Clinical use of azelnidipine in the treatment of hypertension in Chinese patients

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Bi-Lian Chen¹,⁎
Yin-Zhuang Zhang¹,⁎
Jian-Quan Luo²,³
Wei Zhang²,³

¹Department of Geriatrics, Xiangya Hospital, Central South University, Changsha, Hunan, People’s Republic of China; ²Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha, Hunan, People’s Republic of China; ³Institute of Clinical Pharmacology, Central South University, Changsha, Hunan, People’s Republic of China

*These authors contributed equally to this work

Background: Hypertension is the most common chronic disease and the calcium channel antagonist is the most popularly used antihypertensive drug in Chinese patients. Azelnidipine is a third generation and long-acting dihydropyridine calcium channel antagonist. A series of research has demonstrated that azelnidipine produced an effective antihypertensive effect in patients with essential hypertension. Now it is need to summarize clinical use of azelnidipine in the treatment of hypertension in Chinese patients.

Methods: Relevant literature was identified by performing searches in PubMed and CNKI (China National Knowledge Infrastructure), covering the period from January 2003 (the year azelnidipine was launched) to July 2014. We included studies that described pharmacology of azelnidipine, especially the pharmacokinetics, clinical efficacy, and safety and tolerability of azelnidipine in a Chinese population. The full text of each article was strictly reviewed, and data interpretation was performed.

Results: In Chinese healthy volunteers, a single-dose oral administration of azelnidipine 8–16 mg had a peak plasma concentration of 1.66–23.06 ng/mL and time to peak plasma concentration was 2.6–4.0 hours and the area under the plasma concentration versus time curve from time 0 hour to 96 hours was 17.9–429 ng·h/mL and elimination half-life was 16.0–28.0 hours. A number of clinical trials have demonstrated that azelnidipine produced a significant reduction in blood pressure in Chinese patients with mild-to-moderate hypertension, which was similar to that of other effective antihypertensive drugs such as amlodipine, zofenopril, and nifedipine. In addition to its antihypertensive effect, azelnidipine had other cardiovascular protective effects as well, like anti-oxidative action, decreasing heart rate, and improving systolic and diastolic function. Azelnidipine was generally well tolerated in Chinese patients and no severe adverse events were observed.

Conclusion: Azelnidipine is effective and safe in the treatment of hypertension in Chinese patients.

Keywords: azelnidipine, hypertension, Chinese, pharmacology, pharmacokinetics, efficacy

Introduction to the management issues in the treatment of hypertension in Chinese patients

Hypertension is the most common chronic disease in the People’s Republic of China and a major risk factor for cardiovascular disease, stroke, and kidney disease. The mortality rate of stroke is the major complication of hypertension in Chinese patients. The 2010 Chinese guideline for the management of hypertension is an update of the previous ones in 1999 and 2005, and it has covered blood pressure (BP) measurement, diagnosis, epidemiologic studies, assessment of risk factors, BP monitoring, management of lifestyle, and drug therapy.¹

The prevalence of hypertension had been investigated in the People’s Republic of China in the years 1958, 1979, 1991, and 2002, especially the last one based
on the diagnosis of hypertension according to World Health Organization and International Society of Hypertension: when a person’s systolic blood pressure (SBP) is $\geq 140$ mmHg or diastolic blood pressure (DBP) $\geq 90$ mmHg, or both, on repeated examinations without any anti-hypertensive drug. These standards apply to all adults older than 18 years of age. It was investigated and found that in 2002, nearly 1.6 billion Chinese adults (aged $\geq 18$ years), about one fifth of adults, had high BP. Compared with 1991, the prevalence was increased by 31%. The awareness rate was 30.2% and the drug treatment rate 24.7% and control rate 6.1%. About 90% of adults with high BP have primary hypertension, sometimes called essential hypertension. The cause of primary hypertension is not known clearly. Most patients with hypertension have other risk factors as well, including lipid abnormalities, glucose intolerance or diabetes, a family history of early cardiovascular events, obesity, and cigarette smoking, and so on.

The importance of ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) for the diagnosis and monitoring of hypertension has been recognized and emphasized for a period of time. BP measure at a Doctor’s office is usually higher than ABPM and HBPM. It is recommended that the ABPM and HBPM be used for the diagnosis of isolated office (white coat) hypertension and isolated ambulatory (masked) hypertension.

