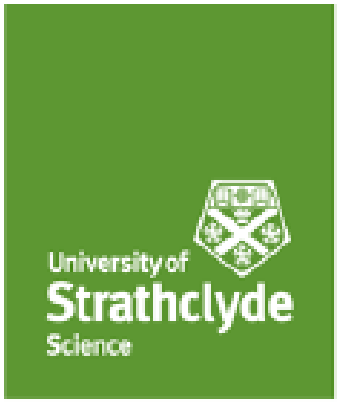
Learnings from cross national aggregated DU studies in Europe

Prepared by Brian Godman



1. Introduction

2. Challenges of cross national studies on medicines and potential ways forward including examples

3. Summary

Growing pressures on pharmaceutical expenditure will continue with ongoing reforms

- Pharmaceutical expenditure grew by 50% in real terms during past decade - 60% of total expenditure in some countries

- This is set to continue unless addressed due to:
  - ageing populations and rising levels of NCDs
  - continued inappropriate prescribing
  - stricter clinical targets
  - continued launch of new premium priced products

- This is resulting in ongoing initiatives across Europe to improve appropriate use of medicines. Initiatives include:
  - Models to optimise the use of new medicines including new expensive oncology medicines
  - Initiatives to enhance the use of low cost generics
  - Initiatives to improve the utilisation of anti-infectives

Ref: Godman et al 2012 to 2016; Moon, Godman et al 2014; Furst et al 2015

Pharmaceutical policy and initiatives incorporate a number of areas

- Pharmaceutical policy is designed to improve the safe and effective use of medicines. This incorporates a number of areas including:
  - issues of unmet need and access to medicines
  - pricing of medicines and cost containment
  - improving the rational use of medicines (RUM)
  - issues of innovation and service provision

- Issues regarding pharmaceutical expenditure can be divided into:
  - **supply-side measures** - principally concerned with the pricing of medicines and associated regulations
  - **demand-side measures** - principally concerned with interventions/activities designed to influence the subsequent utilization of medicines

Ref: Traulsen, Almarsdottir 2005; Seiter 2010; Godman, Kwon et al 2016

European ideals – comprehensive and equitable healthcare for all with limited co-payment

- Challenges are particularly important in Europe where:
  - ❑ Equity and solidarity are key principles
  - ❑ Compulsory contributions (taxation or health insurance) – amount depends on income
  - ❑ Goal is continued universal and comprehensive healthcare

- Concerns with the ever increasing prices of new medicines especially cancer and orphan diseases - despite low cost of goods (as low as 0.1%) and monies spent on R & D considerably lower than current rhetoric of over US$1bn/ new medicine

- Companies need their products reimbursed else limited sales in Europe (near monopoly) – this enhances the bargaining power and initiatives that health authorities/ health insurance agencies can instigate to maintain these ideals

Ref: Godman et al 2013 to 2016; van Woerkom, Pipenbrink, Godman et al 2012

Demand-side measures can be collated under the 4 Es to compare their influence across countries

- Demand side initiatives can be collated under 4 'E's – well accepted by payers and endorsed in publications:
  - **Education** – e.g. Academic detailing, benchmarking, guidelines and formularies
  - **Economics** – e.g. financial incentives for physicians, pharmacists or patients
  - **Engineering** – e.g. prescribing targets - % of PPIs as generics, % of statins as generics, % of patients achieving agreed BP and lipid goals
  - **Enforcement** – e.g. prescribing restrictions, compulsory generic substitution

