

## **Analysis of the influence of recent reforms in China; cardiovascular and cerebrovascular medicines as a case history to provide future direction**

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### **Abstract**

**Background:** Pharmaceutical expenditure has grown by 16% per annum in China, enhanced by incentives for physicians and hospitals. Hospital pharmacies dispense 80% of medicines in China, accounting for 46% of total hospital expenditure. Principal measures to moderate drug expenditure growth include pricing initiatives as limited demand-side measures. **Objective:** Assess current utilization and expenditure including traditional Chinese medicines (TCMs) between 2006 and 2012. **Methods:** Uncontrolled retrospective study of medicines to treat cardiovascular and cerebrovascular (CV) diseases in one of the largest hospitals in Southwest China. **Results:** Utilisation increased 3.3 fold for CV medicines, greatest for TCMs, with expenditure increasing 4.85 fold. Low prices for generics were seen, similar to Europe. However, there was variable utilization of generics at 29% to 31% of total product volumes in recent years. There continued to be irrationality in prescribing with high use of TCMs, and utilization of medicines dropping significantly once low prices. **Conclusion:** Prices still have an appreciable impact on utilization in China. Potential measures similar to those implemented among Western European countries could improve rationality and conserve resources.

Key Words: China, Drug utilisation, generics, demand-side measures, cardio-vascular drugs

## Background

There are ongoing initiatives across countries to improve prescribing efficiency. This is due to continual pressure on resources brought about by ageing populations and the continued launch of new premium priced drugs [1-5]. Initiatives for established drugs include multifaceted demand-side measures to increase the prescribing of low costs generics versus originators and patented products in a class [2-8]. Classes include the proton pump inhibitors (PPIs), statins and the renin-angiotensin inhibiting drugs, with the latter including both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [2-7,9-17]. The combination of low-cost generics and multifaceted demand-side measures has resulted in considerable savings in some European countries without compromising care [2-4,7,9,10].

As a developing and transitional country, China has also seen rapid growth in pharmaceutical expenditure, with growth averaging 16% per annum during the past decade [18]. This growth has been enhanced by increasing health insurance coverage, now covering 90% of the Chinese population [18,19], with the ultimate goal of universal coverage by 2020 [18,20-25]. A number of measures and initiatives have been introduced in China in recent years to try and moderate growth rates to help achieve universal coverage as well as help address the difficulties with seeing physicians and associated costs. These include cutting pharmaceutical prices, introducing essential medicine lists and guidelines and establishing co-payment caps [18-21,24-27]. Having said this, there appear to be currently no universal measures among public insurers to monitor the quality of physician prescribing illustrated for instance by the continued high use of antibiotics and injectables [26, 28-32]. Pharmaceutical expenditure has been a principal target in China since it accounts for 46% of total hospital expenditure in 2010 [18], with hospital pharmacies dispensing more than 80% of the country's total medicines [18,26, 27,33]. Out-of-pocket payments account for 36% of total healthcare expenditure [21]. The principal reasons for the high level of dispensing in hospitals include patient convenience, physician recommendations, the possibility of nonstandardized prescriptions and a greater assurance of pharmaceutical quality [26].

Drug prices are currently determined by the government (state or province) or manufacturers themselves, with actual prices subject to tenders in each province or municipality orchestrated by the local health departments [18, 19, 26]. Since 2006, the margin between the procured and retail price was fixed to approximately 15%. As a result, greatly standardizing the purchasing channels among Chinese hospitals [19,26,27, 33]. For most pharmaceuticals, government control and tendering are the principal forces to decrease prices. Market forces are enhanced by appreciable competition among generic companies, with more than 5,000 pharmaceutical manufacturers in China producing mainly generics [18]. However, there are still no formal pricing mechanisms for generics in China unlike the situation in Europe, which helped achieve generic prices as low as 2% to 10% of patent prices in some countries [2-5,7,14,16]. The current system in China also encourages physicians to overprescribe pharmaceuticals as well

as prescribe those that provide the greatest profit to enhance their income. Hospitals also rely on revenues from medicines for their sustainability. This combination subsequently influences prescribing patterns [18,19,26, 32-35]. Lim and colleagues also found that dispensing doctors prescribed more medicines to patients, and prescribed more originators than generic drugs [36]. This is not helped by similar patient co-payments for an originator or generic. As a result, little increase in the use of generics in China was noted in recent years [18].

Medicines to treat cardiovascular and cerebrovascular diseases are important classes in China due to the increasing incidence and prevalence of these diseases [18]. This includes oxiracetam, which is perceived to improve learning and memory functions of patients with dementia. Jin and colleagues also recently identified cardiovascular drugs among the leading therapeutic classes by volume among hospitals in the Chongqing District of China, alongside anti-infective agents and medicines for the digestive and nervous systems [37], with its population of 28.8 million people (2010 census). This is similar to other districts in China [38]. This also includes over 110 traditional Chinese medicines (TCMs) used to treat these conditions despite increasing awareness of the safety problems associated with TCMs in recent years [39,40]. TCMs generally contain yellow pigment from Carthamine or salvianolic acids, and are typically administered via injections. New TCMs continue to be made available with the active components containing for example ginseng, the root of red-rooted salvia, red ginseng, Folium Ginkgo, pseudo-ginseng and Erigeron breviscapus extract. The manufacturers of these typically apply for new medicine approval. As a result, gain exclusive approval for manufacturing which helps obtain higher procurement prices. This use of traditional medicines is despite attempts to develop guidelines and essential medicine lists in China based on published evidence; enhanced by the increased profitability from injections [18,21,29,31].

The prices of cardiovascular drugs have been adjusted four times between 2006 and 2012 in Chongqing District. There were two changes with tendering, in March 2006 and April 2011, and two national adjustments to the maximum retail prices, in January 2007 and March 2011 [41]. However, there are still considerable incentives for physicians to prescribe expensive originators rather than cheaper generics despite initiatives to enhance INN (International Non-proprietary name) prescribing [18,26,29,33,42].

Consequently, the aims of this study are to firstly to assess changes in the utilisation patterns of cardiovascular and cerebrovascular drugs in recent years, including traditional Chinese medicines, with increasing availability of generic drugs. Secondly, assess changes in the utilisation of selected originator and generic cardiovascular and cerebrovascular drugs over time including TCMs as well as potential factors leading to these patterns. Thirdly, assess changes in cardiovascular and cerebrovascular drug expenditure over time as well as changes in the procurement prices for generic, originator drugs and traditional Chinese medicines. This includes the influence of price reductions as well as potentially increasing competition as more generics become available. Lastly, suggest potential future reforms that China could consider to enhance the rational use of medicines as well as obtain further price reductions.

## Methods

This was an observational uncontrolled retrospective study of prescriptions between 2006 and 2012 [43]. This methodology was chosen since there have been multiple supply- and demand-side measures in China and its various Districts during this period making it difficult to perform an interrupted time series analysis. However where possible, we have performed simple statistical analyses such as the chi-square test.

We will firstly describe why we chose this data set for analysis before describing the methodology chosen for assessing utilisation and expenditure data.

Typically for drug utilisation analyses, data is obtained from health authorities or pharmacy databases [2-7,9,10,12-16]. However in China, most drug utilisation studies are performed with data from hospitals as they incorporate both inpatient and outpatient data [18,39]. In addition, as mentioned, they account for 80% of total drugs currently dispensed in China [18,26,33]. Consequently, hospital procurement data is currently an optimal source of drug utilisation data in China. Accurate data on hospital tendering and procurement is especially important for this type of analysis given the profitability from medicines [29]. This data is not always available from some commercial sources, which can just provide maximum retail price data [33]. In addition, hospitals in China also procure and dispense medicines which are not included in the current reimbursement list. Consequently, comprehensive utilization and expenditure would not be picked up through analyzing reimbursed data sets from the Insurance Department.

Chongqing is a municipality directly under China's central government. In the urban district in Chongqing City, the main public general hospitals include three hospitals affiliated to the Third Military Medical University, two hospitals affiliated to Chongqing Medical University, and 10 municipal hospitals. Every hospital may include different generic drugs, but with the same originator equivalents as part of the tendering process to obtain good prices [18].

