Drug Safety (2021) 44:589–600
https://doi.org/10.1007/s40264-021-01047-1

ORIGINAL RESEARCH ARTICLE

Assessing the Impact on Health of Pharmacovigilance Activities: Example of Four Safety Signals

Florence van Hunsel[1] · Laura Peters[1,2] · Helga Gardarsdottir[2] · Agnes Kant[1]

Accepted: 27 January 2021 / Published online: 19 February 2021

Abstract

Introduction The impact of pharmacovigilance activities on public health remains under-investigated, and measuring the impact on health of pharmacovigilance activities for a specific safety signal is challenging.

Objective To gain more insight into the methodological challenges and the data required, we assessed the impact of pharmacovigilance on public health for four identified product-specific safety signals using publicly available data in the Netherlands. The assessment was on the impact of the intertwined and complementary steps of the pharmacovigilance pathways.

Methods The impact of pharmacovigilance on public health was assessed using the assessment support tool and 'open data' from the Netherlands for four different types of pharmacovigilance safety signals: (1) off-label use of cyproterone acetate/ethinyloestradiol (CPA/EE) and thrombotic risk after pharmacovigilance measures after 2014; (2) pergolide and the risk of cardiac valvulopathy after pharmacovigilance activities in 2003; (3) proton pump inhibitors and the risk of hypomagnesaemia after pharmacovigilance activities in 2011; (4) rosiglitazone withdrawal from the market because of cardiovascular effects in 2010.

Results For the signals on CPA/EE and pergolide, a crude estimation of the impact could be made with varying degrees of assumptions based on the risk described in the literature and utilisation data.

Conclusion This article highlights the methodological challenges and the data required to assess the impact of product-specific safety signals. A structured assessment support tool can be used as a guide for the necessary data elements and steps needed for the measurement or estimation of impact of pharmacovigilance activities on public health, provided that the appropriate data are available.

Key Points

Although the number of studies assessing the impact of pharmacovigilance actions on health at the population level is increasing, the impact of pharmacovigilance activities on public health remains under-investigated.

Measuring the impact on health of pharmacovigilance activities for a specific safety signal is challenging but important.

✉ Florence van Hunsel
f.vanhunsel@lareb.nl

[1] Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands

[2] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

1 Introduction

Pharmacovigilance activities aim to reduce harm by improving the use of medicines. If we can measure or estimate the harm reduced by pharmacovigilance activities, we generate evidence about the effectiveness and show the effect of these activities. Although an increasing number of studies are assessing the impact of pharmacovigilance actions on health at the population level, assessing the impact of pharmacovigilance activities on public health remains under-investigated [1–3].

In 2017, the Pharmacovigilance Risk Assessment Committee (PRAC), the European Medicines Agency (EMA) committee responsible for assessing and monitoring the safety of human medicines, published a strategy that aimed to assess the impact of regulatory actions in order to provide regulators and other stakeholders with insights into which pharmacovigilance activities are the most successful [4]. Knowledge on the impact of pharmacovigilance activities can be used to stimulate proactive pharmacovigilance systems across the EU. The PRAC strategy focussed on measuring the effectiveness of the pharmacovigilance processes and of product-specific risk minimisation. It aimed to identify enablers of effective pharmacovigilance and promote collaboration on developing methodologies for impact research [4]. In addition, in 2018, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) published guidance on methods for pharmacovigilance impact research [5].

The pharmacovigilance process is complex and encompasses different stakeholders and activities [5]. The ENCePP guidance on methods for pharmacovigilance impact research included a visualisation of the various pathways and effects of pharmacovigilance activities [5] (Fig. 1).

Pharmacovigilance activities are, to some extent, intertwined and complementary: safety signals can lead to regulatory actions. However, healthcare professionals (HCPs) are exposed to information on safety issues from both regulators and the scientific community (scientific journals, conferences), which could affect their prescribing behaviour even before regulatory actions have taken place. Furthermore, the knowledge is also shared via the media, which might also affect the behaviour of HCPs and/or patients and thus influence the use of medicines in clinical practice. This could result in safer use of medicines but might also cause harm. Measuring impact should, therefore, include an assessment of not only the intended but also the unintended effects and other simultaneous events such as changes in clinical practice or secular trends in health outcomes. When measuring the impact on health outcomes of a specific safety signal, all those elements in the pharmacovigilance pathway should be accounted for to enable a better estimate of the impact of the signal [5].

Measuring the impact on health of pharmacovigilance activities of a specific safety signal is challenged by various elements, both methodological and in terms of access to and the availability of valid and complete data. Although it is acknowledged that there is a number of options when it concerns electronic health records and other real-world

