Drugs Aging (2015) 32:927–936
DOI 10.1007/s40266-015-0306-5

ORIGINAL RESEARCH ARTICLE

Antihypertensive Medications, Loop Diuretics, and Risk of Hip Fracture in the Elderly: A Population-Based Cohort Study of 81,617 Italian Patients Newly Treated Between 2005 and 2009

Giovanni Corrao[1] · Paolo Mazzola[2] · Matteo Monzio Compagnoni[1] · Federico Rea[1] · Luca Merlino[3] · Giorgio Annoni[2,4] · Giuseppe Mancia[2,5]

Published online: 20 November 2015

Abstract

Objective Our objective was to assess the relationship between antihypertensive drugs, loop diuretics, and the risk of hospitalization for hip fracture (HF).

Design We conducted a population-based study in a cohort of 81,617 patients from Lombardy (Italy) aged 70–90 years who were newly treated with antihypertensive agents or loop diuretics between 2005 and 2009. Cases were the 2153 patients who experienced the outcome (hospitalization for HF before 31 December 2012). For each case, up to three controls were randomly selected from the cohort to be matched for sex, age at cohort entry, and date of initial prescription. The case–control and case-crossover designs and the logistic regression for matched sets were used to measure the strength of the association between current use of an antihypertensive drug (within 30 days before the HF hospitalization) and the risk of outcome.

Results Case–control and case-crossover odds ratios (ORs) for current use of loop diuretics were 1.67 (95 % confidence interval [CI] 1.28–2.18) and 1.49 (95 % CI 1.05–2.10), respectively. Among patients aged 81–90 years, case–control and case-crossover ORs were 1.52 (95 % CI 1.04–2.21) and 1.82 (95 % CI 1.10–3.00) for current use of loop diuretics and 1.86 (95 % CI 1.03–3.35) and 1.88 (95 % CI 1.01–3.48) for α-blockers. No other agent was associated with the outcome.

Conclusions Evidence that loop diuretics and α-blockers are associated with a higher risk of HF was consistent in the two observational approaches. Clinicians should carefully consider the risk of falls in their selection of drugs for hypertension and in the clinical use of loop diuretics.

Key Points

Newly prescribed antihypertensive medications, when considered together as a whole class, do not determine a greater risk of hip fracture in older patients.

However, particularly in the oldest patients, α-blockers and loop diuretics may increase this risk.

Rapid reduction of circulating fluid volume and/or systematic vasodilatation should be avoided in the elderly because these mechanisms are highly likely to cause a fall and consequent hip fracture.

1 Introduction

Randomized clinical trials have repeatedly shown that antihypertensive drug treatment reduces the risk of hypertension-related morbid and fatal events in older patients

Electronic supplementary material The online version of this article (doi:10.1007/s40266-015-0306-5) contains supplementary material, which is available to authorized users.

✉ Giovanni Corrao
giovanni.corrao@unimib.it

[1] Division of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milan, Italy

[2] Department of Health Sciences, University of Milano-Bicocca, Milan, Italy

[3] Operative Unit of Territorial Health Services, Lombardy Region, Milan, Italy

[4] Geriatric Clinic, San Gerardo University Hospital, Monza, Italy

[5] Istituto Auxologico Italiano, Milan, Italy

[1], including subjects aged ≥80 years, who show a favorable benefit–harm ratio for antihypertensive treatments [2, 3]. However, elderly hypertensive patients recruited for randomized clinical trials have almost invariably been characterized by better health status than those in real-life practice. This difference is particularly marked in the as-yet sole trial addressing octogenarian hypertensive subjects [4–6]. Furthermore, in randomized clinical trials, the expertise of physicians and the close follow-up afforded patients favor optimal treatment delivery, minimizing its side effects [7], but the real-life tolerability profile of elderly patients may differ [8].

Falls are a well-known geriatric syndrome that often lead to serious injuries such as fractures. Among them, hip fracture (HF) is considered a key proxy of falls [9]. Major risk factors for falls are balance and gait impairment, dizziness, and postural hypotension, which are among the most common adverse effects of antihypertensive medications [10–12]. A meta-analysis of observational studies showed a 24 % increased odds of falling associated with the use of antihypertensive agents [13], even though the studies varied in the extent of adjustment for confounding factors. As a result, whether (and the extent to which) these findings are attributable to differences between individuals—i.e. comorbidity and other confounders—or to the effect of antihypertensive agents per se is unclear [14].

Data are conflicting concerning the effect of different antihypertensive medications on the occurrence of falls and fractures [13–19]. Reports of a reduction in fracture risk with β-blockers [20–24], calcium channel blockers (CCBs) [15], angiotensin-converting enzyme (ACE) inhibitors [16, 17], and angiotensin receptor antagonists (angiotensin receptor blockers [ARBs]) [25] are inconsistent. Loop diuretics as a class have been associated with an increased risk of HF in some [17, 26, 27], but not all [28, 29], studies.

We performed a large population-based investigation nested into a cohort of individuals aged between 70 and 90 years newly treated with antihypertensive drugs or loop diuretics, to assess whether current exposure to these agents increases the risk of HF.

2 Methods

2.1 Setting

Lombardy is a Northern Italian region that accounts for about 16 % (almost 10 million) of the total Italian population. All Italian citizens are covered by the National Health Service (NHS); in Lombardy, this has been associated since 1997 with an automated system of databases to collect a variety of information. We retrieved data from the Lombardy healthcare utilization databases, the details of which and uses in the field of hypertension are reported elsewhere [30–34].

