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Original research paper

Fall risk-increasing drugs and associated health outcomes among community-dwelling older patients: A cross-sectional study in Croatian cohort of the EuroAgeism H2020 project

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ABSTRACT

Our study aimed to assess the prevalence of fall risk-increasing drugs (FRIDs) in a sample of community-residing older patients in Croatia and its association with negative health outcomes. An observational, cross-sectional study was conducted on older patients (65+) visiting community pharmacies in three regionally different study sites in Croatia. Data were collected using a questionnaire developed for that purpose and included components of comprehensive geriatric assessment. Prevalence of FRIDs was identified using the "Screening Tool of Older Persons Prescriptions in older adults with high fall risk" (STOPPFall). In the sample of 407 participants (median age 73 (IQR 69–70) years; 63.9 % females), 79.1 % used at least one FRID. The most common drug classes were diuretics, benzodiazepines, and opioids (in 51.1 %, 38.1 %, and 17.2 % participants, respectively). More FRIDs were prescribed to the oldest old patients (85+) and participants from poorer regions of Croatia (Slavonia) ($p < 0.05$). Exposition to FRIDs was identified as the significant risk factor associated with falls (OR = 1.24 (1.04–1.50); $p = 0.020$) and higher healthcare utilization (OR = 1.29 (1.10–1.51); $p = 0.001$). Our study highlights the need for rationalization of FRID use. To reduce the unnecessary exposure to FRIDs in older adults, healthcare professionals must consider high individualization of medication schemes regarding selection, dosing, and combinations of only necessary FRIDs.

Keywords: fall risk-increasing drugs (FRIDs), older adults, STOPPFall, fall, deprescribing

INTRODUCTION

Falls present the most recurrent type of accidents among older adults (1). It is known that one in three people aged over 65 years experiences at least one fall every year, and 20 % of falls result in an injury (1). Falls can lead to fractures, head trauma, decreased

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mobility, and increased frailty and mortality, particularly in older adults, and can cause subsequent a fear of falling, leading to social isolation, immobility, and even higher risk of further falls (2, 3). After a serious fall-related injury in older adults, chances for a full recovery are low and the risk of long-term disability and placement to long-term facilities substantially increases (4). Studies also confirmed a higher risk of mortality (5, 6) and Centres for Disease and Control Prevention (CDC) reported that fall death rates among adults aged 65 and older in the United States of America increased about 30 % from 2009 to 2018 (7). According to the World Health Organisation (WHO) report, an estimated 684,000 fatal falls occur each year, making it the second leading cause of unintentional injury death, with the highest prevalence among older adults over the age of 60 years in all regions of the world (8). Based on EuroSafe data, approximately 40,000 older people are reported to be fatally injured from falls every year in the European Union (9).

Falls appear as a result of interaction between multiple risk factors and situations, of which many are fully or partially preventable (10). Some of the risk factors for both falls and fractures consist of older age, poor vision, muscle weakness, difficulties in walking and balancing, various chronic disorders (such as hypertension, diabetes, cardiovascular diseases, stroke, depression, Parkinson's disease, pain, and others), medication use and also the use of polypharmacy and hyperpolypharmacy in multimorbid patients (concurrent use of 5 and more or 10 and more medications) (11). A systematic literature review with meta-analysis that aimed to clarify the risk factors for falls in older adults, analyzed 22 risk factors of falls and identified among those particularly older age, lower education level, polypharmacy, malnutrition, living alone, living in an urban area, smoking, and alcohol consumption (12). It is often challenging to determine whether falls in complex geriatric patients occurred as a negative consequence of a particular medication/medications, polypharmacy, or hyperpolypharmacy or whether they appeared as a direct result of a physical illness or frailty. Most often and particularly in complex geriatric patients, causes of falls are multifactorial with a lot of contributing factors. This was also concluded by the systematic literature review by Deandrea *et al.* in Epidemiology (13). It is only possible to attribute falls to a negative effect of a particular medication/medications when the falls occur within a few days after starting the medication, or whether a cessation of the medication/medications ends in the resolution of falls (14). Among numerous fall risk factors that have been identified, the use of fall-risk-increasing drugs (FRIDs) and mobility problems were documented to be the most important factors (15). The number of FRIDs in the therapy increases with multimorbidity, polypharmacy, or hyperpolypharmacy (16) and these phenomena increase with higher age (17). The commonly prescribed medications causing falls include different drug classes, among which are particularly prominent benzodiazepines, antidepressants, antipsychotic medications, and opiates, but they differ based on the investigated setting of care (18).

