

RESEARCH SUBMISSIONS

Triptans and vascular comorbidity in persons over fifty: Findings from a nationwide insurance database – A cohort study

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Abstract

Objective: To gather information about prescription of triptans and to evaluate whether vascular comorbidity differs in users and nonusers of triptans over the age of 50 years.

Background: Beyond the age of 50 years, migraine is still common—yet the incidence of vascular disorders increases. Triptans, medications for treating migraine attacks, are vasoconstrictive drugs and contraindicated in persons with vascular disorders.

Methods: Based on a nationwide insurance database from 2011, we compared the prescription of vascular drugs (identified by Anatomical Therapeutic Chemical codes), vascular diagnoses and hospitalizations, between triptan users greater than 50 years and a matched control group.

Results: Of the 3,116,000 persons over 50 years, 13,833 (0.44%) had at least one triptan prescription; 11,202 (81%) were women. Thirty percent of the triptan users (13,833/47,336 persons) were over 50 years. Of those over 50 years, 6832 (49.4%) had at least one vascular drug and 870 (6.3%) had at least one inpatient vascular diagnosis; 15.7% (2166 of 13,833 users) overused triptans. We compared triptan-users to 41,400 nonusers, using a 1:3 match. In triptan-users, prescriptions of cardiac therapies and beta blockers were significantly more common (odds ratio [OR] = 1.35, 95% confidence interval [CI] = 1.24–1.47 and OR = 1.19, 95% CI = 1.14–1.25, respectively); whereas prescriptions of calcium channel blockers and renin/angiotensin inhibitors were significantly less common (OR = 0.82, 95% CI = 0.76–0.88 and OR = 0.75, 95% CI = 0.72–0.79, respectively). The prescriptions of antihypertensive, diuretic, and antilipidemic drugs as well as platelet inhibitors and direct thrombin inhibitors did not differ in users and nonusers. Triptan users had significantly more hospital stays (OR = 1.39, 95% CI = 1.33–1.45); however, the number of days spent in the hospital

Abbreviations: ATC, Anatomical Therapeutic Chemical code; 95% CI, 95% confidence interval; DDD, defined daily dose; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Edition; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; WHO, World Health Organization.

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and more importantly the frequency of inpatient vascular diagnoses did not differ statistically significantly between the two groups.

Conclusion: In persons over 50 years of age, a prescription of triptans is common. Vascular comorbidity is comparable in users and nonusers of triptans showing that triptans are prescribed despite vascular comorbidity and suggesting that triptan use does not increase vascular risk in patients with migraine over the age of 50 years. Nevertheless, regular evaluation for contraindications against triptans and for vascular risk factors is recommended in this age group.

KEYWORDS

comorbidity, migraine, pharmacoepidemiological study, triptan overuse, triptans, vascular

INTRODUCTION

Migraine is one of the most debilitating neurological disorders and was ranked as the second largest contributor to disability adjusted life years in the Global Burden of Disease study.¹ Migraine prevalence is about 10%–18% and peaks at the age of 30 to 50 years.² Nonetheless, migraine is still present after the age of 50 years, and migraine in older age will be a growing health issue with the increasing life-expectancy. In a study from the Netherlands,³ the 1-year prevalence of migraine was 12% in women and 6% in men aged greater than or equal to 55 years. In Norway, the 1-year prevalence decreased with age and was 8% and 4% in women and men aged 60–69 years, 4% each in those aged 70–79 years, and 4% and 3% in women and men aged 80 years or older.⁴ In a Swedish study, the prevalence of active migraine decreased from 13% in women aged 55–59 years to 3% in women aged 70–74 years.⁵ A study in the United States found a similar age-related migraine prevalence.⁶

In contrast, the prevalence of vascular diseases increases with age. Austrian data indicate that this increase in prevalence starts at about the age of 50 years. Persons aged 60–69 years have a three-fold increase in the prevalence of cardiovascular diseases and ischemic stroke as well as in the incidence of peripheral artery disease compared with persons younger than 60 years of age.⁷ Similar rates of an age-dependent increase in vascular diseases were reported in Germany.⁸

