Immediate Risk for Cardiovascular Events in Hip Fracture Patients: A Population-Based Cohort Study

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ABSTRACT

Background Emerging evidence showed that bone metabolism and cardiovascular diseases (CVD) are closely related. We previously observed a potential immediate risk of cardiovascular mortality after hip fracture. However, whether there is an immediate risk of cardiovascular events after hip fracture is unclear. The aim of this study was to evaluate the risk for major adverse cardiovascular events (MACEs) between patients having experienced falls with and without hip fracture.

Methods This retrospective population-based cohort study used data from a centralized electronic health record database managed by Hong Kong Hospital Authority. Patients having experienced falls with and without hip fracture were matched by propensity score (PS) at a 1:1 ratio. Adjusted associations between hip fracture and risk of MACEs were evaluated using competing risk regression after accounting for competing risk of death.

Results Competing risk regression showed that hip fracture was associated with increased one-year risk of MACEs (hazard ratio [HR], 1.27; 95% CI, 1.21 to 1.33; $p<0.001$), with a 1-year cumulative incidence difference of 2.40% (1.94% to 2.87%). The HR was the highest in the first 90-day after hip fracture (HR of 1.32), and such an estimate was continuously reduced in 180-day, 270-day, and 1-year after hip fracture.

Conclusions Hip fracture was associated with increased immediate risk of MACEs. This study suggested that a prompt evaluation of MACE among older adults aged 65 years and older who are diagnosed with hip fracture irrespectively of cardiovascular risk factors may be important, as early management may reduce subsequent risk of MACE.

Key words: Unintentional falls, Osteoporosis, Major adverse cardiovascular events, Propensity score matching

Introduction

Emerging evidence shows that there is an association between osteoporosis and cardiovascular diseases (CVD) (1). Meta-analysis of observational studies has shown that low bone mineral density (BMD) is associated with increased risk of coronary heart disease, stroke, and death for CVD (2). Such a relationship could be mediated by factors commonly underlying both diseases, like advancing age, low-density lipoprotein (LDL) cholesterol, calcium, vitamin K, sedentary lifestyle (3-5) and dysregulated calcification (6-8). In addition, several anti-osteoporosis medications are known to be associated with increased (9, 10) or decreased risk (11, 12) of CVD, further reinforcing the close relationship between osteoporosis and CVD. For example, a randomized trial showed evidence of an unfavourable cardiovascular risk profile for the use of romosozumab in patients with osteoporosis (9). A possible explanation is that romosozumab might be associated with increased CVD risk through the promotion of vascular calcification by its sclerostin inhibition property (9). In contrast, there is evidence showing the association between the use of alendronate and decreased risk of CVD (11). Nitrogen-containing bisphosphonates (N-BPs), which includes alendronate, could potentially lower cholesterol levels by targeting the mevalonate pathway (11).

Hip fracture has also been shown to be associated with increased risk of cardiovascular events (2, 13-16). For example, a Denmark study showed that the one-year adjusted hazard ratio (aHR) of stroke and myocardial infarction (MI) for hip fracture patients was 2.23 and 2.34 respectively, when compared to the general population (16). However, most published studies used people with high BMD (relative to patients with hip fracture) or without history of fracture as the

control population. It is unclear if falls, one of the major contributors of hip fracture, confounded the association, since unintentional falls could indicate the presence of undiagnosed CVD (17). Furthermore, the reported increase in the incidence of fall-related hospitalization suggested that unintentional fall is an increasingly important public health issue (18). With unintentional fall being a public health issue and a potential key confounder in the previous studies, there is a need to investigate the association between hip fracture and CVD among patients having experienced falls. We previously reported that there was a possible immediate increased risk of CVD death soon after a patient sustained a hip fracture (30-day risk of CVD death: 22.2%), and such risk continuously dropped to 11.6% 1-year after sustaining a hip fracture (11). Nevertheless, given that this trend was purely descriptive, without accounting for important confounders including falls, whether there is an immediate increased risk of a CVD event soon after hip fracture event remains far from clear.

In this population-based cohort study, we aim to determine the risk of major adverse cardiovascular events [MACEs] (including stroke, MI, atrial fibrillation [AF], heart failure [HF], cardiovascular mortality) in patients with unintentional falls only vs patients with both unintentional falls and hip fracture after propensity score (PS) matching. In addition, the immediate risk of MACEs in hip fracture patients will also be evaluated.

Methods

Data Source

The data used for this study was extracted from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA). The HA is a statutory body managing all the public hospitals and clinics in Hong Kong (19). CDARS is a centralized electronic health record database used for the purposes of recordkeeping and research. Records on demographics information, diagnoses, laboratory tests, procedures, medication prescriptions as well as dates regarding death, hospital admission and discharge could be retrieved from CDARS. Anonymized records were used throughout this study. The database was validated for its accuracy in hip fracture diagnosis coding, with a positive predictive value of 100% (20). CDARS has been widely used for conducting high-quality population-level epidemiological studies, including studies regarding hip fractures (11, 21) and cardiovascular diseases. The study protocol was approved by the institutional review board of the University of Hong Kong and the HA.

Study Cohort

It is well documented that falls are the major cause of hip fracture, so we used a survivor cohort of patients having experienced falls as the control. New patients who were admitted to the hospital due to unintentional falls (International Classification of Diseases, Ninth Revision [ICD-9] Codes E880-E888) between January 1 2006 and December 31 2015 were identified (N= 257,457). Among these patients, new hip fracture patients were further identified using ICD-9 code of 820.XX (N= 54,914). Patients without hip fracture were considered as control. Patients were excluded if they were aged below 65 years-old, or if they had any missing demographic or covariate variables. Since hip fracture patients require surgical treatment, we restricted our analysis to patients who survived to hospital discharge to avoid bias of event due to surgery and

length of hospitalization. Thus, the index date was set to be the date of discharge of the first occurrence of falls or fracture records in the database within the study period, for the control and fracture groups, respectively. In addition, postoperative cardiac complications may increase risk of MACEs shortly after operation, thus we further excluded PS-matched pairs (i.e. one patient with hip fracture and one without) if either one of the patients developed MACEs in the first 30 days after the index date. A sensitivity analysis was conducted by changing the index date from the date hospital discharge to the date of hospital admission. This would include MACEs recorded during hospitalization as outcome events.

Outcomes

The primary outcome of interest was cardiovascular diseases recorded using ICD-9 diagnosis codes in CDARS. We defined CVD using MACEs (22), which included any one of the following events: stroke, MI, AF, HF and cardiovascular death. The independent associations between hip fracture and each of the individual MACEs were also studied. Patients were followed until the occurrence of outcome events or the end of the one year follow up period, whichever came first.

Propensity Score Matching

Since this was an observational study where group allocation was not randomized, propensity score matching was used as a method to address potential selection bias. PS matching allows the balance of baseline characteristics between the treatment and control groups when investigating an outcome of interest, and therefore mimicking the confounders controlling property of a

randomized controlled trial (RCT) (23). The independent variables used in the PS model included all the potential confounding variables which are presented in eTable 1 in the Supplement, which were selected based on reference to a previous study (11). These variables were chosen due to their potential associations (including biological plausibility) with hip fracture and CVD events. For diagnosis and prescription variables, their baseline status was defined by the presence of a record within the one-year period before index date. Logistic regression was applied to compute a propensity score for each patient, and the scores were then used to construct the hip fracture survivor cohort with a matched accidental fall survivor control cohort. Each hip fracture patient was matched with one control patient using a caliper of 0.2 standard deviation, without replacement. Hip fracture patients who could not be matched with any patients in the control cohort were excluded from the study. Kernel density plots of propensity scores before and after PS matching were produced to check for the balance of baseline characteristics between the hip fracture and control groups. Standardized mean differences (SMD) were computed for each covariate to evaluate PS match quality. Covariates with a SMD >0.1 were adjusted in the subsequent regression analysis. A sensitivity analysis was conducted by developing a minimal PS model with age and sex as the only covariates included. The results from the subsequent regression analysis of this minimal PS model served as a reference to be presented alongside the main analysis. To further address the potential of immortal time bias introduced by using hospital discharge date as index date, another sensitivity analysis was conducted by adding the length of hospital stay as an additional covariate in the PS model.

