Original Article

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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)-lowing 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 $\geq$ 160 mmHg and/or DBP $\geq$ 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

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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 2 mmHg, losing ratio was 10–15%, 400 cases in each group were needed to detect a 10 ± 8 mmHg 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

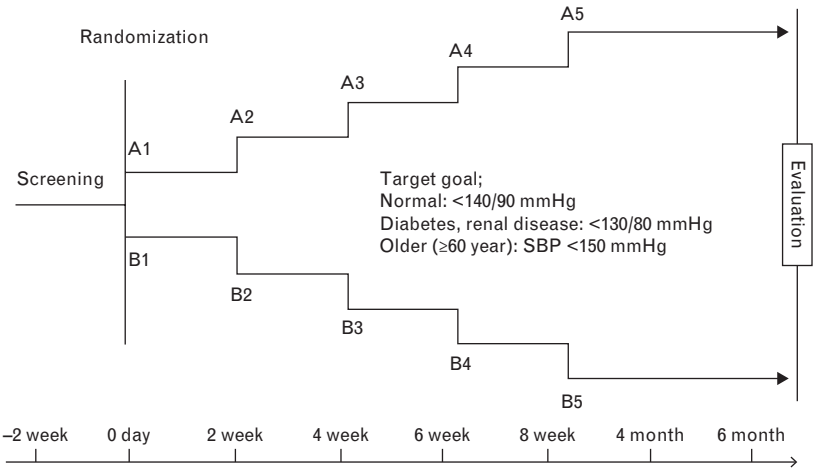

FIGURE 1 Study design for drug titration. A1: nitrendipine 10 mg, q.d.; hydrochlorothiazide 12.5 mg, q.d. A2: nitrendipine 10 mg, b.i.d.; hydrochlorothiazide 12.5 mg, q.d. A3: nitrendipine 10 mg, b.i.d.; hydrochlorothiazide 12.5 mg, b.i.d. A4: captopril, 12.5 mg, b.i.d. A5: captopril, 25 mg, b.i.d. B1: 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/m^2)	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.

