Original Research paper

Ongoing initiatives to improve prescribing efficiency in China; statins as a case history

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Abstract

Introduction: Pharmaceutical expenditure rose by 16% per annum in China during the past decade, and now represents 46% of total health care expenditure. Initiatives to moderate growth include pricing regulations for pharmaceuticals and encouraging INN prescribing. However, there is limited monitoring of physician prescribing and current incentives encourage hospitals and physicians to profit from drug procurement. **Objective**: Assess changes in statin utilisation and expenditure as additional generics are launched. Subsequently, compare results in China with findings among European countries to provide future guidance. **Methods**: Observational retrospective study of statin utilisation and procurement expenditure from 2004 to 2013 in two large teaching hospital groups. **Results**: Statin utilisation rose 32 fold in one hospital group and 54 fold in the other. Expenditure also increased but to a lesser extent, i.e. from just over CNY 0.65 million in 2004 to 15.3 million in 2013 in one hospital group and from CNY 0.49 to 19.3 million in the other. Atorvastatin (originator) was the most utilised statin. Utilisation of each generic statin was typically low, e.g. 10% in 2013 in one hospital group. Procurement prices fell over time, greatest for generic simvastatin (-74 to -91%) mirroring data from European countries. However, no increase in their prescribing was observed. In fact, a significant decrease in generic prescribing was seen in one hospital group between 2004 and 2013. **Conclusion**: There are considerable opportunities to improve prescribing efficiency in China based on European experience. However, current incentives encouraging hospitals and physicians to profit from drug procurement need to be addressed.

Key words: statins; China; generics; health policies; prices; drug utilisation study

Introduction

There is increasing scrutiny of the growth in pharmaceutical expenditures in many countries in recent years. Growth rates averaging 50% in real terms during the past decade (1-3) has resulted in multiple reforms across countries. This growth has been driven by well-known factors including ageing populations and new premium priced drugs (1,2,4-6). Initiatives for new medicines include models to better manage the entry of new medicines to optimise the use of available resources (6-8). Initiatives for established medicines include measures to enhance the utilisation of low cost generics rather than originators and single sourced (patented) products in a single or related class where all products are seen as essentially similar (2,6,9-11). Examples include the proton pump inhibitors (PPIs), statins and renin-angiotensin system inhibiting drugs (2,6,12-20), with the latter including both angiotensin converting enzyme inhibitors (ACEIs) and the angiotensin receptor blockers (ARBs).

Savings can be substantial for the medicines in these classes that are essentially therapeutically equivalent when the medicines are given in appropriate doses, because the prices of generics are as low as 2% to 10% of pre-patent loss prices in some countries (2,12,18,21-23). Multifaceted demand-side measures enacted to achieve these savings include high International non-proprietary name (INN) prescribing, formularies, prescribing guidance, continuous medical education, quality circles, strengthening of drug and therapeutic committees (DTCs), prescribing targets, financial incentives and prescribing restrictions (2,12,13,18,19,21,24-26). Considerable savings can also be achieved in low- and middle-income countries from switching from use of originators to use of the lowest-priced equivalent generic drugs (27-29).

China has also seen considerable increases in pharmaceutical expenditure in recent years which has been growing at over 16% per annum during the past decade (29-32). This has continued into the current decade (33). This growth has been principally driven by increasing insurance coverage (34). The Chinese government has introduced three different types of health insurance in recent years each targeting different populations, with basic coverage reaching over 90% of the population in 2011 (33, 35-37) and 95% in 2013 (33). The ultimate goal is universal coverage by 2020 (35-40). As a result of increased coverage, total 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 (35). Expenditure has increased more rapidly in recent years reaching US$350 per capita in 2011 (33). In 2010, pharmaceutical revenues for Chinese public hospitals was 405.39 billion CNY (approximately US$ 62.4 billion), 46% of total healthcare expenditure (29,41), with out-of-pocket payments accounting for 36% of total healthcare expenditure (35).

As a result, China has introduced a number of measures in recent years to help moderate this growth. These measures have principally been aimed at trying to control pharmaceutical expenditure in hospitals, because more than 80% of total pharmaceutical consumption in China is currently occurring in hospitals (29,35,37,42). For state-priced products, the National Development and Reform Commission (NDRC) sets maximum retail prices (price cap) including mark-ups; for province- or municipality-priced products, the price management department determines the retail prices. For other products, retail prices are determined by the manufacturers (29,35,42,43). For instance, the NDRC has implemented 28 price adjustments between 1997 and 2011 to address high prices for common or expensive medicines such as cardiovascular drugs or anticancer drugs (29,44). There were also eight price cuts for antibiotics between 2000 and 2005 (31).

Medicines in hospitals are subject to tenders in each province and municipality with each hospital pharmacy deciding on its own procurement list. This has resulted in cardiovascular drug prices changing four times between 2006 and 2011 in Chongqing Urban District alone (29). Published studies have suggested these bidding processes reduced the prices of essential medicines by 16.9% between 2009 and 2011 (35). However, there are no formal pricing policies for generics in China unlike the policies introduced across Europe, which have resulted in lower price (2,4,12, 16,10,18,21, 45). This lack of policies is at least partially responsible for the fact that there are more than 5,000 pharmaceutical manufacturers in China producing mainly generics (29,33,42). It is expected, but not yet proven, that greater transparency in pharmaceutical pricing may lead to further price reductions (35).

