

## Research paper

# Are prescribing initiatives readily transferable across classes: the case of generic losartan in Scotland?

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## ABSTRACT

**Background** There are on-going initiatives in Scotland to improve the quality and efficiency of prescribing in primary care. Activities to enhance prescribing of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs) include prescribing guidance, guidelines, benchmarking, prescribing targets and financial incentives. These measures stabilised reimbursed expenditure for renin-angiotensin inhibitor drugs between 2001 and 2007 despite a 159% increase in volumes. Generic losartan was included in the Drug Tariff from July 2010. As there is no appreciable difference between ARBs, and the prices of generic losartan are falling, health boards should be actively encouraging its prescribing.

**Aim** To primarily assess changes in utilisation patterns of losartan versus other ARBs after July 2010. Second, to assess the utilisation of generic versus originator losartan.

**Method** We used an interrupted time series analysis of ARB utilisation, measured in defined daily

doses (DDDs) before and after July 2010. Utilisation data were obtained from the NHS National Services Scotland Corporate Warehouse.

**Results** There was no significant change in the utilisation pattern of losartan or other ARBs combined before or after the introduction of generic losartan. Losartan accounted for 32% of total ARBs 12 months after listing. Between 98 and 99% of losartan was prescribed generically. In March 2012, the price of losartan was 88% below pre-patent prices with potential savings of £8m per year.

**Conclusion** Specific measures are needed to change prescribing habits especially with complex messages. The cost of deriving savings must be weighed against other quality initiatives and other ARBs losing or shortly losing their patents.

**Keywords:** demand-side measures, drug utilisation study, generics, losartan, Scotland

## What this paper adds

### What do we know?

Intensive demand-side measures enhance prescribing efficiency once standard treatments are available as generics. Previously angiotensin-converting enzyme inhibitors (ACEIs) were recommended first-line for the management of hypertension or heart failure with patented angiotensin receptor blockers (ARBs) reserved for patients intolerant to ACEIs. The launch of low-cost generic ARBs has altered this situation.

### What does this paper add?

There was no change in utilisation patterns for losartan versus other ARBs once losartan lost its patent. Specific measures are needed to change physician prescribing habits especially with complex messages. Opportunity costs for any intervention must be weighed against other high priority areas for quality improvement.

## Background

Cardiovascular disease (CVD) is a leading cause of death in Europe, with more than 80 million people estimated to have a >25% risk of a vascular event over a decade.<sup>1–3</sup> Overall, deaths from CVD account for one-quarter of all deaths worldwide, and over 40% of deaths in the EU.<sup>1–3</sup> This has a cost of over €169bn annually in Europe, in addition to the appreciable medical implications.<sup>2,4</sup>

The major drug classes to treat hypertension include the angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics. All drug classes have shown similar beneficial effects for preventing cardiovascular events,<sup>2,3,5,6</sup> with ACEIs and ARBs showing similar effectiveness in reducing blood pressure.<sup>6,7</sup> As a result, renin–angiotensin inhibiting drugs have been incorporated into American and European guidelines for treating hypertension either as a monotherapy or in combination.<sup>6,8</sup> Typically, ACEIs have been advocated first-line ahead of ARBs, especially following the availability of generic ACEIs.<sup>2,3,9–11</sup>

Heart failure is also a priority area among European health authorities in view of its prevalence, morbidity and economic burden, which has been estimated at ~2% of national health expenditure.<sup>2,12</sup> Both ACEIs and ARBs appear equally effective in reducing cardiovascular events in patients with heart failure, and both have been recommended as first-line treatment.<sup>2,11,12</sup> Renin–angiotensin inhibitor drugs are also recommended in patients with diabetes to reduce diabetic nephropathy<sup>8</sup> with generic ACEIs advocated first-line to conserve resources without compromising care.<sup>2,3,9–11</sup>

Prescribing of ARBs has been a target for health authority and health insurance company activities across Europe due to the lower costs of generic ACEIs and studies showing that a dry cough (a major side effect) occurs in only ~10% of patients prescribed ACEIs.<sup>3,11,13–15</sup> In addition, only 2–3% of patients in

