Availability, cost, and prescription patterns of antihypertensive medications in primary health care in China: a nationwide cross-sectional survey

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Summary

Background Around 200 million adults in China have hypertension, but few are treated or achieve adequate control of their blood pressure. Available and affordable medications are important for successfully controlling hypertension, but little is known about current patterns of access to, and use of, antihypertensive medications in Chinese primary health care.

Methods We used data from a nationwide cross-sectional survey (the China Patient-Centered Evaluative Assessment of Cardiac Events Million Persons Project primary health care survey), which was undertaken between November, 2016 and May, 2017, to assess the availability, cost, and prescription patterns of 62 antihypertensive medications at primary health-care sites across 31 Chinese provinces. We surveyed 203 community health centres, 401 community health stations, 284 township health centres, and 2474 village clinics to assess variation in availability, cost, and prescription by economic region and type of site. We also assessed the use of high-value medications, defined as guideline-recommended and low-cost. We also examined the association of medication cost with availability and prescription patterns.

Findings Our study sample included 3362 primary health-care sites and around 1 million people (613 638 people at 2758 rural sites and 478 393 people at 604 urban sites). Of the 3362 sites, 8·1% (95% CI 7·2–9·1) stocked no antihypertensive medications and 33·8% (32·2–35·4) stocked all four classes that were routinely used. Village clinics and sites in the western region of China had the lowest availability. Only 32·7% (32·2–33·3) of all sites stocked high-value medications, and few high-value medications were prescribed (11·2% [10·9–11·6] of all prescription records). High-cost medications were more likely to be prescribed than low-cost alternatives.

Interpretation China has marked deficiencies in the availability, cost, and prescription of antihypertensive medications. High-value medications are not preferentially used. Future efforts to reduce the burden of hypertension, particularly through the work of primary health-care providers, will need to improve access to, and use of, antihypertensive medications, paying particular attention to those with high value.

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Introduction

An estimated 200 million adults in China have hypertension but fewer than 15% are treated.[1–4] Moreover, among those who are treated, about two-thirds do not achieve adequate control of their blood pressure.[5–8] Inadequate management of patients with hypertension might have substantial health and economical consequences; the sequelae of hypertension, including stroke and heart disease, are the leading causes of morbidity and mortality in China,[9,10] and are associated with substantial expense to patients and the health system.

The successful management of hypertension in China requires, in addition to lifestyle and behavioural modifications, affordable and widely available antihypertensive medications prescribed appropriately in primary health-care settings, a main point of contact with the health system in China. Findings from studies have suggested low availability and high costs as major barriers to optimum use and adherence to essential antihypertensive medications, especially in low-income rural areas in China.[3,11]

The Chinese health reform in 2009 strengthened the role of primary health care that serves as gatekeeper to the health-care system.[12] The reform also introduced the National Essential Medicine Program that was designed to provide affordable and equitable basic health care for all by 2020. Pharmaceutical policy has also evolved quickly, such as allowances for primary health-care sites to procure non-essential medicines in 2014 and abolishment of the government price ceiling in 2015 (appendix). Although availability of medications increased after the National Essential Medicine Policy was launched,[13–15] little is known about current patterns of access to antihypertensive medications across Chinese primary health-care settings, where higher financial burdens and few medication choices might

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See Online for appendix

Research in context

Evidence before this study

To assess treatment and control of hypertension in China, we searched PubMed for English-language published articles and the China National Knowledge Infrastructure for Chinese-language articles, published before May, 2016, using the terms "primary health care", "pharmaceutical policy", "essential medication", "essential medicine", "hypertensive medication", OR "hypertension". We also reviewed references from the identified articles and other relevant articles and reports. Awareness, treatment, and control of hypertension were found to be low. The Chinese National Essential Medicine Program, a zero mark-up policy for essential medications, was implemented by all primary health-care sites in 2009 to meet residents' medication needs and reduce their out-of-pocket costs. However, we noted conflicting results for availability and cost, and few studies reported prescription patterns of antihypertensive medications. Previous studies were limited to specific regions, populations, and data sources.

Added value of this study

We used data from a national primary health-care study and a screening study of high risks for cardiovascular disease in China to depict the current status of availability, cost, and prescription patterns of antihypertensive medications in primary health-care settings in China. We collected the data directly from primary health-care sites, rather than analysing secondary data from other reports. We noted marked deficiencies in availability, cost, and prescription of hypertensive medications, and a few health-care pharmacies did not stock any antihypertensive medications. Village clinics and sites in the western region of China had the lowest availability. High-cost medications were more likely to be prescribed than low-cost medications, and high-value medications, those that are guideline-recommended and low-cost, were not preferentially prescribed.

Implications of all the available evidence

Our findings suggest that interventions to improve hypertension treatment and control in China will need to ensure that low-cost antihypertensive medications are adequately available in primary health-care settings. Implementation of the essential medicines policy at the local level is currently inadequate. Use of high-value medications might help to reduce patients' cost burden of hypertension treatment.

result in lower treatment and control rates. This information is essential for developing targets for interventions that are designed to improve national hypertension treatment and control.

Accordingly, to address the need for information about the availability, cost, and prescription of antihypertensive medications in primary health-care settings across China, we analysed data from a national, government-funded study of the primary health-care system and a large national cardiovascular screening project.[16] Our study focused on all four types of primary health-care sites in China—community health centres and community health stations in urban areas, and township health centres and village clinics in rural areas—and also examined how the costs of antihypertensive medications were associated with the availability and prescription of antihypertensive medications, with a particular focus on lower-cost, guideline-recommended treatments.