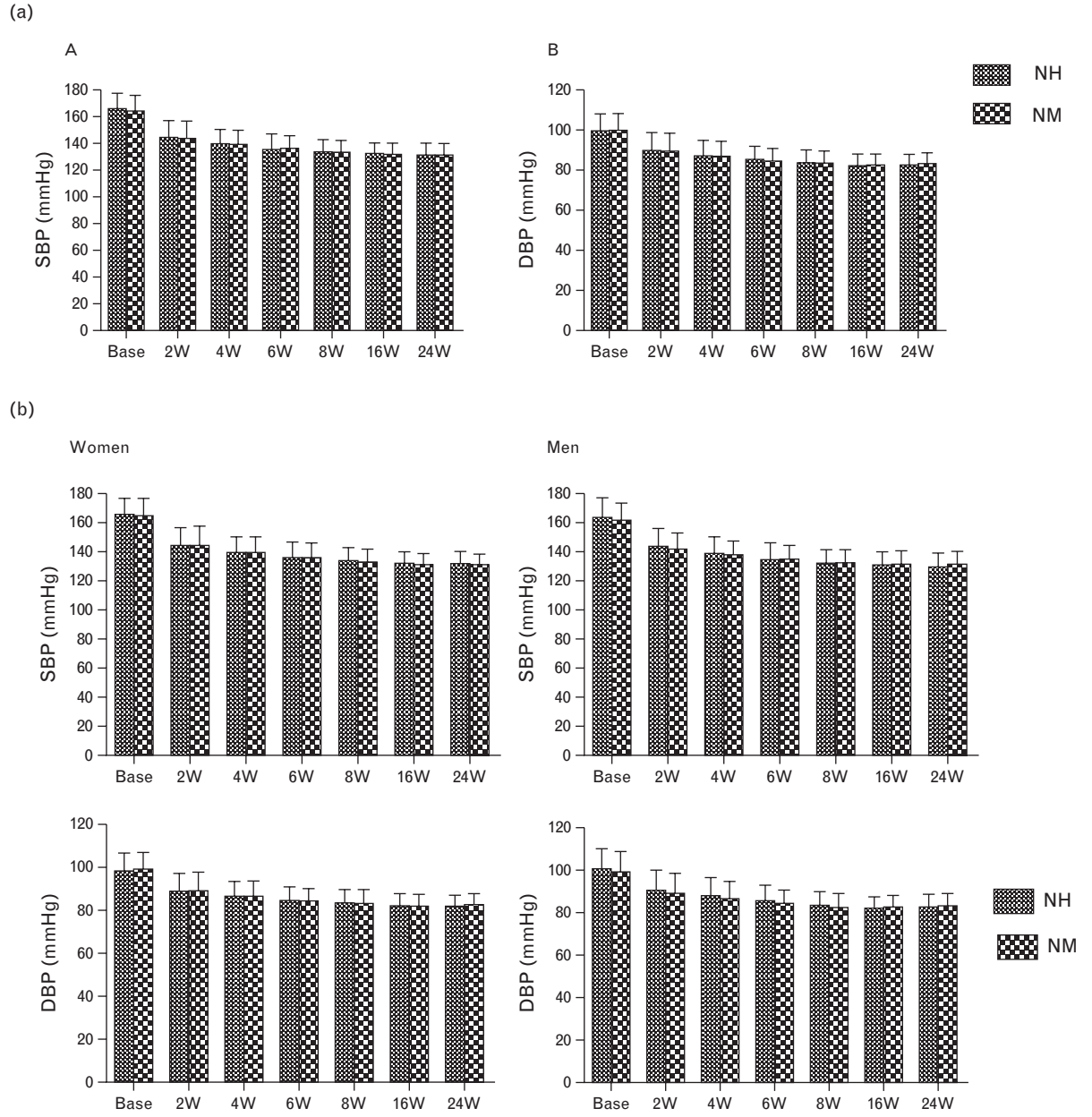

FIGURE 2 (a) BPs at baseline and after treatment. (b) BPs at baseline and after treatment by sex. (c) BPs at baseline and after treatment by age group. BP, blood pressure; NH, nitrendipine+hydrochlorothiazide; NM, nitrendipine+metoprolol.

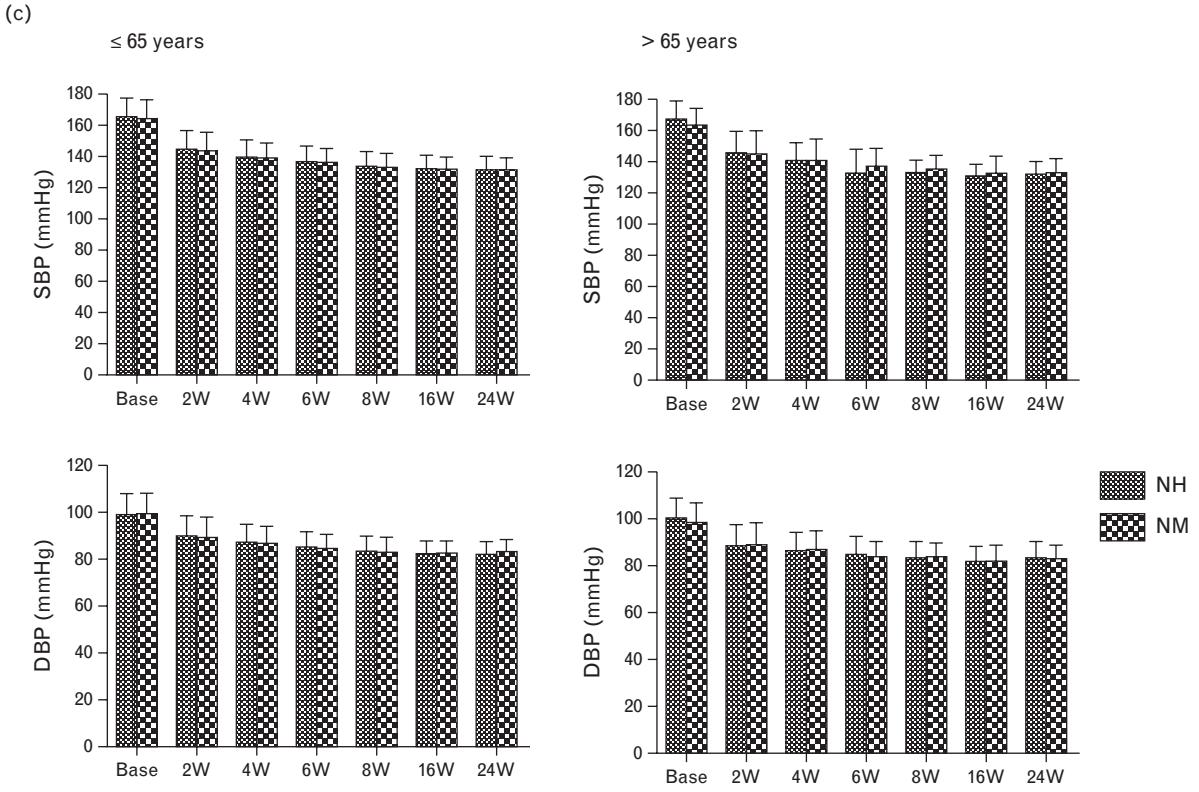

FIGURE 2 (*Continued*).

