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

Péter Elek PhD[a, 1], András Harsányi MSc[b, 2], Tamás Zelei MD[b,c, 3], Kata Csetneki MSc[b,c, 4], Zoltán Kaló PhD[b,c, 5]

[a] Department of Economics, Eötvös Loránd University (ELTE), Budapest, Hungary

[b] Department of Health Policy and Health Economics, Eötvös Loránd University (ELTE), Budapest, Hungary

[c] Syreon Research Institute, Budapest, Hungary

Published under the same title in

Health Policy 121(5), 558-565.

http://dx.doi.org/10.1016/j.healthpol.2017.02.015

[1] Corresponding author. Email: peter.elek@tatk.elte.hu
Mailing address: Department of Economics, Eötvös Loránd University (ELTE), H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary. Phone: +36-30-474 3831. Fax: +36-1-372-2912.
[2] Email: harsanyia@caesar.elte.hu
Mailing address: Department of Health Economics and Health Policy, Eötvös Loránd University (ELTE), H-1117 Budapest, Pázmány Péter sétány 1/A, Hungary.
[3] Email: tamas.zelei@tatk.elte.hu Mailing address: see footnote 2
[4] Email: kata.csetneki@syreon.eu Mailing address: see footnote 2
[5] Email: kalo@tatk.elte.hu Mailing address: see footnote 2

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.

Highlights

- Clopidogrel utilization in Europe was greatly affected by affordability constraints before generic entry.
- Afterwards the gap between the lower- and higher-income countries has been reduced substantially.
- Generic entry increased clopidogrel consumption in lower- and average-income countries but not in the highest-income ones.
- This underlines the investment aspect of generic medicines.

Keywords: Clopidogrel, Generic Drugs, Multilevel Analysis, Patient Access, Pharmaceutical Policy

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 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 Figure A1 in Appendix displays, the share of generic clopidogrel products increased substantially in the vast majority of countries, reaching around 70 per cent of all consumption on average by 2014, with large variability. For instance, this share was essentially 100 per cent in Czech Republic, Denmark, Hungary and Slovakia, while remained below 20 per cent in Luxemburg and Slovenia and below 50 per cent 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 fine for it – the drug maker Sanofi encouraged a campaign to discourage doctors and pharmacists from prescribing or substituting generic versions of its former clopidogrel product Plavix. After the resolution of this issue the generic share in France soon reached 75 per cent by 2013.

Figure 1 displays the evolution of combined (generic and non-generic) clopidogrel utilization in European countries, while Figure A2 in Appendix shows these graphs separately by country. There were very large (more than 100-fold) cross-country differences in clopidogrel utilization in 2004, which decreased to a less than 10-fold difference by 2014. At the beginning of the period the largest utilization was observed in France, Greece and Luxemburg (above 3 DOT per inhabitant per year) and the lowest in Czech Republic, Estonia, Poland and Slovakia (less than 0.06 DOT per inhabitant per year), while at the end of the period countries with largest utilization were Greece, Hungary and Slovakia (above 5 DOT per inhabitant per year) and the ones with lowest utilization were Latvia, Slovenia and Norway (less than 1.5 DOT per inhabitant per year). The right panel of Figure 1 shows that average clopidogrel utilization was very low at the beginning in the lower-income European countries (indicated by a solid line) but afterwards – and especially after the time of the generic entry – these countries experienced a dramatic increase, reaching the average consumption level of higher-income countries (indicated by a dashed line) by the end of the period. Meanwhile, consumption did not change substantially in the latter group. Inspecting the countries separately (see Figure A2 in

Appendix), generic entry seemed to increase utilization only in lower-income countries – most notably in the Czech Republic, Poland and Slovakia.

(Fig. 1 about here)

Before a more formal analysis, Table 1 displays descriptive statistics of country-level clopidogrel utilization data and health need and affordability variables for various years. (From this point we use annual data and omit Bulgaria, Luxemburg, Norway and Slovenia from the analysis.) Figure 2 shows how the correlation between the explanatory variables and logarithmic clopidogrel utilization changed over time between 2004 and 2014. The correlation of logarithmic utilization with logarithmic GDP per capita was around 0.75 in 2004, slightly decreased to 0.5 until 2009 and then dropped to essentially zero after that. Similarly, the correlation with health expenditure per GDP was around 0.75 until 2008 and then dropped to nonsignificant levels by the end of the period. Hence affordability was strongly related to clopidogrel utilization until around 2009, roughly the time of generic entry in most countries, but not thereafter. Meanwhile, interestingly, the proportion of old-age population was positively associated with clopidogrel utilization only until 2009, while SDR from circulatory diseases was even negatively correlated with utilization in this period, suggesting that these variables are not necessarily good proxies for health (clopidogrel) need.