As hypertension is recognized as a “cardiovascular syndrome”, the management strategy should be based on the overall risk of cardiovascular disease estimated with all related risk factors, target organ damage, and co-morbidity of patients. The goal of treating hypertension is set at SBP/DBP $<140/90$ mmHg in uncomplicated hypertension; $<150/90$ mmHg for the elderly ($\geq 65$ years old), or if tolerable, $<140/90$ mmHg; and $<130/80$ mmHg for those with diabetes, coronary heart disease, or renal disease. In general, hypertension is also a “lifestyle disease”. So, such lifestyle modifications as limiting salt intake to 6 g/d, lowering body mass index to 25 kg/m$^2$, smoking cessation, moderation of alcohol consumption, increasing dietary potassium intake, and physical activity, should be implemented for the prevention and control of hypertension. Several hypertensive populations need special attention in the prevention and control of hypertension, such as children and adolescents, the elderly, pregnant women, and patients with various cardiovascular complications. At the same time, it is important to detect and treat secondary hypertension.

Since most patients with hypertension are treated by primary care physicians, it is recognized that strengthening the education and standardized management of hypertension in the community, such as measuring BP at regular intervals, and rational use of drugs, is the basic way to increase the awareness rate and the drug treatment rate and control rate of hypertension.

With regard to the choice of antihypertensive drugs, the 2010 guideline in the People’s Republic of China confirms that a calcium channel antagonist (CCB), diuretic, $\beta$-receptor blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker are all suitable for use as mono-therapy, and in some combinations with each other. A single pill containing these drugs can be administered as initial and maintenance antihypertensive treatment. Selection of the optimal therapy regimen should be based on a person’s individual demographics, BP, cardiovascular risk, co-morbidities, and preference, as well as evidence for preferential beyond-BP-lowering benefits of different antihypertensive agents. The basic principles of drug treatment are a low dosage, priority of long-period drug, a combination of drugs, and individualized therapy. Among these drugs, dihydropyridine CCBs have no absolute contraindications for use and are a preferred drug in mono-therapy and in combination with other agent classes in many Chinese patients.

CCBs, including non-dihydropyridine and dihydropyridine CCB (DHP-CCB), block the calcium channel on vascular smooth cells to dilate the blood vessels to lower the BP. CCB is often used in combination with other agents, especially for elderly hypertensive patients, systolic hypertension, accompanied by stable angina, coronary and carotid atherosclerosis. There are about ten dihydropyridine CCBs used in Chinese patients with hypertension, among which azelnidipine is a new drug.

**Methods**

Papers on the topic of azelnidipine published online between January 2003 (the year azelnidipine was launched) and July 2014 were retrieved from PubMed and CNKI (China National Knowledge Infrastructure) using the search terms ‘azelnidipine’, ‘pharmacology’, ‘pharmacokinetics’, ‘efficacy’, ‘safety’, ‘hypertension’, and ‘Chinese’ in English for the PubMed database and in the Chinese language for the CNKI database. Fifty-four articles were identified. The inclusion criteria included studies that described pharmacology of azelnidipine, especially the pharmacokinetics, clinical efficacy, and safety and tolerability of azelnidipine in the Chinese population. Exclusion criteria consisted of: duplications, not
useful to answer literature review questions after reading the title and the abstract, Chinese review, data being incomplete, and papers with no references. Twenty-three articles were finally included under this search strategy and inclusion/exclusion criteria (Figure 1). The full text of each article was strictly reviewed, and valuable information was summarized by interpretation of the data.

