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Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications

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Aim: the aim of this article was to evaluate the influence of different demand-side measures to enhance the prescribing of generics in ambulatory care based on cross-national comparisons. **Methods:** an observational retrospective study was conducted using administrative databases from across Europe, documenting changes in reimbursed utilization and expenditure of different proton pump inhibitors (PPIs) and statins between 2001 and 2007, alongside different reforms to enhance prescribing efficiency. Utilization was converted to defined daily doses (DDDs) and expenditures were converted to euros. Demand-side measures were collated under the '4 Es' – education, engineering, economics and enforcement – to enable comparisons on the nature and intensity of reforms between countries. **Results:** there were considerable differences in the utilization of generics and patent-protected PPIs and statins among Western European countries. Decreased utilization of omeprazole and simvastatin, alongside increased utilization of esomeprazole, atorvastatin and rosuvastatin, was seen in countries with limited demand-side measures to counteract commercial pressures. Prescribing restrictions, or a combination of education, prescribing targets and financial incentives, had the greatest influence on enhancing the utilization of omeprazole and simvastatin. For example, there was a threefold reduction in the utilization of atorvastatin in Austria following prescribing restrictions. Multiple demand-side interventions generally had a greater influence than single interventions, with the impact appearing additive. Multiple interventions coupled with initiatives to lower prices of generics considerably enhanced prescribing efficiency. **Conclusion:** this cross-national study has demonstrated considerable variation in the utilization and expenditure of PPIs and statins across Europe, providing opportunities to further improve prescribing efficiency. The '4 Es' do provide an understandable methodology to document and compare the influence of different demand-side measures, with the influence varying by their extent and intensity. Further reforms are essential given current financial pressures. Consequently, further research will concentrate on the potential to develop a scoring system to help predict the possible impact of different demand-side measures on future utilization patterns.

KEYWORDS: cross-national studies • demand-side reforms • generic drugs • generic substitution
• prescribing efficiency

Drug therapy is an important treatment option in the management of patients in ambulatory care. The focus on pharmaceutical expenditures is increasing with expenditures having risen rapidly in the 1990s and early 2000s at between 4 and 13% per annum [1–7,101]. This rate is typically faster than that of other components of healthcare [5,6–10],

resulting in pharmaceutical expenditures in ambulatory care now being the largest or equal largest expenditure component in this segment among European countries [1,2,4,10–12].

European governments, health authorities and health insurance agencies have implemented a variety of reforms and initiatives to moderate this unsustainable growth. These include policies

surrounding generics including those that impact on prices (supply-side measures) as well as utilization (demand-side measures).

Supply-side reforms include measures to [2–4,10,13,101]:

- Engineer lower prices for multiple source products helped in many European countries by patients having to cover the costs themselves for a more expensive brand than the reference molecule in addition to any standard co-payment for the dispensed product;
- Engineer low prices for interchangeable products within a class;
- Lower the prices generally of existing medicines through compulsory price cuts.

Alongside this, measures to rapidly reimburse generics once they receive marketing authorization through demonstrating the same qualitative and quantitative composition, as well as bioavailability, as the originator substance and their pricing policy are in line with current directives [13]. However, this is not always the case with appreciable delays occurring in some countries. The pricing

policies for generics and originators (original-brand product once multiple sources are available) in Europe have recently been extensively described by us and others [13–19]. These aspects will therefore not be elaborated further.

Reimbursed prices, especially for high-volume generic drugs, are low in Sweden and the UK. This is helped by compulsory generic substitutions in Sweden [9,13], and high international

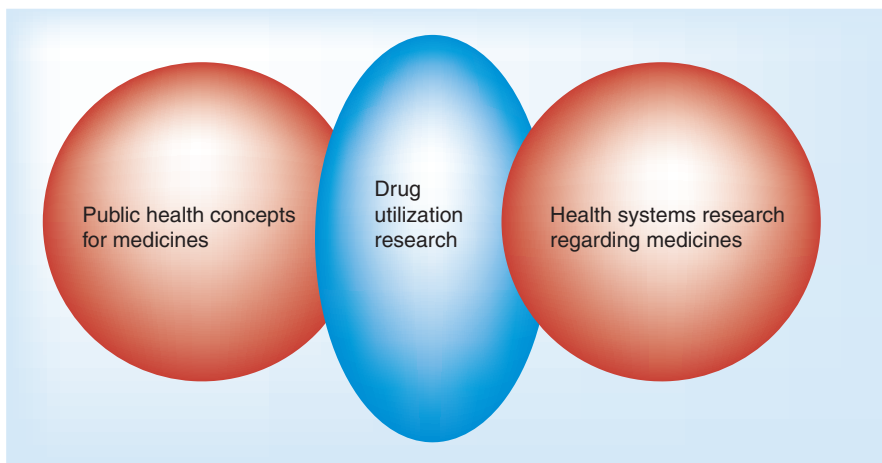


Figure 1. Relationship of drug utilization research with public health and health systems research fields.

Table 1. Country characteristics in 2008 unless stated.

| Characteristics | AT | DE | EE | FR | GB | HR | IE | IT | LT | NO | PO | PT | RS | SE | SI | TR |
|---|------|------|-----|------|------|-----|-----|------|-----|-----|------|------------------|----|-----------|------|------------------|
| Population (millions) | 8.3 | 82.1 | 1.3 | 61.8 | 60.5 | 4.4 | 4.3 | 58.9 | 3.3 | 4.8 | 38.1 | 10.6 | NR | 9.2 | 2.03 | 74.8 |
| % of GDP on healthcare | 10.5 | 10.5 | 6.1 | 11.2 | 8.7 | 7.5 | 8.7 | 9.1 | 5.9 | 8.5 | 7.0 | 9.9 [†] | NR | 9.4 | 8.1 | 6.0 [†] |
| % of GDP on pharmaceuticals and other medical nondurables | 1.4 | 1.6 | 1.3 | 1.8 | NR | NR | 1.5 | 1.7 | NR | 0.7 | 1.6 | 2.2 [†] | NR | 1.2 | NR | NR |
| % of GDP on prescription drugs | 1.1 | 1.4 | 1.0 | 1.5 | NR | NR | NR | NR | 1.2 | 0.6 | 0.9 | NR | NR | 0.9 | 1.2 | NR |
| Taxation-based system | | | | | ✓ | | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| Health insurance-based system | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | | ✓ | | ✓ | | ✓ | |
| Pricing policy for generics | MA | MF | MA | MA | MF | MA | MA | MA | MA | PP | MF | MA | MA | MF | MA | PP |
| Reference pricing – class | VP | ✓ | | | RJT | ✓ | | ✓ | AC | | ✓ | | SP | Only PPIs | | ✓ |

