TITLE: CALCIUM CHANNEL BLOCKERS IN SECONDARY CARDIOVASCULAR PREVENTION AND RISK OF ACUTE EVENTS: REAL-WORLD EVIDENCE FROM NESTED CASE-CONTROL STUDIES ON ITALIAN HYPERTENSIVE ELDERLY

RUNNING HEAD: CALCIUM CHANNEL BLOCKERS AND RISK OF ACUTE EVENTS

AUTHORS:

Alessandra Bettiol [a,b], Ersilia Lucenteforte [a,*], Alfredo Vannacci [a,#], Niccolò Lombardi [a], Graziano Onder [c], Nera Agabiti [d], Cristiana Vitale [e], Gianluca Trifirò [f], Giovanni Corrao [g], Giuseppe Roberto [h], Alessandro Mugelli [a], Alessandro Chinellato [b], for the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE)[i].

AFFILIATIONS:

[a] Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy

[b] Local Health Authority 2 Marca Trevigiana, Treviso, Italy

[c] Department of Geriatrics, Neurosciences, and Orthopaedics, Catholic University of Medicine, Rome, Italy.

[d] Department of Epidemiology, Lazio Regional Health Service, Roma, Italy

[e] Department of Medical Sciences, IRCCS San Raffaele, Roma, Italy.

[f] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy.

[g] Laboratory of Healthcare Research & Pharmacoepidemiology, Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

[h] Regional Agency for Healthcare Services of Tuscany, Epidemiology unit, Florence, Italy.

[i] Members of the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE) are listed in the "Acknowledgments' section".

*CORRESPONDING AUTHOR:

Ersilia Lucenteforte, ScD PhD

Assistant Professor; Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, viale Gaetano Pieraccini, 6 – 50139 Florence, Italy

E-mail address: ersilia.lucenteforte@unifi.it

Telephone number: +39 055 27 58 206

AUTHORS CONTRIBUTION

All authors substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. All author substantially contributed in drafting the work or revising it critically for important intellectual content. All authors approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

This project was made on the behalf of the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE), whose members are: Nera Agabiti , Claudia Bartolini, Roberto Bernabei, Alessandra Bettiol, Stefano Bonassi, Achille Patrizio Caputi, Silvia Cascini, Alessandro Chinellato, Giovanni Corrao, Marina Davoli, Massimo Fini, Rosa Gini, Francesco Giorgianni, Ursula Kirchmayer, Francesco Lapi, Niccolò Lombardi, Ersilia Lucenteforte, Alessandro Mugelli, Graziano Onder, Federico Rea, Giuseppe Roberto, Chiara Sorge, Michele Tari, Gianluca Trifirò, Alfredo Vannacci, Davide Liborio Vetrano, Cristiana Vitale.

FUNDING

This study is part of large program supported by the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE), aimed to assess the appropriateness of outpatient drug prescriptions in the Italian elderly discharged from hospital for cardiovascular (CV) disease.

This work was supported by the Italian Medicines Agency AIFA [AIFA-FARM9LBBBL], which supports the I-GrADE. The funding source had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, nor in the decision to submit the article for publication.

ETHICS APPROVAL

This study was approved by the Ethic Committee of the “Azienda Ospedaliera Universitaria di Careggi”, Florence, Italy, on March 26th 2012; protocol number: 2012/0012643.

Conflict of Interest: All authors have no conflicts of interest to declare.

ABSTRACT

Background and objectives: Antihypertensive treatment with calcium channel blockers (CCBs) is consolidated in clinical practice, however different studies observed increased risks of acute events for short-acting CCBs. This study aimed to provide real-world evidence on risks of acute CV events, hospitalizations and mortality among users of different CCBs classes in secondary CV prevention.

Methods: Three case-control studies were nested in a cohort of Italian elderly hypertensive CV-compromised CCBs users. Cases were subjects with CV events (n=25,204), all-cause hospitalizations (n=19,237), or all-cause mortality (n=17,996) during the follow-up. Up to 4 controls were matched for each case. Current or past exposition to CCBs at index date was defined based on molecule, formulation and daily doses of the last CCBs delivery. The odds ratio (OR) and 95% confidence intervals was estimated using conditional logistic regression models.