(Table 1 about here)

(Fig. 2 about here)

2.3. Methods

Based on the above considerations, we analyzed the longitudinal (panel) clopidogrel utilization data of European countries with a multilevel model (a random intercept – random slope model). These models (also known as hierarchical models) are appropriate to describe the country-specific random trends of clopidogrel utilization, whilst controlling for multiple confounding variables (see e.g. Gelman and Hill [21], for a general review, and Rice and Jones [22], for an early health-specific review of such models). In our analysis we used the following baseline specification:

(1) $$Y_{it} = \alpha_i + \tau_i * t + \theta * t^2 + (\beta_0 + \beta_1 * Z_i) * Aft_{it} + \mathbf{X}_{it}\boldsymbol{\gamma} + \varepsilon_{it}$$

(2) $$\alpha_i = \alpha_0 + \upsilon_i$$

(3) $$\tau_i = \delta_0 + \delta_1 * Z_i + w_i,$$

where i denotes country, t denotes year and $t = 0$ stands for year 2009 (which is the middle of the examined period and the year of generic entry in the majority of countries). The logarithm of

clopidogrel utilization per capita (Y_{it}) was modelled with the time trend, with the vector of the control variables ($\boldsymbol{X}_{it}$) and with the binary variable indicating the years after the generic entry (Aft_{it}). The variable Aft_{it} takes one if the generic entry occurred before year t in country i, takes zero if it occurred after year t and takes 0.25, 0.5 or 0.75 if it occurred within year t, depending on the quarter of the entry. Most importantly, Aft_{it} not only occurs on its own in the equation but its product with Z_i, a measure of the per capita GDP of a country relative to the most developed countries in Europe, was also included. Specifically, Z_i was defined as the logarithmic difference between country i's GDP per capita and the upper decile of the GDP per capita of the countries in the sample in 2009 (the base year). Hence β_0, the parameter of Aft_{it}, measures the effect of generic entry on clopidogrel utilization in the most developed countries (at the upper decile of the income distribution), while β_1, the parameter of $Z_i * Aft_{it}$, measures the heterogenous effect at lower income levels. Since $Z_i < 0$ for the lower-income countries we expect β_1<0 on the basis of the descriptive analysis above. The vector of control variables ($\boldsymbol{X}_{it}$) explaining affordability and health need contains the logarithm of GDP per capita in PPP, health expenditure per GDP, the proportion of old-age population and SDR from circulatory diseases.

The country-specific trend, defined in equation (3), depends on Z_i and thus its parameter δ_1 measures the trend difference between the lower- and higher-income countries. We expect $\delta_1 < 0$ because, on average, lower-income European countries experienced a faster growth rate of clopidogrel utilization than higher-income ones (Figure 1). Finally, equation (1) contains a general quadratic trend in clopidogrel utilization to allow for a possible saturation effect in the given period. We expect θ, the parameter of the quadratic trend, to be slightly negative.

The multilevel structure of the model implies that the country-level intercept α_i and the time trend τ_i vary by country beyond the mere effect of the control variables (equations (2)-(3)). The usual multilevel modelling assumptions apply for the three error terms of the model $(v_i, w_i, \varepsilon_{it})$.

Beyond the baseline model we used two alternative specifications. In the second specification, we restricted the estimation sample to a six-year wide (i.e. ±3 years) time window around the generic entry. By concentrating on periods just preceding and following generic entry, possible longer-term nonlinear trends or longer-term confounding factors could be ruled out. Also, to get rid of possible discrepancies in clopidogrel sales just before the time of generic entry, we omitted the year of generic entry from the sample in this specification.

In the third specification we examined in more detail which aspects of the generic entry affected clopidogrel utilization. We added two more variables to equation (1): the year of generic entry in country i relative to the last quarter of 2009, denoted by R_i, and the logarithm of the number of generic manufacturers in country i in year t, relative to the average number of generic manufacturers

after the generic entries (this logarithmic difference is denoted by M_{it}). Hence our equation (1) became

(1') $$Y_{it} = \alpha_i + \tau_i * t + \theta * t^2 + (\beta_0 + \beta_1 * Z_i + \beta_2 * R_i + \beta_3 * M_{it}) * Aft_{it} + \mathbf{X}_{it}\boldsymbol{\gamma} + \varepsilon_{it}.$$

If earlier generic entry was associated with a larger increase in utilization then $\beta_2 < 0$. If the number of generic manufacturers increased clopidogrel utilization then $\beta_3 > 0$.

3. Results

Table 2 shows the parameter estimates of the multilevel models. According to our baseline specification (first column of Table 2) the generic entry had an essentially zero effect on the level of clopidogrel utilization for the highest-income countries ($\hat{\beta}_0 = -0.02$ in equation (1)) but its effect was substantial for other countries. Our point estimate for β_1 ($\hat{\beta}_1 = -0.82$) suggests that the effect of generic entry on the logarithmic scale was around $-0.02 + 0.82 \times 0.35 = 0.27$ for the average-income country (of which the logarithmic GDP per capita was 0.35 lower than the upper decile) and $-0.02 + 0.82 \times 0.96 = 0.77$ for the lowest-income country in the sample (with logarithmic GDP per capita 0.96 lower than the upper decile). These imply a $100 \times (\exp(0.27) - 1) = 31$ per cent increase of clopidogrel utilization for the average-income country and a $100 \times (\exp(0.77) - 1) = 116$ per cent increase for the lowest-income country.