European Geriatric Medicine Society (EuGMS) Task and Finish group on FRIDs stated in their position paper that there is still not enough awareness among healthcare providers, caregivers, and patients of FRIDs' risks (19). It has been documented by studies that the majority of older patients had not been checked or their FRIDs/medication scheme did not change at all after a fall (20). A systematic literature review by Hart *et al.* that included 10 observational and three randomized controlled studies indicated no reduction in overall FRID use following fall-related healthcare encounters (20). Medications are often not considered a possible risk factor or at least a significantly contributing risk factor among

the other risks. Moreover, older patients have trouble presenting their medication-related problems to doctors because they cannot usually recognize the causality between medication intake and complications increasing the risk of falling (21). However, if the risky medication cannot be fully stopped, even a little adjustment of the drug scheme (timing of drugs, reducing the dosing, *etc*.) may lead to a better quality of life for older persons, with usually preserved efficacy and lower risk of falls. Unfortunately, higher medication intake is usually inappropriately seen as a necessity (19), even if we currently know that drugs are mostly prescribed according to „nongeriatric" guidelines and prescription of polypharmacy is still a common custom. Older patients presenting with multimorbidity should be according to guidelines treated by combinations of multiple medications and currently, following several single-disease guidelines in multimorbid older patients without thorough consideration of multimedication benefits and risks is highly criticized. Due to the lack of "cluster" or specifically "geriatric guidelines", physicians often find it impossible in real clinical practice to prescribe recommended drug schemes, particularly in multimorbid older patients, and individualization of drug regimens is necessary (14).

Considering the importance of medication-related risks of falls and known serious consequences of multimedication schemes in older adults, we aimed our study to document the prevalence of the use of FRIDs in community-residing older patients in Croatia using the Screening Tool of Older Persons Prescriptions in older adults with high risk of falls (STOPPFall) criteria published by Seppala *et al.* (22) and to conduct a comprehensive analysis of the risks associated with the use of FRIDs. In our study, we aimed to explore if patients' characteristics were predictive of some selected negative outcomes such as higher risk of falls, higher rates of acute hospitalizations, and emergency department visits. Based on previous studies, we hypothesized that drug regimens in older patients in Croatia are not yet appropriately individualized, and older adults are exposed to commonly prescribed FRIDs very often which likely increases the risk of falls and higher utilization of healthcare services.

EXPERIMENTAL

Study design

This was an observational, cross-sectional study conducted from June 2019 to May 2021 in regionally different community pharmacies in 3 regions of Croatia, involving patients aged 65 years or over. This study was a part of the EuroAgeism H2020 ESR 7 international project entitled *"Inappropriate prescribing and availability of medication safety and medication management services in older patients in Europe and other countries"*.

Data collection

Data were collected in 3 regions of Croatia (City of Zagreb, Slavonia, and Istria and Kvarner) using the EuroAgeism ESR7 study protocol based on prospective comprehensive geriatric assessment. More than 350 patient-related socio-demographic, economic, clinical, medication-related, and service-use related characteristics were obtained by specific direct patient interviews conducted by trained research staff. The structured, standardized, and piloted research questionnaire was used in this study. The original English version of the

study protocol was translated into Croatian based on the Brislin translation method and minor amendments were made after piloting the questionnaire. Data collection was held in community pharmacies in three geographically different regions of the country, resulting in three regional samples: sample from the City of Zagreb (north-west continental region, $N = 164$), sample from Slavonia (north-east continental region, $N = 124$) and sample from Istria and Kvarner (coastal region, $N = 119$). The sampling of patients in this study was convenient, in each community pharmacy all eligible patients were assessed, based on previously defined inclusion and exclusion criteria. These criteria were: to include all older patients (65 years and older) in stable health status (no intensive care, no acute worsening of health status requiring hospitalization or emergency department visit in the last 3 days, no palliative or terminal care, and life expectancy longer than 12 months). To exclude all older patients having severe dementia and severe communication and hearing disorders (unable to hear or speak). Only patients able and willing to give informed consent were included in the study and the study fully respected GDPR rules and patients' anonymity. Patients' data in protocols and Excel datasets were recorded using patients' individual codes. Refusal rates in our study did not exceed in all regions 5 % of all eligible patients. The comprehensive questionnaire used consisted of 17 sections, 8 of which were utilized for the purpose of this analysis, including data on major sociodemographic characteristics, frailty (using a scale from (1) "very fit" to (9) "terminally ill"), data on self-reported health status (based on a scale ranging from (1) "very poor" to (5) "very good health"), health care utilization (visits of emergency departments and hospitalizations in the previous 12 months), diagnoses, symptoms, occurrence of falls, as well as comprehensive information on medications used in the past 7 days.