Results: Compared to past users, current CCBs users had significant reductions in risks of CV events (OR 0.88 [95%CI: 0.84 – 0.91]), hospitalization (0.90 [0.88 – 0.93]) and mortality (0.48 [0.47 – 0.49]). Current users of long-acting dihydropyridines (DHPs) had the lowest risk (OR 0.87 [0.84 – 0.90], 0.86 [0.83 – 0.90], 0.55 [0.54-0.56] for acute CV events, hospitalizations and mortality), whereas current users of short-acting CCBs had an increased risk of acute CV events (OR 1.77 [1.13– 2.78] for short-acting DHPs; 1.19 [1.07 – 1.31] for short-acting non-DHPs) and hospitalizations (OR 1.84 [0.96 – 3.51] and 1.23 [1.08 – 1.42]).

Conclusions: The already-existing warning on short-acting CCBs should be potentiated, addressing clinicians towards the choice of long-acting formulations.

KEY POINTS

- Real world evidence on CCBs risks of acute events among CV-compromised hypertensive elderly was provided;
- Current use of CCBs significantly reduced risks of CV events, hospitalizations and mortality;
- Current use of short-acting CCBs was associated with higher risks of acute events; clinicians should be addressed towards choice of long-acting formulations.

1. INTRODUCTION

Arterial hypertension affects 33% and 31% of men and women in Italy, with an increasing trend in prevalence, mainly due to population aging [1]. Arterial hypertension is considered an independent, modifiable risk factor for the occurrence of major cardiovascular (CV) events; what's more, the majority of hypertensive patients suffer from additional CV pathologies or risk factors, which further potentiate the risk of acute CV events and mortality [2].

Therefore, the pharmacological management of hypertension is strongly recommended. Among antihypertensive treatments, use of calcium channel blockers (CCBs) is well established in clinical practice, either in primary or secondary CV prevention. According to their chemical structure and to their rapidity of action onset, CCBs can be divided into 4 main classes: short-acting dihydropyridines (DHPs); long-acting DHPs; short-acting non-DHPs CCBs (n-DHPs); and long-acting n-DHPs.

Despite their recognized [3-5] efficacy , the CV safety of CCBs, and in particular of rapid-onset formulations, has been long debated.

Since 1995, different studies correlated CCBs, and in particular short-acting nifedipine (a DHP CCB), with an increased risk of overall mortality and CV events [6-8]. In light of these findings, current Beers criteria classify short-acting nifedipine as an inappropriate drug for elderly patients [9].

Despite this, short-acting nifedipine and rapid-onset CCBs in general are still used in clinical practice, also in elderly subjects at high CV risk.

Given this discrepancy, the present study aimed to provide evidence from the Italian real clinical practice on the risks of acute CV events, all-cause hospitalizations and mortality connected to the different CCBs classes, focusing on a wide population of hypertensive CV-compromised elderly. This study was part of a large program supported by the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE), aimed to assess the appropriateness of outpatient drug prescriptions in the Italian elderly discharged from hospital for CV diseases.

2. SUBJECTS AND METHODS

2.1. Study design

Three case-control studies were nested into a cohort of elderly hypertensive patients diagnosed with CV diseases. The three studies aimed to evaluate the risk of acute CV events (study 1), all-cause hospitalizations (study 2) and mortality (study 3) among current vs past CCBs users.

To limit the possible indication bias, a user-only approach was adopted in all studies, excluding all hypertensive patients never prescribed with CCBs [10].

2.2. Setting

The setting of this study and the methodology for data retrieval have been previously described [11, 12].

Briefly, all data used for the present study were retrieved from the healthcare utilization databases of 3 Italian Regions (Lazio, Lombardy and Tuscany) and 2 Local Health Authorities (Caserta and Treviso), participating to the I-GrADE program.

About 21 million beneficiaries residing in these areas were recorded in the corresponding databases of healthcare services, providing information on nearly 35% of the Italian population.