According to the trend equation the highest-income countries experienced only a modest trend increase of clopidogrel utilization in the given period ($\hat{\delta}_0 = 0.05$ in equation (3)) but the average- and lower-income countries had a substantially higher rate. Since $\hat{\delta}_1 = -0.18$, a one per cent lower per capita GDP implied an around 0.2 per cent higher annual trend increase. Thus the estimated annual trend for the average-income country was around $100 \times (0.05 + 0.18 \times 0.35) = 11$ per cent after controlling for other variables. The quadratic term was significantly negative, implying saturation in clopidogrel consumption by the end of the period.

Among the four control variables the logarithm of per capita GDP and the health expenditure per GDP ratio were significant. On average, in the given period, a one per cent larger GDP per capita was associated with an around 2.2 per cent larger per capita clopidogrel utilization (95% confidence interval: 0.9-3.5 per cent). However, since the country-specific trends strongly depended on income (see Figure 1 and Table 2), this relationship holds only on average. As shown in the descriptive analysis the relationship was very strongly positive at the beginning of the period and decayed until 2014 (see Figure 2). Finally, holding per capita GDP and other factors fixed, a one percentage point larger health expenditure per GDP ratio was associated with 8 per cent larger per capita clopidogrel utilization, suggesting that this variable is an appropriate, partially independent proxy of health need,

affordability and priorities for health care. The parameters of the two other control variables (proportion of old-age population and SDR from circulatory diseases) were not significant.

The conclusions of the second specification, where the model was estimated on the restricted sample, are similar to the baseline results (see the second column of Table 2). The third specification (the third column of Table 2), in which we modeled further heterogeneous effects of the generic entry, shows that a one year earlier appearance of generic versions increased clopidogrel utilization by about 100×(exp(0.29)-1)=34 per cent ($\hat{\beta}_2 = -0.29$) and this effect was highly significant. Since this result was mainly governed by the lower-income country Poland, where generic entry occurred in 2006 (much earlier than in other countries in the sample), the interaction term with logarithmic GDP per capita was lower in magnitude ($\hat{\beta}_1 = -0.52$) in this specification than in the baseline one – nevertheless it was still significant at the 5 per cent level. The specification also shows that the number of generic manufacturers was not significantly associated with the increase of clopidogrel utilization after the generic entry.

(Table 2 about here)

4. Discussion and conclusions

In this paper we analyzed the determinants of clopidogrel utilization in European countries between 2004 and 2014. We found that clopidogrel utilization was strongly affected by affordability constraints (as proxied by GDP per capita) before entrance of generic medicines but this effect decayed by 2014. In line with this, our estimated models found a substantially larger trend increase of clopidogrel utilization in lower-income European countries than in the highest-income ones.

Similarly, the evidence shows that entry of generic medicines increased clopidogrel consumption in lower- and average-income countries but not in the highest-income ones. The data also suggest that an earlier generic entry was associated with a larger effect.

Although we could exploit the variation in the time of generic entry across countries in our estimation strategy, our results were mainly driven by the comparison of clopidogrel utilization levels and trends before and after 2009, the year of generic entry in most countries. Although we controlled for various confounding variables and for a saturation effect in the data, it is still possible that our results were partly governed by external factors we could not control for. In the future it would be worth investigating other pharmaceuticals as well, for which the variation of the time of generic entry was larger, because exploiting this variation would lead to more precise estimates of the effects of generic entry. A similar analysis of 35 generic medicines was carried out by Dylst and Simoens [4], but they focused on the relationship between market share and the price level.

Our research is related to a neglected area, as evaluation of generic drug policies is not a popular field of health policy research. Pharmaceutical policy makers put more emphasis on improving policies of innovative medicines due to pressure from patients, health care professionals and manufacturers to increase patient access to novel therapies. However, the success of public health policies is more dependent on the efficiency of generic drug policies since in disease areas with the most public health burden, such as cardiovascular diseases, the first line treatments are already generic medicines [7]. Hence the importance of generic drug policies has been increasing over time. Generic medicines can improve the sustainability of financing pharmaceuticals by generating savings in health care systems. In addition, off-patent drugs may also generate health gain by improving the accessibility of patients to medicines, especially in countries with cost-containment measures. If volume restrictions were applied for individual prescribers or health care institutions, with generic entry more patients can be treated from the same budget. As generics are more cost-effective than originator medicines, payers may allow first line use of effective generic drugs, if second-line restriction for the originator product in the therapeutic guidelines was implemented only due to economic reasons. Generic price erosion can also result in reduced copayment that may diminish disincentives of patients to access to the most appropriate therapies.

In those countries where cost-containment measures are applied for the originator product payers should equally understand the population health gain and savings in the health care budget due to increased utilization of generic drugs. Patient adherence and persistence are important factors of health gain in chronic diseases, however, policymakers rarely consider these indicators when evaluating generic drug policies, often they just focus on facilitating generic price erosion.

The case of clopidogrel indicates that the utilization of effective patented medicines is affected by affordability constraints. The entrance of generics, however, may increase patient access and improve health outcomes, most notably in lower income countries, thereby reducing inequalities between European patients.