Ref: Wettermark, Godman et al 2009; Godman et al 2012 - 2016

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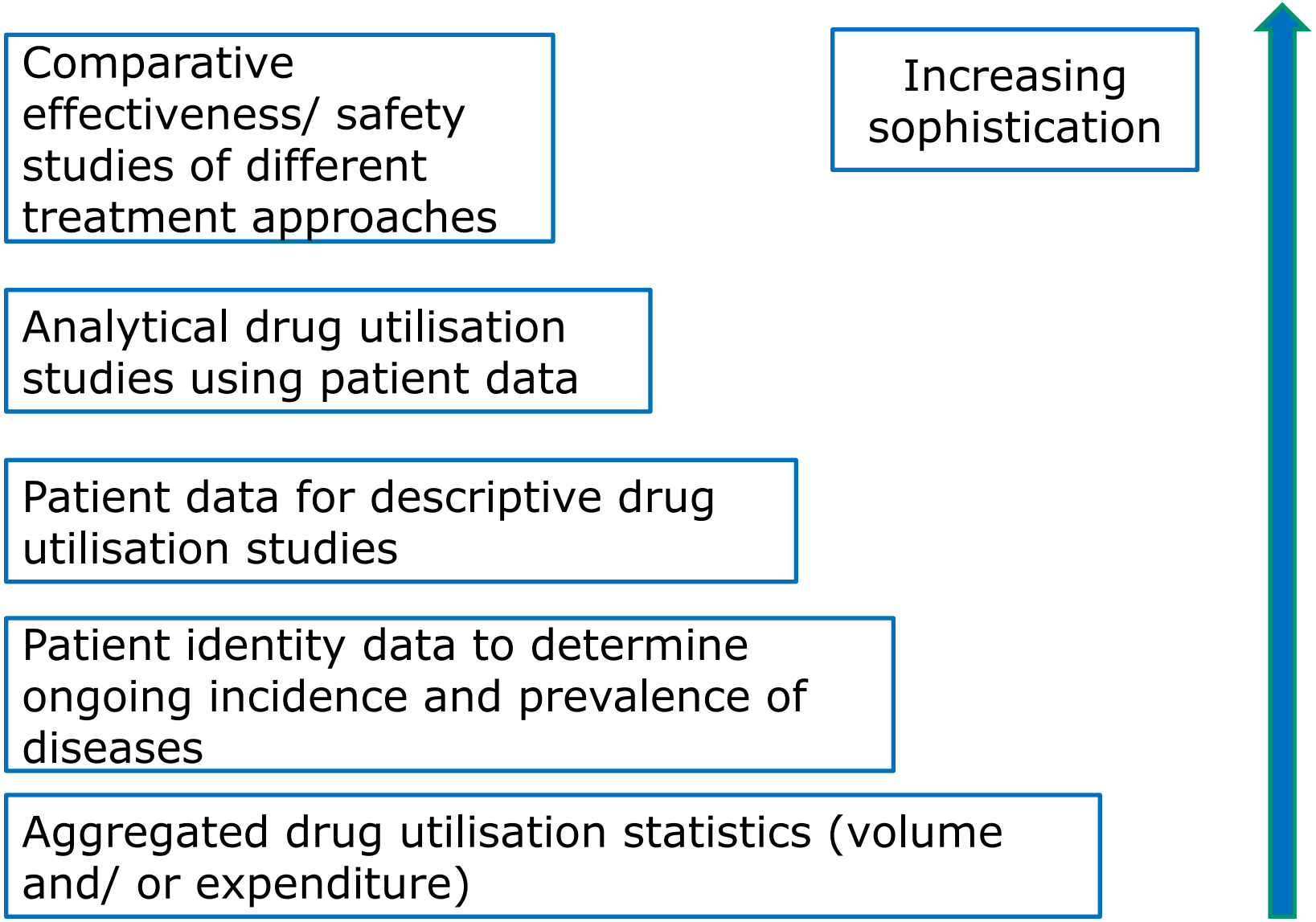
Criteria have been developed to enhance CNC studies. These should be born in mind

- Criteria for undertaking good quality drug utilization and policy cross-country comparative studies have recently been documented

- These include:
  - ❑ Appropriate use of theory
  - ❑ Explicit selection of comparator countries, i.e. the rationale including differences in epidemiology, financing of healthcare and potential policies
  - ❑ Rigour of the comparative design including research approach (although time series analyses difficult if multiple interventions undertaken over time as seen with the PPIs and statins – not so with generic losartan) – the chosen study design will depend on available datasets
  - ❑ Attention to the complexity of cross-national comparisons including ensuring similar datasets, e.g. Lithuania
  - ❑ Contribution of the study to our current knowledge

Ref: Cacace et al 2013



Ref: Godman et al 2016

Why compare cross-country?

- Aggregated DU data can provide insight into local use and policies to further enhance appropriate use of medicines

- Comparison with other countries can give further information/raise issues, e.g.:
  - ❑ Are differences seen?
  - ❑ Why are there differences in utilisation rates/ expenditure?
  - ❑ What does this mean for the efficiency and quality of care? Health care system?
  - ❑ Cross country data can be powerful in advocacy messages to all key stakeholder groups. Examples include cross country antibiotic utilisation patterns as well as generic policies surrounding the PPIs and statins

There are number of challenges with cross national comparisons

- Cross-country comparisons must be undertaken carefully → valid similarities and differences between like medicine utilisation in the same sectors

- Differences context/setting, e.g.:
  - ❑ Different treatment guidelines
  - ❑ Different resistance patterns (antimicrobials)

- Differences in data collection – ensure similar methodology for utilisation data, e.g. DDDs versus commercial/ IMS data sets, reimbursed vs. total utilisation (where pertinent)

- Database content/validity, e.g. Ireland with GMS population

There are several approaches to enhance the quality of CNC studies. These helped by:

- Using standard and comparable methodologies for utilisation, e.g. DDDs and DIDs in ambulatory care (PDDs can be difficult to ascertain if no access to patient specific data)
- Working with pertinent groups, e.g. health authority/ Ministry personnel/ Insurance personnel when describing policy initiatives in given sectors and including them as authors in any study
- Using robust databases for the studies that are regularly audited (as opposed to utilisation data from commercial sources given the expense)
- Using other accepted methodologies if difficult to obtain utilisation data from databases, e.g. qualitative and other approaches
- Accepting that time series analyses may not always be possible – and stating why, e.g. PPI and statin studies

Ref: Godman et al 2010 to 2015

Our recent study in Lithuania showed why important to use similar datasets for CNC studies

Year/ database for PPIs	2004	2007	2010	2012
IMS (Total)	4.9	13.8	17.9	21.2
Health Insurance (reimbursed)	0.7	2.3	2.9	3.0
% reimbursed vs. IMS	14.5	16.5	16.3	14.3

