Review of ongoing initiatives to improve prescribing efficiency in China; angiotensin receptor blockers as a case history

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Abstract

Introduction: Pharmaceutical expenditure is rising by 16% per annum in China and is now 46% of total expenditure. Initiatives to moderate growth include drug pricing regulations and encouraging INN prescribing. However, no monitoring of physician prescribing quality and perverse incentives. Objectives: Assess changes in ARB utilisation and expenditure as more generics become available; compare findings to Europe. Methodology: Observational retrospective study of ARB utilisation and expenditure between 2006 and 2012 in the largest hospital in Chongqing District. Results: Variable and low use of generics versus originators with a maximum of 31% among combined single ARBs. Lower for Fixed Dose Combinations. Prices typically reduced over time, greatest for generic telmisartan (-54%), mirroring price reductions in some European countries. However, no preferential increase in prescribing of lower cost generics. Accumulated savings of 33million CNY for this large provider if adopted European practices. Conclusion: considerable opportunities to improve prescribing efficiency in China.

Introduction

There is increasing scrutiny over pharmaceutical expenditure across countries with growth rates averaging 50% in real terms during the past decade [1,101], driven by well-known factors including ageing populations and new premium priced drugs [1-3, 101]. This has resulted in multiple reforms across countries. Initiatives for established drugs include measures to enhance the utilisation of low cost generics versus originators and single sourced (patented) products in a class or related class where all products are seen as essentially therapeutically similar. Classes include the proton pump inhibitors (PPIs), statins and renin-angiotensin inhibitor drugs [1,3-13], with the latter including both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Savings can be substantial with greater utilisation of generics versus originators and patented products in a class without compromising care, with prices of generics as low as 2% to 10% of pre-patent loss prices in some countries [1,3-8,14-17]. Multifaceted demand-side measures to enhance their prescribing include encouraging high International non-proprietary name (INN) prescribing,

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formularies, prescribing guidance, continuous medical education, quality circles, strengthening of drug and therapeutic committees (DTCs), prescribing targets, financial incentives and prescribing restrictions [1,3-8,10-13,18,19]. Examples of the impact of multifaceted supply- and demand-side measures are included in Table 1.

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Table 1 – Influence of multiple supply- and demand-side measures on the utilisation and expenditure of PPIs, statins and renin-angiotensin inhibitor drugs among selected European countries [1,3,5-8]

Country	Impact of initiatives
Netherlands	• Reimbursed expenditure for the PPIs fell by 58% in 2010 vs. 2000 despite a 3 fold increase in utilisation • Reimbursed expendiure for the statins fell by 14% in 2010 vs. 2000 despite a 3-fold increase in utilisation
Sweden	• Reimbursed expenditure for the PPIs and statins decreased by 49% and 39% in 2007 vs. 2001 respectively despite a 53% and 3.2 fold increase in their utilisation
UK (Scotland)	• Reimbursed expenditure on PPIs in 2010 was 56% below 2001 levels despite a 3 fold increase in utilisation; expenditure would have been GB£159million greater in 2010 for a 5.2 million population without such measures • Reimbursed expenditure on the statins in 2010 was only 7% above 2001 levels despite a 6.2 fold increase in utilisation; expenditure would have been GB£290million greater in 2010 for a 5.2 million population without such measures • Reimbursed expenditure on the renin-angiotensin inhibitor drugs remaining relatively stable between 2001 and 2007 despite a 159% incease in utilisation

Considerable savings can also be achieved in low- and middle income countries from switching originators to the lowest-priced generic drugs [20-22].

China has also seen considerable increases in pharmaceutical expenditure, growing at over 16% per annum during the past decade [22,23]. This growth has been principally driven by increase insurance coverage. The Chinese government has introduced three different types of health insurance targeting different populations, with coverage reaching over 90% of the population by 2011 [24-26]. The ultimate goal is universal coverage by 2020 [24-29]. As a result of increased coverage, healthcare expenditure increased from 3.5% to 5% of GDP between 1995 and 2010, equating to a ten-fold increase in per capita spending from US$21 to 220 [26].

As a result, China has introduced a number of measures in recent years to help moderate this growth [22,23,25,26]. The principal measures have concentrated on trying to control pharmaceutical prices and expenditure in hospitals. This is because more than 80% of total pharmaceutical consumption is currently dispensed in public hospitals in China [22,23,30]. In 2010, pharmaceutical revenues for Chinese public hospitals were 405.39billion CNY (approximately US$62.4billion), 46% of total healthcare expenditure [22,102], with out-of-pocket payments accounting for 36% of total healthcare expenditure [26]. This includes mechanisms to lower the price of drugs [22,23]. For state-priced products, the National Development and Reform Commission (NDRC) sets maximum retail prices (price caps) including mark-ups; for province- or municipality-priced products, the price management department determines the retail prices; and for other products the ex-factory and retail prices are determined by the manufacturers [22,26,31,32]. For instance, the NDRC has implemented 28 price adjustments between 1997 and 2011 to address potentially high prices for common or expensive medicines such as cardiovascular drugs or anticancer drugs [22,33].