Triptans, serotonin_{1B/1D} receptor agonists, are a specific treatment for aborting migraine attacks. Their effect in migraine is currently believed to be mediated by their agonism of 5HT_{1B/1D} receptors on sensory nerves of the trigeminal system and by inhibiting neurotransmitter release, particularly of calcitonin gene-related peptide.⁹ Triptans also have a vasoconstrictive effect, restricting their use in vascular disorders. According to their labeling, triptans are contraindicated in persons with ischemic heart disease, cerebrovascular disease, uncontrolled hypertension, and peripheral artery disease. Some are also contraindicated in moderate to severe hypertension and in significant cardiac arrhythmias. Moreover, triptans are contraindicated (sumatriptan) or not recommended in patients over 65 years. Despite these contraindications and limitations, several studies reported the use of triptans in patients with vascular diseases, including persons

beyond the age of 65 years. A pharmacoepidemiological study in Italy showed that 37% of all first-time triptan users over 65 years had vascular comorbidities and that 5% had absolute contraindications against triptans.¹⁰ Among the long-time triptan users over 65 years of age, 64% had vascular comorbidities, and 6% had absolute contraindications against triptans.¹⁰ However, analyses of the US Food and Drug Administration (FDA) reports, reviews of observational studies, and data from a general practice research database did not reveal an increased risk of vascular incidents in triptan users.^{11–13}

Our analysis of an Austrian nationwide insurance database showed that, in 2007, 33,602 persons (0.45%) of the insured population had at least one triptan prescription.¹⁴ Twenty-nine percent of the triptan users were over 50 years old (23.6% 51–65 years and 5.4% ≥66 years), 5.9% of the triptan users over the age of 50 years overused triptans.¹⁴

Vascular comorbidity and prescription of vascular drugs in triptan users over 50 years of age in Austria has not been studied so far. Previous migraine studies on triptan use and vascular risks did not focus on elderly triptan users, and were based on selected cohorts, or databases comprised only of distinct regions of a country. In contrast, the Austrian database allows for the analysis of nationwide insurance data. The aim of this study was to evaluate the triptan use and overuse in persons over 50 years of age in Austria and to evaluate if triptan use constitutes a risk factor for vascular diseases in patients over 50 years and if adherence to contraindications is supported by population-based data. We hypothesized that due to the contraindications, triptan users over 50 years of age would have lower prescription rates of vascular comorbidities, lower rates of vascular diagnoses, and lower hospitalization rates than control persons, and that triptans do not constitute a vascular risk factor.

METHODS

The study was approved by the ethics committee of the Medical University of Vienna (EK-Nr. 1411/2015). For this cohort study, the Dachverband der Österreichischen Sozialversicherungsträger (Main Association of Austrian Social Insurances) provided a database containing data from 19 Social Security institutions for the year 2011. The

database was the most recent available and is anonymized. Accordingly, informed consent was neither necessary nor feasible. We used the database to analyze the prescription of triptans and vascular medications, inpatient vascular diagnoses, and the number and duration of hospital stays. The database includes all medications covered by the insurance plans and dispensed to patients. For each dispensed package, the patients have to pay a prescription charge, which was 5.10 Euros in 2011. The database does not include over-the-counter medication and prescription medication dispensed free of charge to patients with severe chronic diseases or low income if it is cheaper than the prescription charge, and medication paid by the patients themselves. In Austria, triptans were not available over-the-counter in 2011.

For each insured person, the following descriptors were available: anonymized unique identifier, date of birth and sex, the postal code of the residential address, the Anatomical Therapeutic Chemical (ATC) code and the pharmacy article identifier ("Pharmazentralnummer") of the dispensed drug, the number of packages, number of hospital admissions, duration of hospital stays, and International Statistical Classification of Diseases and Related Health Problems 10th Edition (ICD-10) diagnoses from hospital stays.

We analyzed data of triptan users aged older than 50 years and of a control population matched for age (same year of birth), sex, province of residence, and being alive at index prescription. For each triptan user, we selected three persons without triptan dispensation in 2011. Matching for province was included because Austria shows a declining health gradient from west to east.¹⁵ Matching for being alive at index prescription means that only control persons were matched who were still alive at the date of the triptan users' index prescription in order to produce comparable times at risk. We cannot rule out that control persons had migraine and treated their attacks with other medications than triptans.