Demand-side measures undertaken in China include the development of an essential medicine list, clinical guidance and guidelines (30,33,35,46,47). However, currently there are limited measures being taken by public insurers to monitor the quality of prescribing (48,49). There were reforms introduced in 2007 - the 'Prescription Management Ordinance' - specifying that prescriptions should be written by generic (INN) name. However, to date there has been limited enforcement (29,43). As a consequence, physicians tend to write prescriptions with the generic (INN) name and simultaneously indicate the brand or manufacturer's name; alternatively, they simply choose medicines listed in hospitals' information technology (IT) systems with the corresponding brand name or manufacturer (29,43). This situation is not helped by having similar patient co-payments for an originator or a generic. In addition, in the current system, hospitals typically use the profits from medicine procurement for their sustainability (33,47,49).

Pharmaceutical expenditure in hospitals accounted for between 41.5% to 46% of hospitals' total income between 2006 and 2010 (29,33,41,43,46,48). This is because the financial support from the Chinese Government to public hospitals declined steadily from approximately 40% to 60% of hospital

revenues in 1980s, to 17% in the late 1990s and to 8.2% by 2003 (29,31). Consequently, hospitals use the revenue from a permitted 15% mark-up in drug procurement for their sustainability (29,31,33,35,43). Even after attempts to reduce procurement prices, the actual mark-up of medicines in hospitals in 2005 averaged approximately 42% (43). There are also inducements for physicians to overprescribe drugs as well as prescribe drugs that produce the greatest profit for them and the hospital (29,31,33,49), e.g. bonuses physicians receive directly from the manufacturers from prescribing their products. According to a study of 12 hospitals in Beijing from 1996 to 2005, expenditure on antibacterial medicines increased due to expensive antibiotics being prescribed rather than cheaper alternatives (31). This situation is exacerbated by the low salaries currently paid to physicians in China; with many physicians earning 5000 CNY (US$ 780) a month or less (50,51). This has resulted in considerable irrational prescribing despite the introduction of measures to decrease this such as essential medicine lists (29,31,33,42,43). An example of irrational prescribing is the continued inappropriate use of injectable drugs including injectable traditional Chinese medicines as well as considerable over prescribing of antibiotics including, as mentioned, the use of expensive versus less expensive antibiotic alternatives (31,32,49,52,53).

A number of issues and findings have recently been identified (Box 1) for the use of cardiovascular medicines in the Chongqing Region of China (29).

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

- The market share of generics among 12 leading cardiovascular (CV) drugs decreasing 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 (based on defined daily doses)
- The market share of originators appreciably increasing between 2006 and 2008; however, narrower fluctuations after this
- Generic versions were available for all 12 CV drugs studied from 2006, with the price of originators averaging 63% greater than generic prices in 2011. These included 3 of the statins
- Overall, the prices of generics for the 12 CV drugs studied varied from 0.34 to 0.98 of the originator in 2011, i.e. 2% to 56% price difference
- There was potential for considerable savings with greater use of generics in this region if this could be engineered through additional demand side measures

For a number of reasons (Box 2; references 6,12,15,17,18,20,21,25,40,52), the authors felt a study looking specifically at all the statins procured in China and for a longer time period was justified.

Box 2 – Rationale for studying statin utilization and expenditure in China

- Ischaemic heart disease and cerebrovascular disease are among the leading causes of death in China
- Lack of appreciable therapeutic differences between the various statins or between originator and generic statins.
- Published studies have shown that patients can be successfully switched between statins without compromising care
- The recent expansion of the utilisation of statins with greater use in non-CV disease populations, e.g. patients with diabetes in addition to those with coronary vascular disease
- The fact that some but not all previous studies in China have shown that appreciable price reductions are possible for generics
- The considerable variation in demand-side measures used in Western European countries to encourage the preferential prescribing of low cost generic statins and the appreciable differences in the eventual utilisation of generic and single-sourced statins produced by these measures
- The paucity of data on the economic effects of various measures used in China to encourage statin use
- Between 2006 and 2011, some generic statins were included in hospital lists in China. As a result, providing an opportunity to further evaluate generic penetration rates and savings compared to the situation summarized in Box 1

Consequently, the principal objective of this paper was to assess changes in the utilisation of and expenditure on statins in China when generic statins are included in procurement lists. The authors

hoped to use the data generated to suggest potential future reforms that China could consider to enhance prescribing efficiency as China strives for universal health access such as that which exists in Europe.

Methods

Typically for these types of drug utilisation analyses, data are obtained from health authority, health insurance or pharmacy databases (12,14, 16, 18,19,22,23,25,54). However in China, drug utilisation studies are often performed with data from hospitals as they incorporate both inpatient and outpatient data (29,55). In addition, as mentioned, these data account for 80% of total drugs currently dispensed in China (29,40). This is related to the convenience of hospital dispensing which is based on physician recommendations. Such data also eliminates the possibility of nonstandardized community based prescriptions and there is greater assurance of pharmaceutical quality in hospitals (43). Consequently, hospital procurement data are 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 (43,47,49). These data are not always available from some commercial sources, which provide only maximum retail price data (30). Hospital procurement prices are also not always captured in health insurance data. In addition, hospitals may dispense medicines that are not currently reimbursed. As a result, health insurance data are not the optimal 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 with the Third Military Medical University (TMMU), two hospitals affiliated with Chongqing Medical University (CMU), and 10 municipal hospitals. Each hospital can dispense generic drugs from different manufacturers, but each has the same originator equivalents because there are only a limited number of originator manufacturers (29).