Medicines in hospitals are subject to tenders in each province and municipality with each hospital pharmacy subsequently having its own product list and prices, e.g. for cardiovascular drugs prices have changed four times between 2006 to 2011 in Chongqing Urban District alone [22,33]. Published studies have suggested these bidding processes reduced prices of essential medicines by 16.9% between 2009 and 2011 [26]. However, there are no pricing policies for generics in China unlike measures across Europe which have led to low prices [1,3-8,34]. In addition in the current system, hospitals typically use the profits from medicine procurement for their sustainability [31,103], with pharmaceutical expenditure in hospitals accounting for between 41.5% to 46% of hospitals' total

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income between 2006 and 2010 [22,32,35,36,102]. This is because the financial support of the Chinese government to public hospitals declined steadily from approximately 60% of hospital revenues in 1980s to 8.2% by 2003. Consequently, hospitals use the revenue from drug procurement for their sustainability with a permitted 15% mark-up [26,32]. Even with measures to reduce procurement prices, the actual mark-up of medicines in hospitals in 2005 averaged approximately 42% [32]. There are also inducements for physicians to overprescribe drugs as well as prescribe drugs that produce the greatest profit for them and the hospital [22,31]. This situation is exacerbated by currently low salaries for physicians in China with many physicians earning 5000 CNY (US$780) a month or less [37].

The lack of policies have resulted in more than 5,000 pharmaceutical manufacturers in China producing mainly generics [22,32]. It is envisaged that greater transparency in pharmaceutical pricing may lead to further price reductions [26]. However, this remains to be seen.

Demand-side measures in China include the development of an essential medicine list, clinical guidance and guidelines [23,26,35,38,103]. However, currently there are no measures among public insurers to monitor the quality of prescribing [31,36], with emphasis principally on procurement activities. There were reforms in 2007 - the 'Prescription Management Ordinance' - specifying that prescriptions should be written by INN. However, to date there has been limited enforcement [22,32]. As a consequence, physicians tend to write prescriptions with the generic (INN) name and simultaneously indicate the brand or manufacturer name; alternatively, drugs are listed with the corresponding brand name or manufacturer in hospitals' IT system [22,27]. This is not helped by similar patient co-payments for an originator or generic.

The current incentives as well as limited demand-side measures have resulted in considerable irrationality in prescribing despite some measures to improve this [26,31,32]. This is illustrated by continued appreciable use of injectable drugs in China as well as considerable prescribing of antibiotics [31,39].

These various initiatives in China translated in a variety of outputs (Box 1) when utilisation and expenditure was recently analysed for cardiovascular medicines in the Chongqing Region of China [22].

Box 1 – Findings for cardiovascular medicines in the Chongqing Region in China 2006 to 2011 [22]

- The market share of generics among 12 leading cardiovascular (CV) drugs decreased from 50% in the first half of 2006 to 34% by the end of 2011, with the market share of originators increasing to 66% by the end of 2011 (DDD based)
- The market share of originators appreciably increased between 2006 and 2008. Narrower fluctuations after this
- Generic versions were available for all 12 drugs from 2006
- The price of originators were on average 63% higher than generic prices in 2011
- Prices of generics for the 12 CV drugs varied from 66% to 98% price of the originator in 2011
- There was potential for considerable savings with greater use of generics if this could be engineered alongside obtaining lower prices where possible

We would like to build on these findings looking specifically at angiotensin receptor blockers (ARBs). The reasons for this are included in Box 2.

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Box 2 – Rationale for the current study researching ARBs in China [3,10,11,14,15,18,22,32,41-43,55-57,106]

- Ischaemic heart disease and cerebrovascular disease are now among the leading causes of death in China
- Previous studies have shown appreciable price reductions for generics; however, other studies have shown less of a difference
- Generic losartan recently became available in Western Europe with all angiotensin receptor blockers (ARBs) seen as essentially similar at appropriate doses
- There was considerable variation in demand-side measures among Western European countries to encourage the prescribing of losartan once generics became available, which has resulted in appreciable differences in losartan utilisation post generics without compromising care. There were also appreciable differences in generic losartan prices. Consequently, providing an opportunity to compare the findings with China
- Between 2006 and 2012, some generic ARBs alone or in fixed dose combinations (FDCs) were included in hospital lists in China providing opportunities to further evaluate generic penetration rates and savings building on Box 1

Consequently, the principal objectives of this study are to assess changes in ARB utilisation in China as more generic ARBs are incorporated into hospital procurement lists, which includes assessing changes in the utilisation of originator versus generic ARBs over time; similarly ARB Fixed Dose Combinations (FDCs). Secondly, assess changes in ARB and ARB FDC expenditure over time as well as for generic and originator ARBs and ARB FDCs. This includes price reductions over time

We will subsequently compare the findings with Western European countries with China striving for universal coverage, which is routine among Western European countries. This will provide a basis for suggesting potential future reforms that have been successful in Europe for the authorities in China to consider to achieve their aims without further growth at over 16% per annum.

We would expect to see greater prescribing of originators than generics building on our earlier findings (Box 1). In addition, variable and sometimes limited price reductions for generics versus originators and versus pre-generic inclusion prices. We expect price reductions to be less than those seen among some Western European countries for high volume generics including losartan (Box 1). This is despite multiple generic ARBs being available in China (Table 2) [102].

