ORIGINAL ARTICLE

Tolerability of Antihypertensive Medications: The Influence of Age

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Abstract

Introduction Despite high prevalence of hypertension, few studies have analysed the adverse effects (AEs) of antihypertensive medications, especially in older patients.

Aim To investigate the prevalence and associated factors of antihypertensive-related AEs, focusing on the influence of age on treatment tolerability.

Methods We retrospectively investigated antihypertensive-related AEs in patients evaluated at the Hypertension Clinic of Careggi Hospital, Florence, Italy, between January 2017 and July 2020. Multivariable regression models were generated to analyse variables associated with AEs in the overall sample and in participants ≥75 years.

Results Among 622 subjects (mean age 64.8 years, 51.4% female), the most frequently reported AEs were calcium-channel blockers (CCB)-related ankle swelling (26.8%) and ACEi-induced cough (15.1%). Ankle swelling was more common in older patients (35.7% vs 22.3%, p = 0.001; odds ratio [OR] 1.94, 95%CI 1.289-2.912) and was independently associated with Body Mass Index (BMI, adjOR 1.073) and angiotensin-receptor antagonists (adjOR 1.864). The association with BMI was confirmed in older patients (adjOR 1.134). ACEi-induced cough showed similar prevalence in younger and older patients (13.9% vs 15.6%, p = 0.634), being independently associated with female sex (adjOR 2.118), gastroesophageal reflux disease (GERD, adjOR 2.488) and SNRI therapy (adjOR 8.114). The association with GERD was confirmed in older patients (adjOR 3.238).

Conclusions CCB-related ankle swelling and ACEi-induced cough represent the most common antihypertensive-related AEs, also at old age. Older patients showed a two-fold increased risk of ankle swelling, that was also independently associated with BMI. ACEi-induced cough had similar prevalence at younger and old ages, being independently associated with GERD.

Keywords Blood pressure · Older adults · Cough · Adverse event · Adverse effect

1 Introduction

Hypertension represents one of the leading modifiable risk factors for cardiovascular morbidity and mortality, affecting more than 1.28 billion adults worldwide with increasing prevalence in advancing age [1]. Recent literature has provided clear evidence on the beneficial effects of blood pressure (BP) reduction, also in older adults [2, 3]. Yet, at old age, comorbidities, polypharmacy and age-related changes in pharmacokinetics and pharmacodynamics may contribute to increase the risk of drug-related adverse effects (AEs), i.e., any noxious, undesired, or unintended response to a therapeutic agent, which occur at therapeutic doses [4].

It is estimated that drug-related AEs occur in approximately 20–85% of patients receiving anti-hypertensive medications, with distinct and specific tolerability profiles for different drug classes [5–7]. AEs associated with antihypertensive medications may negatively impact patient's compliance [8], leading to poor BP control and increased cardiovascular risk [9].

The HYVET trial reported a 40% prevalence of drug-related AEs among subjects aged 80 or older receiving antihypertensive therapy [10]. Despite the known predisposition

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of older patients to drug-related AEs, the influence of age on tolerability of antihypertensive medications has been poorly investigated to date, except for the well-known risk of hypotension, electrolyte imbalances and renal function worsening [11, 12]. Therefore, although treatment tolerability can significantly influence patients' compliance and therapeutic management, the risk and predisposing factors for antihypertensive-related AEs in older adults remain currently unclear [13].

The present study analysed the prevalence and associated factors of antihypertensive-related AEs in a sample of hypertensive outpatients, with the final purpose to investigate the influence of age on antihypertensive treatment tolerability.

2 Methods

We conducted a retrospective cross-sectional analysis of data from all treated hypertensive patients evaluated at the Hypertension Clinic of Careggi University Hospital, Florence, Italy, between January 2017 and July 2020. The Hypertension Clinic of Careggi University Hospital evaluates hypertensive adults of all ages from Florence and its surroundings, offering specialized geriatric care for older hypertensive patients. Tolerability of antihypertensive medications and past history of treatment-related AEs are routinely investigated during the visit and any current/previous AE is recorded in medical charts. For the purpose of the present study, a medical chart review was carried out to collect data on medical history, comorbidities and BP values. Detailed information on medical therapy was recorded, focusing on antihypertensive drug classes (ACE–inhibitors [ACEi], angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], beta-blockers, diuretics [loop diuretics, thiazide diuretics, mineralcorticoid receptor antagonists], doxazosin and other alpha receptor blockers). Moreover, tolerability of antihypertensive medications was assessed by recording any current/previous AE spontaneously reported by the patient or detected by the physician during routine visits. Antihypertensive-related AEs were defined as any adverse effect resulting in treatment discontinuation or dose reduction. The prevalence of AEs was assessed based on the total number of patients who were receiving or had previously received a specific drug class, i.e., the total number of patients with ongoing treatment and of those with previous treatment discontinuation because of AE (prior treatment).