Triptan use and overuse, and vascular medications

We identified triptans by the ATC code, and package size (units per package), dose per unit, and route of administration by the pharmacy article identifier. In 2011, sumatriptan tablets and injections, zolmitriptan tablets, melting tablets as well as nasal spray, eletriptan, and frovatriptan were available and reimbursed. Rizatriptan and naratriptan were available but reimbursed only in exceptional cases, almotriptan was not available. We defined triptan use as greater than or equal to one package of a triptan dispensed in 2011, and triptan overuse as greater than or equal to 30 defined daily doses (DDDs; according to the World Health Organization [WHO]),^{14,16} dispensed in at least one quarter. The cutoff dose of 30 DDDs was chosen in line with the International Classification of Headache Disorders,¹⁷ which requires the use of triptans on greater than or equal to 10 days per month over a period of 3 months for diagnosing triptan overuse for headache. As triptan use may fluctuate over time, we assessed triptan overuse in one, two, three, and four quarters of 2011.

We identified vascular medications by the ATC code and analyzed them according to ATC groups: cardiac therapies (antiarrhythmics

classes I and II, cardiac stimulants, vasodilators, glycosides, and other preparations), antihypertensives, diuretics, beta blockers, calcium channel blockers, renin/angiotensin inhibitors, antilipidemic drugs, platelet aggregation inhibitors, phenprocoumon and acenocoumarol, direct thrombin inhibitors, and heparins.

We analyzed vascular diagnoses according to ICD-10 codes: variants of hypertension (I10.- to I13.- and I15.-), variants of ischemic heart disease (I20.- to I25.), cardiomyopathy (I42.-), atrioventricular and left bundle branch block (I44.-), atrial fibrillation and flutter (I48.-), heart failure (I50.-), cerebrovascular diseases (I63.- to I67.-), other atherosclerosis of arteries of native extremities (I70.-), and arterial embolism and thrombosis (I74.-).

Statistics

Data were extracted from the insurance database and then analyzed using SAS 9.4 (SAS Institute Inc., 2016). Two-sided *p* values less than 0.05 were considered statistically significant. In case of multiple tests performed within one research question, the method of Bonferroni-Holm was used to correct for multiple testing (uncorrected *p* values are reported with an indication of significance after correction). Categorical variables were described by counts and percentages, and were compared between subgroups of triptan users using chi-square tests. We compared prescription of vascular medications, presence of vascular diagnoses, and hospital stays (dichotomized as no stay vs. at least one stay due to extremely right skewed distribution) between triptan users and controls using stratified logistic regression models with groups (triptan users vs. controls) as the sole independent variable and strata defined as the quadruple of one triptan user and their three matched controls. Odds ratios (ORs) from these models are reported with 95% confidence intervals (95% CI). The question whether age modifies the differences between triptan users and controls regarding certain outcomes was analyzed by testing the interaction of group and age (using a flexible spline fit with 6 degrees of freedom); age-specific ORs were reduced from the model with interaction. Analyses of the detailed prescription of beta blockers and renin/angiotensin inhibitors were post hoc, all other analyses were preplanned. No statistical power calculation was conducted prior to the study. The sample size for triptan users was based on the available data. The number of three control persons for each triptan user was chosen to balance an increase in power with finding a sufficient number of matching partners. The authors had full access to all study data.

RESULTS

Triptan prescription

The insurance database included 8,346,549 persons (99.3% of Austria's inhabitants), 237 had to be excluded due to missing data (sex, date of birth, or place of residence). Of the remaining 8,346,312

persons, 4,004,653 were men (48%) and 4,341,659 were women (52%); 3,116,220 persons were over 50 years old. Of the whole sample, 47,336 persons (0.57%) were at least once dispensed any triptan in 2011. Among those over 50 years of age, 13,833 persons (0.44%) were at least once dispensed any triptan; thereof 11,202 women (81%) and 2631 men (19%), and 2643 (19.1%) of these triptan users were older than 65 years. The group over 50 years comprised 29.2% of all triptan users in 2011 (13,833/47,336 persons); 11,190 (23.6%) of all triptan users were 51–65 years old, and 2643 (5.6%) were greater than or equal to 66 years old. The control group comprised 41,400 persons; 33,606 women (81%) and 7893 men (19%).

