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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

Running head: Antihypertensive agents and hip fracture

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ABSTRACT

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

Design. A population-based study was carried out 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 2,153 patients who experienced the outcome (hospitalization for HF within December 31, 2012). For each case, up to three controls were randomly selected from the cohort to be matched for gender, 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 for current use of loop diuretics were 1.67 (95% CI: 1.28 to 2.18) and 1.49 (1.05 to 2.10) respectively. Among patients aged 81-90 years, case-control and case-crossover odds ratios were 1.52 (1.04 to 2.21) and 1.82 (1.10 to 3.00) for current use of loop diuretics, 1.86 (1.03 to 3.35) and 1.88 (1.01 to 3.48) for α-blockers. No other agent was associated with the outcome.

Conclusions. Evidence that loop diuretics and α-blockers are associated with higher risk of HF was consistently supplied by 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.

Keywords. Antihypertensive drugs; Loop diuretics; Case-crossover design; Elderly; Healthcare Databases; Hip fracture; Nested case-control study; Risk of falls

KEY POINTS

- Newly prescribed antihypertensive medications, when considered together as a whole class, do not determine a greater risk of hip fracture in the older patients. However, especially in the oldest, 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 they are mechanisms 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 [1], including subjects aged 80 years and older, 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 so far sole trial addressing octogenarian hypertensives [4-6]. Furthermore, in randomized clinical trials physicians' expertise and patients' close follow-up 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, which 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, it is unclear

whether (and to what extent) these findings are attributable to differences between individuals – i.e. comorbidity and other confounders – or to the effect of antihypertensive agents per se [14].

Data are conflicting concerning the effect of different antihypertensive medications on the occurrence of falls and fractures [13-19]. There is inconsistency in reports of a reduction in fracture risk with β-blockers [20-24], calcium channel blockers [15], ACE inhibitors [16,17] and angiotensin receptor antagonists [25]. 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 ten million) of the total population. In Italy, all the citizens are covered by the National Health Service (NHS), and 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, whose details and uses in the fields of hypertension are reported elsewhere [30-34].

2.2 Cohort and follow-up

We included all residents aged 70 to 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, calcium channel blockers (CCBs),

loop- and non-loop diuretics. The complete list of drugs is in the Supplementary Table 1. Although these drugs may be used for treating conditions other than hypertension, and loop diuretics are not indicated as primary antihypertensives, we will refer to them henceforth collectively as blood-pressure lowering medications.

On the basis of the 5-year interval before the initial prescription, patients were excluded if they had already received any blood-pressure lowering medication (to ensure inclusion of newly treated individuals), or displayed characteristics suggestive of 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 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 ATC-codes of outpatient drug prescriptions, consisted of bisphosphonates, calcitonin, raloxifene, corticosteroids, antineoplastic agents, and medications used for thyroid therapy. With the aim of ensuring enough observation for applying exclusion criteria, patients who did not result registered into the NHS from at least five years before the initial prescription were excluded.

The patients included into the final cohort accumulated person-years of follow-up from the initial prescription until the earliest date among hospital admission for HF (outcome), death, emigration, or December 31st, 2012.

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 were selected randomly within the cohort after they were matched on gender, age at cohort entry (± 3 years), date of cohort entry, and did not yet have experienced the outcome at the time of the matched case event (index date).

2.4 Exposure

For each case and control all blood-pressure 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 blood-pressure lowering medication. The last prescription before the outcome onset within the current time was considered for classifying patients according to 1) exposure to specific blood-pressure 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 agents (combined therapy) 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 hypoglycaemic agents [35,36]). Additionally, we recorded the use of statins, which has 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 the postural control (i.e., digoxin, benzodiazepines, antiarrhythmics, and antiepileptics [38]) in the 30-day period before the hip fracture was also included. Finally, the diagnosis available from the inpatient charts over five years before the initial prescription date was used to calculate the Charlson comorbidity index [39].

2.6 Data analysis

Two approaches of data analysis were used (**Figure 1**). One, the case-control approach was used by contrasting the current exposure of each case with that of the 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 blood-pressure lowering medications. Estimates were adjusted for the above reported covariates including drug prescriptions during the 5-year period (i.e., antidepressants, neuroleptics, hypoglycaemic agents, and statins) and

the 30-day period (i.e., digoxin, benzodiazepines, antiarrhythmics, and antiepileptics) before the index date, as well as the Charlson comorbidity index (categorized according to scores 0, 1 or ≥2).

Two, 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 of 30-day width) within each case patient. A wash-out period between the current and the most recent reference period was allowed to avoid a carryover effect. By comparing cases to themselves at different points in time, 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 blood-pressure lowering medications. Estimates were adjusted for the use of digoxin, benzodiazepines, antiarrhythmics, and antiepileptics during the current and referent periods.

It should be considered that, according with the case-crossover design, exposure to blood-pressure 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 wash-out period. We therefore need a long enough time-window before the index date for assessing exposure of all case patients. For this reason, cases who did not reach at least 6 months of follow-up were excluded. Furthermore, although a shorter time-window was requested for the case-control design, we preferred to use the same exclusion criterion for ensuring results comparability.

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 to verify the robustness of case-control and case-crossover findings.