Administrative databases consulted for this study included: i) an archive of demographic and administrative data of residents who receive National Health Service (NHS) assistance; ii) a database on hospital discharge records including information about primary diagnosis and up to five co-existing conditions and procedures (secondary diagnosis fields) coded according to the International Code of Disease, 9^{th} revision (ICD-9 CM) classification system; iii) a prescription database providing information on all community prescriptions reimbursed by the NHS with drugs coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Each subject is identified through a unique identification code, therefore allowing the record linkage among databases. In order to preserve privacy, the original unique identification code was replaced with its digest that is the image of the code through a cryptographic hash function.

2.3. Participants

Beneficiaries of the NHS who i) were residing in the participating healthcare territorial units, ii) were aged 65 years or older, and iii) had been hospitalized with a diagnosis of selected CV diseases in the years 2008-2010 (considering ICD9-CM codes reported in **Supplementary material S1 text**, in primary or secondary diagnosis field), were considered eligible to enter the cohort. The date of the first CV-related hospitalization in the period was considered as the entry date in the study. Subjects were excluded if they i) were discharged dead from the entry hospitalization, ii) had history of malignancies (identified from a discharge diagnosis with ICD9-CM codes 140*-208* in primary or secondary diagnosis) at any time prior to the entry date, and/or iii) did not have at least 2 years of uninterrupted observation prior to the entry date. Of the remaining patients, only subjects that i) had a diagnosis of hypertension (identified from a discharge diagnosis with ICD-9 CM code 401* in primary or secondary diagnosis fields) in the 2 years before the entry date, and ii) had at least one prescription of a CCBs (ATC codes C08* or C09BB* or C09DB*) following the entry date, were included in the final cohort.

For study 1 and 2, members accumulated person-years of follow-up from the first date of CCBs delivery after the entry date, until the occurrence of: i) a further acute CV events, ii) a hospitalization with a diagnosis of cancer, iii) death, and/or iv) end of data availability. For study 3, instead, members accumulated person-years of follow-up until: i) a hospitalization with a diagnosis of cancer, ii) death, and/or iii) end of data availability.

The first date among these events were considered as exit date. Patients who exit the study in the 15 days following the entry date were excluded, since death or re-hospitalizations were probably related to the entry hospitalization rather than to a new event.

2.4. Definition of case subjects and controls

Cases were defined as subjects experiencing the outcome of interest during follow-up: CV-related hospitalization in study 1, identified considering the ICD9-CM coded reported in **Supplementary material**

S2 text; all-cause hospitalizations in study 2; all-cause mortality in study 3. For each case subject, the first date of the outcome of interest was defined as the index date.

Each case was matched to up to 4 controls randomly selected by risk-set sampling from all cohort members whose follow-up did not end prior to the index date of the corresponding case. Matching was performed within each participating healthcare territorial unit according to gender, age, and month and year of entry in the study. Of note, a subject could be considered as a case subject in one study and as a control in the other studies. Cases with no matched controls were excluded from the study.

2.5. Exposure to CCBs

To evaluate whether or not subjects were currently exposed to CCBs at time of index date, the last prescription of CCBs during the follow-up was considered. The amount of defined daily doses (DDD) of the last CCB delivery was considered. A grace period corresponding to the 20% of the amount of the last DDD delivered was given. Patients currently exposed to CCBs at time of index date were considered as current users; on the other hand, patients without CCBs therapeutic coverage at index date were considered as past users. For current users, exposition to the four different CCBs classes was assessed considering the CCB active principle and formulation: long-acting DHP, including amlodipine alone (C08CA01) or in combination with perindopril (C09BB04) or with olmesartan medoxomil (C09DB02), felodipine alone (C08CA02) or in combination with ramipril (C09BB05), isradipine (C08CA03), nimodipine (C08CA06), nisoldipine (C08CA07), nitrendipine (C08CA08), lacidipine (C08CA09), manidipine alone (C08CA11) or in combination with delapril (C09BB12), barnidipine (C08CA12), lercanidipine alone (C08CA13) or in combination with enalapril (C09BB02), and release-modified formulation of nicardipine (C08CA04) and nifedipine (C08CA05); short-acting DHP, including not release-modified formations of nifedipine (C08CA05) and nicardipine (C08CA04); long-acting n-DHPs, including gallopamil (C08DA02), and release-modified formulations of verapamil (C08DA01) or diltiazem (C08DB01); short-acting n-DHP, including not release-modified formulations of verapamil (C08DA01) and diltiazem (C08DB01).