Our results highlighted that for lower income countries the investment aspect of generic drug policies can be equally or even more important than the aspect of disinvestment. Policymakers should also consider this investment aspect of generic medicines when designing and implementing European and national pharmaceutical policies.

Acknowledgments

The authors would like to thank Neelam Patel (IMS Health) for guidance about the data and Pieter Dylst (EGA) for useful comments. Data were provided by IMS Health. The study was funded by the

European Generic and Biosimilar Medicines Association (EGA). Péter Elek was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Conflict of Interest

The writing of this manuscript was supported by EGA. However, authors summarized their independent professional opinion and take full responsibility for potential errors in the manuscript.

References

1. Kutzin J. Health financing policy: a guide for decision-makers. Health Financing Policy Paper 2008/1. WHO. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/78871/E91422.pdf. Accessed 26 Jan 2016.

2. Pharmaceutical Sector Inquiry. Final Report, European Commission. 8 July 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf Accessed 26 Jan 2016.

3. Dylst P, Vulto A, Simoens S. Does increased use of generic medicines by elders in Belgium help to contain escalating health care budgets? J Aging Soc Policy 2014;26(3):266-80. DOI: 10.1080/08959420.2014.899197

4. Dylst P, Simoens S. Does the market share of generic medicines influence the price level? A European analysis. PharmacoEconomics 2011;29:875-82. DOI: 10.2165/11585970-000000000-00000

5. Kanavos P. Measuring performance in off-patent drug markets: a methodological framework and empirical evidence from twelve EU member states. Health Policy 2014;118:229-41. DOI: 10.1016/j.healthpol.2014.08.005

6. Heinze G, Hronsky M, Reichardt B, Baumgärtel C, Müllner M, Bucsics A, Winkelmayer WC. Potential savings in prescription drug costs for hypertension, hyperlipidemia, and diabetes mellitus by equivalent drug substitution in Austria: a nationwide cohort study. Appl Health Econ Health Policy 2015;13(2):193-205. DOI: 10.1007/s40258-014-0143-4

7. Kaló Z, Holtorf AP, Alfonso-Cristancho R, Shen J, Ágh T, Inotai A, Brixner D. Need for multicriteria evaluation of generic drug policies. Value Health 2015;18:346-351. DOI: 10.1016/j.jval.2014.12.012

8. Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrazo S, Berg C, Bishop I, Bucsics A, Campbell S, Finlayson AE, Fürst J, Garuoliene K, Herholz H, Kalaba M, Laius O, Piessnegger J, Sermet C, Schwabe U, Vlahović-Palčevski VV, Markovic-Pekovic V, Vončina L, Malinowska K, Zara C, Gustafsson LL. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Front Pharmacol 2014;5:106. DOI: 10.3389/fphar.2014.00106

9. Dylst P, Vulto A, Simoens S. Societal value of generic medicines beyond cost-saving through reduced prices. Expert Rev Pharmacoecon Outcomes Res 2015;15(4):701-11. DOI: 10.1586/14737167.2015.1017565

10. Gumbs PD, Verschuren WM, Souverein PC, Mantel-Teeuwisse AK, de Wit GA, de Boer A, Klungel OH. Society already achieves economic benefits from generic substitution but fails to do the same for therapeutic substitution. Br J Clin Pharmacol 2007;64(5):680-5. DOI: 10.1111/j.1365-2125.2007.02958.x

11. Chu C, Rudant E, Bonvalet M, Agostini H, Cavalié P, Bonhomme-Faivre L, Frenkiel J, Taillandier J, Boissonnas A, Vittecoq D, Wyplosz B. Generic drug prescriptions following hospital discharge: a prospective study in France. Eur J Intern Med 2011;22(5):e45-9. DOI: 10.1016/j.ejim.2011.01.016

12. McDevitt-Potter LM, Sadaka B, Tichy EM, Rogers CC, Gabardi S. A multicenter experience with generic tacrolimus conversion. Transplantation 2011;92(6):653-7. DOI: 10.1097/TP.0b013e31822a79ad

13. Godman B, Persson M, Miranda J, Skiöld P, Wettermark B, Barbui C, Gustafsson LL. Changes in the utilization of venlafaxine after the introduction of generics in Sweden. Appl Health Econ Health Policy 2013;11(4):383-93. DOI: 10.1007/s40258-013-0037-x

14. European Medicines Agency (EMA). EPAR summary for the public. Plavix (clopidogrel). EMA/765472/2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library /EPAR_Summary_for_the_public/human/000174/WC500042183.pdf Accessed 29 Feb 2016

15. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. Am J Med 2004;116(12):797-806. DOI: 10.1016/j.amjmed.2004.01.014

16. Kolm P, Yuan Y, Veledar E, Mehta SR, O'Brien JA, Weintraub WS. Cost-effectiveness of clopidogrel in acute coronary syndromes in Canada: a long-term analysis based on the CURE trial. Can J Cardiol 2007;23(13):1037-42.