2.2 Cohort and Follow-Up

We included all residents aged 70–90 years. Of these, we identified those who received at least one antihypertensive medication or loop diuretic anytime between 2005 and 2009, defining the first dispensation as the initial prescription. The medications included blockers of the renin-angiotensin system (i.e. ACE inhibitors and ARBs), α-blockers, β-blockers, CCBs, and loop- and non-loop diuretics. The complete list of drugs is available in Table S1 of the Electronic Supplementary Material (ESM). Although these drugs may be used for treating conditions other than hypertension, and loop diuretics are not indicated as primary antihypertensives, we refer to them henceforth collectively as blood pressure (BP)-lowering medications.

On the basis of the 5-year interval before the initial prescription, patients were excluded if they had already received any BP-lowering medication (to ensure inclusion of newly treated individuals), or displayed characteristics suggestive of a high risk of falls and/or bone fracture, such as hospital admissions for selected causes or prescriptions of selected medications. The former, identified by the *International Classification of Diseases*, ninth revision (ICD-9) code for hospital admissions, included malignant neoplasm, traumatic injury, Paget's disease, osteomalacia, Cushing syndrome, coeliac disease, hyperthyroidism, hyper-parathyroidism, Parkinson's disease, orthostatic hypotension, blindness, balance disorders, dementia, cerebrovascular disease, and chronic liver disease. The selected medications, identified by the Anatomical Therapeutic Chemical (ATC) codes on outpatient drug prescriptions, were bisphosphonates, calcitonin, raloxifene, corticosteroids, antineoplastic agents, and medications used for thyroid therapy. To ensure enough observations to apply exclusion criteria, patients who had not been registered with the NHS for at least 5 years before the initial prescription were excluded.

The patients included in the final cohort accumulated person-years of follow-up from the initial prescription until hospital admission for HF (outcome), death, emigration, or 31 December 2012, whichever came first.

2.3 Cases and Controls

Cases were those who experienced the outcome 'hospitalization for HF' during the follow-up, identified by the related ICD-9 code (820.x). The earliest date of hospital admission recorded with this code was considered as the event date. Three controls for each case had not yet

experienced the outcome at the time of the matched case event (index date) and were selected randomly after they were matched on sex, age at cohort entry (±3 years), and date of cohort entry.

2.4 Exposure

For each case and control, all BP-lowering medications dispensed from initial prescription until the index date were identified. Prescriptions during the 30-day period before the index date were considered to identify current exposure to any BP-lowering medication. The last prescription before the outcome onset within the current time was considered to classify patients according to (1) exposure to specific BP-lowering classes, i.e., ACE inhibitors and ARBs together, α-blockers, β-blockers, CCBs, loop diuretics, and non-loop diuretics; (2) antihypertensive treatment strategy, i.e. if one (monotherapy), or two or more (combined therapy) agents were dispensed. Combined therapy was regarded as either a fixed-dose combination or an extemporaneous combination of two or more drugs dispensed at the same date.

2.5 Covariates

We included prescriptions of drugs used for selected diseases known to be associated with increased risk of fall (i.e., antidepressants, neuroleptics, and hypoglycemic agents [35, 36]). We also recorded the use of statins, which have been consistently associated with decreased risk of HF [37]. The prescriptions of these medications were recorded for the 5-year period before the initial prescription. Information about the use of other drugs suspected to affect postural control (i.e., digoxin, benzodiazepines, anti-arrhythmics, and anti-epileptics [38]) in the 30-day period before the HF was also included. Finally, diagnoses available from inpatient charts over 5 years before the initial prescription date were used to calculate the Charlson comorbidity index [39].

2.6 Data Analysis

Two data analysis approaches were used (Fig. 1).

First, the case–control approach was used by contrasting the current exposure of each case with that of three matched controls. A conditional logistic regression for 1:3 matched case–control data was used to estimate the odds ratio (OR) and 95 % confidence interval (CI) of HF associated with the current exposure to BP-lowering medications. Estimates were adjusted for the above-reported covariates, including drug prescriptions during the 5-year period (i.e., antidepressants, neuroleptics, hypoglycemic agents, and statins) and the 30-day period (i.e., digoxin, benzodiazepines, anti-arrhythmics, and anti-epileptics)