We chose two teaching hospital groups in the Chongqing District to conduct our study (CMU and TMMU). These two hospital groups we felt to be both representative of the entire Chongqing District and also able to provide comprehensive datasets on both utilisation and expenditures. In view of the complexity of the procurement process only the largest hospitals, e.g. TMMU, tend to have a comprehensive range of products available for prescribing, which may influence procured prices and utilisation patterns. The dataset was obtained from the company publishing journals, one of which is named *China Pharmacy* The company is located in Chongqing and collects 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 have used a similar approach in a previous study (29).

An observational, uncontrolled, retrospective study of prescriptions between 2004 and 2013 was performed (56). The time period includes the period of the previous study (Box 1). This methodology was chosen because multiple supply- and demand-side measures had been introduced during this period in China making it difficult to perform an interrupted time series analysis. In addition, multiple generic statins are available in China (Table 1) (57) and there were multiple changes to the procurement of statins over this period (Table 2). Both chi-square and the Fischer exact tests were undertaken to assess potentially significant changes in the prescribing of generics versus originators.

Table 1 - Registered number of approvals for the production of generic statin preparations in China in January 2014 (57)

Statin	Registered number of approvals
Simvastatin	156
Rosuvastatin	13
Pravastatin	13
Atorvastatin	9
Pitavastatin	6
Fluvstatin	5

NB Registered approvals for production of raw material drug are excluded.

Table 2 – Procurement availability of statins from 2004 to 2013

Statins	TMMU hospital group		CMU hospital group	
	Originator	Generic	Originator	Generic
Simvastatin	2004	Available in 2004	2004	Available in 2004
Pravastatin	2004	2009(June)	2004	Not available
Fluvastatin	2004	Not available	2004	Not available
Atorvastatin	2004	Available in 2004	2005(June)	Available in 2004
Pitavastatin	2010(July)	2012(April)	Not available	Not available
Rosuvastatin	2008(Feburary)	2009(July)	2010(December)	Not available

NB: Generics may have been available in China during previous years; however, just not included in the hospital procurement process in view of the different choices available

The Chinese currency, the Renminbi "*yuan*" (CNY), was used to determine expenditure and expenditure/ DDD for statins over time. There was no allowance for inflation 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 (58,59) 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 (12,13,18,19, 22,23,25,54,60). We also did not convert CNY data to either US$ or Euros during the course of the study as we did not want the pricing information influenced by currency fluctuations; especially during the recent financial crises in Europe and the US. Originator statins are those products currently or previously possessing intellectual property (patent), which either come from multinational companies or are 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 between a large number of manufacturers (Table 1).

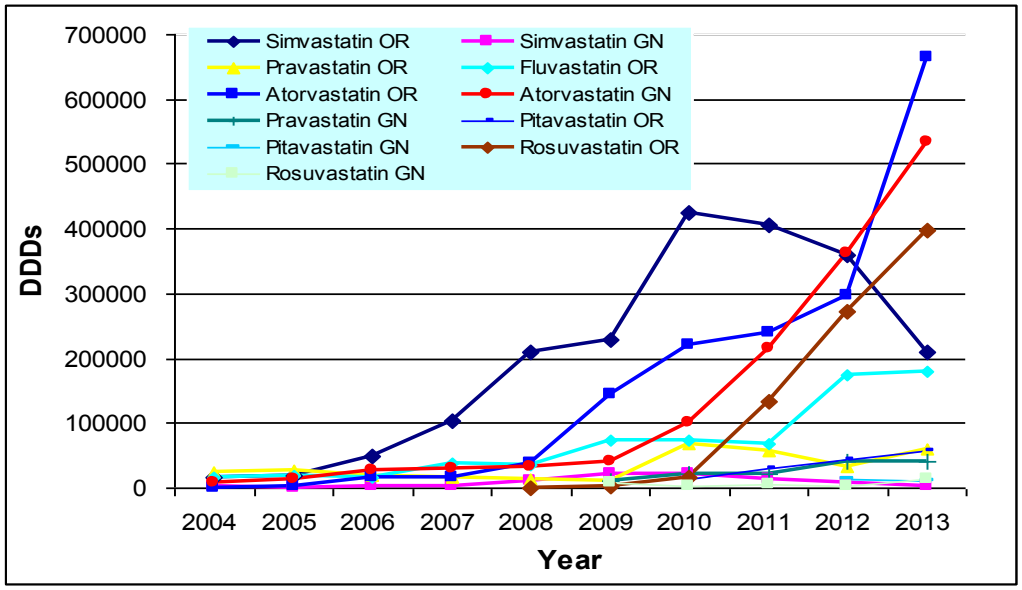
Six statins were available between 2004 and 2013 in the TMMU hospital (ATC C10AA01, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08 (61) and five statins in the CMU hospital (Table 2). Utilisation was measured in terms of Defined Daily Dose (DDDs); defined as '*the average maintenance dose of a drug when used in its major indication in adults*', with this measure recognised as the international standard to assess utilisation patterns within and between countries (62). 2011 DDDs were defined based on international guidance (62-64).