We chose the largest hospital in Chongqing District to conduct our study as it is one of the largest hospitals in Southwest China. It can also provide comprehensive datasets on both utilization and expenditure and is a typical health care provider. The dataset was obtained from the magazine company of China Pharmacy. The company is located in Chongqing and is able to collect detailed information from large hospitals in southwest China. The data contains all individual drug information including product names, purchase dates, dosage forms, specification, manufacturers, unit prices and volumes. This is an authoritative source for drug utilisation statistics in China, which is regularly audited. We used a similar approach in previous studies [18].

The datasets are broken down into three groups:

- **Originator products.** These include products from multinational companies imported into China or manufactured by joint ventures in China founded by multinational pharmaceutical companies. Since these medicines have the original intellectual property and are

considered by some to have better quality, they typically command a premium prices versus generics

- **Generic products.** These are produced by enterprises with local investment, including state-owned and private enterprises. Prices are influenced by the Chinese price control policy, and these products typically face competition from a number of different manufacturers. Their quality has improved in recent years with a number of different measures to enhance manufacturing standards. For instance in 2009, all medicines on the Chinese essential medicine list were required to undergo quality sampling and testing at the provincial level at least annually and at the central level at least every three years [21]. Good Manufacturing (GMP) standards were also revised in 2011 to further improve the quality of generic manufacturing in China [21]
- **Traditional Chinese medicines.** Usually prepared from herbs or other traditional sources, with some preparations involve chemical substances. The main delivery route is via an injection. The characteristics of traditional Chinese medicines are multi target and multi utility. They are believed to provide comprehensive treatment of patients with chronic cardiovascular and cerebrovascular diseases enhanced by a high degree of acceptance among both physicians and patients. They are also believed for instance to improve blood circulation and remove blood stasis and activate collaterals [37].

Volume data was derived from the quantity of drugs dispensed as we considered procurement volume equal to clinical consumption. We chose unit package data as our measurement of utilisation, e.g. one box (e.g., 10 mg × 16) or one bottle (e.g., 0.1 g × 1 ml for an injection or 1g for powder) as opposed to defined daily doses (DDDs) [44]. This is because:

- there is currently no reliable source for DDDs for traditional Chinese medicines (the principal products used) with several authors using different methodologies and figures in their calculations [39]
- most prescribing physicians in China use the package unit (i.e., one box or one bottle) as the charging unit when calculating their patients' expenditure. This is a similar concept to prescription items in the UK, which is a key metric among UK primary care organisations [16]
- the specifications of the products typically did not change during the study period

Calculations to determine procurement prices, prices per unit and overall expenditure were based on Chinese currency *yuan* (CNY). There was no allowance for inflation or deflation as we wanted to compute actual changes over time as a result of the tendering process. This is in line with previous studies [2-7,9,10,12-16]. We have also not converted CNY data to either US\$ or Euros during the course of the study as we did not want the pricing data influenced by currency fluctuations, especially during the recent financial crises in Europe and the US.

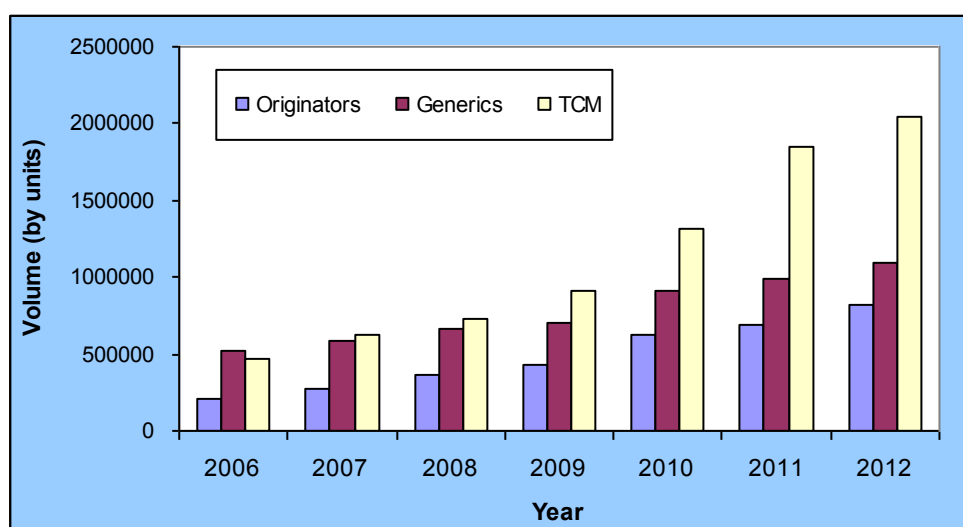
In addition to overall utilisation and expenditure data, we also analysed several individual products separately to improve our understanding of the situation in China. For this, we typically chose to analyse in detail individual products with an average purchase volume of 1,000 packs per month or a procurement price higher than CNY 20, or a total annual value over CNY 1 million.

## Results

### *Utilisation (general)*

Total utilisation of drugs to treat cerebrovascular and cardiovascular diseases increased 3.3 fold between 2006 and 2012, rising from 1.2 million units in 2006 to 3.98 million units in 2012 (Figure 1). This included both single agents and combinations, and was greatest for traditional Chinese medicines at 4.41 fold (Figure 1). Utilisation increased among all product groups apart from ligustrazine. The increase was highest for the statins and the renin-angiotensin inhibiting drugs (Table 1).

Figure 1 – Overall growth in utilisation of the three main categories (by Units) 2006 to 2012 in the Chongqing District



TCM = Traditional Chinese Medicines

Table 1 – Utilisation of different pharmacotherapeutic groups and traditional Chinese medicines (by unit) in the Chongqing District 2006 to 2012

<b>Product/Group</b>	<b>Total utilisation 2006</b>	<b>Total utilisation 2012</b>	<b>Increase (2012 vs. 2006)</b>	
Beta blockers (including combinations)	45253	181208	4.0 fold	
Calcium channel blockers (including combinations)	66098	286700	4.34 fold	
Renin-angiotensin inhibitor drugs (including combinations)	ACEIs	51782	74665	1.44 fold
	ARBs	25662	288160	11.23 fold
Statins	25765	214799	8.34 fold	
Ligustrazine	40119	0	0	
Levocarnitine	40874	76773	1.88 fold	
Oxiracetam	33390	139626	4.18 fold	
Cinepazide	25600	36780	0.44 fold	
Others (consolidated )	379869	610092	1.61	
Total traditional Chinese medicines	464954	2048258	4.41 fold	
<b>Total</b>	<b>1199366</b>	<b>3957061</b>	<b>3.30 fold</b>	

NB Ligustrazine is included separately although it may also be considered a Chinese herbal medicine. Utilisation measured in package units. Fold = times, e.g.4.0 fold = 4 times

Analysis of the 12 single products meeting our definition showed an increase in the utilisation of both originators and generics. However, there was variable utilisation of generics with overall utilisation stabilising at 29% to 31% of total utilisation for these 12 cardiovascular products in recent years (Table 2. Table 1A in the Appendix contains more detailed analysis - broken down by 6 month periods).

Table 2 – Yearly utilisation of both generics and originators for 12 single cardiovascular and cerebrovascular products in the Chongqing District between 2006 to 2012

Product	2006	2007	2008	2009	2010	2011	2012
Metoprolol - Generic	0	0	0	0	0	0	0
Metoprolol - Originator	22637	28302	33680	37920	46080	64150	102240
Bisoprolol – Generic	0	0	0	0	0	0	0
Bisoprolol - Originator	8400	14040	18300	17605	34380	36720	40860
Amlodipine – Generic	9445	17170	21200	34150	47570	60608	66510
Amlodipine – Originator	7900	8900	9600	19466	26200	25700	41850
Nifedipine – Generic	25259	26128	28500	28430	27100	29600	17100
Nifedipine – originator	11880	18650	31621	25380	39330	37170	55620
Felodipine – Generic	248	1120	1080	1050	940	250	1240
Felodipine – Originator	2640	6670	12557	19680	29844	36160	53280
Benazepril – Generic	0	329	1730	3380	14810	12940	15600
Benazepril - Originator	6480	8560	11280	16560	17640	25020	30899
Losartan – Generic	0	0	0	0	0	0	4600
Losartan – Originator	6160	10990	17800	23330	38600	36200	37620
Telmisartan – Generic	252	1500	5312	5600	7600	9800	11175
Telmisartan – Originator	1582	3587	8400	8930	11600	14848	26200
Valsartan – Generic	814	1200	400	1050	1200	1300	1725
Valsartan – Originator	1766	4250	14409	21030	24000	40140	58880
Atorvastatin – Generic	7680	8400	8958	11760	27659	57520	89793
Atorvastatin – Originator	1920	2520	5339	20800	31440	34160	42282
Simvastatin – Generic	384	396	2052	4716	4420	3200	1680
Simvastatin – Originator	7210	15604	31400	34320	63800	60800	38600
Irbesartan – Generic	0	700	11300	18600	25735	19800	25000
Irbesartan – Originator	6650	11500	12686	20520	32920	34200	43200

NB.

