Department of Clinical Epidemiology

An ENCePP study:
Impact of risk minimisation among users of rosiglitazone-containing products

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Vera Ehrenstein, MPH, DSc

Aarhus University Hospital

AARHUS UNIVERSITY

www.kea.au.dk

Risk minimisation measures: two levels of impact

1. Drug utilization patterns of rosiglitazone

- contraindications
- off-label use
- impact of published information

2. Impact in switchers to and from rosiglitazone on

- glycaemic control
- other objective parameters of disease
- acute drug reactions

Study characteristic	Northern Denmark	United Kingdom
Study population	OHA users in northern Denmark (~33% pop. sample)	OHA users recorded in the GPRD (~6% pop. sample)
Health care setting	Universal coverage; GP=gatekeeper	
Study design and period	Historical cohort study 2000-2010	
Use of OHA and other medications	The Aarhus University Prescription Database outpatient prescriptions **dispensed**	The GPRD Drug File Prescriptions **issued**
Contraindications, off-label use, acute events	National Patient Registry (hospital-based events: inpatient, outpatient, ER)	The GPRD Event File (all health related events)
Laboratory data	Laboratory Information Systems of Northern Denmark (hospital-based tests)	The GPRD Laboratory File (all tests)

Drug utilization assessment periods

- **Period 1** July 2000 to 23 May 2007
  (Nissen & Wolski meta-analysis NEJM)

- **Period 2** 24 May 2007 to 24 January 2008
  (EMA: coronary syndrome added as a contraindication; warning about ischemic events)
- **Period 3** 25 January 2008 to 22 September 2010
  (EMA suspends rosiglitazone)

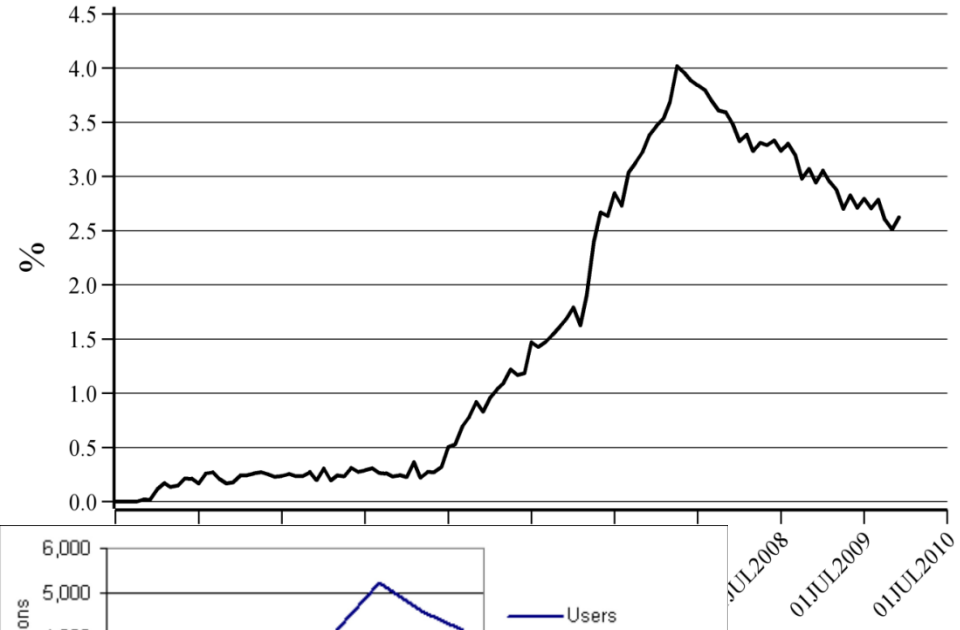
- **Period 4** 23 September 2010 ~ mid 2011

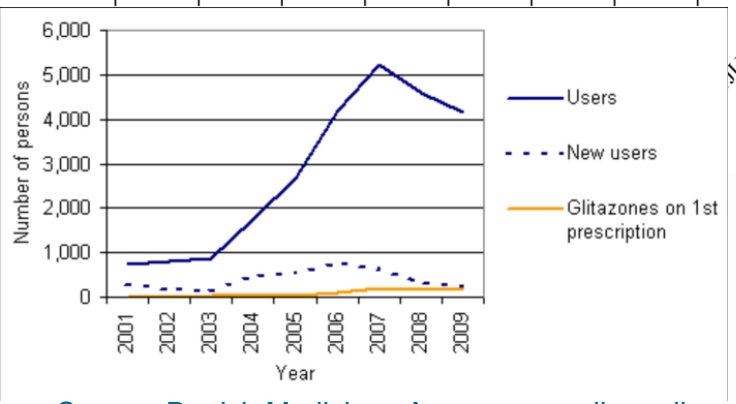
Users of oral hypoglycaemic (OHA) agents in UK and northern Denmark, 2000-2010, n (%)