Results

Utilisation

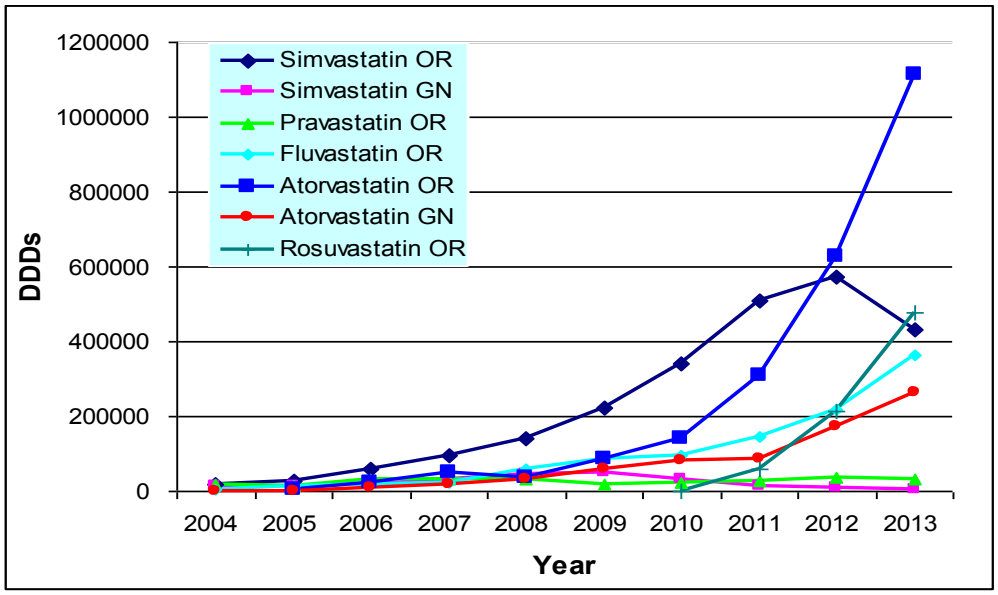
There was an appreciable increase in the prescribing of statins during the study period, increasing 32 fold from just over 67,000 DDDs in 2004 to 2.17 million in 2013 across all products for the TMMU hospitals (Figure 1), and 54 fold from over 49,000 DDDs to 2.69 million for the CMU hospitals (Figure 2).

Figure 1 – Utilisation of statins (DDDs) between 2004 and 2013 in the TMMU hospitals



NB: OR: originator; GN: generic

Figure 2 – Utilisation of statins (DDDs) between 2004 and 2013 in the CMU hospitals



NB: OR: originator; GN: generic

The greatest increase in utilisation was seen with atorvastain (originator and generic in the TMMU hospitals, and only originator in the CMU hospitals) and simvastatin, although the consumption of the later decreased in the most recent years (Figures 1 and 2, Table 3). The utilisation of both rosuvastatin and fluvastatin also increased steadily but to a lesser extent.

Table 3 – Consolidated utilisation of statins (in DDDs) including generics and originators in the two Chongqing hospital groups from 2004 to 2013

TMMU hospitals	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Degree of change
Simvastatin - Originator	15323	18133	48067	104027	209333	228800	425333	405333	360267	210933	
Simvastatin - Generic	2453	560	1792	1848	9576	22008	20627	14933	7840	2240	
Simvastatin - Total	17776	18693	49859	105875	218909	250808	445960	420267	368107	213173	12.0
% Genenric	*13.8%*	*3.0%*	*3.6%*	*1.7%*	*4.4%*	*8.8%*	*4.6%*	*3.6%*	*2.1%*	*1.1%*	
Pravastatin - Originator	23969	27986	19291	15395	14833	11433	67200	56933	31873	58800	
Pravastatin - Generic						11267	21467	22667	41327	39980	
Pravastatin - Total	23969	27986	19291	15395	14833	22700	88667	79600	73200	98780	4.1
% Genenric						*49.6%*	*24.2%*	*28.5%*	*56.5%*	*40.5%*	
Fluvastatin - Originator	15895	19623	17346	38827	34347	74667	74433	68227	175280	179200	11.3
Atorvastatin - Originator	280	2135	15631	17640	37373	145600	220080	239120	295974	665210	
Atorvastatin - Generic	9282	13580	26880	29400	31353	41160	102057	215320	361491	532560	
Atorvastatin - Total	9562	15715	42511	47040	68726	186760	322137	454440	657465	1197770	125.3
% Genenric	*97.1%*	*86.4%*	*63.2%*	*62.5%*	*45.6%*	*22.0%*	*31.7%*	*47.4%*	*55.0%*	*44.5%*	
pitavastatin - Originator							13790	30030	42350	57330	
pitavastatin - Generic									14000	10360	
pitavastatin - Total							13790	30030	56350	67690	
% Genenric									*24.8%*	*15.3%*	
Rosuvastatin - Originator					1134	1400	15400	133497	273413	398160	
Rosuvastatin - Generic						7896	1729	5600	2800	12600	
Rosuvastatin - Total					1134	9296	17129	139097	276213	410760	
% Genenric						*84.9%*	*10.1%*	*4.0%*	*1.0%*	*3.1%*	
Combined total											
Total Generic	11735	14140	28672	31248	40929	82331	145879	258520	427457	597740	50.9
Total Statins	67201	82018	129006	207137	337949	544231	962116	1191660	1606614	2167373	32.3
% Genenric	17.5%	17.2%	22.2%	15.1%	12.1%	15.1%	15.2%	21.7%	26.6%	27.6%	