Methods

Data source and study sample

We derived data on the availability, cost, and prescription of antihypertensive medications from the nationwide China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project (MPP) primary health-care survey, undertaken from November, 2016 through May, 2017. The design of this survey has been described previously.[17] Briefly, we established a nationwide epidemiological collaborative network of the China PEACE MPP, which consisted of 141 county or district-level regions from all 31 provinces in mainland China.[16] The MPP enrolled the eligible study sites according to the number of residents of the catchment area, population stability, local economical conditions, and geographical location. The PHC services are provided by community health centres and community health stations (one level below) in urban areas, and township health centres and village clinics (one level below) in rural areas (appendix). We surveyed 203 community health centres, 401 community health stations, 284 township health centres, and 2474 village clinics to quantify the care-delivery capacity and the quality of primary health care. The distribution of primary health care study sites sampled across rural and urban areas reflects the national ratio.[18]

Data on hypertension treatment and control were derived from the cardiovascular risk screening programme of the China PEACE MPP, which up to June 20, 2017, had enrolled 1·7 million residents, aged 35 to 75 years, who had lived in 141 selected county-level or district-level regions for at least 6 months in the past year. The interview data from China PEACE MPP included information about the history of hypertension diagnosis and treatment, collected by face-to-face administration of a questionnaire. In total, 1·09 million people with information in the MPP lived in the 435 townships or communities that are the focus of this study. We linked the characteristics of primary health-care sites with local population epidemiological data at the township or community level (ie, one level below county or district), China's 2015 National Census data,

and geographical location information from a Chinese web mapping service (AMAP).[19]

Data collection and definitions

We obtained, copied, and reviewed lists of medications in stock at the time of the survey from Nov 1, to Dec 31, 2016, from each participating primary health-care site. For each medication on the list, we obtained information about the generic name, brand name, dosage form, specification, manufacturer, and retail price per sale unit. We cleaned and checked the reported generic names against China Pharmacopoeia 2015,[20] achieving 95% accuracy.

For outpatient prescriptions (from April 1, 2015, to March 31, 2016), we collected information about each patient's age, sex, and diagnosis, which is routinely listed on the prescriptions, as well as the medication name, dosage, and administration. In primary health-care sites with an electronic prescription system, relevant information was directly imported into a digital database. For sites without an electronic prescription system, we included the first 100 outpatient prescriptions in each 10-day period for the 12 months in our analysis (3600 total prescriptions during the study period). We scanned copies and trained staff to manually abstract relevant information, with double-entry methods included as a quality check to ensure an accuracy standard of at least 98%.

In MPP, blood pressure was measured twice during the interview, using a unified electronic blood pressure monitor (Omron HEM-7430; Omron Corporation, Kyoto, Japan) with standardised procedures.[21] Treatment was defined as the proportion of patients in the China PEACE MPP population with hypertension who self-reported use of antihypertensive medications at the baseline interview. Control was defined as the proportion of these patients with a blood pressure of less than 140/90 mm Hg at the baseline interview. Treatment and control of hypertension were assessed by aggregating participant data at the township or community level.

We obtained information on the characteristics of each primary health-care site, including workforce and use of information technology systems, through a survey of site leaders and health-care professionals. We focused on 62 oral medications by generic names listed in the database of guidelines for hypertension management, regardless of whether they were recommended,[2,22,23] and the essential medicine lists.[24] We categorised each of these medicines as angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, diuretics, fixed-dose combination medications, traditional compound drugs, or centrally active drugs; each category was mutually exclusive (ie, a medicine in one category could not be categorised in another). We did not include alpha-blockers or alpha-beta blockers because of their scarcity in the primary care sector.

We ascertained the availability of each antihypertensive medication at any dose in the site pharmacy, calculated as the proportion of all participating sites with a specific antihypertensive medication or medication

	Rural	Urban	Total
Primary health-care site			
Number	..	..	3362
Township health centre	284 (8·4%)	..	..
Village clinic	2474 (73·6%)	..	..
Community health centre	..	203 (6·0%)	..
Community health station	..	401 (11·9%)	..
Eastern region	..	..	31·9% (30·3–33·5)
Township health centre	28·5% (23·3–34·2)	..	..
Village clinic	27·8% (26·0–29·6)	..	..
Community health centre	..	38·9% (32·2–46·0)	..
Community health station	..	56·4% (51·3–61·3)	..
Central region	..	..	35·6% (34·0–37·2)
Township health centre	31·0% (25·7–36·7)	..	..
Village clinic	39·9% (37·9–41·8)	..	..
Community health centre	..	29·1% (22·9–35·8)	..
Community health station	..	15·7% (12·3–19·6)	..
Western region	..	..	32·5% (30·9–34·1)
Township health centre	40·5% (34·7–46·5)	..	..
Village clinic	32·4% (30·5–34·3)	..	..
Community health centre	..	32·0% (25·7–38·9)	..
Community health station	..	27·9% (23·6–32·6)	..
Linked MPP population*			
Number	613 638	478 393	1 092 031
Age (years)	56·2 (9·8)	55·8 (9·8)	56·0 (9·8)
Women	59·6% (59·4–59·7)	60·9% (60·8–61·0)	60·1% (60·1–60·2)
Men	40·4% (40·3–40·6)	39·1% (39·0–39·2)	39·9% (39·8–39·9)
Ethnic Han	88·8% (88·7–88·9)	93·3% (93·2–93·3)	90·8% (90·7–90·8)
12 years of education or more	9·4% (9·3–9·5)	32·3% (32·2–32·5)	19·5% (19·4–19·5)
Current smoker	21·7% (21·6–21·8)	18·4% (18·3–18·5)	20·2% (20·2–20·3)
No insurance	0·2% (0·2–0·2)	1·1% (1·1–1·1)	0·6% (0·6–0·6)
Last-year income >¥50 000	8·6% (8·5–8·6)	18·3% (18·2–18·4)	12·8% (12·7–12·9)
Patients with hypertension	46·4% (46·2–46·5)	44·1% (43·9–44·2)	45·4% (45·3–45·5)
Awareness†	43·8% (43·6–44·0)	48·7% (48·5–48·9)	45·9% (45·8–46·0)
Treatment†	27·1% (27·0–27·3)	34·5% (34·3–34·7)	30·3% (30·1–30·4)
Control†	5·5% (5·4–5·6)	9·8% (9·7–9·9)	7·3% (7·3–7·4)

Data are n (%), % (95% CI), or mean (SD). MPP=Million Persons Project. ..=not applicable. *The population is linked at the township or community level. †Among all patients with hypertension. Awareness was defined as self-reported diagnosis of hypertension at the baseline interview.