Pharmacology, mode of action, pharmacokinetics of azelnidipine

Azelnidipine, ((±)-(3)-(1-diphenylmethylazetidin-3-yl)-5-isopropyl-2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate; CS-905), is a third generation, long-acting dihydropyridine calcium antagonist. Azelnidipine was jointly developed by Ube Industries, Ltd. (Yamaguchi, Japan) and Daiichi Sankyo Co, Ltd (Tokyo, Japan) and launched into the market as Calblock in Japan in 2003. Azelnidipine has two enantiomers (R-(-)- and S-(+)-enantiomers) due to an asymmetric carbon at the 4-position, and the (R)-(-) enantiomer of dihydropyridine calcium antagonists is considered to possess intrinsic pharmacological activity. The antihypertensive effect of azelnidipine is primarily based on the inhibition of trans-membrane Ca$^{2+}$ influx through the voltage-dependent channels of vascular smooth muscles. Ca$^{2+}$ channels are classified into several subtypes, including L-type, T-type, N-type, P/Q-type, and R-type Ca$^{2+}$ channels based on their electrophysiological properties. Azelnidipine is selective for L-type Ca$^{2+}$ channels. Azelnidipine has strong lipophilicity and affinity to membranes of vascular smooth muscle cells. A preclinical study showed that azelnidipine could not be removed from the blood vessels, even by washing. It is retained in the vascular wall after clearance from the blood and continues to elicit a hypotensive effect. Unlike other dihydropyridine CCBs, azelnidipine does not induce reflex tachycardia, probably since it elicits a gradual fall in BP. In addition, clinical studies have demonstrated that azelnidipine significantly reduced heart rate and proteinuria in hypertensive patients by suppressing sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, cerebro-protective, and anti-atherosclerotic effects, and improves insulin resistance.

Azelnidipine is used in the treatment of patients with hypertension, and the recommended dosage is 8–16 mg orally once daily. Oral administration of azelnidipine shows rapid, dose-dependent absorption. A series of research was conducted to investigate the pharmacokinetics of different dosages of azelnidipine in healthy Chinese volunteers (Table 1). After a single-dose oral administration of azelnidipine 8–16 mg in 106 healthy Chinese volunteers, peak plasma concentration ($C_{\text{max}}$) was 1.66–23.06 ng/mL, time to $C_{\text{max}}$ ($T_{\text{max}}$) was 2.6–4.0 hours, and the area under the plasma concentration versus (vs) time curve from time 0 hour to 96 hours (AUC$_{0–96}$) was 17.9–429 ng/mL·h. After administration of azelnidipine 8 mg/day for 5–8 days, mean $C_{\text{max}}$ and AUC$_{0–96}$ values were 2.63–6.62 ng/mL and 43.8–113.0 ng/mL·h; $T_{\text{max}}$ was 2.8–3.5 hours. Steady-state plasma concentration of azelnidipine was achieved after day two. After a single, oral dose of 8–16 mg in healthy Chinese subjects, azelnidipine had an elimination half-life ($t_{1/2}$) of 16.0–28.0 hours. At steady state, the $t_{1/2}$ was 25.2–32.5 hours after administration of azelnidipine 8 mg/day for 5–8 days. Following a single oral dose (4 mg) of $^{14}$C-labeled azelnidipine in humans, approximately 26% of total radioactivity was excreted in urine and 63% in feces over the 7 days post-dosing.
The pharmacokinetics of azelnidipine in patients with hypertension appeared to be similar to those of healthy volunteers. The influence of food on azelnidipine was studied on healthy Japanese volunteers. When a single oral dose (10 mg) of azelnidipine was administered after a meal, the mean Cmax was 2.6-fold higher when compared with the values obtained in the fasted state (18.5 vs 7.1 ng/mL, P<0.05), while mean AUC∞, Tmax, and t1/2 values not statistically different between after-meal and the fasted state. As a result, administration of azelnidipine after a meal is recommended by the manufacturer. Azelnidipine is extensively bound to human plasma proteins (90%-91%). Like most CCBs, azelnidipine undergoes extensive first-pass hepatic metabolism. Azelnidipine is metabolized by cytochrome P450 (CYP) 3A4 in the liver and has no active metabolite. It has the potential for interactions with other drugs or compounds that are substrates for this enzyme. A study was conducted about azelnidipine (8 mg) administered with itraconazole (50 mg), a drug with a strong CYP3A4 inhibitory activity. Cmax and AUC12h values of azelnidipine administered with itraconazole were 1.6 and 2.8 times higher than those with azelnidipine alone. In hypertensive patients with renal dysfunction, the steady-state plasma concentrations of azelnidipine were approximately 2-fold higher than those in healthy volunteers (P<0.01).

Efficacy studies of azelnidipine in Chinese patients

A number of clinical trials in Chinese patients have demonstrated that azelnidipine was effective for treatment of hypertension. Azelnidipine 8–16 mg administered once daily in the morning for 2 months significantly reduced BP over 24 hours in 60 young patients with essential hypertension (P<0.05), as demonstrated with 24-hour ABPM. The loading rate of BP was significantly lower after treatment with azelnidipine (P<0.01). Twenty-seven patients with mild-to-moderate hypertension (mean SBP/DBP 158.2/98.6 mmHg) received azelnidipine 16 mg/day for 12 weeks, and BP was significantly decreased (mean SBP/DBP 124.5/80.2 mmHg at the end of the study, P<0.05).