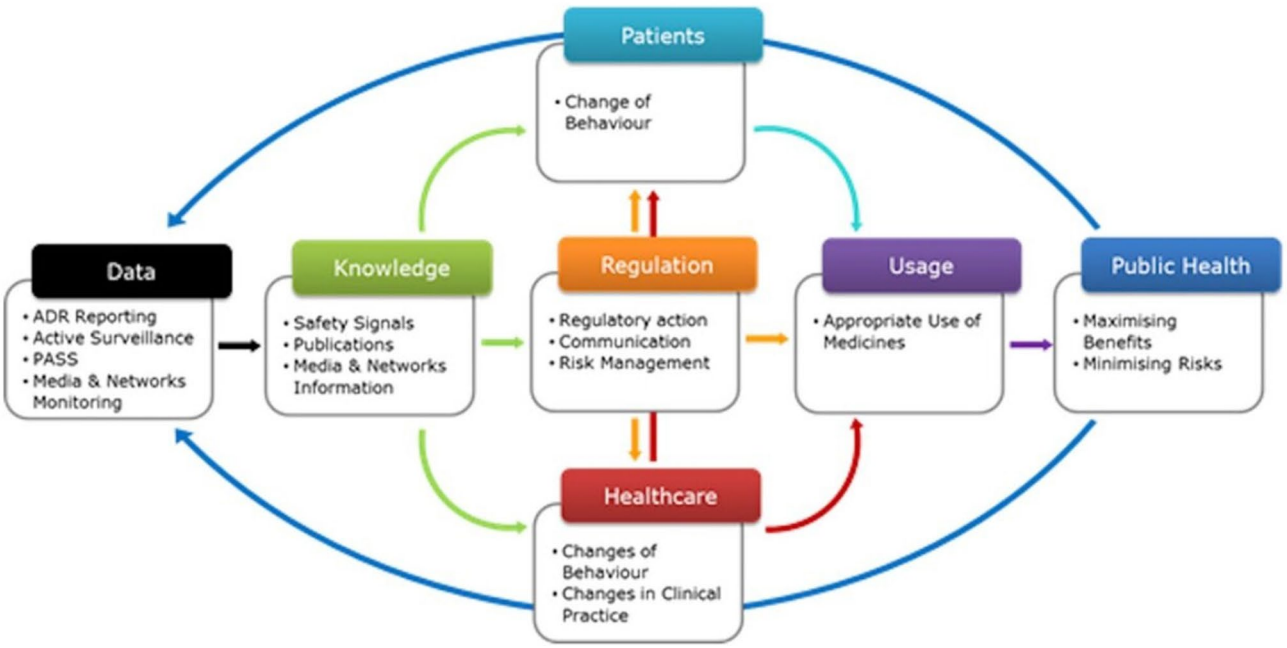

Fig. 1 Model of pathways and effects of pharmacovigilance activities [5]. *ADR* adverse drug reaction, *PASS* post-authorisation safety study

data, these are not always easily accessible to the governmental institutions that should play a role in monitoring the impact of pharmacovigilance activities on health outcomes. To provide insight into the methodological challenges and the data required, we conducted assessments of the impact of four different product-specific safety signals. We used only open-source data in these examples.

1.1 Safety Signals

Four different types of pharmacovigilance safety signals were selected for assessment of their impact. The examples were chosen because they are very diverse, highlighting different aspects of the assessment. No specific reasons or criteria were behind this choice, other than the expectation that the assessment would provide insights into the methodological challenges and the data required. The selected safety signals are as follows:

1. Off-label use of cyproterone acetate (CPA)/ethinyloestradiol (EE) and thrombotic risk after pharmacovigilance measures after 2014.
2. Pergolide and the risk of cardiac valvulopathy after pharmacovigilance activities in 2003.
3. Proton pump inhibitors (PPIs) and the risk of hypomagnesaemia after pharmacovigilance activities in 2011.
4. Withdrawal of rosiglitazone from the market because of cardiovascular effects in 2010.

2 Approach of the Assessment of Impact

An assessment support tool was used to help determine all the information required for the actual assessment in a structured manner, based on the *Model of Pathways and Effects of Pharmacovigilance Activities* in the ENCePP guidance on methods for pharmacovigilance impact research [5]. The assessment scheme is shown in Fig. 2. Because the goal of pharmacovigilance is to reduce harm by more appropriate use of medicines, a broad definition of the impact of pharmacovigilance was used: "the harm prevented by implementing pharmacovigilance activities."

2.1 Steps of the Assessment Tool

2.1.1 Formulate a Definition of Impact on Health of the Signal

The first step of the assessment is to describe the safety signal, the risk involved, and actions that took place after the safety signal was found (Fig. 2; shown in yellow). For the safety signal, a specific definition of the impact needs to be made: which changes in which health outcome during which time frame is suitable? (Fig. 2; shown in grey).

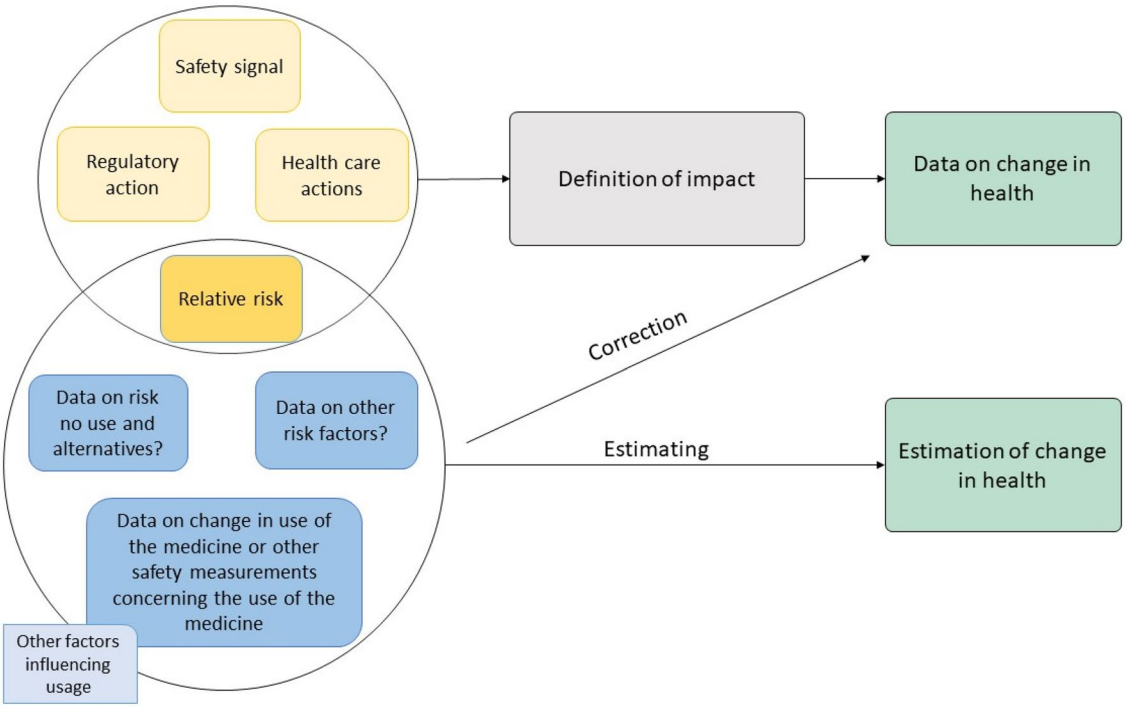

Fig. 2 Assessment support tool for measuring or estimating impact

2.1.2 Based on this Pre-defined Definition of Impact, Search for Data on Change in Health

If these data on the change in health (Fig. 2; shown in green) are available, such as 'the number of myocardial infarctions (MI) in a population of drug users in a specific time frame', these can be used to measure the impact of the pharmacovigilance activities.

