ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (6): 471-480
0114-5916/12/0006-0471/$49.95/0

Prescribing of Rosiglitazone and Pioglitazone Following Safety Signals

Analysis of Trends in Dispensing Patterns in the Netherlands from 1998 to 2008

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Abstract

Background: Relevant safety signals in the EU are regularly communicated in so-called 'Direct Healthcare Professional Communications' (DHPCs) or European Medicines Agency (EMA) press releases. Trends of a decrease in the use of rosiglitazone following regulatory safety warnings have been described in the US. In the EU, however, relatively little is known about dispensing patterns following DHPCs or other safety signals such as EMA press releases.
Objective: The objective of this study was to analyse trends in dispensing patterns of rosiglitazone and pioglitazone following DHPCs and EMA press releases in the EU member state, the Netherlands.
Methods: Data for this study were obtained from the PHARMO Record Linking System, which includes drug dispensing records from community pharmacies of approximately 2.5 million individuals in the Netherlands. Over the period 1998–2008 an *a*uto-*r*egressive, *i*ntegrated, *m*oving *a*verage model (ARIMA) was fitted. The DHPC letters or EMA press releases were used as determinants. Adjustments were made for publication of certain literature. Stratification was performed for dispensings prescribed by general practitioners (GPs) and those prescribed by specialists.
Results: For rosiglitazone, four EMA press releases and two DHPCs were issued; for pioglitazone, one DHPC was issued. The number of rosiglitazone

dispensings prescribed by GPs decreased significantly after publication of DHPCs and EMA press releases concerning the risk of macular oedema and risk of fractures (both p-values 0.001). The number of rosiglitazone dispensings decreased statistically significantly after publication of EMA press releases 2 and 3 concerning cardiovascular risks but not for EMA press release 4. Adjustment for certain publications in the literature reduced the effect of communicated safety issues on the proportion of dispensings.

Conclusions: Although it is difficult to disentangle the effect of DHPCs and EMA press releases from the effect of reports published in the literature, our results suggest that prescribers may react to such safety communications.

Background

The incidence of type 2 diabetes mellitus is increasing throughout the world,[1] including the Netherlands.[2,3] The availability of drugs to treat diabetes mainly depends on pharmaceutical companies developing and marketing such drugs, and on drug regulatory bodies licensing and reimbursing them. In the EU, the European Medicines Agency (EMA) coordinates the centralized authorization procedure for medicinal products.[4] Approval through a centralized procedure facilitates swift and widespread access to the EU market, exposing large groups of patients. This makes it of crucial importance to identify safety concerns as soon as possible. Relevant safety information in the EU is communicated to healthcare professionals in so-called 'Direct Healthcare Professional Communications' (DHPCs) or EMA press releases.

The oral glucose-lowering drugs rosiglitazone and pioglitazone, both thiazolidinediones, have been approved through a central procedure.[4] When these drugs were authorized in the year 2000, thiazolidinediones were already known to be associated with fluid retention and increased risk of heart failure.[5] As a consequence, use was restricted to second-line treatment and contraindicated in patients with known heart failure. Labelling in the EU was different in this regard compared with the labelling in the US.[4] In 2005 and 2006, studies suggested an association between rosiglitazone and an increased risk of macular oedema[6] and an increased risk of fractures in women.[7] Moreover, in 2007 Nissen and Wolski[8] found that rosiglitazone was associated with an increased risk of myocardial infarction and a borderline increased risk of cardiovascular death, although this finding could not be confirmed in an interim analysis of the RECORD study (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes; a company-sponsored clinical trial evaluating cardiovascular outcomes of rosiglitazone) at that time.[9] Analysis of additional recent studies by the EMA's Committee for Medicinal Products for Human Use (CHMP), suggesting an increased risk of cardiovascular diseases in rosiglitazone users,[10,11] together with previous data, has led to the conclusion that the benefits of rosiglitazone no longer outweigh the risks.[12] Therefore, suspension of marketing authorization of all drugs containing the active substance rosiglitazone was recommended in September 2010.[13] Although a safety warning was issued in the US, rosiglitazone was not suspended.