Table 2 - Registered number of approvals for production of generic angiotensin receptor blockerss in China in October 2013 [107]

ARBs	Losartan	Valsartan	Irbesartan	Telmisartan	Candesartan
Registered numbers of approval	34	43	41	117	32

Methodology

This was an observational retrospective study of prescriptions dispensed over a seven year period between 2006 and 2012 [40]. This includes the time period of the previous study (Box 1). This methodology was chosen since multiple supply- and demand-side measures have been introduced during this period in China making it difficult to perform an interrupted time series analysis. In addition, there have been multiple changes to the procurement of single and ARB FDCs over time (Table 3).

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Table 3 – Procurement of single ARBs and ARB fixed-dose combinations (FDCs) in the Chongqing District from 2006 to 2012

ARB single	Date originator available	Date when generics first part of hospital procurement
Candesartan	Not available	Available in 2006
Irbesartan	2006	2007 (October)
Losartan	2006	2012 (March)
Telmisartan	2006	Available in 2006
Valsartan	2006	Available in 2006
ARB FDCs		
Irbesartan FDC	2006	2008 (March)
Losartan FDC	2006	2010 (May)
Valsartan FDC	2006	Not available

NB Generic ARBs and FDCs may be available in China during previous years. However, not included in the procurement process in view of the considerable data that must be provided as part of tendering

Typically for these types of drug utilisation analysis, data is obtained from health authority, health insurance or pharmacy databases [5-8,10,11,15,41-43]. However in China, most drug utilisation studies are performed with data from hospitals as they incorporate both inpatient and outpatient data [22,44]. In addition, as mentioned, they account for 80% of total drugs currently dispensed in China [22]. This is in view of the convenience of hospital dispensing, physician recommendations, possibility of nonstandardized prescriptions and greater assurance of pharmaceutical quality in hospitals [32]. The quality of pharmaceuticals in hospitals is enhanced by strict quality control as part of the tendering process [32]. This builds on reforms to improve the manufacturing standards of generic drugs in China implemented from 2000 onwards [26], e.g. in 2009 all medicines on the Chinese Essential Medicines List (EML) 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 to be considered for procurement [26].

Consequently, hospital procurement data is currently the 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 profit hospitals make from medicines [31,32]. This data is not always available from some commercial sources, which just provide maximum retail price data [23]. Hospital procurement prices are also not always captured in health insurance data. In addition, hospitals may procure medicines that are not currently reimbursed. As a result, further reducing the utility of health insurance data as a data source for comprehensive drug utilisation studies in China.

Chongqing is a municipality directly under China's central government, with a total population of 28.8 million people (2010 census). 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 [22]. However, in view of the complexity of the procurement process only the largest hospitals tend to have a comprehensive range of products available for prescribing.

In view of these factors, we chose the largest hospital in Chongqing District to conduct our study. This is because it is one of the largest hospitals in Southwest China, has a wide range of medicines available for prescribing, can provide comprehensive datasets on both utilisation and expenditure and is a typical health provider to the public. 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 through co-operation with public hospitals. The data contains all individual drug information including product names, purchase dates, dosage forms, specifications, 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 [22].

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The Chinese currency Renminbi "*yuan*" (CNY) was used to determine expenditure and expenditure/ DDD for ARBs and ARB FDCs over time. These were not adjusted for inflation or deflation during this period as we wanted to compute actual changes over time as a result of the tendering process. This is because most health authorities typically decrease prices when budgets are being exceeded [45,46] making adjustments based on factors such as retail price indexes or purchasing price parity difficult to justify when reviewing pharmaceutical prices. This is in line with previous studies [5-8,10,11,41,42]. 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. Originator ARBs are referred to as products currently or previously possessing intellectual property (patent), which are either from multinational companies or manufactured by joint ventures in China founded by multinational pharmaceutical companies. Generic drugs are domestic products produced by Chinese enterprises with local investment, including state-owned and private enterprises. There is strong competition with a number of manufacturers (Table 2).

Five single ARBs and three ARB FDCs were available in the target hospital (ATC C09CA01 to 09, C09DA01 to 05, C09DX01 to 03 [104]) between 2006 and 2012 (Table 3). Utilisation was measured in terms of Defined Daily Dose, with DDDs defined as '*the average maintenance dose of a drug when used in its major indication in adults*', with this measure recognised as the international standard to assess utilisation patterns within and between countries [105]. The data was subsequently aggregated for analysis. 2011 DDDs were used in line with international guidance [47,48,105]. The WHO methodology used to calculate the DDDs for combination products, based on the principle of counting this as one dose [105].

We subsequently divided ARBs into single and ARB FDCs as ARB FDC utilisation varied considerably among Western European countries, ranging from 2% to 3% of ARB/ losartan utilisation in the UK to 50% in Austria [10,41-43]. This was due to issues such as the extent of increased compliance in practice, economics as well as access to diuretics.

A narrative review of published studies to appraise the utilisation and expenditure of ARBs among selected Western European countries was undertaken by one of the co-authors (BBG). The studies selected were based on multiple publications that the co-authors were involved with providing exemplars of potential measures the authorities in China could consider as they move towards universal coverage.

