Cost-effectiveness of nitrendipine and hydrochlorothiazide or metoprolol to treat hypertension in rural community health centers in China

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**Objectives:** The objective of this article is to compare blood pressure (BP)-lowering effects of nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol, and estimate the economic effect of these therapies on hypertension.

**Methods:** Outpatients (N = 793) 18–70 years of age with stage 2 or severe hypertension (SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg) were recruited from four randomly selected rural community health centers in Beijing and Jilin. After drug wash out, they were randomly divided into nitrendipine and hydrochlorothiazide group or nitrendipine and metoprolol group. The costs of drug treatment for hypertension were calculated and general estimation, whereas effectiveness was measured as a reduction in SBP and DBP at the end of a 24-week study period.

**Results:** Overall, 623 patients were eligible for the study and after a 24-week follow-up, SBP and DBP were 131.2/82.2 mmHg for the nitrendipine and hydrochlorothiazide group and 131.4/82.9 mmHg for the nitrendipine and metoprolol group and these were not significantly different (P = 0.7974 SBP and P = 0.1166 DBP). Comparing with nitrendipine and metoprolol, the cost of nitrendipine and hydrochlorothiazide was less, and its effectiveness was similar. The cost/effect ratio (US$/mmHg) was 1.4 for SBP and 2.8 for DBP for the nitrendipine and hydrochlorothiazide group, and 1.9 and 3.8 for the nitrendipine and metoprolol group’s SBP and DBP values, respectively. The incremental cost per patient for achieving target BP was 5.1. Adverse events were mild or moderate and there were no differences between treatment groups.

**Conclusion:** Treating hypertension with nitrendipine and hydrochlorothiazide was cost-effective than nitrendipine and metoprolol, and these data will allow more reasonable and efficient allocation of limited resources in low-income countries.

**Keywords:** β-blockers, calcium channel blocker, cost-effectiveness, diuretics, hypertension, treatment

**Abbreviations:** BP, blood pressure; CCBs, calcium channel blockers; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio

**INTRODUCTION**

Hypertension, a major risk factor for cardiovascular disease is a global public health issue [1,2]. More than 50% of cardiovascular disease is associated with elevated blood pressure (BP) [3], which is becoming one of the most costly health conditions [2], a problem that will only grow to the rising prevalence of obesity, sedentary lifestyles, and an ageing society [4,5].

Reducing BP significantly reduces the risk of major clinical cardiovascular outcomes (fatal and nonfatal stroke, myocardial infarction, and heart failure) and this has been shown in multiple randomized clinical trials [6]. In addition, these trials confirmed that more hypertensive patients require at least two drugs to reduce BP to below 140/90 mmHg [7]. Rational drug combinations at appropriate dose are helpful to improve tolerability and compliance, which are essential for hypertensive control [8]. For many patients in China, low compliance is associated with drug cost.

Synergistic antihypertensive effects of calcium channel blockers (CCBs) and thiazide diuretics or β-blockers and thiazide diuretics have been confirmed [9]. In China, some
CCBs and β-blockers as well as thiazide diuretics are low cost but whether these drugs are efficacious in this population is uncertain. To optimize limited healthcare resources in China or other developing countries, we assessed the pharmacoeconomics of nitrendipine and hydrochlorothiazide or nitrendipine with metoprolol and we measured reductions in hypertension in rural Chinese communities. These data will inform future drug-based decisions for areas with limited resources.

MATERIALS AND METHODS

Study design

This is a randomized, open-label, prospective clinical trial. First, one county was selected from the rural area of Beijing, as well as Jilin. In Beijing, Fangshan County, which has 14 community health centers, was selected. In Jilin, Jingyu County, which has eight community health centers, was selected. Then, two centers were randomly selected from each county. Patients with primary hypertension, BP at least 160/100 mmHg, and aged 18 to 70-years old were recruited from each center. For the first 1–2 weeks of the study, antihypertensive medicines were washed out after drug discontinuation and eligible patients were randomized to receive nitrendipine with hydrochlorothiazide or nitrendipine with metoprolol. If BP control was not achieved (SBP/DBP <140/90 mmHg), treatment was modified as depicted in Fig. 1. During the 24-week follow-up period, study participants made six visits at 2, 4, 6, 8, 16, and 24 weeks after the study commencement. The drug dosage adjustments in the study were described in supplementary Table 1, http://links.lww.com/HJH/A709.