Trends of a decrease in the use of rosiglitazone following regulatory safety warnings have been described in the US.[14-16] In the EU however, relatively little is known about dispensing patterns following DHPCs or other safety signals such as EMA press releases.[17-19] Consequently, it is unknown whether such signals influence prescribing and change dispensing patterns. The objective of this study was to analyse trends in dispensing patterns of rosiglitazone and pioglitazone following DHPCs and EMA press releases in the EU member state, the Netherlands.

Methods

Data for this study were obtained from the PHARMO Record Linking System (PHARMO RLS), a dynamic cohort of participants that includes, among other information, drug dispensing records from community pharmacies concerning approximately 2.5 million individuals in the Netherlands since 1986.[20] The drug dispensing database contains the following information per prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use.[21] All participants with more than two dispensings for drugs used for diabetes (ATC code A10) between 1 January 1998 and 31 December 2008 were included in the study cohort. To ensure a cohort of incident users, participants with a dispensing during the first 6 months of follow-up were considered as prevalent users and excluded from the analysis. In addition, participants who were dispensed their first prescription under the age of 18 years were excluded. Participants were followed until death, movement out of the PHARMO RLS catchment area, or end of study period (31 December 2008), whichever came first.

To verify the trends in dispensings of thiazolidinediones and other drugs used for diabetes, and to assess the impact of introduction of new drugs on the market, the different types of drugs prescribed for diabetes (ATC code A10) were classified into eight mutually exclusive categories: insulin analogues (A10AB05, A10AD05, A10AB06, A10AB04, A10AC04, A10AD04, A10AE04, A10AE05), human insulin (all A10A, excluding those mentioned above), biguanides (A10BA), sulfonylurea derivatives (A10BB), thiazolidinediones (A10BG), dipeptidyl peptidase-4 (DPP-4) inhibitors (A10BH), combinations of oral blood glucose-lowering drugs (A10BD) and other oral blood glucose-lowering drugs (A10B, excluding those mentioned above and A10X).[21] Dispensing figures were calculated per month as a percentage of the total number of A10 prescriptions dispensed to the study cohort over the same period.

The effect on the number of rosiglitazone and pioglitazone dispensings of DHPCs published by the marketing authorization holders and the regulatory bodies, as well as EMA press releases, was assessed. To this end, an *a*uto-*r*egressive, *i*ntegrated, *m*oving *a*verage model, also called an ARIMA (p,d,q) model was fitted. In this model, p represents the lingering effects of preceding scores. The integrated element d represents the trends in the data, and the moving average element q represents the lingering effects of preceding random shocks. The Durbin Watson test statistic was used to test for autocorrelation. Whether the time series were stationary was assessed by using the Dickey Fuller statistic. It was hypothesized that the interventions under study had an abrupt effect with permanent duration (instead of a gradual onset with a temporary duration). The direction and magnitude of the change in level after the intervention is represented by ω, which is presented together with its p-value.

The DHPC letters[22-24] or EMA press releases[25-28] were used as determinants to assess the impact of these safety communications on the number of rosiglitazone and pioglitazone prescriptions. Adjustments were made for publication of certain literature: the first case report on macular oedema,[6] results on the risk of fractures from ADOPT (A Diabetes Outcome Progression Trial),[7] results on the risk of myocardial infarction by Nissen and Wolski[8] and the RECORD trial,[9] and lastly, the recommendation made by the American Diabetes Association (ADA) and the European Association for the Study on Diabetes (EASD) for greater caution on the use of thiazolidinediones.[29] The DHPCs under analysis were sent to general practitioners (GPs), pharmacists and a broad category of specialists. EMA press releases were published on the EMA website; literature was published in the respective journals and online and was available via search engines such as PubMed.