2.1.3 If Not Available, Search for Data Needed to Estimate the Impact on Health

If direct data on change in health are not available, an estimation of the impact can be made (Fig. 2; shown in green). This estimation can be based on data on the change in use of the medicine and the known risk of the safety issue (Fig. 2; shown in dark yellow).

2.1.4 Take into Account Other Factors that Could have Influenced the Health Outcomes

In addition to intended impacts on public health, a pharmacovigilance action can also have unintended effects that may be harmful. To make a correct risk assessment or estimation, other factures influencing the change in health outcome need to be considered (Fig. 2; shown in blue), for instance, the risk of patients using no appropriate medication or switching to alternatives that might involve the same or other risks must be evaluated. When using expenditure data for an estimation, it is also important to note that factors other than the safety signal might influence usage (Fig. 2; shown in light blue), for instance, emerging therapies that patients might be switched to.

Finally, the effects of other simultaneous events, trends, and changes in risk factors affecting the health outcome being measured must also be taken into account (Fig. 2; shown in blue).

2.1.5 Assess or estimate the impact on health

3 Assessment per Signal

3.1 Extensive Off-Label Use of Cyproterone Acetate/Ethinyloestradiol and Thrombotic Risk

3.1.1 Formulate a Definition of Impact on Health of the Signal

CPA is a progestogen with a strong anti-androgen function that suppresses natural ovulation [6, 7]. Therefore, EE is added to the formulation, giving the drug contraceptive characteristics [6, 8]. In the Netherlands, CPA/EE was authorised for marketing in 1987 for the treatment of acne, seborrhoea, or light hirsutism in women of childbearing age if hormonal treatment was considered necessary. Conversely, market authorisation of CPA/EE products was never approved in the USA [6, 9, 10].

The timeline of information on the drug safety signal or other relevant clinical decisions for products containing CPA/EE is available as electronic supplementary material (ESM)-1. Based on the type of signal and pharmacovigilance and clinical activities, the following definition of impact for measures taken regarding products containing CPA/EE was formulated: the reduced number of venous thromboembolism events (VTEs) before and after the pharmacovigilance activities in 2013 in women of childbearing age. As the original signal was dated December 2012, the period before pharmacovigilance activities was defined as < 2013. The implementation of HCP guidelines would also take a few months, so the post-pharmacovigilance activity period was defined as > 2014.

3.1.2 Based on this Pre-defined Definition of Impact, Search for Data on Change in Health

No open-source data on the number of VTEs in the Netherlands were available.

3.1.3 If Not Available, Search for Data Needed to Estimate the Impact on Health

Regarding the use of Diane-35, multiple alternative contraceptive methods are available, including hormonal and non-hormonal treatments. The number of users of combined oral contraceptives (COCs) and CPA/EE in the Netherlands was based on a publication from 2016 [11]. From the literature, a risk estimate for VTE was chosen based on a meta-analysis [12] that found a baseline risk of non-users of 1.9/10,000 women-years. The pooled relative ratio (RR) showed that all COCs increase the risk of developing VTEs, but the third- and fourth-generation COCs are considered high risk and have an RR of 3.8, whereas the second-generation drugs are considered low risk, with an RR of 2.8. The pooled RR of CPA/EE is 3.9 [12].

3.1.4 Take into Account Other Factors that Could have Influenced the Health Outcomes

Other factors could influence the risk of developing VTEs. For instance, previous hormone pill-related scares [13–17] could have led women to choose not to use oral contraception and take the risk of becoming pregnant. Pregnancy itself is also related to a higher risk of VTE [18, 19]. However, women could also use a non-drug intrauterine device (IUD)

as an effective alternative to oral hormonal contraception. The lack of data on this latter category meant we were unable to calculate the effect of women switching to this alternative. Factors such as a change in smoking habits in the user group could also influence the risk of VTEs. Data from the Statistics Netherlands (CBS) StatLine database [20] indicated no large changes in these factors from 2010 to 2015.

3.1.5 Assess or Estimate the Impact on Health

The reduced number of VTEs was estimated using data on the risk of developing adverse drug reactions (ADRs) and user numbers. An estimation was made of the total number of prevented VTE cases in the Netherlands (Table 1). The number of VTEs among COC users pre- and post-pharmacovigilance activity was compared. The overall change in hormonal contraceptive usage is known, comparing utilisation before and after 2013. For each hormonal contraceptive, including CPA/EE, the number of VTE cases/year was calculated based on the RR described by Stegeman et al. [12]. Taking all hormonal contraceptive use into account, the estimated number of prevented thrombosis cases is approximately 165/year. However, since the number of IUD users is unknown, this is an overestimation of the number of prevented VTE cases. It should be noted that we had no data on the number of women who switched from oral contraceptives to IUDs.

The assessment scheme for this signal, with all the included data, is available as ESM-5.

3.2 Risk of Developing Valvular Heart Disease with Pergolide

Pergolide is a ergot-derived dopamine receptor agonist used in the treatment of Parkinson's disease (PD). Pergolide was first authorised for marketing in 1989 in the USA [21] and in 1991 in the Netherlands [22].

