Hypertension Research (2019) 42:1794–1800
https://doi.org/10.1038/s41440-019-0300-0

ARTICLE

Oral short-acting antihypertensive medications and the occurrence of stroke: a nationwide case-crossover study

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Received: 5 January 2019 / Revised: 19 May 2019 / Accepted: 6 June 2019 / Published online: 12 July 2019

Abstract

The purpose of the study was to clarify whether short-acting antihypertensives are associated with the occurrence of ischemic stroke and intracerebral hemorrhage (ICH). This was a retrospective case-crossover study using the Taiwan National Health Insurance Research Database. We identified all adult patients hospitalized with a primary diagnosis of ischemic stroke or ICH between January 2005 and December 2013. For each case, short-term and long-term exposure to short-acting antihypertensives, including nifedipine, labetalol and captopril, during the case vs. control periods were compared, and odd ratios (ORs) and 95% confidence intervals (CIs) for ischemic stroke or ICH were calculated with adjustment for confounders. Among 272785 ischemic stroke and 77798 ICH patients, the mean age was 77.8 ± 14.3 years and 70.8 ± 16.6 years, respectively. The short-term use of the three short-acting antihypertensives were all associated with an increase in the incidence of ischemic stroke (nifedipine: OR 4.51, 95% CIs 3.99–5.11; labetalol: OR 2.07; 95% CIs 1.71–2.51; captopril: OR 1.98, 95% CIs 1.72-2.29) and ICH (nifedipine: OR 2.98, 95% CIs 2.30–3.84; labetalol: OR 2.37; 95% CIs 1.66–3.39; captopril: OR 2.48; 95% CIs 1.69–3.63). The long-term use of short-acting nifedipine for 30 days was associated with a modest increase in the risk for ischemic stroke (OR 1.86; 95% CIs 1.42–2.45). Overall, the short-term use of short-acting antihypertensives is associated with a modest increase in the incidence of stroke, and short-acting nifedipine is linked to a substantial rise in the incidence of ischemic stroke. The long-term use of short-acting nifedipine was also related to an increased incidence of ischemic stroke. Physicians should be cautious of prescribing these short-acting antihypertensives.

Keywords Prevention · Short-acting antihypertensives · Nifedipine · Ischemic stroke · Intracerebral hemorrhage

Introduction

Hypertension is a common chronic medical condition that is related to a higher risk of cardiovascular and cerebrovascular diseases [1]. Chronic hypertension is often managed with various classes of antihypertensive medications, including calcium channel blockers, alpha- or beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [1]. Sustained-release formulas are preferred because they have more stable antihypertensive effects and are easier for patients with regards to maintaining adherence.

Oral short-acting antihypertensive medications are sometimes prescribed to patients with acute elevation of blood pressure (BP). Among these medications, immediate-release nifedipine is generally not recommended because severe adverse effects have been reported, including excessive hypotension, syncope, arrhythmia, myocardial

Supplementary information The online version of this article (https://doi.org/10.1038/s41440-019-0300-0) contains supplementary material, which is available to authorized users.

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infarction, stroke, and mortality [2–8]. Accordingly, the United States Food and Drugs administration issued a warning about its use in the treatment of hypertension in patients at high cardiovascular risk [9]. It has also been put on the list of potentially inappropriate medications for elderly patients [10]. Nevertheless, physicians in several countries around the world still routinely prescribe short-acting nifedipine to their patients [11, 12]. On the other hand, it is not clear if the increased stroke risk is a class effect associated with all short-acting antihypertensive medications or a drug-specific effect only associated with short-acting nifedipine. We therefore conducted a case-crossover study using the Taiwan health insurance database to evaluate the association between stroke occurrence and 3 commonly used short-acting antihypertensive medications (nifedipine, labetalol and captopril).

Methods

Data source

We conducted a retrospective case-crossover study using the Taiwan National Health Insurance Research Database (NHIRD). The Taiwan National Health Insurance program was launched in 1995. It covers 99% of the population and reimburses expenses for outpatient and inpatient services as well as prescription drugs. In the study period, the diagnosis code used in NHIRD was the 9th revision of the International Classification of Diseases (ICD-9). This study was approved by the institutional review board of Chang Gung Memorial Hospital, Chiayi, Taiwan.