Table 1: **Characteristics of primary health-care sites and Million Persons Project population included by rural and urban area**

class in stock. We calculated the annual median cost for each medication, using its median price across different primary health-care sites and the guideline-recommended dose. We defined high-value medications as those that were both recommended by the Chinese Guideline for Hypertension Management

	Essential medicines list*			Guidelines			Availability, % (95% CI), (n=3362)	Class availability, % (95% CI), (n=3362)	Annual cost per patient (RMB), median (IQR)	Prescription frequency, % (95% CI), (n=29 171)
	WHO	NEM	PSEM	Guideline in primary health care 2014	JNC 8 2014	Chinese guideline 2010				
ACE inhibitors	..	..	..	..	..	..	..	62·6% (61·0–64·3)	..	..
Captopril	..	Y	1	Y	Y	Y	44·0% (42·3–45·7)	..	16 (11–43)	2·5% (2·3–2·7)
Enalapril	Y	Y	1	Y	Y	Y	38·9% (37·3–40·6)	..	225 (160–435)	4·3% (4·1–4·5)
Benazepril	..	..	13	Y	..	Y	8·4% (7·5–9·4)	..	1066 (748–1144)	1·2% (1·1–1·3)
Ramipril	..	..	1	..	..	Y	0·4% (0·2–0·6)	..	1819 (1819–2021)	0
Perindopril	..	..	3	..	..	Y	1·0% (0·7–1·4)	..	1255 (1172–1261)	0·2% (0·2–0·3)
Fosinopril	..	..	7	Y	..	Y	3·6% (3·0–4·3)	..	1022 (723–1054)	0·7% (0·6–0·8)
Lisinopril	..	..	2	Y	Y	Y	3·3% (2·8–4·0)	..	659 (469–678)	0·1% (0·1–0·2)
Quinapril	..	..	1	..	..	..	<0·1% (<0·1–0·2)	..	1166 (1166–1166)	<0·1% (<0·1–0·1)
Imidapril	..	..	1	..	..	Y	0·3% (0·1–0·5)	..	1123 (1123–1123)	0
Cilazapril	..	..	0	..	..	Y	0	..	..	0
Angiotensin receptor blockers	..	..	..	..	..	..	..	34·4% (32·7–36·0)	..	..
Valsartan	..	Y	15	Y	Y	Y	21·4% (20·0–22·8)	..	663 (340–1028)	7·4% (7·1–7·7)
Losartan	..	..	7	Y	Y	Y	7·8% (6·9–8·7)	..	1306 (942–1883)	2·1% (1·9–2·3)
Irbesartan	..	..	13	Y	Y	Y	21·1% (19·7–22·5)	..	850 (610–1101)	6·7% (6·4–7·0)
Candesartan	..	..	1	..	Y	Y	4·2% (3·5–4·9)	..	589 (468–751)	1·0% (0·9–1·1)
Eprosartan	..	..	0	..	Y	..	0	..	..	0
Telmisartan	..	..	7	Y	..	Y	10·3% (9·3–11·4)	..	516 (298–801)	4·3% (4·0–4·5)
Olmesartan	..	..	0	..	..	Y	0·9% (0·6–1·2)	..	1833 (1761–2660)	0·2% (0·2–0·3)
ACE inhibitors or angiotensin receptor blockers	..	..	..	..	..	..	..	69·0% (67·4–70·6)	..	..
Beta-blockers	..	..	..	..	..	..	..	47·2% (45·5–48·9)	..	..
Bisoprolol	Y	Y	5	Y	..	Y	8·8% (7·9–9·8)	..	791 (549–1080)	0·9% (0·8–1·0)
Metoprolol	Y	..	8	Y	Y	Y	41·0% (39·4–42·7)	..	251 (171–281)	8·0% (7·7–8·4)
Metoprolol extended release	..	..	0	..	..	Y	3·6% (3·0–4·3)	..	438 (401–440)	0·2% (0·2–0·3)
Atenolol	Y	..	1	Y	Y	Y	5·1% (4·4–5·9)	..	7 (5–8)	0·2% (0·1–0·2)
Propranolol	..	..	2	..	..	Y	7·6% (6·7–8·5)	..	26 (16–86)	<0·1% (<0·1–0·1)
Betaxolol	..	..	0	..	..	Y	0	..	..	0
Calcium channel blockers	..	..	..	..	..	..	..	75·5% (74·0–76·9)	..	..
Amlodipine	Y	Y	23	Y	Y	Y	33·8% (32·2–35·4)	..	369 (206–565)	16·8% (16·3–17·2)
Nifedipine	..	Y	16	Y	..	Y	34·4% (32·8–36·0)	..	9 (5–19)	2·7% (2·5–2·8)
Nifedipine extended release	..	Y	0	Y	..	Y	41·2% (39·5–42·9)	..	413 (266–468)	7·4% (7·1–7·7)
Nifedipine controlled release	..	..	0	Y	..	Y	15·0% (13·8–16·2)	..	1012 (890–1526)	6·0% (5·7–6·3)
Felodipine extended release	..	..	15	Y	..	Y	19·2% (17·9–20·6)	..	425 (313–1049)	3·7% (3·5–3·9)
Levamlodipine	..	..	9	Y	..	Y	11·8% (10·7–12·9)	..	688 (437–904)	7·7% (7·4–8·0)
Nitrendipine	..	Y	1	Y	Y	Y	30·3% (28·7–31·9)	..	12 (7–44)	1·0% (0·9–1·1)
Verapamil	..	..	4	..	..	Y	1·4% (1·1–1·9)	..	302 (288–360)	0
Verapamil extended release	..	..	0	..	..	Y	<0·1% (<0·1–0·2)	..	460 (460–460)	0
Diltiazem	..	..	11	..	..	Y	1·9% (1·5–2·4)	..	507 (269–1117)	0
Diltiazem extended release	..	..	0	..	Y	..	0·7% (0·5–1·1)	..	583 (527–869)	0·1% (<0·1–0·1)
Lacidipine	..	..	7	Y	..	Y	4·0% (3·4–4·8)	..	228 (225–273)	0·3% (0·3–0·4)
Nicardipine	..	..	1	..	..	Y	0	..	..	0
Benidipine	..	..	0	..	..	Y	0·1% (<0·1–0·3)	..	999 (908–1610)	0
Lercanidipine	..	..	0	..	..	Y	0·3% (0·1–0·5)	..	1530 (1509–1530)	0