Prescription of vascular medications

At least one vascular medication was dispensed to 6832 (49.4%) of the triptan users and to 19,541 (47.2%) of the controls. Thus, triptan users showed a small, but statistically significant increase in the odds of being dispensed any vascular medication (OR = 1.10, 95% CI = 1.06–1.15). Table 1 reveals a more varied picture of the prescription rates of vascular medications. Triptan users had statistically significantly increased odds of being dispensed cardiac therapies (35% increase), beta blockers (19% increase), and heparins (28% increase); as well as statistically significant decreased odds of being dispensed calcium channel blockers (18% decrease), renin/angiotensin inhibitors (25% decrease), and vitamin K antagonists (19% decrease). Among calcium channel blockers, flunarizine, which is approved for migraine and vestibular migraine, was dispensed to 421 (3%) triptan users and to 62 controls (0.1%), OR = 20.7. Persons with triptan overuse had similar dispensation rates of vascular medications, but beta blockers were dispensed statistically significantly more often to persons with than without overuse (26.2% vs. 20.3%, $p < 0.001$).

We analyzed propranolol and metoprolol, which are first-line migraine prophylactics, in comparison to bisoprolol (which may be used in migraine prophylaxis). Propranolol (OR = 5.3, 95% CI = 4.4–6.3) and metoprolol (OR = 1.82, 95% CI = 1.65–2.02) were dispensed to triptan users significantly more often than to controls (propranolol 324/2.3% vs. 191/0.46% and metoprolol 613/4.4% vs. 1033/2.5%, respectively); whereas the dispensation of bisoprolol to triptan users was comparable to controls (858/6.2% vs. 2491/6.0%; OR = 1.04, 95% CI = 0.96–1.12, respectively). Lisinopril, a migraine prophylactic with low evidence, was dispensed to triptan users less frequently (464/3.4% vs. 1699/4.1%; OR = 0.81, 95% CI = 0.73–0.90); whereas candesartan, a second-line migraine prophylactic in Austria, was dispensed to triptan users more frequently (381/2.8% vs. 961/2.3%; OR = 1.20, 95% CI = 1.06–1.35).

Triptans were dispensed despite the prescription of vascular medications or the presence of vascular diagnoses. In the second half of 2011, of 11,036 triptan users with a triptan prescription, 4667 (42.3%) had any vascular medication and/or vascular diagnosis in the first half of 2011. Of 11,157 triptan users with a triptan prescription in the first half of the year, 4863 (43.6%) also had a vascular medication or diagnosis during the first half of 2011; thereof, 3431 (70.6%) had at least one triptan prescription in the second half of 2011. In comparison, 6294 of the triptan users with a triptan prescription from January to June were without any vascular medication or vascular diagnosis. Thereof, 4929 (78%) had another triptan prescription from July to December ($p < 0.001$).

Prevalence of vascular diagnoses, and hospital stays

The prevalence of any vascular diagnoses did not differ statistically significantly between triptan users (870, 6.3%) and controls (2603, 6.3%; OR = 1.00, 95% CI = 0.93–1.09; Table 2). Likewise, the

TABLE 1 Triptan users and controls with dispensed vascular medications

Vascular medications	Triptan users $n = 13,833$		Controls $n = 41,499$		OR	95% CI*	p value
	n	%	n	%			
Cardiac therapies	802	5.8	1832	4.4	1.35	1.24–1.47	<0.001*
Antihypertensives	389	2.8	1291	3.1	0.90	0.80–1.01	0.075
Diuretics	603	4.4	1807	4.4	1.00	0.91–1.10	0.980
Beta blockers	2939	21.2	7695	18.5	1.19	1.14–1.25	<0.001*
Calcium channel blockers	997	7.2	3582	8.6	0.82	0.76–0.88	<0.001*
Renin/angiotensin inhibitors	3060	22.1	11,192	27.0	0.75	0.72–0.79	<0.001*
Antilipidemic drugs	2590	18.7	7621	18.4	1.03	0.98–1.08	0.329
Platelet aggregation inhibitors	744	5.4	2145	5.2	1.05	0.96–1.15	0.270
Phenprocoumon + acenocoumarol	273	2.0	990	2.4	0.81	0.71–0.94	0.004*
Direct thrombin inhibitors	28	0.2	44	0.1	1.24	0.80–1.93	0.345
Heparins	909	6.6	2164	5.2	1.28	1.18–1.39	<0.001*

Note: Stratified logistic regression. Vascular medications grouped according to ATC groups.