Sample size was estimated using noninferiority evaluation methods. We assume that noninferiority cutoff value was 2mmHg, losing ratio was 10–15%, 400 cases in each group were needed to detect a 10 ± 8mmHg average difference of DBP (at 2P = 0.05) at least 90% power. Finally, 793 participants were recruited from each center, 623 participants completed the follow-up.

Data collection and measurement

Demographic and clinical characteristics and anthropometric measurements were collected with questionnaires and standardized measurements. Then, a standardized protocol was used for BP measurements and patients avoided smoking or using caffeine at least 30 min before BP data collection. Patients were assessed when remaining in a seated position for at least 5 min prior to BP measurement. Final recorded BP data were determined from an average of three BP readings and all study protocols were approved by the Ethics Committee of Fuwai Hospital.

Cost estimation

Traditionally, economic burden of disease is estimated in terms of direct, indirect, and intangible costs [10]. Direct cost was divided into direct medical and direct nonmedical costs. Direct medical costs were healthcare expenditures for hospitalization fees, outpatient visits, and medications. Costs associated with outpatient visits were estimated by multiplying the number of outpatient visits related to hypertension by outpatient costs. Medication costs were estimated according to the maximum retail price designated by the China’s national development and reform commission. Direct nonmedical costs included transportation for visiting health providers for hypertension evaluation. Indirect costs include resources forgone to participate in an intervention, typically measured as lost wages or lost leisure time. There were no hospitalization or hypertension-related events during the follow-up period. Intangible costs, such as the pain, grief, or suffering associated with an intervention, are difficult to quantify. Therefore, indirect costs and intangible costs were not included in the analysis. All costs presented in US dollars were calculated using the average exchange rate at the time of data collection (2013; $1 = 6.29 RMB).

Definitions

Hypertensive patients were defined as those with a mean SBP of at least 140 mmHg, a mean DBP measurement of at least 90 mmHg, and/or self-reported current use of...

FIGURE 1  Study design for drug titration. A1: nitrendipine 10 mg, q.d.; hydrochlorothiazide 12.5 mg, q.d. A2: nitrendipine 10 mg, b.i.d.; hydrochlorothiazide 12.5 mg, q.d. A3: nitrendipine 10 mg, b.i.d.; hydrochlorothiazide 12.5 mg, b.i.d. A4: captopril, 12.5 mg, b.i.d. A5: captopril, 25 mg, b.i.d. B1: nitrendipine 10 mg, q.d.; metoprolol 12.5 mg, b.i.d. B2: nitrendipine 10 mg, b.i.d.; metoprolol 12.5 mg, b.i.d. B3: nitrendipine 10 mg, b.i.d.; metoprolol 25 mg, b.i.d. B4: captopril, 12.5 mg, b.i.d. B5: captopril, 25 mg, b.i.d. If blood pressure control was still not achieved after 16 weeks for both groups, another antihypertensive drug was added. b.i.d., twice daily; q.d., daily.
TABLE 1. Baseline characteristics

| Characteristic              | NH (n = 318)   | NM (n = 305) | P value |
|----------------------------|----------------|--------------|---------|
| Age (years)                | 56.1 ± 8.4     | 56.4 ± 9.0   | 0.6741  |
| Women (%)                  | 205 (64.5)     | 175 (57.4)   | 0.0698  |
| BMI (kg/m²)                | 26.2 ± 3.6     | 26.1 ± 3.7   | 0.8049  |
| Heart rate (beats/min)     | 75 ± 7.8       | 75.3 ± 7.7   | 0.6112  |
| Smoking (%)                | 69 (21.7)      | 67 (21.9)    | 0.9352  |
| Drinking (%)               | 57 (17.9)      | 49 (16.1)    | 0.5371  |
| Hypercholesterolemia (%)   | 24 (7.6)       | 19 (6.2)     | 0.5166  |
| Diabetes (%)               | 21 (6.6)       | 20 (6.6)     | 0.9814  |
| SBP (mmHg)                 | 165.3 ± 12.1   | 163.9 ± 12.0 | 0.1268  |
| DBP (mmHg)                 | 99.1 ± 9.0     | 99.4 ± 8.5   | 0.7591  |

NH, nitrendipine + hydrochlorothiazide; NM, nitrendipine + metoprolol.