[†]2006.
[†]2007.
 AT: Austria; DE: Germany; EE: Estonia; ES: Spain – Catalonia; FR: France; GB: Great Britain; HR: Croatia; IE: Republic of Ireland; IT: Italy; LT: Lithuania; NO: Norway; PO: Poland; PT: Portugal; RS: Serbia; SE: Sweden; SI: Slovenia; TR: Turkey.
 GDP: Gross domestic product; NR: Not recorded.
 Generic pricing: MA: Mixed approach – combining prescriptive pricing for the first generic or generics followed by market forces; MF: Market forces – where measures are in place to lower prices through market forces; PP: Prescriptive pricing for generics – dictated by health authorities or health insurance agencies.
 Reference pricing – Class: AC: Being actively considered; RJT: Proposed but Rejected; SP: Applies to some product classes but not all; VP: Voluntary reference pricing.

nonproprietary name (INN) prescribing linked with the transparent pricing of generics in the UK [13,20,21]. Reimbursed prices for six high-volume generics in Sweden were between 4 and 13% of the originator prices prepatent loss, with generic simvastatin and generic risperidone being 2% of the originator price in the UK [3,9,20,22]. Despite various initiatives [13], the prices of generics still vary by up to 36-fold across countries depending on the molecule [18]. Consequently, reducing reimbursed prices for generics in some European countries is one way to enhance prescribing efficiency.

Equally, enhancing the prescribing and dispensing of generics will also help to improve prescribing efficiency. Demand-side measures include the following [2–4,9,13,20,23–31]:

- Encouraging pharmacists to substitute, where appropriate, through incentives and other mechanisms;
- Additional patient co-payments for more expensive molecules than the referenced price molecule;
- Prescribing targets coupled with physician financial incentives;
- Budget devolution coupled with financial incentives and penalties;
- Benchmarking physician prescribing patterns against each other coupled with financial penalties for excessive costs.

However, it is recognized that prescribing is a complex process. This typically involves physicians sifting information from a variety of sources, including pharmaceutical companies, as well as balancing a range of personal, social and logistical influences including habitual behaviors in addition to medical and pharmaceutical considerations [29,32–38]. This complexity is reflected, for instance, by pharmaceutical companies having spent over GB£850 million/year in the UK alone in marketing activities in recent years to influence prescribing, with similar rates in other countries [24,38,102].

There have also been initiatives to address concerns regarding the effectiveness and safety of generics when they arise. These include educational initiatives via physicians, pharmacists and the media, not granting reimbursement where concerns with the quality of the generic exist, for example, in Austria, as well as directing prescribing and dispensing [2,4,9,13,21,23,39,40]. Directing

prescribing and dispensing includes prohibiting substitution where concerns are evident, for example, in Sweden, or alternatively, recommending the prescribing of brand names, for example, in the UK with, for instance, ciclosporin, lithium and mesalazine as well as long-acting morphine. Thankfully, concerns over the

Table 2. Details of the administrative databases and data providers (100% coverage of the population unless stated).

| Providers for the cross-national study | Databases |
|--|---|
| Austria | Data Warehouse of the Federation of Austrian Social Insurance Institutions (98% of the population) |
| Germany | GAmSi database, that is, GKV-Arzneimittel Schnellinformation, which covers all prescriptions paid for by the Social Health Insurance Funds (approximately 90% of the population) |
| Estonia | Estonian Health Insurance Fund |
| Spain – Catalonia | DMART (Catalan Health Service) database (all patients in Catalonia) Data only available from 2003 onwards |
| France | Medic'am database (CNAM-TS database for salaried personnel covering 75% of the population) |
| Great Britain – England | Information Centre for Health and Social Care |
| Great Britain – Scotland | PIS from NHS National Services Scotland Corporate Warehouse |
| Croatia | Croatian Institute for Health Insurance |
| Republic of Ireland | HSE-PCRS (GMS population covering approximately 25–30% of the population with higher morbidity than the general population, reflected in consuming approximately 65% of total pharmaceutical expenditure) |
| Italy | OsMed database |
| Lithuania | Electronic database of the National Health Insurance Fund |
| Norway | NorPD Expenditure data only available from 2004 onwards |
| Poland | National Health Fund database |
| Portugal | INFARMED (NHS) database (approximately 75% of the population) |
| Serbia | Republic of Serbia's Health Insurance Fund database |
| Sweden | Apoteket AB (National Corporation of Swedish Pharmacies – monopoly up to 1 January 2010) |
| Slovenia | The National Institute of Public Health and Health Insurance Institute Prescription database |
| Turkey | SGK – single national public payer purchasing approximately 95% of pharmaceutical expenditure in Turkey |

GMS: General Medical Services; HSE-PCRS: Health Service Executive – Primary Care Reimbursement Service; NorPD: Norwegian Prescription Database; PIS: Prescribing Information System, SGK: Social Security Institution.

Table 3. Prescribing indicators used to assess changes in prescribing efficiency.

| Class | Indicator | Rationale |
|---------|--|---|
| PPI | Percentage of generic omeprazole versus all omeprazole in 2007 | Extent of prescribing and dispensing of the generic versus originator drugs after patent loss |
| | Percentage of omeprazole (all) versus all PPIs principally between 2001 and 2007, and in 2007 versus prepatent loss utilization (Western European countries) | Omeprazole was the first PPI to lose its patent; consequently, the principal focus initially for health authority and health insurance company interventions to enhance PPI prescribing efficiency. As a result, the focus of this study was on omeprazole rather than other PPIs, which lost their patents during the course of the study |
| | Percentage of esomeprazole versus all PPIs principally between 2001 and 2007, and in 2007 versus prepatent loss utilization (Western European countries) | Only PPI to be patent protected (single source) during the study period among Western European countries |
| Statins | Percentage of generic simvastatin versus all simvastatin in 2007 | Extent of prescribing and dispensing of the generic versus originator drugs after patent loss |
| | Percentage of simvastatin (all) versus all statins principally between 2001 and 2007, and in 2007 versus prepatent loss utilization (Western European countries) | Simvastatin was the first major statin to lose its patent; consequently, the principal focus initially for health authority and health insurance company interventions to enhance statin prescribing efficiency. As a result, the focus of this study was on simvastatin rather than other statins, which lost their patents during the course of the study |
| | Percentage of atorvastatin and rosuvastatin versus all statins principally between 2001 and 2007, and in 2007 versus prepatent loss utilization (Western European countries) | Only statins to be patent protected (single source) during the study period among Western European countries |

PPI: Proton pump inhibitor.

effectiveness and/or safety of generics among physicians typically only occur in a minority of cases [5,9,41–44]. This situation is not helped by some originator companies questioning the quality of generics as part of their marketing efforts to reduce sales erosion post-patent loss [103].

Concurrent with this, there have been initiatives by European authorities to optimize the prescribing of new premium-priced drugs to further enhance prescribing efficiency. This is because expenditure on new drugs is seen as a major challenge to continued equitable and comprehensive healthcare in Europe [45], exacerbated by the limited health gain with many new products versus current standards [2,4,46–48].