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 **Figure 2**. The 81,617 patients accumulated 406,953 person-years of observation (on average 5.0 years per patient), and generated 2,331 first hospital admissions for HF. Of these, the 178 patients who experienced the outcome within the first six months of follow-up were excluded. The remaining 2,153 HF hospitalizations were included as cases and were matched to 6,450 controls. At the date of the initial prescription mean age (±SD) of cases and controls was 79 years (±5 years), and 24% of them 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 blood-pressure lowering medication treatment in about one third of the cases with no significant difference from controls. There was no evidence that cases and controls differ 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 antiepileptic agents ($p<0.001$). The proportion of patients under statin treatment was lower in cases than in controls ($p=0.008$), whereas the reverse was observed for antidepressants and neuroleptics (both $p<0.001$). Charlson comorbidity index 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 one.

3.2 Case-control estimates

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

3.3 Case-crossover estimates

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

Sensitivity analysis

Results did no substantially change by shortening at 15 days or lengthening at 45 and 90 days the definition of current exposure (results shown in **Supplementary Table 2**).

4. DISCUSSION

This study shows that elderly subjects newly treated with blood-pressure lowering medications as a whole in a real life setting did not exhibit a greater risk of HF. Nevertheless, considering the single classes, current use of loop diuretics resulted consistently associated with an increased HF risk among the entire cohort of patients aged 70 to 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 had also a 1.9-fold increased HF risk.

The mechanism for loop diuretics involves rapid reduction in 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 greater.

Several features of this study should be mentioned to interpret these findings. First of all, 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 doubtless strengthens the validity of our findings.

Because we designed the study to investigate the acute effect of taking blood-pressure 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 sympathetic vascular influences or reducing blood volume [42,43] with associated symptoms such as dizziness, fainting, or syncope [44,45]. Indeed, impaired blood pressure homeostasis [46] and urinary symptoms during night-time [17] could facilitate injurious falls.

We also remark that a case-crossover design needs of a sufficient time frame for retrospectively investigating the exposure of interest. Evidence suggests that initiation of blood-pressure lowering medication in the immediate post-exposure period is largely associated with orthostatic hypotension [42,45,47]. This likely explain 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, which showed a two-fold 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. At our best knowledge, there are no other studies that demonstrated an increased risk of HF with use of α-blockers.

Furthermore, we enlightened 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 hypertensives are attributable to acute use of loop diuretics. Etiological fraction is expected to be about 5% for α-blockers. This means that, in our setting, almost one out of twelve hospital admissions for HF are 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. One, 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. Two, 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. Three, because our HCU 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%), and only about 20% are prescribed for angina pectoris, myocardial infarction and heart failure, and less than 1% for non-chronic indications, such as oedemas [49]. Four, 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 there is no evidence that this aspect might substantially affect antihypertensive therapy. Rather, we cannot exclude that worsening clinical

profile (likely leading to change therapeutic strategy and increase the risk of fall) may partly explain the observed risk excesses.

5. CONCLUSION

This large population-based study in a setting of real practice confirms previous evidence of an increased risk of HF among elderly 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 the individual disability to the 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.

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DISCLOSURES

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P.M., M.M.C., F.R., L.M., G.A. declare that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

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

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Legends of figures

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

Fig. 2 Flow-chart of inclusion and exclusion criteria

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

Footnote: ACEs: Angiotensin-converting enzyme inhibitor ; ARBs: Angiotensin receptor blockers; CCBs: calcium channel blockers

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

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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

Running head: Antihypertensive agents and hip fracture

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ABSTRACT

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

Design. A population-based study was carried out 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 2,153 patients who experienced the outcome (hospitalization for HF within December 31, 2012). For each case, up to three controls were randomly selected from the cohort to be matched for gender, 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 for current use of loop diuretics were 1.67 (95% CI: 1.28 to 2.18) and 1.49 (1.05 to 2.10) respectively. Among patients aged 81-90 years, case-control and case-crossover odds ratios were 1.52 (1.04 to 2.21) and 1.82 (1.10 to 3.00) for current use of loop diuretics, 1.86 (1.03 to 3.35) and 1.88 (1.01 to 3.48) for α-blockers. No other agent was associated with the outcome.

Conclusions. Evidence that loop diuretics and α-blockers are associated with higher risk of HF was consistently supplied by 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.

Keywords. Antihypertensive drugs; Loop diuretics; Case-crossover design; Elderly; Healthcare Databases; Hip fracture; Nested case-control study; Risk of falls

KEY POINTS

- Newly prescribed antihypertensive medications, when considered together as a whole class, do not determine a greater risk of hip fracture in the older patients. However, especially in the oldest, 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 they are mechanisms 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 [1], including subjects aged 80 years and older, 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 so far sole trial addressing octogenarian hypertensives [4-6]. Furthermore, in randomized clinical trials physicians' expertise and patients' close follow-up 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, which 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, it is unclear

whether (and to what extent) these findings are attributable to differences between individuals – i.e. comorbidity and other confounders – or to the effect of antihypertensive agents per se [14].

Data are conflicting concerning the effect of different antihypertensive medications on the occurrence of falls and fractures [13-19]. There is inconsistency in reports of a reduction in fracture risk with β-blockers [20-24], calcium channel blockers [15], ACE inhibitors [16,17] and angiotensin receptor antagonists [25]. 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 ten million) of the total population. In Italy, all the citizens are covered by the National Health Service (NHS), and 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, whose details and uses in the fields of hypertension are reported elsewhere [30-34].

2.2 Cohort and follow-up

We included all residents aged 70 to 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, calcium channel blockers (CCBs),

loop- and non-loop diuretics. The complete list of drugs is in the Supplementary Table 1. Although these drugs may be used for treating conditions other than hypertension, and loop diuretics are not indicated as primary antihypertensives, we will refer to them henceforth collectively as blood-pressure lowering medications.