Ethics considerations

The Ethical Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry (Croatia), and the Ethical Committee of the Charles University, Faculty of Pharmacy in Hradec Kralove (Czech Republic, study centre of the ESR7 EuroAgeism H2020 project) issued ethical approvals for this research. Written informed consent was collected from all participants. Participating subjects were free to decline participation at any time during the study, and data were collected and stored under specific codes with an assurance of anonymity and data confidentiality.

Outcome measures

The primary outcome measure was the prevalence of the use of FRIDs among community-residing older patients in Croatia and the secondary outcome measure was the testing of the associations between exposition to FRIDs and higher risk of falls and healthcare utilization in the studied population.

FRIDs

For the identification of FRIDs, we used the STOPPFall instrument (22). Development of these STOPPFall criteria presented the first wide effort in Europe to create a consensus on FRIDs for older patients. This tool was created based on evidence from the recent meta-analyses and national fall prevention European guidelines, where 24 experts chose their

level of agreement on a Likert scale with the items in three Delphi panel rounds (22). For the purpose of this study, we identified all the medications registered in Croatia classified in one of the categories from STOPPFall tool based on ATC coding (Anatomical Therapeutic Chemical classification system, namely anticholinergics (N04A), diuretics (C03), alpha--blockers used as antihypertensives (C02C), opioids (N02A), antidepressants (N06A), antipsychotics (N05A), antiepileptics (N03A), benzodiazepines (N05B and N05C) and benzodiazepine-related drugs (N05C), alpha-blockers for prostate hyperplasia (G04C), centrally-acting antihypertensives (C02A), antihistamines (R06A), vasodilators used in cardiac diseases (C01D), medications for overactive bladder and urge incontinence (G04B)). Thus, we analyzed all classes of FRIDs stated in the original STOPPFall criteria.

Falls

Data on the history of falls- the time occurrence and the frequency- was collected and four categories on the frequency of the occurrence were used; from category (1) "a fall is experienced daily" to category (4) "a fall is experienced less than twice a month". For the categorization of time from when the last fall occurred, six categories were used, ranging from category (1) "a fall occurred in the last seven days" to category (6) "a fall occurred more than a year ago". The number of falls in the last year was also recorded (1–3 times or ≥ 4 times), as well as subjectively reported cause of the fall (open question where patients could state various causes).

Healthcare utilization

Healthcare utilization was defined as the number of patient visits to the emergency department and the number of hospitalizations in the previous twelve months.

Statistical analysis

Descriptive statistics were conducted to describe the prevalence of FRIDs. The normality of the distribution of numerical variables was tested by the Kolmogorov-Smirnov's test. Non-normally distributed numerical variables were presented as the median and interquartile range (IQR), and the differences between groups were tested with the Mann--Whitney's test for binary variables and with the Kruskal-Wallis test for variables with more than two categories. Categorical variables were presented as percentages and the difference between groups was tested using the Chi-squared test. Multivariable analysis of factors associated with the health outcomes was performed using logistic regression models (enter method). Two models of logistic regression were explored to ascertain the effects of different variables (age, gender, frailty scores, having FRID in the therapy, number of prescribed drugs excluding FRIDs, number of comorbidities, and self-reported health) with the likelihood of having at least 1 fall in the previous twelve months (the first model), and on the increased prevalence of selected healthcare services utilization (specifically acute hospitalization or emergency department visits in the last twelve months – the second model). Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY), and p values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Participants' characteristics

From a total of 407 participants, the majority were female (63.9 %) with a median age of 73 (IQR 69–80) years, a median of 5 (IQR 3–8) diagnosis, and 6 (IQR 3–9) prescribed drugs. As proposed by Lee and co-workers, also for the purpose of our analysis participants were classified into three age groups: youngest-old (65–74), middle-old (75–84), and oldest-old age (≥ 85) (23). More than half of the participants were distributed in the early senior age group and most of the participants were found not to be frail (72 %). Table I represents a detailed overview of the participants' general characteristics and variables describing their health condition (*i.e.*, scores on the frailty test, symptoms that participants had experienced, and their self-reported health).