3.2.1 Formulate a Definition of Impact on Health of the Signal

Relatively soon after marketing authorisation, cases of fibrotic reactions (retroperitoneal, pericardial, and pleural) were reported. In 2002, the first cases of valvulopathy were published [23–25]. Information on the drug safety signal is available as ESM-2. Based on the signal and pharmacovigilance activities, the following definition of impact was formulated: reduced number of cardiac valvulopathy in patients with PD after pharmacovigilance activities (2003).

3.2.2 Based on this Pre-defined Definition of Impact, Search for Data on Change in Health

Data on change in health (the number of valvulopathy events per year) from electronic health records or clinical data were not publicly available, nor was published literature available on the change in the number of valvulopathy cases in the Netherlands.

3.2.3 If Not Available, Search for Data Needed to Estimate the Impact on Health

The number of pergolide users decreased from 34,048 in 2003 to 4133 in 2013, a decrease of 87.9%. Considering that, during the same period, the total use of anti-Parkinson drugs increased, the relative pergolide use has decreased even more: from 6.12 to 0.27%. A trend analysis of utilisation in the Netherlands before and after the pharmacovigilance activities showed that a gradual decline was already occurring before the regulatory actions in Europe [26].

Multiple studies examined the risk of developing valvulopathy when using pergolide. Although a causal relationship between pergolide use and valvulopathy was confirmed, with an established mechanism, the reported risk varied largely between studies (8.7–21.8%) [27–30]. The meta-analysis by Rasmussen et al. [30] found a relative risk of 3.05 for developing valvulopathy in pergolide users compared with non-users.

Table 1 Usage of hormonal contraceptives and venous thromboembolism cases per year

Hormonal contraceptive	Usage pre-2013	RR[a]	VTE cases/year	Usage 2015	RR	VTE cases/year
Diane-35	180,000	3.9	130	44,000	3.9	32
High-risk COCs	430,200	3.8	310	322,200	3.8	233
Low-risk COCs	1,419,800	2.8	755	1,437,800	2.8	765
Total	2,030,000		1195	1,804,000		1030

The baseline risk of non-users was 1.9/10.000 women years

COC combined oral contraceptive, *RR* relative risk, *VTE* venous thromboembolism

[a]RR based on Stegeman et al. [12]

3.2.4 Take into Account Other Factors that Could have Influenced the Health Outcomes

Patients with PD who stop using pergolide are likely to switch to other therapies, such as cabergoline and bromocriptine. Cabergoline is not available on the Dutch market [22]. A referral procedure where the risk of valvulopathy in bromocriptine users was assessed could not exclude increased risk, although a risk estimate was not described in the referral [31]. Furthermore, two additional safety issues occurred in 2004 and 2005 that could have influenced the usage of pergolide [32–35]. This could not be accounted for in our impact estimate.

Given the existing evidence, it is difficult to account for all possible factors in our impact estimate. First, the ADR is likely dose dependent, and a number of studies showed that doses above 3 mg/day were associated with an increased risk of valvulopathy [36–39]. However, some studies did not find this dose relationship of the ADR. Therefore, more research is necessary to determine the effect of dose on the development of ADRs [27, 36, 39–44]. There is also some debate on the correlation between duration of treatment and the increased risk of valvulopathy [27, 28, 37, 38, 45–47]. Furthermore, regression of valve abnormalities occurs when discontinuing the treatment, but this is not the case for all fibrotic reactions [27, 36–39, 41, 42, 44, 45, 48–50]. These are all factors that we could not account for in our risk estimation.

3.2.5 Assess or Estimate the Impact on Health

For this signal, it was not realistic to define the time period before and after the activities. Instead, the total amount of pergolide users from 2003 until 2013 per year was estimated. The pharmacovigilance activities prevented approximately 2752 moderate-to-severe valvulopathy cases from 2003 to 2013, approximately 272 moderate-to-severe valvulopathy cases per year.

The assessment scheme for this signal, with all the included data, is available as ESM-5.

3.3 Proton Pump Inhibitors and the Risk of Hypomagnesaemia

PPIs are widely used for peptic ulcers, gastroesophageal reflux disease, and oesophagitis. They also protect the stomach and oesophagus for patients using medicines such as non-steroidal anti-inflammatory drugs. Long-term usage has been associated with an increased risk of developing hypomagnesaemia [51–61].

3.3.1 Formulate a Definition of Impact on Health of the Signal

Long-term usage of PPIs has been associated with an increased risk of developing hypomagnesaemia [51–61]. The timeline of information on the drug safety signal or other relevant clinical decisions is available as ESM-3. Based on the signal and pharmacovigilance activities, the following definition of impact was formulated: reducing the number of hypomagnesaemia cases after the pharmacovigilance activities of 2011 among PPI users.

3.3.2 Based on this Pre-defined Definition of Impact, Search for data on Change in Health

Data on change in health (number of hypomagnesaemia cases) within the PPI user group were unavailable.

3.3.3 If Not Available, Search for Data Needed to Estimate the Impact on Health

The impact of the pharmacovigilance activities could be estimated using a risk assessment and change in utilisation. However, since PPIs are also available over the counter, no suitable Dutch data were available to provide insight into changes in utilisation. When looking at the prescription use of PPIs only, through the Drug Information System of the National Health Care Institute (GIP-data), a decrease in the number of PPI users can be seen from 2011 to 2012 after the pharmacovigilance activities took place, although the number of PPI users slowly rose again from 2012 (Fig. 3). A meta-analysis [59] indicated that the risk of developing hypomagnesaemia was 1.63 times higher in PPI users than nonusers.