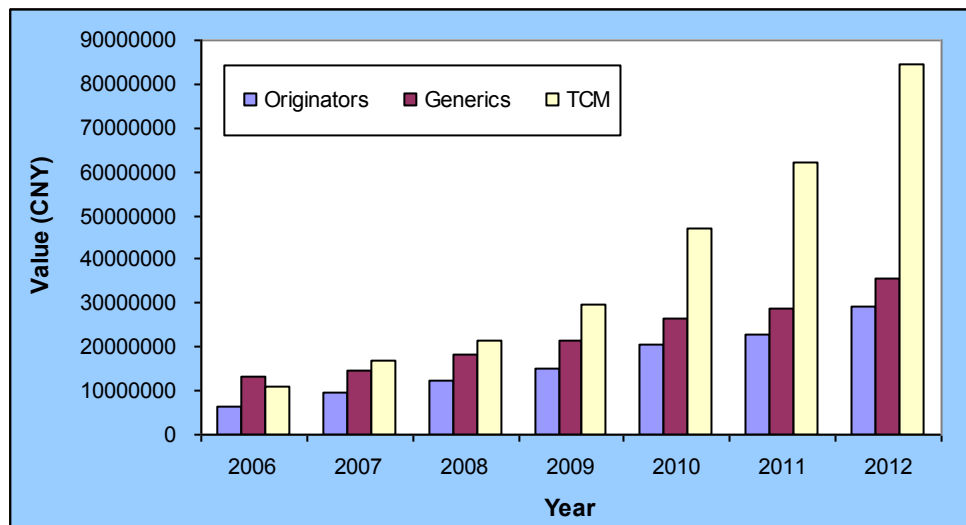
Utilisation measured in package units

### ***Procured expenditure (general)***

Total procurement expenditure on cardiovascular and cerebrovascular medicines increased from 30.76million CNY to 149.29 million, a 4.85-fold increase over the 7 years, representing a compounded annual growth rate of 30% (Figure 2). There was increasing expenditure on traditional Chinese medicines, with their share of total expenditure increasing from 35% in 2006 to 57% in 2012.

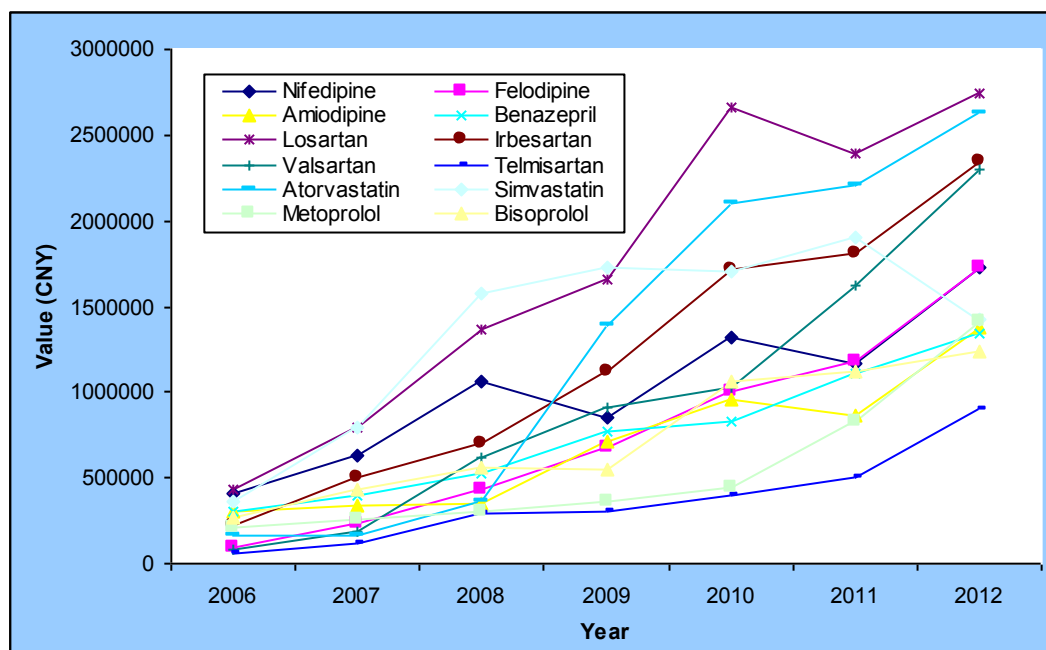


Figure 2 - Total procurement expenditure on cardiovascular and cerebrovascular medicines in CNY in the Chongqing District 2006 to 2012



There was also steady growth in procurement expenditure of originator products with procurement values of more than one million CNY in 2012 (Figure 3).

Figure 3 – Total procurement expenditure of the 12 originator cardiovascular and cerebrovascular medicines in CNY in the Chongqing District 2006 to 2012



NB. We acknowledge the procurement of telmisartan was less than 1millionCNY/ year. However, included in view of the rapid rise in recent years

However, there was a mixed picture regarding procurement prices for generics and originators among the principal 12 products over time (Table 3. More detailed analysis in Table 2A). In

general, procurement prices for both originators and generics decreased over time, although this was not universal.

Table 3 – Change in procurement expenditure/ unit (CNY) for 12 single originator and generic cardiovascular and cerebrovascular drugs in the Chongqing District between 2006 and 2012

Product	2006	2007	2008	2009	2010	2011	2012
Metoprolol - Generic							
Metoprolol - Originator	9.199	9.116	8.848	9.419	9.667	12.836	13.851
Bisoprolol – Generic							
Bisoprolol - Originator	31.594	30.905	30.910	30.910	30.910	30.535	30.400
Amlodipine – Generic	32.048	35.975	36.962	37.892	38.661	38.346	38.668
Amlodipine – Originator	38.372	38.047	36.780	36.763	36.372	33.479	32.929
Nifedipine – Generic	18.783	15.043	14.069	14.245	14.681	13.200	12.894
Nifedipine – originator	34.385	34.018	33.500	33.500	33.476	31.256	31.130
Felodipine – Generic	25.441	25.855	25.390	25.390	25.390	28.306	35.290
Felodipine – Originator	36.120	34.569	34.153	34.137	33.787	32.690	32.500
Benazepril – Generic		35.700	35.700	35.700	35.700	30.662	29.220
Benazepril - Originator	47.508	46.830	46.830	46.830	46.830	44.529	43.633
Losartan – Generic							66.080
Losartan – Originator	48.764	49.210	48.289	49.148	48.874	46.352	47.802
Telmisartan – Generic	22.670	35.924	35.220	35.220	35.220	24.399	20.710
Telmisartan – Originator	34.691	34.150	34.150	34.150	34.150	34.150	34.150
Valsartan – Generic	20.478	19.840	19.840	19.840	19.840	16.886	16.000
Valsartan – Originator	43.727	43.626	42.780	42.780	42.780	40.325	39.096
Atorvastatin – Generic	34.148	30.789	30.090	30.090	31.175	28.938	28.964
Atorvastatin – Originator	67.269	67.000	67.009	67.000	67.000	64.541	62.240
Simvastatin – Generic	27.910	24.943	24.090	23.851	20.867	13.740	11.846
Simvastatin – Originator	50.711	50.687	50.300	50.300	26.683	31.378	36.810
Irbesartan – Generic		22.960	22.950	22.950	22.950	19.271	18.340
Irbesartan – Originator	31.935	31.423	31.259	31.260	31.260	31.260	31.260