On the basis of the 5-year interval before the initial prescription, patients were excluded if they had already received any blood-pressure lowering medication (to ensure inclusion of newly treated individuals), or displayed characteristics suggestive of 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 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 ATC-codes of outpatient drug prescriptions, consisted of bisphosphonates, calcitonin, raloxifene, corticosteroids, antineoplastic agents, and medications used for thyroid therapy. With the aim of ensuring enough observation for applying exclusion criteria, patients who did not result registered into the NHS from at least five years before the initial prescription were excluded.

The patients included into the final cohort accumulated person-years of follow-up from the initial prescription until the earliest date among hospital admission for HF (outcome), death, emigration, or December 31st, 2012.

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 were selected randomly within the cohort after they were matched on gender, age at cohort entry (± 3 years), date of cohort entry, and did not yet have experienced the outcome at the time of the matched case event (index date).

2.4 Exposure

For each case and control all blood-pressure 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 blood-pressure lowering medication. The last prescription before the outcome onset within the current time was considered for classifying patients according to 1) exposure to specific blood-pressure 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 agents (combined therapy) 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 hypoglycaemic agents [35,36]). Additionally, we recorded the use of statins, which has 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 the postural control (i.e., digoxin, benzodiazepines, antiarrhythmics, and antiepileptics [38]) in the 30-day period before the hip fracture was also included. Finally, the diagnosis available from the inpatient charts over five years before the initial prescription date was used to calculate the Charlson comorbidity index [39].

2.6 Data analysis

Two approaches of data analysis were used (**Figure 1**). One, the case-control approach was used by contrasting the current exposure of each case with that of the 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 blood-pressure lowering medications. Estimates were adjusted for the above reported covariates including drug prescriptions during the 5-year period (i.e., antidepressants, neuroleptics, hypoglycaemic agents, and statins) and

the 30-day period (i.e., digoxin, benzodiazepines, antiarrhythmics, and antiepileptics) before the index date, as well as the Charlson comorbidity index (categorized according to scores 0, 1 or ≥2).

Two, 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 of 30-day width) within each case patient. A wash-out period between the current and the most recent reference period was allowed to avoid a carryover effect. By comparing cases to themselves at different points in time, 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 blood-pressure lowering medications. Estimates were adjusted for the use of digoxin, benzodiazepines, antiarrhythmics, and antiepileptics during the current and referent periods.

It should be considered that, according with the case-crossover design, exposure to blood-pressure 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 wash-out period. We therefore need a long enough time-window before the index date for assessing exposure of all case patients. For this reason, cases who did not reach at least 6 months of follow-up were excluded. Furthermore, although a shorter time-window was requested for the case-control design, we preferred to use the same exclusion criterion for ensuring results comparability.

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 to verify the robustness of case-control and case-crossover findings.

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 **Figure 2**. The 81,617 patients accumulated 406,953 person-years of observation (on average 5.0 years per patient), and generated 2,331 first hospital admissions for HF. Of these, the 178 patients who experienced the outcome within the first six months of follow-up were excluded. The remaining 2,153 HF hospitalizations were included as cases and were matched to 6,450 controls. At the date of the initial prescription mean age (±SD) of cases and controls was 79 years (±5 years), and 24% of them 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 blood-pressure lowering medication treatment in about one third of the cases with no significant difference from controls. There was no evidence that cases and controls differ 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 antiepileptic agents ($p<0.001$). The proportion of patients under statin treatment was lower in cases than in controls ($p=0.008$), whereas the reverse was observed for antidepressants and neuroleptics (both $p<0.001$). Charlson comorbidity index 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 one.

3.2 Case-control estimates

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

3.3 Case-crossover estimates

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

Sensitivity analysis

Results did no substantially change by shortening at 15 days or lengthening at 45 and 90 days the definition of current exposure (results shown in **Supplementary Table 2**).

4. DISCUSSION

This study shows that elderly subjects newly treated with blood-pressure lowering medications as a whole in a real life setting did not exhibit a greater risk of HF. Nevertheless, considering the single classes, current use of loop diuretics resulted consistently associated with an increased HF risk among the entire cohort of patients aged 70 to 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 had also a 1.9-fold increased HF risk.

The mechanism for loop diuretics involves rapid reduction in 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 greater.

Several features of this study should be mentioned to interpret these findings. First of all, 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 doubtless strengthens the validity of our findings.

Because we designed the study to investigate the acute effect of taking blood-pressure 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 sympathetic vascular influences or reducing blood volume [42,43] with associated symptoms such as dizziness, fainting, or syncope [44,45]. Indeed, impaired blood pressure homeostasis [46] and urinary symptoms during night-time [17] could facilitate injurious falls.

We also remark that a case-crossover design needs of a sufficient time frame for retrospectively investigating the exposure of interest. Evidence suggests that initiation of blood-pressure lowering medication in the immediate post-exposure period is largely associated with orthostatic hypotension [42,45,47]. This likely explain 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, which showed a two-fold 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. At our best knowledge, there are no other studies that demonstrated an increased risk of HF with use of α-blockers.

Furthermore, we enlightened 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 hypertensives are attributable to acute use of loop diuretics. Etiological fraction is expected to be about 5% for α-blockers. This means that, in our setting, almost one out of twelve hospital admissions for HF are 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. One, 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. Two, 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. Three, because our HCU 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%), and only about 20% are prescribed for angina pectoris, myocardial infarction and heart failure, and less than 1% for non-chronic indications, such as oedemas [49]. Four, 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 there is no evidence that this aspect might substantially affect antihypertensive therapy. Rather, we cannot exclude that worsening clinical

profile (likely leading to change therapeutic strategy and increase the risk of fall) may partly explain the observed risk excesses.