2.6. Covariates

Covariates assessed for each case and control included: i) use to CCBs in the 6 months before the entry in the study; v) severity of the CV disease, assessed considering the occurrence of cardiovascular procedures in the 2 years before entry in the study, identified as reported in **Supplementary material S3 text**; vi) type of CV pathology at entry (identified as reported in **Supplementary material S1 text**); vii) Charlson Comorbidity Index (CCI), calculated in the 2 years before the entry date according to the algorithm reported by Quan et al. [13], and categorized as 0, 1, or ≥ 2; viii) current use of other antihypertensive treatment at time of index date.

2.7. Data analysis

Percentages of all considered covariates among cases and controls were compared using Chi-square tests. A conditional logistic regression model for matched case-control data was used to estimate the Odds Ratio (OR), and 95% confidence interval (CI), of the outcomes of interest associated with current use of CCBs compared with past use. Adjustments were made for the above listed covariates.

All analyses were performed using the software STATA version 14. For all tested hypotheses, two-tailed p-values less than 0.05 were considered statistically significant.

2.8. Sensitivity analyses

A sensitivity analysis was performed to limit the possible unmeasurable bias coming from CCBs deliveries occurred during a hospital stay [14]. In fact, drug deliveries occurring during hospitalizations are not recorded in administrative databases. With this aim, cohort members who experienced hospitalization for whichever cause in the 30 days before index date were excluded. Sensitivity analysis was performed only for study 1 and 3.

3. RESULTS

An initial cohort of 965,903 subjects discharged from a CV-related hospitalization was extracted (**Figure 1**). Following the application of the defined exclusion criteria, a final cohort of 107,533 hypertensive elderly affected by CV pathologies and treated with CCBs was selected.

27,679 subjects experienced a further acute CV event: of them, 2,475 were excluded due to lack of matching controls. 25,204 patients were included as cases subjects and were matched to 55,325 controls (study 1). All-cause hospitalizations occurred instead in 74,488 out of the 107,533 subjects: of them, 55,251 were excluded due to lack of matching controls. 19,237 cases and 20,102 matching subjects were included in study 2. All-cause death occurred in 22,080 patients, of whom 4,084 were excluded due to lack of matching controls. 17,996 were included as cases subjects and were matched to 45,431 controls (study 3).

3.1. Characteristics of cases and controls

Table 1 provides some selected characteristics of cases and controls included in the three studies. According to matching variables (study design), cases were comparable to controls in all studies. Considering the CV disease at entry, more cases than controls were diagnosed with heart failure or cardiac arrhythmia in all studies, with ischemic heart disease in study 1 and 3, and with stroke in study 3. As concern CV procedures, more cases than controls had undergone coronary artery bypass surgery and other heart surgery procedures in study 1 and 2, percutaneous transluminal coronary angioplasty in study 2, and cerebral revascularization in study 1. Based on CCI, case subjects were frailer than controls in all studies. In all studies, use of CCBs in the 6 months before entry was more frequent among cases. On the other hand, current use of CCBs at index date was more frequent among controls in all studies. In particular, in all three studies, more controls than cases were currently exposed to long-acting DHPs. On the other hand, in all studies, current use of short-acting DHPs was more frequent among case subjects. As concerning n-DHPs CCBs, current use of either long- or short-acting formulations was significantly higher among cases than controls in study 1 and 2, while it was higher among controls in study 3.

Focusing on other antihypertensive treatments currently used at index date, diuretics were more used among cases than controls in all studies, beta-blockers were more used among controls in study 3, agents acting on the Renin-Angiotensin system were more used among controls in study 2 and 3, and other anti-hypertensive drugs (ATC code C02*) were more used among cases in study 1 and 2, and among controls in study 3.