Furthermore, a series of clinical trials (most of them published in Chinese magazines) have demonstrated that azelnidipine produced a significant reduction in BP in Chinese patients with essential hypertension when compared with other effective anti-hypertensive drugs such as amlodipine, zofenopril, and nifedipine (extended release). In these studies, azelnidipine 8–16 mg/day was as effective as amlodipine 5–10 mg/day in reducing BP in primary hypertension. Amlodipine is a widely used calcium antagonist and is known to have a slow and persistent hypotensive effect. A double-blind control study was planned to divide 61 patients
| Year of publication | Drug                          | Number of patients | Dose (mg) | Period (weeks) | SBP (mmHg) Baseline | SBP (mmHg) After treatment | DBP (mmHg) Baseline | DBP (mmHg) After treatment | HR (bpm) Baseline | HR (bpm) After treatment |
|---------------------|-------------------------------|--------------------|-----------|----------------|---------------------|--------------------------|----------------------|--------------------------|----------------|--------------------------|
| 200927              | Azelnidipine                  | 27                 | 8–16      | 8              | 151.6±11.4          | 130.4±11.8**            | 100.3±5.1            | 85.0±7.0**               | --             | --                       |
|                     | Amlodipine                    | 28                 | 5–10      | 8              | 150.9±11.4          | 134.8±11.6**            | 101.0±4.7            | 89.1±6.8**               | --             | --                       |
| 201028              | Azelnidipine                  | 101                | 8–16      | 8              | 149.6±12.7          | 129.3±10.6**            | 98.4±3.2             | 85.5±7.0**               | 74.6±6.6       | 73.6±7.1                 |
|                     | Amlodipine                    | 101                | 5–10      | 8              | 149.3±13.2          | 134.3±11.7**            | 98.6±3.5             | 88.8±8.5**               | 74.3±8.3       | 73.2±7.1                 |
| 201129              | Azelnidipine                  | 40                 | 8–16      | 8              | 155.8±10.9          | 136.3±8.9*              | 101.0±4.3            | 89.9±6.1*                | --             | --                       |
|                     | Amlodipine                    | 21                 | 5–10      | 8              | 150.9±11.4          | 134.8±11.6*             | 100.3±3.7            | 85.5±8.2*                | --             | --                       |
| 201130              | Azelnidipine                  | 30                 | 8         | 12             | 149.3±21.1          | 132.4±12.7*             | 90.8±7.6             | 81.4±8.5*                | --             | --                       |
|                     | Amlodipine                    | 30                 | 5         | 12             | 148.9±19.7          | 134.1±11.9*             | 89.9±8.2             | 83.7±9.4*                | --             | --                       |
| 201131              | Azelnidipine                  | 62                 | 8         | 8              | 146.9±14.7          | 133.0±10.3*             | 96.7±10.5            | 88.9±8.4*                | --             | --                       |
|                     | Zofenopril                    | 62                 | 15        | 8              | 141.1±14.4          | 129.4±4.0*              | 93.0±10.0            | 86.4±9.9*                | --             | --                       |
| 201232              | Azelnidipine                  | 24                 | 8–16      | 8              | 155.9±16.1          | 126.6±12.7**            | 99.9±4.1             | 84.4±6.4**               | 73.3±9.2       | 63.8±6.4**               |
|                     | Amlodipine                    | 24                 | 5–10      | 8              | 155.8±13.0          | 127.1±8.8**             | 96.1±20.3            | 85.0±6.7**               | 72.3±8.6       | 67.5±7.7                 |
| 201233              | Azelnidipine                  | 35                 | 8         | 12             | 148.9±14.8          | 135.1±12.9**            | 102.1±20.2           | 87.8±10.5**              | --             | --                       |
|                     | Amlodipine                    | 36                 | 5         | 12             | 148.4±15.1          | 130.4±8.0**             | 96.8±12.0            | 84.0±8.2**               | --             | --                       |
| 201234              | Azelnidipine (extended release) | 43               | 8         | 8              | 152.2±14.6          | 127.5±10.4*             | 102.4±13.2           | 84.5±9.6*                | --             | --                       |
| 201335              | Azelnidipine (extended release) | 43               | 30        | 8              | 151.7±13.8          | 132.3±12.3*             | 100.3±11.6           | 89.7±10.2*               | --             | --                       |
| 201336              | Azelnidipine                  | 112                | 8–16      | 8              | 151.0±10.6          | 134.5±8.8**             | 97.3±4.9             | 83.7±8.1**               | 69.2±9.0       | 68.0±9.3                 |
|                     | Amlodipine                    | 109                | 5–10      | 8              | 152.0±9.8           | 135.4±3.1**             | 97.2±4.2             | 84.3±3.3**               | 69.3±8.3       | 69.2±4.8                 |
| 201337              | Azelnidipine                  | 31                 | 8         | 8              | 150.2±12.6          | 135.2±13.3**            | 97.7±7.9             | 86.1±10.8**              | --             | --                       |
|                     | Amlodipine                    | 31                 | 5         | 8              | 148.8±15.4          | 130.0±8.2**             | 95.7±8.1             | 83.4±8.8**               | --             | --                       |
| 201338              | Azelnidipine                  | 47                 | 8–16      | 20             | 152.2±8.9           | 133.7±8.1**             | 99.8±4.6             | 85.7±6.1**               | 73.2±2.8       | 74.3±3.2                 |
|                     | Amlodipine                    | 45                 | 5–10      | 20             | 153.2±9.5           | 132.9±9.0**             | 100.0±6.8            | 85.4±6.9**               | --             | --                       |
| 201439              | Azelnidipine                  | 35                 | 8         | 12             | 152.9±8.9           | 134.6±8.2**             | 99.5±4.2             | 85.6±4.4**               | 73.2±2.8       | 74.3±3.2                 |
|                     | Amlodipine                    | 36                 | 5         | 12             | 153.3±10.2          | 131.9±8.5**             | 100.0±6.0            | 84.9±5.6**               | 72.3±3.3       | 76.3±3.4                 |