(Table 2 continues on next page)

	Essential medicines list*			Guidelines			Availability, % (95% CI), (n=3362)	Class availability, % (95% CI), (n=3362)	Annual cost per patient (RMB), median (IQR)	Prescription frequency, % (95% CI), (n=29 171)
	WHO	NEM	PSEM	Guideline in primary health care 2014	JNC 8 2014	Chinese guideline 2010				
(Continued from previous page)										
Diuretics	..	..	..	..	..	..	..	59·9% (58·2–61·5)	..	..
Indapamide	..	Y	1	Y	Y	Y	32·5% (31·0–34·2)	..	42 (18–99)	1·2% (1·1–1·3)
Indapamide extended release	..	..	0	..	..	Y	12·6% (11·5–13·8)	..	279 (197–389)	1·3% (1·2–1·4)
Hydrochlorothiazide	Y	..	1	Y	Y	Y	34·7% (33·1–36·3)	..	3 (1–5)	1·0% (0·9–1·1)
Bendroflumethiazide	..	..	0	..	Y	..	0	..	..	0
Chlortalidone	..	..	0	..	Y	..	0	..	..	0
Spironolactone	..	..	2	..	..	Y	22·3% (20·9–23·7)	..	41 (28–56)	0·5% (0·5–0·6)
Furosemide	..	..	1	..	..	Y	14·1% (13·0–15·4)	..	17 (16–25)	0·5% (0·5–0·6)
Triamterene	..	..	1	..	..	Y	3·3% (2·7–4·0)	..	115 (58–158)	0
Amiloride	..	..	1	..	..	Y	1·2% (0·9–1·7)	..	232 (232–232)	0
Traditional compound drugs†	..	..	..	..	..	..	..	55·6% (53·9–57·3)	..	..
Compound reserpine triamterene	..	Y	1	Y	..	Y	36·6% (35·0–38·2)	..	414 (299–435)	2·7% (2·5–2·9)
Compound reserpine	..	Y	1	Y	..	Y	34·9% (33·3–36·6)	..	80 (54–158)	0·6% (0·5–0·7)
Compound dihydralazine sulfate	..	..	2	..	..	..	1·2% (0·9–1·7)	..	137 (137–158)	<0·1% (<0·1–0·1)
Compound trizin and rutinum	..	..	1	..	..	..	0·1% (<0·1–0·2)	..	..	0
Compound kendir	..	..	1	..	..	..	2·5% (2·0–3·1)	..	65 (63–194)	0
Zhenju jiangya tablet	..	..	7	Y	..	Y	8·2% (7·3–9·2)	..	178 (130–269)	0·8% (0·7–0·9)
Fixed-dose combination drugs	..	..	..	..	..	..	..	10·4% (9·4–11·5)	..	..
Amiloride compounds	..	..	2	Y	..		0·1% (<0·1–0·3)	..	116 (116–116)	<0·1% (<0·1–0·1)
Losartan potassium and hydrochlorothiazide	..	..	1	Y	..	Y	2·7% (2·2–3·3)	..	1983 (895–2427)	1·6% (1·4–1·7)
Valsartan and hydrochlorothiazide	..	..	0	Y	..	Y	1·2% (0·9–1·7)	..	3750 (1726–4720)	<0·1% (<0·1–0·1)
Irbesartan and hydrochlorothiazide	..	..	1	..	..	Y	6·1% (5·3–6·9)	..	1136 (805–1609)	3·1% (2·9–3·3)
Captopril and hydrochlorothiazide	..	..	6	Y	..	Y	5·5% (4·8–6·4)	..	147 (66–197)	0·2% (0·1–0·2)
Nitrendipine and atenolol	..	..	0	Y	..	Y	0	..	..	0
Centrally active drugs	..	..	..	..	..	..	..	2·3% (1·9–2·9)	..	..
Rauwofia	..	..	1	..	..	Y	0·1% (<0·1–0·2)	..	588 (588–588)	0·1% (0·1–0·1)
Clonidine	..	..	2	..	..	Y	1·5% (1·1–2·0)	..	104 (104–104)	0
Reserpine	..	..	15	..	..	Y	0·4% (0·2–0·7)	..	45 (45–45)	0·2% (0·2–0·3)

.. =not applicable. NEM=National Essential Medicine List. PSEM=provincial supplementary essential medicine lists (value refers to the number of provinces that had this medication in its provincial list). *Essential lists: WHO=WHO Model Lists of Essential Medicines. †Ingredients per tablet forTraditional compound drugs: compound reserpine triamterene: reserpine 0·1 mg, triamterene 12·5 mg, hydrochlorothiazide 12·5 mg, dihydralazine 12·5 mg. Compound reserpine: reserpine 0·032 mg, hydrochlorothiazide 3·1 mg, dihydralazine 4·2 mg, promethazine 2·1 mg. Compound dihydralazine sulfate: dihydralazine sulfate 10·0 mg, hydrochlorothiazide 12·5 mg, reserpine 0·1 mg. Compound trizin and rutinum: hydrochlorothiazide 2·0 mg, dihydralazine sulfate 1·5 mg, rutinum 5·0 mg, reserpine 0·03 mg. Compound kendir: kendir 220 mg, dihydralazine sulfate 1·6 mg, hydrochlorothiazide 1·6 mg, promethazine 1·05 mg. Zhenju jiangya tablet: clonidine hydrochloride 0·03 mg, hydrochlorothiazide 5·0 mg, rutinum 20·0 mg, chrysanthemum indicum powder, nacre powder.