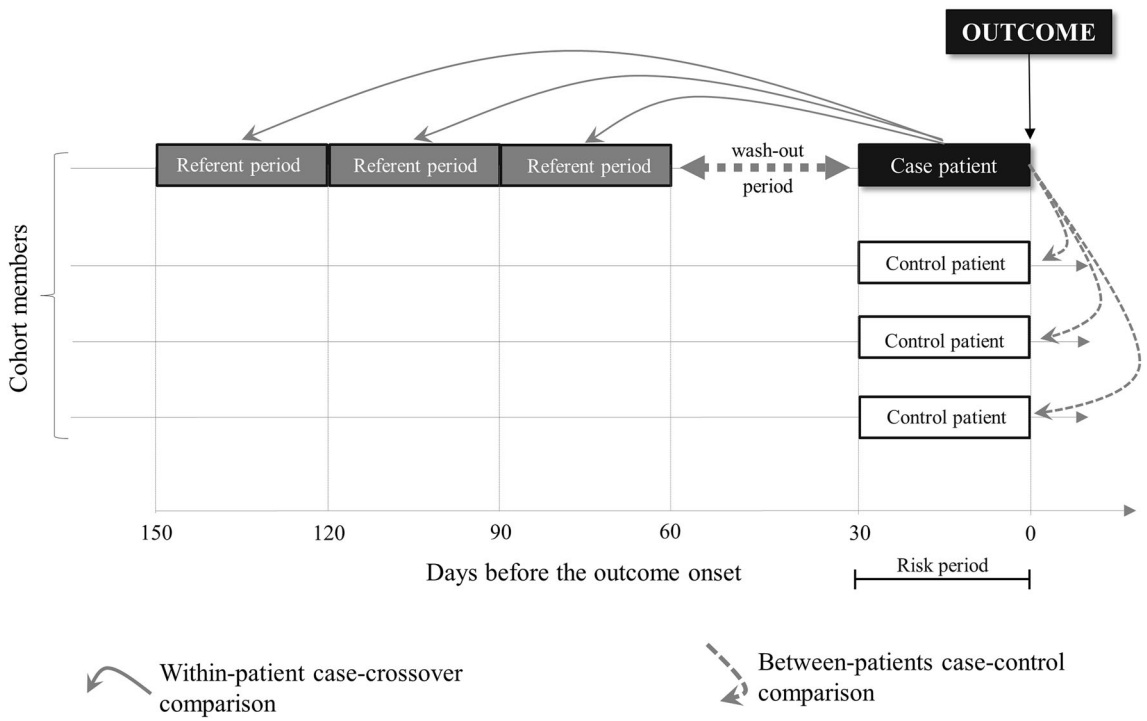

Fig. 1 Case–control and case-crossover comparison studying the effect of antihypertensive drug use (exposure) on the acute risk of hip fracture (outcome)

before the index date, as well as the Charlson comorbidity index (categorized according to scores 0, 1, or ≥2).

Second, the case-crossover approach was used to estimate the effect of current exposure on the considered outcome [40]. To this end, the current exposure of each case was contrasted with three previous reference periods (each 30 days) within each case patient. A washout period between the current and the most recent reference period was allowed to avoid a carryover effect. By comparing cases with themselves at different time points, the case-crossover approach automatically controls for confounding by attributes that are constant over time. A conditional logistic regression model for 1:3 matched data was again used to estimate the OR for current exposure to BP-lowering medications. Estimates were adjusted for the use of digoxin, benzodiazepines, anti-arrhythmics, and anti-epileptics during the current and referent periods.

It should be considered that, according to the case-crossover design, exposure to BP-lowering medications and other agents must to be assessed during a time window large enough to include current and referent periods, as well as the washout period. We therefore needed a time window long enough before the index date to assess exposure of all case patients. Thus, cases who did not reach at least 6 months of follow-up were excluded. Furthermore, although a shorter time window was required for the case–control design, we preferred to use the same exclusion criterion to ensure comparability of results.

Data were separately analysed for two age subgroups (70–80 and 81–90 years). Shorter (15 days) and longer (45 and 90 days) definitions of exposure were also considered so the robustness of case–control and case-crossover findings could be verified.

All analyses were performed using the Statistical Analysis System software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p values were two-sided.

3 Results

3.1 Patients

The selection of the final cohort is detailed in Fig. 2. The 81,617 patients accumulated 406,953 person-years of observation (average of 5.0 years per patient), and generated 2331 first hospital admissions for HF. Of these, the 178 patients who experienced the outcome within the first