Notes: *P<0.05, **P<0.01 compared with baseline.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute.
into two groups in which one received azelnidipine 8–16 mg or amlodipine 5–10 mg once daily for a period of 8 weeks. The SBP and DBP decreased significantly in both azelnidipine group and amlodipine group at 2 weeks, 4 weeks, 6 weeks, and 8 weeks after the treatment (P<0.05). The SBP and DBP between the azelnidipine group and the amlodipine group had no significant difference (P>0.05) at all time-points. In another multicenter, double-blind, randomized study in 231 patients with mild-to-moderate essential hypertension, after azelnidipine 8–16 mg or amlodipine 5–10 mg once daily for 8 weeks, the DBP of the patients at sitting position in both groups was lower than that at their baseline after 8 weeks of treatment (13.56±6.22 mmHg vs 12.94±5.50 mmHg). No significant differences were observed in the two groups. In studies assessed by ABPM, azelnidipine and amlodipine also showed a comparable 24-hour anti-hypertensive effect.

Although the anti-hypertensive effect of azelnidipine is similar to that of amlodipine, azelnidipine has its own advantages. In 76 Chinese patients with mild-to-moderate essential hypertension, the administration of azelnidipine 8–16 mg or amlodipine 5–10 mg once daily for 8 weeks significantly decreased SBP and DBP and the indexes of 24-hour ABPM when compared with those at baseline, and no significant differences were observed in the two groups. In this study, the number of patients with normal dipper circadian rhythm BP after treatment was higher in the azelnidipine group when compared with that in the amlodipine group. Meanwhile, azelnidipine has a comparable anti-hypertension effect to angiotensin-converting enzyme inhibitor. Azelnidipine 8–16 mg/day for 8 weeks controlled 24-hour BP (assessed by ABPM) to a similar extent as zofenopril 15–30 mg/day in a randomized and double-blind study in 130 patients with mild-to-moderate hypertension. There were no significant differences between these two groups with regard to the 24-hour BP control. The anti-hypertension effect of azelnidipine is also superior to second generation of dihydropyridine calcium antagonist. After the administration of azelnidipine (8 mg/day) or extended release nifedipine (30 mg/day) for 8 weeks, patients had a significant decrease in SBP and DBP (P<0.05). Meanwhile, the decline of SBP and DBP was significantly greater in the azelnidipine group than those in the extended release nifedipine group.

