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COMMENT

Can calcium channel blockers prevent ischemic stroke in nonvalvular atrial fibrillation patients?—the optimal choice of antihypertensive drug for subtype-specific stroke prevention

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Nonvalvular atrial fibrillation (NVAF) is a major cause of cardioembolic stroke [1], and the number of patients with NVAF is expected to increase with the growth of the elderly population [2]. Cardioembolic stroke is the most severe stroke subtype, often leading to death or being bed-ridden, particularly in elderly patients. To prevent cardioembolic stroke, NVAF patients are recommended to take oral anticoagulants (OACs) despite the risk of hemorrhagic complications, such as hemorrhagic stroke [1]. Hypertension is the most important risk factor for hemorrhagic and ischemic stroke, including cardioembolic stroke, and it increases the burden of atrial fibrillation. Therefore, optimal blood pressure lowering using appropriate antihypertensive drugs (AHDs) is an important strategy to prevent cardioembolic and hemorrhagic stroke in NVAF patients taking OACs [3].

Several randomized controlled trials (RCTs) have established the efficacy of lowering blood pressure and the optimal blood pressure level for the primary [4] and secondary [5, 6] prevention of ischemic stroke, regardless of subtype. Based on this evidence, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) [7] recommend an optimal blood pressure level of <130/80 mmHg for stroke prevention in patients taking antithrombotic agents, considering the high incidence of hemorrhagic stroke in the Japanese population. The guidelines also recommend the preferential choice among four classes of AHDs, i.e., a calcium channel blocker (CCB), angiotensin II receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACE-I), or diuretic as the first-line AHD and their combination for hypertensive patients resistant to the use of a single AHD [7]. However, there is little evidence regarding the superiority of a specific class of AHD for stroke prevention. Renin-angiotensin system (RAS) blockers [8] and β-blockers [9] are expected to be more effective for the primary prevention of NVAF in patients with left ventricular hypertrophy and congestive heart failure (CHF). However, the superiority of RAS blockers over other AHDs, including dihydropyridine CCBs, has not been demonstrated in the secondary prevention of NVAF (to decrease the frequency of attacks and transition to a chronic state) in large RCTs [10, 11]. Guidelines recommend the use of β-blockers or nondihydropyridine CCBs to prevent the development and/or worsening of CHF in NVAF patients [7]. A recent meta-analysis of general hypertension patients demonstrated that dihydropyridine CCBs were more effective in the primary prevention of stroke but less effective in preventing heart failure than other AHDs [4]. Regarding the secondary prevention of stroke, the benefit of intensive blood pressure lowering with the combined use of ACE-Is and diuretics has been established in PROGRESS [5]. However, based on real-world data from the Fukuoka Stroke Registry, a multicenter prospective registry of acute stroke in Japan [12], diuretics are not commonly used for the prevention of ischemic stroke except for cardioembolic stroke. Moreover, ACE-Is are completely replaced by ARBs, particularly in noncardioembolic stroke, at least in Japan (Fig. 1). Stroke physicians prefer CCBs and/or ARBs in patients with noncardioembolic stroke, such as atherothrombotic brain infarction and lacunar infarction, while CCBs with β-blockers and others are commonly used for secondary prevention in patients with cardioembolic stroke (Fig. 1). CCBs may have advantages in glucose and lipid metabolism, blood pressure variability reduction, and autoregulatory maintenance of cerebral blood flow for stroke prevention, particularly in elderly patients [7, 12].

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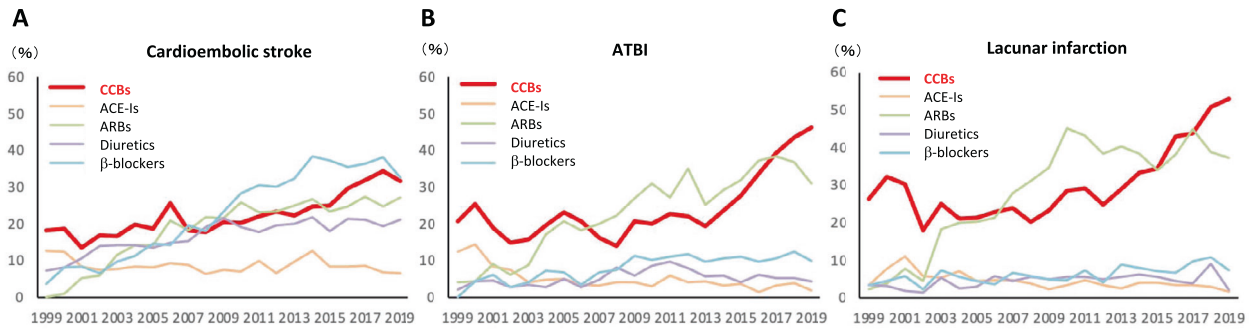

Fig. 1 Frequency of antihypertensive drug use for secondary prevention following acute ischemic stroke in the Fukuoka Stroke Registry. The use of antihypertensive drugs, including CCBs, ACE-Is, ARBs, diuretics, and β-blockers, at discharge following acute ischemic stroke from 1999 to 2019 in the Fukuoka Stroke Registry, a multicenter prospective registry of patients with acute stroke in Japan. The frequency is shown according to the subtypes of ischemic stroke: **A** cardioembolic stroke ($n = 5224$), **B** atherothrombotic brain infarction (ATBI) ($n = 4352$), and **C** lacunar infarction ($n = 4921$). CCB calcium channel blocker, ACE-I angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker

To date, CCBs are the major AHDs for either primary or secondary stroke prevention, regardless of subtype; however, the overall benefits of CCBs for stroke prevention remain unknown in NVAF patients at risk for cardiac failure.