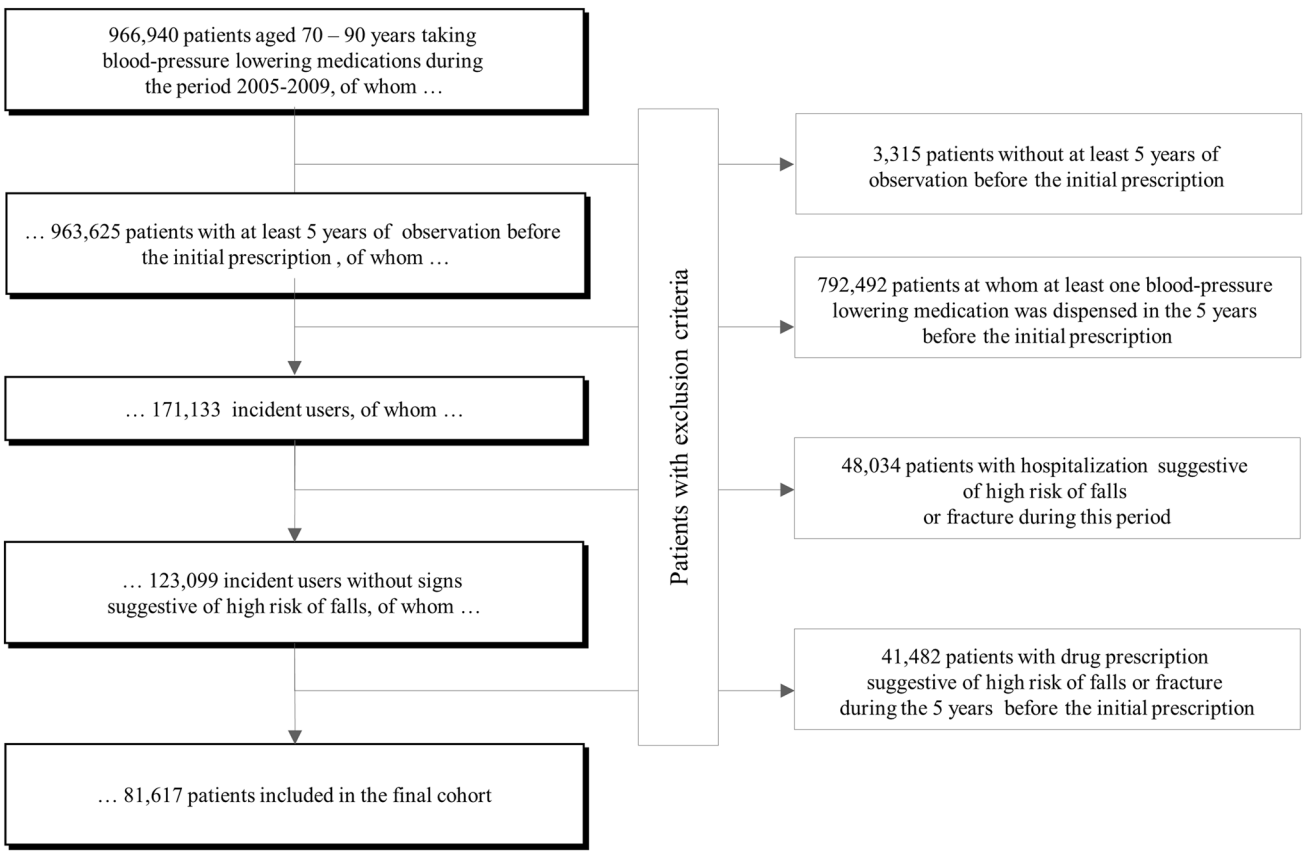

Fig. 2 Flow-chart of inclusion and exclusion criteria

6 months of follow-up were excluded. The remaining 2153 HF hospitalizations were included as cases and were matched to 6450 controls. At the date of the initial prescription, mean age (±standard deviation [SD]) of cases and controls was 79 years (±5), and 24 % were men.

Some selected characteristics of the study population, as well as of risk and referent periods within cases, are summarized in Table 1. HF was preceded by a 30-day BP-lowering medication treatment in about one-third of the cases, with no significant difference from controls. There was no evidence that cases and controls differed for the currently employed treatment strategy. A higher proportion of cases than controls was currently exposed to α-blockers ($p = 0.036$), loop diuretics ($p < 0.001$), benzodiazepines ($p < 0.001$), and anti-epileptic agents ($p < 0.001$). The proportion of patients receiving statin treatment was lower in cases than in controls ($p = 0.008$), whereas the reverse was observed for antidepressants and neuroleptics (both $p < 0.001$). The Charlson comorbidity index score was similar in cases and controls. Cases were more frequently exposed to loop diuretics ($p = 0.021$) during the current period than during the referent period.

Table 1 Comparison between the 2153 case patients hospitalized for hip fracture and the corresponding 6450 controls included in the study

	Cases (A)	Controls (B)	Referent periods (C)	*p* value[a] (A vs. B)	*p* value[a] (A vs. C)
Current prescriptions of BP-lowering medication[b]					
ACEI or ARB	368 (17.1)	1207 (18.7)	1169 (18.1)	0.092	0.291
CCB	122 (5.7)	389 (6.0)	349 (5.4)	0.536	0.642
β-Blocker	118 (5.5)	353 (5.5)	388 (6.0)	0.989	0.368
α-Blocker	26 (1.2)	47 (0.7)	60 (0.9)	0.036	0.260
Loop diuretic	94 (4.4)	171 (2.7)	213 (3.3)	<0.001	0.021
Non-loop diuretic	169 (7.9)	587 (9.1)	487 (7.5)	0.076	0.639
Any agent	663 (30.8)	2131 (33.0)	1939 (30.0)	0.054	0.473
Monotherapy	440 (20.4)	1381 (21.4)	1259 (19.5)	0.338	0.317
Combined therapy	223 (10.4)	750 (11.6)	680 (10.5)	0.107	0.823
Any agent with the exception of loop diuretics	614 (28.5)	1910 (29.6)	1811 (28.0)	0.334	0.678
Monotherapy	417 (19.4)	1247 (19.3)	1188 (18.4)	0.972	0.322
Combined therapy	197 (9.1)	663 (10.3)	623 (9.6)	0.131	0.525
Concomitant treatment[b]					
Digoxin	23 (1.1)	73 (1.1)	76 (1.2)	0.808	0.683
Benzodiazepine	8 (0.4)	2 (0.0)	19 (0.3)	<0.001	0.578
Anti-arrhythmic	51 (2.4)	115 (1.8)	153 (2.4)	0.087	0.999
Anti-epileptic agent	36 (1.7)	40 (0.6)	95 (1.5)	<0.001	0.509
Previous treatment[c]					
Statin	313 (14.5)	1096 (17.0)	NA	0.008	NA
Hypoglycemic agent	206 (9.6)	590 (9.2)	NA	0.560	NA
Antidepressant agent	460 (21.4)	926 (14.4)	NA	<0.001	NA
Neuroleptic agent	114 (5.3)	185 (2.9)	NA	<0.001	NA
Charlson comorbidity index score[c]					
0	2014 (93.6)	6107 (94.7)	NA	0.073	NA
1	91 (4.2)	221 (3.4)	NA		
≥2	48 (2.2)	122 (1.9)	NA		