2.1 Statistical Analysis

Continuous variables were expressed as means and standard deviations (SD) or as medians and interquartile ranges (IQRs, 25th–75th percentiles), according to what was most

appropriate based on variables distribution. Categorical variables were expressed as absolute frequencies with percentages.

To investigate the influence of age on treatment tolerability, the prevalence of antihypertensive-related AEs was analysed in two age-stratified subgroups (< 75 and ≥ 75 years). Moreover, for the most frequently reported AEs, bivariate analyses were performed to compare patients with and without each adverse effect, in the overall sample and in the subgroup ≥ 75 years. The Pearson chi-square test was used for comparison of categorical variables between groups, while the T-test for independent samples (parametrical) or the Mann-Whitney test (non-parametrical) were used as appropriate for comparison of continuous variables. Multivariable binary logistic regression models were generated with backward stepwise selection approach to identify factors independently associated with each adverse effect. Logistic regression models were adjusted for demographics and other clinical variables of interest including those showing an association with the outcome in univariate analysis. To avoid multicollinearity, inter-correlations among the tested variables were verified by using a correlation matrix of the Spearman's Rho correlation coefficients on two sides; variables with a correlation coefficient equal or superior to 0.50 were excluded from the model. Results of logistic regression were expressed as odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS Statistics software version 26 (SPSS Inc. IBM, Chicago, IL).

3 Results

The study sample included 622 patients (mean age 64.8 ± 14.8 years, 51.4% female). Their characteristics are detailed in Table 1. The study participants were receiving a median number of 2 antihypertensive medications, with renin-angiotensin system inhibitors (79.4%) and CCBs (57.2%) being the most commonly prescribed drug classes.

Table 2 describes antihypertensive-related AEs observed in our study sample. CCB-related ankle swelling (26.8% of patients receiving prior/ongoing CCBs treatment) and ACEi-induced cough (15.1% of patients receiving prior/ongoing ACEi treatment) were the most frequently reported, while other AEs were rare.

CCBs-related ankle swelling was significantly more common in older than in younger patients (35.7% vs 22.3%, p = 0.001), with an OR of 1.94 (95% CI 1.289–2.912, p = 0.002). Prevalence of ACEi-induced cough was similar in the two age groups (13.9% vs 15.6%, p = 0.634) (Fig. 1).

Table 1 Clinical characteristics of the study sample.

	Overall sample (n = 622)
Age (years), mean (SD)	64.8 (14.8), range 18–95
Female sex, n (%)	320 (51.4)
Body Mass Index (kg/m^2), mean (SD) (n = 431)	27.6 (4.7)
Hypertension profile, n (%)	
Systolic-diastolic hypertension	488 (78.5)
Isolated systolic hypertension	97 (15.6)
Isolated diastolic hypertension	37 (5.9)
Office SBP/DBP (mmHg), mean (SD)	138.3 (18.5)/79.2 (10.4)
Home SBP (n = 529)/DBP (n = 501) (mmHg), mean (SD)	130.1 (12.4)/76.6 (9.1)
Orthostatic hypotension, n (%)(n = 556)	228 (41.0)
Current smoking	80 (12.9)
Diabetes, n (%)	105 (16.9)
Coronary artery disease, n (%)	44 (7.1)
Heart failure, n (%)	19 (3.1)
Previous stroke or transient ischemic attack, n (%)	73 (11.7)
Chronic kidney disease, n (%)	168 (27.0)
COPD, n (%)	38 (6.1)
Asthma, n (%)	33 (5.3)
Gastroesophageal reflux disease, n (%)	64 (10.3)
Chronic venous insufficiency, n (%)	67 (10.8)
Antihypertensive drugs number, median (IQR)	2 (2-3)
ACE-inhibitors, n (%)	272 (43.7)
ARBs, n (%)	222 (35.7)
CCBs, n (%)	356 (57.2)
Diuretics, n (%)	247 (39.7)
Loop diuretics	48 (7.7)
Thiazide diuretics	187 (30.1)
MRAs	44 (7.1)
Beta-blockers, n (%)	229 (36.8)
Doxazosin, n (%)	68 (10.9)
Other alpha blockers, n (%)	38 (6.1)
Clonidine, n (%)	21 (3.4)
Benzodiazepines, n (%)	75 (12.1)
SSRIs, n (%)	45 (7.2)
SNRIs, n (%)	13 (2.1)