Results

Utilisation

There was an appreciable increase in the prescribing of ARBs alone or as FDCs, rising 12 fold from just over 209,000 DDDs in 2006 to 2.45million in 2012 across all products (Figure 1).

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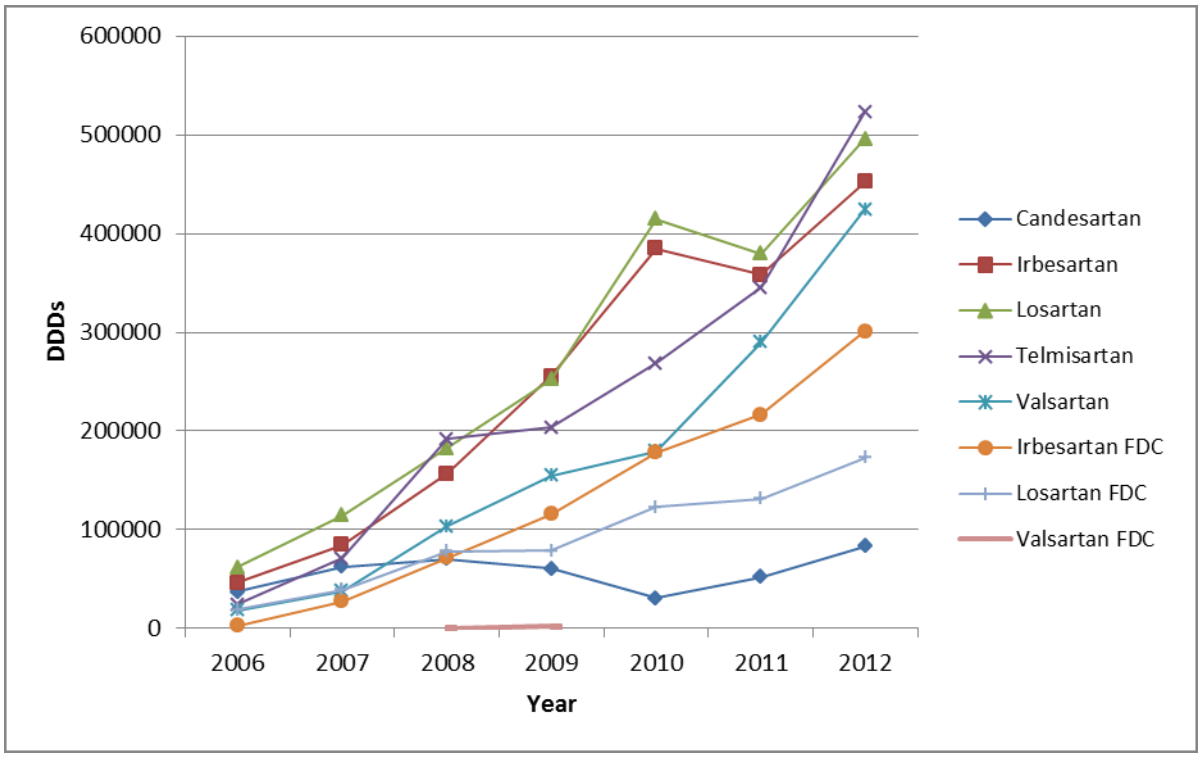
Figure 1 – Utilisation of single and FDC ARBs (DDDs) between 2006 and 2012 in the Chongqing District from 2006 to 2012



NB. FDCs = Fixed Dose Combinations.

The greatest increase in utilisation was seen for both telmisartan and valsartan among the single ARBs and for irbesartan among the FDCs (Figure 1, Table 4). However, there was variable use of generic versus originator ARBs, i.e. there was a rapid increase in the use of generic irbesartan peaking at 44% of total irbesartan in 2009 before declining to 33%. A similar pattern was seen for telmisartan peaking at 40% of total telmisartan utilisation in 2011 before falling to 30% in 2012. There was also an increase in generic candesartan in 2012 vs. 2006, although this varied by year (Figure 1) resulting in its share of total single ARBs falling from 20% in 2006 to between 2% to 4% between 2010 and 2012 (Figure 1, Table 4).

The variable use of generics among the single ARBs led to their overall utilisation increasing from 24% of total single ARBs in 2006 to 31% in 2008 before falling to between 22% and 24% between 2010 and 2012 (Table 4). This was despite increasing availability of generic ARBs (Tables 2 and 3).

There was also a 21.5 fold increase in ARB FDC utilisation between 2006 and 2012, greatest for irbesartan FDC (108 fold) (Figure 1, Table 4). As a result, there was increasing use of ARB FDCs as a % of total ARBs, rising from 11% in 2006 to stabilising at 19% to 20% between 2010 and 2012. There was also increasing use of generic ARB FDCs reaching 19% of total ARB FDCs in 2012.