Year/ database for statins	2004	2007	2010	2012
IMS total	2.4	4.5	8.3	12.9
Health Insurance (reimbursed)	0.6	0.8	3.5	7.3
% of NHIF database vs. IMS	23.2	17.5	42.2	56.8

Ref: Garuoliene, Godman et al 2016

Principally health authority personnel from across Europe demonstrated multiple demand-side measures increased the prescribing of generic PPIs and statins. Findings communicated to provide future guidance

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Appreciable differences in generic utilisation (PPIs and statins) leading to considerable differences in efficiency

Country	Class	Utilisation 2007 vs. 2001	Expenditure 2007 vs. 2001	€/1000 inhabitants/ year in 2007
AT	PPI	↑3.6 fold	↑ 2.1 fold	€19299
	Statins	↑ 2.4 fold	↓ 3%	€9555
DE	PPIs	↑ 3.2 fold	↑ 1.4 fold	€13864
	Statins	↑ 2.1 fold	↓ 54%	€6833
FR*	PPI	↑ 2.1 fold	↑ 38%	€15194
	Statin	↑ 72%	↑ 19%	€14896
GB – Eng	PPI	↑ 2.3 fold	↓ 38%	€6186
	Statin	↑ 5.1 fold	↑ 20%	€13439
IE	PPI	↑2.4 fold	↑ 2.6 fold	Over €60,000
	Statin	↑7.1 fold	↑4.9 fold	Over €60,000
SE	PPI	↑ 42%	↓ 48%	€5832
	Statins	↑ 2.5 fold	↓ 51%	€5192

A retrospective drug utilisation study was undertaken documenting changes in utilisation patterns and costs before and after generic simvastatin as multiple measures introduced in most countries over time preventing time series analyses

Ref: Godman, Shrank et al 2010

Typically multiple interventions over time making time series analyses difficult, e.g. UK PCT

Year	2004	2005	2006	2007
General				
Education - Regional	Practice based Pharmacists provided by PCTs to monitor prescribing and provide educational input to GPs			
Engineering - national			Better Care, Better Value Metric for statins and PPIs	
Engineering - Regional	Generic switch programmes initiated by practice pharmacists to enhance prescribing and dispensing of generics			
			ScriptSwitch software installed	
Economics	Prescribing incentive scheme based on prescribing targets for PPIs and statins and PPI doses prescribed			Practice based commissioning
PPIs				
Education - Regional	NICE Technology Appraisal PPIs including dose reduction, guidance on dyspepsia including PPIs first line and dropping to maintenance doses. MeReC Bulletins and drug information on esomeprazole			
Statins				
Education	Blackpool, Fylde and Wyre HEPAC Guidelines on lipids			
			NICE and MeReC guidance on statin prescribing encouraging generics	
Engineering			Information to practices on potential savings from prescribing generics	
Engineering	QoF targets including clinical indicators CHD 8, Stroke 8, Diabetes 17			

The second publication also involved central and eastern European (CEE) countries documenting changes in expenditure and utilisation of PPIs and statins over time (2007 vs. 2001)

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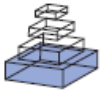

Policies to enhance prescribing efficiency in Europe: findings and future implications