FIGURE 2 (a) BPs at baseline and after treatment. (b) BPs at baseline and after treatment by sex. (c) BPs at baseline and after treatment by age group. BP, blood pressure; NH, nitrendipine + hydrochlorothiazide; NM, nitrendipine + metoprolol.
antihypertensive medications. Diabetes was defined as fasting plasma glucose at least 7.0 mmol/l (126 mg/dl) or a current treatment of insulin or oral hypoglycemic agents. Study participants who smoked one cigarette per day for at least 1 year were classified as smokers. Alcohol consumption was positive if an individual consumed at least one alcoholic beverage per week in the past year. Hypertensive control was calculated as the number of treated patients who had SBP less than 140 mmHg and DBP less than 90 mmHg and these data were divided by the total number of hypertension individuals studied.

Statistical analysis
Continuous variables are descriptively expressed as the means ± SDs and categorical variables are expressed as percentages or frequencies. Comparisons of characteristics were performed using a Student’s t-test or a χ² test. An intent-to-treat analysis was used for comparing treatment groups. The treatment’s effectiveness was calculated as follows:

Effectiveness (E) = Final BP – Baseline BP

The cost-effectiveness ratio (CER) was calculated as the ratio of the cost divided by effectiveness in nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol treatment groups; the incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the cost difference to the difference in effectiveness between nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol treatment groups, which represents an additional cost and effectiveness gained when nitrendipine and metoprolol (NM) is compared with nitrendipine and hydrochlorothiazide (NH):

\[
\text{ICER} = \frac{\Delta C}{\Delta E}
\]

\[
= \frac{(\text{NM cost} - \text{NH cost})}{(\text{NM effectiveness} - \text{NH effectiveness})}
\]

The cost-effectiveness of nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol for treating hypertension was studied as follows: the average and incremental cost per mmHg reduction in BP after 24 weeks of treatment; and the average and incremental cost per patient achieving target BP (BP < 140/90 mmHg) after 24 weeks. All statistically significant decisions confirmed with two-tailed P values. All analyses were conducted with SAS software, version 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS
Table 1 shows the demographic and clinical characteristics of study participants and both groups were well balanced, although nearly to significance for sex \((P = 0.0698)\).

After a 24-week follow-up, SBP and DBP were 131.2/82.2 mmHg for the nitrendipine and hydrochlorothiazide group and 131.4/82.9 mmHg for the nitrendipine and metoprolol group were not different (Fig. 2a); neither were that in stratum by sex groups (131.5/81.8 mmHg vs. 130.5/82.4 mmHg for women; 130.6/83.1 mmHg vs. 130.1/83.7 mmHg for men).
132.5/83.6 mmHg for men; Fig. 2b) and by age groups (131.1/82.1 mmHg vs. 131.0/82.9 mmHg for the ≤ 65-year-old group; 131.9/85.5 mmHg vs. 133.1/83.1 mmHg for the > 65-year-old group; Fig. 2c). And there was no difference in the percentage of patients with controlled BP between the two treatment regimens at the end of the study (80.8% vs. 82.3%, \( P = 0.360 \); Fig. 3a), the results were same when stratified by sex groups (84.2% vs. 88.3% for women \( P = 0.257 \); 77.5% vs. 79.7% for men \( P = 0.678 \)), and by age groups (82.9% vs. 85.8% for the ≤ 65-year-old group \( P = 0.360 \); 74.4% vs. 78.9% for the > 65-year-old group \( P = 0.615 \); Fig. 3b).

In terms of SBP lowering, CER (US$/mmHg, the cost of reducing BP by 1 mmHg at the end of the study) was 1.4 for nitrendipine and hydrochlorothiazide and 1.9 for nitrendipine and metoprolol, ICERs reducing BP by 1 mmHg of –8.5; about DBP lowering, CER was 2.8 for nitrendipine and hydrochlorothiazide and 3.8 for nitrendipine and metoprolol, ICERs was –28.8 (Table 2). When stratified by sex or age group, nitrendipine and hydrochlorothiazide cost less than nitrendipine and metoprolol for BP lowering in all subgroups; whereas nitrendipine and hydrochlorothiazide are slightly more effective than nitrendipine and metoprolol for BP lowering in subgroups except women, but ICERs was 51 for SBP, 30.6 for DBP (Table 2).

The CER per patient for achieving target BP was 0.6 for the nitrendipine and hydrochlorothiazide group and 0.7 for the nitrendipine and metoprolol group, the ICERs per
patient for achieving target BP was 5.1 (Table 3). When stratified by sex and age group, ICERs were 3.9 in women, 5.8 in men, 5.0 in 65-year or less group, 2.7 in more than 65-year group, respectively (Table 3).