Study population

We identified all hospitalized patients (≥20 years) who were admitted with a primary diagnosis of ischemic stroke (ICD-9 codes 433. X1, 434. X1, 436) or intracerebral hemorrhage (ICH) (ICD-9 431) between January 1, 2005, and December 31, 2013. Patients hospitalized due to transient ischemic stroke (ICD-9 435.9) and subarachnoid hemorrhage (ICD-9 430) were not included. For each case, the first stroke episode during the study period was defined as the index stroke (or index hospitalization). Because we only had the data from 2005 to 2013, the index stroke may not have been the first stroke experienced by the individual. The index date was defined as one day before the first date of the index hospitalization (including both the time in the emergency room and the ward) because some patients may already have had stroke symptoms on the day before the index date. We excluded patients who had no computed tomography or magnetic resonance imaging of the brain during the index hospitalization or within the 3 days before the index hospitalization because the diagnosis of stroke may have been uncertain. We also excluded patients who had been hospitalized for any reason in the ward or emergency room within 90 days prior to the index hospitalization because the medication use during hospitalization may have been more complicated and had the potential to confound our analysis. This was a nationwide study that included all available and eligible patients. The requirement of informed consent from subjects included in this study was waived.

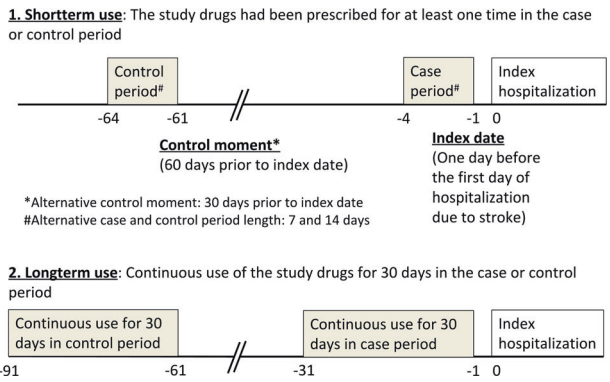

Fig. 1 The case-crossover study design

Case-crossover study design

The study design was a case-crossover study in which a case was used as its own control in a different time period Fig. 1. Two periods were defined for comparison for each case, namely, the case period and the control period. The case period was defined as a 3-day period before the index date, and the control period was defined as a 3-day period before the control moment (that is, 60 days before the index date). To test the robustness of the results, we also used different case and control period lengths (7 days and 14 days) and different control moment (30 days before the index date).

The study drugs were short-acting, immediate-release antihypertensive medications, namely, nifedipine 10 mg, labetalol 200 mg and captopril 25 mg. The patient was defined as "exposed" to a study drug if the drug was prescribed at least once during the case or control period. To evaluate the effect of the long-term use of these study drugs, we also compared the continuous use of the drugs for 30 days within the case and control periods. Because we excluded patients who had other hospitalizations within 90 days prior to the index stroke, all of these study drugs were prescribed in outpatient clinics.

Comorbidity information was extracted by ICD-9 codes within 2 years prior to the index stroke for each case, including hypertension (ICD-9 401-405), ischemic heart disease (ICD-9 410-414), diabetes mellitus (ICD-9 250), dyslipidemia (ICD-9 272), atrial fibrillation (ICD-9 427.31),

heart failure (ICD-9 428), chronic liver disease (ICD-9 571, 070.41, 070.44, 070.51, 070.54, V02.62, 070.22, 070.23, 070.33, V02.61, 291.××, 303.0×, 303.9×, 305.0×), cancer (ICD-9 140-208), chronic kidney disease (ICD-9 585, 403), subarachnoid hemorrhage (ICD-9 430), unruptured cerebral aneurysm (ICD-9 437.30), and cerebrovascular malformation (ICD-9 747.81).

Statistical analysis

We analyzed the characteristics of the ischemic stroke and ICH patient populations, including age, sex, and comorbidities. Exposure to the short-acting antihypertensive medications during the case period and the control periods were compared. Odd ratios (ORs) and 95% confidence intervals (CIs) for ischemic stroke or ICH episodes associated with the use of short-acting antihypertensive medications were calculated by conditional logistic regression.

Subgroup analyses according to sex, age groups, hypertension known before the prescription of the drugs of interest, additional antihypertensive drug use, diabetes mellitus, hyperlipidemia, ischemic heart disease, chronic kidney disease, atrial fibrillation, and heart failure were performed to assess the interactive effect between different patient characteristics and drug use.