Statistical Analysis

Mean and standard deviation (SD) were used for the descriptive reporting of the continuous baseline variables, while frequencies and percentages were used for reporting categorical variables. The cumulative incidence differences (CID) of MACEs were calculated, allowing a comparison of MACEs incidences between the hip fracture and fall control groups. The 95% confidence intervals (CI) of CID were estimated using the percentile bootstrap method, with 1000 bootstrap samples (24). The CID plot allows a visual comparison of MACEs incidences at various time points during the one-year follow-up period. Adjusted hazard ratios and the 95% CIs were estimated using the competing risk regression model (25), with death being the competing event of hip fracture. A two-sided p-value <0.05 was considered statistically significant. The statistical software R was used in all statistical analyses (26).

Results

Patient Characteristics

In this study, 54,914 patients having experienced falls with newly diagnosed hip fracture between January 1 2005 and December 31 2016 were identified (Figure 1). For the control cohort, 202,543 patients who were admitted to hospital with newly diagnosed accidental falls, but without hip fracture, were identified. After PS matching, 34,334 hip fracture patients and 34,334 patients having experienced falls (controls) were included. The mean age for the matched hip fracture and control cohorts were 81.75 years (SD=7.04) and 81.94 years (SD=7.55), respectively (eTable 2 in the Supplement). The kernel density plot after PS match showed that the PS score distributions were nearly identical when comparing the hip fracture and control groups (eFigure 1a-b in the Supplement). This showed that the balance of baseline characteristics

between hip fracture and control groups was considerably improved after the PS matching procedure accounting for the covariates. Prior to PS matching, there were 14 baseline variables with a standardized mean difference of >0.1, ranging from 0.101 to 0.641. After PS matching, all variables were well matched with a SMD <0.1, with the highest SMD being 0.027. Thus, no adjustment was done in the subsequent analysis.

Hip Fracture and risk of MACEs

A total of 7,297, 2,538, 3,398, 880, 2,033 and 754 cases of MACEs, AF, HF, MI, stroke and cardiovascular mortality were identified during 1-year follow up. The incidence rates of these events in both hip fracture and fall control cohorts are provided in Table 1.

At 1-year, significant CID between hip fracture and fall control groups was observed for MACEs, AF, HF, MI, and stroke with an estimate of 2.4% (95% CI, 1.94% to 2.87%), 0.93% (95% CI, 0.65% to 1.20%), 1.39% (95% CI, 1.07% to 1.70%), 0.42% (95% CI, 0.24% to 0.59%), and 0.45% (95% CI: 0.19% to 0.71%) respectively (Table 2). The CID was not significant for cardiovascular mortality (Table 2). eFigure 2a in the Supplement shows the cumulative incidence curve of MACEs between hip fracture and control groups, and the curves for other CVD outcomes are provided in eFigure 2b-f in the Supplement.

The competing risk regression analysis after accounting for competing risk of death showed that hip fracture was associated with the increased one-year risk of MACEs (hazard ratio [HR], 1.27; 95% CI, 1.21 to 1.33; eTable 3 in the Supplement). Similar significant association was observed for individual cardiovascular events, including AF (HR, 1.29; 95% CI, 1.20 to 1.40), HF (HR, 1.34; 95% CI, 1.25 to 1.43), MI (HR, 1.40; 95% CI, 1.22 to 1.60), and stroke (HR, 1.16; 95% CI, 1.07 to 1.27). However, null association was observed for hip fracture with cardiovascular mortality (HR, 0.90; 95% CI, 0.78 to 1.04). The sensitivity analysis using hospital admission date as index date showed similar results across all outcomes, except for cardiovascular mortality (eTable 4 in the Supplement). In this analysis, significant association was observed for hip fracture with cardiovascular mortality (HR, 1.13; 95% CI, 1.01 to 1.25). Another sensitivity analysis with length of hospital stay added to the PS model showed that the conclusions were essentially unchanged when compared to that of the PS model without the length of hospital stay (eTable 5 in the Supplement versus Table 3). The HRs computed based on the minimal PS model with age and sex as the only covariates included also showed consistent conclusions across all the cardiovascular outcomes studied, when compared to the main analysis using the full PS model (eTable 6 in the Supplement).

Risks of cardiovascular events for hip fracture patients were compared to fall control cohort at 90, 180, 270, and 365 days after hospital discharge (index date) (Table 3 and Figure 2). Among all the time points studied, the highest HR was observed at 90 days after hospital discharge for MACEs, AF, HF, and MI (Table 3). The HRs decreased progressively at 180, 270, and 365 days after hospital discharge, and the associations were significant at all time points studied. For stroke, null association was observed in the first 180 days, and the association became

statistically significant for day 270 and 1 year, with the HR of 1.12 (95% CI, 1.01 to 1.23) and 1.16 (95% CI, 1.07 to 1.27), respectively. No significant association was observed between hip fracture and cardiovascular mortality at all time points studied.

Discussion

In this population-based study with 68,668 hospitalized patients having experienced falls, hip fracture was shown to be associated with an increased risk of MACEs. The immediate risk of MACEs was the highest near the time of hip fracture (during the first 90 days after index date), and such risk decreased continuously although it remained statistically significant in 1 year.

To the best of our knowledge, this is the first study using patients having experienced falls as the control group to address the potential overestimation of the effect of hip fracture that could arise from using the general population as the control group. A previous meta-analysis summarized studies that evaluated the association between fracture and CVD (2). Based on the data from eight studies, there was a significant association between hip fracture and increased risk of CVD, with a pooled HR of 1.48 (95% CI, 1.22 to 1.80) (2). Although published studies involved differences in study design (such as different definitions of CVD, age groups of interest, control group), our estimate (HR of 1.27) was in line with the published meta-analysis, with the corresponding CID of 2.40% when compared to the fall control cohort. We observed null association for hip fracture with MACEs mortality. We therefore performed a sensitivity analysis using admission date as the index date, and observed that hip fracture was significantly

associated with MACEs mortality with a HR of 1.13 (95% CI, 1.01 to 1.25). These data suggested that the excessive cardiovascular mortality during hospitalization may lead to underestimation of the risk in the current study.

Our study further showed that there is an immediate risk of MACEs after hip fracture. While most, if not all, non-traumatic hip fractures resulted from falls from standing height, fall *per se* could be due to the presence of undiagnosed CVD or other conditions that are known to be associated with increased risk of CVD, such as frailty, physical inactivity, and diabetes. A previous Danish study found that hip fracture patients had a significantly increased risk of MI and stroke in the first 30 days after the diagnosis of hip fracture, with a HR of 12.97 (95% CI, 11.56 to 14.55) and 9.42 (95% CI, 8.71 to 10.19) respectively, when compared to the general population, after adjustment for age, sex, Charlson comorbidity index, previous osteoporotic fracture, and calendar year of diagnosis. The HR for MI and stroke in the first 90 days observed in the current study was 1.79 (95% CI, 1.36 to 2.35) and 0.98 (95% CI, 0.85 to 1.14), respectively. Such discrepancy in the estimates could be driven by the control cohort (general population in the Danish study vs. hospitalized patients having experienced falls in this study), different definition of index date (diagnosis date in the Danish study vs. hospital discharge date in this study), and statistical methods (adjustment for 5 variables in the Danish study vs. propensity score matching based on 41 variables in this study). Since postoperative complications are commonly defined as complications occurring in the first 30 days after an operation, the estimates observed in the previous study could be over-estimated and biased. Likewise, using admission date as the index date in the present study yielded null association between hip fracture and stroke in the first 30 follow-up days (HR, 0.97; 95% CI, 0.88 to 1.07).