Table 2: **Availability of individual and classes of medications among all primary health-care sites**

in Primary Health Care 2014 and cost no more than 200 Chinese RMB, a threshold corresponding to 1% of the average annual disposable income per person in China in 2015.[25,26] The guideline recommends medicines based on clinical effectiveness. We used the 2014 guideline as a framework to guide our investigation of a wide range of antihypertensive medications expected for routine use.

Statistical analysis

First, to examine availability, cost, and prescription of antihypertensive medications at different types of primary health-care sites, we calculated percentages for categorical variables, and mean (SD) or median (IQR) for continuous variables, as appropriate. To determine site-specific characteristics associated with the availability of antihypertensive medications, we fitted a mixed model

with township or community as random effects and a logit-link function. The model included a spherical covariate structure to account for spatial autocorrelation and differences among townships or communities. The final model included six characteristics other than the type of sites and regions—ie, the number of health-care professionals, licensed physicians, physicians with a medical bachelor degree (5-year medical education), physicians who took a continuing-education course in the past year, social insurances for contracted health-care professionals, and healthcare professionals who routinely used IT systems (appendix).

Second, we modelled the prescribed medication as a function of its cost, both overall and in rural or urban subgroups. To address potential sampling variation and imbalances in numbers between electronic prescriptions and prescriptions taken from scanned copies, we adapted a resampling approach to undertake a simulation analysis with a non-parametric bootstrap, with replacement, method.[27,28] Specifically, for prescription data taken from scanned copies, we randomly selected records with a sample size equal to the total number of records; for electronic prescription data, we randomly selected a sample size equal to the sample size of the prescription data from the scanned copy. We then appended the two resampled datasets together and fitted the mixed model to estimate the association between the medication's prescription and its cost. We repeated this process 10 000 times to obtain the distributions of the estimated associations and their 95% CIs. All analyses were done using SAS 9.4, and all statistical testing was two-sided, at a significance level of 0·05. The Fuwai Hospital Institutional Review Board approved the study; the site survey was deemed exempt; and informed consent was obtained from all MPP study participants.

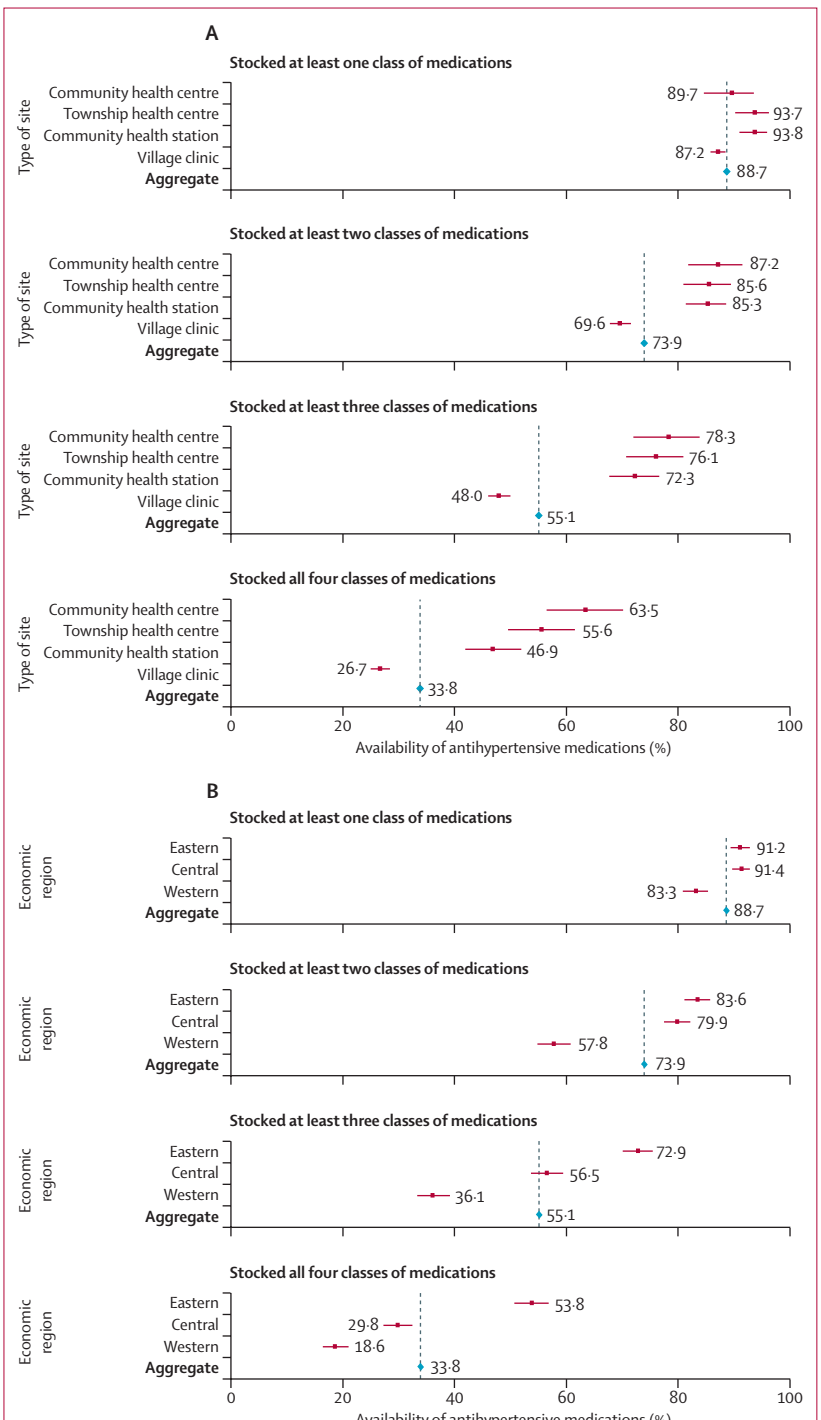


Figure 1: **Availability of antihypertensive medicines in China by type of site and economic region**
Data are percentage (95% CI). The four classes of antihypertensive medicines assessed were angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, and diuretics. Definitions of the three economic regions are in the appendix.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding and lead authors had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