5. CONCLUSION

This large population-based study in a setting of real practice confirms previous evidence of an increased risk of HF among elderly 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 the individual disability to the 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.

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P.M., M.M.C., F.R., L.M., G.A. declare that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

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

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Legends of figures

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

Fig. 2 Flow-chart of inclusion and exclusion criteria

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

Footnote: ACEs: Angiotensin-converting enzyme inhibitor ; ARBs: Angiotensin receptor blockers; CCBs: calcium channel blockers

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

Table 1
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Table 1. Comparison between the 2,153 case patients hospitalized for hip fracture and the corresponding 6,450 controls included into the study. Selected characteristics of cases and controls observed during the current period (A vs B, between-patients case-control comparison), and within each case observed during the current and the referent periods (A vs C, within-patient case-crossover comparison) are reported

	Case	Control	Referent	p-value[a]	p-value[a]
Current prescriptions of blood-pressure lowering medication[b]					
ACEs or ARBs	368 (17.1%)	1,207 (18.7%)	1,169 (18.1%)	0.092	0.291
CCBs	122 (5.7%)	389 (6.0%)	349 (5.4%)	0.536	0.642
β-blockers	118 (5.5%)	353 (5.5%)	388 (6.0%)	0.989	0.368
α-blockers	26 (1.2%)	47 (0.7%)	60 (0.9%)	0.036	0.260
Loop diuretics	94 (4.4%)	171 (2.7%)	213 (3.3%)	<0.001	0.021
Non-loop diuretics	169 (7.9%)	587 (9.1%)	487 (7.5%)	0.076	0.639
Any agent	663 (30.8%)	2,131 (33.0%)	1,939 (30.0%)	0.054	0.473
Monotherapy	440 (20.4%)	1,381 (21.4%)	1,259 (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%)	1,910 (29.6%)	1,811 (28.0%)	0.334	0.678
Monotherapy	417 (19.4%)	1,247 (19.3%)	1,188 (18.4%)	0.972	0.322
Combined therapy	197 (9.1%)	663 (10.3%)	623 (9.6%)	0.131	0.525
Concomitant treatments[b]					
Digoxin	23 (1.1%)	73 (1.1%)	76 (1.2%)	0.808	0.683
Benzodiazepines	8 (0.4%)	2 (0.0%)	19 (0.3%)	<0.001	0.578
Antiarrhythmics	51 (2.4%)	115 (1.8%)	153 (2.4%)	0.087	0.999
Antiepileptic agents	36 (1.7%)	40 (0.6%)	95 (1.5%)	<0.001	0.509
Previous treatments[c]					
Statins	313 (14.5%)	1,096 (17.0%)	-	0.008	-
Hypoglycaemic agents	206 (9.6%)	590 (9.2%)	-	0.560	-
Antidepressant agents	460 (21.4%)	926 (14.4%)	-	<0.001	-
Neuroleptic agents	114 (5.3%)	185 (2.9%)	-	<0.001	-
Charlson Comorbidity Index score[c]					
0	2,014 (93.6%)	6,107 (94.7%)	-	0.073	-
1	91 (4.2%)	221 (3.4%)	-		
≥2	48 (2.2%)	122 (1.9%)	-		

ACEs: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blockers; CCBs: calcium channel blockers.

a According to chi-square test or its version for the trend (categories of the Charlson comorbidity index score).

b Within 30 days before the index date.

c Within five years before the index date.

Table 2
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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 (70 to 80 years old) and older (81-90 years old) patients

		Younger patients OR (95% CI)	Older patients OR (95% CI)
ACEs or ARBs	Case-control	0.69 (0.58 to 0.82)	0.82 (0.67 to 1.01)
	Case crossover	0.91 (0.73 to 1.13)	0.89 (0.69 to 1.15)
CCBs	Case-control	1.08 (0.82 to 1.43)	0.84 (0.60 to 1.18)
	Case crossover	0.95 (0.66 to 1.36)	1.44 (0.89 to 2.35)
β-blockers	Case-control	0.99 (0.75 to 1.32)	1.21 (0.85 to 1.72)
	Case crossover	0.78 (0.56 to 1.10)	1.03 (0.67 to 1.58)
α-blockers	Case-control	1.39 (0.57 to 3.39)	1.86 (1.03 to 3.35)
	Case crossover	1.40 (0.47 to 4.15)	1.88 (1.01 to 3.48)
Loop diuretics	Case-control	1.88 (1.28 to 2.74)	1.52 (1.04 to 2.21)
	Case crossover	1.36 (0.84 to 2.19)	1.82 (1.10 to 3.00)
Non-loop diuretics	Case-control	0.79 (0.63 to 1.00)	0.89 (0.68 to 1.17)
	Case crossover	0.94 (0.69 to 1.29)	1.31 (0.92 to 1.88)
Any agent	Case-control	0.93 (0.80 to 1.08)	0.95 (0.80 to 1.12)
	Case crossover	1.03 (0.86 to 1.23)	1.16 (0.94 to 1.43)
Monotherapy	Case-control	1.10 (0.92 to 1.30)	0.96 (0.79 to 1.17)
	Case crossover	1.10 (0.90 to 1.34)	1.13 (0.88 to 1.44)
Combined therapy	Case-control	0.71 (0.57 to 0.88)	0.92 (0.72 to 1.18)
	Case crossover	0.90 (0.68 to 1.17)	1.21 (0.89 to 1.65)
Any agent with the exception of loop diuretics	Case-control	0.87 (0.75 to 1.01)	0.91 (0.77 to 1.08)
	Case crossover	1.00 (0.83 to 1.19)	1.13 (0.91 to 1.40)
Monotherapy	Case-control	1.01 (0.85 to 1.20)	0.95 (0.78 to 1.16)
	Case crossover	1.07 (0.87 to 1.31)	1.16 (0.90 to 1.49)
Combined therapy	Case-control	0.78 (0.62 to 0.97)	0.84 (0.65 to 1.09)
	Case crossover	0.86 (0.65 to 1.14)	1.08 (0.78 to 1.49)