ARBs angiotensin receptor blockers, *CCBs* calcium channel blockers, *COPD* chronic obstructive pulmonary disease, *DBP* diastolic blood pressure, *MRA* mineralcorticoid receptor antagonist, *SBP* systolic blood pressure, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitors, *SNRI* serotonin-norepinephrine reuptake inhibitor

3.1 ACEi-induced cough

Patients suffering from ACEi-induced cough were more frequently female (65.7% vs 45.5%, p = 0.002) and showed a higher prevalence of gastroesophageal reflux disease (20.9% vs 9.5%, p = 0.007). Moreover, they were more commonly receiving benzodiazepines (19.4% vs 10.1%, p = 0.027) and SNRI antidepressants (6% vs 0.8%, p = 0.002) (Supplementary table 1).

In a multivariable logistic regression model adjusted for benzodiazepine therapy, COPD and current smoking, ACEi-induced cough remained significantly associated with female sex (OR 2.118, 95% CI 1.218–3.683, p = 0.008), gastroesophageal reflux disease (GERD) (OR 2.488, 95% CI 1.241–4.987, p = 0.01) and SNRI therapy (OR 8.114, 95% CI 1.723–38.202, p = 0.008). Age was not associated with ACEi-induced cough.

In the subgroup of older patients, univariate analysis provided similar results, showing the association of ACEi-induced cough with GERD, benzodiazepines and SNRI antidepressants (Table 3). GERD was the only variable independently associated with ACEi-induced cough

Table 2 Antihypertensive-related adverse effects observed in the study sample

| Adverse effects, n (%)	All patients	Age < 75	Age 75+
ACE-inhibitors	N = 445	N = 301	N = 144
Cough	67 (15.1)	47 (15.6) *	20 (13.9) *
Erectile dysfunction	3 (0.7)	3 (1.0)	–
Headache	1 (0.2)	1 (0.3)	–
Flushing	1 (0.2)	–	1 (0.7)
Constipation	1 (0.2)	1 (0.3)	–
Angiotensin receptor antagonists	N = 222	N = 118	N = 104
Cough	3 (1.3)	2 (1.7)	1 (1.0)
Myalgia	1 (0.4)	1 (0.8)	–
Erectile dysfunction	1 (0.4)	1 (0.8)	–
Calcium channel blockers	N = 496	N = 328	N = 168
Ankle swelling	133 (26.8)	73 (22.3) **	60 (35.7) **
Constipation	4 (0.8)	1 (0.3)	3 (1.8)
Headache	9 (1.8)	8 (2.4)	1 (0.6)
Palpitations	13 (2.6)	13 (4.0)	–
Flushing	8 (1.6)	4 (1.2)	4 (2.3)
Erectile dysfunction	6 (1.2)	5 (1.5)	1 (0.6)
Abdominal pain	3 (0.6)	1 (0.3)	2 (0.6)
Myalgia	2 (0.4)	1 (0.3)	1 (0.6)
Mineralcorticoid receptor antagonists	N = 77	N = 44	N = 33
Gynecomastia	3 (3.9)	–	3 (9.1)
Myalgia	1 (1.3)	–	1 (3.0)
Beta-blockers	N = 229	N = 143	N = 86
Erectile dysfunction	5 (2.1)	5 (3.4)	–
Alopecia	3 (1.3)	3 (2.1)	–
Headache	2 (0.9)	1 (0.7)	1 (1.2)
Alpha-blockers	N = 106	N = 57	N = 49
Palpitations	3 (2.8)	3 (5.2)	–
Headache	3 (2.8)	2 (3.5)	1 (2.0)