Selected characteristics of cases and controls observed during the current period (A vs. B, between-patient case–control comparison), and within each case observed during the current and the referent periods (A vs. C, within-patient case-crossover comparison)

Data are presented as *n* (%) unless otherwise indicated

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BP* blood pressure, *CCB* calcium channel blocker, *NA* not applicable

[a] According to the Chi squared test or its version for the trend (categories of the Charlson comorbidity index score)

[b] Within 30 days before the index date

[c] Within 5 years before the index date

3.2 Case–Control Estimates

Statistical evidence suggested that current exposure to α-blockers and loop diuretics increased the risk of HF by 69 % (95 % CI 4–176) and 67 % (95 % CI 28–118), respectively (Fig. 3). Current exposure to loop diuretics was significantly associated with HF risk among both younger and older patients, whereas evidence that α-blockers exert their action on the considered outcome was found only for older patients (Table 2). There was no evidence that current exposure to BP-lowering medications as a whole (including or excluding loop diuretics), as well as BP-lowering medication dispensed as monotherapy or combined therapy, affected HF risk (Fig. 4).

3.3 Case-Crossover Estimates

Figure 3 shows that current exposure to loop diuretics significantly increased HF risk by 49 % (95 % CI 5–110). The risk associated with current use of α-blockers observed from case–control estimates was not confirmed by the case-crossover estimate. However, older patients currently using α-blockers and loop diuretics had increased HF risks of 88 % (95 % CI 1–248) and 82 % (95 % CI 10–200), respectively (Table 2). Similarly, there was no evidence that current exposure to BP-lowering medications as a whole (including or excluding loop diuretics), as well as treatment strategy affected the HF risk (Fig. 4).

3.4 Sensitivity Analysis

Results did not substantially change with shortening (15 days) or lengthening (45 and 90 days) of the definition of current exposure (results shown in Table S2 of the ESM).

4 Discussion

This study shows that elderly subjects newly treated with BP-lowering medications as a whole in a real-life setting did not exhibit a greater risk of HF. Nevertheless, when considering the single classes, current use of loop diuretics was consistently associated with an increased HF risk among the entire cohort of patients aged 70–90 years (1.5-fold increased risk), as well as among those aged 81–90 years (1.8-fold increased risk). The category of older patients currently exposed to α-blockers also had a 1.9-fold increased HF risk.

The mechanism for loop diuretics involves rapid reduction of circulating plasma volume and for α-blockers, vasodilatation due to α-adrenergic blockade [41]. Because advanced age is associated with diminished organ and homeostatic reserve, the susceptibility of older people to the adverse effects of these mechanisms is correspondingly increased.

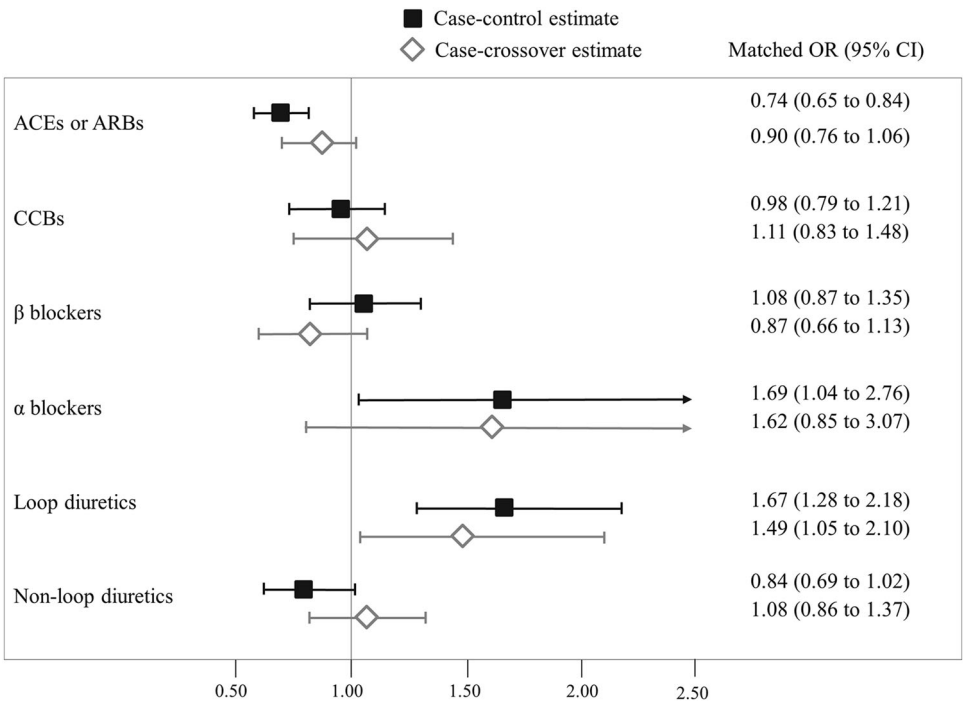

Fig. 3 Case–control and case-crossover estimates of the relationship between current exposure to classes of antihypertensive drug therapy and the risk of hip fracture. *ACE* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *CI* confidence interval, *OR* odds ratio

Table 2 Case–control and case-crossover estimate of the relationship between current use of blood pressure-lowering medications and the risk of hip fracture in younger (aged 70–80 years) and older (aged 81–90 years) patients