CMU hospitals	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Degree of change
Simvastatin - Originator	16053	27733	57700	95020	143060	223803	338800	505067	552533	431200	
Simvastatin - Generic	11627	12333	19036	30053	46422	50003	33150	11867	7667	5950	
Simvastatin - Total	27680	40066	76736	125073	189482	273807	371950	516933	560200	437150	15.8
% Genenric	*42.0%*	*30.8%*	*24.8%*	*24.0%*	*24.5%*	*18.3%*	*8.9%*	*2.3%*	*1.4%*	*1.4%*	
Pravastatin - Originator	17096	14026	33250	33500	31477	18877	24383	27067	37800	30800	1.8
Fluvastatin - Originator	4247	14933	16427	23893	56929	86613	96740	146347	216907	363440	85.6
Atorvastatin - Originator		3080	21077	49980	35658	84140	140910	308140	626080	1113910	
Atorvastatin - Generic	350	1820	7070	17710	33180	59640	82320	88200	172200	263760	
Atorvastatin - Total	350	4900	28147	67690	68838	143780	223230	396340	798280	1377670	3936.2
% Genenric	*100.0%*	*37.1%*	*25.1%*	*26.2%*	*48.2%*	*41.5%*	*36.9%*	*22.3%*	*21.6%*	*19.1%*	
Rosuvastatin - Originator							350	57890	212940	478800	
Combined total											
Total Generic	11977	14153	26106	47763	79602	109643	115470	100067	179867	269710	22.5
Total Statins	49373	73925	154560	250156	346725	523077	716653	1144577	1826127	2687860	54.4
% Genenric	24.3%	19.1%	16.9%	19.1%	23.0%	21.0%	16.1%	8.7%	9.8%	10.0%	

In January 2010, the originator manufacturer adjusted its price of simvastatin tablets 40 mg × 5's from CNY 50.30 to 26.70 in TMMU Hospitals (slightly changed to CNY 26.61 in February 2011) and its utilisation subsequently increased (Table 3). In September 2011 (November 2011 in CMU hospitals), the manufacturer changed the specification to 40 mg × 7's, and priced at CNY 36.81. Its utilization subsequently decreased in the TMMU hospitals and in 2013 in the CMU hospital. Meanwhile the utilisation of atorvastatin and rosuvastatin increased (Figures 1 and 2, Table 3).

There was variable use of generic statins in the two hospitals. In the TMMU hospitals, there was a rapid increase in the use of generics. The utilisation of generic atorvastatin peaked at 97% of total atrovastatin in 2004 before declining to 22% in 2009, and subsequently increased to between 45% and 55% in recent years. A similar pattern was seen for generic pravastatin once it was procured, peaking at 50% of total pravastatin utilisation in 2009 before falling to 24% in 2010 and subsequently increasing to between 41% and 57% in recent years (Figure 1, Table 3). However, there was limited use of generic pitavastatin and rosuvastatin in recent years (Table 3). The variable use of generics among the statins led to their overall utilisation increasing from 18% of total statins in 2004 to 28% in 2013 in the TMMU hospitals (Table 3). However, the difference in the utilisation of generic vs.

originator statins between 2004 and 2013 was not significant by chi-square test ($p>0.05$) despite the increasing availability of generic statins (Tables 2 and 3).

In the CMU hospitals, the greatest increase was for atorvastatin (3936 fold) (Figure 2, Table 3). However, owing to decreasing utilisation of generic atorvastatin as a percentage of total atorvastatin, there was decreasing use of generic statins to 9% to 10 % of total statins in recent years (Table 3). In this hospital group, there was a significant difference in the utilisation of generic vs. originator statins between 2004 and 2013 ($p<0.01$ using the chi-square test).

Expenditure

Total expenditure on the statins increased appreciably in both hospitals, rising from just over 650,000 CNY in 2004 to 15.3 million CNY in 2013 for the TMMU hospitals, and from 493,000 to 19.3 million CNY for the CMU hospitals (Figures 3 and 4). The greatest expenditure was on atorvastatin, amounting to 60-61% of total statin expenditure in the two hospitals (Figures 3 and 4).

Figure 3 – Total expenditure of statins in CNY in the TMMU hospitals from 2004 to 2013