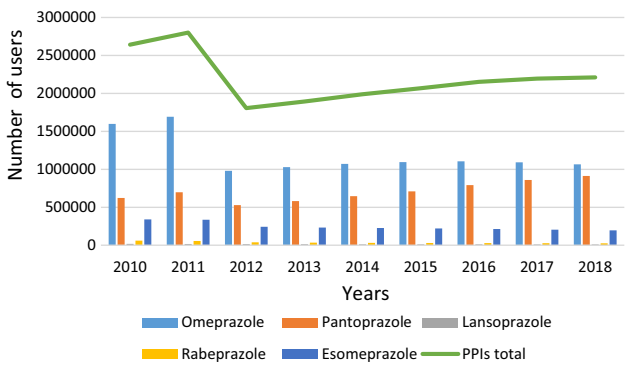

Fig. 3 Number of users of proton pump inhibitors (PPIs) on prescription from 2010 to 2018

3.3.4 Take into Account Other Factors that Could have Influenced the Health Outcomes

Many other factors could be attributed to the development of hypomagnesaemia, such as low intake of magnesium, vomiting and diarrhoea, alcoholism, and renal losses [62]. In the chosen time frame, other signals concerning PPIs also might have influenced a change in utilisation. Multiple observational studies found that PPIs modestly increased the risk of hip, spine, and any-site fractures [63, 64].

3.4 Assess or Estimate the Impact on Health

Without data on changes in use, it is not possible to estimate the impact.

The assessment scheme for this signal, with all the included data, is available as ESM-5.

3.5 Rosiglitazone Withdrawal due to Cardiovascular Effects

Rosiglitazone (Avandia®) is a thiazolidinedione antidiabetic agent that improves glycaemic control by improving insulin sensitivity. The drug was approved by the US FDA in May 1999 for the treatment of type 2 diabetes mellitus (T2DM) as first-line monotherapy or in combination with metformin. At the time of marketing authorisation in the EU (March 2000), rosiglitazone usage was restricted to second-line oral combination therapy.

3.5.1 Formulate a Definition of Impact on Health of the Signal

In September 2010, the EMA suspended the market authorisation of rosiglitazone, while the FDA restricted its use to patients without established New York Heart Association functional classification class III or IV heart failure (HF). Further, rosiglitazone is not recommended in patients with symptomatic HF [65]. These actions were taken approximately 10 years after the introduction of rosiglitazone because rosiglitazone might be associated with an increased risk of ischaemic heart disease [66]. The timeline of information on the drug safety signal or other relevant clinical decisions is available as ESM-4. Based on the signal and pharmacovigilance activities, the following definition of impact was formulated: a reduction in the number of cardiovascular-related events among patients with T2DM after withdrawal of rosiglitazone from the market in 2010. The cardiovascular events most often associated with rosiglitazone are HF, MI, and cardiovascular-related deaths, so these will be the main outcomes.

3.5.2 Based on this Pre-defined Definition of Impact Search for Data on Change of Health

Data on change in health (the number of cardiovascular events among patients with T2DM per year) were not publicly available.

3.5.3 If Not Available, Search for Data Needed to Estimate the Impact on Health

Data on change in use were available from the Drug Information System of the National Health Care Institute [26]. The number of defined daily doses (DDD)/month shows that utilisation of rosiglitazone gradually decreased, starting after the first safety signal in 2006 and decreasing further after more pharmacovigilance measures took place. Two drops in the user numbers were measured: from April 2007 to January 2008, a decrease of 333,331 DDDs/year (− 49.9%) was seen. From August 2010 to December 2010, a decline of 220,709 DDDs/year (− 98.0%) was measured. An autoregressive integrated moving average model for trend analysis [67] showed two significant changes in trends after the regulatory actions. The safety signal of 2006 regarding oedema caused a significant decrease in trend directly after the regulatory action; second, the safety warning in 2007 stating the increased risk of cardiovascular events while using rosiglitazone caused a significant decrease in utilisation trend after 2 months. Conversely, the number of users of pioglitazone seemed to steadily increase (Fig. 4).

The available literature gave conflicting results regarding the increased risk of cardiovascular events: some showed an increased risk of MI, HF, and even cardiovascular-related death, whereas others showed a decreased risk [68–73].

3.5.4 Take into Account Other Factors that Could have Influenced the Health Outcomes

Many other factors increase the risk of cardiovascular events, such as obesity, smoking, sodium intake, lack of physical activity, family history, and diabetes. None of these risk factors changed significantly from 2006 to 2010 [74]. Some other pharmacovigilance activities for rosiglitazone occurred in the same period, such as a safety warning on rosiglitazone and the development of macular edema in 2006 that could have influenced drug utilisation [75, 76].

3.5.5 Assess or Estimate the Impact on Health

Although we noted a change in the usage of rosiglitazone and pioglitazone, we were unable to estimate the impact of this change on the health of patients, because no risk estimation from the literature was possible.