Maximizing prescribing efficiency for both new and existing drugs will help address the continual pressures on pharmaceutical budgets driven by demographic changes, rising patient expectations, stricter clinical targets, the continued launch of new innovative premium-priced drugs and the growth in individualized medicines [8,45,47,49]. European countries are already learning from each other [27], which needs to continue to avoid prohibitive increases in either taxes or health insurance premiums in order to maintain comprehensive and equitable healthcare. Cross-national comparisons of drug utilization is one method for identifying possible measures that countries could introduce, as they help identify potential areas for improving prescribing efficiency through evaluating the consumption of medicines using standard methodologies and possible rationales for patterns observed (FIGURE 1). They also enable analytical studies, linking datasets between countries and matching changes in utilization and expenditure patterns with reforms to guide future initiatives.

The objectives of this paper are:

- First, to analyze changes in drug utilization and expenditure of high-volume ambulatory care drugs in recent years across Europe;
- Second, to try and match the changes seen with ongoing demand-side measures, collated into understandable subgroups in order to enhance comparisons;
- Third, to identify possible future demand-side measures that European countries could instigate in addition to current measures to further enhance the utilization of generics.

As a result, we would be able to add to the existing literature, as there are currently only a limited number of publications assessing the impact of different demand-side measures on future prescribing patterns apart from those concerning guideline production and dissemination, academic detailing or audits combined with feedback and financial incentives [26,30,31,50,51]. This is not helped by health authorities and health insurance agencies typically instigating a range of measures simultaneously or in quick succession, making such analyses difficult.

Methodology

This was an observational uncontrolled retrospective study [52], involving an analysis of reimbursed prescriptions from administrative databases. This methodology was used as there was no opportunity for a controlled study with data analyzed retrospectively. In addition, health authorities and health insurance agencies typically instigate a number of measures simultaneously or in quick succession. These may also last over time, with some applying nationally while others

vary in intensity between regions within a country. As a result, there was no opportunity to perform more sophisticated analytical studies. We acknowledge the limitations of the chosen study design.

A total of 18 European countries and regions were included in the analysis: Austria, Croatia, Estonia, France, Germany, Italy, Lithuania, Norway, Portugal, Poland, the Republic of Ireland, Serbia, Slovenia, Spain (Catalonia), Sweden, Turkey and the UK (England and Scotland). The countries reflect differences in geography, epidemiology, financing of healthcare, available resources for healthcare including pharmaceuticals, approaches to the pricing of generics, originators and single-sourced products, as well as differences in measures to enhance the prescribing of generics (TABLE 1) [1,13,53,104].

A total of 9% of gross domestic product is currently spent on healthcare in Spain, with 1.8% spent on pharmaceuticals [104]. Catalonia was chosen to represent Spain in this study as it is one of the principal autonomous communities in Spain that has been active over a number of years, instigating a range of measures to enhance the prescribing of generics [10].

As stated, only administrative databases from health authorities of health insurance groups were used for the analyses (TABLE 2) to ensure consistency as well as reflect the public health perspective

of this paper. Using administrative databases also ensured that all reimbursed prescriptions were captured for the respective country populations as commercial sources can sometimes include only a sample of pharmacies or, alternatively, only data from wholesalers. The latter does not include any products sold directly from generic manufacturers to community pharmacies.

Two classes of drugs were chosen for in-depth analysis of the potential influence of different demand-side measures on ambulatory care prescribing. These were the proton pump inhibitors (PPIs) – anatomical therapeutic chemical (ATC) group A02BC [105] – and the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) – ATC group C10AA [105]. They were chosen as they are both high-volume prescribing areas in ambulatory care. They also contain a mixture of generics, originators and single-sourced products in a class with single-sourced products marketed as major developments at premium prices, even though health authorities and health insurance agencies generally view these developments as minor at best for the majority of patients [24,53,102,106–111]. There may be some evidence suggesting greater effectiveness for very high doses of atorvastatin, but this should only apply to a minority of patients [54]. Lastly, PPIs and statins are typically

Table 4. Dates when generic omeprazole and generic simvastatin were first reimbursed in Western European countries.

| Country | Year when generic omeprazole was dispensed and reimbursed | Baseline year for assessing utilization patterns of PPIs | Year when generic simvastatin was dispensed and reimbursed | Baseline year for assessing utilization patterns of statins | Comments |
|---------------------|---|--|--|---|--|
| Austria | 2003 | 2002 | 2002 | 2001 | – |
| Germany | 2002 | 2001 | 2003 | 2002 | – |
| Spain – Catalonia | Available in 2003 | 2003 | Available in 2003 | 2003 | Data only available after 2003 for analysis |
| France | 2004 | 2003 | 2005 | 2004 | – |
| GB – England | 2002 | 2001 | 2003 | 2002 | – |
| GB – Scotland | 2002 | 2001 | 2003 | 2002 | – |
| Republic of Ireland | 2002 | 2001 | 2003 | 2002 | – |
| Italy | 2007 | 2006 | 2007 | 2006 | 2008 data compared with 2006 as generics only recently became available |
| Norway | Available in 2004 | 2004 | Available in 2004 | 2004 | Prescription expenditure data only available from 2004; consequently, start of data analysis |
| Portugal | Available in 2000 | 2000 | 2001 | 2000 | Data only available from 2000, that is, after generic omeprazole was launched |
| Sweden | 2003 | 2002 | 2003 | 2002 | – |

GB: Great Britain; PPI: Proton pump inhibitor.

Table 5. '4 E' categorization of demand-side initiatives across Europe.

| 4 'E' category | Definition | Examples |
|----------------|---|--|
| Education | Programs that influence prescribing through dissemination of material, which can be passive or active | Simple distribution of printed treatment guidance Intensive strategies such as educational outreach visits and the monitoring of prescribing against agreed guidance or guidelines coupled with feedback |
| Engineering | Organizational or managerial interventions | Price: volume agreements for existing drugs Disease management programs Prescribing targets, for example, the percentage of prescriptions for generic omeprazole versus all PPIs and percentage generic simvastatin versus all statins and goals for INN prescribing when this is not obligatory or enforced |
| Economics | Financial interventions (positive and negative) | Patient co-payments for more-expensive drugs than the current reference molecule Positive and negative financial incentives for physicians Devolved budgets to physicians |
| Enforcement | Regulations including those enforced by law | Mandatory generic substitution in pharmacies Prescribing restrictions such as prior authorization schemes, for example, atorvastatin in Austria, or alternatively, prescribing restrictions with follow-up only where concerns arise, for example, in Norway and Sweden |

'4 Es': Education, engineering, economics and enforcement; INN: International nonproprietary name; PPI: Proton pump inhibitor.
Data taken from [26].

the subject of many country and/or regional initiatives to enhance efficiency.