Because a guideline of the Dutch Foundation of General Practitioners on the treatment of diabetes (March 2006)[30] and consequent remedial activities of healthcare insurance companies on GP prescribing might have had an impact on the dispensing figures, analyses were stratified for dispensings prescribed by specialists versus those prescribed by GPs.[30] Furthermore, it has been

shown earlier that safety warnings for rosiglitazone led to a decrease in the dispensings of rosiglitazone but initially to an increase in the number of dispensings of pioglitazone which later levelled out.[15,16] It has been estimated that after safety warnings for rosiglitazone, 23–41% of the patients receiving rosiglitazone switched to pioglitazone.[31,32] Therefore, results were separately analysed for the use of pioglitazone and rosiglitazone.

As determinants of dispensing pattern variance during the period 1998–2008, the introduction to or withdrawal from the Dutch market of innovator drugs used for diabetes (ATC code A10)[33] was visualized as well.

All analyses were performed using SAS software (version 9.2, Cary, NC, USA.); p-values are two-sided and were considered statistically significant if $p < 0.05$.

Results

6 165 341 prescriptions with an ATC code for drugs used for diabetes (A10) were dispensed to 158 599 participants during the period 1998–2008. Of these, 2 443 090 prescriptions (39.6%) were dispensed to 36 305 participants (22.9%) who did not have a baseline prescription-free period of 6 months and were considered as participants with prevalent diabetes. Another 304 094 (4.9%) prescriptions were excluded from participants who received only one prescription, participants with a first prescription at <18 years of age or participants with inconsistencies of dates in the database (i.e. more than one date of death, prescription date after date of death or missing date of cohort entry or end of follow-up). Since participants and their prescriptions could be excluded for more than one of these reasons, 3 579 810 (58.1%) dispensed prescriptions for 112 105 (70.7%) participants (incident users) remained for the analysis. Characteristics of this study population are presented in table I.

Table I. Characteristics of the study population (n = 112 105)

Characteristic	
Sex [n (%)]	
Male	51 657 (46.1)
Female	60 448 (53.9)
Age at first dispensed drug used for diabetes mellitus [y (SD)]	62.6 (14.5)
Number of dispensed prescriptions per patient [median (IQR)]	20 (9–43)
Type of prescriber [no. of prescriptions (%)]	
General practitioner	3 071 686 (85.8)
Specialist	452 987 (12.7)
Other or unknown	55 137 (1.5)

IQR = interquartile range; **SD** = standard deviation.

As can be seen from figure 1, the proportion of insulin and oral glucose-lowering drugs to the total number of drugs dispensed for diabetes remained constant over the 10-year study period. However, within the insulin category, the proportion of insulin analogues increased while the proportion of human insulin decreased. With regard to oral glucose-lowering drugs, the proportion of biguanides increased at the expense of the sulfonylurea derivatives. During the period January 1998–December 2008, 107 new generic drugs and seven new active substances (repaglinide, nateglinide, exenatide, sitagliptin, vildagliptin, pioglitazone and rosiglitazone) were introduced on the Dutch market. One drug was withdrawn from the market (Exubera®, human insulin for inhalation). Unfortunately, dispensing numbers of repaglinide (0.1%), nateglinide (0.1%), exenatide (<0.1%), sitagliptin (<0.1%), vildagliptin (<0.1%) and Exubera® (<0.1%) were too low to further evaluate the dispensing patterns. After the introduction of rosiglitazone and pioglitazone to the market in 2000, the contributed proportion of these two drugs to the total number increased. Over the whole period of availability of rosiglitazone and pioglitazone on the Dutch market, their contributed proportion to the total number of prescriptions dispensed for diabetes was 2.7% and 1.7%, respectively. For rosiglitazone, four EMA press releases and two DHPCs were issued; for pioglitazone, one DHPC was issued. In figure 2, we visualized the possible effect of DHPCs,[22-24] EMA press releases[25-28] and literature[6-9] on the dispensing patterns of rosiglitazone and pioglitazone. As can be seen from figure 2, the general pattern is similar for thiazolidinediones prescribed by GPs and those prescribed by specialists. How-

ever, as presented in table II, the impact of regulatory risk communications on the dispensing proportion differs per prescriber type.