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Table 4 – Consolidated utilisation of single and FDC ARBs (in DDDs) including generics and originators in the Chongqing District from 2006 to 2012

Single ARBs	2006	2007	2008	2009	2010	2011	2012	Degree of change
Candersartan Generic	36960	62580	70560	60480	30880	52400	83190	2.3
Losartan								
Losartan - Originator	61740	114597	182700	252210	414400	379400	431340	
Losartan - Generic							64400	
Losartan - Total	61740	114597	182700	252210	414400	379400	495740	8.0
% Generic							*13*	
Irbesartan								
Irbesartan – Originator	46550	80500	88802	143640	230440	239400	302400	
Irbesartan - Generic		4200	67800	111600	154410	118800	150000	
Irbesartan – Total	46550	84700	156602	255240	384850	358200	452400	10
% Generic		*5*	*43*	*44*	*40*	*33*	*33*	
Telmisartan								
Telmisartan – Originator	22148	50218	117600	125020	162400	207872	366800	
Telmisartan – Generic	1764	21000	74368	78400	106400	137200	156450	
Telmisartan – Total	23912	71218	191968	203420	268800	345072	523250	22
% Generic	*7*	*29*	*39*	*39*	*40*	*40*	*30*	
Valsartan								
Valsartan – Originator	12362	29750	100863	147210	168000	280980	412160	
Valsartan – Generic	5698	8400	2800	7350	11200	9100	12075	
Valsartan – Total	18060	38150	103663	154560	179200	290080	424235	23.5
% Generic	*32*	*22*	*3*	*5*	*6*	*3*	*3*	
Combined total								
Total Generic Single ARBs	44422	96180	215528	257830	302890	317500	466115	10.5
Total Single ARBs	187222	371245	705493	925910	1278130	1425152	1978815	11
% Generic	*24*	*26*	*31*	*28*	*24*	*22*	*23*	
FDC ARBs								
Irbesartan FDCs								
Irbesartan FDC – Originator	2800	27314	58100	92960	133560	166320	223440	
Irbesartan FDC – Generic			13510	23100	44520	50400	77840	
Irbesartan FDC – Total	2800	27314	71610	116060	178080	216720	301280	108
% Generic FDC			*19*	*20*	*25*	*23*	*26*	
Losartan FDCs								
Losartan FDC – Originator	19306	38850	78400	79100	119490	121800	160370	
Losartan FDC – Generic					3500	9800	12880	
Losartan FDC – Total	19306	38850	78400	79100	122990	131600	173250	9
% Generic FDC					*3*	*7*	*7*	
Valsartan FDC – originator			350	1960				
Combined total								
Total generic FDCs			13510	23100	48020	60200	90720	
Total FDCs	22106	66164	150360	197120	301070	348320	474530	21.5
% Generic FDCs			*9*	*12*	*16*	*17*	*19*	
All ARBs								
Total ARBs (all)	209328	437409	855853	1123030	1579200	1773472	2453345	12
Total single ARBs (%)	89	85	82	82	81	80	81	

NB. FDCs = Fixed Dose Combinations. % Single ARBs = % single ARBs vs. total ARBs

Expenditure

Total ARB expenditure (single and FDCs) also increased appreciably, rising from just over 1million CNY in 2006 to 9.87million CNY in 2012 (Figure 2).

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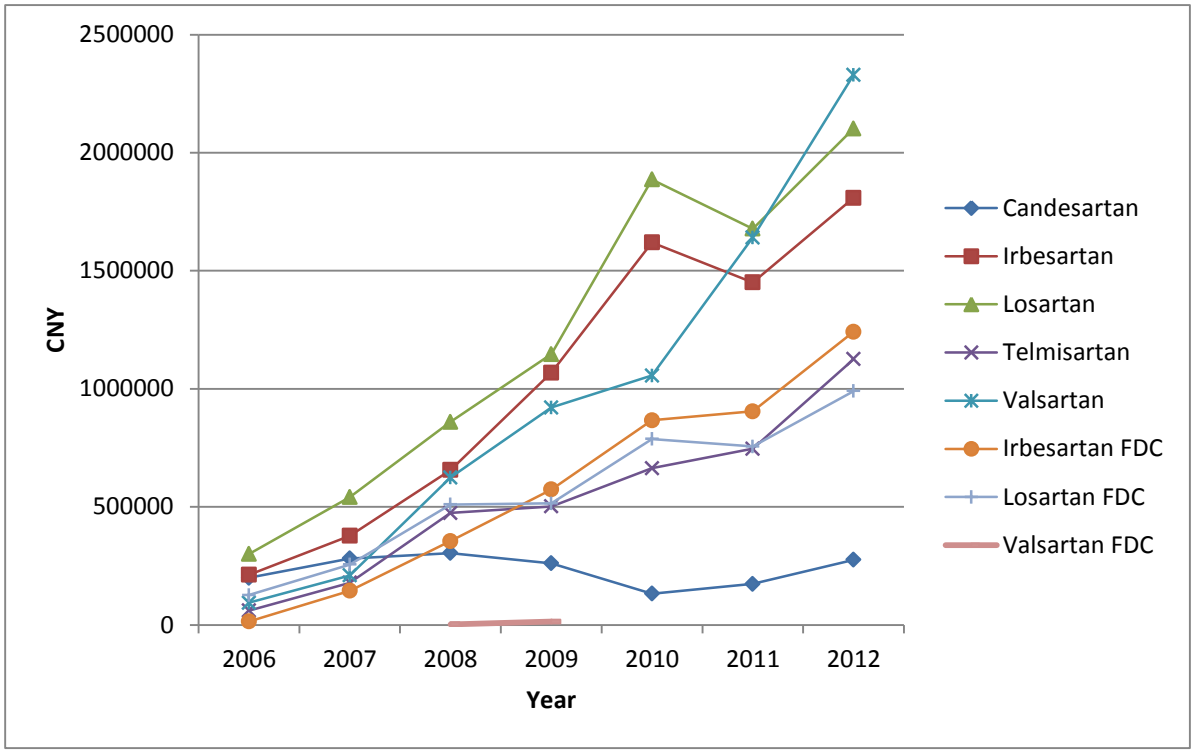
Figure 2 – Total expenditure of ARBs (single and FDCs) 2006 to 2012 in Renminbi "*yuan*" (CNY) in the Chongqing District from 2006 to 2012