	Younger patients	Older patients
ACE or ARB		
Case–control	0.69 (0.58–0.82)	0.82 (0.67–1.01)
Case crossover	0.91 (0.73–1.13)	0.89 (0.69–1.15)
CCB		
Case–control	1.08 (0.82–1.43)	0.84 (0.60–1.18)
Case crossover	0.95 (0.66–1.36)	1.44 (0.89–2.35)
β-Blocker		
Case–control	0.99 (0.75–1.32)	1.21 (0.85–1.72)
Case crossover	0.78 (0.56–1.10)	1.03 (0.67–1.58)
α-Blocker		
Case–control	1.39 (0.57–3.39)	1.86 (1.03–3.35)
Case crossover	1.40 (0.47–4.15)	1.88 (1.01–3.48)
Loop diuretic		
Case–control	1.88 (1.28–2.74)	1.52 (1.04–2.21)
Case crossover	1.36 (0.84–2.19)	1.82 (1.10–3.00)
Non-loop diuretic		
Case–control	0.79 (0.63–1.00)	0.89 (0.68–1.17)
Case crossover	0.94 (0.69–1.29)	1.31 (0.92–1.88)
Any agent		
Case–control	0.93 (0.80–1.08)	0.95 (0.80–1.12)
Case crossover	1.03 (0.86–1.23)	1.16 (0.94–1.43)
Monotherapy		
Case–control	1.10 (0.92–1.30)	0.96 (0.79–1.17)
Case crossover	1.10 (0.90–1.34)	1.13 (0.88–1.44)
Combined therapy		
Case–control	0.71 (0.57–0.88)	0.92 (0.72–1.18)
Case crossover	0.90 (0.68–1.17)	1.21 (0.89–1.65)
Any agent with the exception of loop diuretics		
Case–control	0.87 (0.75–1.01)	0.91 (0.77–1.08)
Case crossover	1.00 (0.83–1.19)	1.13 (0.91–1.40)
Monotherapy		
Case–control	1.01 (0.85–1.20)	0.95 (0.78–1.16)
Case crossover	1.07 (0.87–1.31)	1.16 (0.90–1.49)
Combined therapy		
Case-control	0.78 (0.62–0.97)	0.84 (0.65–1.09)
Case crossover	0.86 (0.65–1.14)	1.08 (0.78–1.49)

Data are presented as odds ratio (95 % confidence interval)

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker

Several features of this study should be mentioned to interpret these findings. First, the increased risk was observed using two different approaches, namely case–control and case-crossover designs. Case–control is vulnerable to confounding, including confounding due to physical and cognitive conditions typical of advanced age, which often remain unmeasured. The case-crossover design is not vulnerable to confounding by factors that remain constant within individuals, but is vulnerable to confounding arising from time trends in exposure or confounders. Although these designs use entirely different sets of controls, very similar results were obtained in the current application. This undoubtedly strengthens the validity of our findings.

Because we designed the study to investigate the acute effect of taking BP-lowering medications in the period before the HF outcome, the findings do not indicate a longer-term lowering effect of loop diuretics or antihypertensive agents on bone mineral density [18, 23]. Rather, they likely reflect the hypotensive effect of impairing

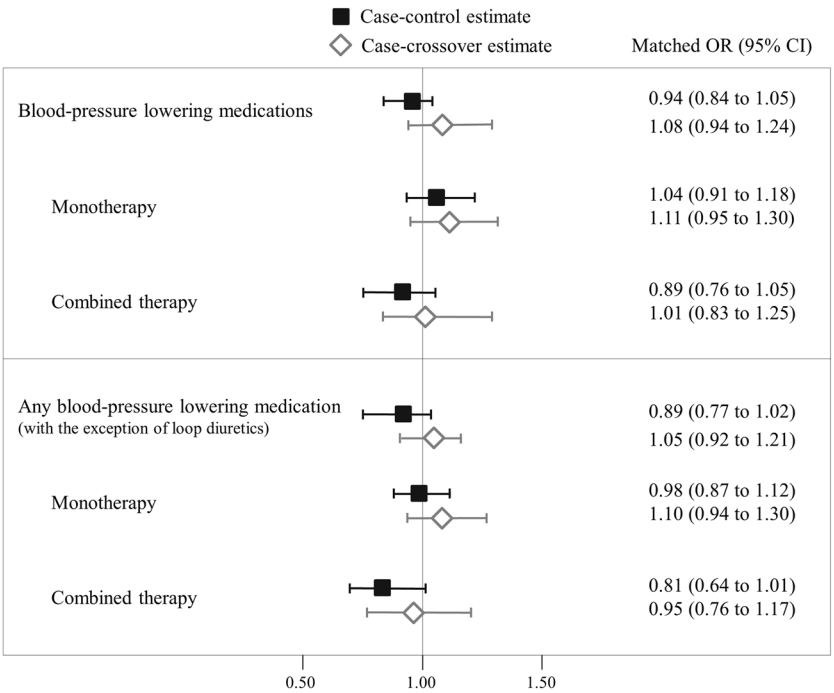

Fig. 4 Case-control and case-crossover estimates of the relationship between current exposure to any antihypertensive therapy, with or without loop diuretics, and the risk of hip fracture. *CI* confidence interval, *OR* odds ratio

sympathetic vascular influences or reducing blood volume [42, 43] with associated symptoms such as dizziness, fainting, or syncope [44, 45]. Indeed, impaired BP homeostasis [46] and urinary symptoms at night [17] could facilitate injurious falls.

