

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

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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

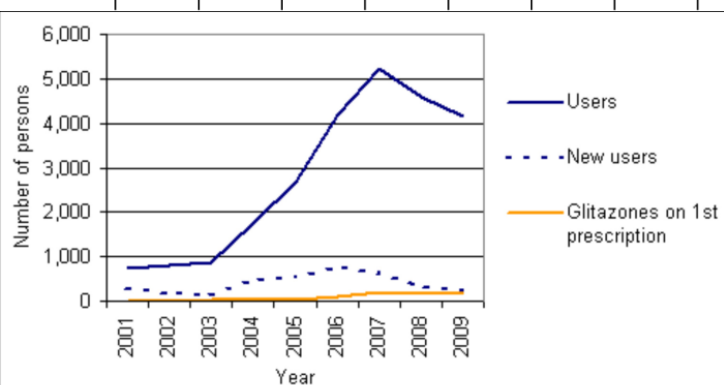
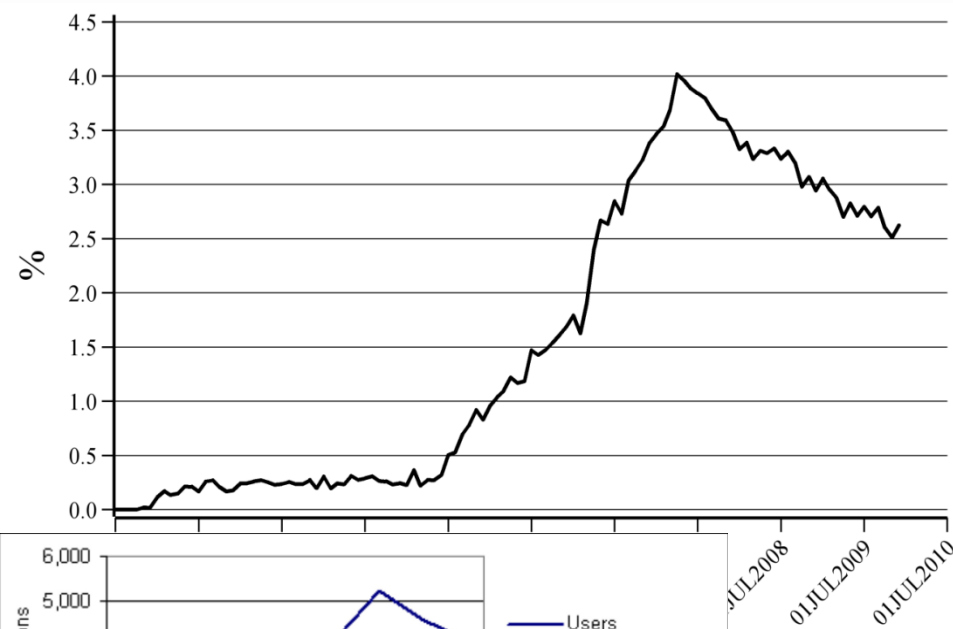
- **Period 1** July 2000 to 23 May 2007
(Nissen & Wolski meta-analysis NEJM)
- **Period 2** 24 May 2007 to 24 January 2008
(EMA: coronary syndrome added as a contraindication; warning about ischemic events)
- **Period 3** 25 January 2008 to 22 September 2010
(EMA suspends rosiglitazone)
- **Period 4** 23 September 2010 ~ mid 2011

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

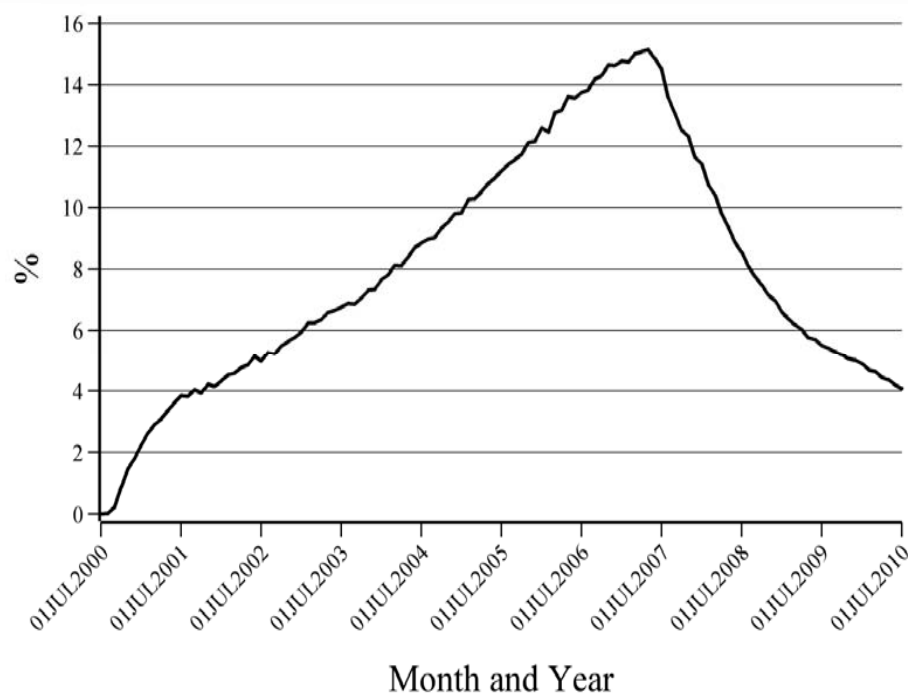
Characteristic	United Kingdom N=191,276		Northern Denmark N=60,897	
	Rosiglitazone N = 25,428	Other OHA N = 165,848	Rosiglitazone N=2,251	Other OHA N=58,646
Age group				
< 35 y	589 (2.3)	9,358 (5.6)	81 (3.6)	3,473 (5.9)
35 – <45 y	2,469 (9.7)	13,192 (8.0)	277 (12)	4,429 (7.6)
45 – <55 y	5,513 (22)	25,023 (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



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)
Sitagliptin	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

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