An ARIMA (1,1,0) model was fitted to analyse the change in attributable proportion of rosiglitazone and pioglitazone to the total number of dispensings prescribed for diabetes. Using the Durbin Watson test statistic, no (seasonal) autocorrelation could be detected for either rosiglitazone or for pioglitazone. The Dickey Fuller test yielded statistically significant p-values for the change in attributable proportion for rosiglitazone and pioglitazone, indicating that the time series were stationary and analysable in the specified model.

After the first EMA press release[25] and DHPC[24] for rosiglitazone, which were issued in December 2005 and January 2006, respectively, for a suspected increased risk of macular oedema, the number of dispensings decreased significantly for those prescribed by GPs (p-values 0.001; table II). A statistically significant decrease in dispensings following these safety warnings could not be found for dispensings prescribed by specialists (p-values 0.06 and 0.09, respectively). In addition, following the case report on macular oedema, the decrease in dispensings was statistically significant for dispensings prescribed by GPs (p-value 0.001) but not for those prescribed by specialists (p-value 0.08; data not shown).[6] Additionally, we adjusted for

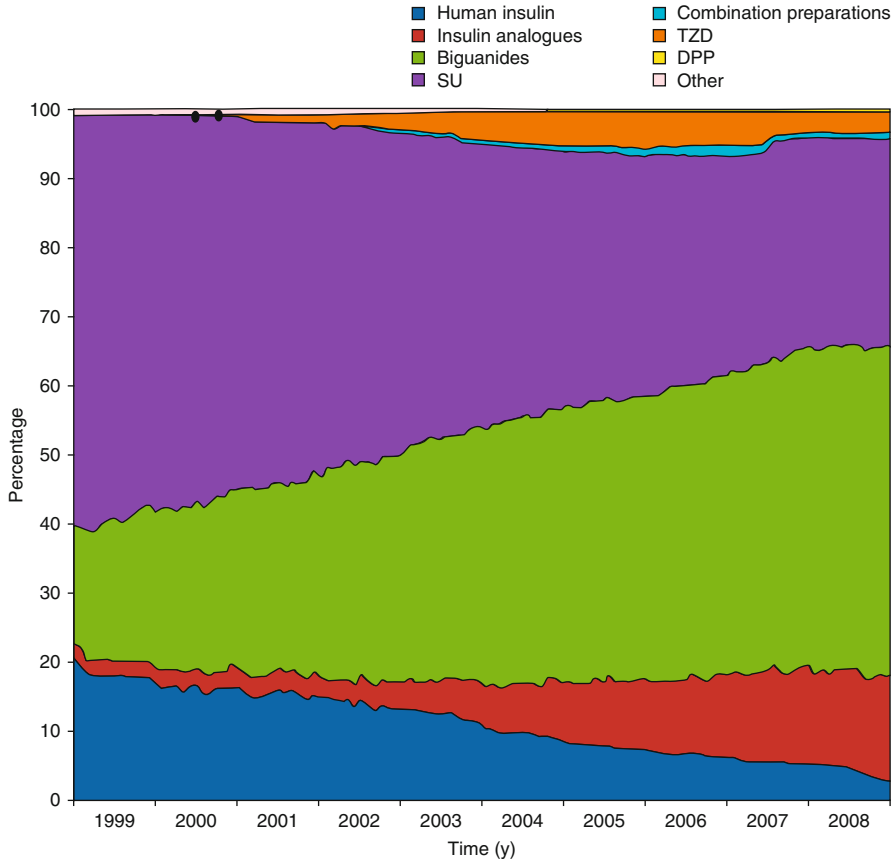

Fig. 1. Percentage contribution per drug category to the total number of drugs used for diabetes dispensed per month in a cohort of incident users of drugs dispensed for diabetes mellitus. The black dots represent the introduction of rosiglitazone and pioglitazone, respectively, to the market. **DPP** = dipeptidyl peptidase-4 inhibitors; **SU** = sulfonylurea derivatives; **TZD** = thiazolidinediones.