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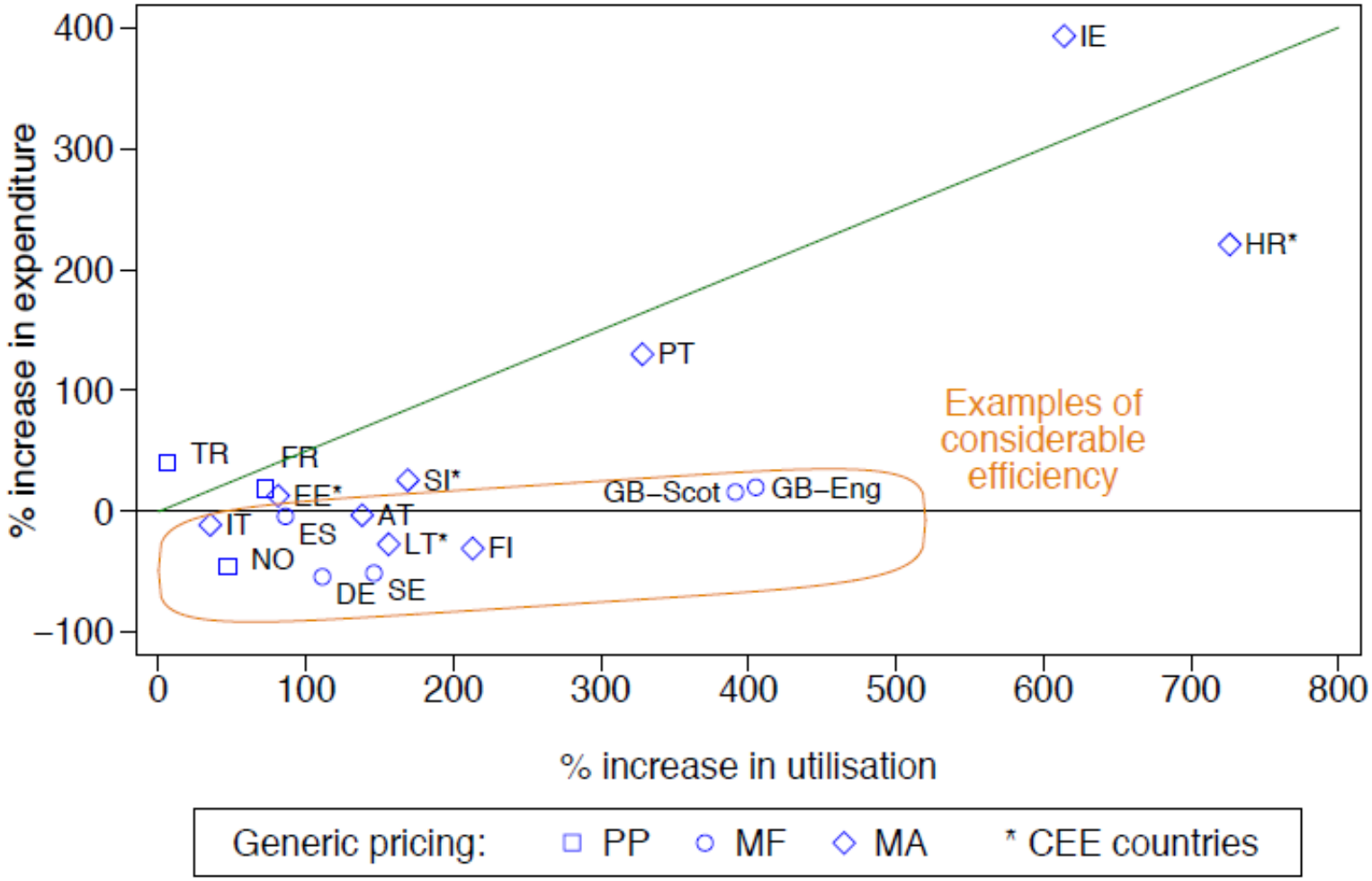
The study again showed that multiple demand-side measures greater influence on statin prescribing of generics/ efficiency. Limited change in CEE countries as typically only generics reimbursed (2007 vs 2001)