Utilization rates for the substances in each class were computed using defined daily doses (DDDs) [112]. The concepts of ATC classification and DDDs were developed to facilitate comparisons in drug utilization between countries, especially where there are differences in pack sizes and available tablet strengths [55,56]. The ATC/DDD index from 2010 has been used in line with recommendations [57].

A number of prescribing indicators were selected to assess the influence of the various demand-side reforms and initiatives on improving prescribing efficiency. These were based on current measures used by health authorities across Europe [9,10,20,102]. Their details and rationale are included in TABLE 3.

Lovastatin was available in some European countries; however, its utilization was limited even in these countries, especially with the increasing utilization of simvastatin. Consequently, simvastatin was the major focus of health authority and health insurance company activity, and is the statin chosen in this study.

As seen in TABLE 3, the analysis principally focused on the years between 2001 and 2007, as typically both generic omeprazole and generic simvastatin became available and were reimbursed during this time period in Western European countries (TABLE 4). Only Western European countries were included in this particular analysis as generic omeprazole was either the only available PPI in former Central and Eastern European countries during some or all of the study period, or was available here earlier than in Western European countries. There was a similar situation with the statins, with generic simvastatin again being available earlier in Central and Eastern Europe than in Western European countries. In addition, generic atorvastatin also became available in Central and Eastern European countries during the study period. All these factors impact on the utilization patterns in former Central and Eastern European countries compared with those in Western European countries.

Reimbursed expenditures, principally from 2001 to 2007, were also captured for each product and class along with changes in utilization to try and assess the influence of the various reforms and initiatives on overall prescribing efficiency from a public health/payer perspective. The only exceptions were Austria, Germany and Norway, where it was difficult to separate reimbursed from total expenditure.

We acknowledge that there are differences in co-payments, pharmacy and wholesaler remunerations as well as value-added tax (VAT) between European countries. In addition, we are aware that community pharmacists may receive discounts and rebates directly from generic manufacturers to preferentially dispense their generics, and in some countries, there is appreciable dispensing of parallel imported products. However, reimbursed expenditure reflects the recorded situation among the health authorities and health insurance agencies.

Reimbursed expenditures were initially calculated in the local currencies and were subsequently converted to euros in 2007 to facilitate comparisons: €1 = GB£0.734 and SEK9.25 (2007). There was no allowance for inflation as typically generic prices were compared with prepatent loss prices by the various authorities [13]. In addition, the prices of generics do not generally rise and may also be subjected to price cuts; however, this is not always the case [13,113].

Details of the various supply- and demand-side reforms in each selected European country were collated with the help of the considerable expertise of the co-authors, from published papers, web-based publications or internal documents known to the co-authors. Details of the reforms were subsequently re-validated with the co-authors to add robustness to the analyses. A narrative review of identified papers was subsequently conducted by one of the co-authors (Brian Godman).

The various demand-side measures have been collated under the '4 Es' methodology – that is, education, engineering, economics and enforcement – to simplify comparisons between countries (TABLE 5),

given the extensive range of measures that have been introduced across Europe. This approach has been used in other settings and adapted to healthcare [9,10,20,26,58].

Finally, there has been no analysis of the initial rationale behind the appropriateness of prescribing either a PPI or statin, as this would require access to patient databases and would detract from the main focus of the paper, which is the identification of potential measures to further enhance prescribing efficiency once physicians have decided to prescribe either a PPI or lipid-lowering drug. However, these issues have been discussed in individual country publications [10,20,58].

Results

The various European countries have implemented a range of different demand-side reforms to try and enhance prescribing efficiency generally and for the PPIs and statins (TABLE 6). Details of general measures to enhance prescribing efficiency and their intensity, as well as specific measures for the PPIs and statins, are summarized in SUPPLEMENTARY TABLE 1 [114].

FIGURE 2 depicts the utilization of generic omeprazole versus all omeprazole, and generic simvastatin versus all statins, in 2007 in selected Western European countries. As stated, reimbursed prices for both generics and originators are typically the same across Europe, with patients being required to fund the additional costs themselves for a more expensive product [13].

FIGURE 3 depicts the changes in utilization for omeprazole and esomeprazole as a percentage of all PPI utilization in 2007 versus utilization rates seen just prior to patent loss of omeprazole (TABLE 2) unless stated. The various demand-side measures influencing the utilization patterns for omeprazole and esomeprazole are documented in TABLE 1 [114]. SUPPLEMENTARY TABLE 2 [114] documents the actual changes in utilization patterns for omeprazole and esomeprazole as a percentage of all PPI utilization on a DDD basis over time among Western European countries.

FIGURE 4 depicts the changes in utilization for simvastatin, atorvastatin and rosuvastatin as a percentage of all statin utilization in 2007 versus utilization rates seen just prior to patent loss of simvastatin (TABLE 2) unless stated. The various demand-side measures influencing the utilization are again documented in SUPPLEMENTARY TABLE 1 [114]. SUPPLEMENTARY TABLE 3 [114] documents the changes in utilization patterns for simvastatin, atorvastatin and rosuvastatin as a percentage of all statin utilization on a DDD basis over time among the Western European countries.

In France, there has been greater utilization of pravastatin than simvastatin. The combined utilization of simvastatin and pravastatin, which lost its patent shortly after simvastatin, was

Table 6. Summary of the different demand-side reforms and initiatives among European countries categorized under the '4 E's'.

| Country | Education | Engineering | Economics | Enforcement |
|----------------|-----------|-------------|-----------|----------------|
| AT | ✓ | | ✓ | ✓ |
| DE/states | ✓ | ✓ | ✓ | ✓ |
| EE | ✓ | ✓ | ✓ | ✓ |
| ES/Catalonia | ✓ | ✓ | ✓ | ✓ |
| FR* | ✓ | ✓ | ✓ | ✓ |
| GB – England | ✓ | ✓ | ✓ | |
| GB – Scotland† | ✓ | ✓ | ✓ | |
| IE | ✓ | | | |
| IT/regions | ✓ | ✓ | ✓ | ✓ |
| LT | ✓ | ✓ | ✓ | ✓ |
| HR | ✓ | ✓ | ✓ | ✓ |
| NO | ✓ | | | ✓ |
| PO | ✓ | | ✓ | ✓ |
| PT | ✓ | ✓ | ✓ | ✓ |
| RS | | | ✓ | Selected drugs |
| SE | ✓ | ✓ | ✓ | ✓ |
| SI | ✓ | | ✓ | Selected drugs |
| TR | ✓ | | | |

*Contrats d'amélioration des pratiques individuelles (CAPI) in France for prescribing targets linked with incentives was only introduced in 2009 [2].

†Differences between England and Scotland are principally in terms of drug budget devolution/accountability (see SUPPLEMENTARY TABLE 1) [114].