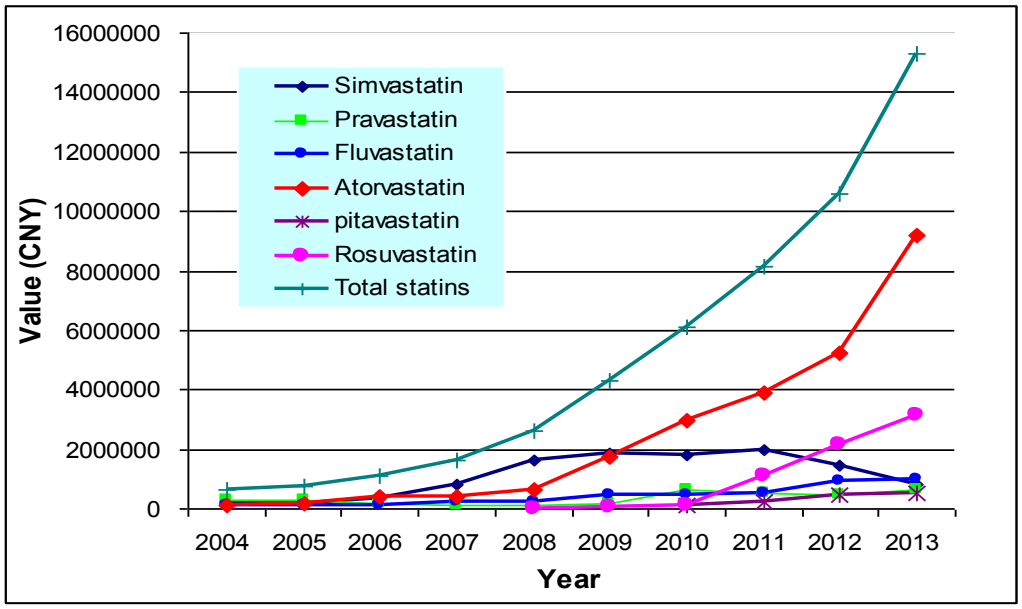
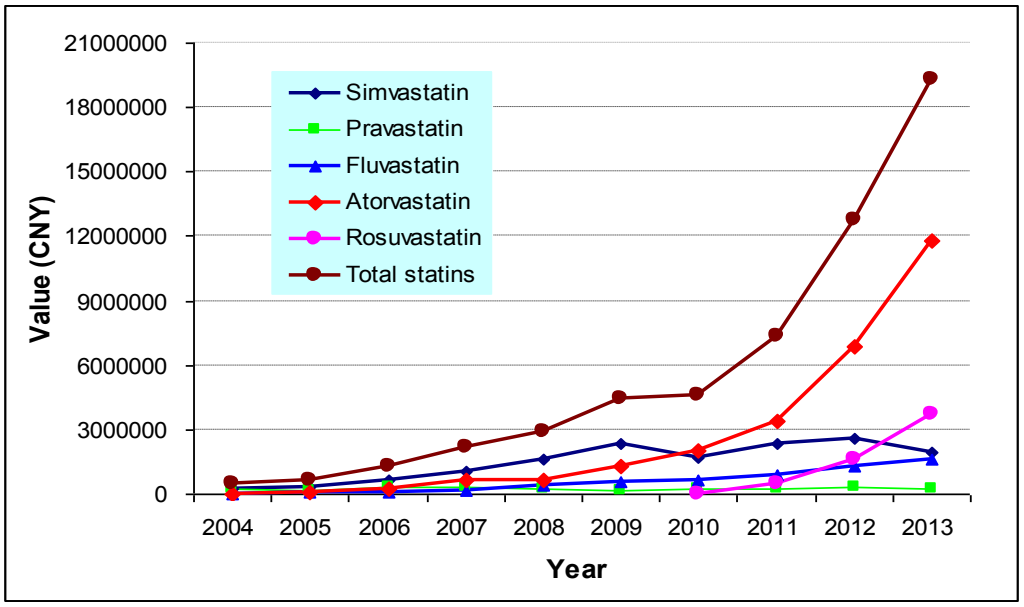


Figure 4 - Total expenditure of statins in CNY in the CMU hospitals from 2004 to 2013



In the TMMU hospitals, the lower increase in total expenditure (24 fold) versus utilisation (32 fold) was helped by reducing expenditure/ DDD for the various statins (Table 4). There was a numerically smaller but statistically insignificant ($p>0.05$ using Fisher exact test) decrease of 23% for originator statins combined in 2013 vs. 2004 compared with a 38% decrease for generics. This resulted in an overall 27% price reduction for combined statins between 2004 and 2013 (Table 4).

Table 4 – Expenditure/ DDD for statins (generic and originator) in the two Chongqing hospitals from 2004 to 2013