Potential time-varying confounders included the concurrent use of other antihypertensive medications, anticoagulants, antiplatelets, and other antithrombotic agents and the diagnosis of infective endocarditis (ICD-9 4210, 4211), valvular heart disease (ICD-9 390-398, 424), acute myocardial infarction (ICD-9 410, 412), thyrotoxicosis (ICD-9 242), pneumonia (ICD-9 480-487), thromboembolism (ICD-9 4151, 451, 453), and atrial fibrillation (ICD-9 427.31). We included variables achieving statistical significance in the univariate analysis as the adjusting variables in the multivariate analysis, including valvular heart disease, acute myocardial infarction, thyrotoxicosis, pneumonia, atrial fibrillation, thromboembolism, and the concurrent use of other antihypertensive medications, anticoagulants, antiplatelets, and other antithrombotic agents. Adjusted odds ratios were calculated after controlling for the above time-varying confounding variables.

Statistical significance was determined using 95% CIs or a P value < 0.05. The statistical analysis was performed using the SAS statistical package (release 9.4, SAS Institute Inc, Cary, NC).

Results

During the study period, 306184 and 85649 patients (≥20 years) were hospitalized with the primary diagnoses of ischemic stroke and ICH, respectively. After excluding the patients who had been hospitalized within 3 months before the index stroke, 272785 patients with a first ischemic stroke episode and 77797 patients with a first ICH episode during the study period were identified. Of the ischemic stroke patients, 59.5% were male, and the mean age was 77.8 ± 14.3 years. Of the ICH patients, 64% were male, and the mean age was 70.8 ± 16.6 years. Of the ischemic stroke and ICH patients, 55.0% and 43.1% had hypertension, respectively. Other characteristics and comorbidities of these patients are shown in Table 1.

Table 1 Characteristics of patients with ischemic stroke and intracerebral hemorrhage

Characteristics	Ischemic stroke $N = 272,785$ n (%) or mean (SD)	Intracerebral hemorrhage $N = 77,797$ n (%) or mean (SD)
Age, year	77.8 (14.31)	70.8 (16.58)
<60	32631 (12.0)	21746 (28.0)
60–79	106701 (39.1)	30580 (39.3)
80+	133453 (48.9)	25471 (32.7)
Male	162239 (59.5)	49805 (64.0)
Comorbidities		
Hypertension	150129 (55.0)	33565 (43.1)
Diabetes mellitus	80829 (29.6)	12392 (15.9)
Dyslipidemia	47118 (17.3)	8012 (10.3)
Ischemic heart disease	42142 (15.4)	7061 (9.1)
Heart failure	16316 (6.0)	2705 (3.5)
Atrial fibrillation	9212 (3.4)	1176 (1.5)
Liver cirrhosis	12860 (4.7)	4999 (6.4)
Chronic renal failure	9576 (3.5)	3453 (4.4)
Cancer	10710 (3.9)	2570 (3.3)
Unruptured cerebral aneurysm	0 (0.0)	0 (0.0)
Subarachnoid hemorrhage	299 (0.1)	141 (0.2)
Cerebrovascular malformation	0 (0.0)	0 (0.0)
Additional antihypertensive drugs		
≥2 kinds	20617 (7.6)	3044 (3.9)
1 kind	15003 (5.5)	2371 (3.1)
0	237165 (86.9)	72382 (93.0)

SD standard deviation

Tables 2 and 3 show the risks of ischemic stroke and ICH associated with the exposure to short-acting antihypertensive medications, respectively. Comparing the case period (3 days before index date) and control period (3 days preceding 60 days before the index date), the use of short-acting nifedipine was associated with a substantial rise in the risk of ischemic stroke (OR 4.51, 95% CIs 3.99–5.11)

Table 2 Risk of ischemic stroke associated with exposure to short-acting nifedipine, labetalol, and captopril

