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Policy objective of generic medicines from the investment perspective: The case of clopidogrel

Péter Elek[a,*], András Harsányi[b], Tamás Zelei[b,c], Kata Csetneki[c], Zoltán Kaló[b,c]

[a] Department of Economics, Eötvös Loránd University (ELTE), H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary
[b] Department of Health Policy and Health Economics, Eötvös Loránd University (ELTE), H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary
[c] Syreon Research Institute, H-1142 Budapest, Mexikói út 65A, Hungary

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ABSTRACT

The objective of generic drug policies in most countries is defined from a disinvestment perspective: reduction in expenditures without compromising health outcomes. However, in countries with restricted access of patients to original patented drugs, the objective of generic drug policies can also be defined from an investment perspective: health gain by improved patient access without need for additional health budget.

This study examines the investment aspect of generic medicines by analyzing clopidogrel utilization in European countries between 2004 and 2014 using multilevel panel data models. We find that clopidogrel consumption was strongly affected by affordability constraints before the generic entry around 2009, but this effect decayed by 2014. After controlling for other variables, utilization had a substantially larger trend increase in lower-income European countries than in the higher-income ones. Generic entry increased clopidogrel consumption only in lower- and average-income countries but not in the highest-income ones. An earlier generic entry was associated with a larger effect.

The case of clopidogrel indicates that the entrance of generics may increase patient access to effective medicines, most notably in lower-income countries, thereby reducing inequalities between European patients. Policymakers should also consider this investment aspect of generic medicines when designing pharmaceutical policies.

1. Introduction

The main policy objective of health care decision-makers is to maximize health gain for the population by efficiently allocating limited resources [1]. Off-patent medicines, such as generic and biosimilar medicines, can support this objective by offering equally high-quality treatment at lower costs [2,3]. An increased use of generic medicines can generate significant savings in the health care budget [3–6]. The objective of generic drug policies is usually defined as reduction in expenditures without compromising health outcomes [7].

However, the objective of generic drug policies can be defined differently in countries with significant resource constraints, where the accessibility of patients to high-cost patented medicines may be limited. In these countries third-party payers implement different cost-containment measures, including incentives to different stakeholders to restrict the utilization of high-cost medicines [8]. Volume limits for individual physicians or health care institutions

* Corresponding author. Fax: +36 1 372 2912.
E-mail addresses: peter.elek@tatk.elte.hu (P. Elek), harsanyia@caesar.elte.hu (A. Harsányi), tamas.zelei@tatk.elte.hu (T. Zelei), kata.csetneki@syreon.eu (K. Csetneki), kalo@tatk.elte.hu (Z. Kaló).

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may prevent prescribers to propose the most optimal drug therapy for all eligible patients. Alternatively, high-cost medicines may be reimbursed only as second-line therapies after the failure of first-line therapies. Significant copayment can increase the price sensitivity of patients, and therefore limit their accessibility to high-cost medicines compared to the full reimbursement scenario. Payback mechanisms may reduce the profitability of manufacturers with increased drug utilization, and therefore create disincentives to promotional activities.

Such restrictions may be alleviated due to generic price erosion, and consequently patient access can be improved significantly after patent expiry [9]. In such cases the most important benefit of generic medicines is not cost-savings, but increased health gain. In countries with restricted access of patients to original patented medicines the objective of generic drug policies can be also defined from an investment perspective: health gain by improved patient access without need for additional health budget [7]. The majority of scientific publications support the cost-saving potential of generic medicines [10–12], but empirical evidence related to increased patient access is limited [13].

Our objective was to explore whether increased utilization of clopidogrel after the market entry of generic medicines is associated with affordability constraints (i.e. GDP per capita) in European countries. Clopidogrel is used to prevent problems caused by blood clots in patients with significant risk for vascular events, such as recent myocardial infarction or stroke, established peripheral arterial disease, acute coronary syndrome [14].

We selected clopidogrel based on several criteria. Firstly, patent expiry between 2005 and 2010 ensured that we had sufficient follow-up period after the entry of first generic alternatives in major European countries. Secondly, significant health gain of clopidogrel (i.e. >0.1 QALYs) compared to previous standard therapies was calculated in several studies [15–19], hence we assumed that increased patient access could be translated to health gain. Thirdly, clopidogrel was a first-in-class product with no relevant therapeutic alternatives, therefore increased utilization after patent expiry could not be related to cannibalization of the market share of similar products. Finally, clopidogrel is mainly distributed through retails pharmacies, and so the IMS database could provide reliable longitudinal data on sales volumes.

2. Data and methods

2.1. Data

We made use of detailed product-level clopidogrel sales data that were provided to us by IMS Health. The database of our analysis contained quarterly sales information of clopidogrel products (measured in standard units) between 2004 and 2014 from 27 countries (all members of the European Union except Croatia, Cyprus and Malta, together with Norway and Switzerland). Cyprus and Malta were not present in the original database, and we omitted Croatia, Russia and Turkey because – for Croatia – no data were available before the generic entry and – for the two other countries – regulatory practice and economic development differed much from the other part of the sample. Name, manufacturer, strength (mostly 75 mg and sometimes 300 mg) and generic/non-generic category were also shown for the products in the database.

In our analysis we used a country- and annual- (or quarter-) level longitudinal database aggregated from the product-level data. The dependent variable was the aggregated DOT (days of treatment) sales of clopidogrel, divided by the population of the country. DOT sales were obtained by multiplying standard units by strength and dividing by the DDD (daily defined dose) of 75 mg.

The main explanatory variables of interest were (1) the binary variable indicating the periods after the first appearance of a generic clopidogrel product in the given country, and (2) the number of different generic manufacturers in the given country in the given year. We also used control variables that describe affordability, health need and priorities for health care in a country, hence may influence drug utilization. Taking into account the time series availability of the data and the indications for clopidogrel, we measured these factors with GDP per capita in PPP, the health expenditure per GDP ratio, the proportion of old-age population (above 65 years) and the age-standardized death rate (SDR) from diseases of circulatory system (for all ages). The latter variable was not available after 2012 and for some other sporadic country–years hence its missing values were imputed by simple country-specific log-linear trends. The source of data was World Bank and – for SDR from circulatory diseases – the HFA–WHO database. We note that, not surprisingly, the parameter estimates of our interest do not change if we use health expenditure per capita instead of the health expenditure per GDP ratio in the equations.

2.2. Descriptive analysis

The first generic clopidogrel product entered the market in 2009 in the majority of countries (20 out of the 27 cases). The exceptions were: Italy, Luxemburg, Switzerland (2010), Germany (2008), Bulgaria (2007), Poland and Slovenia (2006). Afterwards, as Supplementary Fig. A1 in Appendix displays, the share of generic clopidogrel products increased substantially in the vast majority of countries, reaching around 70% of all consumption on average by 2014, with large variability. For instance, this share was essentially 100% in Czech Republic, Denmark, Hungary and Slovakia, while remained below 20% in Luxemburg and Slovenia and below 50% in Belgium and Italy.

Most countries experienced a monotonous increase in the generic share after the generic entry. Notable exceptions are Bulgaria, Norway and Slovenia, where generic clopidogrel was temporarily removed from the market after its first introduction because of patent problems (see Baumgartel et al. [20] for details of these events). Due to these specific events these three countries were omitted from the regression analysis below. Luxemburg was also omitted because of its small size and its special relationship with Belgium with regard to pharmaceutical sales.

There was also a small temporary decrease in the generic ratio in France around 2010–2011 because – as the French Competition Authority later ruled and issued a