Results
The study sample included 3362 primary health-care sites (18·0% urban, 82·0% rural) across China (appendix). Township health centres constituted 8·4% of sites, village clinics 73·6%, community health centres 6·0%, and stations 11·9% (table 1). The 435 townships or communities, which collectively enrolled 1·09 million people in the China PEACE MPP, served as the study sample for determining hypertension treatment and control rates. The median sample size of participants at the township or community level was 2128 (IQR 1165–3103).

Among the 3362 PHC sites, the most widely available antihypertensives were calcium-channel blockers, of which nifedipine extended release was the most commonly stocked (table 2).

The patterns of medication availability varied by site. Overall, 8·1% (273/3362, 95% CI 7·2–9·1) of primary health-care pharmacies did not have any antihypertensive

medications; 88·7% (2982/3362, 87·6–89·7) stocked either ACE inhibitors or angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, or diuretics; and 33·8% (1136/3362, 32·2–35·4) had all four classes of antihypertensive medications (figure 1). Availability, defined as having any class of medication, was associated with the type of site and economic region (appendix)—township health centres were more likely, and sites in the western region were less likely, to stock any kind of antihypertensive medication, and village clinics and sites in the western region were also less likely to have all four classes (figure 1; appendix). No characteristic specific for primary health-care sites other than the type of sites and region was strongly associated with antihypertensive availability (appendix).

Median annual costs per patient for individual medications varied substantially (table 2). Figure 2 shows the medications in value quadrants, according to their guideline-recommended status and cost. Only 32·7% (95% CI 32·2–33·3) of sites stocked medications in the high-value category.

Across 396 townships or communities, we sampled 26159 of 518915 hypertension prescriptions. The most commonly prescribed individual medication was amlodipine (16·8% [95% CI 16·3–17·2]), and the most frequently prescribed antihypertensive classes were calcium-channel blockers (45·6% [45·1–46·2]), angiotensin-receptor blockers (21·7% [21·3–22·2]) and beta-blockers (9·4% [9·1–9·7]; appendix). Overall, 86·2% (85·7–86·6) of prescriptions were for one medication, whereas less than 1% were for three or more medications. When two medications were used, fixed-dose combinations (38·9% [95% CI 37·2–40·5]), ACE inhibitors plus calcium-channel blockers (18·3% [17·0–19·7]), and angiotensin-receptor blockers plus calcium-channel blockers (17·0% [15·8–18·3]) were most commonly prescribed together (appendix). 2234 prescription records (7·7% [95% CI 7·4–8·0]) were for non-guideline-recommended medications, 3276 (11·2% [10·9–11·6]) for high-value medications, and 23603 (81·1% [80·6–81·5]) for higher-cost, guideline-recommended medications (figure 2).

The sites varied by treatment and control (appendix). The median risk-standardised treatment and control rates were 35·7% (IQR 19·6–52·1) and 8·3% (3·6–16·1), respectively. The worst 10% of sites had rates of 4·1% (1·6–5·8) and 1·1% (0·8–1·5), respectively, whereas the best 10% had rates of 72·5% (69·3–77·3) and 30·6% (26·5–35·4).

The cost of a medication was associated with being prescribed (figure 3, appendix), but not with its availability (figure 3). On average, high-cost medications were more likely than low-cost medications to be prescribed in primary health-care sites. Low-cost medications accounted for 40·5% (95% CI 39·9–41·1) of the medications in the pharmacies. Of all the prescriptions, 12·6% (12·3–13·0) were for low-cost medications and 4·7% (4·4–4·9) were for diuretics, the lowest-cost medication.