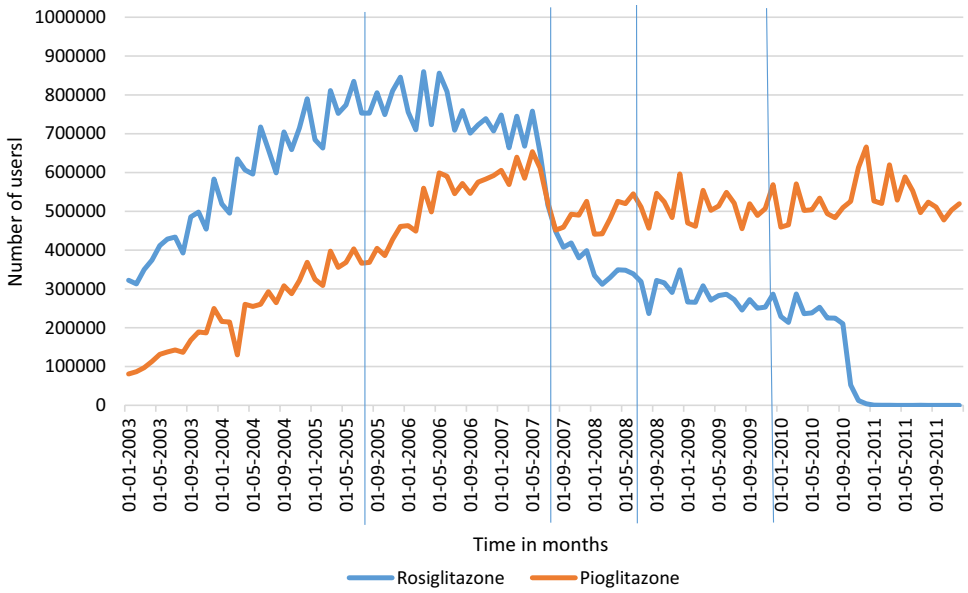

Fig. 4 User numbers of rosiglitazone and pioglitazone, expressed in defined daily dose per month, for 2003–2011. The four vertical lines are indicators of European Medicines Agency communication regarding drug safety and rosiglitazone

The assessment scheme for this signal, with all the included data, is available as ESM-5.

4 Discussion

With this article, we wanted to highlight the methodological challenges and the data required to assess the impact of product-specific safety signals using health outcomes from electronic health records and estimations based on data on risk of the event and change in usage. For this, we took four diverse safety signals into account. An assessment support tool was used, considering elements from the ENCePP guidance on methods for pharmacovigilance impact research [5]. This assessment support tool is meant as a guide for the necessary data elements and steps needed for the measurement or estimation of impact of pharmacovigilance activities on public health. A specific definition of the impact is essential: which changes in which health outcome in which time frame are suitable? Importantly, the ENCePP guidance on methods for pharmacovigilance impact research [5] mentioned that "outcomes to be studied in impact research are closely tied to the nature and objective of the pharmacovigilance activities. Because regulatory actions are mostly tailored to individual medicinal products, there is no standard outcome that could be measured for each activity."

4.1 Insights from Assessments

For impact assessments, often data are needed on health outcomes within specific population groups, for example, data on health outcomes for women of childbearing age or data on cardiac valvulopathy in patients with PD. In the signal examples we used to assess the impact, only open-access data were used to show how the assessment scheme could be used. For instance, for health outcomes, we used the open-source CBS StatLine database [20]. However, this source only contains open-source data on an aggregated population level per year and for specific population groups. Data on changes in use of pergolide, rosiglitazone, and prescription-based PPIs were more readily available from the Drug Information System of the National Health Care Institute. However, drugs that can be purchased over the counter without a medical prescription or that are not reimbursed are rarely covered in secondary data sources [5], as was the case with our PPI signal.

To a large extent, it was possible to consider the risk of patients using no appropriate medication or switching to alternatives that might have the same or other risks for the signal on CE/EE. However, data on switches to (non-hormonal) IUDs were lacking. Without correcting for the risks of developing VTEs for the alternative hormonal contraceptives, an estimation will be incorrect.

When assessing the extent to which patients are deprived of the benefit of a drug (compared with the next best alternative) after a safety warning, the loss of benefit compared with the remaining best alternative should be considered. In our assessments, although highlighted as one of the steps to give an assessment of impact, we could not perform this counterbalancing calculation of loss of benefit for the selected signals. Spillover effects are also hard to catch. For instance, an FDA warning in 2003 of an association between selective serotonin reuptake inhibitor prescription and suicidality in paediatric patients also led to decreased prescriptions in adults and

possibly suboptimal treatment [77]. It is challenging to consider all other possible factors that can influence the risk of an event or usage of a drug, other than pharmacovigilance activities, such as the decline in smoking for the risk of VTEs or other newly available drugs for the treatment of PD in the signal examples. Estimating the risk for a signal also gets complicated if results in the available literature regarding the increased risk are conflicting, which was the case for cardiovascular events associated with rosiglitazone. Therefore, although we noted a change in the usage of rosiglitazone, we were unable to estimate the impact of this change on the health of patients.

4.2 Studies on Impact

When performing research to address comparative safety and effectiveness questions, fit-for-purpose data should be used to ensure the validity of outcomes. A clinical trial or prospective cohort would be ideal in this respect, but once a risk has been identified, this could be considered no longer ethical. In addition, such research is expensive and very time consuming. Gathering appropriate data on changes in health outcomes, for example from electronic healthcare databases, is an alternative approach to assess the impact of pharmacovigilance activities, provided the data are representative of the population. If specific data are available on changes in health in a specific time frame, these can be used to measure the impact of the pharmacovigilance activities. However, if these data are lacking, an estimation of the impact can be made based on data on the risk of the event and changes in usage of a drug.

In addition, studies investigating impact should aim to include assessment of both the intended and the unintended health outcomes of the pharmacovigilance activities on which they are focusing. A review of impact studies by Goedecke et al. [1] showed that the most often used outcome measures in studies were related to drug utilisation. Health outcomes such as morbidity, mortality, pregnancy-related outcomes, or changes in laboratory values were measured as surrogate values in only 27% of the studies [1]. Weatherburn et al. [78] performed a systematic review of studies that assessed the impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes. In studies examining health outcomes, they found a mean decrease of 10% in intended and a 7% increase in unintended health outcomes. Briesacher et al. [79] performed a critical review of methods to evaluate the impact of FDA regulatory actions and found that less than one-quarter (22%) included control groups in these assessments. Only 56% assessed changes in use of substitute products/services, and 11% examined patient health outcomes. Interrupted time series (ITS) regression is a strong tool to evaluate an intervention's effect. The systematic review of studies on impact also created an inventory of the methodological approaches used [1]. The methods used were very diverse, but the use of ITS regression is increasing. An example of ITS is a study on the long-term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales [80].

Although some of the impact studies may have had methodological challenges, it is important that more research on impact is performed to provide the necessary evidence for the effectiveness of pharmacovigilance activities [2].