17. Heeg BM, Peters RJ, Botteman M, van Hout BA. Long-term clopidogrel therapy in patients receiving percutaneous coronary intervention. PharmacoEconomics 2007;25(9):769-82. DOI: 10.2165/00019053-200725090-00005

18. Berg J, Fidan D, Lindgren P. Cost-effectiveness of clopidogrel treatment in percutaneous coronary intervention: a European model based on a meta-analysis of the PCI-CURE, CREDO and PCI-CLARITY trials. Curr Med Res Opin 2008;24(7):2089-101. DOI: 10.1185/03007990802222261

19. Karnon J, Holmes MW, Williams R, Bakhai A, Brennan A. A cost-utility analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK. Int J Cardiol 2010;140(3):315-22. DOI: 10.1016/j.ijcard.2008.11.105

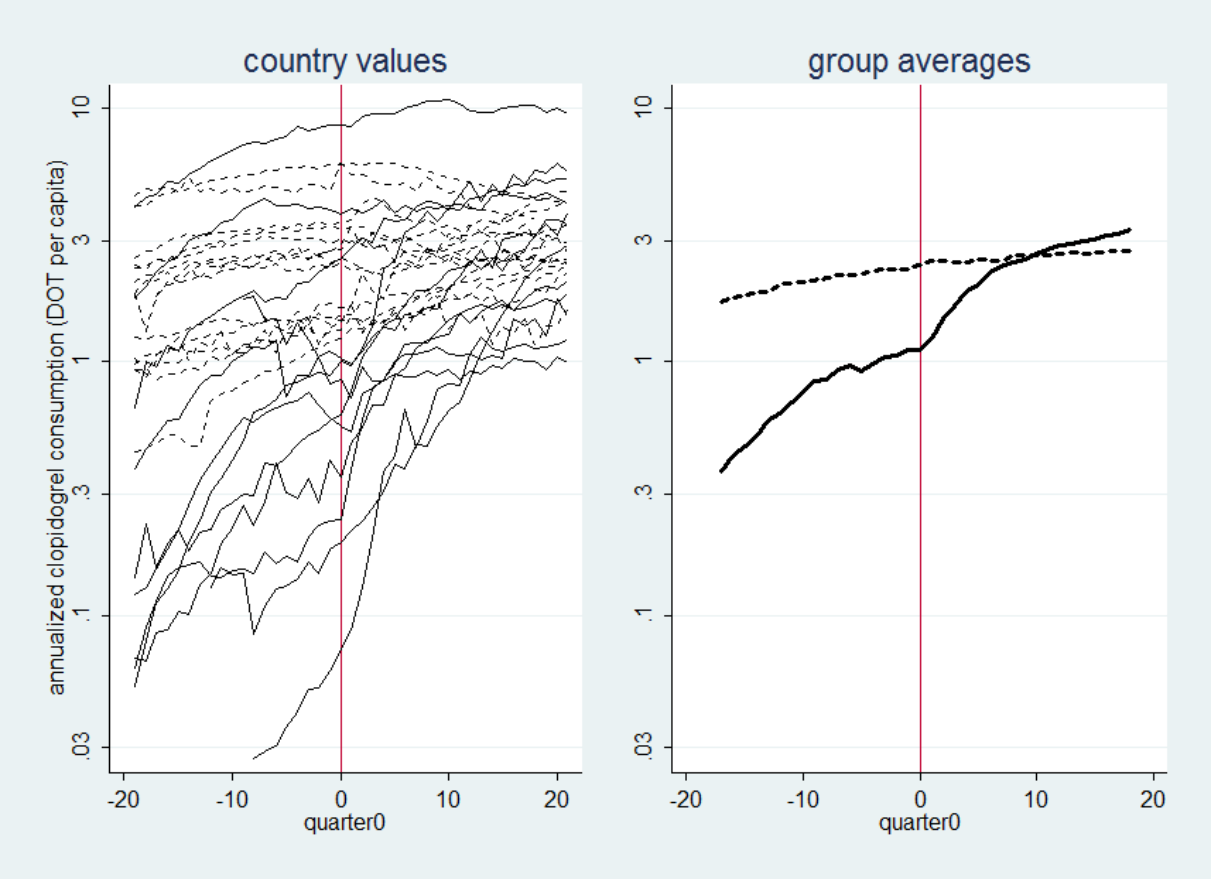
20. Baumgartel C, Godman B, Vitry A, Ringerud AM. Sermet C, Zara C, Koskinen H, Herholz H, Bennie M. What lessons can be learned from the launch of generic clopidogrel? GaBi Journal. 2012;1(2):58-68. DOI: 10.5639/gabij.2012.0102.016

21. Gelman A, Hill J. Data Analysis Using Regression and Multilevel / Hierarchical Models. 1st ed. Cambridge University Press; 2007.