Adverse events during the study were mild or moderate and there were no differences between treatment groups but chief adverse events were dry mouth in the nitrendipine and hydrochlorothiazide group (Table 4).

DISCUSSION

We measured the efficacy and cost-effectiveness of nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol treatments in rural community health centers in China and noted that both treatments reduced BP and neither was significantly different. The nitrendipine and hydrochlorothiazide presented a cost-effective combination related to nitrendipine and metoprolol for treating individuals with stage 2 or severe hypertension, no matter for the whole study participants or for sex groups or age groups. Hyper-tension treatment has been studied for cost-effectiveness and nurse-administered, tailored behavioral interventions in the United States [11]; the national hypertension treatment program in Germany [12] and the elderly health examination program including hypertension screening in Taiwan [13] had been shown to be useful but to date the use of nitrendipine and hydrochlorothiazide and nitrendipine and metoprolol has not been compared for cost and efficacy.

CCBs are established as effective and well tolerated for treating Asians with hypertension and CCBs and thiazide diuretics or β-blockers are recommended by Joint National Committee (JNC 8) guidelines and the 2013 European Society of Hypertension and of European Society of Cardiology [14,15]. The Nordic Diltiazem study compared the effects of CCBs, diuretics, and β-blockers on cardiovascular morbidity and mortality related to hypertension and noted that diuretics and β-blockers significantly reduced SBP (3mmHg) compared with CCB treatment alone [16].

Diuretics and β-blockers, whether administered as monotherapy or as a combination in associations, are acceptable low-cost treatments for hypertensive individuals [17–19]. Also, price variations within drug classes may be exploited to find the least expensive option. For example the incremental cost for nitrendipine and metoprolol is US$5.1 and it was a well tolerated therapy.

### TABLE 2. Cost-effectiveness analysis and incremental cost-effectiveness ratios with regard to lowering blood pressure

|                       | SBP | DBP | C/E | ΔC/ΔE |
|-----------------------|-----|-----|-----|-------|
| **Women (n = 380)**   |     |     |     |       |
| NH                    | 47.2| 33.8| 16.3| 8.9   |
| NM                    | 62.5| 34.1| 16.8| 8.8   |
| **Men (n = 243)**     |     |     |     |       |
| NH                    | 49.5| 35.1| 17.9| 10.3  |
| NM                    | 62.2| 30.0| 16.0| 10.0  |
| **<65 years (n = 530)**|   |     |     |       |
| NH                    | 47.1| 34.1| 16.9| 9.5   |
| NM                    | 61.7| 33.1| 16.7| 9.2   |
| **>65 years (n = 93)**|   |     |     |       |
| NH                    | 53.9| 35.7| 17.0| 9.1   |
| NM                    | 66.1| 30.2| 15.2| 10.0  |
| **Total (n = 623)**   |     |     |     |       |
| NH                    | 48.0| 34.3| 16.9| 9.6   |
| NM                    | 63.4| 32.6| 16.4| 9.4   |

C, average cost per patient; E, effectiveness; ND, no data; NH, nitrendipine + hydrochlorothiazide; NM, nitrendipine + metoprolol.

### TABLE 3. Cost-effectiveness analysis and incremental cost-effectiveness ratios with regard to pertinent achieving target blood pressure

|                       | E (%) | C/E | ΔC/ΔE |
|-----------------------|-------|-----|-------|
| **Women (n = 380)**   |       |     |       |
| NH                    | 84.2  | 0.6 | ND    |
| NM                    | 88.3  | 0.7 | 3.9   |
| **Men (n = 243)**     |       |     |       |
| NH                    | 77.5  | 0.6 | ND    |
| NM                    | 79.7  | 0.8 | 5.8   |
| **<65 years (n = 530)**| |     |     |       |
| NH                    | 82.9  | 0.6 | ND    |
| NM                    | 85.8  | 0.7 | 5.0   |
| **>65 years (n = 93)**| |     |     |       |
| NH                    | 74.4  | 0.7 | ND    |
| NM                    | 78.9  | 0.8 | 2.7   |
| **Total (n = 623)**   |       |     |       |
| NH                    | 81.8  | 0.6 | ND    |
| NM                    | 84.6  | 0.7 | 5.1   |

C, average cost per patient; E, effectiveness; ND, no data; NH, nitrendipine + hydrochlorothiazide; NM, nitrendipine + metoprolol.