ACEs: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blockers; CCBs: calcium channel blockers

Figure 1
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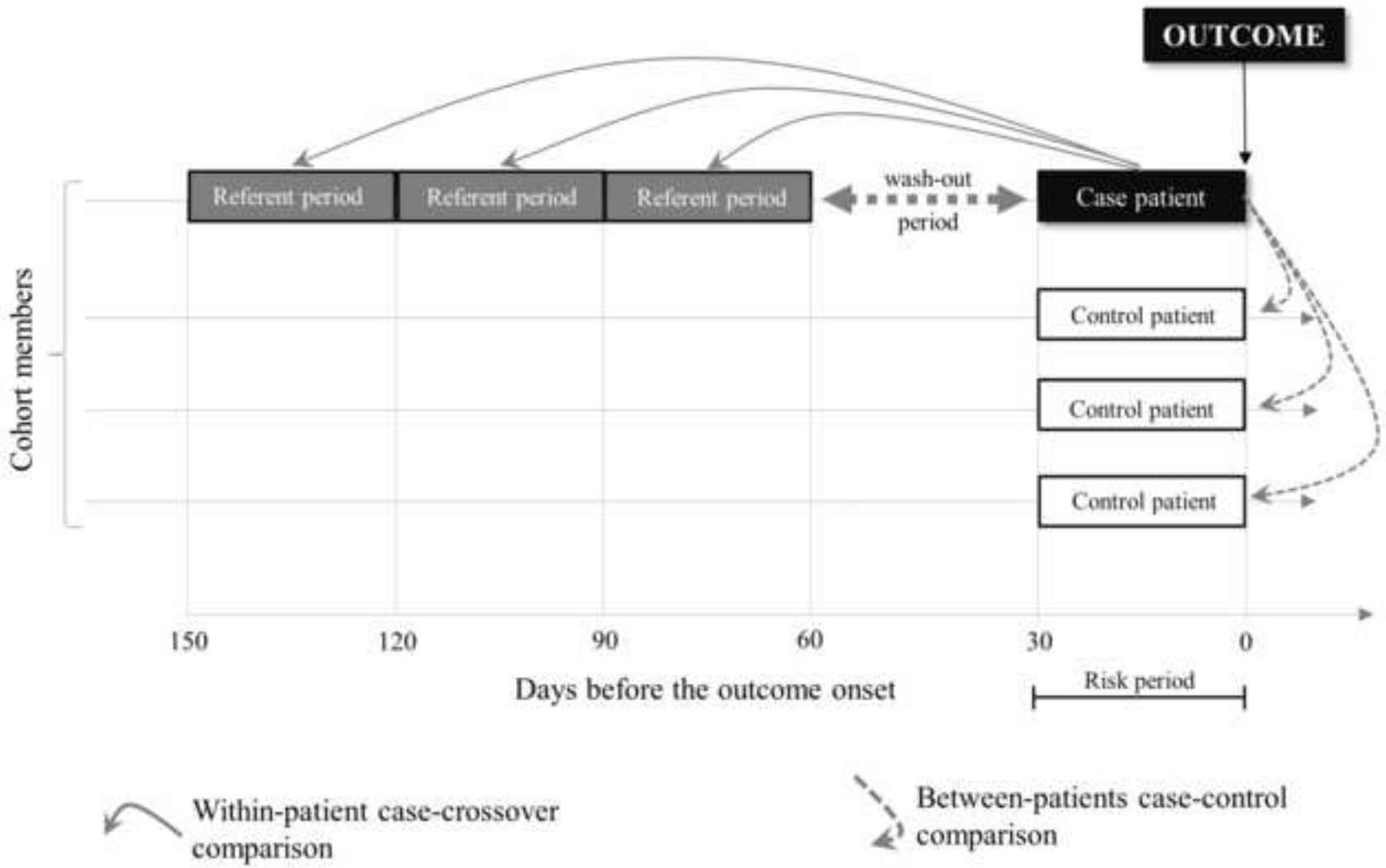
Figure 1