### **Specific classes and products**

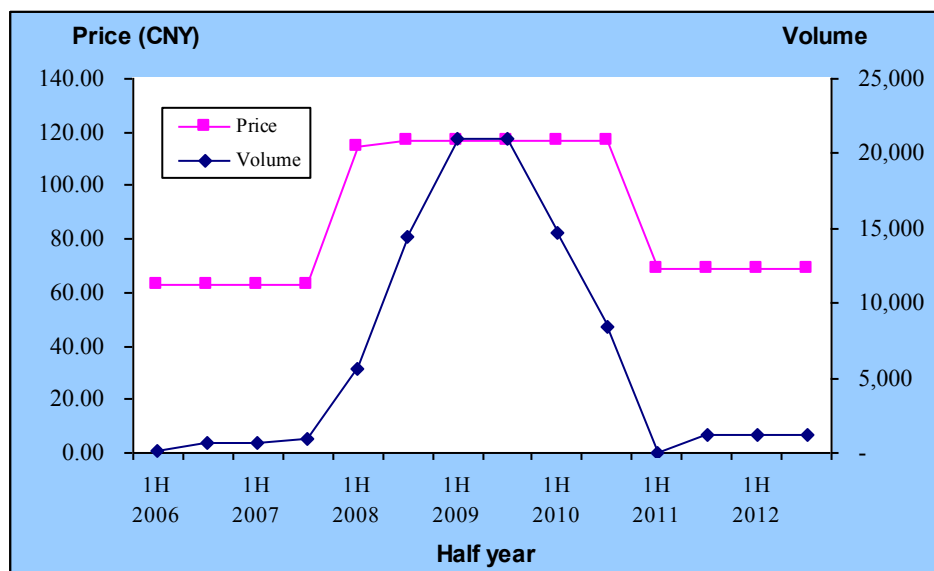
#### *β- Adrenergic receptor blockers*

Nogenerics were procured for either of the two higher volume beta blockers over time (Table 2).

There was an increase in the utilisation of esmolol hydrochloride injections during part of the study period. The main esmolol injection was launched in July 2006 with a specification of 0.1 g × 1 ml priced 62.80 CNY per bottle. Only a limited amount was used: 788 bottles in 2006 and 1,685 in 2007 (Figure 4). In April 2008 after the specification was adjusted to 0.2 g × 2 ml with a higher price of 116.52CNY, the procurement volume increased from 5,600 bottles in the first half of 2008 to 21,000 bottles in the first and second half of 2009. After its price decreased to 68.84CNY per bottle, consumption decreased. This reduced to 1,150 bottles in the second half

of 2012, a 94.5% decrease from the peak. Concurrently, the utilization of both originator metoprolol and bisoprolol increased (Table 2 and 1A).

Figure 4 – Volume and procurement prices (CNY) of esmolol injections 2006 to 2012 in the Chongqing District 2006 to 2012



NB Specification of esomol injections were adjusted from 0.1 g × 1 ml to 0.2 g × 2 ml in April 2008

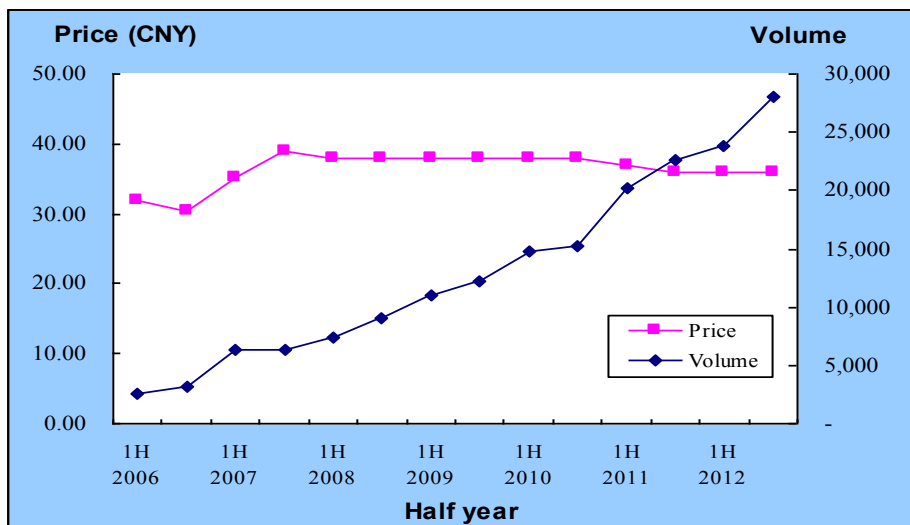
#### *Calcium channel blockers*

There was variable utilisation of generic versus originator calcium channel blockers. Utilisation of amlodipine and felodipine increased whilst utilisation of nifedipine decreased (Tables 2 and 1A).

There was increasing utilisation of both generic and originator amlodipine besylate (2.5mg x 14 tablets) over time. However, there was no significant difference between the utilisation of either the generic or originator during the study period (P>0.05).

There were generally stable pack prices during this period ((Figure 5, Tables 3 and 2A).

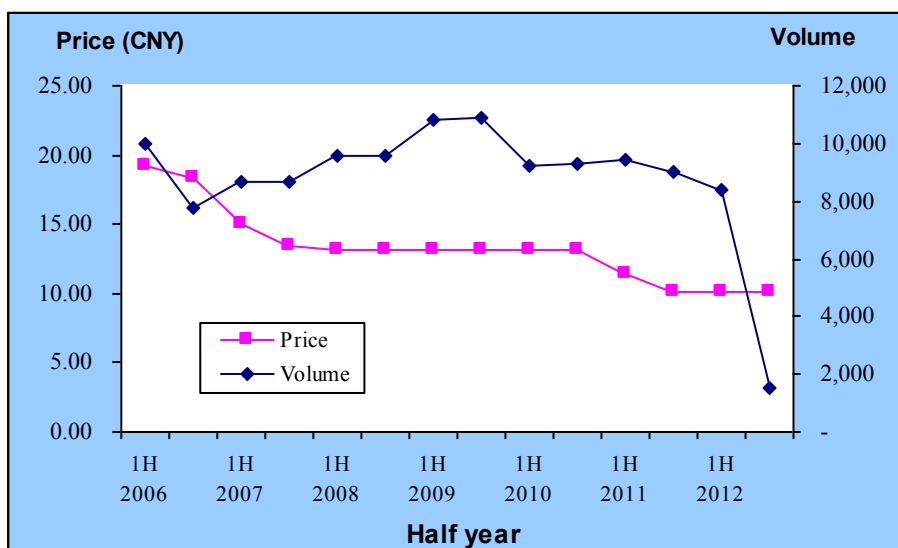
Figure 5 – Procurement volume and prices (CNY) of generic besylate amlodipine (2.5mg besylate tablets x 14) 2006 to 2012 in the Chongqing District



There was decreasing utilisation of generic sustained release tablet nifedipine in the last half of 2012. In the same period, procurement prices decreased (Figure 6). There was a corresponding increase in the consumption of the originator (Tables 2 and 1A). This led to a significant difference in the utilisation of originator vs. generic nifedipine during the course of the study ( $p < 0.005$  using the chi-square test).

There was an overall 59% price differential (expenditure/ unit) for generic nifedipine vs. the originator by the second half of 2012 (Tables 3 and 2A).

Figure 6 – Procured price-volume of sustained release generic nifedipine 20 mg × 20 tablets in the Chongqing District of China 2006 to 2012



#### *HMG Co-A reductase inhibitors (Statins)*

There was increased utilisation of both generic and originator atorvastatin and simvastatin over time (Tables 2 and 1A). Overall, there was low utilisation of generic vs. originator simvastatin at only 5% of total units during the past 2.5 years. Expenditure/ unit for generic simvastatin was only 34% and 25% originator prices in early 2006 and by the end of 2012 respectively (Table 3 and 2A).