Table I. Participant characteristics

Characteristic	*N* (%) participants
Gender	
female	260 (63.9)
male	147 (36.1)
Region	
city of Zagreb	164 (40.3)
Slavonia	124 (30.5)
Istria and Kvarner	119 (29.2)
Age group	
early age (65–74)	226 (55.5)
middle age (75–84)	147 (36.1)
oldest age (≥ 85)	34 (8.4)
Number of diagnoses	
≤ 2 diagnoses	65 (16.0)
3–5 diagnoses	162 (39.8)
≥ 6 diagnoses	180 (44.2)
Number of prescribed drugs[a]	
1–4 drugs	114 (28.0)
5–9 drugs	211 (51.9)
≥ 10 drugs	82 (20.1)
Frailty test[b]	
very fit	49 (12.0)
well	66 (16.2)
managing well	178 (43.7)
vulnerable	73 (17.9)
mildly frail	21 (5.2)
moderately frail	10 (2.5)

severely frail	3 (0.7)
very severely frail	2 (0.5)
terminally frail	1 (0.2)
Reported symptoms[c]	
light-headedness	63 (15.5)
vertigo	118 (29.0)
syncope	6 (1.5)
hypotension	60 (14.7)
bradycardia	17 (4.2)
unsteady gait	113 (27.8)
Self-reported health	
very poor or poor	45 (11.1)
moderate	163 (40.1)
good or very good	198 (48.8)

Percentages calculated from non-missing values (missing values: *N* = 6 (bradycardia); *N* = 5 (age, syncope, hypotension); *N* = 2 (vertigo, light-headedness); *N* = 1 (self-reported health)). [a] None of the participants used zero (0) drugs. [b] Participants being very fit, well or managing well on frailty tests were considered as not being frail. [c] From the complete list of clinical symptoms available in the EuroAgeism H2020 ESR7 research tool were selected only those that might be associated with falls (light-headedness, vertigo, syncope, hypotension, bradycardia, unsteady gait).

Falls were reported in 198 (49.0 %) participants, while 14 (3.5 %) participants experienced a fall one week before data collection (more detailed overview see in Table II). Only 9 participants (2.2 %) reported recurrence falls- they have been falling more than twice a month. In the previous twelve months, falls were reported in 74 (18.3 %) participants. Eight (2 %) participants fell ≥ 4 times during this period while others fell 1–3 times in the past year. Falls, which occurred more than a year ago before data collection, were documented in 124 (30.7 %) participants. The most reported causes of falls were slipping, vertigo, and loss of balance.

Table II. History of falls among older patients

Variable	*N* (%)
Last fall	
in the last 7 days	14 (3.5 %)
in the last 7–14 days	3 (0.7 %)
in the last 14 days– 1 month	10 (2.5 %)
in the last 1–3 months	10 (2.5 %)
in the last 3 months –1 year	37 (9.2 %)
more than one year ago	124 (30.7 %)
did not experience a fall	206 (51.0 %)

Percentages calculated from non-missing values (missing values, *N* = 2).

Prevalence of FRIDs

The use of at least one FRID was observed in a total of 318 (79.1 %) participants with a median number of prescribed FRIDs of 1 (IQR 1–2). It has been shown that 123 (30.2 %) participants had one prescribed FRID, while 195 (47.9 %) were prescribed two or more FRIDs. The maximum number of prescribed FRIDs for individual patients was seven and was found in 1 (0.2 %) participant. The most common drug classes identified as FRIDs were diuretics, used by a total of 51.1 % of participants, followed by benzodiazepines (38.1 %) and opioids (17.2 %) (see Table III). The most frequently used FRIDs were hydrochlorothiazide (19.2 %), indapamide (17.7 %), diazepam (15.7 %), and tramadol (15.2 %). Prevalence between 4 % and 15 % was observed in our study for prescribing the following FRIDs: alprazolam, furosemide, tamsulosin, moxonidine, zolpidem, and oxazepam. Other FRIDs medications were prescribed rarely (prevalence less than 2.5 %). A detailed overview of specific FRID medications identified in the sample and their prevalence is presented in the Supplementary Material.