NB. FDCs = Fixed Dose Combinations.

The lower increase in total expenditure (9.8 fold) versus utilisation (12 fold) was helped by reducing expenditure/ DDD for the various ARBs (Table 5). However, there was only a marginal decrease for single originator ARBs combined at 7% in 2012 vs. 2006 compared with a 44% procured price reduction for generics. This resulted in an overall 17% price reduction for single ARBs combined between 2006 and 2012 (Table 5).

There was also considerable variation in procured price reductions for individual generic ARBs over the course of the study. These ranged from 22% for generic valsartan to 39% for candesartan and 54% for telmisartan. Expenditure/ DDD for generic irbesartan was 33% below pre-inclusion prices in 2012 (Table 5). There were also variable differences in procured prices of generic versus originator single ARBs. This was greatest for valsartan reaching 59% in 2012. This compares to a maximum of 32% for irbesartan in 2012, with the difference steadily growing over time. There was considerable variation for telmisartan, ranging from a 31% increase in 2006 to a 39% decrease in 2012, with again a greater decrease in recent years.

There was a greater procured price reduction for combined originator FDCs at 21% during the study period versus single originator ARBs at 7%. Expenditure/ DDD for generic FDCs combined reduced by 49% in 2012 vs. combined originator FDC prices in 2006 (Table 5).

One reason for increased utilisation of irbesartan FDCs in recent years (Table 4) could be the limited procured price differential between originator and generic single drugs and corresponding FDCs in 2011 and 2012, with a maximum 18% difference between originator single and FDCs in 2007. However, there were no appreciable price differences between generic single and FDC irbesartan between 2008 and 2012. In fact in 2011 expenditure/ DDD for the generic FDC irbesartan was lower than single irbesartan (Table 5).

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Table 5 – Expenditure/ DDD for single ARBs (generic and originator) and FDC ARBs (generic and originator) in the Chongqing District from 2006 to 2012

ARB single	2006	2007	2008	2009	2010	2011	2012	% change 2012 vs. 2006	% change in 2012 vs. pre-patent loss
Candesartan (generic)	5.397	4.492	4.310	4.310	4.294	3.313	3.315	-39	
Irbesartan – Originator	4.562	4.489	4.466	4.466	4.466	4.466	4.466	-2	-2
Irbesartan – Generic		3.827	3.825	3.825	3.825	3.212	3.057		-33
Irbesartan % Difference		***-15***	***-14***	***-14***	***-14***	***-28***	***-32***		
Losartan (Originator)	4.865	4.719	4.705	4.546	4.552	4.423	4.169	-14	-6
Losartan (Generic)							4.720		7
% Losartan Difference							***13***		
Telmisartan – Originator	2.478	2.480	2.439	2.439	2.439	2.439	2.439	-2	
Telmisartan – Generic	3.239	2.566	2.516	2.516	2.516	1.743	1.479	-54	
Telmisartan % Difference	***31***	***3***	***3***	***3***	***3***	***-29***	***-39***		
Valsartan – Originator	6.247	6.232	6.111	6.111	6.111	5.761	5.585	-11	
Valsartan – Generic	2.925	2.834	2.834	2.834	2.630	2.412	2.286	-22	
Valsartan % Difference	***-53***	***-55***	***-54***	***-54***	***-57***	***-58***	***-59***		
Total Single ARBs – originator	4.516	4.407	4.407	4.480	4.449	4.399	4.195	-7	
Total single ARBs – Generic	4.994	3.898	3.519	3.512	3.369	2.571	2.783	-44	
Total single ARBs	***4.629***	***4.275***	***4.136***	***4.210***	***4.193***	***3.992***	***3.862***	-17	
ARB FDCs									
Irbesartan FDC – Originator	5.196	5.296	5.196	5.196	5.184	4.471	4.471	-14	-16
Irbesartan FDC – Generic			3.913	3.913	3.913	3.194	3.114		-41
% Irbesartan Difference			***-25***	***-25***	***-25***	***-29***	***-30***		
Losartan FDC – Originator	6.548	6.577	6.507	6.507	6.476	5.892	5.863	-10	-10
Losartan FDC – Generic					3.897	3.897	3.897		-40
% Losartan FDC Difference					***-40***	***-34***	***-34***		
Valsartan FDC – originator			6.963	6.963					
Total generic FDCs			3.913	3.913	3.912	3.309	3.225		-49
Total originator FDCs	6.377	6.048	5.952	5.812	5.794	5.072	5.053	-21	

NB. FDCs = Fixed Dose Combinations. Pre-patent loss = pre-procurement of generics (although may have been available for procurement before this)

There were considerable differences in the utilisation of losartan among selected Western European countries post generics (Table 6). Similarly for price reductions for generic losartan over time versus pre-patent loss prices.