22. Rice N, Jones A. Multilevel models and health economics. Health Econ 1997;6(6):561-75.

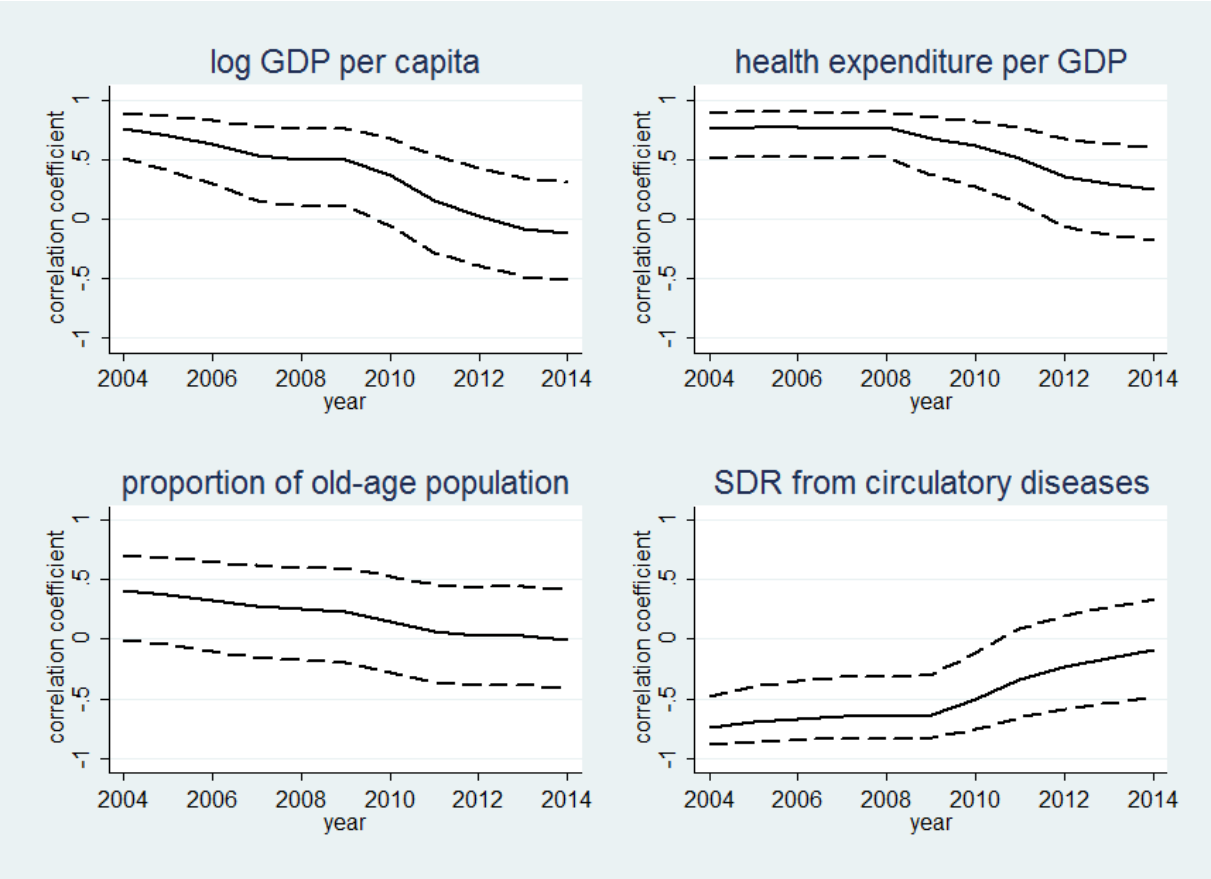
Figures and tables

Figure 1: Clopidogrel consumption in lower- and higher-income European countries relative to the quarter of generic entry (quarter0)



Source: own calculations based on data from IMS Health.
Quarterly clopidogrel consumption is annualized and displayed in logarithmic scale.
Solid lines indicate lower-income, dashed-lines higher-income countries (categorized according to the average GDP per capita in PPP in 2009). Left panel shows individual country values and right panel displays logarithmic averages in the lower- and the higher-income group. To ensure rough comparability, we calculated averages after omitting three countries where generic entry occurred before 2008 (Bulgaria, Poland, Slovenia).

Figure 2: Correlation coefficient of logarithmic clopidogrel utilization per capita and various control variables in European countries by year (2004-2014)



Source: own calculations based on data from IMS Health.
Solid lines indicate correlation coefficients and dashed-lines give 90% confidence intervals. All calculations are based on 23 European countries.

Table 1: Descriptive statistics of clopidogrel utilization and the explanatory variables in European countries in various years

Variable / Year	**2004**		**2009**		**2014**	
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
Clopidogrel variables						
Clopidogrel utilization (DOT per capita)	1.30	(1.16)	2.37	(1.96)	3.43	(1.83)
Log clopidogrel utilization (DOT per capita)	-0.47	(1.55)	0.54	(0.86)	1.13	(0.46)
Generic / total clopidogrel ratio (per cent)	0.0	(0.0)	13.3	(17.4)	74.9	(19.6)
Explanatory variables						
Log GDP per capita in PPP (constant price international USD)	10.28	(0.40)	10.35	(0.33)	10.40	(0.30)
Health expenditure / GDP (per cent)	8.34	(1.79)	9.44	(1.81)	9.39	(2.04)
Proportion of old-age population (per cent)	15.7	(2.1)	16.5	(2.2)	17.3	(2.5)
SDR from circulatory diseases (all ages, per 1,000 inhabitants)	3.22	(1.53)	2.70	(1.36)	2.32	(1.34)

Source: own calculations based on data from IMS Health.
All means and standard deviations (S.D.) are for 23 European countries.