5 Conclusion

This article highlights the methodological challenges and the data required to assess the impact of product-specific safety signals. A structured assessment support tool can be used as a guide for the necessary data elements and steps needed for the measurement or estimation of the impact of pharmacovigilance activities on public health, provided that the appropriate data are available.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-021-01047-1.

Declarations

Funding No sources of funding were used to assist in the preparation of this article.

Conflict of interest Florence van Hunsel, Laura Peters, Helga Gardarsdottir, and Agnes Kant have no conflicts of interest that are directly relevant to the content of this study.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Publicly available data were used for this research. The data used during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions FH, LP, HG, and AK contributed to the article. LP eters performed the assessments of the impact, with input from the other authors. FH wrote the first draft of the manuscript with input from all other authors. All authors contributed to manuscript revision and read and approved the submitted version.

References

1. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions—systematic review and methodological considerations. Br J Clin Pharmacol. 2018;84(3):419–33. https://doi.org/10.1111/bcp.13469.
2. van Hunsel F, Gardarsdottir H, de Boer A, Kant A. Measuring the impact of pharmacovigilance activities, challenging but important. Br J Clin Pharmacol. 2019. https://doi.org/10.1111/bcp.14042.
3. Kesselheim AS, Campbell EG, Schneeweiss S, Rausch P, Lappin BM, Zhou EH, et al. Methodological approaches to evaluate the impact of FDA drug safety communications. Drug Saf. 2015;38(6):565–75. https://doi.org/10.1007/s40264-015-0291-y.
4. (PRAC). PRAC. PRAC strategy measuring impact pharmacovigilance activities (Rev 1). 2017.
5. European Network of Centres for Pharmacoepidemiology, Pharmacovigilance. ENCePP guide on methodological standards in pharmacoepidemiology—annex 2. Guidance on methods for pharmacovigilance impact research. 2018. http://www.encepeu/standards_and_guidances/methodologicalGuideAnnex2shtml. Accessed 21 Nov 2019.
6. Bitzer J, Amy JJ, Beerthuizen R, Birkhauser M, Bombas T, Creinin M, et al. Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism. J Fam Plann Reprod Health Care. 2013;39(3):156–9. https://doi.org/10.1136/jfprhc-2013-100624.
7. Bitzer J. Comment on "Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism": author's response. J Fam Plann Reprod Health Care. 2013;39(4):304–5. https://doi.org/10.1136/jfprhc-2013-100710.
8. Martinez F, Avecilla A. Combined hormonal contraception and venous thromboembolism. Eur J Contracept Reprod Health Care. 2007;12(2):97–106. https://doi.org/10.1080/13625180701300194.
9. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. J Am Coll Cardiol. 2009;53(3):221–31. https://doi.org/10.1016/j.jacc.2008.09.042.
10. Mintzes B. Drug regulatory failure in Canada, the case of Diane-35. women and health protection. 2004.
11. Stichting Farmaceutische Kengetallen (SFK). Aandeel risicopillen in vijf jaar met kwart afgenomen. 2006. https://www.sfk.nl/publicaties/PW/2016/aandeel-risicopillen-in-vijf-jaar-met-kwart-afgenomen. Accessed 21 Aug 2019.
12. Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama VA, Helmerhorst FM, Stijnen T, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ. 2013;347:f5298. https://doi.org/10.1136/bmj.f5298.
13. Furedi A. The public health implications of the 1999 pil scare. Hum Reprod Update. 1999;5(6):7.
14. Farmer RD, Williams TJ, Simpson EL, Nightingale ALE, of, . pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. BMJ. 1995;2000(321):3.
15. Martin RM, Hilton,S.R., Kerry, S.M.. The impact of the October 1995 'Pil Scare' on oral contaceptive use in the United Kingdom; analysis of a general practice automated database. Fam Pract. 1997;14(4):6.
16. Mills A. Avoiding problems in clinical practice after the pill scare. Hum Reprod Update. 1999;5(6):639.
17. de Vries CS, van den Berg,P.B., van den Berg, L.T.W.,. Oral contraceptive use before and after the latest pill scare in the Netherlands. Contraception. 1998;57:3.
18. Zambrano MD, Miller EC. Maternal stroke: an update. Curr Atheroscler Rep. 2019;21(9):33. https://doi.org/10.1007/s11883-019-0798-2.
19. Chen GC, Gao H, Zhang L, Tong T. Evaluation of therapeutic efficacy of anticoagulant drugs for patients with venous thromboembolism during pregnancy: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2019;238:7–11. https://doi.org/10.1016/j.ejogrb.2019.04.038.
20. Statistics Netherlands. 2019. http://www.cbs.nl. https://opendata.cbs.nl/statline/#/CBS/nl/. Accessed 21 Nov 2019.
21. US Food and Drug Administration (FDA). Drugs@FDA: FDA Approved Drug Products—pergolide. 2019. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019385. Accessed 23 Aug 2019.
22. College ter Beoordeling van Geneesmiddelen (CBG-MEB). 2019. https://www.geneesmiddeleninformatiebank.nl/nl/. https://www.geneesmiddeleninformatiebank.nl/nl/. Accessed 21 Aug 2019.
23. Shaunak S, Wilkins A, Pilling JB, Dick DJ. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. J Neurol Neurosurg Psychiatry. 1999;66(1):79–81. https://doi.org/10.1136/jnnp.66.1.79.
24. Flowers CM, Racoosin JA, Lu SL, Beitz JG. The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. Mayo Clin Proc. 2003;78(6):730–1. https://doi.org/10.4065/78.6.730.
25. Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. Mayo Clin Proc. 2002;77(12):1280–6. https://doi.org/10.4065/77.12.1280.
26. Zorginstituut Nederland (ZIN). The Drug Information System of the National Health Care Institute. 2019. https://www.gipdatabank.nl/servicepagina/engelse-informatie. Accessed 21 Aug 2019.
27. Corvol JC, Anzouan-Kacou JB, Fauveau E, Bonnet AM, Lebrun-Vignes B, Girault C, Agid Y, Lechat P, Isnard R, Lacomblez L. Heart valve regurgitation, pergolide use, and Parkinson disease. Arch Neurol. 2007;64(12):5.
28. Tran T, Brophy JM, Suissa S, Renoux C. Risks of cardiac valve regurgitation and heart failure associated with ergot- and non-ergot-derived dopamine agonist use in patients with Parkinson's disease: a systematic review of observational studies. CNS Drugs. 2015;29(12):985–98. https://doi.org/10.1007/s40263-015-0293-4.
29. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet Neurol. 2009;8(10):929–37. https://doi.org/10.1016/s1474-4422(09)70225-x.
30. Rasmussen VG, Østergaard K, Dupont E, Poulsen SH. The risk of valvular regurgitation in patients with Parkinson's disease treated with dopamine receptor agonists. Mov Disord. 2011;26(5):801–6. https://doi.org/10.1002/mds.23470.
31. European Medicines Agency (EMA). Overall summary of the scientific evaluation of bromocriptine, dihydroergocryptine and lisuride and associated names. 2008. https://www.ema.europa.eu/en/documents/referral/bromocriptine-dihydroergocryptine-lisuride-article-31-referral-annex-ii_en.pdf. Accessed 23 Aug 2019.
32. Fahn S, Parkinson Study G. Does levodopa slow or hasten the rate of progression of Parkinson's disease? J Neurol. 2005;252(Suppl 4):IV37–IV42. https://doi.org/10.1007/s00415-005-4008-5.
33. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004;351(24):2498–508. https://doi.org/10.1056/NEJMoa033447.