* Comparison between age groups p = 0.634

** Comparison between age groups p = 0.001

Fig. 1 Prevalence of ACEi-induced cough and CCB-related ankle swelling in the overall sample and by age subgroups (<75 vs ≥75 years: p = 0.63 for ACEi-induced cough; p = 0.002 for CCB-related ankle swelling)
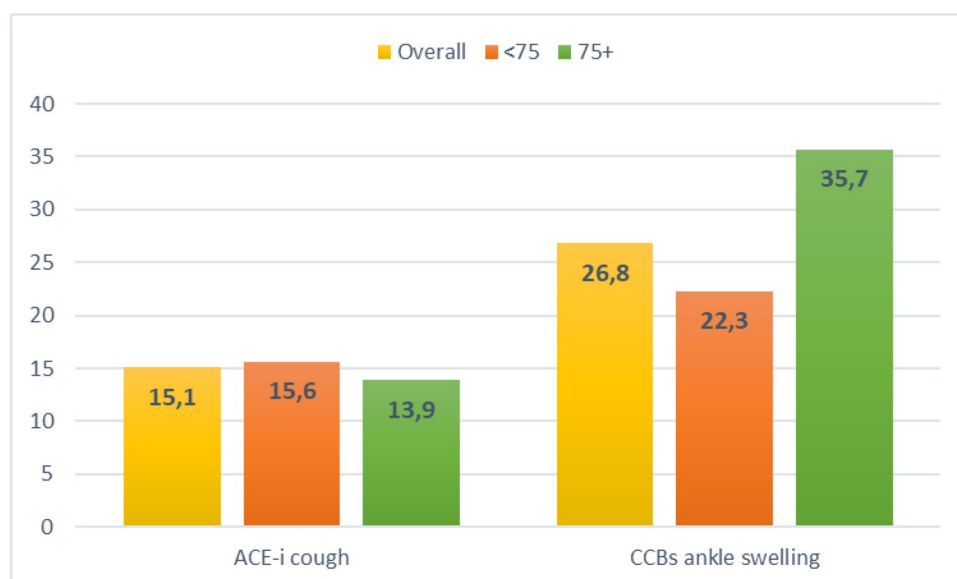
Table 3 Bivariate analysis for ACEi-induced cough and CCB-related ankle swelling among participants aged ≥75 years.