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Table 6 – Differences in demand-side measures among selected European countries to enhance losartan utilisation post generics and their impact [10,11,39,41,55,56]

Country	Summary demand-side measures	% losartan utilisation time 0	% losartan utilisation at the study end	% price generic losartan vs. originator
Austria	• Prescribing restrictions removed for losartan but not the other ARBs • Potential sanctions for physician abuse including financial penalties	10%	17%*	17%
Belgium	• Prescribing restrictions removed for losartan but not for patented ARBs • Patented ARBs still needed prior approval from health insurers - otherwise a 100% co-payment	20%	24%*	54%
Denmark	• Delisting of all other ARBs other than losartan from the reimbursed list • Patients can be prescribed another ARB. However the prescription must be justified and accepted – otherwise 100% co-payment	35%	93%*	12% (total losartan)
Ireland	• No specific activities undertaken	24%	23%	56%
Scotland	• No specific activities undertaken • However, losartan 99% generic due to high voluntary INN prescribing	33%	34%**	12%
Spain (Catalonia)	• No specific activities undertaken	17%	19%	32%
Sweden	• Multiple demand-side measures including formularies recommending losartan; academic detailing; prescribing targets for % losartan, therapeutic switching programmes among some Counties (regions) and physician or practice based financial incentive schemes • Ongoing compulsory generic substitution in pharmacies (resulting in losartan 97% generic) • From May 2011, prescribing restrictions lifted for losartan but not the other ARBs	27%	39%*	10%

NB. Utilisation measured in DDDs and % refers to % losartan vs. other single ARBs. Time 0 = time when generic losartan first reimbursed. Study end varied from 13 to 30 months post generic losartan. % price generic losartan = % price by the study end vs. the pre-patent loss price of the originator (typically reimbursed expenditure/ DDD). ARBs = angiotensin receptor blockers. * = statistically significant difference. ** Not statistically significant

A similar situation was seen in one Primary Care Organisation in the UK to that in Scotland and Sweden [10,15,43]. Initially, there was no immediate change in losartan utilisation following generics with no specific demand-side measures similar to Scotland. However, subsequent multiple demand-side measures similar to Sweden (Table 6) resulted in losartan increasing from 26% of all single ARBs to 65% 7 months later, leading to appreciable savings [15].

Discussion

We will initially discuss utilisation and expenditure patterns in the Chongqing District before comparing the findings with Western European countries (Table 6) as a basis for suggesting future initiatives in the region. As expected, there was variable utilisation of originator ARBs as more multiple sourced ARBs become available (Tables 3 and 4).

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However, there appeared to be variable rationality in prescribing with the utilisation of both valsartan (most expensive originator) and telmisartan (cheapest originator varying between 56% to 60% lower than valsartan between 2010 and 2012) growing substantially during the study period with telmisartan accounting for 26% of total single ARBs by 2012 and valsartan 21% (Tables 4 and 5). In addition, the utilisation of both candesartan and irbesartan, with the prices of originators between valsartan and telmisartan, decreased as a percentage of total single ACEIs during the study period (Tables 4 and 5). This irrationality continued with generic ARBs with their utilisation reaching a maximum 28% to 31% of total single ARBs between 2008 and 2009 before falling to 22% to 24% between 2010 and 2012 (Table 4), with the price difference between the most expensive originator ARB and cheapest generic ARB being 59% in 2010 and 74% in 2012 (Table 5).
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This was different for the FDCs. The combined utilisation of generic FDCs rose steadily throughout the study, reaching 19% of total ARB FDCs in 2012 (Table 4). Overall, there was a steady increase in FDC utilisation, stabilising at 19% to 20% of total ARBs by 2012 (Figure 1, Table 4). This may be facilitated by similar prices for single ARBs and FDCs in some cases as seen with irbesartan (Table 5). However, it is difficult to comment further without specific research.

The various findings appear to confirm continued irrationality in the prescribing of single ARBs, mirroring the findings in other classes and with injectables versus oral drugs [22,31,39,49]. Having said this, there appears to be progress with obtaining reasonable price reductions for generics versus originators in hospitals in China, building on the many supply-side measures and initiatives described earlier. This can be seen with procured price reductions for generic single ARBs versus pre-patent loss prices (Table 5) matching some of those seen among some Western European countries (Table 6). This can also be seen with a 54% reduction in the procured price of generic telmisartan over time as well as a 33% to 41% price reduction for irbesartan generics and irbesartan FDCs respectively in 2012 vs. pre-patent loss prices. We believe the procured price reduction for generic temisartan would have been greater if we were able to obtain earlier procured prices. This matched some of the price reductions seen with the earlier research (Box 2).