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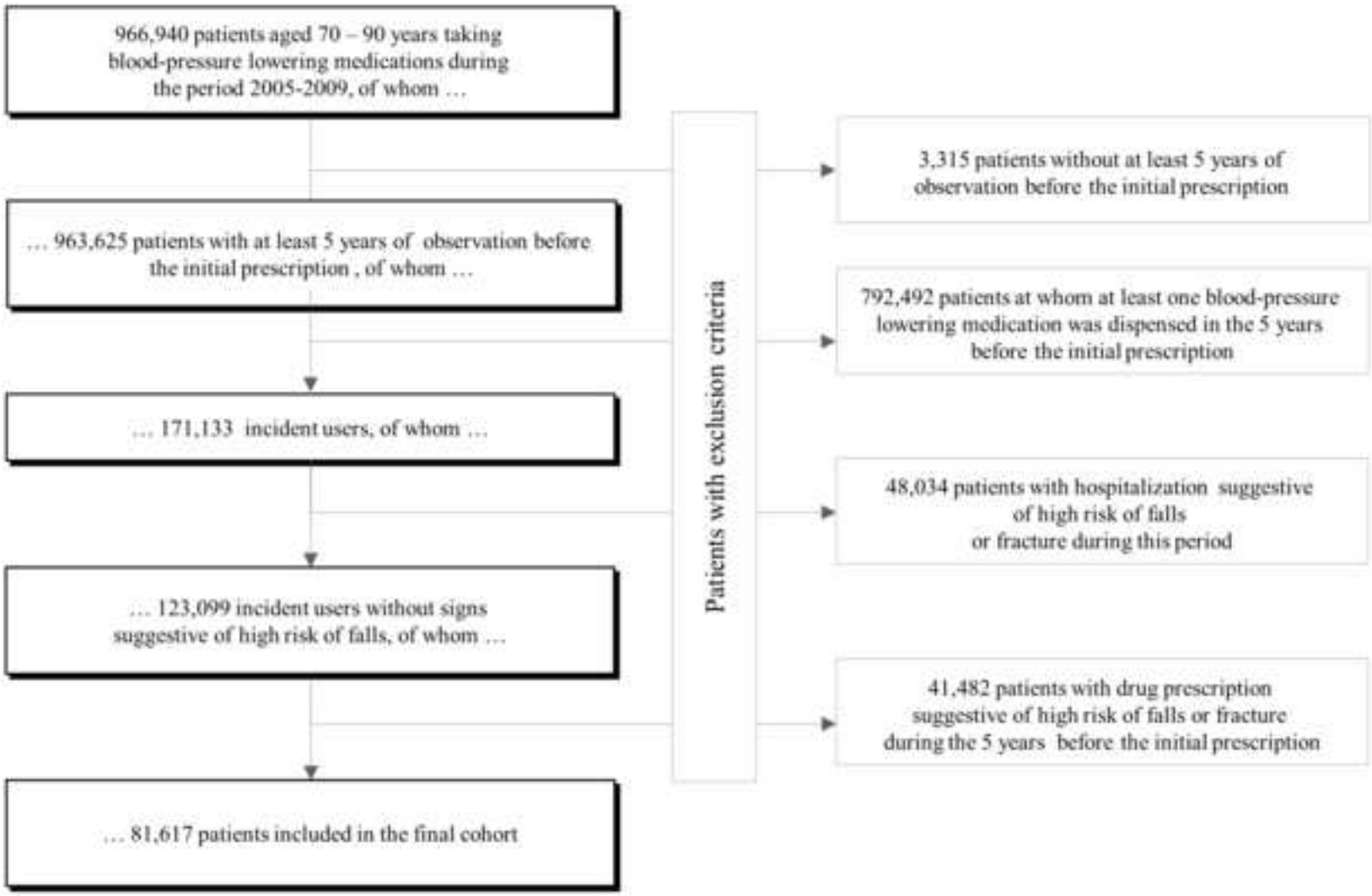

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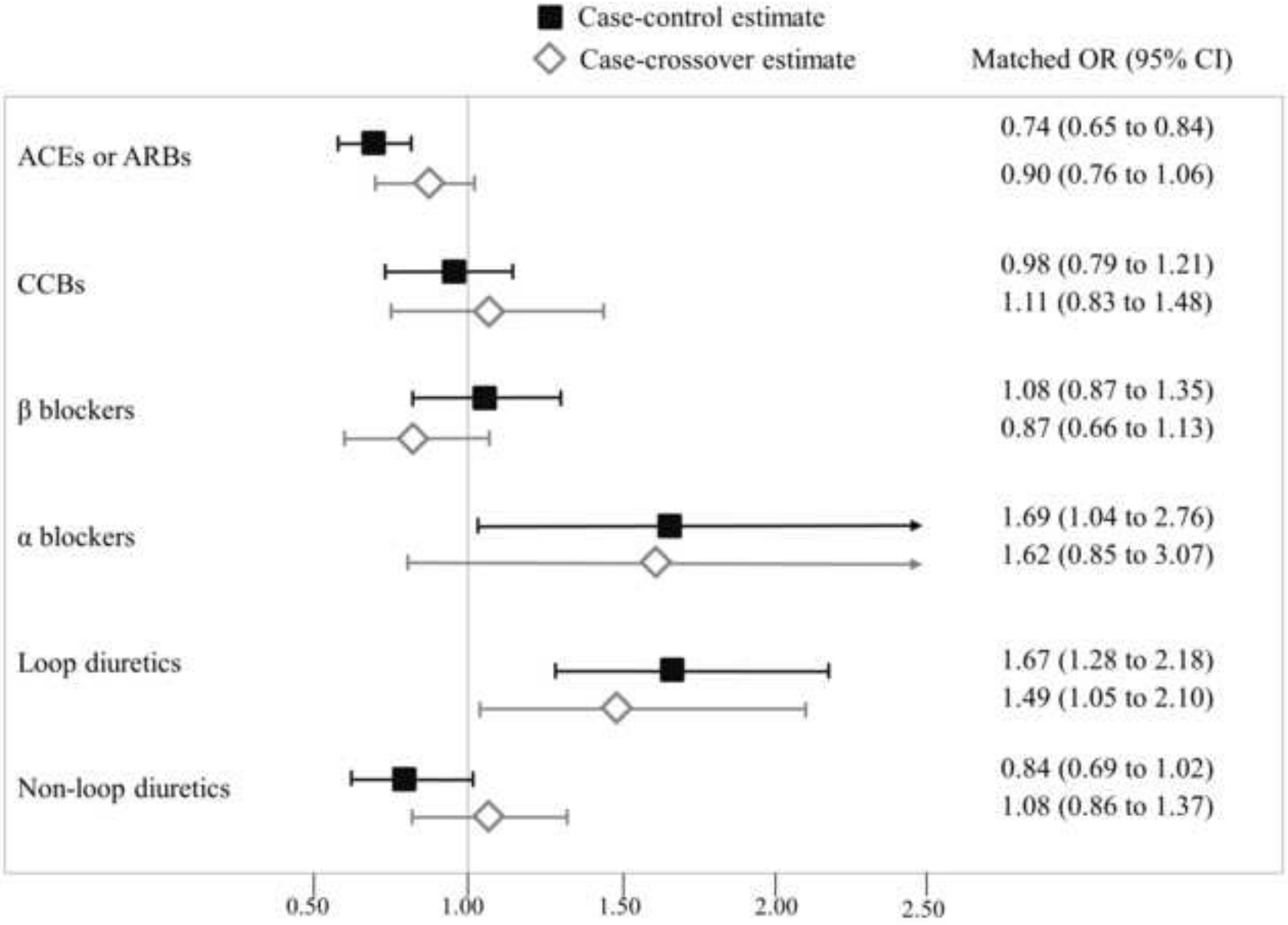