AT: Austria; DE: Germany; EE: Estonia; ES: Spain – Catalonia; FR: France; GB: Great Britain; HR: Croatia; IE: Republic of Ireland; IT: Italy; LT: Lithuania; NO: Norway; PO: Poland; PT: Portugal; RS: Serbia; SE: Sweden; SI: Slovenia; TR: Turkey.

also lower in 2007, at 42% of all statins versus 55% in 2004. TABLE 7 documents the changes in the utilization patterns of the PPIs and statins in selected Western European countries brought about by the various demand-side initiatives (TABLE 5 & SUPPLEMENTARY TABLE 1), combined with initiatives to lower generic prices in each country [13], and their impact on overall efficiency. Only half the countries have been documented for illustrative purposes.

The various reforms in Italy (SUPPLEMENTARY TABLE 1) [114] led to reimbursed expenditure for the PPIs in 2008 decreasing by 24% versus 2006, despite a 35% increase in volumes. Reimbursed expenditure for the statins fell by 11% during the same period, despite a similar 35% increase in volume.

In Turkey, with currently only limited demand-side measures (SUPPLEMENTARY TABLE 1) [114], differences in utilization and expenditure of PPIs and statins in 2009 versus 2007 were as follows:

- PPIs: PPI utilization increased by 26% while reimbursed expenditure increased by 61% through a 5.5-fold increase in the utilization of esomeprazole (from 2 to 7% of total PPI utilization), while omeprazole utilization decreased from 10 to 5% of total PPI utilization;
- Statins: statin utilization increased by 6% while expenditure increased by 41%, with greater utilization of atorvastatin (76%

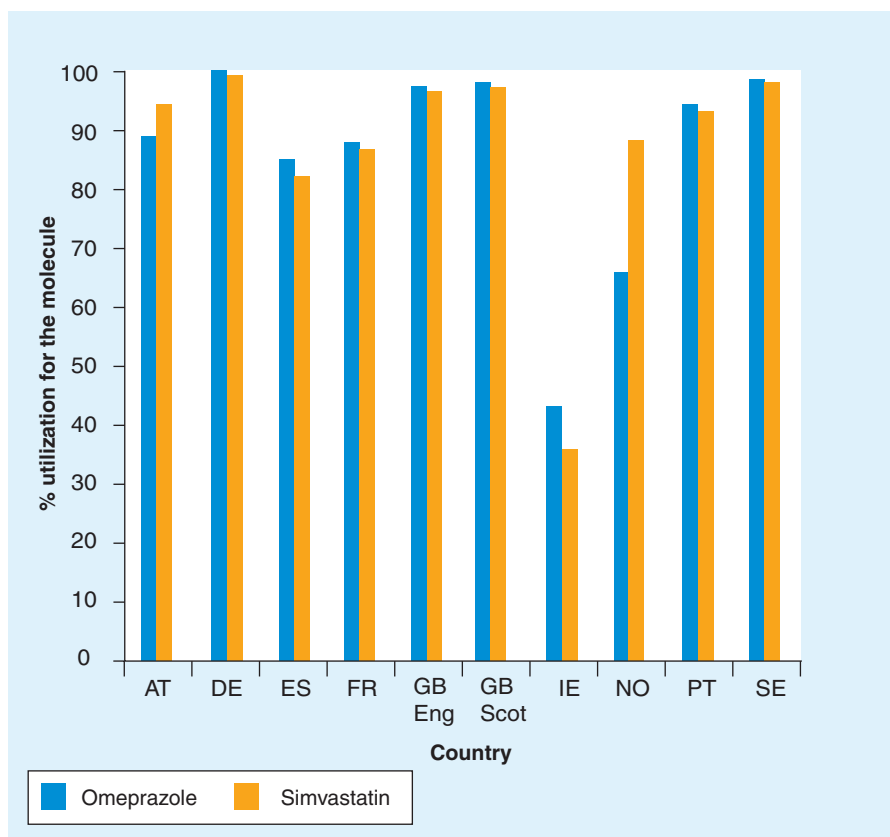


Figure 2. Utilization of generic omeprazole versus all omeprazole and generic simvastatin versus all simvastatin in 2007 in selected European countries (defined daily dose basis).

AT: Austria; DE: Germany; ES: Spain; FR: France; GB Eng: England; GB Scot: Scotland; IE: Republic of Ireland; NO: Norway; PT: Portugal; SE: Sweden. Reproduced from [13].

of total statin utilization in 2007 rising to 84% in 2009), and simvastatin utilization decreasing from 9% of the total statin utilization to 5% during this period.

TABLE 8 documents the impact of the various reforms (TABLE 6 & SUPPLEMENTARY TABLE 1) [114] on PPI and statin prescribing efficiency amongst former Central and Eastern European countries in recent years. As previously discussed, generic PPIs and statins, including generic atorvastatin, were typically available earlier in these countries, making comparisons difficult with Western European countries.

In Poland in 2007 versus 2001, there was nearly a twofold difference in the rate of increase in the utilization of PPIs versus the increase in expenditure. At the same time, there was a 4.5-fold difference between the rate of increase in the utilization of statins versus that seen for expenditure.

The situation in Serbia is complicated by generic PPIs and statins having been on the market before comprehensive datasets became available in 2005. The various policies led to overall expenditure for the PPIs only increasing 1.7-fold between 2005 and 2009, while utilization increased 2.1-fold. Reimbursed expenditure for the statins increased sixfold during this period while utilization increased 6.5-fold.

Discussion including likely future developments over the next 5 years in Europe

The first comprehensive list of DDDs was published in Norway in 1975 and has developed since then. As a result, DDDs are now the internationally accepted methodology for comparing drug utilization across countries, especially where there are different packs and tablet strengths between countries [57,59,60,112]. Consequently, the ATC/DDD methodology was employed in these two cross-national comparisons.

The plethora of demand-side initiatives (TABLE 6 AND SUPPLEMENTARY TABLE 1) [114] appears to have resulted in considerable utilization of generic drugs versus the respective originators, with utilization rates of over 80% typically being achieved for the generic drugs (FIGURE 2). The major exception among the Western European countries is the Republic of Ireland, with currently limited measures to enhance the prescribing of generics even in this selected population. This will change with the planned introduction of reference pricing for the molecule in 2011 [12]. However, it is difficult at this stage to fully predict the outcome.

The different demand-side measures, their extent and intensity collated under the '4 Es' (SUPPLEMENTARY TABLE 1) [114] do appear to lead to considerable differences in the utilization of omeprazole and simvastatin, as well as single-sourced PPIs (e.g., esomeprazole) and statins (e.g., rosuvastatin and atorvastatin), among Western European countries over time (SUPPLEMENTARY TABLES 2 & 3) [114], and in 2007 versus patterns seen before the patent loss of either omeprazole or simvastatin (FIGURES 3 & 4).