ACEI clinical trials discontinued their treatment due to a dry cough.<sup>11,13,16</sup> As a result, the Office of Fair Trading (OFT) in the UK suggested in 2007 that ARBs should only account for a maximum of 5% of total renin–angiotensin inhibitor drug prescriptions.<sup>15</sup>

Health authority and health insurance demand-side activities in Europe have ranged from prescribing restrictions limiting ARBs to patients experiencing unacceptable side effects from or being intolerant to ACEIs,<sup>2,3,11,16,17</sup> to educational activities including prescribing guidance, benchmarking, academic detailing, prescribing targets for ACEIs and ARBs, as well as financial incentives.<sup>2,3,9–11</sup> There have also been initiatives to successfully switch patients between different ARBs to further conserve resources.<sup>18,19</sup>

Activities in Scotland to enhance the prescribing of ACEIs versus ARBs included national and local prescribing guidance such as guidance from the Scottish Inter-collegiate Guideline Network (SIGN), benchmarking among general practitioners (GPs), academic detailing, financial incentive schemes, as well as prescribing targets initiated as part of Audit Scotland in 2003, i.e. >25% by prescribing volume for ARBs versus all renin–angiotensin inhibitor drugs in the Lothian Health Board.<sup>11</sup> These measures stabilised reimbursed expenditure on renin–angiotensin inhibitor drugs in Scotland between 2001 and 2007 despite a 159% increase in utilisation (using defined daily doses [DDD]), helped by low prices for generic ACEIs and limited utilisation of ARBs.<sup>11</sup> The low utilisation of ARBs in Scotland mirrored the low rates seen in countries who had introduced formal prescribing restrictions for ARBs.<sup>11,16,17</sup> The increase in renin–angiotensin inhibitor utilisation was in part due to GPs trying to attain blood pressure goals as part of a Quality and Outcomes Framework target, which is similar to the situation with statins in Scotland in recent years.<sup>20</sup> In essence, this improves care quality without adding to costs.

Losartan's patent expired in the UK in March 2010, with the first generics reimbursed in Scotland in July 2010 when listed on the Drug Tariff. Consequently,

health boards should be active in encouraging GPs to start patients on losartan when an ARB is indicated, as well as switching patients on other ARBs to losartan.<sup>19</sup> This was particularly important as £26.27m was spent on ARBs in Scotland in 2009, making ARBs the seventh most expensive drug class in Scotland, and the price of losartan fell rapidly following its generic availability.<sup>19</sup> Alongside this, only a minority of patients prescribed ARBs were being prescribed losartan before its loss of patent. A Cochrane Review concluded that all ARBs have a statistically equivalent effect on blood pressure. This was endorsed by the National Institute for Health and Clinical Excellence (NICE) in their August 2011 guidance that patients with hypertension can be started on an ACEI or low-cost ARB.<sup>19,21,22</sup> In addition, there have been no head-to-head trials showing any difference in effectiveness between the various ARBs for heart failure, although higher doses are typically needed in heart failure than hypertension. A recent cohort study demonstrated that, in patients with heart failure, higher doses of losartan (100 mg/day) were not associated with increased mortality versus candesartan, which is different for lower doses.<sup>19,23,24</sup> Alongside this, patients in the UK have been successfully switched between ARBs without compromising care,<sup>18,19</sup> although greater care may be needed when switching patients between different ARBs when treating heart failure.<sup>25</sup>

In view of the many initiatives in Scotland to enhance the prescribing of generics within a class or related classes, we would expect there to be an increase in the prescribing of losartan following its loss of patent for patients newly started on an ARB, as well as potentially switching patients from other ARBs to losartan to conserve resources. This is despite there being no active programme among the health boards or NHS Scotland to specifically encourage such activities. This is in recognition of the Hawthorne effect, with on-going multiple demand-side measures encouraging the prescribing of generic ACEIs versus premium-priced patented ARBs.<sup>26</sup>