	Prior/ongoing ACEi treatment (N = 144)			Prior/ongoing CCBs treatment (N = 168)		
	Cough (n = 20)	No cough (n = 124)	p	Ankle swelling (n = 60)	No ankle swelling (n = 108)	p
Age, mean (SD)	80.6 (2.8)	80.2 (4.1)	0.656	80.5 (4.1)	81.0 (4.5)	0.494
Female sex, n (%)	15 (75.0)	65 (52.4)	0.059	38 (63.3)	57 (52.8)	0.186
Body Mass Index (kg/m2), mean (SD)	29.2 (6.4) (n = 77)	27.1 (4.0) (n = 77)	0.230	28.8 (4.0) (n = 91)	26.9 (4.6) (n = 91)	0.058
Office SBP (mmHg), mean (SD)	138.6 (18.7)	145.1 (17.7)	0.132	143.3 (17.4)	146.4 (19.2)	0.307
Office DBP (mmHg), mean (SD)	75.4 (9.2)	75.6 (11.4)	0.934	74.8 (75.3)	75.3 (11.1)	0.769
Home SBP (mmHg), mean (SD)	135.0 (14.6) (n = 126)	133.4 (10.6) (n = 126)	0.615	134.9 (9.3) (n = 145)	134.2 (12.2) (n = 145)	0.704
Home DBP (mmHg), mean (SD)	68.2 (5.1) (n = 103)	71.7 (9.1) (n = 103)	0.208	72.5 (8.7) (n = 123)	69.8 (8.8) (n = 123)	0.097
Orthostatic hypotension, n (%)	11 (57.9) (n = 129)	53 (48.2) (n = 129)	0.434	22 (41.5) (n = 152)	57 (57.6) (n = 152)	0.059
Current smoking, n (%)	1 (5.0)	8 (6.5)	0.803	3 (5.0)	6 (5.6)	0.878
Diabetes, n (%)	5 (25.0)	35 (28.2)	0.765	17 (28.3)	28 (25.9)	0.736
CAD, n (%)	1 (5.0)	12 (9.7)	0.498	6 (10.0)	14 (13.0)	0.570
Heart failure, n (%)	1 (5.0)	10 (8.1)	0.632	5 (8.3)	10 (9.3)	0.840
Chronic kidney disease, n (%)	8 (40.0)	44 (35.5)	0.696	23 (38.3)	46 (42.6)	0.591
COPD, n (%)	2 (10.0)	22 (17.7)	0.389	6 (10.0)	21 (19.4)	0.110
Asthma, n (%)	0 (0.0)	6 (4.8)	0.315	4 (6.7)	5 (4.6)	0.574
GERD, n(%)	6 (30.0)	14 (11.3)	**0.025**	7 (11.7)	14 (13.0)	0.808
Venous insufficiency, n (%)	1 (5.0)	14 (11.3)	0.393	9 (15.0)	10 (9.3)	0.260
Antihypertensive medications, median (IQR)	3 (2-4)	3 (2-4)	0.603	3 (2-4)	3 (2-4)	0.907
CCBs/ACEi, n (%)	16 (80.0)	80 (64.5)	0.173	19 (31.7)	46 (42.6)	0.164
ARB	20 (100.0)	29 (23.4)	< 0.001	34 (56.7)	46 (42.6)	0.080
Diuretics, n (%)						
Loop diuretics	3 (15.0)	19 (15.3)	0.970	8 (13.3)	20 (18.5)	0.388
Thiazide diuretics	8 (40.0)	45 (36.3)	0.750	24 (40.0)	39 (36.1)	0.618
MRA	3 (15.0)	7 (5.6)	0.127	3 (5.0)	9 (8.3)	0.421
Beta-blockers, n (%)	7 (35.0)	57 (46.0)	0.360	28 (46.7)	49 (45.4)	0.872
Doxazosin, n (%)	1 (5.0)	26 (21.0)	0.090	13 (21.7)	17 (15.7)	0.337
Other alpha blockers, n (%)	1 (5.0)	10 (8.1)	0.632	4 (6.7)	11 (10.2)	0.443
Clonidine, n (%)	0 (0.0)	6 (4.8)	0.315	4 (6.7)	6 (5.6)	0.771
Benzodiazepines, n (%)	6 (30.0)	15 (12.1)	**0.035**	12 (20.0)	16 (14.8)	0.388
SSRIs, n (%)	3 (15.0)	12 (9.7)	0.470	4 (6.7)	10 (9.3)	0.560
SNRIs, n (%)	2 (10.0)	0 (0.0)	**< 0.001**	2 (3.3)	3 (2.8)	0.839

ARB angiotensin receptor blocker, *CAD* coronary artery disease, *CCBs* calcium channel blockers, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *DBP* diastolic blood pressure, *GERD* gastroesophageal reflux disease, *HF* heart failure, *MRA* mineralcorticoid receptor antagonist, *SBP* systolic blood pressure, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitors, *SNRI* serotonin-norepinephrine reuptake inhibitor

in older patients (OR 3.238, 95% CI 1.046–10.022, p = 0.042).

3.2 CCBs-Related Ankle Swelling

Patients reporting CCB-related ankle swelling were older (mean age 69.2 vs 64.9 years, p = 0.003) and showed higher mean Body Mass Index (BMI) values (29.1 vs 27.5 kg/m²,

p = 0.004). Moreover, these patients were more likely to receive ARBs (47.4% vs 32.8%, p = 0.003), thiazide diuretics (40.6% vs 30%, p = 0.026) and doxazosin (18% vs 10.5%, p = 0.024). By contrast, ACEi therapy was less common among patients with CCB-related ankle swelling (38.3% vs 49.9%, p = 0.023) (Supplementary Table 2). The association between CCB-related ankle swelling and ARBs was also confirmed in a multivariable logistic regression model adjusted for demographics, doxazosin and diuretic therapy, heart failure and venous insufficiency (OR for ARBs 1.864, 95% CI 1.127–3.082, p = 0.015). Additional variables independently associated with ankle swelling included age (OR 1.020, 95% CI 1.002–1.038, p = 0.030) and BMI (OR 1.073, 95% CI 1.016–1.133, p = 0.012), but not ACEi (OR 0.411, 95% CI 0.155–1.094, p = 0.075) (Supplementary Table 3).