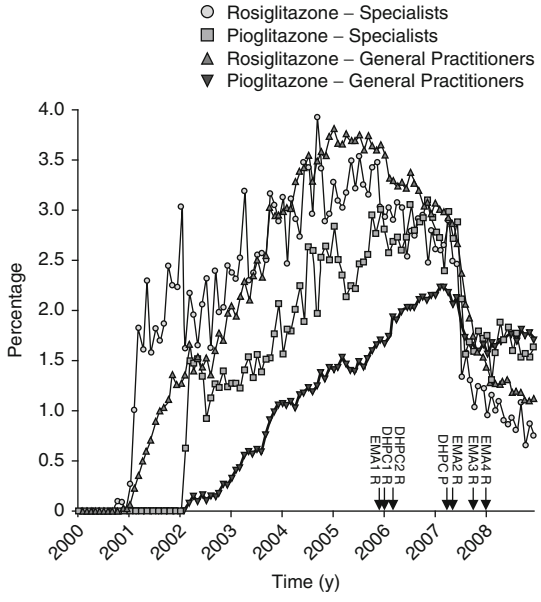

Fig. 2. Contribution (%) for rosiglitazone and pioglitazone to the total number of drugs used for diabetes dispensed per month in a cohort of incident users of drugs dispensed for diabetes mellitus. The arrows represent the subsequent Direct Healthcare Professional Communication and European Medicines Agency press releases for either rosiglitazone (R) or pioglitazone (P) [see also table II]. The percentage is calculated separately for each prescriber type (e.g. rosiglitazone dispensings prescribed by the general practitioner are divided by all prescriptions prescribed by the general practitioner over the same time period). **DHPC** = Direct Healthcare Professional Communication; **EMA** = European Medicines Agency.

availability of this first case report concerning macular oedema following rosiglitazone treatment.[6] This resulted in a non-statistically significant decrease in dispensings following both the first EMA press release and the first DHPC for dispensings prescribed by specialists as well as GPs.

After the second DHPC for rosiglitazone,[22] which was issued for a suspected increased risk of fractures in March 2006, the number of dispensings decreased further, with a total decline in the contributed proportion of around 50% (p-value for dispensings prescribed by GPs 0.001 and by specialists 0.08). This DHPC was preceded by the outcomes of the ADOPT study which, by itself, also influenced the number of dispensings prescribed by GPs (p-value 0.002; data not shown).[7] In contrast, no effect was found from this publication[7] on the number of dispensings prescribed by specialists (p-value 0.10). After adjusting the effect of the second DHPC for the availability of the results of ADOPT, the decrease in the number of dispensings prescribed by specialists as well as those prescribed by GPs did not remain statistically significant.

The number of dispensings decreased further after press releases 2 (May 2007), 3 (October 2007) and 4 (January 2008) issued by the EMA concerning cardiovascular risk (p-values for dispensings prescribed by GPs 0.001, 0.12 and 0.37, respectively; for those prescribed by specialists, p-values 0.05, <0.001 and 0.62, respectively).[26-28] Publications about cardiovascular risks also had a statistically significant effect on the number of dispensings but this was dependent on prescriber type.[8,9] Adjustment of the effect of EMA press release number 2[26] for the paper by Nissen and Wolski[8] was not possible due to co-linearity. For EMA press release 3,[27] the effect of the regulatory risk communication continued to have a statistically significant effect on the proportion of dispensings prescribed by specialists but not by GPs when additionally adjusted for certain literature[8,9] and EMA press release 2 (table II).[26] For EMA press release number 4,[28] however, after adjusting for the previous EMA press release regarding cardiovascular risk (number 3[27]) and for certain literature,[8,9] the effect did not remain statistically significant (table II).

Following the DHPC[23] issued for pioglitazone and a possible increased risk of fractures, a decrease can be seen in the number of dispensings which was not statistically significant for either dispensings prescribed by specialists or those prescribed by GPs. In addition, the ADOPT study[7] did not have a statistically significant effect on the number of dispensings prescribed.