We consider that despite the study design limitations, prescribing restrictions (enforcement) as a single entity appear to appreciably influence utilization. This is depicted by the considerable reduction in the utilization of atorvastatin and rosuvastatin in Austria, Germany and Norway in 2007 versus prepatent loss rates (FIGURE 4, SUPPLEMENTARY TABLES 1 & 3) [114] compared with increased utilization of these single-sourced statins France, the Republic of Ireland, Portugal and Turkey, where there are currently fewer demand-side reforms to counteract pharmaceutical company marketing pressures (SUPPLEMENTARY TABLE 1) [114]. However, it is difficult to substantiate this within the study design. This is starting to change in France with the introduction of prescribing targets such as the percentage of prescriptions for generic PPIs and statins linked with financial incentives [2].

The nature of the enforcement (SUPPLEMENTARY TABLE 1) [114] also appears to impact on subsequent utilization patterns with a

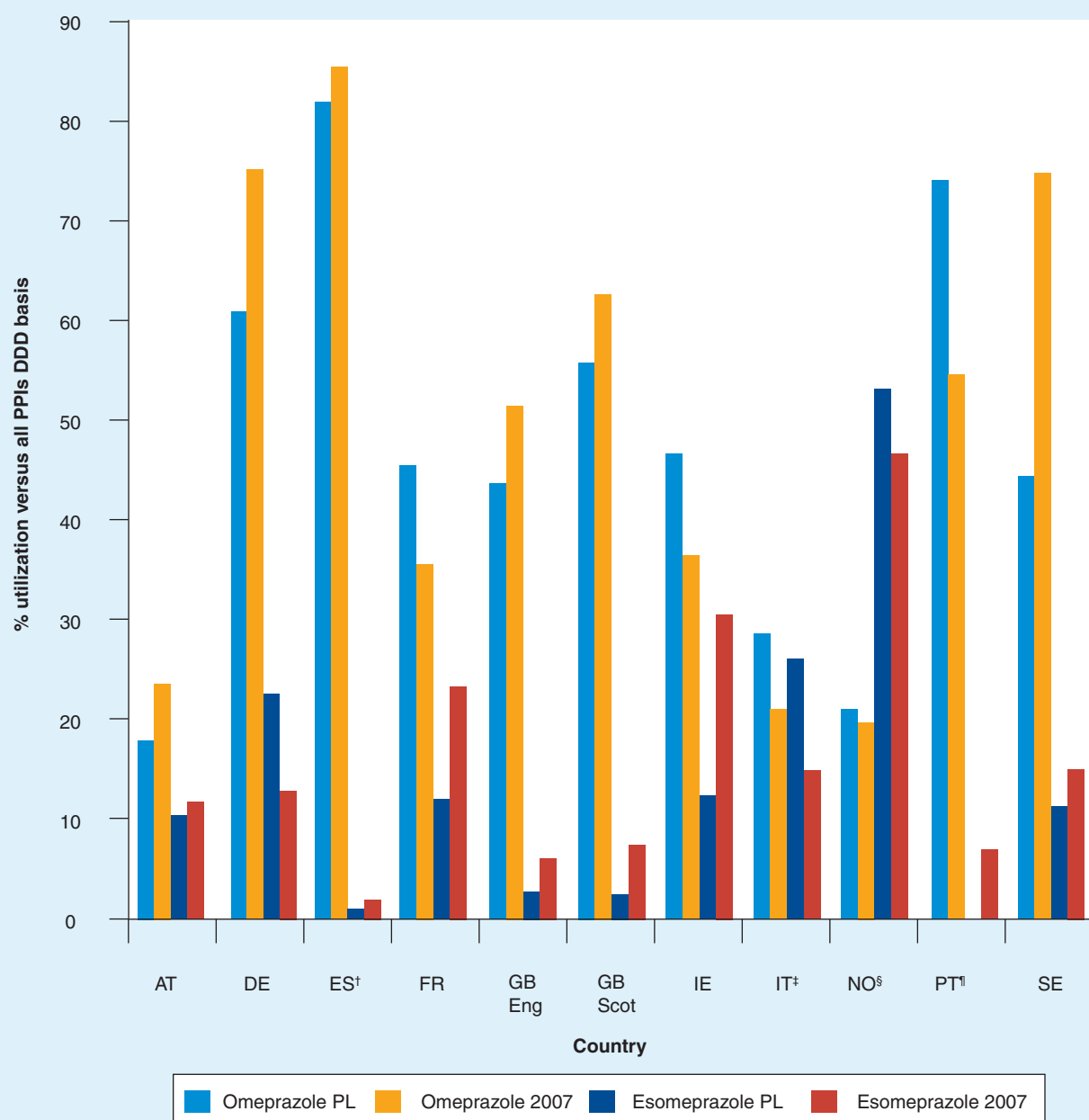


Figure 3. Utilization patterns on a DDDs basis in 2007 for omeprazole and esomeprazole versus prepatent loss of omeprazole (unless stated) among Western European countries.

†Baseline = 2003; Catalonia = Spain.

‡2006 vs 2008.

§Baseline = 2004.

¶Baseline = 2000.

DDD: Defined daily dose; PL: Before patent loss.

AT: Austria; DE: Germany; ES: Spain; FR: France; GB Eng: England; GB Scot: Scotland; IE: Republic of Ireland; IT: Italy; NO: Norway; PT: Portugal; SE: Sweden.

seemingly greater fall in the utilization of atorvastatin and simvastatin following prescribing restrictions in Austria compared with Norway when factoring in baseline levels for the utilization of atorvastatin and rosuvastatin (FIGURE 4). This phenomenon will be explored further in future papers.

The combination of education, engineering and economics also appreciably influences the future utilization of multiple versus patent-protected products within a class. This can be seen when comparing the changes in PPI (omeprazole and esomeprazole) and statin (simvastatin, atorvastatin and rosuvastatin) utilization