In the older patient subgroup, the association of CCB-related ankle swelling with BMI values and ARBs was marginally significant at univariate analysis (Table 3). At multivariable logistic regression analysis, the occurrence of ankle swelling was independently associated with BMI values (OR 1.134, 95% CI 1.017–1.264, p = 0.023) and inversely associated with loop diuretics (OR 0.206, 95% CI 0.048–0.879, p = 0.033). Similar results were reported when adjusting for ACEi, while ARBs were not retained in the multivariable model (Supplementary Table 3).

4 Discussion

AEs associated with antihypertensive medications represent a common concern for both patients and physicians and might negatively impact treatment compliance and effectiveness. The occurrence and unfavourable consequences of antihypertensive-related AEs might be magnified in older patients, who typically present an increased risk of both cardiovascular events and drug-related AEs [14, 15]. Although some previous studies have investigated antihypertensive-related AEs, data referring to older hypertensive patients remain scarce.

The present study analysed antihypertensive treatment tolerability in a sample of 622 hypertensive outpatients evaluated at a specialised hypertension clinic. The most frequently reported AEs were CCB-related ankle swelling and ACEi-induced cough, also in older patients. Patients aged ≥75 years showed a two-fold increased risk of CCB-related ankle swelling, with approximately one third of patients in this subgroup reporting consequent CCB discontinuation or dose reduction. By contrast, prevalence of ACEi-induced cough was not influenced by age. Other antihypertensive-related AEs were rare both in younger and in older patients.

ACEi-induced cough occurred in the 15.1% of patients receiving ACEi, consistently with previous literature reports [16, 17]. However, available data on ACEi-induced cough

are highly variable and inconsistent, due to different characteristics of the study samples and different methods of assessment of AEs. Indeed, some studies reported significantly higher incidence rates [18, 19], while others described a much lower incidence, particularly among patients presenting with chronic cough. Moreover, some data indicate that, in a minority of patients, cough may not recur if ACEi therapy is reintroduced [20–22]. It follows that cough reported during ACEi treatment may not always be attributable to the drug, and other causes of the symptom should be considered. In our study sample, ACEi-induced cough was found to be associated with GERD independently of other conditions potentially predisposing to cough, such as chronic obstructive pulmonary disease and smoking. This result supports the hypothesis that cough reported during ACEi treatment may be promoted or caused by different clinical conditions, such as GERD. Prospective studies are needed to confirm this hypothesis.

ACEi-induced cough was more common in female patients, confirming previous literature results [23]. We also observed an association between ACEi-induced cough and SNRI antidepressants. To our knowledge, no similar data are available in the literature. A possible explanation involves the mechanism of action of SNRIs, which induce an increase in blood levels of norepinephrine and serotonin. Increased serotonin levels have been described in patients with asthma [24] and a pathogenetic role of serotonin in asthma exacerbations has been hypothesized, although the underlying mechanism remains unknown. We could thus speculate that the increase in serotonin levels induced by SNRIs could favour the occurrence of cough in patients receiving ACEi. However, given the limited number of patients treated with SNRIs in our sample, this association should be further investigated in larger studies.

A randomised controlled trial involving 27,492 hypertensive patients showed an increased risk of ACEi-induced cough in individuals aged 65 or older as compared to younger subjects [25]. The present study did not identify an association between ACEi-induced cough and age, consistently with other literature data [26]. Moreover, the independent association between cough and GERD was confirmed in the older subgroup, implying that ACEi therapy might be only partially causative of this symptom also at old age.