Table III. Prevalence of classes of drugs identified as FRIDs

Drug class	*N* (%) participants
Diuretics[a]	208 (51.1)
Benzodiazepines[a]	155 (38.1)
Opioids[a]	70 (17.2)
Antidepressants[a]	40 (9.8)
Alpha-blockers for prostate hyperplasia[b]	39 (9.6)
Benzodiazepines related drugs[a]	32 (7.9)
Antihistamines[b]	32 (7.9)
Centrally acting antihypertensives[b]	25 (6.1)
Vasodilators used in cardiac diseases[b]	22 (5.4)
Medications for overactive bladder and urge incontinence[c]	13 (3.4)
Antiepileptics[a]	11 (2.7)
Antipsychotics[a]	11 (2.7)
Alpha-blockers used as antihypertensives[a]	8 (2.0)
Anticholinergics[a]	0 (0)

[a] Drug classes agreed in the first Delphi round of the STOPPFall tool. [b] Drug classes agreed in the second Delphi round of the STOPPFall tool. [c] Drug classes agreed in the third Delphi round of the STOPPFall tool

The high prevalence of FRIDs (79 %) that we identified in the participants in this study calls for establishing better medication-safety measures in Croatia and for reducing inappropriate prescribing in high-risk populations of older adults in our country. Only few studies that we found in the scientific literature applied the STOPPFall tool for determining the prevalence and risk factors and the prevalence of FRIDs in these studies were: 71.3 %

in outpatients suffering from multiple myeloma (a cross-sectional study conducted in outpatient oncology and hematology services in a south-eastern part of the Brazilian capital) (24), 73 % in older people with upper limb fragility fractures (in observational prospective study conducted in three fracture clinics in England) (25) and 85.4 % in a retrospective observational matching study using an electronic health records dataset of patients (≥ 70 years) admitted to an academic hospital in the Netherlands (26). Other studies used different tools or definitions to assess FRIDs and observed prevalence in these studies ranged between 65 and 93 % (27–29) in older inpatients and between 34.5 and 87 % in older outpatients (30, 31).

Furthermore, an important finding is regarding the class of FRIDs that were most prescribed – diuretics and benzodiazepines, the latter being of particular concern due to the long-term risks in older patients. Almost half of the participants in our sample of community-residing older patients reported being prescribed benzodiazepines or benzodiazepine--related drugs (Z-drugs), medicines with an unfavorable ratio of benefit and risk in older adults. A meta-analysis estimated that the number needed to treat (NNT) in the older population was 13 for a benzodiazepine or Z-drug to obtain a benefit; whereas the number needed to harm (NNH) was 6 (32, 33). Panelists in Delphi round during the development of a STOPPFall tool reached the highest agreement on benzodiazepines as the fall risk-increasing drugs and recognized the high need for deprescribing for this drug class (22). Benzodiazepines increase the risk of falls (32), but also the risk of dementia (34, 35) and higher mortality (36). Only short-term prescription of benzodiazepines is rational in older age. Among the benzodiazepine portfolio, patients of this study were mostly prescribed diazepam, due to its long half-life, less favorable for older patients than some other benzodiazepines (*i.e.* oxazepam or lorazepam) (37, 38). Therefore, our results call for appropriate actions in reducing benzodiazepine prescribing in older patients in Croatia, especially diazepam. The existing evidence on benzodiazepine deprescribing suggests that multi-component interventions are usually necessary to support the difficult work of patients and clinicians in changing behaviors in the prescribing and use of these drugs by patients (39).

Factors significantly associated with the use of FRIDs

Statistically significant differences in the number of prescribed FRIDs were observed between age groups and different regions (Table IV). Patients in the oldest age group and those from the northeastern part of Croatia were prescribed significantly more FRIDs compared to other groups. Regarding age, several authors found that being 85+ is a risk factor for polypharmacy (40–42) while others detected that 85+ is a protective factor for excessive polypharmacy (43–45), with one of the explanations that in very old people with shorter life expectancy, preventive medications are usually stopped to improve the patients' current well-being (46). The fact that in our study FRIDs were frequently used in the cohort of older patients 85+, highlights the importance of the need for more individualized pharmacotherapy in this cohort of patients and to recognize the oldest old as a target group for therapy optimization with an emphasis on reducing prescription of potentially inappropriate drugs, with a special focus on FRIDs. Furthermore, an important finding is that a higher prevalence of FRIDs was observed in Slavonia, the most eastern region of Croatia, which is one of the poorest regions in the European Union with the lowest GDP, highest unemployment rate, and the lowest average salaries in Croatia. It has also one of the highest poverty levels. Previously has been documented that potentially inappropriate medications were more

frequently prescribed in poorer older patients when compared between different European regions (47). Our results indicate that prescribing culture as well as patients' needs could differ even between different areas in a small country such as Croatia and that a greater need for specific measures ensuring appropriate prescribing of medicines to older patients is in poorer regions.