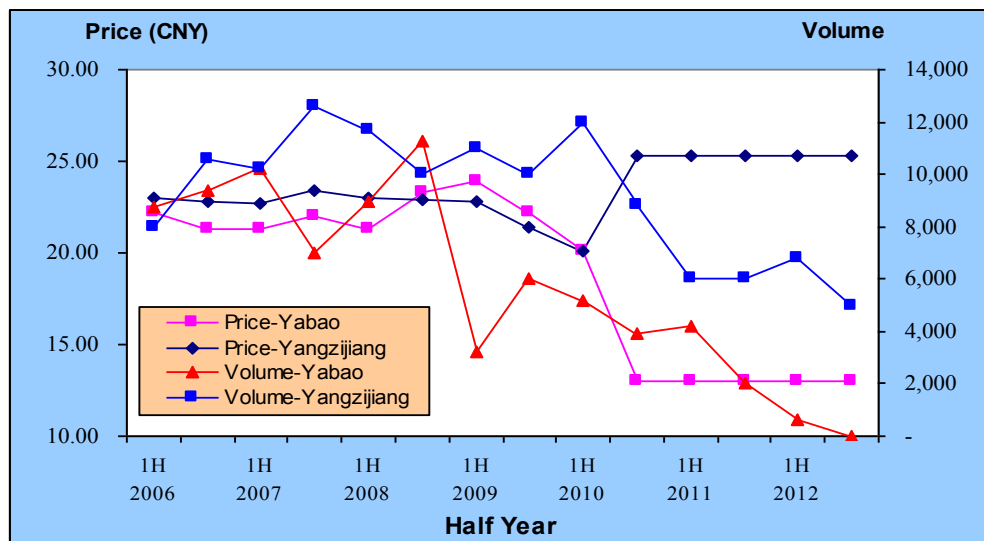
There was high utilisation of generic atorvastatin versus total atorvastatin over time (Tables 2 and 1A) compared with the situation for simvastatin. The procurement price for generic atorvastatin was 47% of the originator price in the last half of 2012 (Tables 3 and 2A). The price decline for generic atorvastatin was modest over time and there was no significant difference in the price changes for generic vs. originator atorvastatin between 2006 and 2012 ( $p>0.05$ ).

#### *Renin-angiotensin inhibiting drugs*

Generally, ARBs were more prescribed than ACEIs (Table 2). There was variable utilisation of generic renin-angiotensin inhibiting drugs over time (Tables 2 and 1A). The utilisation of generic irbesartan and telmisartan increased over the study period whilst the utilisation of generic valsartan remained low. Overall, there were no significant difference in the evolution of generic benazepril, irbesartan, and telmisartan versus originators between 2006 and 2012 (Fischer exact test -  $p>0.05$ ).

Expenditure/ unit for generic telmisartan and generic valsartan in late 2012 was 41% and 64% respectively below early 2006 procurement prices, and expenditure/ unit for generic irbesartan in the second half of 2012 was 41% below pre-generic procurement prices (Tables 3 and 2A). The procurement price of enalapril maleate tablets moderated at the beginning of 2006 with similar consumption until 2010 (Figure 7). After its procurement price per unit decreased from CNY 22.08 to 13.04, utilisation also decreased. Later one of the manufacturers, *Yangtze River Pharmaceuticals*, changed its specification from 10 mg × 16 tablets to 10mg x 32 tablets combined with an increased price (CNY 25.30). The same overall volume was maintained based on the number tablets dispensed although the number of packages decreased. Concurrent with this, another manufacturer (*Yabao Pharmaceuticals*) lost much of its market share and stopped selling from February 2012.

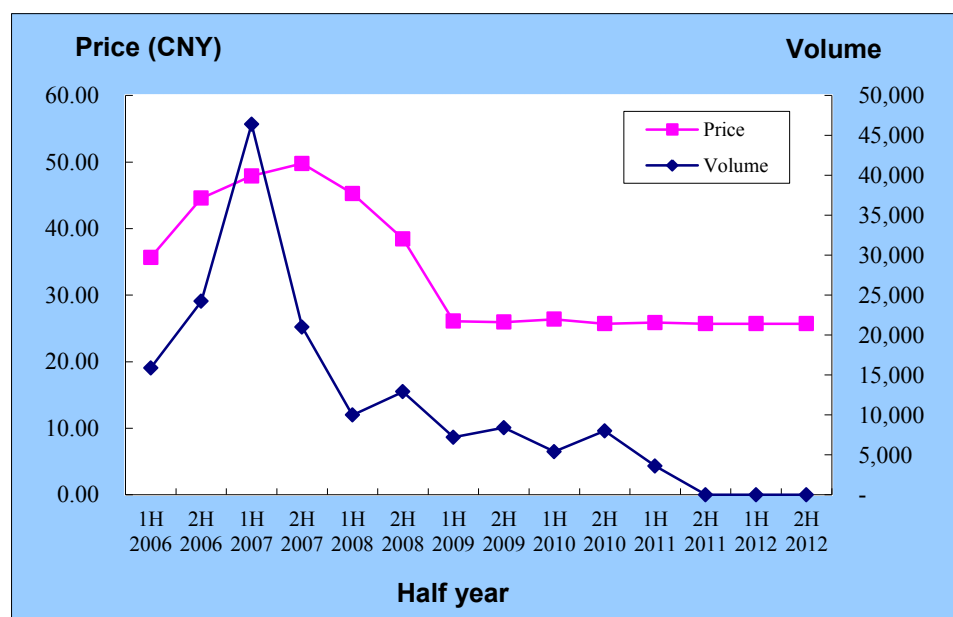
Figure 7 – Procurement price-volume of enalapril maleate tablets in the Chongqing District of China 2006 to 2012



*Ligustrazine*

Ligustrazine injection was initially provided by four different manufacturers, and reached a peak of 46,400 bottles in 2007 before falling to 3,600 bottles in the first half of 2011 with procurement terminated in the second half of 2011. The procurement price decreased to CNY 25.70 in the first half of 2009 and has been maintained at this price level (Figure 8).

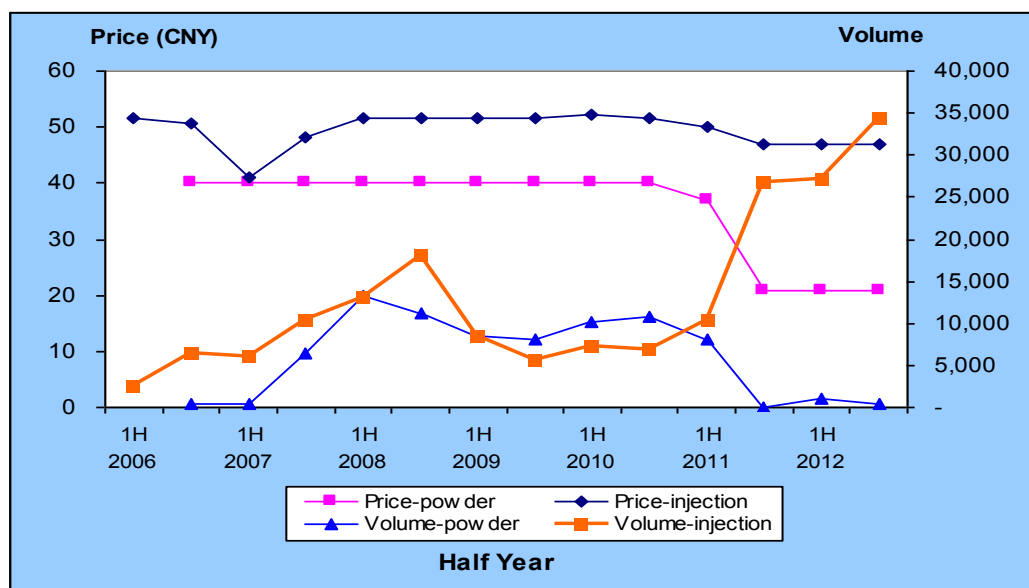
Figure 8 – Procurement price and volume of ligustrazine injections (CNY) in Chongqing District 2006 to 2012



### Levocarnitine

Expenditure on levocarnitine remained high throughout the 7-year period, at more than CNY 2 million a year. The utilisation of levocarnitine powder for injection (1g) decreased appreciably after the procurement price almost halved from CNY 40.00 to 20.90. The price of the second preparation, levocarnitine injection 1 g × 5 ml, was only modestly reduced from CNY 51.48 to 46.88 (Figure 9). This injection subsequently increased its utilisation at the expense of the powder plus injection.