Length of risk window	Case periods *n* (%)	Control periods *n* (%)	OR (95% CI)	Adjusted OR[a] (95% CI)
Short-acting nifedipine				
Control moment: 30 days before stroke				
3 days	2250 (0.8)	374 (0.1)	6.74 (6.00–7.57)	3.93 (3.48–4.44)
7 days	3204 (1.2)	855 (0.3)	4.57 (4.20–4.97)	3.01 (2.76–3.29)
14 days	4162 (1.5)	1672 (0.6)	3.13 (2.93–3.34)	2.39 (2.23–2.56)
Control moment: 60 days before stroke				
3 days	2250 (0.8)	329 (0.1)	7.30 (6.48–8.23)	4.51 (3.99–5.11)
7 days	3204 (1.2)	790 (0.3)	4.89 (4.48–5.33)	3.24 (2.96–3.54)
14 days	4162 (1.5)	1594 (0.6)	3.29 (3.08–3.52)	2.47 (2.30–2.64)
Continuous use for 30 days[b]	189 (0.1)	87 (0.03)	2.80 (2.15–3.65)	1.86 (1.42–2.45)
Short-acting labetalol				
Control moment: 30 days before stroke				
3 days	760 (0.3)	150 (0.1)	5.62 (4.67–6.77)	2.07 (1.71–2.51)
7 days	1064 (0.4)	355 (0.1)	3.95 (3.43–4.56)	1.91 (1.65–2.21)
14 days	1433 (0.5)	687 (0.3)	2.74 (2.45–3.06)	1.68 (1.50–1.88)
Control moment: 60 days before stroke				
3 days	760 (0.3)	160 (0.1)	4.87 (4.10–5.79)	1.92 (1.60–2.30)
7 days	1064 (0.4)	364 (0.1)	3.52 (3.08–4.02)	1.72 (1.50–1.97)
14 days	1433 (0.5)	716 (0.3)	2.60 (2.34–2.90)	1.57 (1.41–1.76)
Continuous use for 30 days[b]	83 (0.03)	41 (0.02)	2.64 (1.79–3.90)	1.27 (0.84–1.90)
Short-acting captopril				
Control moment: 30 days before stroke				
3 days	1039 (0.4)	263 (0.1)	4.53 (3.91–5.24)	2.03 (1.74–2.36)
7 days	1547 (0.6)	564 (0.2)	3.54 (3.16–3.96)	1.94 (1.73–2.18)
14 days	2133 (0.8)	1104 (0.4)	2.52 (2.31–2.76)	1.67 (1.53–1.83)
Control moment: 60 days before stroke				
3 days	1039 (0.4)	265 (0.1)	4.06 (3.54–4.66)	1.98 (1.72–2.29)
7 days	1547 (0.6)	614 (0.2)	3.01 (2.71–3.34)	1.68 (1.50–1.87)
14 days	2133 (0.8)	1131 (0.4)	2.41 (2.21–2.63)	1.60 (1.46–1.75)
Continuous use for 30 days[b]	131 (0.1)	87 (0.03)	1.91 (1.44–2.54)	1.00 (0.75–1.34)

OR odds ratio, *CI* confidence interval

[a]Model adjusted for valvular heart disease, acute myocardial infarction, thyrotoxicosis, pneumonia, atrial fibrillation, thromboembolism, antihypertensive, anticoagulant, antiplatelet, other antithrombotic agent

[b]The reference group is nonuser. Continuous use means continuously used 1–30 days preceding index date and control moment. Control moment was 60 days before index date

and a moderate increase in the risk of ICH (OR 2.98, 95% CIs 2.30–3.84); the use of labetalol was associated with a moderate rise in the risk of ischemic stroke (OR 2.07; 95% CIs 1.71–2.51) and the risk of ICH (OR 2.37; 95% CIs 1.66–3.39); and the use of captopril was linked to a moderate increase in the risk of ischemic stroke (OR 1.98; 95% CIs 1.72–2.29) and the risk of ICH (OR 2.48; 95% CIs 1.69–3.63), after adjustment for confounders. The sensitivity analysis showed that using different case and control period lengths (7 and 14 days) or using different control moment (30 days prior to index date) did not change the main results.

When comparing the continuous use of short-acting antihypertensive drugs for 30 days in the case period and control period, only nifedipine was associated with a modest increase in the risk of ischemic stroke (OR 1.86; 95% CIs 1.42–2.45).