	United Kingdom N=191,276		Northern Denmark N=60,897	
Characteristic	Rosiglitazone N = 25,428	Other OHA N = 165,848	Rosiglitazone N=2,251	Other OHA N=58,646
Age group				
< 35 y	589 (2.3)	9,358 (5.6)	81 (3.6)	3,473 (5.9)
35 – <45 y	2,469 (9.7)	13,192 (8.0)	277 (12)	4,429 (7.6)
45 – <55 y	5,513 (22)	25,023 (15)	576 (26)	9,099 (16)
55 – <65 y	7,661 (30)	38,668 (23)	734 (33)	15,022 (26)
65 – <75 y	6,434 (25)	42,030 (25)	433 (19)	14,068 (24)
75 – <85 y	2,426 (9.5)	28,430 (17)	141 (6.3)	9,639 (16)
≥ 85 y	336 (1.3)	9,147 (5.5)	9 (0.4)	2,916 (5.0)
Sex				
Male	14,169 (56)	87,076 (53)	1,299 (58)	30,857 (53)
Female	11,259 (44)	78,772 (48)	952 (42)	27,789 (47)
Charlson comorbidity index				
0 (none)	16,646 (65)	95,607 (58)	1,649 (73)	36,937 (63)
1 – 2 (medium)	7,925 (31)	57,984 (35)	538 (24)	17,595 (30)
≥ 3 (high)	857 (3.4)	12,257 (7.4)	64 (2.8)	4,114 (7.0)
Stopped rosiglitazone	19,498 (77)	--	1,466 (65)	

Users of rosiglitazone preparations as proportion of all OHA users, 2000-2010

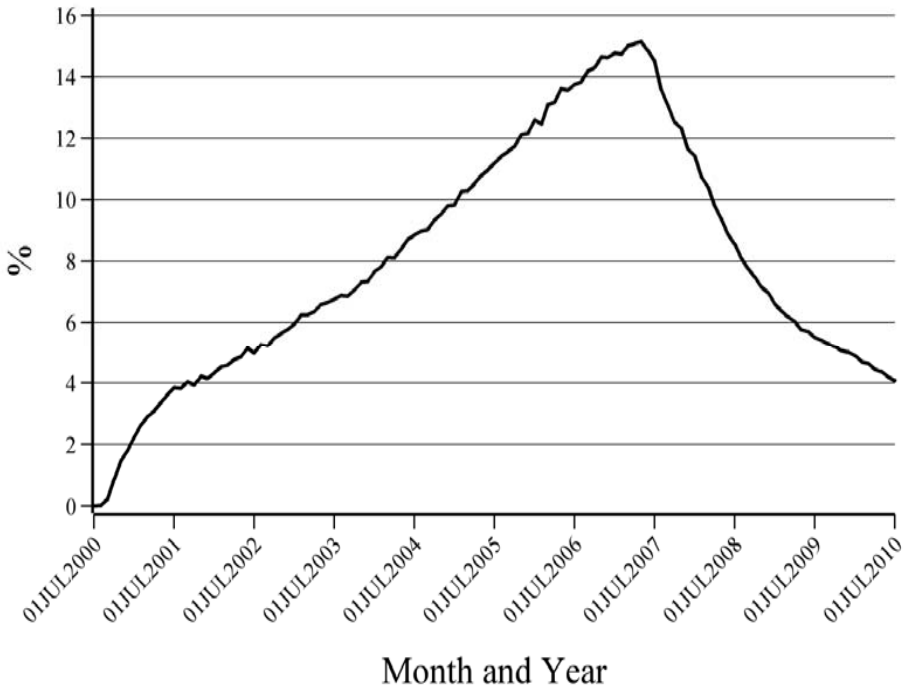
Northern Denmark





Source: Danish Medicines Agency www.dkma.dk

United Kingdom (GPRD)



*NB: y-axes have different scales

Prevalence of persons with contraindications among persons treated with rosiglitazone-containing products. Numbers are percent (95% confidence intervals).

	Diagnoses recorded since database inception (1977 DK/1987 UK)	Diagnoses recorded in the 12 months before the first rosiglitazone prescription (DK)
Any cardiac contraindication*, northern Denmark (2000-2009)		
Time Period 1	19.3 (17.3;21.4)	6.0 (4.8;7.2)
Time Period 2	20.0 (17.7;22.2)	6.9 (5.5;8.3)
Time Period 3	19.4 (17.3;21.4)	8.2 (6.7;9.6)
Any cardiac contraindication, United Kingdom (2000-2010)		
Time Period 1	24.6 (24.0;25.1)	
Time Period 2	21.6 (20.9;22.3)	
Time Period 3	19.6 (18.9;20.3)	
Time Period 4	13.8 (11.6;16.0)	

*Defined as a record of heart failure or acute coronary syndrome, or acute myocardial infarction, or ischemic heart disease before the first prescription for rosiglitazone

Glycated haemoglobin (HbA1c) before and after initiation of rosiglitazone-containing products

Post-initiation period	3 months	6 months	12 months
Northern Denmark			
Available records, N	1,107	1,299	1,039
Baseline mean (std), %	8.54 (1.52)	8.53 (1.53)	8.55 (1.55)
Change from baseline, mean (std), %	-0.81 (1.55)	-0.88 (1.53)	-1.01 (1.57)
Proportion with a meaningful decrease*	51%	53%	59%
United Kingdom			
Available records, N	11,815	16,059	11,889
Baseline mean (std), %	8.91 (1.58)	8.90 (1.59)	8.88 (1.56)
Change from baseline, mean (std), %	-0.87 (1.61)	-0.96 (1.65)	-0.97 (1.67)
Proportion with a meaningful decrease*	56%	58%	58%