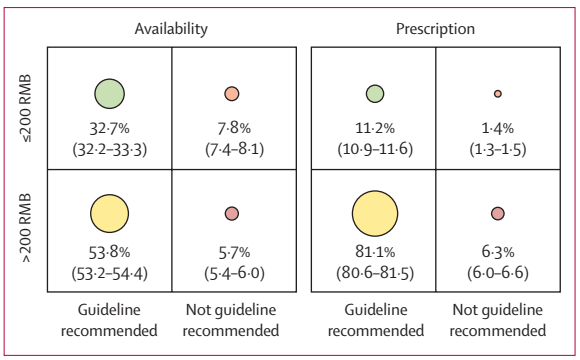


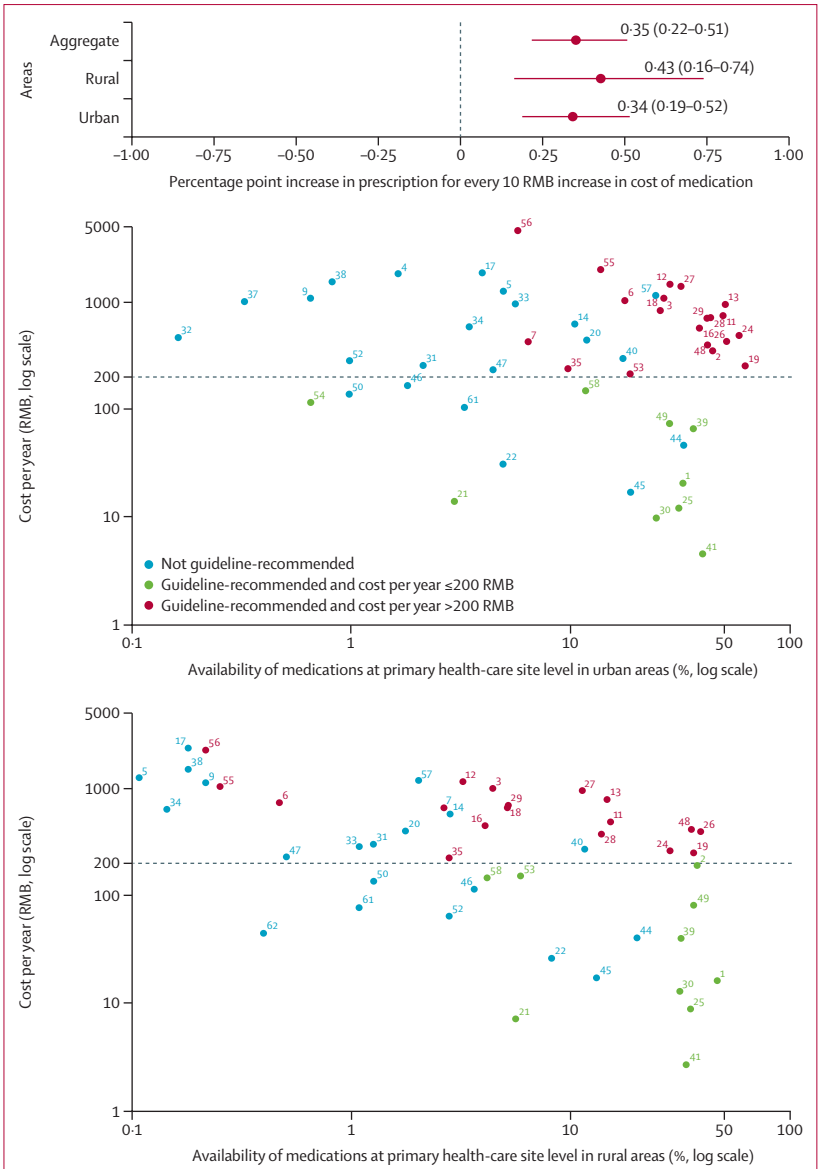
Figure 2: **Availability and prescription of medications in China by value quadrants**
Data are percentage (95% CI). x-axis: Chinese Guideline for Hypertension Management in Primary Health Care, 2014. y-axis: Annual cost of medication per patient (RMB).

Discussion

This national study of antihypertensive medications in China revealed marked deficiencies in their availability, cost, and prescription. First, hypertension medications are inconsistently available in primary health-care pharmacies across China, and one in 12 did not stock any antihypertensive medications. Second, despite the availability of low-cost antihypertensive medications, higher-cost medications were more often prescribed. In fact, the higher the cost of the medication, the more likely that it was prescribed; however, this did not necessarily mean that the most expensive drug was the one that was most frequently prescribed. The higher-cost medications did not represent medications with higher effectiveness.

This study adds to the scientific literature in several ways: it is the first national study of the availability, cost, and prescription of antihypertensive medications in China, involving all provinces. National policies with regard to essential medications and reimbursement might aim to improve access;[29] this study provides a contemporary assessment of the availability and use of antihypertensive therapies in primary health-care sites around the country and shows that deficiencies exist at the point of care. This study was based on actual investigations of the pharmacies and inspection of the prescriptions, and required government support, partnership with providers and administrators of primary health care, and site access to inspect pharmacies and examine prescriptions. The study did not depend on reports from the sites but, rather, involved direct data collection. Previous studies were limited to specific regions, populations, and data sources.[14,30–32]

The reasons for gaps in the availability and prescription of antihypertensive medications are not clear. Chinese national policies state that essential medications should be available and affordable. However, we uncovered problems



1 Captopril
2 Enalapril
3 Benazepril
4 Ramipril
5 Perindopril
6 Fosinopril
7 Lisinopril
8 Quinapril
9 Imidapril
10 Cilazapril
11 Valsartan
12 Losartan
13 Irbesartan
14 Candesartan
15 Eprosartan
16 Telmisartan
17 Olmesartan
18 Bisoprolol
19 Metoprolol
20 Metoprolol extended release
21 Atenolol
22 Propranolol
23 Betaxolol
24 Amlodipine
25 Nifedipine
26 Nifedipine extended release
27 Nifedipine controlled release
28 Felodipine extended release
29 Levamlodipine
30 Nitrendipine
31 Verapamil
32 Verapamil extended release
33 Diltiazem
34 Diltiazem extended release
35 Lacidipine
36 Nicardipine
37 Benidipine
38 Lercanidipine
39 Indapamide
40 Indapamide extended release
41 Hydrochlorothiazide
42 Bendroflumethiazide
43 Chlortalidone
44 Spironolactone
45 Furosemide
46 Triamterene
47 Amiloride
48 Compound reserpine triamterene
49 Compound reserpine
50 Compound dihydralazine sulfate
51 Compound trizin and rutinum
52 Compound kendir
53 Zhenju jiangya tablet
54 Amiloride compound
55 Losartan potassium and hydrochlorothiazide
56 Valsartan and hydrochlorothiazide
57 Irbesartan and hydrochlorothiazide
58 Captopril and hydrochlorothiazide
59 Nitrendipine and atenolol
60 Rauwolfia
61 Clonidine
62 Reserpine

Figure 3: **Annual costs per patient compared with availability and prescription patterns of antihypertensive medications**
Data are (A) percentage point increase (95% CI) and (B) and (C) percentages.