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; OR, odds ratio.

*Statistically significant after correction for testing 11 classes (Bonferroni-Holm).

prevalence of vascular diagnoses in persons with triptan overuse did not differ statistically significantly from that of other triptan users ($p = 0.239$). According to package information leaflets, ischemic heart disease, atrial fibrillation and flutter (interpreted as significant rhythm disorder), cerebrovascular disease, atherosclerosis of arteries of native extremities, and arterial embolism and thrombosis can be considered as absolute contraindications against triptans. Hence, 383 (2.7%) of the triptan users and 53 (2.5%) of those with triptan overuse had an absolute contraindication against triptans. Hypertension is seen as a contraindication only if it is not well controlled or untreated. The database does not tell if the 5.2% of triptan users with hypertension or the triptan users with medications with antihypertensive potential had well or insufficiently controlled hypertension. The odds of having at least one hospital admission as an inpatient was increased by 39% in triptan users compared with controls: 3740 triptan users (27%) and 8715 controls (21%) with at least one hospital stay (OR = 1.39, 95% CI = 1.33–1.45). The duration of hospital stays did not differ significantly between triptan users and controls.

Interaction of age and triptan use with respect to vascular factors

Age did not significantly modify the differences between triptan users and controls concerning the prevalence of vascular diagnoses (OR at age 55 = 0.92, 95% CI = 0.78–1.08 and OR at age 70 = 1.00, 95% CI = 0.86–1.16, respectively; interaction $p = 0.605$), and hospitalization rate (OR at age 55 = 1.39, 95% CI = 1.29–1.51 and OR at age 70 = 1.33, 95% CI = 1.20–1.48, respectively; interaction $p = 0.510$). In contrast, age significantly modified the differences between triptan users and controls regarding vascular medication (OR at age 55 = 1.17, 95% CI = 1.09–1.25 and OR at age 70 = 0.97, 95% CI = 0.86–1.09, respectively; interaction $p < 0.001$); descriptive details are given in [Table 3](#).

Triptan overuse, triptan use with respect to residency

In 2166 triptan users over 50 years of age (15.7%; 1747 women and 419 men), we identified indications of triptan overuse with a prescription of at least 30 DDDs within one quarter of 2011; thereof, 814 (37.6%) had a triptan overuse in one quarter, 438 (20.2%) in two quarters, 362 (16.7%) in three quarters, and 552 (25.5%) in four quarters, and 995 persons were dispensed greater than or equal to 120 defined daily doses in 2011. The rate of triptan overuse in the groups aged 51–65 and greater than or equal to 66 years did not differ statistically significantly (1761/15.7% vs. 405/15.3%).

Compared to the proportion of Austria's population (in 2011: 8,401,940¹⁸), triptan users were under- or over-represented in two provinces. In Upper Austria, 13.9% of triptan users (1922) accounted for 16.8% of the population (1,413,762 persons), whereas in Vienna, 24% of triptan users (3320) accounted for 20.4% of the population

(1,714,227 persons). Triptan overuse was most common in Vorarlberg (20%; 91 of 455 triptan users) and ranged from 13.4% (147 of 1093 triptans users) to 16.8% (559 of 3320 triptan users) in the other provinces. These differences were not statistically significant.

DISCUSSION

To our knowledge, this was the first study in the Austrian population looking at the use of triptans and its association to vascular factors in persons over 50 years of age. Use of triptans was common in those over 50 years and accounted for 29% of all triptan users in 2011. This proportion was stable compared to 2007.¹⁴

Vascular medications and vascular diagnoses

The overall rate of vascular medications differed significantly in users (49.4%) and nonusers (47.2%) of triptans and was higher than in other studies. In an Italian cohort, 12% of all first-time triptan users and 37% of those over 65 years had vascular comedications; and 0.6% and 5%, respectively, had absolute contraindications against triptans.¹⁰ Among all long-time triptan users, 27% had vascular comedications, among those over 65 years, 64% had vascular comedications; and 0.8% and 6%, respectively, had absolute contraindications against triptans.¹⁰ From the ATC-oriented grouping of vascular medications, we could not infer on absolute contraindications against triptans. However, in 2.7% of our triptan users, vascular diagnoses implicated contraindications against triptans, which is a lower rate than in the Italian study.¹⁰ We have to bear in mind that the comparison of health claims databases is limited by different methodologies of data inclusion and extraction, as well as different insurance and billing regulations.