Furthermore, participants in this study using FRIDs reported more symptoms potentially associated with falls (*e.g.* unsteady gait, vertigo, and light-headedness), as well as worse health, more falls, and more healthcare utilization (higher rates of hospitalizations and emergency department visits during the past 12 months) (Table IV). This confirms also another known fact that poorer prescribing may lead to higher healthcare costs due to higher utilization of healthcare services (48–50).

Table IV. Patient characteristics and health determinants associated with the average number of FRIDs used

Variable	Average number of FRIDs used	*p*-value
Gender		
male (147)	1.65 ± 1.368	0.776
female (260	1.63 ± 1.370	
Age group		
Early age (65–74)	1.56 ± 1.439	
Middle age (75–84)	1.67 ± 1.283	0.003*
Oldest age (≥ 85)	2.06 ± 1.179	
Region		
City of Zagreb (164)	1.60 ± 1.360	
Slavonia (124)	1.91 ± 1.301	0.003*
Istria and Kvarner (119)	1.42 ± 1.411	
Light-headedness		
yes (63)	2.19 ± 1.533	0.001*
no (342)	1.54 ± 1.308	
Vertigo		
yes (118)	1.97 ± 1.396	0.001*
no (287)	1.50 ± 1.332	
Syncope		
yes (6)	2.67 ± 2.066	0.175
no (396)	1.62 ± 1.351	
Hypotension		
yes (60)	1.80 ± 1.350	0.327
no (342)	1.62 ± 1.377	

Bradycardia		
yes (384)	1.41 ± 1.064	0.708
no (17)	1.65 ± 1.380	
Unsteady gait		
yes (113)	2.03 ± 1.550	0.001*
no (293)	1.49 ± 1.262	
Fall in last twelve months		
yes (73)	1.76 ± 1.366	0.011*
no (331)	1.50 ± 1.332	
Healthcare utilisation[a]		
yes (122)	1.98 ± 1.474	0.002*
no (274)	1.47 ± 1.273	
Number of diagnoses		
≤ 2 diagnoses	1.60 ± 1.378	
3–5 diagnoses	1.65 ± 1.451	0.831
≥ 6 diagnoses	1.65 ± 1.292	
Self-reported health		
very poor or poor	2.67 ± 1.261	
moderate	1.81 ± 1.464	< 0.001*
good or very good	1.28 ± 1.153	

[a] Number of hospitalizations and emergency department visits in the last twelve months; * $p < 0.05$ is considered statistically significant. Non-parametric tests were used; Mann Whitney U test for binary variables and the Kruskal-Wallis test for variables with more than two categories (age, region, self-reported health, number of diseases).

Logistic regression models predicting falls and healthcare utilization

We explored two logistic regression models- one for the association of different variables with the falls and the other for testing the associations with healthcare utilization (specifically the number of hospitalizations and emergency department visits in the last twelve months). Both regression models were statistically significant ($\chi^2(5) = 18.665$, $p = 0.002$, for falls as dependent variable; and $\chi^2(5) = 11.660$, $p = 0.040$ for healthcare utilization as a dependent variable). Tables V and VI present the results of the two logistic regression models.

Predictive factors for falls

The only factors associated with falls in the examined model analyzing the risk of falls were FRIDs and higher age. Participants using FRIDs were 1.24 times more likely to experience falls in the last twelve months ($p = 0.020$). Increasing age was associated with an increased likelihood of experiencing falls (1.06 times; $p = 0.002$). Other variables in the model

Table V. Logistic regression for the dependent variable experiencing fall in the last twelve months

Predictor	B	SE	Wald	df	OR (95 %CI)	*p*-value
Age (year)	0.062	0.020	10.050	1	1.064 (1.024–1.105)	0.002*
Gender (female)	0.405	0.289	1.961	1	1.499 (0.851–2.640)	0.161
Frailty scores	0.000	0.001	0.090	1	1.000 (0.997–1.002)	0.764
Comorbidities	0.017	0.038	0.195	1	1.017 (0.944–1.096)	0.659
Number of FRIDs	0.219	0.094	5.408	1	1.244 (1.035–1.496)	0.020*

Overall model fit ($\chi^2(5) = 18.665$, $p = 0.002$). FRID – fall risk increasing drug, OR – odds ratio, CI – confidence interval. * $p < 0.05$ is considered statistically significant.