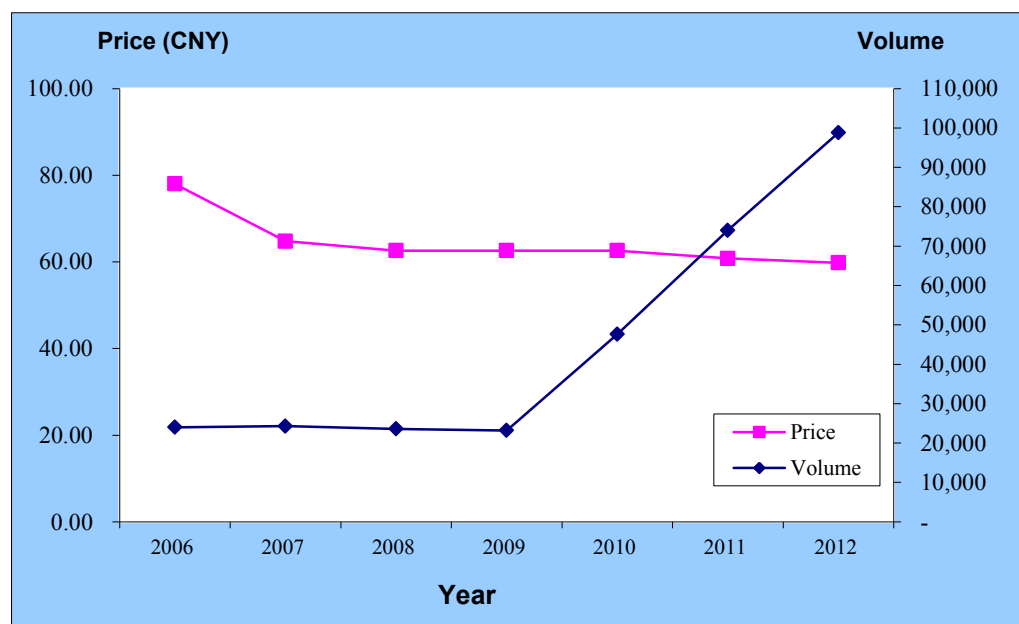
Figure 9 - Price-volume of levocarnitine powder 1g and levocarnitine injection 1 g × 5 ml (CNY) 2006 to 2012 in the Chongqing District



### Oxiracetam

Oxiracetam had the highest utilisation of any cardiovascular or cerebrovascular drug, increasing from 33.4 thousand units in 2006 to 139.6 thousand units in 2012 (Table 1). This was increasingly the injection (Figure 10), which had a higher relative price than the capsules.

Figure 10 - Price-volume of oxiracetam injection 1 mg × 5 ml in the Chongqing District of China 2006 to 2012



#### *Cinepazide*

There was appreciable fluctuation in the utilisation of cinepazide maleate injection during the study period as a result of neutropenia. This side-effect resulted in some countries refusing market authorisation; alternatively removing it from the market. The WHO also suggested compensating patients for adverse events caused by the drug [45,46]. During the study period, its procurement price remained relatively stable

#### *Traditional Chinese medicines*

There was a 4.41 fold increase in the utilisation of traditional Chinese medicines during the study period (Figure 1, Table 1). Three leading preparations currently account for 45% of the total market share of traditional Chinese medicines with a package price varying from CNY 42.78 to 135.96. High prices appear to be achieved and maintained with limited competition. The rising costs of Chinese materials contributed to these prices, especially at the end of 2009. This resulted in procured expenditure/ unit for traditional Chinese medicines increasing from 23.41 CNY in the 2006 to 41.32 in 2012, corresponding to a 1.77 fold increase. As a result, procurement costs rose 7.78 fold. Some older products have now been transferred to community pharmacies where prices have fallen

#### **Discussion**

We will initially discuss utilisation and expenditure patterns in the Chongqing District including general findings as well as those for traditional Chinese medicines. Secondly, suggest the implications for the utilisation and expenditure for domestically produced products. Finally, we will suggest potential future reforms that could be considered by the authorities in China. These are based on successful measures among Western European countries, who have



already achieved equitable and comprehensive healthcare for their citizens. However, we are aware that any future demand-side measures will have only limited success unless the perverse incentives for physicians and hospitals are substantially reduced, e.g. addressing physician salaries who currently earn 5000 CNY (US\$780) a month or less [42].

Firstly, as expected, there was an appreciable increase in the utilisation and expenditure on medicines to treat cardiovascular and cerebrovascular diseases in the Chongqing District of China between 2006 and 2012 (Figures 1 and 2, Table 1). We believe this considerable increase can be attributed to many factors. These include urbanization, an aging population, the expanding scope of medical insurance and improving living standards. However, we are unable to comment further without specific research. This increase though mirrors the considerable increase in utilisation of statins and renin-angiotensin inhibiting drugs seen among Western European countries during the past decade [2-4,6,7,9-11,14-16]

Authorities across countries have generally cut drug prices when faced with higher than expected expenditure or following a financial crisis [47-50]. China is no exception. The main measures introduced by the authorities to try and contain drug expenditure have been price reductions. This has been seen in practice especially for the generics apart from a minority of situations (Tables 3 and 2A), with some price reductions mirroring those among Western European countries [4,9,15]. However, price reduction policies implemented in isolation have not been effective in containing overall drug expenditure (Figure 2). These findings are similar to those of other authors in China [18,31,33] as well as other Asian countries. For instance in South Korea, policies concentrating on price controls without addressing demand-side measures did not achieve their desired result [49, 51].

Secondly, we believe the considerable growth in the utilisation and expenditure on traditional Chinese medicines (Figures 1 and 2, Table 1) is an important finding. Traditional Chinese medicines accounted for 57% of total procured expenditure by the end of 2012. We believe this increase may have been facilitated by the launch of new products with higher prices, relatively limited competition, and the fact that these are typically administered by injection [29,31,41]. However, the lack of published data for many of these products, coupled with their high relative prices, suggests continued irrationality in prescribing in China despite the development of essential medicine lists [21].

Concerns with irrationality in prescribing are further endorsed by the continued growth in the utilisation of originator medicines despite generics being available at reduced prices, which can be substantial (Tables 2 and 3, 1A and 2A). The reduction in the price of generics over time mirror some of those seen among Western European countries for ARBs and statins [1-5] when compared with earlier originator prices (Tables 3 and 2A). This suggests competition among generic companies has helped reduce procurement prices over time. However, hospitals and authorities will only realise the savings if this price reduction is accompanied by their appreciably increased utilisation where generics are available for procurement. Such activities could be facilitated by enforcement of the Prescription Management Ordinance in 2007 specifying that prescriptions should be written by INN [18, 26], especially with recent

regulations improving the quality of generic medicines in China [21]. High voluntary INN prescribing rates of 98% to 99% have been achieved among a range of products and classes in Scotland through a variety of demand-side measures [2,9,10].

Thirdly, we believe based on our findings that there appear to be four different models in operation for domestically produced pharmaceuticals (Table 5).

Table 5 – Four different models for domestically produced pharmaceuticals

Model	Details
1	<ul style="list-style-type: none"> <li>• A substantial drop in drug prices does appear to affect their subsequent use</li> <li>• This was illustrated by some products no longer purchased or with limited procurement after a significant price decline, e.g. generic nifedipine, enalapril of <i>Yabao Pharmaceuticals</i>, esmolol, levocarnitine powder for injection and ligustrazine (Figures 4, 6 to 9)</li> <li>• This was also illustrated by generic simvastatin - where there was limited use (Tables 2, 1A) versus the originator. Alongside this, substantial procurement price reductions (67% over the study period)</li> <li>• The procurement price of the originator simvastatin also reduced over time but to a lesser extent (29%) (Tables 3 and 2A)</li> <li>• This may be attributable to the fact that higher prices may translate into higher profits and conversely lower prices with lower profits, with lower prices adversely affecting hospital profitability and physician salaries</li> </ul>
2	<ul style="list-style-type: none"> <li>• A small decrease in the procured price per pack, e.g.10%, did not appear to generally change utilisation trends. There may also be an increase</li> <li>• We believe this was because the whole supply chain including manufacturers and prescribing doctors could adjust their profitability mix accordingly</li> <li>• This is illustrated by generic benazepril and telmisartan as well as both originator and generic atorvastatin with increased utilisation over time despite limited decreases in procurement expenditure/ unit (Tables 2 and 3, 1A and 2A)</li> </ul>
3	<ul style="list-style-type: none"> <li>• Some drugs maintained a relatively high price during the study period and their consumption substantially increased, e.g. originator metoprolol and bisoprolol with the procurement price of metoprolol increasing during the study period (Tables 2 and 3, 1A and 2A)</li> <li>• This was also seen for oxiracetam</li> <li>• Other products with a relatively stable price over time also increased their volume in line with market growth, e.g. amlodipine besylate tablet (Figure 5) and cinepazide maleate injection (before its severe side effect became broadly known)</li> </ul>
4	<ul style="list-style-type: none"> <li>• There appears to be a “CNY 20 phenomenon”, i.e. when the procurement price per pack drops to near or below CNY 20, utilization rates usually decreased (or at least stopped increasing)</li> <li>• Examples include generic nifedipine (Figure 6), generic enalapril and generic simvastatin</li> </ul>