3.2. Use of CCBs and risks of acute CV events, all-cause hospitalizations and mortality

The effect of CCBs on the risk of acute CV events, all-cause hospitalizations and mortality is shown in **Figure 2**. Focusing on acute CV events, current users of CCBs exhibited a risk reduction of 12% (OR 0.88 [95% CI: 0.84-0.91]) compared to past CCBs users. In particular, stratifying according to the different CCBs classes, only long-acting DHPs were associated with a significant reduction in risk (OR 0.87 [0.84 – 0.90]); on the other hand, current users of either short-acting DHPs or n-DHPs resulted to be at increased risk of acute CV events (OR 1.77 [1.13 – 2.78] and 1.19 [1.07 – 1.31]), respectively).

The occurrence of the different CV outcomes among current users of the different CCBs classes is reported in **Figure 3**. The most frequent CV outcome was cardiac arrhythmia, which was experienced by 10.74% of current CCBs users, followed by heart failure (6.61%), ischemic stroke (5.77%), acute myocardial infarction (4.52%), transient ischemic attack (1.62%) and haemorrhagic stroke (0.90%). Of note, occurrence of acute myocardial infarction, cardiac arrhythmia and heart failure was significantly higher among current users of short-acting DHPs compared to long-acting DHPs ($p<0.05$). Similarly, occurrence of cardiac arrhythmia and heart failure was significantly higher among current users of short-acting n-DHPs compared to long-acting n-DHPs ($p<0.05$), whereas the occurrence of acute myocardial infarction was significantly higher among users of long-acting n-DHPs ($p<0.05$).

Focusing on all-cause hospitalizations, current use of CCBs resulted to play a protective role compared to past use (OR 0.90 [0.88 – 0.93]) (**Figure 2**). Stratifying according to CCBs classes, only long-acting DHPs were associated with a significant reduction in risk (OR 0.88 [0.83 - 0.90]). On the other hand, both long- and short-acting n-DHPs were associated with an increased risk of hospitalizations (OR 1.15 [1.04 – 1.27] and 1.23 [1.08 – 1.42]).

Considering all-cause mortality, current CCBs users exhibited a risk reduction of 52% (OR 0.48 [0.47-0.49]) compared to past CCBs users. In particular, all CCB classes except short-acting DHPs were associated with a significant reduction in risk (OR of 0.55 [0.54 – 0.58] for long-acting DHPs; 0.62 [0.58 – 0.66] for long-acting n-DHPs; 0.83 [0.75 – 0.91] for short-acting n-DHPs).

3.3. Sensitivity analysis

In the sensitivity analysis of study 1, 11,672 case subjects who experienced acute CV events where matched to 22,543 controls. Results of this analysis confirmed a protective role of current use of CCBs towards acute CV events (OR 0.89 [0.85 – 0.92]) (**Supplementary Table S1**). In particular, current users of long-acting DHPs were at the lowest risk (OR 0.87 [0.84 – 0.91]), whereas current users of either short-acting DHPs or n-DHPs were at significantly higher risk (OR 1.75 [1.32 – 2.31] and 1.17 [1.07 – 1.28], respectively). In the sensitivity analysis of study 3, 8,427 case subjects who died for whichever cause were matched to 20,394 controls. Current users of CCBs resulted to be at significantly lower risk of mortality (OR 0.40 [0.38 – 0.43]). In particular, current exposition to all CCBs classes, except short-acting DHPs, resulted to be protective towards all-cause mortality.

4. DISCUSSION

In this large population-based study of elderly hypertensive patients formerly experiencing a major CV hospital admission, we found that current use of CCBs significantly decrease the risk of both hospitalizations (for acute CV events or for whichever cause) and mortality, compared to past CCBs use. In particular, current users of long-acting DHPs were found to be at the lowest risk of all considered events. Our results add further evidence supporting the effectiveness of CCBs in secondary CV prevention, therefore highlighting the importance of a strict adherence to this treatment.

On the other hand, we found that current users of either short-acting DHPs or n-DHPs were at significantly higher risk of hospital admission for both acute CV events and all causes, compared to past CCBs users.