Nevertheless, our study showed that the immediate increase in risk was observed not only for MI, but also AF, HF, and MACEs.

Increasing evidence showed that bone metabolism and risk of CVD are closely related. In patients with hip fracture, immobilization, especially soon after hip fracture, can lead to hypercalcemia, which was a causal factor of coronary heart disease (27), MI (27), and lower BMD (28) as demonstrated in Mendelian Randomization studies. Nevertheless, such elevation in serum calcium could be progressively reduced in 3 months (29). On the other hand, there are common risk factors underlying both osteoporosis and CVD risk (1, 30), such as physical inactivity, older age, smoking and drinking, increased inflammation, LDL-cholesterol (31), vitamin K (32, 33) etc. Randomized controlled trials provided evidence on the association between increased risk of CVD and non-steroidal anti-inflammatory drugs (NSAIDs), which could be used for pain management for patients after hip fracture surgery (34). A meta-analysis investigating the association between use of NSAIDs and acute MI showed that the risk of acute MI was greatest in the first month of NSAIDs use (35). These factors could potentially explain why there was an overall increase in both 1-year risk and immediate risk for MACEs after hip fracture.

Our study has important clinical implications. The immediate risk of MACEs after hip fracture suggested a prompt evaluation of MACEs among older adults aged 65 years and older who are diagnosed with hip fracture irrespectively of cardiovascular risk factors may be important, as early management may reduce subsequent risk of MACEs. It also suggested that close

monitoring of MACEs risk in hip fracture patients is required, which may lead to a better prognosis.

This study was conducted based on a large survivor cohort identified from a population-based electronic health record system. The fracture diagnoses in the CDARS were validated (20), and this database has been previously used to conduct high quality observational studies (11, 21). In addition to the availability of a large sample size in this study, the use of a fall control cohort combined with PS matching provided a robust method to estimate the independent effect of hip fracture on CVD risk among the population of older adults who are susceptible to falls. While many previous studies included a few basic demographic covariates (e.g. age and gender) for matching cases and controls, this study included a detailed list of important variables, including baseline diagnosis and medication variables, in the PS generation and matching. We also addressed the issue of competing risk of death on the outcome estimations. Furthermore, a wide range of CVDs were evaluated, including HF, which is rarely reported in the literature but is a common disease in older adult populations (2). We also considered the issue of postoperative cardiac complication in the analysis to avoid bias and over-estimation.

There are limitations in this study. Although an extensive list of covariates was controlled for in the analysis, data on BMD which is an important risk factor of CVD were not available. Nevertheless, we used a diagnosis code of osteoporosis at baseline as a surrogate indicator of BMD. Similarly, blood pressure, blood lipid and body mass index were unavailable, while hyperlipidemia, obesity and hypertensive diseases statuses at baseline were used as surrogate

indicators (11). As data on HBA1c levels which could be used to evaluate glycemic control were not available, diabetes mellitus status at baseline was considered. Another limitation is that only inpatient records within the public hospital system were included in this study, while outpatient and general practice events were not captured. However, using a centralized population database provided the advantage of large sample size and a relatively high level of data consistency. The use of hospital discharge rather than admission date as index date meant that MACEs recorded during hospitalization would not be considered as outcome events. Treatment of hip fracture typically involves surgeries which may be associated with postoperative CVD events and mortality. For example, the use of antithrombotic drugs after hip fracture surgery could provide a protective effect towards risk of CVD while the drugs are administered, but such an effect could be lost after termination from drug treatment. The estimates observed in this study could have been under-estimated, due to our stringent definition of postoperative cardiac complications (cardiac events that happened within 30 days after the index date), thus it is expected that non postoperative cardiac complications could have been excluded. This issue was addressed through the sensitivity analysis using hospital admission index date, which captured in-hospital events.

Using hospital discharge date as index date could introduce immortal time bias, which would be in favor of a protective effect (i.e. HR<1) of the exposure (hip fracture) (36). Under our stringent definition of cardiovascular outcomes, significant associations between hip fracture and increased risk of MACE outcomes were observed except for MACE mortality. Although immortal time bias could indeed lead to underestimation of the associations between hip fracture and cardiovascular outcomes, it would not lead to false-positive associations (i.e. associations of hip fracture and increased risk of MACEs) in the current study.

When the definition of index date changed from hospital discharge to admission date, the association between hip fracture and MACE mortality changed from null to significant. This observation suggested that MACE mortality may be elevated soon after sustaining a hip fracture and immortal time bias under the hospital discharge index date setting could potentially be present. Therefore, a sensitivity analysis with length of hospital stay included in the PS model was conducted to investigate whether this variable mediated the association between hip fracture and MACE mortality. However, the association with MACE mortality was still insignificant under this setting. Collectively, these findings suggested that length of stay may not explain the null association with MACE mortality after the hip fracture when discharge date was used as the index date. The null association could be due to lower sample event number and hence power, after excluding patients who died from cardiac causes happened during hospitalization.

Comparing to the results of the minimal PS model with age and sex as the only covariates, accounting for the detailed list of potential covariates did not alter the conclusions, suggesting that the other covariates included in the PS model played a minimal role in the association of hip fracture with MACE outcomes. Although the results showed that including the large number of covariates in the propensity score model may be unnecessary in the current study, we aimed to create a cohort with balanced baseline characteristics for a better comparison between the hip fracture and control groups. PS matching mimicking randomization in a randomized controlled trial is a statistical technique that addresses bias in non-experimental settings, thus we consider it

is still a good practice to perform PS matching and considered covariates based on biological plausibility in the current study.

In conclusion, this study identified a robust association between hip fracture and increased risk of MACEs in the older adult population. We further showed that the risk of MACEs is the highest near the time of hip fracture (during the first 90 days after index date), suggesting there is an immediate risk of MACEs after fracture. These findings might be used to support CVD risk assessment and health management of older adults who are diagnosed with hip fracture irrespectively of cardiovascular risk factors.

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Table 1. Incidence rates of CVD events in the hip fracture and fall control cohorts.

	Hip Fracture Events (n)	Control Events (n)	Hip Fracture n = 34,334 Incidence rate, per 1,000 person-years	Control n = 34,334 Incidence rate, per 1,000 person-years
MACEs	4,061	3,236	133.10	105.19
Atrial Fibrillation	1,428	1,110	45.37	35.17
Heart Failure	1,937	1,461	61.94	46.47
Myocardial Infarction	512	368	16.03	11.51
Stroke	1,093	940	34.51	29.71
MACEs Mortality	358	396	11.16	12.35

Notes: MACEs = Major Adverse Cardiovascular Events.

Table 2. Estimated 1-year Cumulative Incidences of CVD events in the hip fracture and fall control cohorts.