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 χ^2 test. An intent-to-treat analysis was used for comparing treatment groups. The treatment's effectiveness was calculated as follows:

$$\text{Effectiveness (E)} = \text{Final BP} - \text{Baseline BP}$$

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):

$$\begin{aligned}\text{ICER} &= \Delta C/\Delta E \\ &= (\text{NM cost} - \text{NH cost})/(\text{NM effectiveness} \\ &\quad - \text{NH effectiveness})\end{aligned}$$

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.

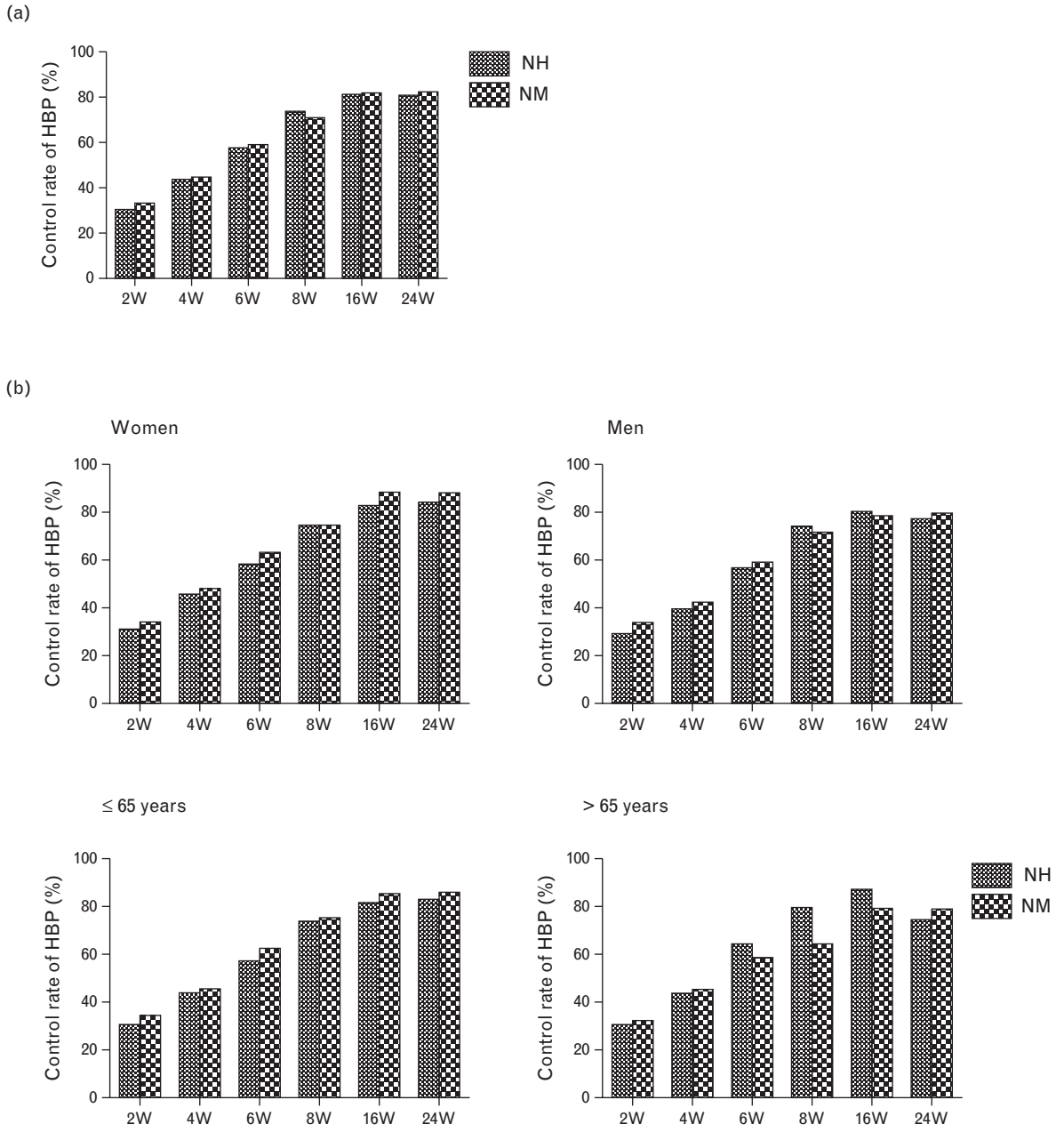

FIGURE 3 (a) Control of hypertension between groups. (b) Control of hypertension between groups by sex and age group. HBP, high blood pressure; NH, nitrendipine+hydrochlorothiazide; NM, nitrendipine+metoprolol.

