by using a new-user design[10] to avoid biases related to the study of prevalent users, and compared several different methods to potentially reduce the immeasurable time bias.

The study has some limitations. First, we assessed the immeasurable time bias in only one case study, and thus its generalizability to other pharmacoepidemiological studies is unclear. However, this is a clinically relevant example that has been the focus of several trials and observational studies.[21–23] In addition, we repeated analyses using two other drug classes (ACEi and ARBs) and obtained similar results. Second, 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. However, a previous validation study reported an overall positive predictive value of 82% for reported diagnoses of HF when compared with patients' electronic medical records obtained from hospitals or clinic chart reviews.[24] Moreover, our sensitivity analyses found consistent results when varying the inclusion criteria of patients with HF (Supplementary Table S13, available as Supplementary data at *IJE* online). Third, given our observational design, residual confounding from unmeasured confounders may be present. However, such confounding should be similar in all analyses and thus not impact onour study conclusions.

In conclusion, the immeasurable time bias caused by the lack of availability of in-hospital drug information can result in substantial bias in pharmacoepidemiological studies and the exaggeration of the benefits of prescription drugs. Our findings suggest that the time-varying adjustment for hospitalization may reduce immeasurable time bias in the absence of inpatient medication data in cohort studies.

The data underlying this article cannot be shared publicly, due to laws and regulations that prohibit the distribution of individual's data. The data will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *IJE* online.

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Author contributions

All authors contributed to the study design and interpretation of the data. J.Y.S .designed the study, supervised the statistical analyses, interpreted the data and wrote the manuscript. I-S.O. collected the data, conducted the statistical analyses, interpreted the data and wrote the manuscript. Y.H.B. and H.E.J. contributed to the design of the study, interpreted the data and wrote the manuscript. K.B.F. designed the study, interpreted the data and critically revised the manuscript. All authors reviewed and commented on drafts and approved the final manuscript and the decision to submit it for publication.

Conflict of interest

None declared.

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