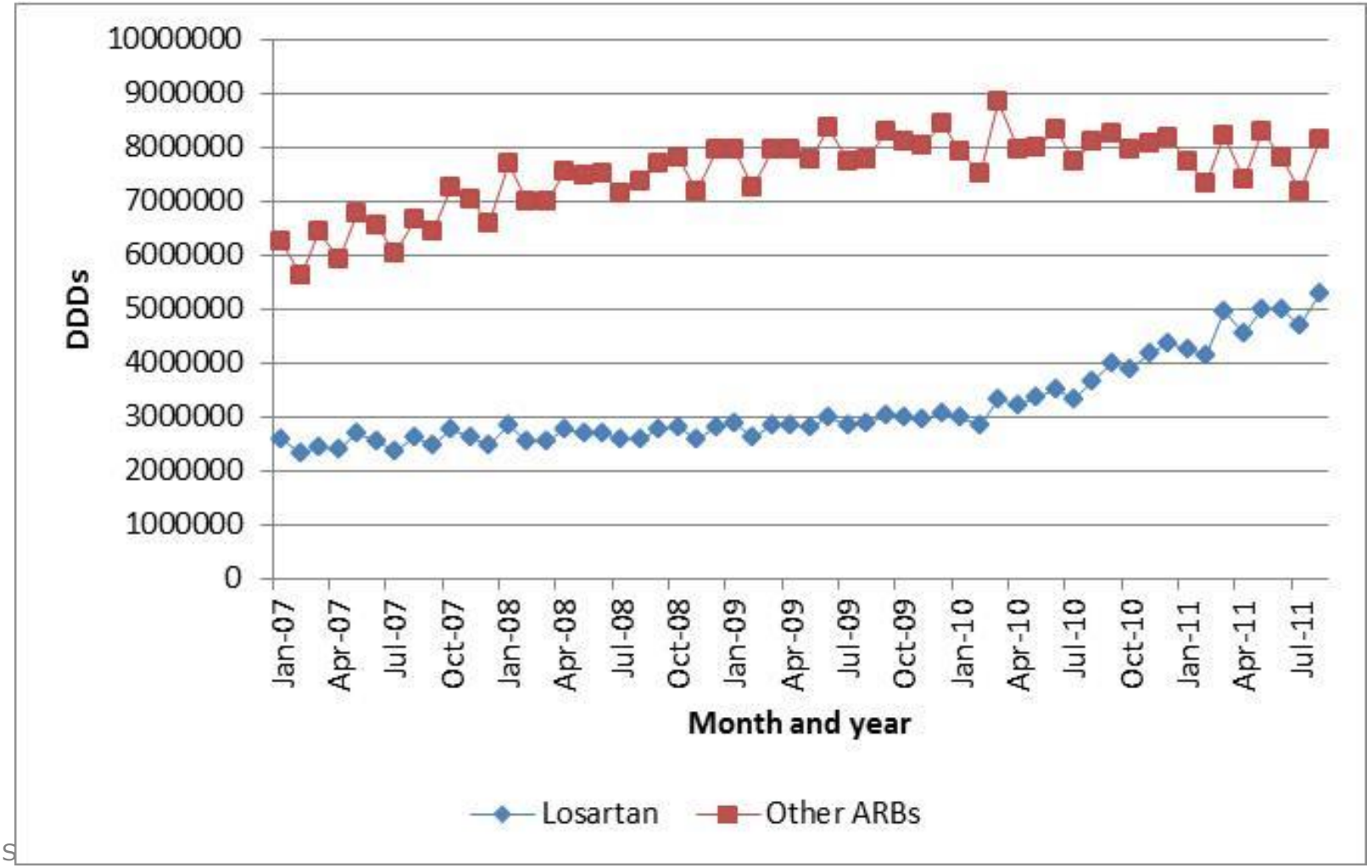
Ref: Godman, Shrank et al 2011

Different activities were undertaken by health authorities in Western European countries in response to generic losartan (first generic ARB) – typically initially or not at all (allowing time series)

Country	Generic losartan reimbursed	Activities
Austria	October 2008	Prescribing restrictions removed for losartan but not the other ARBs. Potential sanctions for abuse
Belgium	July 2010	Prescribing restrictions removed for losartan; prior authorisation for other ARBs (otherwise 100% co-payment). General co-payment 25%
Bury PCT	July 2010	No immediate measures. This changed in March 2011 with multiple measures including educational activities, switching programmes, prescribing targets and financial incentives
Denmark	April 2010	Delisting of all other ARBs from the reimbursed list apart from losartan
Ireland	March 2010	No specific activities were undertaken to enhance losartan utilisation
Scotland	July 2010	No specific activities as high INN prescribing rates, other priorities and the imminent launch of generics of other ARBs
Spain (Catalonia)	July 2006	No specific activities regarding losartan - apart from general activities enhancing the prescribing of generics
Sweden	March 2010	Multiple activities among the counties including educational programmes, switching programmes and financial incentives