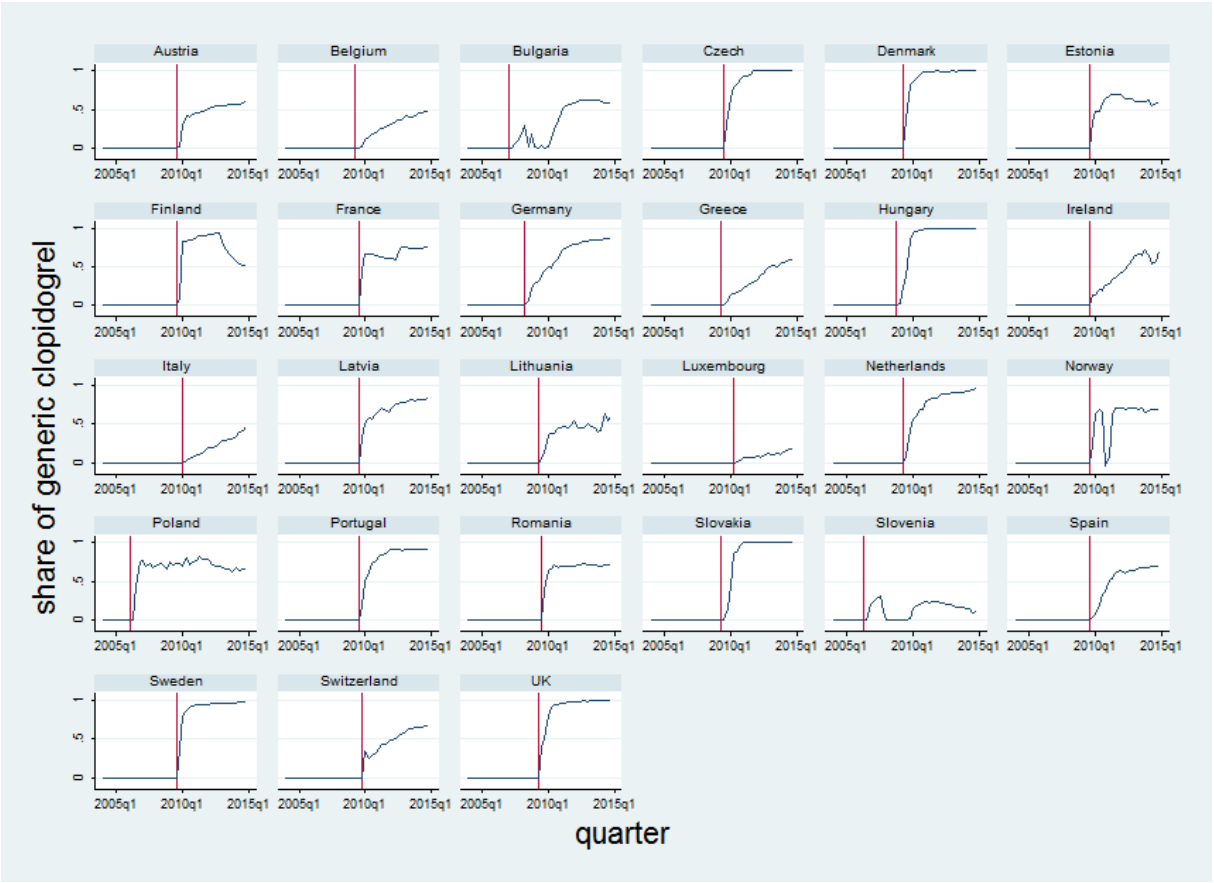
Table 2: Estimation results from multilevel models

Dependent variable: **log clopidogrel utilization (DOT per capita)**		**Baseline** **eq. (1)-(3)**	**Restricted** **eq. (1)-(3)**	**Alternative** **eq. (1')-(3)**
Parameters				
After generic entry	β_0	-0.018 (0.066)	-0.006 (0.055)	-0.042 (0.071)
After generic entry x log GDP per capita in 2009 (relative to upper decile)	β_1	-0.82** (0.34)	-0.63** (0.27)	-0.52** (0.24)
After generic entry x year of generic entry (relative to 2009)	β_2			-0.29*** (0.09)
After generic entry x log number of generic manuf. (relative to average)	β_3			0.053 (0.052)
Log GDP per capita in PPP	γ_1	2.25*** (0.66)	1.56*** (0.60)	1.91*** (0.48)
Health expenditure / GDP (per cent)	γ_2	0.078** (0.038)	0.043 (0.052)	0.078* (0.043)
Proportion of old-age population (per cent)	γ_3	-0.022 (0.055)	-0.019 (0.045)	-0.012 (0.053)
SDR from circulatory diseases (all ages, per 1,000 inhabitants)		0.20 (0.13)	0.03 (0.09)	0.18 (0.13)
Trend (relative to 2009)	δ_0	0.054** (0.022)	0.028 (0.027)	0.054** (0.022)
Trend (relative to 2009) x log GDP per capita in 2009 (relative to upper decile)	δ_1	-0.183*** (0.046)	-0.258*** (0.063)	-0.193*** (0.043)
Trend squared (relative to 2009)	θ	-0.0070*** (0.0023)	-0.0014 (0.0044)	-0.0069*** (0.0024)
Constant	α_0	-23.8*** (7.2)	-15.9** (6.2)	-20.3*** (5.4)
Standard deviation of error terms				
Standard deviation of v	σ_v	0.71*** (0.14)	0.66*** (0.13)	0.72*** (0.11)
Standard deviation of w	σ_w	0.089*** (0.010)	0.128*** (0.020)	0.092*** (0.011)
Standard deviation of ε	σ_ε	0.169*** (0.022)	0.109*** (0.017)	0.158*** (0.018)
Correlation of v and w	λ	-0.57*** (0.17)	-0.54*** (0.17)	-0.56*** (0.14)
Number of observations		253	137	253
Number of countries		23	23	23