In subgroup analyses, the increased odds of ischemic stroke and ICH among patients taking short-acting antihypertensive medications were consistent among groups stratified by different characteristics (Supplemental Tables 1–3). Using short-acting antihypertensive drugs once or more than once daily were both related to increased risks of ischemic stroke and ICH. Once daily dosing was related

Table 3 Risk of intracerebral hemorrhage associated with exposure to short-acting nifedipine, labetalol, and captopril

Length of risk window	Case periods *n* (%)	Control periods *n* (%)	OR (95% CI)	Adjusted OR[a] (95% CI)
Short-acting nifedipine				
Control moment: 30 days before stroke				
3 days	355 (0.5)	73 (0.1)	5.27 (4.05–6.86)	3.24 (2.47–4.25)
7 days	521 (0.7)	184 (0.2)	3.20 (2.67–3.84)	2.36 (1.96–2.85)
14 days	681 (0.9)	359 (0.5)	2.11 (1.84–2.43)	1.85 (1.60–2.14)
Control moment: 60 days before stroke				
3 days	355 (0.5)	78 (0.1)	4.65 (3.63–5.95)	2.98 (2.30–3.84)
7 days	521 (0.7)	158 (0.2)	3.56 (2.95–4.28)	2.75 (2.27–3.33)
14 days	681 (0.9)	325 (0.4)	2.37 (2.05–2.74)	2.13 (1.84–2.48)
Continuous use for 30 days[b]	38 (0.1)	21 (0.03)	1.94 (1.13–3.35)	1.26 (0.73–2.17)
Short-acting labetalol				
Control moment: 30 days before stroke				
3 days	166 (0.2)	46 (0.1)	4.08 (2.87–5.79)	2.37 (1.66–3.39)
7 days	232 (0.3)	99 (0.1)	2.80 (2.15–3.65)	1.99 (1.52–2.60)
14 days	334 (0.4)	208 (0.3)	1.92 (1.56–2.36)	1.64 (1.33–2.02)
Control moment: 60 days before stroke				
3 days	166 (0.2)	54 (0.1)	3.15 (2.31–4.31)	1.95 (1.42–2.68)
7 days	232 (0.3)	99 (0.1)	2.68 (2.07–3.48)	1.99 (1.53–2.59)
14 days	334 (0.4)	214 (0.3)	1.84 (1.50–2.26)	1.60 (1.30–1.97)
Continuous use for 30 days[b]	14 (0.02)	19 (0.02)	1.01 (0.49–2.07)	0.65 (0.32–1.34)
Short-acting captopril				
Control moment: 30 days before stroke				
3 days	141 (0.2)	45 (0.1)	3.46 (2.42–4.94)	1.99 (1.38–2.86)
7 days	215 (0.3)	114 (0.2)	2.16 (1.68–2.79)	1.51 (1.17–1.96)
14 days	324 (0.4)	218 (0.3)	1.74 (1.42–2.14)	1.47 (1.19–1.81)
Control moment: 60 days before stroke				
3 days	141 (0.2)	37 (0.1)	4.06 (2.79–5.91)	2.48 (1.69–3.63)
7 days	215 (0.3)	100 (0.1)	2.51 (1.93–3.28)	1.85 (1.42–2.43)
14 days	324 (0.4)	208 (0.3)	1.87 (1.52–2.31)	1.63 (1.32–2.02)
Continuous use for 30 days[b]	16 (0.02)	10 (0.01)	1.65 (0.72–3.81)	1.00 (0.43–2.31)

OR odds ratio, *CI* confidence interval

[a]model adjusted for valvular heart disease, acute myocardial infarction, thyrotoxicosis, pneumonia, atrial fibrillation, thromboembolism, antihypertensive, anticoagulant, antiplatelet, other antithrombotic agent

[b]The reference group is nonuser. Continuous use means continuously used 1–30 days preceding index date and control moment. Control moment was 60 days before index date

to a higher odd of strokes than was twice or more daily dosing (Supplemental Table 4).

Discussion

This case crossover study using the Taiwan NHIRD revealed that short-term use of short-acting antihypertensive agents (nifedipine, labetalol and captopril) in the past 2 weeks was associated with a significant increase in the odds of ischemic stroke and ICH, and short-acting nifedipine was associated with substantially greater odds of an ischemic stroke. Moreover, the long-term use of short-acting nifedipine for 30 days was associated with a significantly increased risk of ischemic stroke, while the long-term use of short-acting labetalol and captopril for 30 days was not.