Discussion

We presented a statistically significant decrease in the total number of dispensings of rosiglitazone following DHPCs or EMA press releases in a cohort of incident users of drugs dispensed for diabetes. Our results are comparable to figures published in the US.[14-16] However, since the use

Table II. Content of the Direct Healthcare Professional Communications, European Medicines Agency press releases, and certain literature and their effect on the proportion of dispensings prescribed by general practitioners and specialists in a cohort of incident users of drugs dispensed for diabetes mellitus

Determinant	Date (month-year)	Content	Other interventions in the model	GPs		Specialists	
				ω	p-Value[a]	ω	p-Value[a]
Rosiglitazone							
EMA press release 1[25]	12-2005	Risk of macular oedema	None	−3.41	**0.001**	−1.87	0.06
			Adjusted for case report on macular oedema[6]	−0.89	0.38	−0.72	0.46
DHPC 1[24]	01-2006	Risk of macular oedema	None	−3.52	**0.001**	−1.69	0.09
			Adjusted for EMA press release 1[25]	−0.93	0.35	−1.50	0.13
			Adjusted for case report[6]	−1.23	0.22	−0.11	0.90
			Adjusted for EMA press release 1[25] and case report[6]	−0.93	0.36	−1.51	0.13
DHPC 2[22]	03-2006	Risk of fractures	None	−3.38	**0.001**	−1.71	0.08
			Adjusted for ADOPT[7]	−0.90	0.37	−0.03	0.97
EMA press release 2[26]	05-2007	Cardiovascular risks	None	−3.38	**0.001**	−1.97	**0.05**
EMA press release 3[27]	10-2007	Cardiovascular risks	None	−1.57	0.12	−5.14	<**0.001**
			Adjusted for the RECORD study[9]	−1.31	0.19	−3.04	**0.003**
			Adjusted for Nissen and Wolski[8]	−1.30	0.20	−3.08	**0.002**
			Adjusted for EMA press release 2[26]	−1.30	0.20	−3.08	**0.003**
			Adjusted for the RECORD study[9] and Nissen and Wolski[8]	−1.32	0.19	−5.73	<**0.001**
			As above + adjusted for the standard of the Dutch Foundation of GPs[30]	−1.49	0.14	−5.72	<**0.001**
EMA press release 4[28]	01-2008	Cardiovascular risks	None	−0.90	0.37	−0.49	0.62
			Adjusted for the RECORD study[9]	−1.26	0.21	−0.86	0.39
			Adjusted for Nissen and Wolski[8]	−1.33	0.19	−2.57	**0.01**
			Adjusted for the statement by the ADA and EASD[29]	0.35	0.72	−2.42	**0.01**
			Adjusted for EMA press release 2[26]	−1.33	0.19	−2.57	**0.01**
			Adjusted for EMA press release 3[27]	−0.04	0.97	−0.34	0.73
			Adjusted for the RECORD study[9], Nissen and Wolski[8] and the statement by the ADA and EASD[29]	−1.28	0.20	−0.06	0.95
			Adjusted for EMA press release 2[26] and EMA press release 3[27]	−1.41	0.17	−0.41	0.68
			Adjusted for the RECORD study[9], Nissen and Wolski[8], the statement by the ADA and EASD[29] and EMA press release 3[27]	−1.35	0.18	−0.41	0.67
			As above + adjusted for the standard of the Dutch Foundation of GPs[30]	−1.33	0.18	−0.44	0.66
Pioglitazone							
DHPC[23]	04-2007	Risk of fractures	None	−0.47	0.64	−1.16	0.25
			Adjusted for ADOPT[7]	−1.11	0.27	−0.95	0.34

a Statistically significant p-values are presented in bold.

