The evidence base of health policy decisions has been increased in the last decades, as societies require more objective and verifiable criteria for the allocation of scarce public resources. This is especially true for the purchasing decisions of innovative pharmaceuticals (1). In addition to the main drug registration criteria, including efficacy, safety and quality, public payers in many countries mandate cost-effectiveness evidence and budget impact analysis prior to the pricing and reimbursement decisions of new pharmaceuticals (2-4).

As opposed to public investment decisions related to new drugs, the evidence base of pharmaceutical disinvestment decisions, such as increased utilization of generic medicines is more limited (5, 6). Policy makers often measure the success of generic drug policies by the market share of generics and their price erosion (7, 8). These two easy-to-measure indicators are important to estimate savings in the pharmaceutical budget; however, they cannot provide information on savings in total health expenditure or on maintaining equal health outcomes. In general, from public health perspective generic drug policies are successful, if savings in the health care budget are achieved without any deterioration in health outcomes of patients (9).

In chronic diseases, such as hypertension, the most crucial factor in the implementation of generic drug policies is the continuation of antihypertensive therapy after patent expiry of the original product. If generic reference pricing system is applied to facilitate the implementation of generic antihypertensive drugs, a policy maker is interested in the continuation of antihypertensive therapy. This can be measured by the number of patients treated by a particular antihypertensive drug in the period after patent expiry. This indicator is important to estimate savings in the health care budget; however, it cannot provide information on savings in total health expenditure or on maintaining equal health outcomes. In general, from public health perspective generic drug policies are successful, if savings in the health care budget are achieved without any deterioration in health outcomes of patients (9).
tate generic price erosion (10), the reference generic product may change frequently (11).

**Generic medicine policy in Hungary: internal price referencing system**

In Hungary, internal price referencing is applied for generic drugs. Until 2011, the generic drug with the lowest price became the reference product, and a new reference product was announced in every 3 months. Products with significant price differential over the reference drug were delisted from the reimbursement list. Products with minor price differential compared to the reference product had the same amount of reimbursement but increased copayment (i.e., resulting lower % of reimbursement). Before 2011 entrance of new generic drugs was the main driver of generic price erosion with a predefined mandatory reduction for new entrants of 30-10-10% for the first, second and third generic product. Manufacturers of already marketed generic products had less incentive to reduce drug prices.

From 2011, a new blind bidding procedure for the generic reference pricing scheme has been introduced to further facilitate price erosion for all manufacturers. Every 6 months generic manufacturers have to submit price reduction proposals via an online application system operated by the Hungarian National Health Insurance Fund (NHIF) for their drugs, but without knowing proposals by their competitors. After the closure of the bidding process, the lowest price drug becomes the reference product. Products with less than 15% price differential compared to the reference product have equal amount of reimbursement with the reference product, which translates to a relatively higher percentage of copayment due to higher total price. Products with more than 15% price differential to the reference product can have only 85% reimbursement of the reference product, so there is significant penalty for minor price reductions. The blind bidding procedure has been proved to be a very efficient tool to facilitate price erosion of generic medicines resulting regularly changing generic reference products.

**Potential treatment scenarios after patent expiry**

In any internal price referencing systems chronic patients on antihypertensive drug therapy may choose from several options, if the reference product changes over time. The most specific case is when the patent of a successful antihypertensive medicine expires, and the first generic products enter the market.

In such cases patients may stay on the original brand, if they are willing to pay higher copayment or even the full public price once the original product is delisted from reimbursement (Option 1). In real world some patients may also discontinue drug therapy after the copayment of their original medication increases rapidly, although this option does not make sense from the clinical point of view (Option 2). Alternatively they may switch to another patented original medicine which is not subject internal price referencing or generic substitution at pharmacy level (Option 3). Patients can also switch to a generic product with the same active ingredient of

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**Figure 1. Study design; MACEs: major cardiovascular events.**
their original drug therapy (Option 4); or they can maximize savings from generic price erosion by always choosing the generic product with the lowest actual copayment (Option 5).