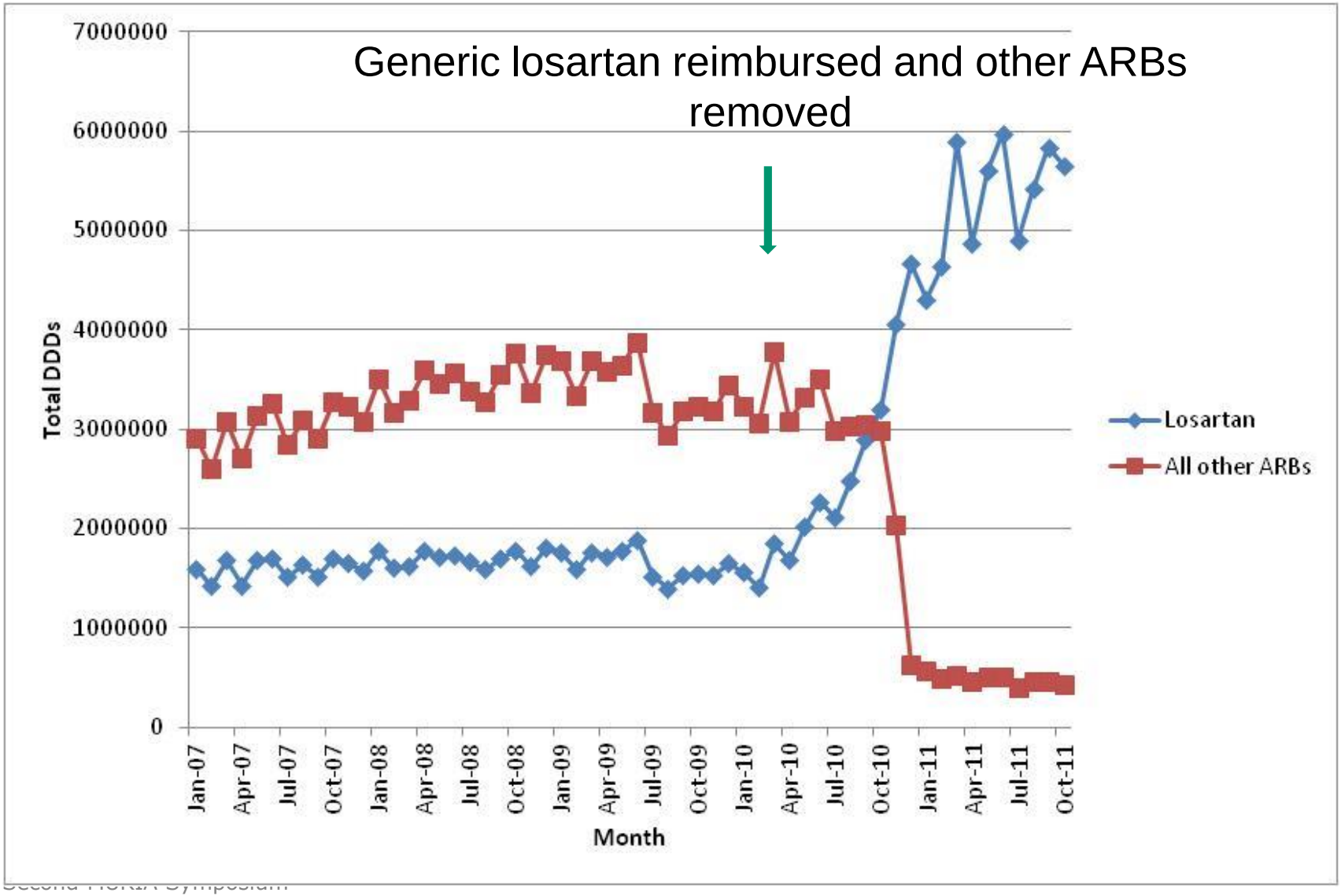
Ref: Moon, Godman et al 2014

Multiple demand side measures among the Counties in Sweden including guidelines, prescribing targets, financial incentives and therapeutic switching significantly increased losartan utilisation post generics (March 2010) reducing costs (costs⬇ by 26%; utilisation ⬆16%)



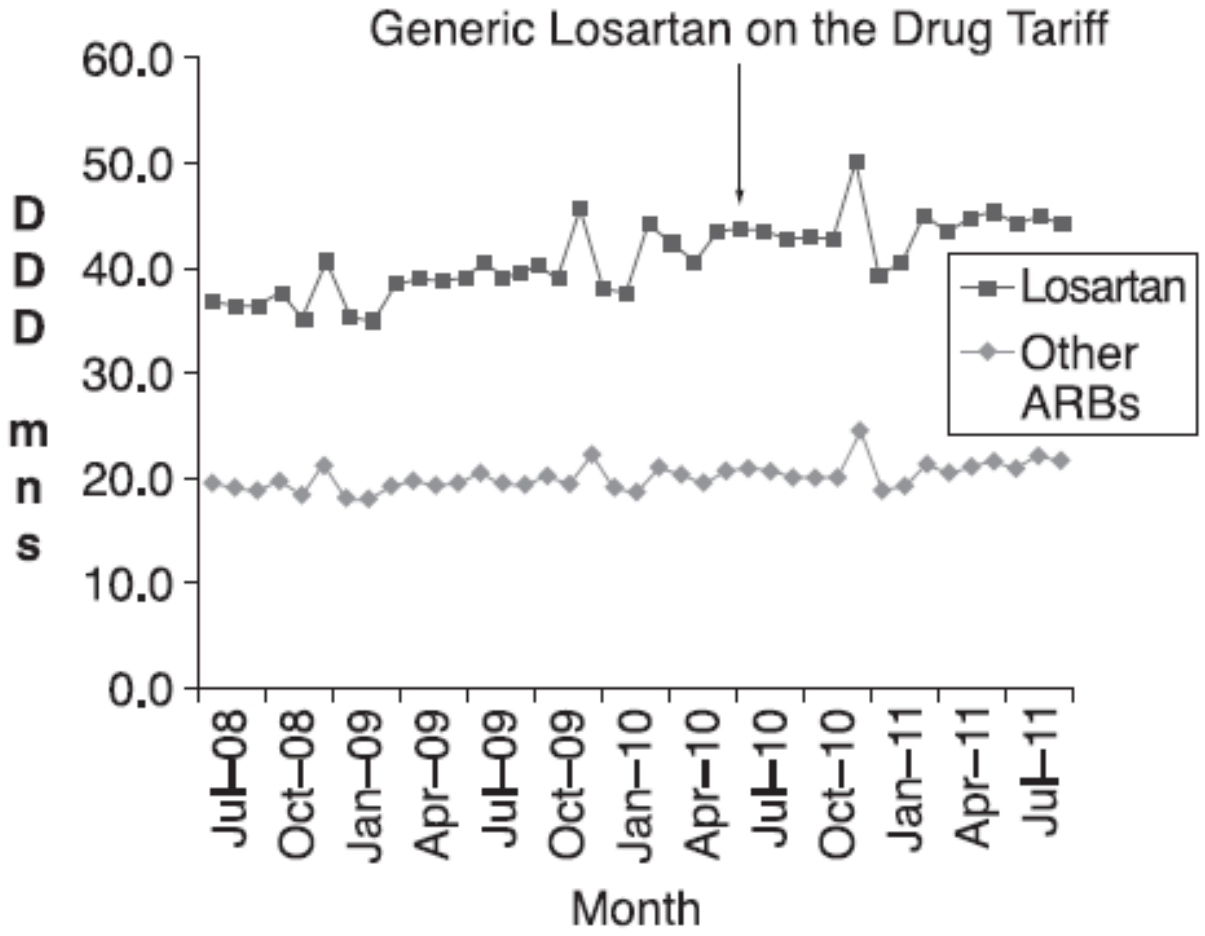
Ref: Godman, Wettermark, Miranda et al 2013

A greater change in utilisation was seen in Denmark where all ARBs apart from losartan were removed from the reimbursement list (apart from medical grounds)