Age influenced the odds of being dispensed vascular medications. The increased odds of having vascular medications in triptan users compared with controls was further increased by being younger. This may point out that in older persons with migraine triptans are given less often due to vascular comorbidities, thus withholding an efficacious therapy from these patients.

The increased odds of being dispensed vascular medications compared with controls has to be interpreted cautiously. The dispensation of different vascular medications varied in detail, and beta blockers may be used by triptan users as migraine prophylaxis. This could explain the even higher prescription rate of beta blockers in those overusing triptans. In fact, metoprolol and propranolol (first-line migraine prophylactics) were significantly more often dispensed to triptan users, whereas bisoprolol was dispensed in triptan users as frequently as in controls. This underlines the assumption that metoprolol and propranolol were used as migraine prophylactics in a considerable number of cases. However, the database does not contain indications for certain medications, and it does not include diagnoses from outpatient visits, therefore, we do not know the indication of beta blockers with certainty. Some renin/angiotensin inhibitors could also be used for migraine prophylaxis. In fact, candesartan was dispensed

TABLE 2 Prevalence of vascular diagnoses in triptan users and controls

Vascular diagnosis	Triptan users n = 13,833		Controls n = 41,499	
	n	%	n	%
Hypertension	713	5.2	2175	5.2
Ischemic heart disease	169	1.2	595	1.4
Cardiomyopathy	20	0.1	72	0.2
Atrioventricular and left bundle branch block	20	0.1	61	0.1
Other conduction disorders	6	0.04	19	0.05
Atrial fibrillation and flutter	98	0.7	361	0.9
Heart failure	35	0.3	151	0.4
Cerebrovascular diseases	75	0.5	241	0.6
Other atherosclerosis of arteries of native extremities	36	0.3	124	0.3
Arterial embolism and thrombosis	5	0.04	15	0.04

Note: Vascular diagnoses grouped by ICD-10 codes.

Abbreviation: ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Edition.

TABLE 3 Comparison of dispensed vascular medications, vascular diagnoses, and rate of hospitalized patients between triptan users and controls in the age groups of 51–65 years and ≥66 years

	Triptan users 51–65 years n = 11,190				Triptan users ≥66 years n = 2643				p value*
	Triptan users	Controls	OR ^a	95% CI	Triptan users	Controls	OR ^a	95% CI	
Vascular medication	4943 44.2%	13,903 41.4%	1.17	1.09–1.25	1889 71.5%	5680 71.6%	0.97	0.86–1.09	<0.001**
Vascular diagnosis	490 4.4%	1504 4.5%	0.92	0.78–1.08	380 14.4%	1099 13.9%	1.00	0.86–1.16	0.605
Rate of hospitalized patients	2762 24.7%	6345 18.9%	1.39	1.29–1.51	978 37.0%	2446 30.9%	1.33	1.20–1.48	0.510

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOdds ratios (OR) are reported at age-group specific median (55 years for first, 70 years for second age-group).

*For interaction of group (triptan users vs. controls) and age, that is for the null hypothesis of equal odds ratios at all ages.

**Statistically significant after correction for testing three outcomes (Bonferroni-Holm).

to triptan users significantly more often. It could have been used to treat hypertension and migraine at the same time. However, we found no such effect for lisinopril, another antihypertensive drug possibly effective in migraine prophylaxis. Flunarizine was dispensed almost entirely to triptan users, because it is used exclusively for migraine prophylaxis. Most probably, the few controls with flunarizine dispensation are persons with migraine, but do not use triptans.