In the latest issue of *Hypertension Research*, Sakakibara et al. [13]. examined whether dihydropyridine CCBs have beneficial or adverse effects in the prevention of ischemic stroke in a large-scale historical registry of 7826 Japanese patients with NVAF taking vitamin K antagonists. The patients were divided into two groups: the CCB ($N = 2693$) and No-CCB ($N = 5133$) groups. The cumulative incidences of ischemic stroke at 4 years in the CCB and No-CCB groups were 5.9% and 5.2%, respectively; dihydropyridine CCBs significantly increased the incidence of ischemic stroke (multivariable-adjusted hazard ratio [95% confidence interval] 1.32 [1.02–1.71]) in the anticoagulated NVAF patients. However, dihydropyridine CCBs were not associated with the development of all-cause mortality, major bleeding, or hemorrhagic strokes (0.85 [0.69–1.04], 1.12 [0.92–1.35], and 1.08 [0.62–1.88], respectively). The authors also reported that dihydropyridine CCBs increased the risk of ischemic strokes, particularly in patients at lower risk for cerebrovascular disease, such as those aged <75 years, with no stroke history, and a $CHADS_2$ score <2 [13]. These results are interesting and may contribute to the knowledge of antihypertensive therapeutic strategies for NVAF patients taking OACs. However, this study had several limitations.

First, the CCB and No-CCB groups were partially disparate populations because the CCB group comprised almost entirely hypertensive patients, while 30% of patients in the No-CCB group were normotensive. The prevalence of other vascular risk factors was also significantly different between the two groups. Thus, it is unclear whether the authors could suitably adjust for the population difference between the two groups even after adjusting for the $CHADS_2$ score and a systolic blood pressure ≥ 140 mmHg in Cox proportional hazard models. The inclusion of normotensive (low-risk) and hypertensive (high-risk) patients in the No-CCB group may have underestimated the risk of ischemic events. Thus, the results should be validated by an additional sensitivity analysis excluding normotensive patients from the No-CCB group.

Second, there was no information on CHF and the subtypes of ischemic stroke that developed during the follow-up period in the study. A possible explanation for this is that dihydropyridine CCBs might exacerbate CHF, which is an intermediate risk factor for cardioembolic stroke, thereby increasing the risk of cardioembolic stroke. If cardioembolic stroke was increased in the CCB group accompanied by worsening CHF, the incidence of poor functional outcomes, including death, might also increase; however, the risk of all-cause mortality was decreased in the CCB group, although the difference was not statistically significant. The higher time in the therapeutic range of warfarin in both the CCB and No-CCB groups in the study (median [interquartile range] 85% [41–100%] and 83% [38–100%], respectively) may possibly explain the lack of a significant difference in the risk of mortality. Alternatively, we may have to consider the possibility that the risk of noncardioembolic stroke was increased in the CCB group because it included a higher proportion of patients with arteriosclerotic diseases, such as coronary artery diseases, peripheral arterial diseases, and strokes, than the No-CCB group. CCB-induced cardiac output reduction or excessive blood pressure lowering might decrease cerebral blood flow, thereby increasing the risk of noncardioembolic stroke in NVAF patients. Therefore, the difference between the frequency of extracranial and intracranial arterial diseases in the CCB and No-CCB groups should be described in the study.

Third, it would be interesting to examine whether similar results would be found in NVAF patients taking direct OACs (DOACs), since they are now predominantly used in NVAF patients instead of warfarin. The Japanese guidelines recommend the preferential administration of DOACs in NVAF patients with a $CHADS_2$ score of ≥1 [14]. Since the authors demonstrated that dihydropyridine CCBs increased the risk of ischemic stroke in patients with a lower risk of cerebrovascular disease with a $CHADS_2$ score < 2 in the study [13], it is possible that dihydropyridine CCBs may also increase the risk of ischemic stroke in NVAF patients taking DOACs.

Sakakibara et al. [13]. raised an important issue regarding the choice of AHDs for stroke prevention in NVAF patients taking oral vitamin K antagonists. Since ischemic stroke comprises several subtypes with different pathophysiologies, the optimal management of risk factors such as hypertension may be different among the subtypes; that is, "how" blood pressure should be lowered may also be a matter of importance. Currently, we have new classes of AHDs, such as angiotensin receptor-neprilysin inhibitors and mineralocorticoid receptor antagonists, both targeting hypertension and CHF. Therefore, it may be necessary to reconsider the choice and combination of AHDs suitable for stroke prevention according to its subtype, which will enable us to provide better personalized medicine for individuals with hypertension.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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