CCB-related ankle swelling was the most common AEs in our sample, being reported by one in four patients receiving CCBs (26.8%). Lower rates have been described in previous studies, ranging from 1 to 15% [27, 28]. Again, this difference might be related to different assessment methods and different clinical characteristics of the studied populations. Our study focused on older hypertensive patients, showing a significantly higher probability of ankle swelling in subjects ≥75 years (35.7% vs 22.2%). Indeed, age was significantly associated with the occurrence of CCB-related ankle

swelling, independently of other predisposing conditions and therapies, such as heart failure, venous insufficiency and vasodilators. This finding agrees with previous literature results [29] and might be explained by ageing phenomena of vascular endothelium that promote vascular hyperpermeability [30] and fluid accumulation in interstitial spaces [31]. Moreover, in older patients, concomitant conditions may be present, such as low protein levels, venous insufficiency and heart disease, which further contribute to swelling.

Our results also indicate an independent association between BMI and CCB-related ankle swelling, which was confirmed in the older subgroup. It can be hypothesised that subjects with higher BMI have an increased abdominal pressure which might hamper venous return, predisposing to peripheral swelling. Indeed, an association between BMI and body swelling has been previously described in hypertensive patients [32], although not in reference to CCBs therapy.

It is known that inhibitors of the renin-angiotensin-aldosterone system may reduce the incidence of CCB-related ankle swelling [33, 34], probably due to a reduction of intracapillary hydrostatic pressure [29]. In our study, however, CCB-related swelling was found to be directly and independently associated with ARBs. By contrast, an inverse association was observed between ankle swelling and ACEi, although not confirmed in multivariable analysis. A possible explanation for this result is provided by the different pharmacokinetics of these drug classes. Indeed, ACEi act through a reduction of angiotensin II levels, while ARBs act as antagonists of angiotensin type 1 receptors, thus allowing for and favouring the stimulation of type 2 receptors, which mediate vasodilation and, possibly, vasodilatory oedema [35].

The association between ankle swelling and diuretics was conflicting in our study, showing a direct association with thiazide diuretics in the overall sample and an inverse association with loop diuretics in the older subgroup. The cross-sectional design of our research did not allow to further explore this association. However, it is likely that patients reporting CCB-related swelling had received thiazide diuretics as alternative therapy to achieve blood pressure control. By contrast, a concomitant therapy with loop diuretics might have reduced the risk of swelling in older patients, although a prescriptive cascade (i.e., prescription of loop diuretics to avoid/treat swelling) cannot be excluded.

Other antihypertensive-related AEs were rare in the present study. CCB-induced headache was reported by the 1.8% of the overall sample and by the 0.6% of subjects ≥ 75 years, less frequently than observed in previous studies [17, 36]. Similarly, the occurrence of CCB-related palpitations was uncommon, consistently with a previous meta-analysis [37]. Notably, CCB-related palpitations were not described in any patients of the older subgroup, suggesting an age-related

reduction of this AE. Indeed, CCB-related palpitations likely derive from a compensatory heart rate increase induced by vasodilation. It might thus be supposed that this response less commonly occurs at old age, due to a less efficient autonomic nervous system function and blunted chronotropic responses. Constipation related to CCB was observed in the 0.8% of the study population and in the 1.8% of the older subgroup. However, as constipation is common at old age, it cannot be excluded that this drug-related AE might have been underestimated. Gynecomastia was reported by the 3.9% of patients receiving mineralcorticoid receptor antagonists, a lower prevalence than previously described [38]. Gynecomastia was observed only in patients ≥ 75 years, probably due to the reduction of testosterone levels occurring at old age [39, 40].

4.1 Limitations

Our results must be interpreted in the context of some study limitations. First, the cross-sectional design of the study did not allow for drawing conclusions on causal factors of AEs. Second, AEs were assessed based on medical records and patient reports, so an underreport of events cannot be excluded. Moreover, detailed information on treatment adherence was not available, so patients with low adherence could not be excluded from the analysis. As rates of low adherence are known to be considerable among hypertensive patients, we cannot exclude that this might have influenced our estimate of AEs prevalence. Finally, the retrospective analysis approach limited the investigation of some common antihypertensive-related AEs, such as electrolyte disorders, hypotensive events, renal worsening, metabolic effects.

5 Conclusions

CCB-related ankle swelling and ACEi-induced cough represent the most common AEs of antihypertensive therapy, also at old age. Older patients showed a two-fold increased risk of CCB-related ankle swelling, that was also independently associated with BMI values. ACEi-induced cough had similar prevalence at young and old ages, being independently associated with gastro-oesophageal reflux disease.

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