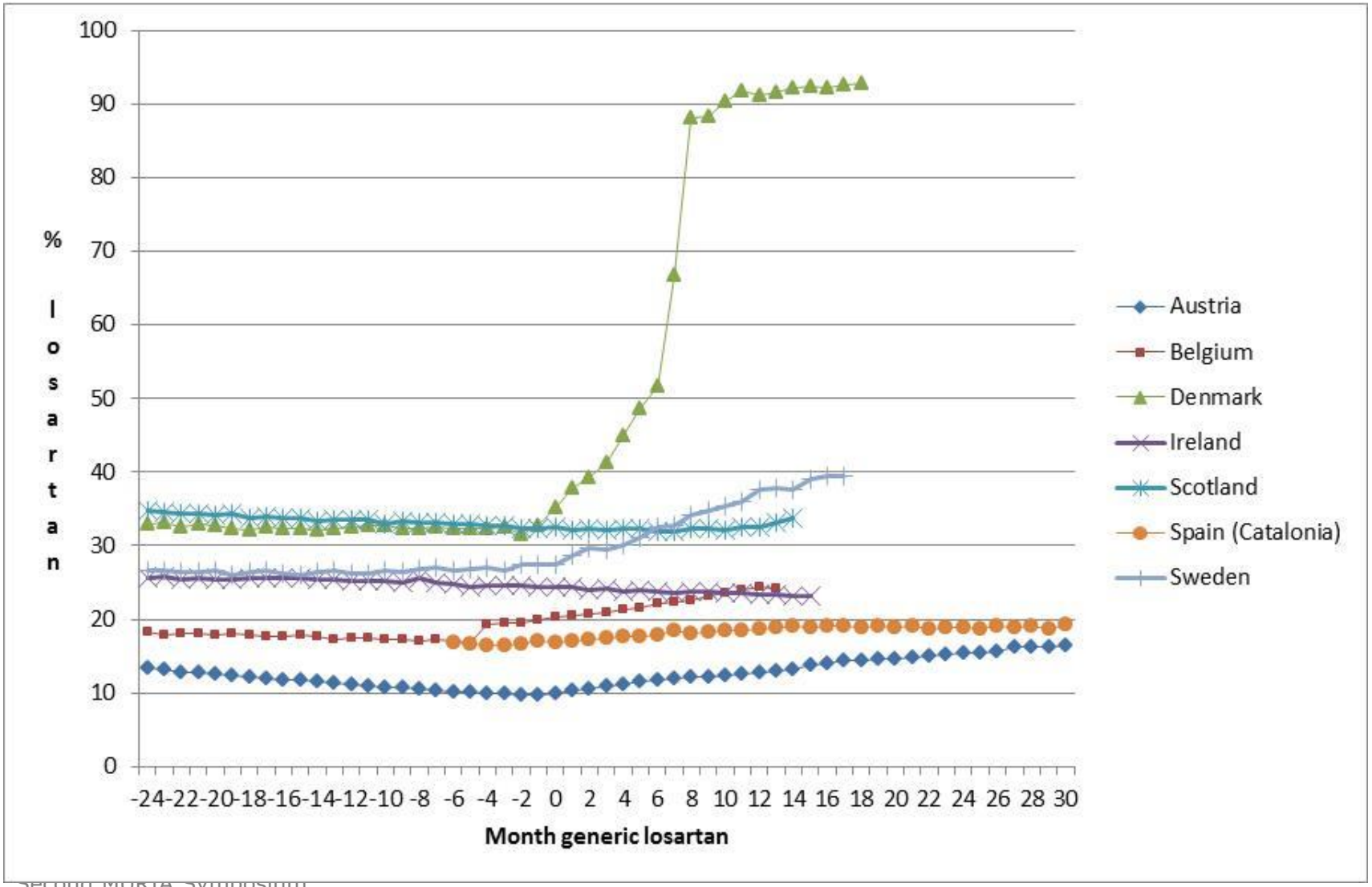
Ref: Hesse, Godman et al 2013

However no specific measures undertaken in Scotland (deliberate policy) leading to no change in the utilisation of losartan following generics in Scotland even with measures encouraging generic ACEIs (exacerbated by a more complex message) – suggests no 'spill over' effect



Ref: Bennie, Bishop, Godman et al 2013

Multiple demand-side activities in Austria, Belgium, Denmark and Sweden increased losartan use once available as generics vs. Ireland, Scotland and Spain