	Hip Fracture n = 34,334 Estimated 1-year Cumulative Incidence	Control n = 34,334 Estimated 1-year Cumulative Incidence	Estimated 1-year Cumulative Incidence Difference (Bootstrap CI)[a]
MACEs	11.83%	9.43%	2.40% (1.94% to 2.87%)
Atrial Fibrillation	4.16%	3.23%	0.93% (0.65% to 1.20%)
Heart Failure	5.64%	4.26%	1.39% (1.07% to 1.70%)
Myocardial Infarction	1.49%	1.07%	0.42% (0.24% to 0.59%)
Stroke	3.18%	2.74%	0.45% (0.19% to 0.71%)
MACEs Mortality	1.04%	1.15%	-0.11% (-0.28% to 0.05%)

Notes: MACEs = Major Adverse Cardiovascular Events; CI = Confidence Interval.

[a] Confidence Interval estimated using 1000 bootstrap samples.

Table 3. Risk of MACEs outcomes of hip fracture patients within one year after index date, compared with fall control cohort patients.

Hazard Ratios from Competing Risk Regression (95% CI) p-value				
	90 days	180 days	270 days	1 year
MACEs	1.32 (1.23 – 1.43) p < 0.001	1.26 (1.19 – 1.34) p < 0.001	1.27 (1.21 – 1.34) p < 0.001	1.27 (1.21 – 1.33) p < 0.001
Atrial Fibrillation	1.41 (1.23 – 1.61) p < 0.001	1.30 (1.17 – 1.43) p < 0.001	1.30 (1.19 – 1.42) p < 0.001	1.29 (1.20 – 1.40) p < 0.001
Heart Failure	1.48 (1.32 – 1.66) p < 0.001	1.37 (1.26 – 1.49) p < 0.001	1.33 (1.24 – 1.44) p < 0.001	1.34 (1.25 – 1.43) p < 0.001
Myocardial Infarction	1.79 (1.36 – 2.35) p < 0.001	1.67 (1.39 – 2.01) p < 0.001	1.50 (1.29 – 1.75) p < 0.001	1.40 (1.22 – 1.60) p < 0.001

Stroke	0.98 (0.85 – 1.14) p = 0.82	1.04 (0.93 – 1.17) p = 0.45	1.12 (1.01 – 1.23) p = 0.028	1.16 (1.07 – 1.27) p < 0.001
MACEs Mortality	0.90 (0.68 – 1.19) p = 0.48	0.94 (0.77 – 1.13) p = 0.49	0.97 (0.82 – 1.14) p = 0.67	0.90 (0.78 – 1.04) p = 0.17

Notes: A sample size of 68,668 after PS Match (Hip fracture: 34,334, Control: 34,334).

MACEs = Major Adverse Cardiovascular Events; CI = Confidence Interval.

Figure 1. Cohort selection flowchart for this study. Postoperative cardiac complications were defined as MACEs recorded in the first 30 days after the index date.

Figure 2. Changes in hazard ratios for CVD outcomes within one year follow-up. Risk of MACEs outcomes with follow-up up to one year after discharge from hospital.

Supplemental Materials

Contents

eTable 1. Covariates included in the propensity score model.

Demographics	
Sex	
Age on index date	
Calendar year on index date	
Institution Cluster	

Diagnoses	**ICD9 Codes**
Cardiovascular diseases	
Coronary heart disease	410, 411, 412, 413, 414, 429.2, 429.71, 429.79
Congestive Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Cerebrovascular diseases	430-437
Hypertensive diseases	401-405
Arrhythmia and conduction disorders	426-427
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447
Respiratory related diseases	
Chronic obstructive pulmonary disease	490-492, 493, 494, 495, 496, 500-505, 506.4
Endocrine and metabolic disorders	
Overweight and obesity	278.0
Hyperlipidaemia	272.0-272.2, 272.4
Diabetes	250
Thyroid disorders	242-244
Renal diseases	
Chronic renal disease	403, 404, 582, 585, 590.0

Liver diseases

Esophageal varices, chronic liver disease, hepatic failure, cirrhosis	456.0, 456.1, 456.2, 571.2, 571.4, 571.5, 571.6, 572.2, 572.3, 572.4, 572.8

Bone related diseases

Osteoporosis	733.0
Paget's disease of bone	731.0
Major fractures other than hip fracture	805, 812, 813, 814

Other diseases

Dementia	290
Connective tissue disease	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725

Medication History
Osteoporosis drugs
Angiotensin II receptor blockers / Angiotensin-converting enzyme-I
Calcium channel blockers
Loop diuretics
Other diuretics
Beta-blockers
Anti-arrhythmics class I and II
Cardiac glycosides
Nitrates
Platelet inhibitors
Anticoagulants
Peripheral vasodilators
Lipid regulating drugs

Antidiabetic drugs (including insulins)

Antidepressants

Antipsychotics

Oral corticosteroids

Nonsteroidal anti-inflammatory drug (NSAIDs)

Proton pump inhibitors

eTable 2. Baseline characteristics of the study cohort.

	Pre-matched Cohort			Matched Cohort		
Variables	Control	Hip Fracture	Standardized Mean Differences	Control	Hip Fracture	Standardized Mean Differences
n	79230	48488		34334	34334	
Males, n (%)	27768 (35.0)	15064 (31.1)	0.085	11418 (33.3)	11485 (33.5)	0.004
Age, mean (SD)	79.73 (7.96)	83.22 (7.37)	0.455	81.94 (7.55)	81.75 (7.04)	0.027
Hospital Cluster, n (%)			0.137			0.02
HKE	11347 (14.3)	5926 (12.2)		4377 (12.7)	4392 (12.8)	
HKW	7491 (9.5)	3940 (8.1)		3013 (8.8)	3154 (9.2)	
KC	15090 (19.0)	9475 (19.5)		6984 (20.3)	7044 (20.5)	
KE	10029 (12.7)	6836 (14.1)		4543 (13.2)	4407 (12.8)	
KW	16958 (21.4)	9131 (18.8)		6850 (20.0)	6815 (19.8)	
NTE	10674 (13.5)	8082 (16.7)		5006 (14.6)	5049 (14.7)	
NTW	7613 (9.6)	5098 (10.5)		3561 (10.4)	3473 (10.1)	
Other	28 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Year of Index Date, n (%)			0.131			0.016
2006	6004 (7.6)	4469 (9.2)		3053 (8.9)	3039 (8.9)	
2007	6332 (8.0)	4543 (9.4)		3182 (9.3)	3161 (9.2)	
2008	6794 (8.6)	4835 (10.0)		3362 (9.8)	3270 (9.5)	
2009	7811 (9.9)	4678 (9.6)		3446 (10.0)	3483 (10.1)	
2010	8505 (10.7)	4746 (9.8)		3519 (10.2)	3500 (10.2)	
2011	8260 (10.4)	5046 (10.4)		3478 (10.1)	3537 (10.3)	
2012	8947 (11.3)	4925 (10.2)		3561 (10.4)	3589 (10.5)	
2013	9579 (12.1)	4935 (10.2)		3506 (10.2)	3611 (10.5)	
2014	9911 (12.5)	5290 (10.9)		3934 (11.5)	3923 (11.4)	
2015	7087 (8.9)	5021 (10.4)		3293 (9.6)	3221 (9.4)	

eTable 2 (Continued)