Should the patient choose either of these scenarios, it is not sufficient to evaluate the success of generic drug policy only in terms of savings in drug budget, changes in health outcomes and overall health care expenditures also have to be taken into account (12). If significant proportion of patients discontinue the antihypertensive therapy after patent expiry or maintain their treatment on the delisted original product, the generic drug policy cannot be considered successful even despite significant savings in drug budget (Option 1-2). Also, switching to another patented original medicine without price erosion cannot be considered as a successful generic drug policy (Option 3). However, it is difficult to choose between those two policy scenarios in which patients are switched to generic products only once or multiple times (Option 4-5).

Objective

Our objective was to estimate the impact of multiple switching of generic antihypertensive drug therapy on health outcomes and total health expenditure for those patients, who had been adherent and persistent with their chronic maintenance antihypertensive losartan therapy before its patent expiry by comparing to patients with only a single switch to a generic losartan brand after the patent expiry.

MATERIALS AND METHODS

Study design, inclusion and exclusion criteria

A retrospective analysis of NHIF database was applied with a full coverage of health care data of all insured Hungarian citizens. We selected those patients from the database into our analysis who had at least 304 days of losartan or losartan/hydrochlorothiazide (HCT) treatment (DOT) with International Statistical Classification of Diseases and Related Health Problems (ICD) I10-I15 codes on prescriptions in the 12 months prior to patent expiry of losartan in July 2007 or losartan/HCT January 2009, respectively (see inclusion period in Fig. 1). ICD-10 codes are mandated on prescriptions in Hungary to indicate primary disease according to the ICD, and these codes confirmed drugs were prescribed to treat hypertension of patients. More than 10 months of treatment was assumed to indicate that patients were persistent with their mono or combination losartan therapy before its patent expiry. We excluded those patients from the analysis who had major myocardial infarct or stroke within 12 months after patent expiry, as for these patients any changes in antihypertensive drug therapy could be attributable to deterioration in their medical status.

Patient allocation

We allocated patients to 5 groups based on switching history in 12 months after patent expiry (see allocation period in Fig. 1) similarly to the theoretical scenarios described above (Options 1-5). Patients in Group 1 stayed on the original brand in the next 12 months after patent expiry. Patients in Group 2 discontinued reimbursed medical treatment for hypertension. Group 3 patients were switched to other original antihypertensive products. Group 4 patients were switched to generic losartan or losartan/HCT, but did not change the generic brand in 12 months. Group 5 patients were switched at least twice among different generic products in 12 months after patent expiry.

As original losartan and losartan/HCT were delisted from reimbursement after 11 and 9 months to patent expiry, respectively, patients in Group 1 could not be tracked in the NHIF database after delisting of original losartan or losartan/HCT (no reimbursement consequences of delisted products). Therefore, we reallocated Group 1 patients between Groups 2-5 based on their prescription history in 12 months after their last original losartan or losartan/HCT prescription (see dotted lines in the allocation period in Fig. 1). Those patients who had no subsequent records of any reimbursed antihypertensive drugs were moved to Group 2. Those patients who were switched to another original antihypertensive drug, were reallocated to Group 3. Those patients who were switched to generic losartan or losartan/HCT, but did not change the generic brand in the next 12 months were moved to Group 4. Those patients who had multiple switch among different generic antihypertensive products at in the next 12 months were moved to Group 5. Group 2 and Group 3 patients provided evidence for the failure of generic drug policy, as they did not continue their antihypertensive therapy on a cheaper alternative medicine, therefore were also excluded from further analysis.

Cost and health outcomes

For patients in Group 4 and 5 we retrieved clinical records of major cardiac events (MACEs), including myocardial infarction, stroke or death for an additional 36 months period in the NHIF database, and calculated the odds ratio for MACEs in Group 4 compared to Group 5.
Total treatment costs after the allocation period over the additional 36 months were also estimated for Group 4 and 5. Treatment costs were censored after death for those patients who died during the 3-year study period. Average annual treatment costs were calculated in the following categories: antihypertensive drugs, other cardiovascular drugs (excluding antihypertensive drugs), cardiovascular treatments excluding non-hospital drugs (e.g., acute or chronic inpatient health services, hospital drugs related to cardiovascular indication defined as ICD I10-I15), non-cardiovascular drugs, non-cardiovascular services excluding non-hospital drugs (e.g., acute or chronic inpatient health services, hospital drugs related to non-cardiovascular indication). As NIHF database has no payment records on non-reimbursed medicines (e.g., over-the-counter drugs), only drugs with partial or full reimbursement could be included into the analysis. Drug costs were calculated at public price, which included NHIF reimbursement and copayment of patients. As services in the primary care are reimbursed by capitation, cost of general practitioner visits was excluded from the analysis. A third party payer’s perspective was applied for health services.