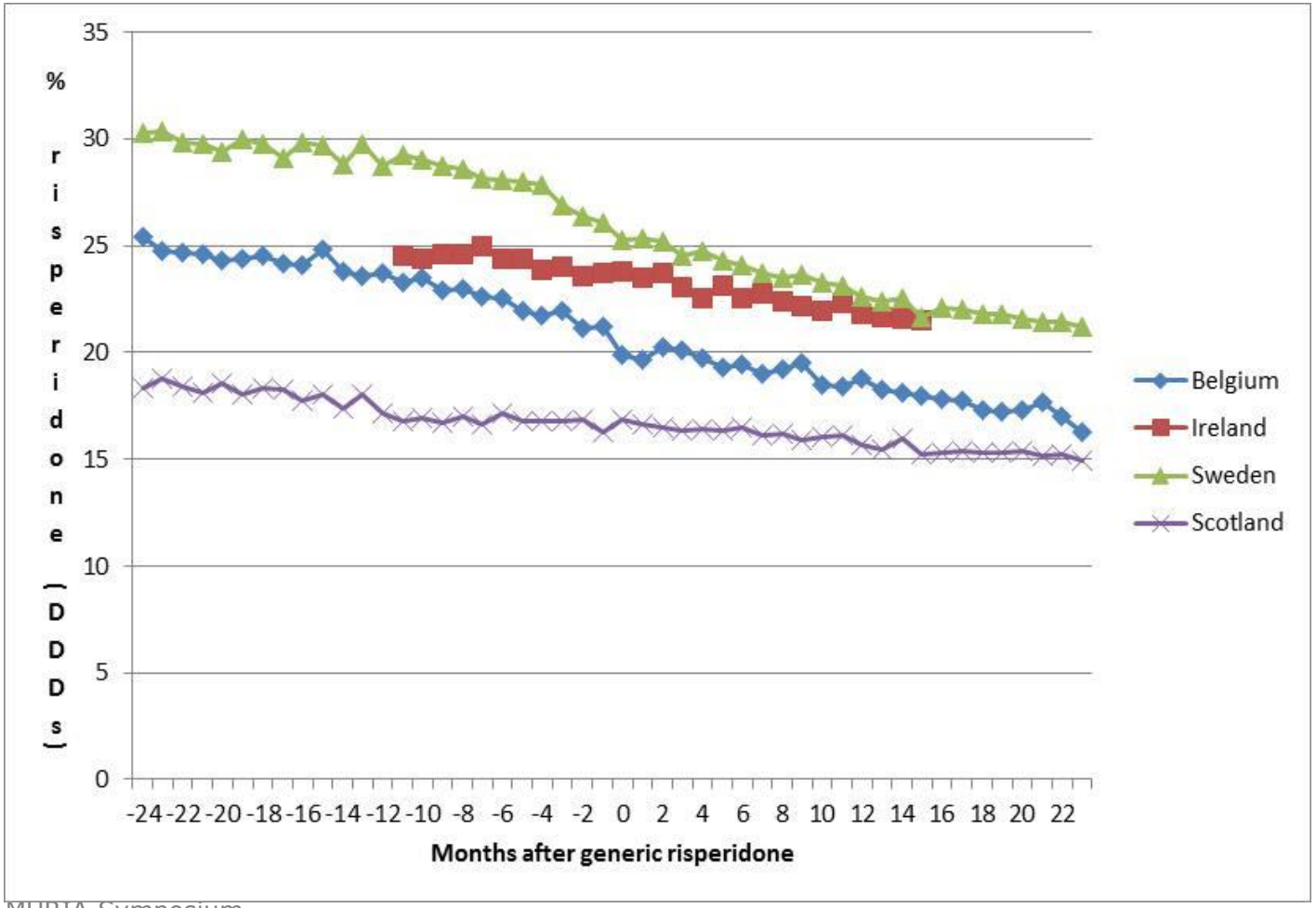
Ref: Moon, Godman et al 2014

Good consistency in the change in slope for the 3 countries with limited/ no demand-side measures (Ireland, Scotland and Spain) following generic losartan applying linear random coefficient models with country specific intercepts and slopes adds robustness to 'no spill over' suggestion

Countries	Change in slope % units per month (95% CI)	Standard deviation of the change in slope Sd (95% CI)
All	0.82 (-0.17 to 1.82)	1.33 (0.78 to 2.26)
Excluding Denmark	0.30 (0.04 to 0.56)	0.32 (0.18 to 0.57)
Excluding Denmark and Sweden	0.22 (0.02 to 0.43)	0.23 (0.12 to 0.43)
Excluding Denmark, Sweden, Austria, Belgium	0.10 (0.01 to 0.20)	0.08 (0.03 to 0.19)

Ref: Moon, Godman et al 2014

Greater need to tailor treatments for patients with schizophrenia and few demand side measures meant no change in risperidone utilisation following generics across Europe



Ref: Godman et al 2014

Good consistency in the rate of change in the slope for risperidone utilisation post generics (considerable variability before this). As a result can make robust conclusions that limited change in utilisation patterns post generics with few demand side measures in schizophrenia

Consolidated atypical antipsychotics following generic risperidone

	Coefficient value (95% CI)	*P*-value
Initial intercept	22.70 (18.58 to 26.82)	<0.001
Change in intercept at month 0	−0.0774 (−1.080 to 0.925)	0.880
Initial slope	−0.144 (−0.158 to -0.130)	<0.001
Change in slope after month 0	−0.00548 (−0.0545 to 0.0436)	0.827

Ref: Godman, Petzold et al 2014

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Drug utilisation and policy studies provide a good platform for implementing future policies

We have shown that:

- 4Es help document demand side measures for comparison purposes within and across countries

- Multiple demand-side measures can favourably influence prescribing patterns across classes and countries with no 'spill over' effect from one class to another

- Challenges do exist – but these can be overcome through persistence and seeking to publish findings as the first step to influence future changes in prescribing patterns. In addition, awareness of the limitations of the research

- Important to have a good mix of countries (and similar context) for cross national comparative (CNC) studies to enhance the robustness of the findings and their generalisability

Thank You

Any Questions!

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