In addition to its antihypertensive effect, azelnidipine also features other cardiovascular protective effects. Previous studies have demonstrated that azelnidipine, unlike other dihydropyridine CCBs, did not increase, but probably decreased, heart rate in clinical settings. In a clinical trial, 27 hypertensive patients complicated with tachycardia were treated with azelnidipine 16 mg/day for 12 weeks. After the treatment, the heart rate declined from 106.7±18.7 beats per minute to 86.3±19.1 beats per minute (P<0.05). In a randomized controlled study among 48 patients with essential hypertension, administration of azelnidipine (8–16 mg/day once daily for 8 weeks) significantly decreased the heart rate. However, patients who received amlodipine (5–10 mg/day once daily for 8 weeks) did not have significantly decreased heart rate after the treatment. Azelnidipine can also prevent left ventricular remodeling and improve systolic and diastolic function. Ninety-two patients with mild-to-moderate essential hypertension were administered azelnidipine 8–16 mg or amlodipine 5–10 mg once daily for 5 months. The left ventricular diastolic function was improved in both groups after the treatment. Compared with that in the amlodipine group, the plasma level of brain natriuretic peptide (BNP) was significantly lower in the azelnidipine group (P<0.05).

Recent research has also demonstrated that azelnidipine has anti-atherosclerotic properties. Azelnidipine 8–16 mg once daily for 8 weeks significantly increased brachial-ankle pulse wave velocity in hypertensive patients. The brachial-ankle pulse wave velocity is an index of arterial stiffness and wave reflection. As a result, azelnidipine achieved significant improvements in arterial stiffness. As for other possible mechanisms, azelnidipine has been reported to elicit anti-atherosclerotic effects by anti-oxidative action. In a clinical trial, 24 patients with hypertension received azelnidipine 8–16 mg once daily for 8 weeks. After the treatment the plasma SOD (an antioxidant enzyme) was significantly increased (P<0.05) when compared with that at baseline. In this study, azelnidipine also significantly decreased plasma Hs-CRP (P<0.05) concentration and increased 6-keto-PGF1α level to inhibit the formation and development of atherosclerosis. In addition, some previous literature has reported that azelnidipine featured renno-protective, improving insulin resistance, and cerebro-protective effects. However there is no relevant research in Chinese.

Safety and tolerability in use of azelnidipine in Chinese patients

There are 14 clinical studies published in Chinese (Table 3). Patients were all diagnosed with essential hypertension and most had mild-to-moderate hypertension. Patients included women and men, the young and the older. Most of the follow-up periods were 8 weeks and the longest was 5 months. No severe adverse events were observed, and nobody dropped out of the therapy because of the adverse events. The most common adverse events were dizziness,
headache, and edema. CCB-related edema is a side effect that may reduce patient compliance or cause necessary switch to another drug. Among these clinical studies, four cases of CCB-related edema occurred in total after treatment with azelnidipine (one ankle edema, one leg edema, two sites without explanation). In studies about comparison of azelnidipine and amlodipine, two patients in the azelnidipine group complained about edema (one ankle edema, one leg edema). Meanwhile, two patients in the amlodipine group suffered from CCB-related edema (one leg edema, one palpebral edema). When compared with extended release nifedipine, two patients in the azelnidipine group and one patient in the extended release nifedipine group were reported to suffer from edema (both were “site unknown”). So, the difference of edema incidence rate between azelnidipine and other CCBs needs further investigation.

Table 3 Safety and tolerability in use of azelnidipine in Chinese patients with hypertension