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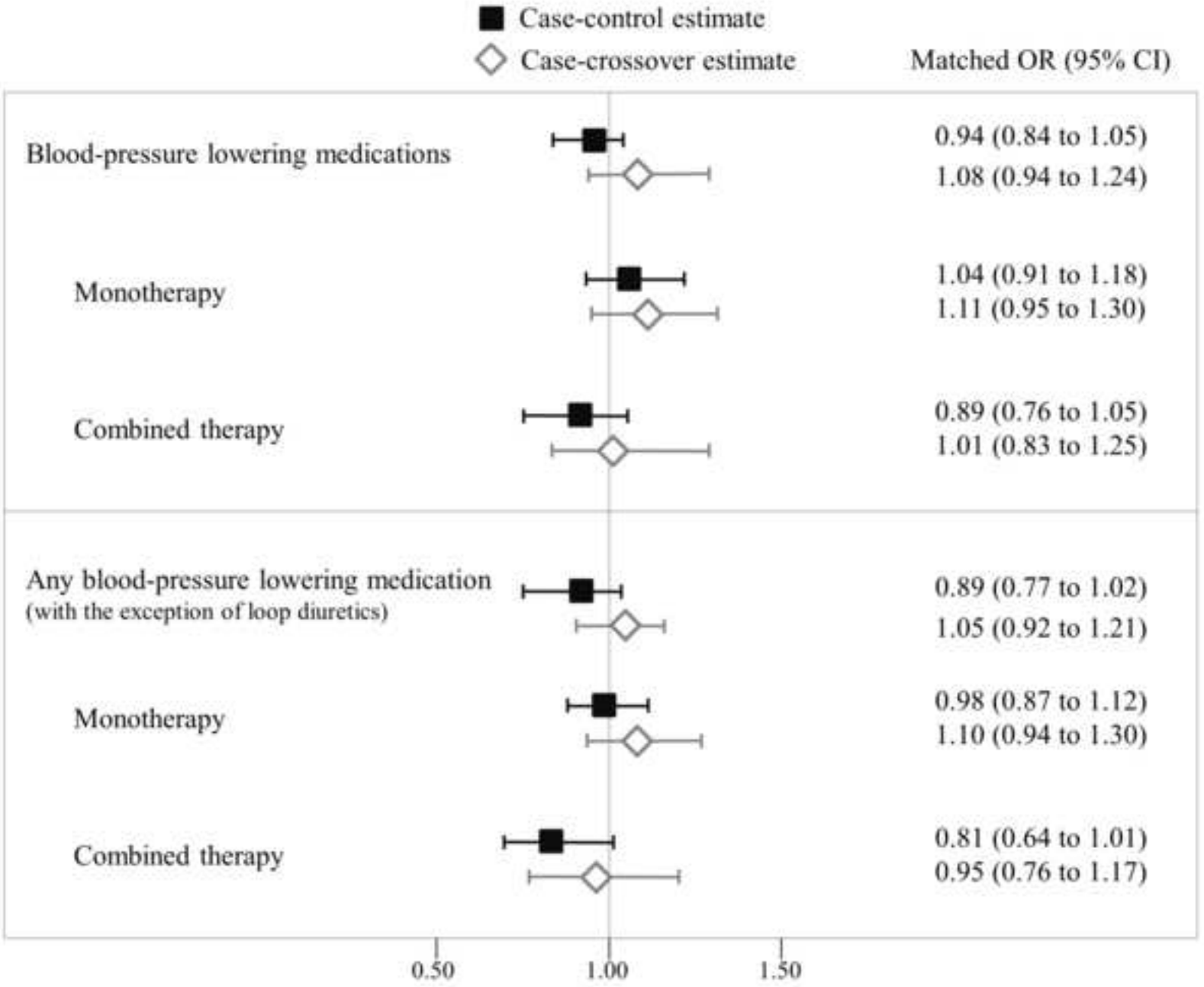

Supplementary materials
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Antihypertensive medications, loop diuretics, and risk of hip fracture in the elderly: a population-based cohort study of 81,617 Italian patients newly treated between 2005 and 2009