The increase in risks connected to the use of short-acting CCBs could be attributable to the rapid mechanism of action of these formulations, which may lead to severe blood pressure fluctuations, unpredictable episodes of severe hypotension, and to tachycardia [15]. Our findings are consistent with previous evidences showing an increased risk of death and acute CV events in patients exposed to rapid-onset CCBs in secondary CV prevention. Already in 1995, a first meta-analysis on 16 randomized secondary-prevention trials on nifedipine was published, reporting a dose-related increased risk of overall mortality among patients exposed to short-acting nifedipine (risk ratio of 1.16 [95% CI: 1.01 to 1.33] [6].

Later on, another meta-analysis on 60 randomized controlled trials evaluated the risk of CV event in patients affected by stable angina and treated with nifedipine in mono- or combination therapy compared to control patients treated with other active drugs in monotherapy [7]. Treatment with immediate-release nifedipine was found to significantly increase the risk of angina (OR of 4.19 [95% CI: 1.41 to 12.49]) as well as of all events combined (OR of 3.09 [95% CI: 1.39 to 6.88].

More recently, a case-crossover study was conducted on 16,069 elderly hypertensive patients experiencing a first stroke events; a significant increase in both ischemic and haemorrhagic stroke associated to the use of short-acting nifedipine was reported (OR 2.56 [95% CI: 1.89–3.47] and 5.16 [95% CI: 2.29–11.66], respectively) [8].

298 Despite the well-known risk associated to short-acting CCBs, we found that rapid-onset CCBs were still
299 in use in the real clinical practice, although the design of this study did not allow to estimate the entity of
300 the overall population exposed to these formulations. However, considering the CV burden and the old
301 age of the study population, antihypertensive treatment with short-acting DHPs was probably
302 inappropriate in these patients.

303 Comparing current use of long-acting formulations of DHPs vs n-DHPs, we found that n-DHPs were
304 associated with higher risk of all considered outcomes. However, this difference in safety profile is likely
305 to be ascribable more to patients' related characteristics than to the molecules themselves, given the
306 differences in therapeutic indications among these two drug classes [16].

307 Our study included a large and unselected cohort of CCBs users aged 65 years or older with a
308 hospitalization for major CV events and diagnosed with hypertension. This means that our findings can
309 be generalised only to elderly suffering of CV disease and elected for an antihypertensive treatment with
310 CCBs in secondary CV prevention. All eligible patients were included, so no bias due to non-response
311 was present, and no recall bias occurred because data on their characteristics (including drug use) were
312 recorded before the outcomes occurred. The drug prescription database provided highly accurate data,
313 because pharmacists are required to report prescriptions in detail in order to obtain reimbursement, and
314 incorrect reports about the dispensed drugs have legal consequences. In addition, the user-only design
315 adopted in this study allowed to control for possible indication bias coming from variability in indications
316 of use of CCBs [10, 14]. Finally, the performed sensitivity analyses confirmed the data provided by the
317 main analysis.

318 However, our study has limitations. First, results of blood pressure monitoring were not available in our
319 data sources; occurrence of CV events, as well as of all-cause hospitalizations and death, could be
320 therefore related to a non-response to antihypertensive treatment, rather than to the anti-hypertensive
321 drug. Second, no information was available on the current health and CV condition of subjects: current
322 users of CCBs (and in particular of short-acting formulations) at time of index date could have been
323 prescribed with short-acting CCBs, following the onset of a CV complication not recorded on
324 administrative databases. Third, evaluation of CCBs use was based on pharmacy-dispensing information.

This method assumes that prescription corresponds to medication use, which may not be invariably true. Although data on dispensing history have shown to be consistent with other adherence measures [17], medication dispensing as a measure of drug use remains a source of uncertainty of our estimates. Fourth, both comorbidities and events were retrieved based on ICD9-CM codes; however, problems related to incomplete or wrong coding may be present. In addition,
ICD-9-CM codes do not indicate degree of severity. Fifth, less than 0.5% of the entire considered population was exposed to short-acting DHPs at time of index date; therefore, results concerning this drug class could be influenced by the small size of this sample. Finally, as for any observational study, residual confounding linked for example with unmeasured disease severity, comorbidity, socio-economic status and various lifestyle factors, cannot be fully eliminated.