*EMA's definition of a meaningful change > 0.6% (% here is the test unit)

Glycated haemoglobin (HbA1c) before and after termination of rosiglitazone-containing products

Post-termination period	3 months	6 months	12 months
Northern Denmark			
Available records, N	580	659	480
Baseline mean (std), %	8.36 (1.78)	8.34 (1.80)	8.49 (1.84)
Change from baseline, mean (std), %	-0.43 (1.57)	-0.39 (1.70)	-0.63 (1.77)
Proportion with a meaningful decrease*	39%	38%	43%
United Kingdom			
Available records, N	7,676	11,068	8,063
Baseline mean (std), %	8.42 (1.98)	8.36 (1.92)	8.30 (1.85)
Change from baseline, mean (std), %	-0.27 (1.89)	-0.15 (1.92)	-0.10 (1.94)
Proportion with a meaningful decrease*	33%	33%	33%

*EMA's definition of a meaningful change > 0.6% (% here is the test unit)

Distribution of OHA prescribed after rosiglitazone, northern Denmark

First oral glucose-lowering agent prescribed after termination of rosiglitazone-containing products	First OHA prescribed at any time after terminating rosiglitazone-containing products	
	N	Percent (95% CI)
Metformin	764	52.1 (49.6;54.7)
Glimepiride	282	19.2 (17.2;21.5)
Sitagliptin	95	6.5 (5.2;7.7)
Gliclazide	46	3.1 (2.2;4.0)
Glibenclamide	44	3.0 (2.1;3.8)
Metformin and sitagliptin	28	1.9 (1.2;2.6)
Exenatide	22	1.5 (0.9;2.1)
Glipizide	21	1.4 (0.8;2.0)
Metformin and vildagliptin	16	1.1 (0.6; 1.6)
Repaglinide	11	0.8 (0.3;1.2)
Acarbose	9	0.6 (0.2;1.0)
Liraglutide	6	0.4 (0.1;0.7)
Tolbutamide	5	0.3 (0.0;0.6)
Pioglitazone	3	0.2 (0.0;0.4)
Vildagliptin	3	0.2 (0.0;0.4)
Unspecified blood glucose lowering agent	1	<0.1 (0.0; 0.2)

Distribution of OHA prescribed after rosiglitazone, United Kingdom

First oral glucose-lowering agent prescribed after termination of rosiglitazone-containing products	First OHA prescribed at any time after terminating rosiglitazone-containing products	
	N	Percent (95% CI)
Metformin	9456	48.5 (47.8;49.2)
Gliclazide	4270	21.9 (21.3;22.5)
Pioglitazone	2699	13.8 (13.4;14.3)
Pioglitazone/Metformin	1081	5.5 (5.2; 5.9)
Glimepiride	703	3.6 (3.3;3.9)
Glibenclamide	388	2.0 (1.8; 2.2)
Sitaglipitin	305	1.6 (1.4; 1.7)
Glipizide	184	0.9 (0.8;1.1)
Tolbutamide	123	0.6 (0.5; 0.7)
Repaglinide	122	0.6 (0.5;0.7)
Acarbose	106	0.5 (0.4;0.6)
Nateglinide	61	0.3 (0.2;0.4)

Conclusions

- The 2007 NEJM meta-analysis by Nissen & Wolski and the following regulatory action was followed by a sharp and irreversible decrease in use of rosiglitazone-containing products

- There was a larger decrease of glycated hemoglobin, on average, following initiation than following termination of rosiglitazone-containing products

- Metformin is prescribed to about half of the patients terminating rosiglitazone

Conducting an ENCePP study

- "To **submit an application** for an ENCePP study seal"
- Tender received 23 Sep 2010
- **Tender awarded** **15 Nov 2010**
- Contract signed 10 Dec 2010
- ENCePP protocol Dr. 1 14 Dec 2010
- Applied for ENCePP seal 14 Jan 2011
- Clarification addressed 20 Jan 2011 (CoC language not in EMA contract)
- **ENCePP seal awarded** **15 Feb 2011**

The study team

Rohini Khorana Hernandez, PhD, Epidemiologist

Sinna Pilgaard Ulrichsen, MSc, Statistician

Jørgen Rungby, MD, DMSc, Professor of Clinical Pharmacology and Toxicology

Timothy L. Lash, MPH, DSc, Professor of Cancer Epidemiology

Anders Riis, MSc, Lector, Senior Statistician

Susan S. Jick, DSc, Professor of Epidemiology and Biostatistics

Henrik Toft Sørensen, MD, PhD, Professor, Department Chair

Department of Clinical Epidemiology and

Department of Endocrinology C, both in Aarhus University Hospital, Aarhus, Denmark

Boston Collaborative Drug Surveillance Program (BCDSP), Boston University School of Public Health, Lexington, MA, USA