## Aim

The principal objective is to assess the change in the utilisation patterns of losartan and the other ARBs alone or in combination in fixed doses (fixed dose combination; FDC) following the listing of generic losartan in the Drug Tariff. Second, to assess the level of prescribing of generic versus originator losartan once available. Third, to assess the utilisation of single versus FDC ARBs. Finally, to suggest measures that could be instigated if needed to further improve ARB prescribing efficiency in Scotland, with reimbursed

prices of generic losartan expected to fall rapidly following inclusion in the Drug Tariff. Prescribing efficiency is defined on this occasion as utilisation growing more rapidly than expenditure with all ARBs seen as essentially similar.<sup>18,19,21,22,24</sup> The prices of omeprazole and simvastatin fell rapidly following patent expiry to 9 and 3%, respectively, of originator pre-patent loss prices in 2010.<sup>20</sup>

We would expect high utilisation of generic losartan versus the originator with high rates of international non-proprietary name (INN) prescribing, averaging over 80% in Scotland for all prescriptions and higher following the availability of generics, e.g. 98% of all omeprazole and simvastatin utilisation on a DDD basis since 2006.<sup>20</sup> DDDs are defined as 'the average maintenance dose of a drug when used in its major indication in adults'.<sup>27,28</sup> We would also expect continuing low utilisation of ARB FDCs as the utilisation of renin-angiotensin inhibitor FDCs has been historically low in Scotland, accounting for just under 2% of all renin-angiotensin inhibitor utilisation in 2007.<sup>2,11</sup> This in view of the accepted need to titrate patients, and the continual controversy surrounding the actual influence of FDCs with improving compliance in routine clinical practice.<sup>2,11,29</sup>

## Method

We used an interrupted time series design to analyse the changes in monthly reimbursed prescriptions of all patients in Scotland dispensed at least one ARB (C09DA01 to 09)<sup>28</sup> between July 2008, i.e. two years before both generic losartan was listed in the Drug Tariff price list, to September 2011, some 15 months after generic losartan was listed, contained in the administrative database of NHS National Services Scotland Corporate Warehouse. We also conducted an observational study on the utilisation of ARB FDCs (C09DA01 to 09, C09DB01 to 05, C09DX01 to 03),<sup>28</sup> again between July 2008 and September 2011. The reason for the different design is that the principal emphasis of this paper is on single ARBs, with anticipated very low utilisation of ARB FDCs. The database covers all patients in Scotland, and is regularly audited to ensure the robustness of the data. Accuracy is assured by a service level agreement with the Pharmaceutical Services Division in NHS Scotland specifying a minimum standard of 98% accuracy.

ARB utilisation in both studies was assessed using DDDs, as this measure is recognised as the international standard to assess utilisation patterns within and between countries.<sup>27,28</sup> DDDs for 2011 were used in line with international guidance,<sup>28,30</sup> with the World Health Organization (WHO) methodology

used to calculate the DDDs for the FDC products. This was based on the principle of counting the FDC as one dose.<sup>29</sup>

Serial autocorrelations of losartan DDDs were assessed in the interrupted time series design using an ARIMA model and a Box–Jenkins–Tiao strategy.<sup>31</sup> DDDs were plotted over time in months. The graphs were visually inspected to assess the trends or the non-stationarity of the data. Alongside this, a segmented regression analysis of the interrupted time series was used to assess the effect of the inclusion of generic losartan in the Drug Tariff in July 2010. Common segmented regression models were used to fit a least-squares regression line to each segment of the independent variable (time  $t$ ), assuming a linear relationship between time and the outcome within each segment. The effect of the intervention (losartan listed in the Drug Tariff) was assessed with using the model:  $Y_t = \beta_0 + \beta_1 (\text{time}_t = 0, 1, 2, \dots, 24) + \beta_2 (\text{intervention } 1t) + \beta_3 (\text{time after intervention } 1t) + \beta_4 \beta_2 (\text{intervention } 2t) + \beta_5 (\text{time after intervention } 2t) + e_t$ , where  $Y_t$  was losartan's DDDs per month  $t$ , time is a continuous variable indicating time (in months) at time  $t$  from the start until the end of the observation period, intervention is an indicator variable for time  $t$  occurring before ( $t = 0$  month) or after ( $t = 1$  month) the inclusion of losartan in the Drug Tariff, and  $e_t$  is the error term at time  $t$ .<sup>32</sup> The time after the intervention (months) is a continuous variable that counts the number of months after the intervention at time  $t$ , coded time 0 before the intervention (July 2010). The Durbin–Watson statistic was calculated to test for a serial autocorrelation of the error terms in the regression models.<sup>33</sup> The statistical package IBM SPSS Statistics version 19.0 was used for all analyses. A  $P$  value of  $<0.05$  was considered significant.<sup>34</sup>