Average annual treatment costs in the study period were compared to the annual treatment costs in the inclusion period prior to patent expiry (see study period in Fig. 1). Difference-in-differences in annual treatment costs compared to baseline year were calculated between Group 4 and 5 (13).

We employed 174.5 HUF/EUR purchasing power parity exchange rate (2012) to report treatment costs in Euro (14). Fisher’s exact test and Welch two sample t-test were used to compare the two groups. The levels of significance were set to 0.05 unless stated otherwise. Statistical analyses were performed in R statistical software.

**RESULTS**

Figure 1 summarizes the allocation of patients, who were persistent with losartan or losartan/HCT treatment prior to its patent expiry, to 5 different groups listed in the Materials and Methods section. Approximately one-third of patients had a single switch to generic losartan during the 12-month allocation period (Group 4), and another one-third of patients had multiple switches among different generic products (Group 5) resulting a total study population of 3101 + 3280, respectively.

9.8% of patients with single switch had MACEs over the 3 year study period, 10.7% of patients in the multiple switch group had MACEs, with no statistically significant difference between the two groups (p = 0.247) (see Table 1).

As patients became older and their disease progressed, the annual treatment costs were increased in both groups compared to baseline year (see Table 2). The difference in total treatment costs, however, were significantly higher by 461 € among those patients with multiple switches among generic products in 12-month after patent expiry (p < 0.001), and the same was true for all cost categories except cardiovascular treatments excluding non-hospital drugs. Interestingly, the annual savings in antihypertensive drug costs were less for patients in Group 5 than in Group 4.

**DISCUSSION AND CONCLUSION**

The policy objective of switching stable chronic patients to generic drugs after patent expiry is to reduce health care costs without compromising health outcomes (i.e., same health gain at lower costs) (Group 4). However, current Hungarian generic medicines policy incentivizes multiple

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**Table 1. Impact of treatment scenarios on major cardiovascular events (MACE).**

<table>
<thead>
<tr>
<th></th>
<th>Single switch to reference generic drug</th>
<th>Multiple switches to generic drugs</th>
<th>Difference between groups</th>
<th>Odds ratio</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3,101</td>
<td>3,280</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarct n(%)</td>
<td>60 (1.93%)</td>
<td>74 (2.26%)</td>
<td>0.32%</td>
<td>0.855</td>
<td>0.384</td>
</tr>
<tr>
<td>Stroke n(%)</td>
<td>115 (3.71%)</td>
<td>125 (3.81%)</td>
<td>0.10%</td>
<td>0.972</td>
<td>0.844</td>
</tr>
<tr>
<td>Death n(%)</td>
<td>187 (6.03%)</td>
<td>208 (6.34%)</td>
<td>0.31%</td>
<td>0.948</td>
<td>0.640</td>
</tr>
<tr>
<td><strong>Total MACEs n(%)</strong></td>
<td><strong>303 (9.77%)</strong></td>
<td><strong>350 (10.67%)</strong></td>
<td><strong>0.90%</strong></td>
<td><strong>0.907</strong></td>
<td><strong>0.247</strong></td>
</tr>
</tbody>
</table>

* Fisher's exact test
switching of drug therapy which may not result in reduction of total health expenditure (Group 5). Regular switch of chronic drug therapies may lead to poorer adherence and persistence (15, 16) and increase in hospitalization events (13, 17-19). Frequent substitution of generic drugs may result in increased side-effects and decreased tolerability (20) and patient confusion (21-23) especially among patients with several comorbidities.