Statins	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**% change 2013 vs. 2004**
TMMU hospitals											
Simvastatin - Originator	8.543	8.203	7.607	7.603	7.545	7.545	4.003	4.707	3.944	3.944	-54%
Simvastatin - Generic	7.719	7.378	5.981	5.345	5.162	5.111	4.471	2.944	2.538	1.997	-74%
Simvastatin % Difference	*-10%*	*-10%*	*-21%*	*-30%*	*-32%*	*-32%*	*12%*	*-37%*	*-36%*	*-49%*	
Pravastatin - Originator	11.607	9.930	9.102	8.773	8.754	7.114	7.021	7.042	6.857	6.857	-41%
Pravastatin - Generic						8.661	8.661	5.800	5.621	5.621	
Pravastatin % Difference						*22%*	*23%*	*-18%*	*-18%*	*-18%*	
Fluvastatin - Originator	7.206	7.225	6.519	6.371	6.334	6.334	6.316	7.367	5.200	5.603	-22%
Atorvastatin - Originator	15.154	15.154	10.370	9.571	9.573	9.571	9.571	9.220	8.891	8.569	-43%
Atorvastatin - Generic	11.154	10.775	9.756	8.797	8.597	8.597	8.449	7.730	7.195	6.523	-42%
Atorvastatin % Difference	*-26%*	*-29%*	*-6%*	*-8%*	*-10%*	*-10%*	*-12%*	*-16%*	*-19%*	*-24%*	
Pitavastatin - Originator							7.669	7.668	7.666	7.666	
Pitavastatin - Generic									8.019	8.019	
Pitavastatin % Difference									*5%*	*5%*	
Rosuvastatin - Originator					7.886	7.886	7.886	7.736	7.714	7.714	
Rosuvastatin - Generic						8.606	8.606	8.205	8.071	7.267	
Rosuvastatin % Difference						*9%*	*9%*	*6%*	*5%*	*-6%*	
Total Statins - Originator	9.517	8.851	8.137	7.631	7.722	7.978	6.099	6.729	6.459	7.295	-23%
Total Statins - Generic	10.436	10.640	9.520	8.593	7.793	7.675	7.920	7.295	6.990	6.487	-38%
Total Statins	9.678	9.159	8.444	7.776	7.730	7.932	6.375	6.852	6.600	7.072	-27%
CMU hospitals											
Simvastatin - Originator	10.210	8.796	8.866	9.222	9.279	9.311	4.663	4.602	4.718	4.522	-56%
Simvastatin - Generic	7.038	6.930	6.988	6.130	6.073	5.928	4.658	1.404	0.968	0.633	-91%
Simvastatin % Difference	*-31%*	*-21%*	*-21%*	*-34%*	*-35%*	*-36%*	*0%*	*-69%*	*-79%*	*-86%*	
Pravastatin - Originator	12.350	11.415	9.026	8.921	8.755	8.841	8.737	8.649	8.644	8.644	-30%
Fluvastatin - Originator	7.699	6.567	6.516	6.516	6.516	6.516	6.516	6.131	6.131	4.541	-41%
Atorvastatin - Originator		8.841	9.571	9.573	9.571	9.571	9.571	8.891	8.891	8.889	
Atorvastatin - Generic	10.463	9.858	9.714	8.703	8.597	8.597	8.597	7.811	7.356	7.049	-33%
Atorvastatin % Difference		*12%*	*1%*	*-9%*	*-10%*	*-10%*	*-10%*	*-12%*	*-17%*	*-21%*	
Rosuvastatin - Originator							8.571	7.719	7.714	7.714	
Total Statins - Originator	10.903	8.856	8.723	8.940	8.668	8.757	6.279	6.359	6.969	7.221	-34%
Total Statins - Generic	7.139	7.307	7.726	7.084	7.125	7.380	7.466	7.051	7.084	6.907	-3%
Total Statins	9.990	8.559	8.554	8.585	8.313	8.468	6.471	6.420	6.980	7.189	-28%

NB: % differences reflect differences in procurement prices between originators and generics

In the CMU hospitals, the smaller increase in total expenditure (39 fold) versus utilisation (54 fold) was again helped by reducing expenditure/ DDD for the various statins (Table 4). There was a

numerically greater decrease for originator statins combined at 34% in 2013 vs. 2004 compared with only 3% for generics. However this difference also did not reach statistical significance ($p>0.05$ using Fisher exact test). These changes resulted however in an overall 28% price reduction for combined statins between 2004 and 2013 (Table 4).

There was considerable variation in price reductions for individual generic and originator statins over the course of the study. The greatest price decline was observed for simvastatin. Prices of the originator declined by 54-56% in the two hospital groups over the course of the study, with prices for generic simvastatin declining even further (Table 4).

Whilst the two hospital groups participate in the pharmaceutical tendering process in Chongqing District, the displayed expenditure/DDD of statins showed differences (Table 4). These are mainly attributable to the different specifications during the procurement process between the two hospitals, e.g. 40mg × 7's in TMMU hospital and 40mg × 7's & 20mg × 7's in CMU hospitals for originator simvastatin, 20mg × 7's in TMMU hospital and 10mg × 7's in CMU hospitals for generic atorvastatin in 2013. In addition, some products with different dosage forms and manufacturers were procured differently by the two hospital groups, e.g. capsules in the TMMU hospitals and tablets in the CMU hospital for generic simvastatin.

Discussion

There appears to be progress with obtaining reasonable price reductions for generics versus originators in hospitals in China. This can be seen with procurement price reductions over time for generic statins as well as for originator prices (Table 4). However, some prices of the generics appeared initially higher than originators, e.g. pravastatin, pitavastatin and rosuvastatin in the TMMU hospitals and atorvastatin in the CMU hospitals (Table 4). This could due to a limited price differential policy between the manufacturers of originator and generic drugs initially. At the first requested procurement opportunity, prices were self-determined by manufacturers and the whole supply chain prefers higher prices with higher profits. Subsequently, the products entered the medicine insurance list and their prices decreased either through government control or greater competition from multiple manufacturers.

The price reductions for generics over time mirror some of those seen in Western European countries (2,12,18,21,54,60). However, there are still opportunities for further price reductions with generic simvastatin which is priced at between 2% to 4% of patented prices in the Netherlands, Sweden and UK for example (12,13, 18, 21). 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 priced at just 3% of pre-patent loss prices in recent years (6,12,25).