Consequently, we believe we can speculate on drug utilisation patterns based on these combined findings. Traditional Chinese medicines have generally been preferred first for treatment. This is followed by originators and generics with relatively procurement high prices. One generic medicine in each class typically retains reasonable utilisation, e.g. amlodipine, atorvastatin and irbesartan (Table 2) among the calcium channel blockers, statins and ARBs respectively, although their volume might be lower than the originator. A substantial drop in prices subsequently adversely affects utilisation especially if prices drop to near or below CNY 20 per pack (Table 5).

However, we acknowledge that we will have to perform specific quantitative and qualitative research with defined hypotheses before we can provide specific guidance on drug utilisation patterns alongside changes in expenditure.

With respect to the future, potential measures to enhance patient access to medicines without prohibitive increases in expenditure include enhancing INN prescribing as precisely described. They also include additional measures to further lower the price of generics given some of the low prices seen in Europe [2,3,7,10]. Alongside this, there must also be measures to enhance the rational use of medicines, which builds on the essential medicine list concept [21]. This includes encouraging the preferential prescribing of evidenced based low cost and equally effective generics versus more expensive originators. Another potential measure is to restrict prescribing choices within a class. As a result, enhance physician familiarity with the medicines they prescribe. This could potentially reduce adverse drug reactions and drug: drug interactions. This was the philosophy behind the generation of the Wise List in the Stockholm Healthcare Region, which contains approximately 200 drugs including first and second line choices covering most of the therapeutic needs in ambulatory care [52-54]. High adherence rates at 80 to 90%% to the voluntary Wise List are enhanced by the involvement of prescribers in the selection process, robust methodologies for selecting the drugs based principally on published evidence of effectiveness and safety, a comprehensive communication programme including a separate Wise List for both patients and physicians, physician trust in the guidance as well as regular feedback [52-55]. Research findings have also shown that increased adherence to the Wise List also reduces costs since medicines that have the most robust data tend to be well established medicines [52,55,56]. There are similar examples in Spain and Scotland [9,10,53].

Other initiatives include potentially introducing prescribing quality indicators, which are increasingly used in healthcare as a tool to achieve safe and quality clinical care and cost-effective therapy, as well as for professional learning, remuneration, and accreditation along with financial incentives [56-60]. Any developed indicators must have (a) content validity; (b) face validity, i.e. relevance, credibility & acceptability (c); concurrent validity – compared with the gold standard (d) construct validity – theoretical construct of quality and (e) predictive validity to be effective and sustainable in practice [61].

We are already seeing a reduction in the procurement of traditional Chinese Medicines in the Chongqing District. This will now be monitored, along with the introduction of potential suggestions to further enhance the rational use of medicines. This includes addressing current perverse incentives. As a result, ascertain whether any additional measures are still needed in the future in China to further enhance access to medicines without significantly increasing overall expenditure.

We acknowledge there are some limitations in this research. These include the fact that the utilisation and procurement data was collected from just one leading hospital in one District in China. In addition, we did not use DDDs for the reasons stated. However, we are aware that other authors have not always used DDDs in this type of research. For instance, Hoyle used a market share weighted average price to analyse cost-effectiveness [62], and Danzon and Kim defined standard units as one tablet, one capsule, or one gram, to compare the price of products in different life cycles [63]. Despite these limitations, we believe our findings are robust and transferable across hospitals and drug classes given our choice of hospital and our methodology based on actual procurement data. However, we acknowledge that follow-up studies will be needed in this and other Districts to substantiate some of the findings.

## **Conclusions**

Traditional Chinese medicines have occupied the largest market share by volume and expenditure in this District, with originators from multinational companies preferred to generics from local manufacturers in view of their relatively higher price. The findings also suggest that price alterations had an appreciable influence on subsequent utilisation patterns, especially when these were significantly decreased. However, further research is needed in this area before we can make any definitive statements. We do believe a number of measures are needed in China to moderate future growth of pharmaceutical expenditure whilst expanding healthcare access. Authorities must seek to enhance the rational use of medicines as well as address some of the barriers. These include addressing the current perverse incentives. This already appears to be happening with a recent reduction in the procurement of traditional Chinese medicines. Suggested measures also include greater encouragement of INN prescribing build on experiences among European countries.

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## Appendix

Table 1A – Utilisation of both generics and originators for 12 single cardiovascular products in the Chongqing District between 2006 to 2012