We also remark that a case-crossover design needs a sufficient time frame to retrospectively investigate the exposure of interest. Evidence suggests that initiation of BP-lowering medication in the immediate post-exposure period is largely associated with orthostatic hypotension [42, 45, 47]. This likely explains why, in contrast with other studies involving elderly patients [16], we did not find that antihypertensive drug treatment as a whole increased the risk of HF. Rather, the case-crossover design sheds light on the differential effect of switching between drug classes. Similar findings were reported by a recent case-crossover study that showed a twofold increased risk of HF shortly after starting loop diuretic treatment [17]. On the other hand, we did not confirm results from case-only studies reporting significant associations between transitory use of β-blockers [14], ACE inhibitors [16], ARBs [25], and CCBs [48] with the risk of falls. To the best of our knowledge, no other studies have demonstrated an increased risk of HF with the use of α-blockers.

Furthermore, we highlighted that the risk of HF is significantly increased among users of benzodiazepines, antiepileptics, antidepressants, and neuroleptics, confirming the increased risk of falls during treatment with psychotropic drugs [38].

Finally, the size of the observed association, jointly with the prevalence of loop diuretic prescriptions in our patient sample (slightly less than 3 %), suggests that less than 3 % of HFs in elderly hypertensive patients are attributable to the acute use of loop diuretics. The etiological fraction is expected to be about 5 % for α-blockers. This means that, in our setting, almost 1 in 12 hospital admissions for HF is probably due to current exposure to antihypertensive drugs. This represents a warning that should always remind physicians of the possibility of accidental falls and their related consequences when antihypertensive treatment is prescribed in the elderly.

This study has some limitations. First, we were unable to determine whether participants adhered with drug prescriptions. However, reliable measures of adherence can hardly be employed in large-scale population studies. Furthermore, poor adherence would have made the adverse effects even greater with respect to α-blockers and loop diuretics. Second, it is impossible to determine whether the observed HFs were related to falls. However, a study on post-menopausal women showed that more than 95 % of HFs are linked to a fall [9], which suggests that this was indeed the main risk factor for the considered outcome. Third, because our healthcare utilization databases did not report diagnostic information, patients may have had conditions other than hypertension. This clearly applies in the case of loop diuretic use, for which the commonest indication is congestive heart failure. However, if we consider the clinical indications of the use of antihypertensive drugs in Italy, hypertension per se represents by far the most common diagnosis (73 %). Only about 20 % are prescribed for angina pectoris, myocardial infarction, and heart failure, and less than 1 %

for non-chronic indications, such as edemas [49]. Fourth, case-crossover estimates are open to bias from confounders that vary with time, including, in the present study, seasonality of HF risk [50]. However, although a certain seasonality in the risk of fractures has been reported [51], to the best of our knowledge no evidence exists that this aspect might substantially affect antihypertensive therapy. Rather, we cannot exclude that worsening clinical profile (likely leading to changed therapeutic strategy and increased risk of fall) may partly explain the observed risk excesses.

5 Conclusions

This large population-based study in a real-life setting confirms previous evidence of an increased risk of HF among elderly subjects who newly use loop diuretics. Some evidence that α-blockers might play a causal role in the onset of HF has been also supplied. Given the potential for bias, and the conflicting results from the existing literature on this issue, additional high-quality studies are needed. Meanwhile, with the aim of reducing the burden of HF, which ranges from individual disability to social costs, it is important to direct every effort to counteract the worldwide increasing trend. In this scenario, the careful consideration of the most appropriate antihypertensive drug strategy plays a fundamental role.

Compliance with Ethical Standards

Funding Support for this study come from the Italian Ministry of Education, University and Research grants ("Fondo d'Ateneo per la Ricerca" portion, year 2014).

Disclosures GC has received research support from the European Community (EC), the Italian Agency of Drugs (AIFA), and the Italian Ministry for University and Research (MIUR). He has taken part in a variety of projects funded by pharmaceutical companies (i.e., Novartis and GSK). He has also received honoraria as member of Advisory Board from Roche.
GM has received honoraria for participation as speaker/chairman in national/international meetings from Bayer, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini Int., Merck, Novartis, Recordati, and Servier.
PM, MMC, FR, LM, and GA declare that they have no conflicts of interest.

Research involving human participants and/or animals The present research did not involve any trials on human participants or animals.