No attempt was made to concomitantly assess changes in reimbursed expenditure during this period as we would expect the reimbursed price for generic

losartan to rapidly fall after its inclusion in the Drug Tariff, mirroring the situation with generic simvastatin (3% of pre-patent loss prices in 2010), generic clopidogrel (7% of pre-patent loss prices soon after its availability) and generic omeprazole (9% of pre-patent loss prices in 2010).<sup>20,35</sup>

## Results

The utilisation of losartan has continued to increase in recent years. However, there was no significant increase in the utilisation of losartan following its listing in the Drug Tariff (Figures 1 and 2, Table 1). Similarly, there was no appreciable change in the utilisation patterns of the other ARBs (Figure 1).

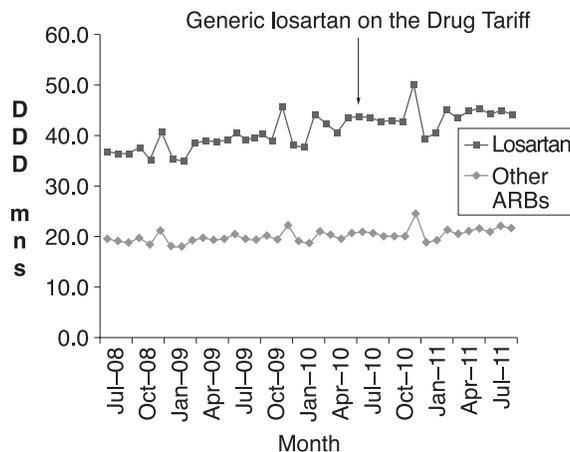
There was greater growth in the utilisation of candesartan post-generic losartan (Table 2), maintaining its dominance as the most utilised ARB. This was compensated for by decreased utilisation of eprosartan and telmisartan after the availability of generic losartan (Table 2).

Overall, there appeared to be no appreciable change in the utilisation of losartan as a percentage of total single ARB utilisation on a DDD moving annual total (MAT) basis after the availability of generic losartan compared with 12 months before generic losartan became available (Table 2).

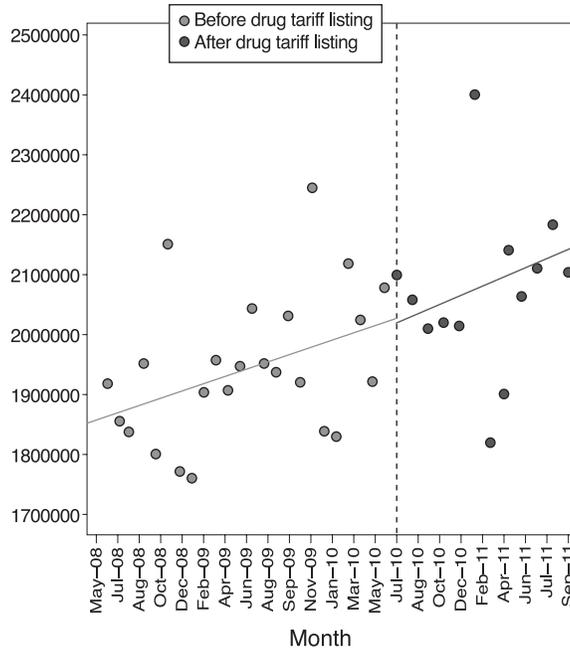
Losartan was typically generic losartan after its launch, averaging between 98 and 99% of all losartan DDDs from August 2010 through INN prescribing.

Throughout the study period, there was limited utilisation of ARB FDCs, averaging  $\sim 2\%$  of total ARB utilisation on a DDD basis.