Source: own calculations based on data from IMS Health.
Cluster-robust standard errors are reported in parentheses.
*** p<0.01, ** p<0.05, * p<0.1
All models were estimated on country-level longitudinal data.
Years: 2004-2014 for the baseline and alternative models, and a six-year wide time window around the generic entry (excluding the year of generic entry) for the restricted sample.

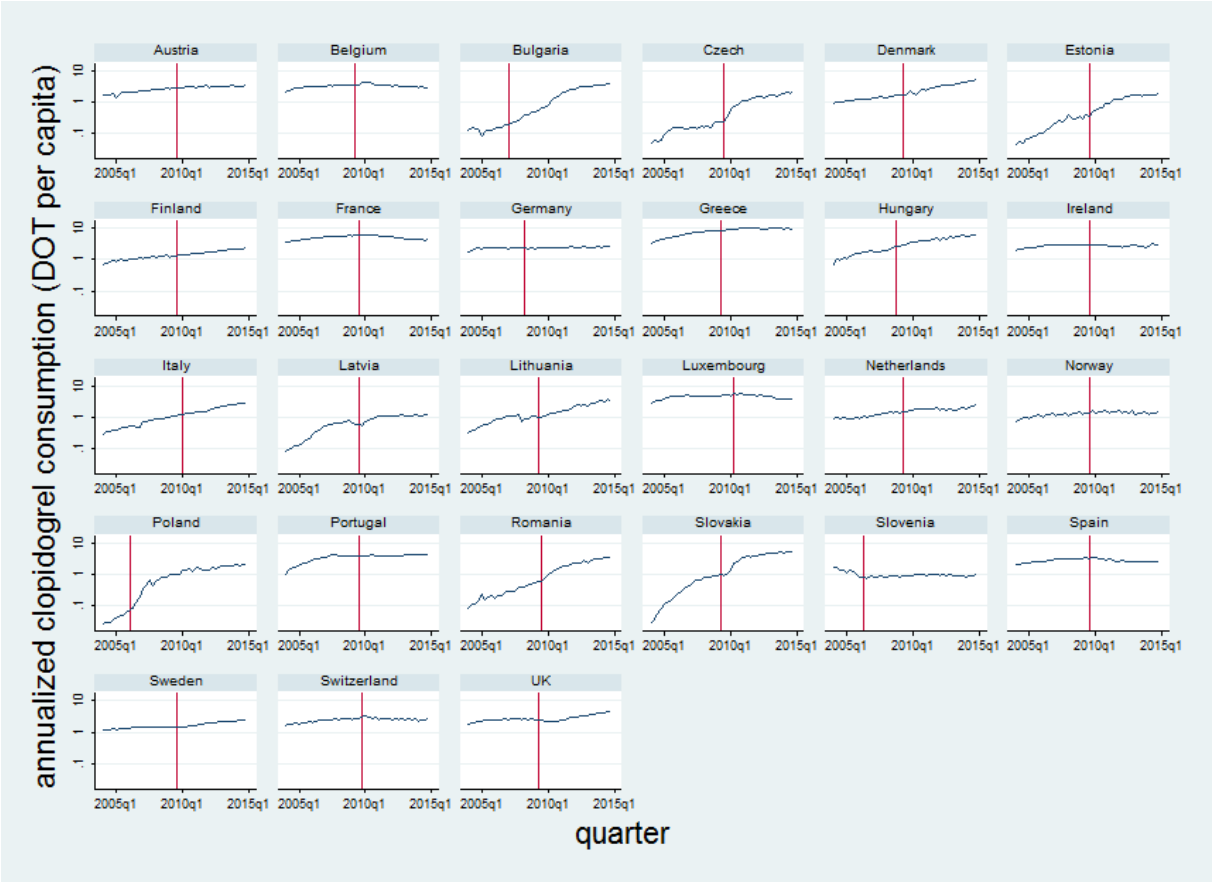
Appendix

Figure A1: The share of generic sales in total clopidogrel sales in European countries (2004-2014)



Source: own calculations based on data from IMS Health.
Vertical lines indicate the quarters of generic entry.

Figure A2: Annualized clopidogrel consumption in European countries (2004-2014)



Source: own calculations based on data from IMS Health.
Vertical lines indicate the quarters of generic entry. Quarterly clopidogrel consumption is annualized and displayed in logarithmic scale.