(gender, frailty, and number of comorbidities) were not significantly associated with an increased likelihood of experiencing a fall ($p > 0.05$) (Table V.). The model explained 7.4 % (Nagelkerke R2) of the variance in the occurrence of falls and correctly classified 81.7 % of cases.

Predictive factors for healthcare utilization

For the second tested model, the only factor associated with the healthcare utilization in the studied sample was the number of prescribed FRIDs in older patients. Participants using FRIDs were 1.29 times more likely to utilize healthcare services in the last twelve months ($p = 0.001$). Other variables in the model (age, gender, frailty, and number of comorbidities) were not statistically significantly associated with the higher likelihood of utilizing healthcare services ($p > 0.05$), tested as a sum of acute hospitalization and emergency department visits in the past 12 months (Table VI). The model explained 4.1 % (Nagelkerke R2) of the variance in healthcare utilization and correctly classified 69.1 % of cases.

As our results indicate, the number of FRIDs showed to be the only factor associated with both a higher prevalence of falls and higher healthcare utilization. These findings reveal the importance of focusing on the prevention of these negative outcomes mainly or also in FRIDs as frequently used potentially inappropriate medications.

Table VI. Logistic regression for the dependent variable healthcare utilization in the last twelve months[a]

Predictor	B	SE	Wald	df	OR (95 %CI)	*p*-value
Age (year)	0.011	0.017	.452	1	1.011 (0.978–1.046)	0.501
Gender (female)	–0.163	0.230	.505	1	0.850 (0.542–1.332)	0.477
Frailty scores	0.000	0.001	.049	1	1.000 (0.998–1.003)	0.825
Comorbidities	–0.002	0.032	.004	1	0.998 (0.937–1.063)	0.949
Number of FRIDs	0.256	0.080	10.139	1	1.292 (1.104–1.513)	0.001*

[a] Number of hospitalization and emergency department visits in the last twelve months. Overall model fit ($\chi^2(5) = 11.660$, $p = 0.040$). FRID – fall risk increasing drug, OR – odds ratio, CI – confidence interval. * $p < 0.05$ is considered statistically significant.

Insights and implications of the study

To our knowledge, this is the first study to examine the prevalence of the use of FRIDs in community-residing older adults using the STOPPFall tool in Croatia. Moreover, this is also the first study using the STOPPFall tool for determining the prevalence and risk factors of falls and associated utilization of healthcare services (particularly acute hospitalizations and emergency department visits) in community-dwelling older patients in Europe.

The applied STOPPFall tool has an important advantage – it was developed as a deprescribing tool and in addition to identifying FRIDs it also provides recommendations on deprescribing. The panelists were asked in which cases to consider deprescribing FRIDs, whether stepwise withdrawal is needed, and how to monitor patients during the deprescribing process (22). The recommendations for most common FRIDs in our study (diuretics and benzodiazepines), based on the STOPPFall tool are the following: stepwise withdrawal is in general recommended for benzodiazepines and should be considered for diuretics; deprescribing of both drug classes should be monitored (in case of benzodiazepines for anxiety, insomnia, and agitation, while in case of diuretics for heart failure, hypertension and signs of fluid retention). All this makes the deprescribing of these commonly used FRIDs a challenging process and requires the active involvement of patients and healthcare professionals, as well as healthcare resources, especially time and healthcare professionals competent in deprescribing and skilled in multidisciplinary collaboration.