	Pre-matched Cohort			Matched Cohort		
Variables	Control	Hip Fracture	Standardized Mean Differences	Control	Hip Fracture	Standardized Mean Differences
Medical record within 365 days before index date, n (%)						
Coronary heart disease	4159 (5.2)	3692 (7.6)	0.097	1808 (5.3)	1865 (5.4)	0.007
Congestive heart failure	3456 (4.4)	3255 (6.7)	0.103	1324 (3.9)	1402 (4.1)	0.012
Cerebrovascular diseases	2767 (3.5)	2302 (4.7)	0.063	1148 (3.3)	1316 (3.8)	0.026
Hypertensive diseases	14780 (18.7)	13010 (26.8)	0.196	6823 (19.9)	7169 (20.9)	0.025
Arrhythmia and conduction disorders	4151 (5.2)	3785 (7.8)	0.104	1660 (4.8)	1742 (5.1)	0.011
Arterial disease	959 (1.2)	1060 (2.2)	0.076	437 (1.3)	509 (1.5)	0.018
Chronic obstructive pulmonary disease	2764 (3.5)	3078 (6.3)	0.133	1194 (3.5)	1367 (4.0)	0.027
Hyperlipidemia	3485 (4.4)	2303 (4.7)	0.017	1428 (4.2)	1469 (4.3)	0.006
Obesity	157 (0.2)	41 (0.1)	0.03	34 (0.1)	34 (0.1)	<0.001
Diabetes	10360 (13.1)	6859 (14.1)	0.031	4709 (13.7)	4715 (13.7)	0.001
Thyroid disorders	647 (0.8)	552 (1.1)	0.033	268 (0.8)	299 (0.9)	0.01
Chronic renal disease	2300 (2.9)	1989 (4.1)	0.065	1000 (2.9)	1082 (3.2)	0.014
Liver diseases	284 (0.4)	227 (0.5)	0.017	124 (0.4)	123 (0.4)	<0.001
Osteoporosis	1917 (2.4)	1543 (3.2)	0.046	644 (1.9)	740 (2.2)	0.02
Paget's disease of bone	9 (0.0)	7 (0.0)	0.003	2 (0.0)	4 (0.0)	0.006
Major fractures other than hip fracture	20856 (26.3)	2100 (4.3)	0.641	1675 (4.9)	1679 (4.9)	0.001
Dementia	1520 (1.9)	2374 (4.9)	0.165	666 (1.9)	784 (2.3)	0.024
Connective tissue disease	271 (0.3)	202 (0.4)	0.012	114 (0.3)	130 (0.4)	0.008

eTable 2 (Continued)

	Pre-matched Cohort			Matched Cohort		
Variables	Control	Hip Fracture	Standardized Mean Differences	Control	Hip Fracture	Standardized Mean Differences
Prescription record within 365 days before index date, n (%)						
Cardiac glycosides	3139 (4.0)	2063 (4.3)	0.015	1291 (3.8)	1144 (3.3)	0.023
Loop diuretics	12479 (15.8)	9901 (20.4)	0.122	5741 (16.7)	5688 (16.6)	0.004
Other diuretics	8666 (10.9)	4765 (9.8)	0.036	3482 (10.1)	3534 (10.3)	0.005
Anti-arrhythmics class I and II	1403 (1.8)	1391 (2.9)	0.073	660 (1.9)	582 (1.7)	0.017
Beta-blocker	22558 (28.5)	13376 (27.6)	0.02	9398 (27.4)	9304 (27.1)	0.006
Angiotensin II receptor blockers / Angiotensin-converting enzyme-I	24291 (30.7)	14895 (30.7)	0.001	10229 (29.8)	10238 (29.8)	0.001
Nitrates	10953 (13.8)	6667 (13.7)	0.002	4397 (12.8)	4360 (12.7)	0.003
Calcium channel blockers	37207 (47.0)	24344 (50.2)	0.065	16469 (48.0)	16578 (48.3)	0.006
Peripheral vasodilators	1289 (1.6)	1027 (2.1)	0.036	652 (1.9)	634 (1.8)	0.004
Anticoagulants	4823 (6.1)	4239 (8.7)	0.101	2329 (6.8)	2291 (6.7)	0.004
Platelet inhibitors	26582 (33.6)	17220 (35.5)	0.041	11685 (34.0)	11528 (33.6)	0.01
Lipid regulating drugs	19369 (24.4)	9908 (20.4)	0.096	7331 (21.4)	7396 (21.5)	0.005
Antipsychotics	6226 (7.9)	5743 (11.8)	0.134	3241 (9.4)	3240 (9.4)	<0.001
Antidepressants	7691 (9.7)	5721 (11.8)	0.068	3626 (10.6)	3617 (10.5)	0.001
Antidiabetic drugs (including insulins)	19518 (24.6)	11693 (24.1)	0.012	8529 (24.8)	8708 (25.4)	0.012
Oral corticosteroids	7365 (9.3)	4193 (8.6)	0.023	2681 (7.8)	2718 (7.9)	0.004
Nonsteroidal anti-inflammatory drug (NSAIDs)	16076 (20.3)	6584 (13.6)	0.18	5291 (15.4)	5382 (15.7)	0.007
Proton pump inhibitors	12127 (15.3)	8976 (18.5)	0.086	5382 (15.7)	5496 (16.0)	0.009
Osteoporosis drugs	2951 (3.7)	612 (1.3)	0.158	492 (1.4)	508 (1.5)	0.004

Notes: SD = Standard Deviation; HKE = Hong Kong East; HKW = Hong Kong West; KC = Kowloon Central; KE = Kowloon East; KW = Kowloon West; NTE = New Territories East; NTW = New Territories West.

eTable 3. Competing risk regression analysis in evaluating the association between hip fracture with one-year risk of MACEs, compared with the fall control cohort patients.

	Hazard Ratio (95% CI)	p-value	E-value[a]
MACEs	1.27 (1.21 to 1.33)	<0.001	1.86
Atrial Fibrillation	1.29 (1.20 to 1.40)	<0.001	1.90
Heart Failure	1.34 (1.25 to 1.43)	<0.001	2.01
Myocardial Infarction	1.40 (1.22 to 1.60)	<0.001	2.15
Stroke	1.16 (1.07 to 1.27)	<0.001	1.59
MACEs Mortality	0.90 (0.78 to 1.04)	0.17	NA

Notes: A sample size of 68,668 after PS Match (Hip fracture cohort: 34,334, Control cohort: 34,334). CI = Confidence Interval.
[a] E-value computed for the observed hazard ratio estimate. NA is assigned when the association of interest is not statistically significant.

eTable 4. Risk of MACEs after propensity score matching with index date being hospital admission date.

	Hazard Ratio (95% CI)	p-value	E-value[a]
MACEs	1.28 (1.23 to 1.32)	<0.001	1.88
Atrial Fibrillation	1.25 (1.19 to 1.32)	<0.001	1.81
Heart Failure	1.37 (1.30 to 1.44)	<0.001	2.08
Myocardial Infarction	1.52 (1.38 to 1.67)	<0.001	2.41
Stroke	1.07 (1.00 to 1.14)	0.039	1.34
MACEs Mortality	1.13 (1.01 to 1.25)	0.028	1.51

Notes: A sample size of 80,170 after PS Match using 1:1 match, without replacement (Hip fracture: 40,085, Control: 40,085). CI = Confidence Interval.

[a] E-value computed for the observed hazard ratio estimate. NA is assigned when the association of interest is not statistically significant.

eTable 5. Risk of MACEs with length of hospital stay added to propensity score model (Hospital discharge date as index date).