ω = estimate of direction and magnitude of the change in number after the intervention; **ADA** = American Diabetes Association; **ADOPT** = A Diabetes Outcome Progression Trial; **DHPC** = Direct Healthcare Professional Communication; **EASD** = European Association for the Study on Diabetes; **EMA** = European Medicines Agency; **GPs** = general practitioners; **RECORD** = Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes.

of thiazolidinediones in the Netherlands is relatively low in comparison with the US and Canada, this might explain why we did not find a statistically significant effect for all regulatory risk communications issued. However, it should also be considered that these regulatory risk communications were preceded by articles from literature on the same issue.[6-8] We were not able to fully assess which part of the decrease might be due to the DHPCs[22-24] or EMA releases[25-28] and which part might be due to the information in the literature.[6-9,29] However, it seems likely that the DHPCs and press releases contributed substantially to the decline, not in the least because of their widespread character and direct address to prescribers who may have missed the literature reports. Also, a DHPC may be more readily followed by doctors who fear the legal consequences of not following such advices.

As mentioned in the Background section, besides communicated safety issues, the introduction of new drugs can influence prescribing and dispensing patterns. Furthermore, implementation of guidelines can be a reason for variation in dispensing patterns. In March 2006, a new guideline was implemented by the Dutch Foundation for General Practitioners.[30] This guideline recommends metformin as first choice pharmacological therapy for patients with type 2 diabetes and, in our opinion, explains the increase we saw in the proportion of biguanides with reference to the total use of oral glucose-lowering drugs. As this guideline was actively promoted by the professional societies, it may have had a large impact on prescribing patterns of GPs in the Netherlands. Therefore, it was chosen to assess the decrease in dispensings prescribed by GPs separately from those prescribed by specialists.

The centralized authorization procedure allows swift and widespread access of new drugs to the European market, making it of crucial importance to recognize problems with these drugs as soon as possible. Safety signals issued by regulatory bodies are frequently preceded by reports presented in literature. To fully disentangle the effect of DHPCs and EMA press releases from the effect of reports published in literature remains difficult since the time in between is often limited. Furthermore, the actual impact of safety warnings may also vary according to explicitness regarding the seriousness of the safety issue. However, as can be seen from table II, adjustment for available literature did still result in a statistically significant effect of EMA press release 3 concerning cardiovascular issues on the proportion of dispensings prescribed by specialists, but not for safety communications released for macular oedema and the risk of fractures or other regulatory safety communication regarding cardiovascular risks. Nevertheless, as DHPCs are sent to all potential prescribers, whereas international medical journals are not read by all prescribers, it is not unreasonable to believe that DHPCs can affect prescribing patterns.

One of the strengths of our study is the large number of participants and prescriptions included over time. Furthermore, since we included only those with a prescription-free period of 6 months, the pattern presented is considered representative of those with newly diagnosed diabetes. However, note must be made that in the light of the ecological nature of this study, no direct conclusions can be drawn from the presented associations. Consequently, whether prescribers indeed took cardiovascular risk factors into account when initiating therapy on thiazolidinediones in individual patients could not be verified.

Conclusions

Our results showed that some DHPCs and EMA press releases were associated with a significant decrease in dispensing proportions of rosiglitazone in a cohort of incident users of drugs dispensed for diabetes. Differences were present between the effects of regulatory risk communication on dispensings prescribed by GPs and those prescribed by specialists. Furthermore, after additional adjustment for certain publications, only the effect of EMA press release 3 issued for cardiovascular risk continued to have a statistically significant effect on dispensings prescribed by specialists. Therefore, our study suggests that prescribers may also react to regulatory alerts with a consequent change in dispensing number.

Acknowledgements

M. van Herk-Sukel and R.M.C. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities, and for pharmaceutical companies. However, this study is not financially supported by a pharmaceutical company. R. Ruiter and B.H.Ch. Stricker work at the Dutch Inspectorate of Healthcare, a governmental organization. S. de Bie, S. Straus and P. Mol work at the Dutch Medicines Evaluation Board. None of the authors has declared any other support from any organization for the submitted work, financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, or other relationships or activities that could appear to have influenced the submitted work.

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