Running head: Antihypertensive agents and hip fracture

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1 **Table S1**

Blood pressure lowering class	Active ingredient
	Single agent
ACEs or ARBs	Captopril, enalapril, lisinopril. Perindopril, ramipril, quinapril, benazepril, cilazapril, fosinopril, trandolapril, spirapril, delapril, moexipril, zofenopril, losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan medoxomil.
CCBs	Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, manidipine, barnidipine, lercanidipine, verapamil, gallopamil, diltiazem.
β-blockers	Pindolol, propranolol, timolol, sotalol, nadolol, metoprolol, atenolol, acebutolol, betaxolol, bisoprolol, celiprolol, nebivolol, labetalol, carvedilol.
α-blockers	Methyldopa (levorotatory), clonidine, moxonidine, doxazosin.
Loop diuretics	Furosemide, piretanide, torasemide.
Non-Loop diuretics	Hydrochlorothiazide, chlortalidone, metolazone, indapamide, spironolactone, potassium canrenoate, canrenone, hydrochlorothiazide and potassium-sparing agents, butizide and potassium-sparing agents, furosemide and potassium-sparing agents.
	Fixed combination
ACEs + CCBs	Enalapril and lercanidipine, perindopril and amlodipine, ramipril and felodipine, delapril and manidipine.
β-blockers + diuretics	Bisoprolol and thiazides, nebivolol and thiazides, metoprolol and thiazides combinations, oxprenolol and other diuretics, atenolol and other diuretics combinations, atenolol and other diuretics.
ACEs + diuretics	Captopril and diuretics, enalapril and diuretics, lisinopril and diuretics, perindopril and diuretics, ramipril and diuretics, quinapril and diuretics, benazepril and diuretics, cilazapril and diuretics, fosinopril and diuretics, delapril and diuretics, moexipril and diuretics, zofenopril and diuretics.
ARBs + CCBs	Olmesartan medoxomil and amlodipine.
ARBs + diuretics	Losartan and diuretics, eprosartan and diuretics, valsartan and diuretics, irbesartan and diuretics, candesartan and diuretics, olmesartan medoxomil and diuretics, azilsartan medoxomil and diuretics.

2

Table S2.

		OR (95% CI)		
		15 days	45 days	90 days
Any agent	Case-control	0.93 (0.82 to 1.07)	0.86 (0.78 to 0.95)	0.80 (0.73 to 0.89)
	Case crossover	0.98 (0.85 to 1.14)	1.08 (0.93 to 1.24)	1.03 (0.89 to 1.21)
Monotherapy	Case-control	1.08 (0.92 to 1.26)	0.95 (0.85 to 1.07)	0.90 (0.80 to 1.00)
	Case crossover	1.03 (0.87 to 1.23)	1.11 (0.95 to 1.30)	1.07 (0.91 to 1.27)
Combined therapy	Case-control	0.73 (0.59 to 0.90)	0.72 (0.62 to 0.84)	0.67 (0.58 to 0.77)
	Case crossover	0.90 (0.71 to 1.13)	1.01 (0.83 to 1.25)	0.96 (0.78 to 1.18)
Any agent with the exception of loop diuretics	Case-control	0.88 (0.77 to 1.01)	0.82 (0.74 to 0.91)	0.76 (0.69 to 0.84)
	Case crossover	0.97 (0.84 to 1.13)	1.06 (0.92 to 1.23)	0.99 (0.85 to 1.16)
Monotherapy	Case-control	1.01 (0.86 to 1.19)	0.92 (0.82 to 1.04)	0.85 (0.76 to 0.95)
	Case crossover	1.02 (0.86 to 1.21)	1.12 (0.95 to 1.32)	1.06 (0.89 to 1.25)
Combined therapy	Case-control	0.69 (0.55 to 0.86)	0.67 (0.58 to 0.79)	0.62 (0.54 to 0.72)
	Case crossover	0.88 (0.69 to 1.13)	0.95 (0.77 to 1.17)	0.86 (0.70 to 1.07)
ACEs or ARBs	Case-control	0.72 (0.61 to 0.85)	0.72 (0.64 to 0.81)	0.70 (0.63 to 0.78)
	Case crossover	0.86 (0.71 to 1.03)	0.90 (0.76 to 1.07)	0.81 (0.68 to 0.97)
CCBs	Case-control	1.02 (0.77 to 1.37)	0.85 (0.70 to 1.03)	0.80 (0.68 to 0.96)
	Case crossover	1.18 (0.85 to 1.63)	0.96 (0.72 to 1.28)	1.13 (0.85 to 1.50)
β-blockers	Case-control	1.09 (0.82 to 1.45)	1.02 (0.85 to 1.24)	1.06 (0.89 to 1.25)
	Case crossover	0.94 (0.69 to 1.27)	1.01 (0.78 to 1.31)	1.38 (1.06 to 1.80)
α-blockers	Case-control	1.36 (0.71 to 2.61)	1.50 (0.96 to 2.34)	1.37 (0.91 to 2.06)
	Case crossover	1.35 (0.64 to 2.84)	0.97 (0.52 to 1.81)	1.09 (0.60 to 1.97)
Loop diuretics	Case-control	1.83 (1.30 to 2.57)	1.55 (1.21 to 1.98)	1.56 (1.25 to 1.95)
	Case crossover	1.24 (0.86 to 1.79)	1.33 (0.97 to 1.83)	1.64 (1.22 to 2.21)
Non-Loop diuretics	Case-control	0.67 (0.52 to 0.85)	0.71 (0.61 to 0.83)	0.67 (0.58 to 0.77)
	Case crossover	0.91 (0.69 to 1.19)	1.14 (0.90 to 1.43)	0.87 (0.70 to 1.08)

Adis

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