Hazard Ratios from Competing Risk Regression (95% CI) p-value				
	90 days	180 days	270 days	1 year
MACEs	1.26 (1.16 – 1.38) p < 0.001	1.21 (1.13 – 1.29) p < 0.001	1.23 (1.16 – 1.31) p < 0.001	1.25 (1.19 – 1.32) p < 0.001
Atrial Fibrillation	1.25 (1.08 – 1.45) p = 0.0036	1.19 (1.06 – 1.33) p = 0.0027	1.20 (1.08 – 1.32) p < 0.001	1.19 (1.09 – 1.30) p < 0.001
Heart Failure	1.43 (1.26 – 1.64) p < 0.001	1.32 (1.20 – 1.45) p < 0.001	1.29 (1.18 – 1.40) p < 0.001	1.33 (1.23 – 1.44) p < 0.001
Myocardial Infarction	1.81 (1.33 – 2.47) p < 0.001	1.58 (1.28 – 1.95) p < 0.001	1.51 (1.27 – 1.80) p < 0.001	1.41 (1.21 – 1.64) p < 0.001
Stroke	0.92 (0.78 – 1.09) p = 0.36	1.01 (0.89 – 1.15) p = 0.87	1.10 (0.99 – 1.23) p = 0.08	1.16 (1.05 – 1.28) p = 0.0041
MACEs Mortality	1.06 (0.77 – 1.46) p = 0.74	0.98 (0.78 – 1.23) p = 0.86	1.05 (0.87 – 1.27) p = 0.59	1.02 (0.87 – 1.21) p = 0.80

Notes: A sample size of 51,448 after PS Match (Hip fracture: 25,724, Control: 25,724).
MACEs = Major Adverse Cardiovascular Events; CI = Confidence Interval.

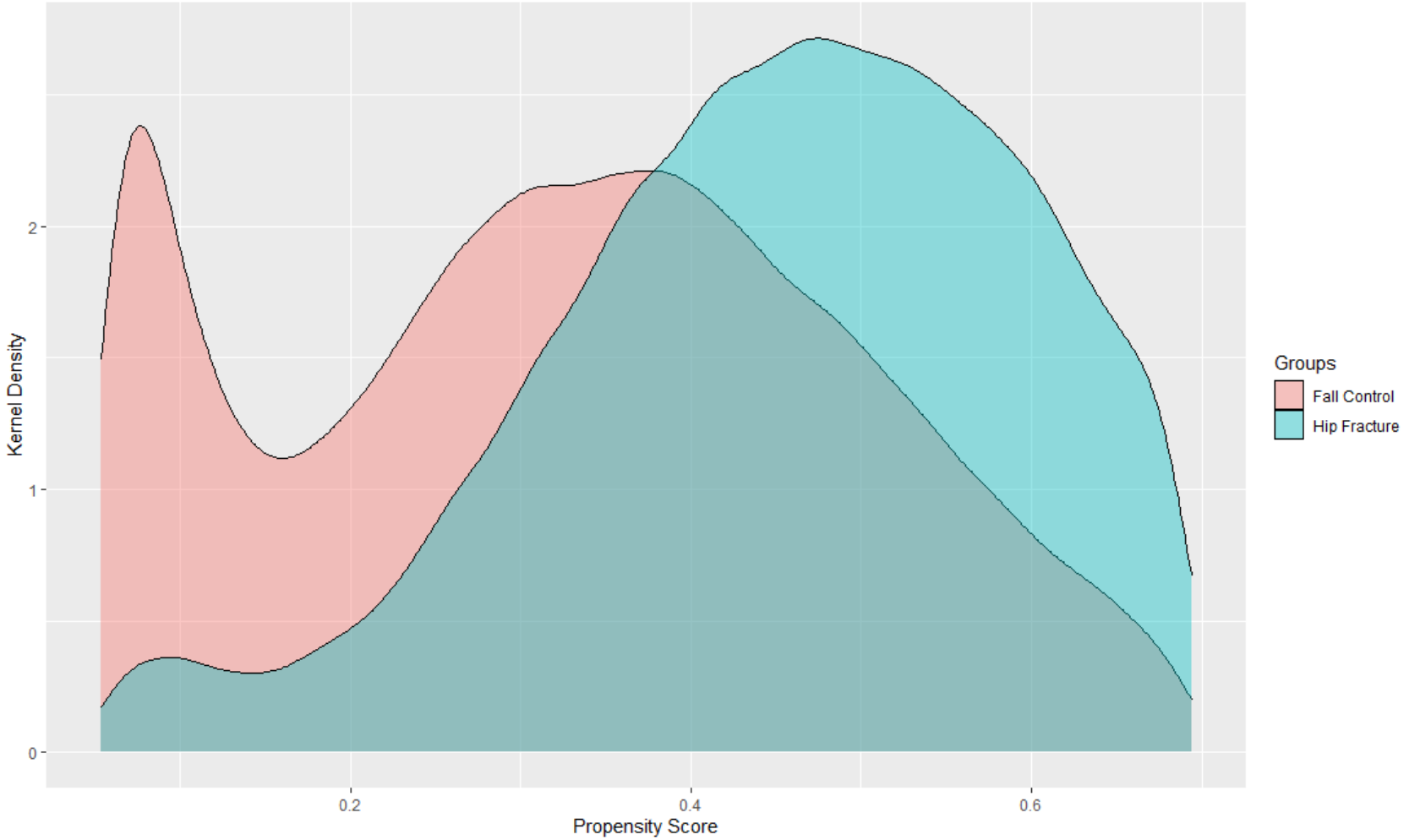
eTable 6. Risk of MACEs after propensity score matching with only age and sex included in the propensity score model (index date being hospital discharge date).

	Hazard Ratio (95% CI)	p-value	E-value[a]
MACEs	1.29 (1.24 to 1.35)	<0.001	1.90
Atrial Fibrillation	1.26 (1.17 to 1.35)	<0.001	1.83
Heart Failure	1.32 (1.24 to 1.41)	<0.001	1.97
Myocardial Infarction	1.27 (1.13 to 1.44)	<0.001	1.86
Stroke	1.22 (1.13 to 1.32)	<0.001	1.74
MACEs Mortality	1.06 (0.92 to 1.21)	0.44	NA