There continued to be irrationality in the prescribing of statins over time. This included the limited and variable prescribing of generic statins versus originators despite appreciably lower prices (Tables 3 and 4). Generic utilisation reached a maximum of 27-28% of total statins between 2012 and 2013 in the TMMU hospital group having fallen to between 12% and 15% of total statins between 2008 and 2010 (Table 3). However, utilisation decreased from 24% of total statins in 2004 to 10% in 2013 in the CMU hospitals (Table 3). Continued irrationality was also seen by the growing utilisation of atorvastatin versus simvastatin, and limited use of generic simvastatin (Figures 1 and 2, Table 3), with both seen as therapeutically similar at appropriate doses (12,15,16-18). Simvastatin originator (cheapest) was priced between 49% and 58% lower than atorvastatin originator (most expensive) between 2010 and 2013 in the TMMU hospitals (47% to 51% in the CMU hospitals), and simvastatin generic (cheapest) was between 68% and 77% cheaper than originator atorvastatin in the TMMU hospitals in recent years (84% to 93% in CMU hospitals).

Overall, there appear to be considerable opportunities to enhance the utilisation of low cost generics versus originators, especially following recent reforms in China to improve manufacturing standards for generics. These new standards include strict quality control for generics as part of the tendering process (35,40). A number of quality control measures were introduced after 2000 in China (35). For instance as of 2009, all medicines on the Chinese EML are 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 eligible for procurement (35). Good Manufacturing Practice (GMP) standards were also

revised in 2011 to further improve the quality of generic manufacturing in China, adding to the potential trust in generics (35).

However, it is likely future demand-side measures will have only limited success unless the current incentives encouraging physicians and hospitals to prescribe and dispense premium priced originators versus lower cost generics are addressed (29,31,33,53). Once these are adequately addressed, potential additional 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 (60).

There are also opportunities to enhance the rational use of medicines in China, building on the essential medicine list concept (33,35, 49). This includes encouraging the preferential prescribing of low cost multiple sourced drugs versus more expensive patented products or originators, and building on INN prescribing. Restricting prescribing choices should enhance physician familiarity with the medicines they prescribe. This could potentially reduce adverse drug reactions and drug: drug interactions as well as strengthen the procurement process. This was the philosophy behind the generation of the Wise List in the Stockholm Healthcare Region, Sweden, which contains approximately 200 drugs including first and second line choices covering most of the needs in ambulatory care (21,24,65). 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 program including a separate list for both patients and physicians, physician trust in the guidance, as well as regular feedback (24,65). Increased adherence also reduces costs (21,24,66). There are similar examples in Spain and Scotland (12,60,65).

Such a system could be introduced throughout the hospitals in the Chongqing District along with continuous medical education and strengthening of hospital DTCs. This could provide an example to other provinces and municipalities throughout China as they grapple with similar issues. This will require strong leadership to achieve this, including instigating quality measures and involving prescribers (67) but the potential economic benefits are great. Restricting the formulary to just one statin based on the cheapest statin (simvastatin) would have saved an accumulated 27 million CNY for the TMMU hospitals alone between 2004 and 2013. Accumulated savings could increase to 49 million CNY with the attainment of generic prices similar to low prices achieved in some Western European countries. Simvastatin is recommended in the ‘Wise List’ in Stockholm County Council (66). In addition, SIGN (Scottish Intercollegiate Guidelines Network) in Scotland advocate the use of only 40 mg simvastatin for the prevention of cardiovascular disease (68,69) as well as for primary prevention of cardiovascular disease in patients with Type 1 diabetes. In addition, 40mg simvastatin or 10mg atorvastatin are used for the prevention of cardiovascular disease in patients with Type 2 diabetes irrespective of starting lipid levels (69,70). The IDEAL study failed to show a significant reduction in coronary vascular events for patients prescribed high dose atorvastatin (80mg/ day) versus low dose simvastatin (20mg/ day) further endorsing the choice of generic simvastatin in such patients (71). However, we concede that initially it may be better to offer a choice, e.g. simvastatin and atorvastatin, based on current utilisation patterns and guidance.

While it remains to be proven, we believe these findings are generalizable to other drug classes and other hospitals in China based on the merits of our methodology as well as the realities of current regulations and tendering systems in China. However, this is a recognised weakness of our approach. Never-the-less, we believe our conclusions that ongoing reforms in China are leading to price reductions, mirroring those seen in other countries, are justified. We also feel that there is still an opportunity to achieve further substantial price reductions and that there are also considerable opportunities to enhance the rational use of medicines, achieving further savings without compromising care. We believe these can be achieved through active formulary management and an increase in continuous physician medical education. This includes benchmarking physician prescribing habits similar to what has been achieved by initiatives in Scotland, Spain and Sweden (60,65). However, as discussed, for long term, sustained rational use of medicines in China, there must be changes in the remuneration system for hospitals and physicians to reduce their reliance on the profitability from drug procurement for their continued sustainability. This would build on current contracting initiatives in hospitals in other districts and settings (31,72). In addition, professionalism must be improved in all aspects of hospital management (73) and perhaps introducing regulations

and laws to reduce unethical practices. These could mirror recent regulations and laws in Europe, Korea and the US (6,19,74,75). When combined, these potential changes should also enhance patient access to essential medicines as well as reduce their co-payments without increasing costs to the Chinese authorities or compromising patient care. As a result, help the Chinese authorities achieve their long term goal of providing universal health care access.

In conclusion, we believe we have demonstrated that despite recent measures there is still considerable irrationality in prescribing in China. There are also considerable opportunities to conserve resources without compromising care.

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