The utilisation of both losartan FDCs, as well as all other ARB FDCs, appeared to fall after the availability of generic losartan (Figure 3). However, the percentage



**Figure 1** Utilisation of losartan vs. other ARBs combined in DDDs (months) July 2009 to September 2011



**Figure 2** Change in utilisation patterns for losartan in defined daily doses over time before and after inclusion in the Drug Tariff

**Table 1** Parameter estimates, standard errors and *P*-values from the segmented regression model predicting the extent of losartan DDDs before and after losartan was included in the Drug Tariff (coefficient variable is losartan DDDs)

Model		Unstandardised coefficients		Standardised coefficients			95.0% confidence interval for B	
		B	SE	Beta	<i>t</i>	Sig.	Lower bound	Upper bound
1	(Constant)	1 859 910.38	50 867.67		36.564	0.000	1 756 643.51	1 963 177.26
	Time	7056.11	3559.996	0.55	1.982	0.06	-171.067	14 283.29
	Reim- bursement	-21 731.93	81 156.23	-0.07	-0.268	0.79	-186 487.84	143 023.98
	Time after reim- bursement	4135.53	8045.23	0.14	0.514	0.61	-12 197.15	20 468.22

<sup>a</sup> Dependent variable: losartan DDDs. Significance (Sig.) only when *p* < 0.05.

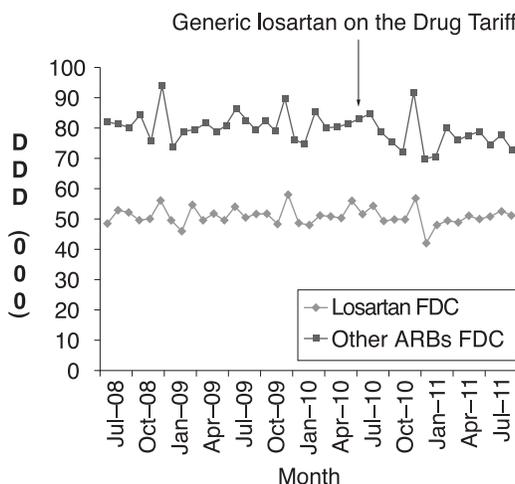
utilisation of losartan FDCs versus all other ARB FDCs remained steady on a MAT basis throughout the study period (Table 3).

There was an increase in the utilisation of some individual FDCs after the availability of generic losartan FDC, with a greater fall in the utilisation of irbesartan and diuretic FDCs that that seen with losartan FDCs (Table 3).

In March 2012, the reimbursed price (Drug Tariff price) of losartan 50 mg in Scotland was 5.6p per day, which was 88% below prices before loss of the patent. This compares with 8 mg candesartan at 32p per day and 150 mg irbesartan at 42.3p per day.

**Table 2** Total DDDs (months) as 12-month MAT figures of individual ARBs 12 months before and after the inclusion of generic losartan in the Drug Tariff

ARB	Total DDDs (month) MAT 12 months before generic losartan	12 months MAT (DDD month) at launch of generic losartan	MAT 12 months after generic losartan (DDD month)	Percent change (12 months after launch)
Losartan	22.77	23.99	24.87	4
Candesartan	21.18	24.9	28.06	13
Eprosatan	0.158	0.149	0.138	-7
Ibresartan	11.52	12.12	12.478	3
Olmesartan	0.656	0.65	0.605	-7
Telmisartan	1.89	1.96	1.92	-2
Valsartan	8.69	8.94	8.97	0
Total	56.28	61.81	66.15	7
Losartan % total	40.5	38.8	37.6	

**Figure 3** Utilisation of losartan FDCs versus other ARB FDCs from July 2008 to September 2011 in DDDs (000s)

## Discussion

There was no appreciable increase in the utilisation of losartan versus other single ARBs following its availability as a generic, which was different to changes seen for some of the other single ARBs following generic losartan. This would suggest no 'spill-over' or Hawthorne effect to increase the utilisation of generic versus patented ARBs, even with continuing multiple measures to increase the prescribing of generic renin-angiotensin inhibitor drugs (in this case generic ACEIs) versus ARBs.<sup>11</sup> As a result, specific measures

will be needed to increase the prescribing of losartan versus other ARBs. These could include prescribing targets linked with financial incentives, and/or active switching programmes. This builds on the experiences with the proton pump inhibitors (PPIs), statins and ACEIs versus ARBs in Scotland.<sup>18,20,36</sup> This is a key learning point, especially given the appreciable influence of on-going intensive demand-side measures in Scotland to enhance prescribing efficiency for the proton pump inhibitors, statins and renin-angiotensin drugs.<sup>11,20</sup> The message to use either ACEIs or low-cost ARBs first-line is more complex than simply