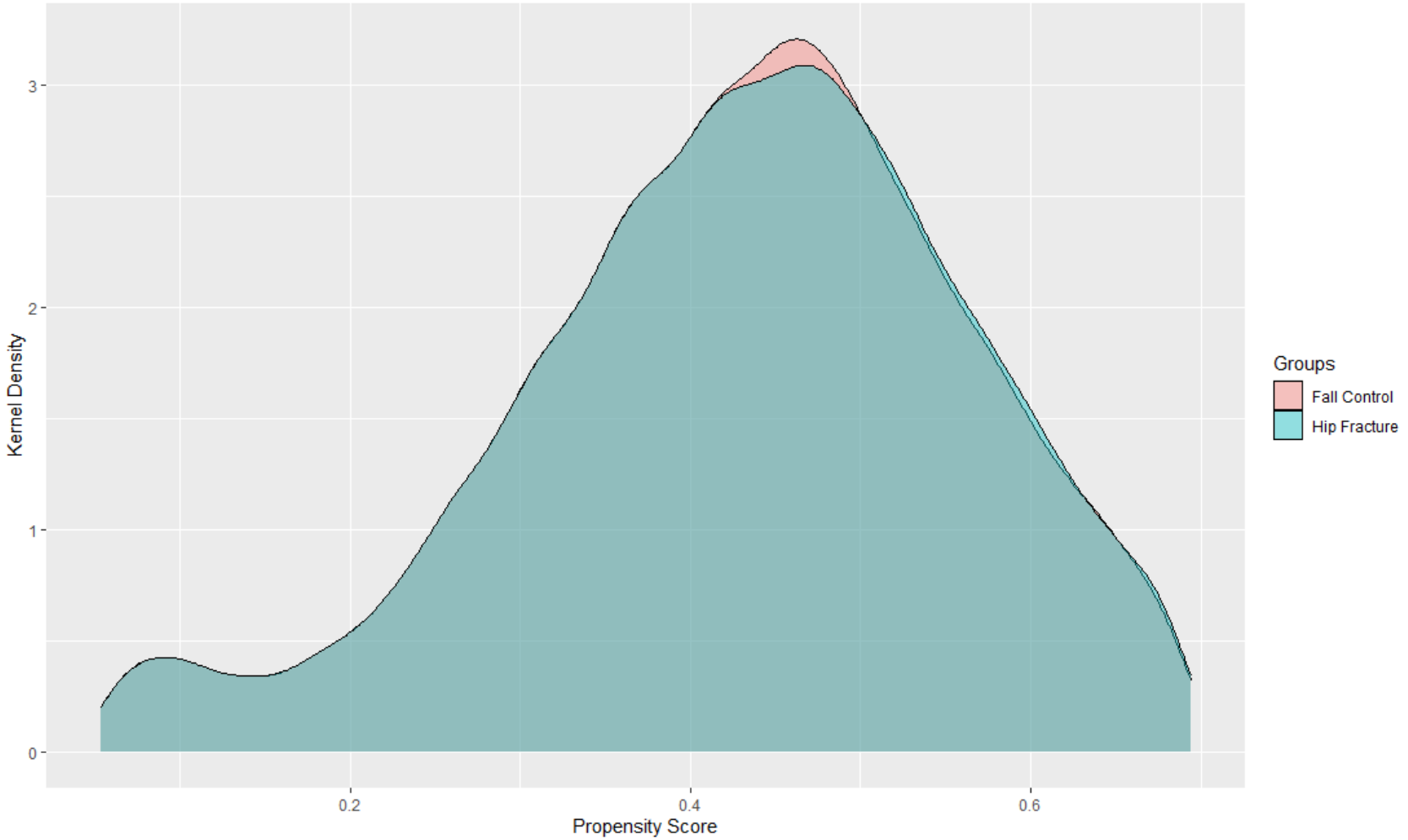
Notes: A sample size of 77,024 after PS Match (Hip fracture cohort: 38,512, Control cohort: 38,512). CI = Confidence Interval.
[a] E-value computed for the observed hazard ratio estimate. NA is assigned when the association of interest is not statistically significant.

eFigure 1. Kernel density plots comparing the hip fracture and fall control groups.

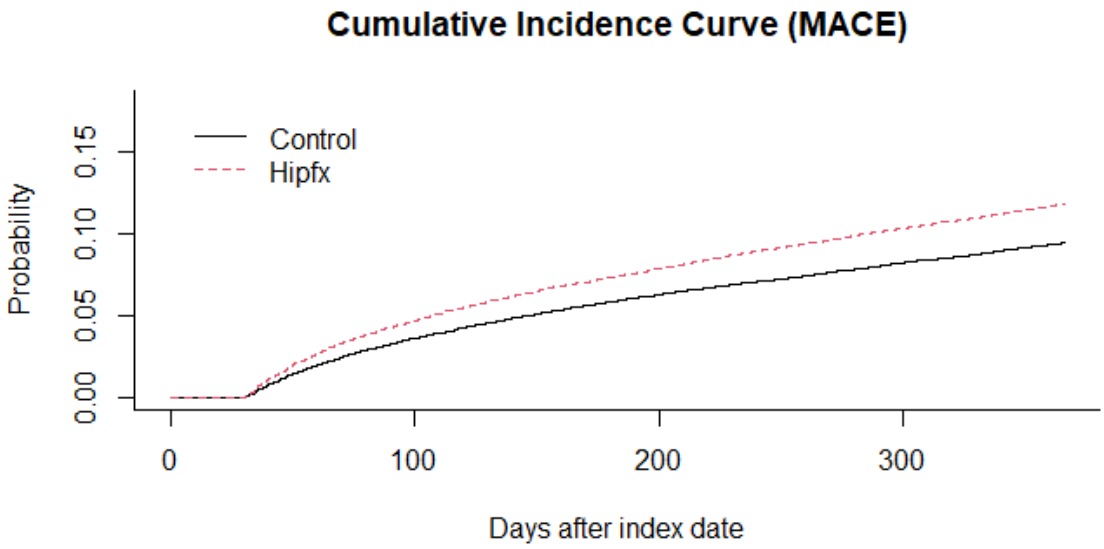
(a) Kernel density plot before propensity score matching.



(b) Kernel density plot after propensity score matching.



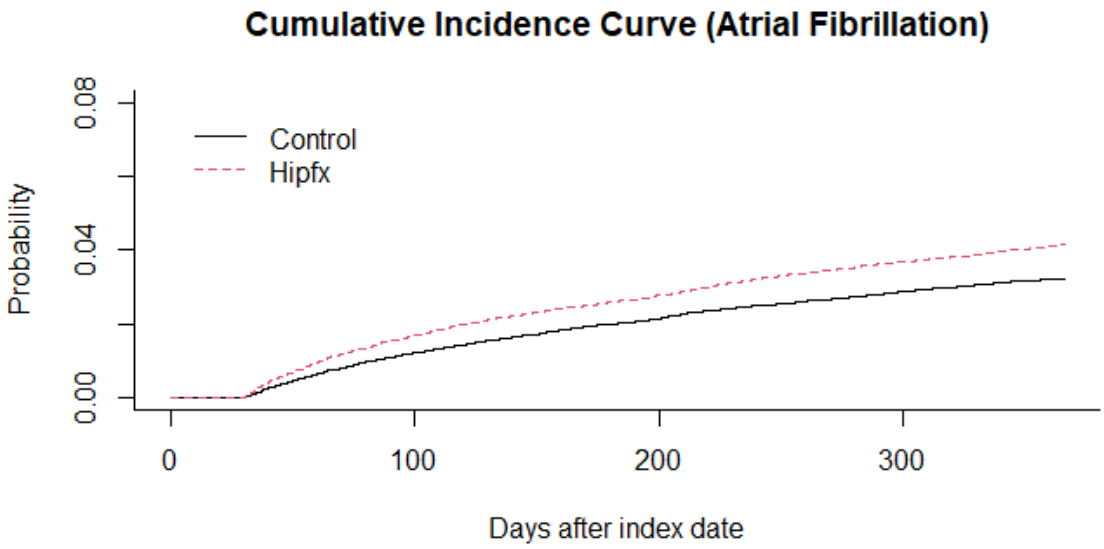
eFigure 2a. Cumulative Incidence Curve of MACEs.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.