The number of any vascular diagnoses in triptan users (6.3%) did not differ statistically significantly from that in controls, and was lower than in previous studies. In a study based on data of two commercial insurances in the United States, 12% of the persons with triptan prescriptions had contraindications against triptans and 8% had any other cardiovascular disease.¹⁸ Moreover, the authors found that even in patients up to 64 years of age and without an explicit vascular disease, 25% had at least one vascular risk factor; and 10% had at least three vascular risk factors.¹⁸ In a population-based US study, 22% of patients with episodic migraine over the age of 60 years self-reported any vascular condition or event.¹⁹ The lower prevalence of vascular diagnoses in our cohort, as well as the lower prevalence of absolute contraindications against triptans may point

to a bias, as outpatient diagnoses were not included in our database. In addition, the prescription rate of vascular medications points to a higher rate of vascular comorbidity.

It is remarkable, that 42% of the persons with a triptan prescription in the second half of the year had any vascular medication or vascular diagnosis in the preceding 6 months, and nearly 71% of the triptan users of the first half of 2011 with any vascular diagnosis or medication were dispensed further triptans in the second half of 2011. That may either point to a high comorbidity in patients with migraine, or it may highlight that the prescribing physicians do not take into account vascular comorbidities in persons with migraine. In contrast to such considerations, the increased dispensation of beta blockers and candesartan in triptan users could also reflect a more elaborate care, in order to obtain a well-controlled hypertension.

Hospital admissions

Triptan users had increased odds by 39% of being admitted to the hospital compared with controls. To our knowledge, data on

hospital admissions among triptan users were not available up to now. Because even patients with severe migraine attacks are usually treated on an outpatient basis (also in emergency departments), we do not assume that this difference was caused by migraine-related admission; but we cannot rule out that triptan use was a risk factor for hospital admission.

Vascular risk of triptans

The vasoconstrictive potential of triptans has led to the exclusion of patients with vascular diseases from phase III studies. In addition, persons over 65 years were not included. Consequently, all triptans were labeled as contraindicated in patients with various vascular diseases, to be used cautiously when vascular risk factors are present, and as contraindicated or not recommended in persons over 65 years of age. In early years, several individual cases of acute myocardial infarction in close temporal relationship with sumatriptan were reported.²⁰ However, a review of case series showed that in many of the cardiac events the event happened more than five half-lives after the administration of the triptan.²¹ In addition, analyses of the FDA reports, reviews of observational studies, the analysis of a general practice research database, and the analysis of claims data did not reveal an increased risk of vascular incidents in triptan users.^{11-13,22,23} Moreover, experimental studies with the administration of triptans during coronary angiography, looking at electrocardiographic changes, or alterations in troponin levels did not show signs of acute coronary syndrome induced by triptans.²⁴⁻²⁶ Most acute coronary artery syndromes are caused by the rupture of atherosclerotic plaques or the occlusion of the coronary artery by a thrombus and not by vasoconstriction. In addition, the most common causes for stroke are large vessel disease, cardio-embolic infarction, and cerebral small vessel disease but not vasospasm. Moreover, experimental studies showed that triptans have a vasoconstrictive effect on extracranial instead of the intracranial arteries.^{27,28} We could conclude that triptans may not be strictly contraindicated in patients with cardiovascular or cerebrovascular disease, and could be safe in healthy elderly persons with migraine.²⁸ Nevertheless, the risk of administration of triptans in patients with vascular diseases must be considered according to their regulatory approval. Until recently, the alternatives to triptans were nonsteroidal inflammatory drugs (NSAIDs) and other non-opioid analgesics. However, NSAIDs increase the risk of acute cardiovascular events²⁹ and also have to be considered carefully; particularly, in elderly patients. Non-vasoconstrictive alternatives, like ditans or gepants, are already available in some countries or will be available in the future,³⁰ but gepants inhibit vasodilation and the knowledge on their vascular risk is limited. Although triptans were used in spite of contraindications in our cohort, we found no increase in vascular comorbidities in triptan users compared with nonusers. This may point out that they could be used more often, if they were indicated.