Product	1H 2006	2H 2006	1H 2007	2H 2007	1H 2008	2H 2008	1H 2009	2H 2009	1H 2010	2H 2010	1H 2011	2H 2011	1H 2012	2H 2012
<b>Beta Blockers</b>														
Metoprolol - Generic	0	0	0	0	0	0	0	0	0	0	0	0	0	0
*Metoprolol - Originator	9660	12977	13251	15051	17040	16640	18000	19920	22800	23280	26710	37440	51840	50400
Bisoprolol – Generic	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bisoprolol - Originator	4020	4380	7200	6840	8460	9840	7200	10405	15480	18900	19260	17460	20880	19980
<b>Total beta blockers</b>	<b>13680</b>	<b>17357</b>	<b>20451</b>	<b>21891</b>	<b>25500</b>	<b>26480</b>	<b>25200</b>	<b>30325</b>	<b>38280</b>	<b>42180</b>	<b>45970</b>	<b>54900</b>	<b>72720</b>	<b>70380</b>
<b>Calcium Channel blockers</b>														
**Amlodipine – Generic	4245	5200	8600	8570	9400	11800	15210	18940	23900	23670	30708	29900	31440	35070
Amlodipine – Originator	5100	2800	4500	4400	4200	5400	7866	11600	12000	14200	14900	10800	15600	26250
Nifedipine – Generic	13509	11750	12767	13361	14600	13900	14600	13830	13900	13200	14400	15200	13800	3300
Nifedipine – originator	5400	6480	9120	9530	19201	12420	15390	9990	21240	18090	18540	18630	27000	28620
Felodipine – Generic	8	240	340	780	280	800	550	500	450	490	50	200	340	900
Felodipine – Originator	2160	480	2400	4270	6317	6240	9600	10080	16464	13380	16960	19200	28560	24720
<b>Total calcium channel blockers</b>	<b>30422</b>	<b>26950</b>	<b>37727</b>	<b>40911</b>	<b>53998</b>	<b>50560</b>	<b>63216</b>	<b>64940</b>	<b>87954</b>	<b>83030</b>	<b>95558</b>	<b>93930</b>	<b>116740</b>	<b>118860</b>
Total generics	17762	17190	21707	22711	24280	26500	30360	33270	38250	37360	45158	45300	45580	39270
<b>% generics</b>	<b>58</b>	<b>64</b>	<b>58</b>	<b>56</b>	<b>45</b>	<b>52</b>	<b>48</b>	<b>51</b>	<b>43</b>	<b>45</b>	<b>47</b>	<b>48</b>	<b>39</b>	<b>33</b>
<b>Renin-angiotensin inhibitors</b>														
Benazepril – Generic				329	1080	650	200	3180	7480	7330	6240	6700	8160	7440
Benazepril – Originator	3600	2880	3520	5040	3600	7680	7560	9000	8640	9000	11460	13560	14700	16199
Irbesartan – Generic				700	4300	7000	8600	10000	15565	10170	8000	11800	11000	14000
Irbesartan – Originator	3050	3600	6700	4800	7156	5530	7880	12640	15120	17800	16920	17280	21960	21240
Losartan – Generic													1400	3200
Losartan – Originator	2760	3400	5000	5990	8000	9800	14500	8830	21800	16800	14600	21600	20800	16820
Telmisartan – Generic	252		150	1350	2753	2559	2800	2800	3600	4000	5000	4800	5575	5600
Telmisartan – Originator	982	600	1150	2437	4000	4400	5530	3400	6700	4900	5448	9400	14200	12000
Valsartan – Generic	614	200	500	700		400	450	600	750	450	800	500	775	950
Valsartan – Originator	600	1166	540	3710	6744	7665	9450	11580	11520	12480	17060	23080	28800	30080
<b>Total renin-angiotensin inhibitors</b>	<b>11858</b>	<b>11846</b>	<b>17560</b>	<b>25056</b>	<b>37633</b>	<b>45684</b>	<b>56970</b>	<b>62030</b>	<b>91175</b>	<b>82930</b>	<b>85528</b>	<b>108720</b>	<b>127370</b>	<b>127529</b>
Total generics	866	200	650	3079	8133	10609	12050	16580	27395	21950	20040	23800	26910	31190
<b>% generics (all)</b>	<b>7</b>	<b>2</b>	<b>4</b>	<b>12</b>	<b>22</b>	<b>23</b>	<b>21</b>	<b>27</b>	<b>30</b>	<b>26</b>	<b>23</b>	<b>22</b>	<b>21</b>	<b>24</b>
% generic benazepril vs. all benazepril				6	23	8	3	26	46	45	35	33	36	31
% generic irbesartan vs all irbesartan	0	0	0	13	38	56	52	44	51	36	32	41	33	40
% generic telmisartan	20	0	12	36	41	37	34	45	35	45	48	34	28	32
<b>Statins</b>														
***Atorvastatin – Generic	3840	3840	4080	4320	4460	4498	5040	6720	11039	16620	24480	33040	40010	49783
Atorvastatin – Originator	720	1200	1680	840	2455	2884	8200	12600	13920	17520	17760	16400	17520	24762
Simvastatin – Generic	268	116	96	300	912	1140	2736	1980	2640	1780	1760	1440	960	720
Simvastatin – Originator	1950	5260	7805	7799	15600	15800	15800	18520	31200	32600	31600	29200	20000	18600
<b>Total Statins</b>	<b>6778</b>	<b>10416</b>	<b>13661</b>	<b>13259</b>	<b>23427</b>	<b>24322</b>	<b>31776</b>	<b>39820</b>	<b>58799</b>	<b>68520</b>	<b>75600</b>	<b>80080</b>	<b>78490</b>	<b>93865</b>
Total generics	4108	3956	4176	4620	5372	5638	7776	8700	13679	18400	26240	34480	40970	50503
<b>% generics</b>	<b>61</b>	<b>38</b>	<b>31</b>	<b>35</b>	<b>23</b>	<b>23</b>	<b>24</b>	<b>22</b>	<b>23</b>	<b>27</b>	<b>35</b>	<b>43</b>	<b>52</b>	<b>54</b>
<b>Total all products</b>	<b>62738</b>	<b>66569</b>	<b>89399</b>	<b>101117</b>	<b>140558</b>	<b>147046</b>	<b>177162</b>	<b>197115</b>	<b>276208</b>	<b>276660</b>	<b>302656</b>	<b>337630</b>	<b>395320</b>	<b>410634</b>
Total generics	22736	21346	26533	30410	37785	42747	50186	58550	79324	77710	91438	103580	113460	120963
<b>% generics</b>	<b>36</b>	<b>32</b>	<b>30</b>	<b>30</b>	<b>27</b>	<b>29</b>	<b>28</b>	<b>30</b>	<b>29</b>	<b>28</b>	<b>30</b>	<b>31</b>	<b>29</b>	<b>29</b>

NB. Utilisation measured in package units, \* = 2 Specifications; \*\* = several manufacturers and specifications. \*\*\*= Different specification to the originator. 1H = first half of the year; 2H = second half of the year

**Table 2A – Change in procurement expenditure/ unit (CNY) for 12 single originator and generic cardiovascular and cerebrovascular drugs in the Chongqing District between 2006 and 2012**

Product	1H 2006	2H 2006	1H 2007	2H 2007	1H 2008	2H 2008	1H 2009	2H 2009	1H 2010	2H 2010	1H 2011	2H 2011	1H 2012	2H 2012	% change	2H 2012 % vs. pre- originator loss prices	% difference generic 2H 2012 generic vs. originator 1H2006
*Metoprolol - Originator	10.02	8.59	8.67	9.51	8.68	9.02	9.22	9.60	9.70	9.63	12.72	12.92	13.92	13.78	37		
Bisoprolol - Originator	32.35	30.90	30.90	30.91	30.91	30.91	30.91	30.91	30.91	30.63	30.43	30.40	30.40	30.40	-6		
**Amlodipine - Generic	32.77	31.46	34.56	37.40	36.94	36.98	37.21	38.44	39.11	38.20	38.32	38.37	38.19	39.10	19		0
Amlodipine - Originator	39.03	37.17	36.83	39.29	36.78	36.78	36.77	36.76	36.78	36.03	33.73	33.13	33.13	32.81	-16		
Nifedipine - Generic	19.31	18.18	15.85	14.27	14.43	13.69	14.38	14.10	14.74	14.61	13.58	12.84	12.91	12.84	-34		-64
Nifedipine - Originator	35.45	33.50	33.50	34.51	33.50	33.50	33.50	33.50	33.50	33.45	31.38	31.13	31.13	31.13	-12		
Felodipine - Generic	14.68	25.80	25.80	25.88	25.39	25.39	25.39	25.39	25.39	25.39	25.39	29.04	35.29	35.29	140		-3.4
Felodipine - Originator	36.55	34.20	34.20	34.78	34.20	34.11	34.07	34.20	33.99	33.54	33.12	32.31	32.50	32.50	-11		
Benazepril - Generic				35.70	35.70	35.70	35.70	35.70	35.70	35.70	32.21	29.22	29.22	29.22	-18	-38	
Benazepril - Originator	48.05	46.83	46.83	46.83	46.83	46.83	46.83	46.83	46.83	46.83	45.16	44.00	44.00	43.30	-10		
Irbesartan - Generic				22.96	22.95	22.95	22.95	22.95	22.95	22.95	20.65	18.34	18.34	18.34		-41	
Irbesartan - Originator	32.73	31.26	31.26	31.65	31.26	31.26	31.26	31.26	31.26	31.26	31.26	31.26	31.26	31.26			
Losartan - Generic													66.08	66.08	0	42	
Losartan - Originator	49.29	48.34	48.44	49.85	48.25	48.32	49.30	48.89	49.72	47.78	45.93	46.63	45.93	50.11	2		
Telmisartan - Generic	22.67		35.22	36.00	35.22	35.22	35.22	35.22	35.22	35.22	28.11	20.53	20.71	20.71	-9		-41
Telmisartan - Originator	35.02	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	34.15	-2		
Valsartan - Generic	20.69	19.84	19.84	19.84		19.84	19.84	19.84	19.84	19.84	17.44	16.00	16.00	16.00	-23		-64
Valsartan - Originator	44.60	43.28	42.78	43.75	42.78	42.78	42.78	42.78	42.78	42.78	41.10	39.75	39.60	38.61	-13		
***Atorvastatin - Generic	35.09	33.21	31.00	30.59	30.09	30.09	30.09	30.09	30.09	31.90	30.14	28.05	28.92	29.00	-17		-57
Atorvastatin - Originator	67.72	67.00	67.00	67.00	67.00	67.02	67.00	67.00	67.00	67.00	66.67	62.24	62.24	62.24	-8		
Simvastatin - Generic	28.07	27.54	25.81	24.67	24.09	24.09	24.09	23.52	21.74	19.57	13.74	13.74	13.74	9.32	-67		-82
Simvastatin - Originator	51.82	50.30	50.30	51.07	50.30	50.30	50.30	50.30	26.70	26.67	26.62	36.53	36.81	36.81	-29		

NB. \* = 2 Specifications; \*\* = several manufacturers and specifications. \*\*\*= Different specification to the originator. 1H = first half of the year; 2H = second half of the year