| Year of publication | Number of patients | Degree of hypertension | Dose (mg) | Period | Adverse events and number |
|--------------------|--------------------|------------------------|-----------|--------|--------------------------|
| 2009†              | 27                 | Mild-to-moderate       | 8–16      | 8 weeks| Dizzy 1, palpitation 1, nausea 1, ankle edema 1, depression 1 |
| 2010†              | 24                 | Mild-to-moderate       | 16        | 12 weeks| Nausea, tiredness without number |
| 2011†              | 40                 | Mild-to-moderate       | 8         | 8 weeks| Headache 1, flush 2 |
| 2011†              | 30                 | Mild-to-moderate       | 8         | 12 weeks| None reported |
| 2011‡              | 27                 | Mild-to-moderate       | 8–16      | 8 weeks| None reported |
| 2011‡              | 62                 | Mild-to-moderate       | 8         | 8 weeks| Headache 4, flush 4 |
| 2012¶              | 48                 | Mild-to-moderate       | 8–16      | 8 weeks| Dizzy 2, headache 1, toothache 1, constipation 1, oppression in chest 1 |
| 2012¶              | 38                 | Mild-to-moderate       | 8         | 12 weeks| None reported |
| 2012¶              | 43                 | Mild-to-moderate       | 8         | 8 weeks| Dizzy 2, palpitation 3, nausea 4, edema 2, arthralgia 1 |
| 2013†              | 60                 | Mild-to-severe         | 8–16      | 2 months| Palpitation 2, flush 1 |
| 2013†              | 116                | Mild-to-moderate       | 8–16      | 8 weeks| Dizzy and headache 8, lower limbs edema 1 |
| 2013‡              | 32                 | Mild-to-moderate       | 8         | 8 weeks| None reported |
| 2013‡              | 47                 | Mild-to-moderate       | 8–16      | 5 months| None reported |
| 2014†              | 38                 | Mild-to-moderate       | 8         | 8 weeks| None reported |

**Patient-focused perspectives such as quality of life, patient satisfaction/acceptability, adherence, and uptake**

Hypertension is a common public health problem in the People’s Republic of China, and it is recognized as a lifestyle disease and greatly affects the quality of life of patients. With the change from the biomedical mode to the biological-social-psychological medical model, more and more studies have analyzed the relationship between hypertension and health-related quality of life (HRQL) in Chinese patients with hypertension. These researchers often used the SF-36 table to assess the HRQL and have demonstrated that individuals with hypertension have a lower score of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health than normotensive individuals. In perspective of hypertensive patients, the number of symptoms had a great negative impact on HRQL. The sources of symptoms might be the perceived symptoms related to hypertension or the side effects from antihypertensive medication. Previous studies also reported that increasing comorbidity, including cerebrovascular disorder, ischemic heart disease, and renal disorder, influenced subjects with hypertension in rating their HRQL. In addition, some socio-demographic factors including sex, age, educational level, region of residence, marital status, frequency of activities, family monthly income, occupations, attitudes toward hypertension, and knowledge of hypertension influenced HRQL of patients with hypertension. Successful control of BP can improve the quality of life of hypertensive
patients. Poor drug adherence is a major contributor to poor BP control. A number of studies evaluated the adherence levels of antihypertensive pharmacotherapies among the Chinese population. These studies have reported that almost 29.7%–53.8% of patients had good adherence to antihypertensive agents in Chinese mainland. The percentage of patients with good adherence (approximately 65.1%–86.8%) was higher in patients in Hong Kong, People’s Republic of China. Some researchers also have investigated the factors associated with antihypertensive drug adherence. Among Chinese patients with hypertension, low income, side effects of antihypertensive drugs, dosing frequency, complex medication regimens, bad behavioral factors, lack of knowledge of hypertension and the treatment, employment status, and a self-perceived health status of “poor” were recognized to contribute to antihypertensive drug discontinuation. In addition, poor doctor–patient relationship and lack of social support were also associated with poor adherence to antihypertensive agents. Users of β-receptor blockers were significantly more likely to have their drugs discontinued than users of CCB in both male and female patients. However, patients of an older age, female sex, and longer duration of antihypertensive agents used (over 10 years) were reported to have better adherence. Previous literature has also proposed methods to improve medication adherence, such as reinforcement of HBPM, formulating a proper treatment plan, strengthening patients’ individualized health education, sending reminders about appointments and continued compliance to medications, making good use of the social support system, organizing health care to provide easy access to health professionals, and building a good doctor–patient relationship. In this way, more patients with hypertension can achieve successful BP control and good quality of life.

**Conclusion (place in therapy)**

In this review, we addressed the management issues in the treatment of hypertension in Chinese patients and especially emphasized the DHP-CCB azelnidipine, including the pharmacology, pharmacokinetics, and a series of clinical studies of azelnidipine in a Chinese population. From the current data, azelnidipine has shown to be as effective in lowering high BP and as safe alternative antihypertensive drugs. Especially, this drug could lower tachycardia in patients. During clinical practice we should focus on national or regional people characteristics and evidence-based medical research in a Chinese population, so as to better arrange individualized treatment in patients with hypertension.

**Disclosure**

The authors have no conflicts of interest to disclose.

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