Triptan overuse

Remarkably, 15.7% of the triptan users over 50 years of age showed signs of triptan overuse. Based on this dataset, we cannot provide an explanation why the proportion of those with triptan overuse increased compared to 2007. The data on triptan overuse in 2011 seems robust, because 62% had signs of overuse in at least two quarters. Triptan overuse in the older age cohort is not negligible, as data from other claims studies showed. In a French cohort, 6.9% of the triptan users were over 65 years of age; thereof 12% overused triptans.³¹ In an Italian cohort, only 0.7-1% of the triptan users were over 60 years, but 15-23% of them were frequent users.³² Most important, we found that even triptan overuse was not associated with an increased rate of vascular comorbidity.

Differences in the prescription rates and in the proportion of persons with triptan overuse between the provinces may be associated with the different availability of neurologists (for example, 20.7 neurologists per 100,000 inhabitants in Vienna and 8.6/100,000 in Vorarlberg).¹⁵

Strengths and limitations

A strength of our study is that it is based on a nationwide insurance database, including 99% of the population irrespective of socio-economic conditions. Second, triptans were not available over the counter; therefore, all triptan prescriptions are included. Prescriptions for patients with low income or other severe chronic diseases (413,471 persons/4.9% of the insured population) are not included if they are cheaper than the prescription charge. Because triptans and the majority of vascular medications cost more than the prescription charge, this has no substantial influence on the results. Third, we compared triptan users to a matched control group of triptan nonusers. Fourth, we could compare triptan use and overuse in persons over 50 years of age with data from 2007.

This study has several limitations. First, due to the high number of cases, some of the statistically significant results may not be of clinical relevance. In particular, we interpreted the dispensation of vascular medications with caution and used descriptive analyses. Second, the database does not include diagnoses from outpatient visits; therefore, there is a high chance we underestimated vascular morbidities in triptan users and controls. However, the analysis of vascular medications compensates for this shortcoming because we found more dispensed vascular medications than vascular diagnoses. Third, the database does not allow us to link inpatient diagnoses with prescriptions and indications of medications. We could not tell if newly diagnosed vascular conditions led to any consequences in triptan prescription. Fourth, we could not differentiate from the database if a vascular event or disease occurred in close temporal relationship with the triptan dispensation. Moreover, claims data are subject to coding errors and do not include medical reports to support diagnoses. Furthermore, the database gives no information whether persons with triptan overuse (based on the prescription

rate) had medication overuse headache. Finally, this was a retrospective review of data and no cause-and-effect conclusions can be drawn.

CONCLUSION

Migraine still plays a role with increasing age. A considerable number of persons over 50 years of age use triptans to treat migraine attacks—and a considerable number of them overuse triptans. Cardiovascular diagnoses and vascular comedications are as frequent as in the overall population of the same age. We found no increase in the prevalence of vascular diseases among triptan users over 50 years of age; implying that the risk of vascular events is not increased by triptan use, and not even by triptan overuse, in this age group. These data and our previous study¹⁴ showed that triptans are generally underprescribed in Austria, perhaps also because of the fear of vascular complications. However, this study supports the safety of triptans, even in persons over 50 years of age and with vascular comorbidities. Nonetheless, neurologists and general practitioners should have an eye on patients over 50 who have migraine. Treatment options and indications have to be re-evaluated regularly. Older age, per se, is not a reason to not prescribe triptans, although they are officially contraindicated in persons older than 65 years. But patients' histories have to be checked for emerging vascular comorbidities regularly.

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CONFLICT OF INTEREST

K.Z. received honoraria for advisory boards from Pfizer, Stada, and Grünenthal. C.W. received honoraria for advisory boards from Pfizer and Grünenthal. W.G., A.G., and A.R.P. declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Study concept and design: Karin Zebenholzer, Walter Gall, Andreas Gleiss, Christian Wöber. *Acquisition of data:* Karin Zebenholzer, Walter Gall, Andreas Gleiss. *Analysis and interpretation of data:* Karin Zebenholzer, Walter Gall, Andreas Gleiss, Antun R. Pavelic, Christian Wöber. *Drafting of the manuscript:* Karin Zebenholzer. *Revising it for intellectual content:* Walter Gall, Andreas Gleiss, Antun R. Pavelic, Christian Wöber. *Final approval of the completed manuscript:* Karin Zebenholzer, Walter Gall, Andreas Gleiss, Antun R. Pavelic, Christian Wöber.

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