### TABLE 4. Number of patients showing side-effects

| Side-effect           | NH | NM | P value |
|-----------------------|----|----|---------|
| Dizziness             | 12 | 7  | 0.28    |
| Somnolence            | 8  | 4  | 0.27    |
| Headache              | 6  | 5  | 0.80    |
| Dry mouth             | 4  | 1  | 0.05    |
| Edema                 | 7  | 4  | 0.39    |
| Cough                 | 5  | 3  | 0.51    |
| Elevated creatinine   | 1  | 0  | 0.33    |
| Elevated cholesterol  | 2  | 3  | 0.63    |
| Waist pain            | 4  | 1  | 0.22    |
| Elevated triglycerides| 7  | 2  | 0.74    |
| Elevated glucose      | 11 | 8  | 0.53    |
| Sexual dysfunction    | 0  | 0  | 0.33    |
| Arthralgia            | 7  | 8  | 0.74    |
| Miscellaneous         | 17 | 16 | 0.13    |

NH, nitrendipine + hydrochlorothiazide; NM, nitrendipine + metoprolol.
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Some study limitations were a short follow-up period; 6 months may be insufficient for fully realizing beneficial and adverse effects of treatment regimens studied. Second, we only used BP as a health outcome, were unable to evaluate the effect of the antihypertensive agents on cardiovascular disease, stroke, or quality-adjusted life years. However, decrease in BP was found to be of major importance for the prevention of cardiovascular events [6]. Therefore, higher proportion of patients reaching target BP in our study may imply long-term mortality and morbidity advantages for hypertensive patients. Third, the current result was somewhat limited by small sample sizes. Finally, the findings may not be transferable to general practice, because the patients from selected centers could not represent the whole China population.

In conclusion, treatment of hypertension with nitrendipine and hydrochlorothiazide was cost-effective than using nitrendipine with metoprolol, and these data may be useful for future resource allocation for treating hypertension in rural communities.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D’Agostino RB, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA 2002; 287:1003–1010.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K,二人eH., et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2224–2260.
3. Wang W, Hu SS, Kong LZ, Gao RL, Zha ML, Wang WY, et al. Summary of report on cardiovascular diseases in China, 2012. Biomed Environ Sci 2014; 27:552–558.
4. Dong B, Ding Q. Aging in China: a challenge or an opportunity? J Am Med Dir Assoc 2009; 10:456–458.
5. Little MO. Hypertension: how does management change with aging? Med Clin North Am 2011; 95:525–537.
6. Chalmers J. The importance of drug combinations for effective control of hypertension. Clin Exp Hypertens 1999; 21:875–884.
7. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28:1462–1536.
8. Neutel JM. Low-dose antihypertensive combination therapy: its rational and role in cardiovascular risk management. Am J Hypertens 1999; 12:735–798.
9. Gradman AH, Basile JN, Carter BL, Bakris GL, Materson BJ, Black HR, et al. Combination therapy in hypertension. J Am Soc Hypertens 2010; 4:90–98.
10. Le C, Zhanikun S, Jun D, Keying Z. The economic burden of hypertension in rural south-west China. Trop Med Int Health 2012; 17:1541–1551.
11. Datta SK, Oddone EZ, Olsen MK, Orr M, McCant F, Gentry P, et al. Economic analysis of a tailored behavioral intervention to improve blood pressure control for primary care patients. Am Heart J 2010; 160:257–269.
12. Gandjour A, Stock S. A national hypertension treatment program in Germany and its estimated impact on costs, life expectancy, and cost-effectiveness. Health Policy 2007; 85:257–267.
13. Deng BH, Liu HW, Pan PC, Mao LW, Chiu HC. Cost-effectiveness of elderly health examination program: the example of hypertension screening. Kaohsiung J Med Sci 2007; 23:17–24.
14. 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; 311:507–520.
15. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34:2159–2219.
16. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000; 356:559–565.
17. Hilleman DE, Mohiuddin SM, Lucas BD Jr, Stading JA, Stoutich AM, Rychon K. Cost-minimization analysis of initial antihypertensive therapy in patients with mild-to-moderate essential diastolic hypertension. Clin Ther 1994; 16:88–102.
18. Dias da Costa JS, Fuchs SC, Olinto MT, Gigante DP, Menezes AM, Macedo S, et al. Cost-effectiveness of hypertension treatment: a population-based study. Sao Paulo Med J 2002; 120:100–104.
19. Ambrosioni E. Pharmacoeconomic challenges in disease management of hypertension. J Hypertens Suppl 2001; 19:535–540.