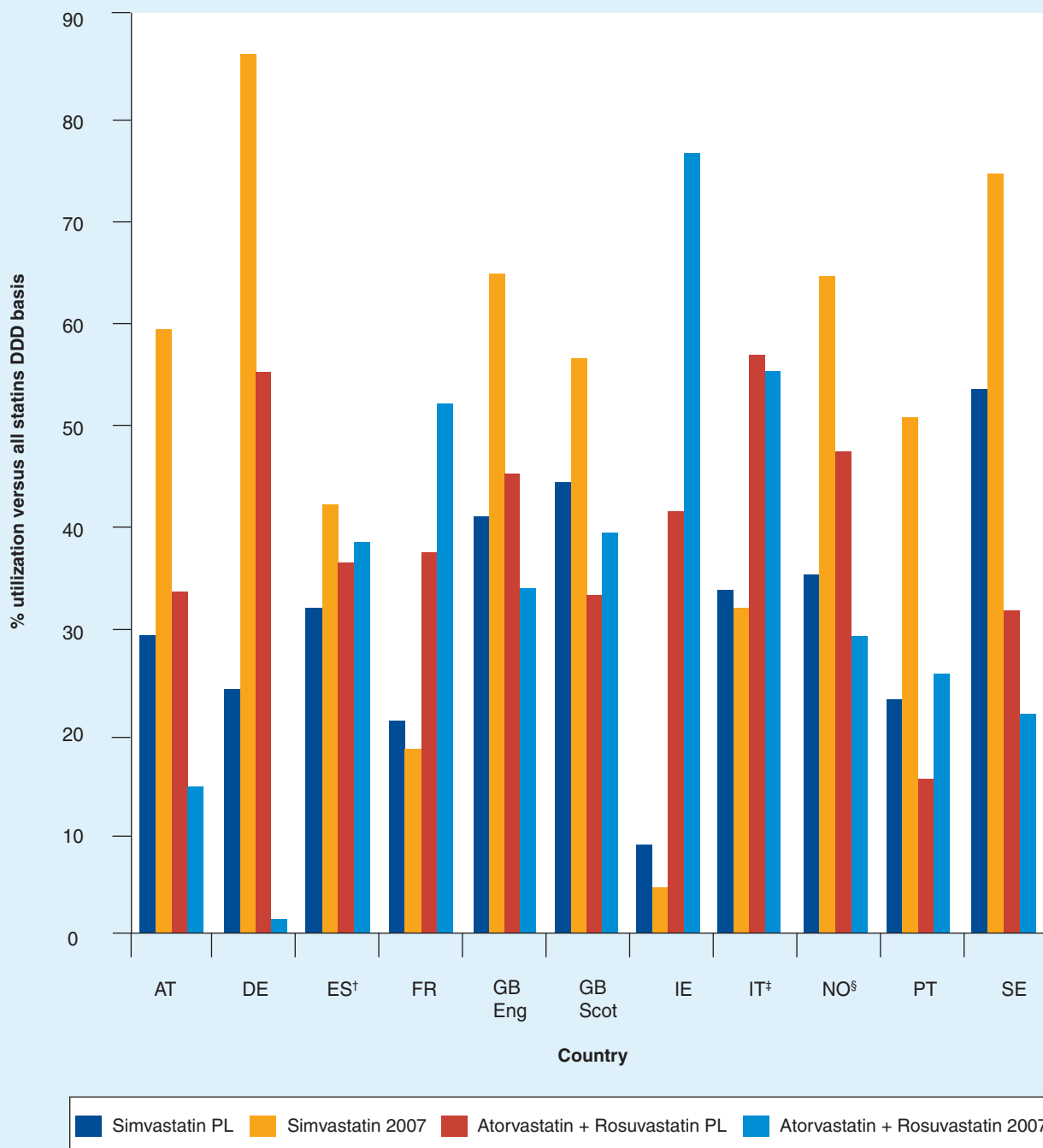


Figure 4. Utilization of simvastatin, atorvastatin and rosuvastatin prior to the availability of generic simvastatin and in 2007 on a DDD basis in Western European countries.

[†]Baseline = 2003; Spain is Catalonia.

[‡]2006 vs 2008.

[§]Baseline = 2004.

DDD: Defined daily dose; PL: Before patent loss.

AT: Austria; DE: Germany; ES: Spain; FR: France; GB Eng: England; GB Scot: Scotland; IE: Republic of Ireland; IT: Italy; NO: Norway; PT: Portugal; SE: Sweden.

in Sweden and the UK (England and Scotland), where all three approaches are combined, with France, Portugal, the Republic of Ireland (FIGURE 4, SUPPLEMENTARY TABLES 1–3) [114] and Turkey. The

differences in the observed utilization patterns for the different statins between England and Scotland (FIGURES 3 & 4) may well reflect differences in economic intensity (SUPPLEMENTARY TABLE 1) [114].

Table 7. Influence of supply and demand measures on prescribing efficiency between 2001 and 2007 among selected Western European countries.

| Country | Class | Utilization 2007 vs 2001 | Expenditure 2007 vs 2001 | €/1000 inhabitants/year in 2007 |
|-------------------------|---------|--------------------------|--------------------------|---------------------------------|
| Austria | PPI | ↑ 3.6-fold | ↑ 2.1-fold | €19,299 |
| | Statins | ↑ 2.4-fold | ↓ 3% | €9555 |
| Germany | PPI | ↑ 3.2-fold | ↑ 1.4-fold | €13,864 |
| | Statins | ↑ 2.1-fold | ↓ 54% | €6833 |
| France [†] | PPI | ↑ 2.1-fold | ↑ 38% | €15,194 |
| | Statins | ↑ 72% | ↑ 19% | €14,896 |
| Great Britain – England | PPI | ↑ 2.3-fold | ↓ 38% | €6186 |
| | Statins | ↑ 5.1-fold | ↑ 20% | €13,439 |
| Republic of Ireland | PPI | ↑ 2.4-fold | ↑ 2.6-fold | Over €60,000 |
| | Statins | ↑ 7.1-fold | ↑ 4.9-fold | Over €60,000 |
| Sweden | PPI | ↑ 42% | ↓ 48% | €5832 |
| | Statins | ↑ 2.5-fold | ↓ 51% | €5192 |

[†]In France there can be co-pays up to 35% for each class (SUPPLEMENTARY TABLE 1). In the Republic of Ireland, the General Medical Services population is highly selected with greater morbidity than the general population.
PPI: Proton pump inhibitor.

This again will be explored further in future papers. Overall, this combination of intensive demand-side measures together with measures to lower generic prices does enhance PPI and statin prescribing efficiency (TABLE 7), as seen when comparing expenditure (€/1000 inhabitants/year) for the PPIs and statins in England and Sweden in 2007 and the statins in Austria and Germany with those of countries with fewer demand-side measures (TABLE 7 & SUPPLEMENTARY TABLE 1) [114]. In Turkey, expenditures for both the PPIs and statins rose at a faster rate than utilization despite recent measures to lower generic prices [13], facilitated by currently limited demand-side initiatives (SUPPLEMENTARY TABLE 1) [114]. This demonstrates that increased prescribing efficiency can be achieved by combining initiatives to lower generic prices where possible with those to enhance generic utilization. We acknowledge this may well be difficult in practice given the complexities of changing physician prescribing behavior.

Prescribing efficiencies have also been seen among former Central and Eastern European countries, especially among the statins in Croatia and Poland (TABLE 8), helped by reference-price initiatives among both classes with typically only a limited number of demand-side measures in operation (SUPPLEMENTARY TABLE 1) [114]. However, the extent of the prescribing efficiencies seen in practice has been compromised by the availability of generic omeprazole and simvastatin, particularly before 2000 and 2001.