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; 131.9/83.5 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

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

	C (US$)	E		C/E		ΔC/ΔE	
		SBP	DBP	SBP	DBP	SBP	DBP
Women ($n=380$)							
NH	47.2	33.8 ± 14.9	16.3 ± 8.9	1.4	2.9	ND	ND
NM	62.5	34.1 ± 14.7	16.8 ± 8.8	1.8	3.7	51.0	30.6
Men ($n=243$)							
NH	49.5	35.1 ± 17.5	17.9 ± 10.3	1.4	2.8	ND	ND
NM	62.2	30.6 ± 16.9	16.0 ± 10.0	2.0	3.9	−2.8	−6.7
≤65 years ($n=530$)							
NH	47.1	34.1 ± 16.0	16.9 ± 9.5	1.4	2.8	ND	ND
NM	61.7	33.1 ± 15.9	16.7 ± 9.2	1.9	3.7	−14.6	−73
>65 years ($n=93$)							
NH	53.9	35.7 ± 15.1	17.0 ± 9.1	1.5	3.2	ND	ND
NM	66.1	30.2 ± 15.2	15.2 ± 10.0	2.2	4.3	−2.2	−6.7
Total ($n=623$)							
NH	48.0	34.3 ± 15.9	16.9 ± 9.6	1.4	2.8	Null	Null
NM	63.4	32.6 ± 15.8	16.4 ± 9.4	1.9	3.8	−8.5	−28.8

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

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. Hypertension 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 (3 mmHg) 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 3. Cost-effectiveness analysis and incremental cost-effectiveness ratios with regard to pertinent achieving target blood pressure

	C (US$)	E (%)	C/E	ΔC/ΔE
Women ($n=380$)				
NH	47.2	84.2	0.6	ND
NM	62.5	88.3	0.7	3.9
Men ($n=243$)				
NH	49.5	77.5	0.6	ND
NM	62.2	79.7	0.8	5.8
≤65 years ($n=530$)				
NH	47.1	82.9	0.6	ND
NM	61.7	85.8	0.7	5.0
>65 years ($n=93$)				
NH	53.9	74.4	0.7	ND
NM	66.1	78.9	0.8	2.7
Total ($n=623$)				
NH	48.0	81.8	0.6	ND
NM	62.4	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 (4%)	7 (2.4%)	0.28
Somnolence	8 (2.7%)	4 (1.4%)	0.27
Headache	6 (2%)	5 (1.7%)	0.80
Dry mouth	4 (1.3%)	0 (0%)	0.05
Edema	7 (2.3%)	4 (1.4%)	0.39
Cough	5 (1.7%)	3 (1%)	0.51
Elevated creatinine	1 (0.3%)	0 (0%)	0.33
Elevated cholesterol	2 (0.7%)	3 (1%)	0.63
Waist pain	4 (1.3%)	8 (2.7%)	0.22
Elevated triglycerides	7 (2.3%)	8 (2.7%)	0.74
Elevated glucose	11 (3.7%)	8 (2.7%)	0.53
Sexual dysfunction	1 (0.3%)	0 (0%)	0.33
Arthralgia	7 (2.3%)	8 (2.7%)	0.74
Miscellaneous	17 (5.5%)	16 (5.5%)	0.13

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

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.

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Reviewers' Summary Evaluations

Referee 1

STRENGTHS The study provides new data on cost-effectiveness of drug treatment of hypertension in rural communities in China. In clinical practice the combination nitrendipine–hydrochlorothiazide resulted more effective and less expensive than nitrendipine–metoprolol and thus should be preferred as antihypertensive drug treatment. WEAKNESSES There is no classification of stage of hypertension. No information is provided on the percentage of hypertensive patients lost at follow-up

Referee 2

The study explored the cost effectiveness of the combination of a thiazide-like diuretic or of atenolol with nitrendipine and the results were favorable for the diuretic combination. According to the study data, use of the diuretic was equally effective and less expensive. Despite that, more than 15% of the patients treated with the two drugs remained undertreated and will need more than two drugs to normalize their BP.