in the inventory of antihypertensive medication that can be supplied to patients at primary health-care sites. Despite the national focus on blood pressure control—and the responsibility of many of the sites for hypertension management[33]—a substantial proportion of these pharmacies had no or only a few antihypertensive medications, especially the low-cost drugs.[14] The zero mark-up policy might be a possible contributor to our finding that high-value medications are not frequently prescribed. Initiated in 2009, this policy prohibits health-care providers from selling essential medicines at prices higher than their wholesale cost. This policy reportedly exerted a large net effect on the revenue of village clinics, despite government subsidies being increased to compensate for revenue loss.[34,35] These reforms have been suggested to have led to a less-reliable drug supply system in China; for instance, village clinics might no longer provide essential medicines at zero mark-up because of the absence of a profit.[36] With respect to drug-prescribing patterns, there has been an increase in the use of expensive medications since implementation of the Chinese National Essential Medicine Program.[11] Refinements to this policy might provide stronger incentives for the use of low-cost medications. Mandating the availability of medicines might not be sufficient to improve the prevalence of hypertension, but their availability is arguably a necessary component of disease management programmes. Additional studies are needed to carefully examine the effect of zero mark-up policies on access to antihypertensive medicines throughout Chinese primary health-care centres.[12,37] Additionally, some patients and doctors might prefer antihypertensive traditional Chinese medicines, though their use was generally low in our study.

The implications of this study for hypertension management in China are substantial. The reality of care delivery in the clinics is not consistent with the health needs of the nation, and the deficiencies in primary care pharmacies have implications for patient health, as evidenced by suboptimal treatment and control rates. As such, interventions to improve hypertension treatment and control will need to focus not only on bolstering education, screening, and protocols, but also on ensuring that antihypertensive medications are adequately stocked by primary health-care pharmacies.[38] The adequacy of the medication inventory is not sufficient for progress in hypertension treatment and control, but it is certainly a fundamental component. Policy makers will need to ascertain why the aspiration of national policies is being stymied at a local level and probably thwarting efforts by practitioners to address hypertension in their patients.

The study has other important implications. The use of high-value medications—those that are guideline-recommended and reasonably priced—should be a priority for all countries, especially those with few resources.[39] Our study showed that high-value medications are not preferentially used in Chinese primary health-care settings, even though there is no evidence that

higher-priced medications are more effective.[40] A greater emphasis on high-value antihypertensive medications has the potential to mitigate the cost burden of increasing the rates of treatment and providing more value to the country. In this respect, diuretics might be particularly cost-effective. Findings from previous studies have suggested that drugs such as chlorthalidone might even be better than drugs from other classes.[23] However, few comparative effectiveness studies of antihypertensive drugs have been done,[41] and it might be beneficial for China to prioritise such studies. Identifying the higher-priced medications with known marginal benefits over lower-cost alternatives would provide the basis for high-quality and cost-efficient care.

The availability of antihypertensive medications varied among types of sites and economic regions, but inadequacies were not confined to certain types of centres. Site characteristics were not strongly associated with the availability of antihypertensive medications. This finding indicates the need for a broad-based strategy that would address problems that almost all types of primary health-care centres throughout China face.

Our study had several limitations. First, the study sites were not a representative sample despite spanning the entire country geographically and being so large in number. The treatment and control rates, however, were very similar to national estimates.[5] Second, we used a convenience sample and excluded people who were not residents. Those who were excluded would probably have had less access to care and would likely have had even lower control rates. Nevertheless, any inaccuracies in this study would be a bias toward the null, suggesting that our findings might have even underestimated the relationship. Of note, the prescription information reflected all prescriptions, including those provided to migrants. Third, this study focused on pharmacies in primary health-care sites, and people might go elsewhere for their prescriptions. However, half of private pharmacies impose fees that individuals must pay out of pocket.[42] Therefore, we expected that most patients would have a strong preference to obtain their medications from the clinic pharmacy. Future studies should build on these and other emerging primary datasets in China to examine the association between access to antihypertensive medicines and clinical outcomes, including control rates. Fourth, our choice of the 200 RMB threshold for cost might be arbitrary (ie, it was a general value that was not region-specific), and the threshold of 1% of annual disposal income might be higher for rural populations. Applying a lower-cost threshold, however, would further restrict the sample of medicines that could be defined as high-value, and lower the percentage of high-value drugs prescribed, further strengthening our findings. Finally, the inventory and prescription data that were collected covered slightly different periods. If any large-scale change in prescription drug inventories and prescribing behaviours are assumed to be marginal over the span of several months, the effect on this study from similar, albeit non-overlapping periods for data collection might be negligible.

In conclusion, this study revealed key obstacles to progress in mitigating hypertension in China. Despite advances in health-care coverage and policy to limit financial risks and improve health outcomes,[43] this study highlighted deficiencies in the availability, cost, and prescription of antihypertensive medications. Future policies aimed at alleviating the burden of hypertension in China, particularly through the work of primary health-care providers, will need to improve access to high-value antihypertensive medications.

Contributors

LJ and HMK conceived the study and take responsibility for all its aspects. LJ, HMK, MS, and QZ initially designed the survey, with support from EM, GAM, XL, and JL. MS, JL and XL led the data collection. HMK, LJ, MS, and QZ conceived this article. HMK, LJ, MS, and QZ wrote the manuscript, with further contributions from LJ, HMK, EM, GAM, FAM, SS-V, AZ, KN, and YLu. XB, CW, YLi, SS-V, and AZ provided data management and statistical analysis. All authors interpreted data, contributed to critical revisions, and approved the final version of the Article.

Declaration of interests

HMK is a recipient of research agreements from Medtronic and from Johnson & Johnson (Janssen), through Yale, to develop methods of clinical trial data sharing; is the recipient of a grant from the US Food and Drug Administration and Medtronic, through Yale, to develop methods for post-market surveillance of medical devices; works under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures; chairs a cardiac scientific advisory board for UnitedHealth; is a participant or participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science and the Physician Advisory Board for Aetna; and is the founder of Hugo, a personal health information platform. All other authors declare no competing interests.

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