The impact of the various demand-side initiatives in Western European countries also appears to be additive. The prescribing restrictions introduced for atorvastatin in Austria (SUPPLEMENTARY TABLE 1) [114] further

accelerated the prescribing of generic simvastatin [58]. This is also seen when comparing the differences in subsequent utilization of omeprazole and esomeprazole in Austria, where there is currently no prior authorization for the PPIs (SUPPLEMENTARY TABLE 1) [114], with changes in the utilization of simvastatin, atorvastatin and rosuvastatin following the availability of generic omeprazole and simvastatin, respectively (FIGURES 3 & 4, SUPPLEMENTARY TABLES 2 & 3) [114], with both being subject to educational and economic measures. In Sweden, the regions (counties) have introduced prescribing targets and financial incentives in addition to educational activities to further enhance the prescribing of generic PPIs and statins [9,61]. Recently, the national reimbursement agency in Sweden (TLV) introduced prescribing restrictions for atorvastatin [108]. This should further enhance the prescribing of generic simvastatin, mirroring the situation when the TLV introduced prescribing restrictions for angiotensin receptor

Table 8. Impact of supply- and demand-side measures on prescribing efficiency of PPIs and statins in former Central and former Eastern European countries.

| Country | Class | Increase in utilization | Increase in expenditure |
|-------------------|---------|-------------------------|-------------------------|
| EE (2007 vs 2004) | PPI | 2.5-fold | 1.5-fold |
| | Statins | 1.8-fold | 18% |
| HR (2007 vs 2000) | PPI | 4.4-fold | 2.9-fold |
| | Statins | 8.3-fold | 3.2-fold |
| LT (2007 vs 2000) | PPI | 32.2-fold | 14.7-fold |
| | Statins | 6.1-fold | 1.9-fold |
| SI (2007 vs 2001) | PPI | 4.1-fold | 2.8-fold |
| | Statins | 2.7-fold | 26% |

EE: Estonia; HR: Croatia; LT: Lithuania; PPI: Proton pump inhibitor; SI: Slovenia.

blockers (ARBs) [62] in addition to existing demand-side measures. This substantiates the findings in previous publications regarding the additive impact of demand-side measures [63,64]. It also endorses current health authority and health insurance company activities to introduce a range of measures over time.

However, care may be needed if enforcement is undertaken without necessarily considering the impact on the utilization and expenditure of products in related classes. For example, the reimbursement change with atorvastatin in Germany (SUPPLEMENTARY TABLE 1) [114] resulted initially in appreciable expenditure for ezetimibe alone or in combination, as no originator companies were promoting statins (€192 million vs €480.5 million for the statins in 2007) [53]. This situation is now changing through further demand-side initiatives (SUPPLEMENTARY TABLE 1) [114] in view of the concerns with the effectiveness of ezetimibe in practice [53]. There has also been appreciable utilization and expenditure of ezetimibe in France (€139.6 million in 2008 among the salaried population; 8% of statin and ezetimibe utilization) with the propensity of French physicians to prescribe new drugs versus those in England (3% of total utilization of statins and ezetimibe) and Sweden (3% of total utilization of statins and ezetimibe), which further demonstrates the influence of multiple interventions in helping counteract pharmaceutical company marketing activities.

As discussed, we accept that there are limitations with the study design. In addition to those described, there has been no link between indications and actual doses prescribed in order to calculate prescribed daily doses (PDD) [65]. This is particularly important for the statins given the recent guidance advocating higher doses [66–68]. We also acknowledge that we did not include over-the-counter (OTC) or hospital sales when assessing utilization. However, we were more concerned with changes in utilization patterns in ambulatory care than absolute utilization levels. We are aware that there can be differences in utilization figures between information management system (IMS) and administrative databases, especially where there are high co-payments and/or significant prescribing restrictions for the class [69]. We have seen this in practice [KRISTINA NATIONAL HEALTH INSURANCE FUND, VILNIUS, LITHUANIA, PERS. COMM.], building on previous studies with statins [69]. However, this should only have a limited impact when assessing changes in utilization patterns.

Despite these limitations, we believe we have added to the paper by Ostoni and colleagues [50] by showing that different demand-side measures can be used in addition to academic detailing, benchmarking and auditing to further influence prescribing. We have also seen countries learning from each other with, for example, the introduction of prescribing targets and financial incentives in France and Spain (Catalonia), as well as the introduction of prescribing restrictions for atorvastatin and ARBs in Sweden following the challenge when reference pricing was introduced for single-source PPIs [3,9,24], which is still being debated in the courts. Switching programs and prior authorization schemes for the statins are also being successfully introduced in Primary Care Trusts in the UK in line with national guidance [20].

Despite the outcome from the various initiatives to date (SUPPLEMENTARY TABLE 1) [114], further measures are essential. The next stage of the research will be to try and develop a robust scoring system that can help predict the outcome of different demand-side intervention strategies alone or in combination at discrete time points following the availability of generics in a class. These will build on existing measures as well as on the tremendous variation currently seen following the different demand-side measures and their intensities among Western European countries (FIGURES 3 & 4, SUPPLEMENTARY TABLES 1–3) [114]. This should also help to address the shortcomings in the current literature highlighted by Ostoni and colleagues [50].

In conclusion, a number of demand-side initiatives have been introduced across Europe to try and limit the growth in pharmaceutical expenditure. These can be categorized under the '4 Es', with different measures and their intensities appearing to have a considerable influence on utilization patterns and overall prescribing efficiency. Multiple interventions appear to have a greater influence than single interventions, building on previous findings. Further measures are essential, mandating European countries to continue learning from each other. This also includes successfully addressing tactics used by pharmaceutical companies to delay the entry of generics [103], which is to the detriment of all key stakeholder groups as it compromises the funding of new innovative drugs.

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Key issues

- Supply- and demand-side reforms surrounding generics can play a key role with increasing prescribing efficiency for ambulatory care drugs. Both measures are essential to maximize efficiency.
- Increased utilization of premium-priced single-sourced proton pump inhibitors and statins is seen in countries where there are currently limited demand-side reforms to counteract commercial pressures, for example, in France, Portugal, the Republic of Ireland and Turkey. Increased utilization of generic omeprazole and simvastatin, along with reductions or only limited increased utilization of esomeprazole or atorvastatin and rosuvastatin combined, is seen in countries with multiple demand-side measures.
- The impact of the interventions appears to be additive with multiple demand-side interventions having a greater influence with changing utilization than single measures, with the exception of prescribing restrictions (enforcement). This led to appreciable improvements in prescribing efficiency when coupled with initiatives to obtain low prices for generics. However, this is difficult to substantiate given the limitations of the study design.
- Further reforms are essential across Europe to increase prescribing efficiency to avoid prohibitive increases in either taxation or health insurance premiums to continue funding comprehensive and equitable healthcare. Countries are learning from each other but this will need to accelerate.

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