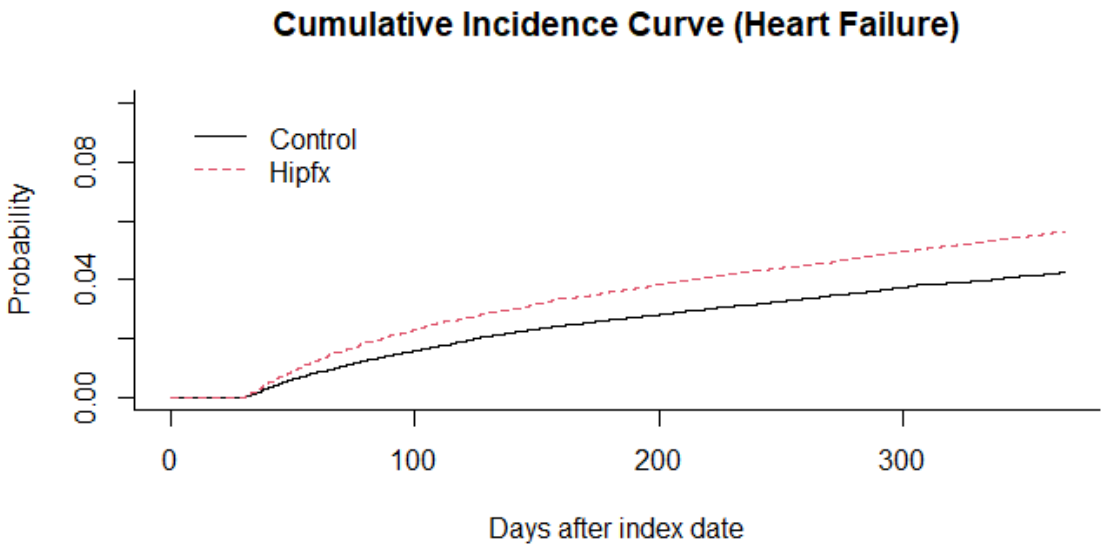
eFigure 2b. Cumulative Incidence Curve of Atrial Fibrillation.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.

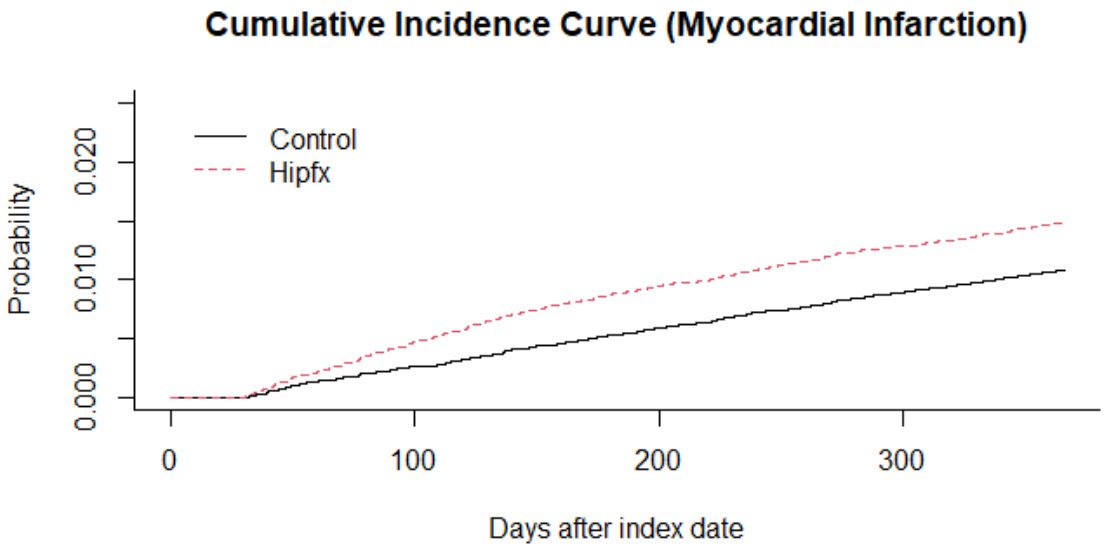
eFigure 2c. Cumulative Incidence Curve of Heart Failure.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.

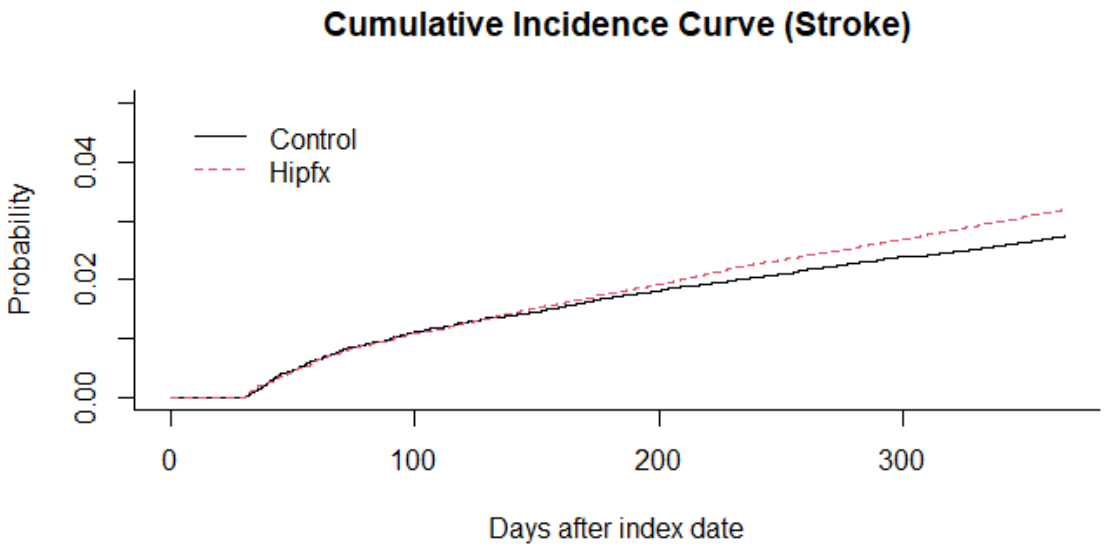
eFigure 2d. Cumulative Incidence Curve of Myocardial Infarction.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.

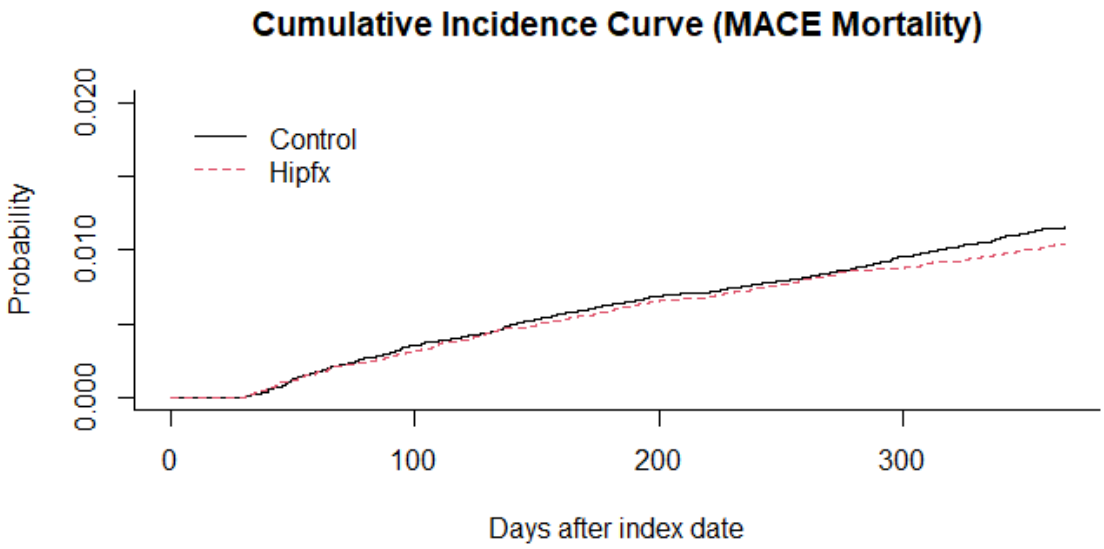
eFigure 2e. Cumulative Incidence Curve of Stroke.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.

eFigure 2f. Cumulative Incidence Curve of MACEs Mortality.



Key:

Control: falls patients without hip fracture;
Hipfx: falls patients with hip fracture.