**Table 3** Total DDDs of ARBFDCs (000s) from 12 months before the availability of generic losartan to 12 months after

ARB FDC	Total DDDs (000) MAT 12 months before generic losartan was listed in the Drug Tariff	Total DDDs (000) MAT at listing of generic losartan	Total DDDs (000) MAT 12 months after generic losartan listed	Percent change
Losartan + diuretic	613.4	623.17	594.81	-4.6
Irbesartan + diuretic	618.57	608.52	564.64	-7.2
Olmesartan + combination	12.5	12.09	12.2	1.0
Olmesartan + amlodipine	0	1.26	4	
Olmesartan + others	0	0	56	
Telmisartan + combination	108.36	108.8	104	-4.4
Valsartan + diuretic	226.94	242.82	244.52	0.7
Total	1579.78	1596.66	1524.24	-4.5
Losartan % total	38.8	39.0	39.0	

encouraging ACEIs alone, requiring additional measures to change physician prescribing habits.

One reason for the lack of specific activity among the health boards and NHS Scotland, even though ARBs were the seventh highest drug expenditure class in 2009 coupled with the continued need to conserve resources, is the estimated savings of nearly £8m just from the availability of generic losartan. In addition, active switching programmes would likely be needed to accrue another £8m to £10m from increased use of losartan. This would entail considerable health board resources at a time when generic valsartan and generic candesartan become available on the Drug Tariff in Scotland by mid-2012 and irbesartan in October 2012. Other higher priority areas have already been identified to improve the quality and efficiency of primary care prescribing in Scotland in 2012,<sup>37</sup> and multiple measures had already been successful in limiting ARB utilisation in Scotland.<sup>11</sup> The emphasis has recently changed in England, with NICE endorsing the utilisation of low-cost (generic) ARBs first-line alongside ACEIs,<sup>21</sup> which may have a spill-over effect in Scotland.

There was high generic prescribing of losartan mirroring the situation with generic ACEIs, omeprazole and simvastatin in Scotland.<sup>11,20</sup> This has the potential to reduce patient confusion and pharmacist time addressing this, especially in countries with branded generics where patients could be dispensed differently named drugs at each prescription.<sup>19,20,35</sup> Education simply encouraging generic prescribing appears to be working well.<sup>20</sup>

As envisaged, there was extremely low utilisation of ARB FDCs in Scotland given concerns with their actual value in practice. This endorsed our approach to principally concentrate on the analysis of single ARBs in this paper.

## Conclusion

ACEIs should remain the first choice for therapy in the management of hypertension and heart failure, with patented ARBs reserved for second-line treatment. Studies have shown that patients can be successfully switched between ARBs without compromising care to lower the cost of ARB treatment, although greater attention may be needed in patients with heart failure. This study has shown that specific and intensive measures will be needed to appreciably enhance ARB prescribing efficiency once ARBs lose their patent, mirroring the findings across Europe for the PPIs and statins.<sup>36</sup> This is important for other health authorities and health insurance companies across Europe as they decide upon future initiatives to improve the quality and efficiency of prescribing from the range of options open to them. However, the resources needed to implement multiple initiatives must be considered alongside those needed for other quality improvement programmes.

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## FUNDING

The study was in part funded by a grant from the Karolinska Institutet.

## ETHICAL APPROVAL

The study involved analysis of routinely collected data.

## PEER REVIEW

Not commissioned; externally peer reviewed.

## CONFLICTS OF INTEREST

MB and IB are employed by NHS Scotland. Otherwise the authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript.

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Received 31 July 2012

Accepted 10 December 2012