References

1. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev. 2009;4:CD000028.
2. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–98.
3. Mukhtar O, Jackson SH. The hypertension in the very elderly trial—latest data. Br J Clin Pharmacol. 2012;75:951–4.
4. Messerli FH, Sulicka J, Gryglewska B. Treatment of hypertension in the elderly. N Engl J Med. 2008;359:972–3.
5. Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. Arch Intern Med. 2008;168:136–40.
6. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297:1233–40.
7. Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases. Hypertension. 2015;65:490–8.
8. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174:588–95.
9. Nyberg L, Gustafson Y, Berggren D, et al. Falls leading to femoral neck fractures in lucid older people. J Am Geriatr Soc. 1996;44:156–60.
10. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med. 2003;348:1556–64.
11. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA. 2003;289:1107–16.
12. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004;52:1349–54.
13. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009;169:1952–60.
14. Gribbin J, Hubbard R, Gladman J, et al. Risk of falls associated with antihypertensive medication: self-controlled case series. Pharmacoepidemiol DS. 2011;20:879–84.
15. Gribbin J, Hubbard R, Gladman JRF, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: population-based case-control study. Age Ageing. 2010;39:592–7.
16. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med. 2012;172:1739–44.
17. Berry SD, Zhu Y, Choi H, Kiel DP, Zhang Y. Diuretic initiation and the acute risk of hip fracture. Osteoporos Int. 2013;24:689–95.
18. Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res. 2011;26:1561–7.
19. Heidrich FE, Stergachis A, Gross KM. Diuretic drug use and the risk for hip fracture. Ann Intern Med. 1991;115:1–6.
20. Song HJ, Lee J, Y-j Kim, et al. β1 selectivity of β-blockers and reduced risk of fractures in elderly hypertension patients. Bone. 2012;51:1008–15.
21. Wiens M, Etminan M, Gill SS, Takkouche B. Effects of antihypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. J Intern Med. 2006;260:350–62.
22. de Vries F, Souverein PC, Cooper C, et al. Use of β-blockers and the risk of hip/femur fracture in the United Kingdom and The Netherlands. Calcif Tissue Int. 2007;80:69–75.
23. Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of β-blockers and risk of fractures. JAMA. 2004;292:1326–32.
24. Thorell K, Ranstad K, Midlöv P, et al. Is use of fall risk-increasing drugs in an elderly population associated with an increased risk of hip fracture, after adjustment for multimorbidity level: a cohort study. BMC Geriatr. 2014;14:131.

25. Shuto H, Imakyure O, Matsumoto J, et al. Medication use as a risk factor for inpatient falls in an acute care hospital: a case-crossover study. Br J Clin Pharmacol. 2010;69:535–42.
26. Taggart HM. Do drugs affect the risk of hip fracture in elderly women? J Am Geriatr Soc. 1988;36:1006–10.
27. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in patients treated with loop diuretics. J Intern Med. 2006;259: 117–24.
28. Lim LS, Fink HA, Blackwell T, et al. Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. J Am Geriatr Soc. 2009;57:855–62.
29. Carbone LD, Johnson KC, Bush AJ, et al. Loop diuretic use and fracture in postmenopausal women: findings from the Women's Health Initiative. Arch Intern Med. 2009;169:132–40.
30. Corrao G, Nicotra F, Parodi A, et al. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension. 2011;58:566–72.
31. Mancia G, Parodi A, Merlino L, Corrao G. Heterogeneity in antihypertensive treatment discontinuation between drugs belonging to the same class. J Hypertens. 2011;29:1012–8.
32. Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29:610–8.
33. Corrao G, Zambon A, Parodi A, et al. Incidence of cardiovascular events in Italian patients with early discontinuations of antihypertensive, lipid-lowering, and antidiabetic treatments. Am J Hypertens. 2012;25:549–55.
34. Corrao G, Soranna D, La Vecchia C, et al. Medication persistence and the use of generic and brand-name blood pressure-lowering agents. J Hypertens. 2014;32:1146–53.
35. Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med. 2003;348:42–9.
36. Malabu UH, Vangaveti VN, Kennedy RL. Disease burden evaluation of fall-related events in the elderly due to hypoglycemia and other diabetic complications: a clinical review. Clin Epidemiol. 2014;6:287–94.
37. Helin-Salmivaara A, Korhonen MJ, Lehenkari P, et al. Statins and hip fracture prevention—a population based cohort study in women. PLoS One. 2012;7:e48095.
38. de Groot MH, van Campen JP, Moek MA, et al. The effects of fall-risk-increasing drugs on postural control: a literature review. Drugs Aging. 2013;30:901–20.
39. Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol. 2008;61:1234–40.
40. Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. Stat Methods Med Res. 2009;18:53–65.
41. Lambert DG, Thomas GD. {alpha}-Adrenoceptor constrictor responses and their modulation in slow-twitch and fast-twitch mouse skeletal muscle. J Physiol. 2005;563:821–9.
42. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. J Clin Pharm Ther. 2005;30:173–8.
43. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. J Am Geriatr Soc. 2011;59:383–9.
44. Capewell S, Capewell A. "First dose" hypotension and venodilatation. Br J Clin Pharmacol. 1991;31:213–5.
45. Slavachevsky I, Rachmani R, Levi Z, Brosh D, Lidar M, Ravid M. Effect of enalapril and nifedipine on orthostatic hypotension in older hypertensive patients. J Am Geriatr Soc. 2000;48: 807–10.
46. Lipsitz LA. Abnormalities in blood pressure homeostasis that contribute to falls in the elderly. Clin Geriatr Med. 1985;1: 637–48.
47. Pool JL, Glazer R, Chiang YT, Gatlin M. Dose-response efficacy of valsartan, a new angiotensin II receptor blocker. J Hum Hypertens. 1999;13:275–81.
48. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of falls on initiation of antihypertensive drugs in the elderly. Osteoporos Int. 2013;24:2649–57.
49. Poluzzi E, Strahinja P, Vargiu A, et al. Initial treatment of hypertension and adherence to therapy in general practice in Italy. Eur J Clin Pharmacol. 2005;61:603–9.
50. Hallas J, Pottegård A. Use of self-controlled designs in pharmacoepidemiology. J Intern Med. 2014;275:581–9.
51. Román Ortiz C, Tenías JM, Estarlich M, Ballester F. Systematic review of the association between climate and hip fractures. Int J Biometeorol. 2015;59:1511–22.