However, we believe there are still opportunities for further price reductions to match those for generic losartan in Denmark, Sweden and the UK (Scotland) (Table 6). Potential initiatives could include new regulations encouraging greater transparency in the pricing of generics. In the UK, this resulted in the prices of generics falling by 32.4% in the first year of the introduction and generic simvastatin just 3% of pre-patent loss prices in recent years [1,3,7,34].

There are also considerable opportunities to enhance the utilisation of low cost generics versus originators especially following the reforms to improve manufacturing standards for generics [26,32]. However, it is likely future demand-side measures will have only limited success unless the perverse incentives for physicians and hospitals are substantially reduced, which currently encourage the prescribing and dispensing of premium priced originators versus generics (Tables 4 and 5). Once addressed, potential demand-side measures could include greater enforcement of INN prescribing. Voluntary INN prescribing in Scotland, achieved through a variety of demand side measures, including physician training in medical schools and follow-up in ambulatory care, resulted in INN prescribing rates of 98% to 99% of total utilisation among a range of classes and drugs [34]. There are also potential measures to enhance the rational use of medicines building on the essential medicine list concept [26,31]. This includes encouraging the preferential prescribing of low cost multiple sourced drugs versus more expensive originators. Restricting prescribing choices will enhance physician familiarity with the medicines they prescribe. As a result, reduce potential adverse drug reactions and drug: drug interactions as well as strengthening the procurement process. 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 needs in ambulatory care [4,19,50]. An additional 100 drugs are included in a separate list reserved for common needs in specialist in- and out-patient care. High adherence rates at 80 to 90%% to the voluntary Wise List are enhanced by the involvement of prescribers in the selection process, a comprehensive communication programme including a separate list for both patients and physicians, physician trust in the guidance as well as regular feedback [4, 19,50]. Increased adherence also reduces costs [4,16,19]. There are similar examples in Spain and Scotland [7,34,50].

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Such a system could be introduced in Chongqing District along with continuous medical education and strengthening of hospital DTCs, providing an exemplar to other provinces and municipalities throughout China as they tackle similar issues. However, this will need strong leadership including instigating quality measures and involving prescribers to attain success [51]. Restricting the formulary to just one ARB and one ARB FDC based on the cheapest ARB (telmisartan for single ARBs and irbesartan for FDCs) would have saved an accumulated17million CNY for this leading hospital alone between 2006 and 2012. This is in line with Denmark as well as Sweden and NHS Bury (UK) with their active switching policies along with other measures (Table 6) without affecting care [10,11,14,15,17]. Accumulated savings increase to 33million CNY with generic pricing similar to Scotland (Table 6).

We believe these findings are generalizable to other classes and other hospitals in China given our methodology as well as the current regulations and tendering system in China. However, this remains to be seen and is a recognised weakness of our approach. Another weakness of our paper is that we have not accessed patient records to see if the changes in ARB utilisation patterns affect subsequent quality of care. However, we do not believe this will be the case based on the findings that all ARBs are seen as essentially similar in clinical practice at appropriate doses [14-17].

Never-the-less, we believe our findings that ongoing reforms in China are leading to price reductions, mirroring those seen in other countries, are justified. There is still though a considerable opportunity for the hospitals and authorities in China to achieve further substantial price reductions for generics as well as enhance their use. Both will be needed if China is to achieve its aim of universal coverage without further substantial increases in pharmaceutical expenditure. We believe this can be achieved through active formulary management and the increase in physician continuous medical education including benchmarking physician prescribing similar to practices seen among Western European countries. However for long term sustainability, there must be changes in the remuneration system for hospitals and physicians. This builds on current contracting initiatives in some hospitals and regions [52]. There must also be regulations and laws to reduce unethical practices including rebate practices similar to recent regulations and laws in Europe, Korea and the US [6,53,54].

In conclusion, we believe we have demonstrated that there is still considerable irrationality in prescribing in China despite recent measures and that there are considerable opportunities to save costs without compromising care. We believe China can achieve this by learning from exemplars among Western European countries and successfully implementing these. However, this needs changes in the remuneration system to hospitals and physicians. Without such measures, China is unlikely to attain its goal of universal insurance coverage by 2020.

Key issues

- Pharmaceutical expenditure rose steadily at over 16% per annum during the past decade with medicines accounting for 46% of total expenditure in 2010. 80% of medicines are currently dispensed in hospitals
- Physicians and hospitals currently use the prescribing and procurement of medicines to enhance their income, with the average mark-up on medicines in hospitals at 42% in 2005. This has resulted in considerable irrationality in prescribing despite initiatives such as Essential Medicine Lists
- This irrationality was also seen when the utilisation of ARBs and their expenditure was examined in the largest hospital in Chongqing District of China and one of the largest hospitals in South West China
- The utilisation of ARBs increased substantially between 2006 and 2012. However, the utilisation patterns for different originator ARBs was variable and did not reflect their procured prices. There was also typically low utilisation of cheaper generics versus originators
- The reduction in the procured prices for generics over time were similar to those seen among some Western European countries. However, there are still considerable opportunities to further lower prices of generics as well as enhance their utilisation vs. originators

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- Introducing supply- and demand-side measures in China similar to Western European countries would enhance the potential for China to achieve its desired goal of universal coverage by 2020. However, this will need substantial changes to the remuneration system for physicians and hospitals to achieve this

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