This study was conducted in community pharmacies and confirms that patients at risk of FRIDs can be identified in this primary setting of care and that the involvement of clinically trained community pharmacists in recognizing patients who need deprescribing of specific classes of drugs might be valuable. Nevertheless, fall prevention strategies represent a complex multifactorial field in healthcare (51) and the involvement of clinically trained pharmacists in the community setting could be highly beneficial in drug risk prevention. In a study from the Netherlands, exploring patients' perspective of pharmacists--led fall prevention services, participants were unaware pharmacists could provide such services, nor that medications could cause falls, but were willing to consider deprescribing if necessary to increase safety (52). On the other hand, a study investigating community pharmacists' perception of contribution to fall prevention showed that even though pharmacists considered themselves capable of preventing falls by FRID deprescribing, there are many major barriers including insufficient interdisciplinary collaboration, patient aversion to FRID deprescribing and lack of time (53). These findings could be the reason for the lack of positive results in FRIDs deprescribing trials, and should not discourage clinically trained pharmacists in ambulatory care from collaboration in interdisciplinary deprescribing of FRIDs and/or providing fall prevention services as they could increase other health benefits in older adults such as reduction in adverse reactions, improved mobility, self-performance and independence (54). Interventions including complementary components such as deprescribing and patient education (*i.e.* on medication-related fall risks, home safety measures, *etc.*) are more useful (55, 56). Furthermore, the IMPROveFALL trial on deprescribing indicated that FRIDs-withdrawal is difficult to maintain over 1 year, in a population of complex, multimorbid older fallers and the single intervention of only FRIDs-withdrawal was not effective in reducing falls (57) or it led to a reduction in total health-care costs, reduced medication costs and was associated with less decline in the

health-related quality of life (58). These results show that more complex interventions and patient follow-up are necessary components of appropriate deprescribing services aimed at reducing falls, especially in older patients using psychiatric medications (57). Moreover, a systematic literature review and meta-analysis by Lee *et al.* published in BMJ Open, states that there is a lack of robust evidence regarding the effectiveness of FRIDs deprescribing as the only strategy to prevent falls or fall-related injury in older adults. Patient-important outcomes are also scarcely reported and should be included in FRIDs deprescribing trials (59).

Different tools are currently available for FRIDs identification, and it is expected that with the development of health technologies and integration of such tools in e-health applications, the use of these tools will become simplified and less time-consuming. However, the importance of an individualized approach will remain irreplaceable, and highly individualized clinical reasoning using a holistic approach cannot be substituted with any screening tool. In concordance with this, Seppala *et al.* also pointed out, that it is challenging to characterize the groups of medicines included in STOPPFall exclusively as FRIDs, given that they have great benefits in the prevention and treatment of several frequent disorders also in older patients (22). Therefore, the decision to withdraw any drug identified as FRID remains always a complex task.

Limitations of the study

The relationship between risk factors and negative outcomes was tested using cross-sectional data (one-time data) with an unsure time sequence of the factors and negative consequences. Therefore, the question if tested factors are rather predictors or consequences of falls and healthcare utilization, remains unanswered. Furthermore, when interpreting results, one should keep in mind that we used the STOPPFall tool in mostly fit patients who were in relatively good health conditions. Patients at higher risk of falls, *e.g.* older residents in nursing homes or older patients acutely hospitalized, may have different (more severe or more frequent) health outcomes when using FRIDs compared to our studied population. Moreover, it can be assumed that the findings could indicate an even higher prevalence of FRIDs if the data were collected in secondary and tertiary care settings. Consequently, our conclusions may not be generalizable for facilities that substantially differ from community pharmacy settings and for older patients with substantially different characteristics. Furthermore, the STOPPFall tool is a relatively recently developed tool, and currently, the lack of evidence from other cross-sectional studies using STOPPFall does not allow us a full comparison, only with a few already published studies.

CONCLUSIONS

This study warrants the high prevalence of FRIDs in the community-dwelling older population in Croatia and its potential association with negative health-related outcomes, namely falls, acute hospitalizations, and emergency department visits. Patient characteristics associated with FRIDs were mainly older age, living in poorer regions, and experiencing symptoms often associated with falls such as light-headedness, unsteady gait, and vertigo. It is necessary to encourage healthcare providers to rationally prescribe FRIDs and to get involved in rational strategies of deprescribing in patients where such strategies may

be beneficial and appropriate, with special attention to benzodiazepines. The results of this study provide initial evidence that may be useful for healthcare professionals in primary care settings and for intensifying the cooperation of healthcare professionals on patient care in this setting of care. It also urges the provision of specific policies and guidelines for appropriate prescribing and deprescribing FRIDs in older adults.

Ethics approval. – Ethical approval for this study was obtained from the Ethical Committees of Charles University (Czech Republic, EuroAgeism H2020 ESR7 study centre) and the Ethical Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry (Croatia, national study centre). Participating subjects were free to decline participation at any time during the study. Data were collected and stored under specific codes with an assurance of anonymity and data confidentiality. All methods were carried out in accordance with relevant project guidelines and regulations.

Consent to participate. – Informed consent on participation was obtained from all subjects before data collection.

Availability of data and materials. – The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest. – The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be viewed as a potential conflict of interest.

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