Unfortunately, persistence of delisted products could not be directly assessed in the NHIF database, as these products have no reimbursement impact to be recorded. However, when we designed the study we assumed that poorer adherence potentially translates to negative health outcomes, and the impact of MACEs on total treatment cost may be greater than potential savings from multiple switching of generic drugs (24-27).

Direct causal relationship between multiple switching and increased total health care costs or negative health outcomes cannot be proven in real world database analysis. Patients with longer treatment period (i.e., better persistence) have higher chance for multiple switching, especially if several previous reference products are delisted. In order to prevent such bias, we stratified our study into separate time periods. Patient allocation into treatment groups based on their switching history over 12 months after patent expiry preceded the measurement of total treatment costs and health outcomes.

Overall, our observational study was not powered enough to detect statistically significant increase in 3-year MACEs in patients with multiple generic switch compared to those patients with single switch to generic losartan in the allocation period. However, increase in annual treatment costs were significantly greater in the multiple switch group compared to the single switch group.

Potential confounding factors may limit the generalizability of our conclusions. Higher treatment costs in Group 5 compared to Group 4 might be attributable to additional factors beyond frequency of switching drug therapy, including differences in baseline risks and switch of patients to antihypertensive medicines with different active ingredient(s). Unfortunately, no data on health state factors could be retrieved from the NHIF database. However, we still need to answer why patients who had strong persistence with a chronic antihypertensive drug therapy during the inclusion period were switched back and forth among different generic products after patent expiry.

The impact of potential confounding variables could have been minimized by multiple regression analysis based on individual patient records, or additional subgroup analyses. Unfortunately, the NHIF provides only aggregate results in order to protect privacy of personal data. Therefore, we were unable to conduct multiple regression analysis controlling for disease severity, individual compliance, demographic characteristics or comorbidities. NHIF even cannot disclose aggregate results for outcomes with less than 10 cases. Consequently, we could not make further subgroup analyses, including separation of losartan patients from losartan/HCT patients, or reporting separately those patients in the multiple switching group, who took several different brands of the same active ingredient.

### Table 2. Annual treatment costs and incremental annual costs compared to baseline period per patient.

<table>
<thead>
<tr>
<th>Treatment categories</th>
<th>Single switch to reference drug</th>
<th>Multiple switches to generic drugs</th>
<th>Difference in differences between groups</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual treatment costs</td>
<td>Increase to baseline year</td>
<td>Annual treatment costs</td>
<td>Increase to baseline year</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>€311</td>
<td>-€201</td>
<td>€385</td>
<td>-€156</td>
</tr>
<tr>
<td>Other cardiovascular drugs</td>
<td>€292</td>
<td>€108</td>
<td>€336</td>
<td>€139</td>
</tr>
<tr>
<td>Cardiovascular treatments excluding non-hospital drugs</td>
<td>€329</td>
<td>€198</td>
<td>€527</td>
<td>€361</td>
</tr>
<tr>
<td>Non-cardiovascular drugs</td>
<td>€908</td>
<td>€478</td>
<td>€1,096</td>
<td>€610</td>
</tr>
<tr>
<td>Non-cardiovascular services excluding non-hospital drugs</td>
<td>€492</td>
<td>€240</td>
<td>€631</td>
<td>€330</td>
</tr>
<tr>
<td>Total annual treatment costs</td>
<td>€2,332</td>
<td>€823</td>
<td>€2,976</td>
<td>€1,284</td>
</tr>
</tbody>
</table>

*Welch two sample t test
In conclusion, the evidence base of pharmaceutical disinvestment decisions has to be strengthened. Further studies are needed to better understand the negative implications of multiple switching of generic drugs on health outcomes and total treatment costs in other chronic conditions. Real world data analysis can provide complementary evidence in addition to randomized controlled clinical trials, as prospective trials are not suitable to estimate costs (protocol driven costs) or persistence.

Conflict of interest

The study was financially supported by Abbott; however, authors summarized their independent professional opinion and take full responsibility for potential errors in the manuscript. Abbott had no influence on the review process, nor were they involved in writing the manuscript.

REFERENCES


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