5. CONCLUSION

Although suffering from the above-mentioned limitations, our study provided key information from the real clinical practice on the effectiveness of antihypertensive treatment with long-acting CCBs as well as on the possible risk associated with short-acting CCBs formulations. Since any potential increased risk may result in a considerable public health impact, the risk estimates of short-acting CCBs provided by this study may support both clinical practitioners and regulatory activities. From our point of view, the already-existing warning on short-acting CCBs should be potentiate, addressing clinicians towards the choice of long-acting formulations.

REFERENCES

1. (SIIA) SIdIA. Ipertensione: i numeri in Italia http://siia.it/i-numeri-in-italia-2/; last access February 2nd 2017

2. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European heart journal. 2013;34(28):2159-219. doi:10.1093/eurheartj/eht151.

3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Bmj. 2009;338:b1665. doi:10.1136/bmj.b1665.

4. Turnbull F, Blood Pressure Lowering Treatment Trialists C. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527-35.

5. Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension. 2005;46(2):386-92. doi:10.1161/01.HYP.0000174591.42889.a2.

6. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995;92(5):1326-31.

7. Stason WB, Schmid CH, Niedzwiecki D, Whiting GW, Caubet JF, Cory D et al. Safety of nifedipine in angina pectoris: a meta-analysis. Hypertension. 1999;33(1):24-31.

8. Jung SY, Choi NK, Kim JY, Chang Y, Song HJ, Lee J et al. Short-acting nifedipine and risk of stroke in elderly hypertensive patients. Neurology. 2011;77(13):1229-34. doi:10.1212/WNL.0b013e318230201a.

9. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2015;63(11):2227-46. doi:10.1111/jgs.13702.

10. Corrao G, Ghirardi A, Segafredo G, Zambon A, Della Vedova G, Lapi F et al. User-only design to assess drug effectiveness in clinical practice: application to bisphosphonates and secondary prevention of fractures. Pharmacoepidemiology and drug safety. 2014;23(8):859-67. doi:10.1002/pds.3650.

11. Vetrano DL, La Carpia D, Grande G, Casucci P, Bacelli T, Bernabei R et al. Anticholinergic Medication Burden and 5-Year Risk of Hospitalization and Death in Nursing Home Elderly Residents With Coronary Artery Disease. Journal of the American Medical Directors Association. 2016;17(11):1056-9. doi:10.1016/j.jamda.2016.07.012.

12. Rea F, Bonassi S, Vitale C, Trifiro G, Cascini S, Roberto G et al. Exposure to statins is associated to fracture risk reduction in elderly people with cardiovascular disease: evidence from the AIFA-I-GrADE observational project. Pharmacoepidemiology and drug safety. 2017;26(7):775-84. doi:10.1002/pds.4206.

13. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care. 2005;43(11):1130-9.

14. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. American journal of epidemiology. 2008;168(3):329-35. doi:10.1093/aje/kwn135.

15. Buonanno FS, Spence JD. Short-acting nifedipine and risk of stroke. Neurology. 2011;77(13):1216-7. doi:10.1212/WNL.0b013e3182311fdf.

16. Godfraind T. Calcium channel blockers in cardiovascular pharmacotherapy. Journal of cardiovascular pharmacology and therapeutics. 2014;19(6):501-15. doi:10.1177/1074248414530508.

17. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. Journal of clinical epidemiology. 1997;50(1):105-16.

FIGURE LEGENDS

Fig. 1 Flow-diagrams of the three user-only nested case-control studies

CCB= Calcium Channel Blockers; CV= Cardiovascular

Fig. 2 Risks of acute cardiovascular events, hospitalizations and mortality for current vs past users of the different Calcium Channel Blockers classes

CCB= Calcium Channel Blockers; CI= Confidence Intervals; CV= Cardiovascular; DHPs= Dihydropyridines; n-DHPs=non- Dihydropyridines; OR= Odds Ratio

Fig. 3 Occurrence of the acute CV outcomes in exam among users of the different Calcium Channel Blockers classes

CCB= Calcium Channel Blockers; DHPs= Dihydropyridines; n-DHPs=non- Dihydropyridines