Our results showed that short-acting antihypertensives had a class effect in that they modestly increased the risk of ischemic stroke. Short-acting antihypertensives are frequently prescribed to patients with acutely elevated BP. However, when the BP is acutely elevated, the lower limit of cerebral blood flow autoregulation may increase from 60-70 mmHg to 120 mmHg. In this situation, a rapid BP reduction induced by short-acting antihypertensive agents may cause cerebral hypoperfusion [13]. Gleen et al.

reported six acutely severe hypertensive patients who had ischemic strokes after a moderate BP reduction of 18–36% due to various short-acting antihypertensive drugs. In all six cases, the posttreatment BP was within the normotensive range [14]. Accordingly, acutely elevated BP should be controlled slowly over hours to days, and the BP should be reduced by not more than 20% in the first hour. However, in outpatient clinics, it is difficult to closely monitor the patients' BP changes after prescribing oral short-acting antihypertensive agents.

Among the short-acting antihypertensives, short-acting nifedipine is differentially linked to greater odds of ischemic stroke compared to short-acting labetalol and captopril. There are some possible reasons. First, short-acting nifedipine has a more rapid onset (after 5 min) and peak effect (after 30–60 min) than short-acting labetalol (onset after 30–60 min and peak effect after 2–4 h) and captopril (onset after 15–30 minutes and peak effect after 60–90 min) [15]. Therefore, short-acting nifedipine is prone to reducing BP too rapidly. Second, nifedipine is a dihydropyridine calcium channel blocker that has a hypotensive effect through vasodilatation of the peripheral arteries. In the presence of cerebral arterial stenosis, the vasodilatation of the cerebral vessels may not compensate for the decrease in blood flow caused by the vasodilatation of the peripheral vessels [14]. It may also steal blood from the marginally perfused regions in the brain by shunting blood to the normal regions with a greater vasodilatory reserve [14]. Third, nifedipine has a negative inotropic effect and may decrease cardiac output and cause watershed infarction, especially in the presence of cerebral artery stenosis [4]. Fourth, nifedipine increases sympathetic stimulation and causes reflex tachycardia [4]. It may potentiate the occurrence of arrhythmia and increase the risk of arrhythmia-related embolic stroke [4].

Moreover, we found that long-term short-acting nifedipine use for 30 days was linked to a higher risk of ischemic stroke, while long-term short-acting labetalol and captopril use for 30 days were not. The duration of the drug effect of short-acting nifedipine is approximately 4–6 h, which is shorter than that of short-acting labetalol (8–12 h) and captopril (6–8 h). Therefore, in the usual practice of twice or three times daily dosing, short-acting captopril and labetalol could reach a steady-state effect of reducing the BP, while short-acting nifedipine may cause BP fluctuation, a known risk factor for ischemic stroke [16].

We found that all of these short-acting antihypertensive medications modestly increased the odds of ICH. These drugs may cause BP fluctuations that cause vulnerable stiff cerebral vessels to rupture, resulting in ICH. Rebound hypertension after rapid BP lowering may also cause ICH. Moreover, both nifedipine and captopril had some antiplatelet effects [17, 18]. On the other hand, some causes of acute BP elevation, such as sympathomimetic drug use, eclampsia or preeclampsia, and pheochromocytoma, may increase ICH risk [19]. An acute surge in BP per se may cause the rupture of cerebral perforating vessels [19]. Episodic hypertension is also reported to be a risk factor for ICH [20]. Therefore, both the short-acting antihypertensive medication and the underlying condition (acute hypertension) that precipitate the prescription of these medications may contribute to the increased ICH risk.

In this study, 55% of ischemic stroke patients had hypertension, but only 13% had regularly taken antihypertensive medication before ischemic stroke. Additionally, 43% of ICH patients had hypertension, but only 7% had regularly taken antihypertensive medication before ICH. Such a scenario suggested that a substantial proportion of hypertensive patients did not receive regular antihypertensive therapy before stroke. This study highlighted the importance of regular blood pressure control once hypertension was found.

This study has limitations. First, the accuracy of stroke was not validated by a medical chart review. However, the ischemic stroke diagnosis in NHIRD has been validated with an accuracy up to 94.5% [21]. Second, the pretreatment and posttreatment BP value for each subject could not be obtained from the database. Therefore, we could not evaluate the relationship between BP changes and stroke occurrence after the administration of these medications. Third, we did not evaluate the dose effect of these medications because it may be influenced by the body mass index, renal function and drug-drug interactions. Such data were not available from the current insurance database. Fourth, we could not confirm the patient's compliance with these medications. It is possible that some patients may not have taken the medications prescribed by the physicians. However, because the compliance for each patient was assumed to be the same in the control and case period, it would have limited the influence on the results. Fifth, this study was performed in Taiwan, and the results of the study may not be generalizable to other populations. Although a nationwide study from Korea and many case reports from white populations showed an association between short-acting nifedipine and the occurrence of ischemic strokes [2–8], the generalizability of the current results needs to be confirmed by further studies conducted in other countries and populations.

In summary, our findings show that the short-term use of short-acting antihypertensive medications is associated with moderately greater odds of ischemic stroke and ICH, and short-acting nifedipine in particular is differentially associated with substantially greater odds of ischemic stroke. Long-term short-acting nifedipine use for 30 days is still harmful with regard to the risk of

ischemic stroke. Based on the results of this study, physicians should avoid prescribing short-acting nifedipine and closely monitor patients who start to take short-acting labetalol and captopril.

Funding This work was supported by the Ministry of Science and Technology, Taiwan, grant number: MOST105-2628-B-182-008-MY2 and the Chang Gung Memorial Hospital, Taiwan, grant number: CORPG6D0101, CORPG6D0102, CORPG6D0103. The sponsors played no role in the design and conduct of the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.
2. Schwartz M, Naschitz JE, Yeshurun D, Sharf B. Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. Arch Intern Med. 1990;150:686–7.
3. Morton C, Hickey-Dwyer M. Cortical blindness after nifedipine treatment. Brit Med J. 1992;305:693.
4. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation 1995;92:1326–31.
5. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? J Am Med Assoc. 1996;276:1328–31.
6. Cheng JW, Behar L. Calcium channel blockers: association with myocardial infarction, mortality, and cancer. Clin Ther. 1997;19:1255–68.
7. Ishibashi Y, Shimada T, Yoshitomi H, Sano K, Oyake N, Umeno T, et al. Sublingual nifedipine in elderly patients: even a low dose induces myocardial ischaemia. Clin Exp Pharm Physiol. 1999;26:404–10.
8. Jung SY, Choi NK, Kim JY, Chang Y, Song HJ, Lee J, et al. Short-acting nifedipine and risk of stroke in elderly hypertensive patients. Neurology 2011;77:1229–34.
9. Marwick C. FDA gives calcium channel blockers clean bill of health but warns of short-acting nifedipine hazards. J Am Med Assoc. 1996;275:423–4.
10. Renom-Guiteras A, Meyer G, Thurmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharm. 2015;71:861–75.
11. Chou CL, Chou CY, Hsu CC, Chou YC, Chen TJ, Chou LF. Old habits die hard: a nationwide utilization study of short-acting nifedipine in Taiwan. PLoS ONE 2014;9:e91858.
12. Schubert I, Hein R, Abbas S, Thurmann P. The frequency of prescription of immediate-release nifedipine for elderly patients in Germany: utilization analysis of a substance on the PRISCUS list of potentially inappropriate medications. Dtsch Arztebl Int. 2012;109:215–9.
13. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. Br Med J. 1973;1:507–10.
14. Fischberg GM, Lozano E, Rajamani K, Ameriso S, Fisher MJ. Stroke precipitated by moderate blood pressure reduction. J Emerg Med. 2000;19:339–46.
15. Vidt DG. Emergency room management of hypertensive urgencies and emergencies. J Clin Hypertens. 2001;3:158–64.
16. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. Arch Neurol. 2010;67:564–9.
17. Skowasch D, Viktor A, Schneider-Schmitt M, Luderitz B, Nickenig G, Bauriedel G. Differential antiplatelet effects of angiotensin converting enzyme inhibitors: comparison of ex vivo platelet aggregation in cardiovascular patients with ramipril, captopril and enalapril. Clin Res Cardiol. 2006;95:212–6.
18. Shih CY, Lin IH, Ding JC, Chen FC, Chou TC. Antiplatelet activity of nifedipine is mediated by inhibition of NF-kappaB activation caused by enhancement of PPAR-beta/-gamma activity. Br J Pharm. 2014;171:1490–1500.
19. Caplan L. Intracerebral hemorrhage revisited. Neurology. 1988;38:624–7.
20. Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension 2006;47:149–54.
21. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf. 2011;20:236–42.