34. Netherlands Pharmacovigilance Centre Lareb. Pergolide and pathologic gambling addiction. 2005. https://databankws.lareb.nl/Downloads/kwb_2005_3_pergo.pdf. Accessed 22 Aug 2019.
35. Lemmens T, Gibson S. Decreasing the data deficit: improving post-market surveillance in pharmaceutical regulation. McGill Law J. 2014;59(4):943–88.
36. Yamashiro K, Komine-Kobayashi M, Hatano T, Urabe T, Mochizuki H, Hattori N, et al. The frequency of cardiac valvular regurgitation in Parkinson's disease. Mov Disord. 2008;23(7):935–41. https://doi.org/10.1002/mds.22036.
37. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. NEJM. 2007;356:29.
38. Oeda T, Masaki M, Yamamoto K, Mizuta E, Kitagawa N, Isono T, et al. High risk factors for valvular heart disease from dopamine agonists in patients with Parkinson's disease. J Neural Transm (Vienna). 2009;116(2):171–8. https://doi.org/10.1007/s00702-008-0160-2.
39. Van Camp GF A, Cosyns D, Goldstein J, Perdaens Schoors D. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. Neurology. 2003;61:859.
40. Kim JY, Chung EJ, Park SW, Lee WY. Valvular heart disease in Parkinson's disease treated with ergot derivative dopamine agonists. Mov Disord. 2006;21(8):1261–4. https://doi.org/10.1002/mds.20931.
41. Kenangil G, Ozekmekci S, Koldas L, Sahin T, Erginoz E. Assessment of valvulopathy in Parkinson's disease patients on pergolide and/or cabergoline. Clin Neurol Neurosurg. 2007;109(4):350–3. https://doi.org/10.1016/j.clineuro.2007.01.011.
42. Ruzicka E, Linkova H, Penicka M, Ulmanova O, Novakova L, Roth J. Low incidence of restrictive valvulopathy in patients with Parkinson's disease on moderate dose of pergolide. J Neurol. 2007;254(11):1575–8. https://doi.org/10.1007/s00415-007-0592-x.
43. Trifiro G, Mokhles MM, Dieleman JP, van Soest EM, Verhamme K, Mazzaglia G, et al. Risk of cardiac valve regurgitation with dopamine agonist use in Parkinson's disease and hyperprolactinaemia: a multi-country, nested case-control study. Drug Saf. 2012;35(2):159–71. https://doi.org/10.2165/11594940-000000000-00000.
44. Yamamoto M, Uesugi T. Dopamine agonists and valvular heart disease in patients with Parkinson's disease: evidence and mystery. J Neurol. 2007;254(S5):74–8. https://doi.org/10.1007/s00415-007-5012-8.
45. Peralta C, Wolf E, Alber H, Seppi K, Muller S, Bosch S, et al. Valvular heart disease in Parkinson's disease vs. controls: an echocardiographic study. Mov Disord. 2006;21(8):1109–13. https://doi.org/10.1002/mds.20887.
46. Ozer F, Tiras R, Cetin S, Ozturk O, Aydemir T, Ozben S, et al. Valvular heart disease in patients with Parkinson's disease treated with pergolide, levodopa or both. J Clin Neurosci. 2009;16(1):83–7. https://doi.org/10.1016/j.jocn.2008.02.005.
47. Martin WR. Dopamine agonists and the risk of valvular heart disease. Nat Clin Pract Neurol. 2007;3(8):426–7. https://doi.org/10.1038/ncpneuro0534.
48. Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Regression of cardiac valvulopathy related to ergot-derived dopamine agonists. Cardiovasc Ther. 2011;29(6):404–10. https://doi.org/10.1111/j.1755-5922.2010.00169.x.
49. Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. Neurology. 2006;67(7):1225–9. https://doi.org/10.1212/01.wnl.0000238508.68593.1d.
50. Zadikoff C, Duong-Hua M, Sykora K, Marras C, Lang A, Rochon P. Pergolide associated cardiac valvulopathy based on Ontario administrative data. Can J Neurol Sci. 2014;35(2):173–8. https://doi.org/10.1017/s0317167100008593.
51. Gau JT, Yang YX, Chen R, Kao TC. Uses of proton pump inhibitors and hypomagnesemia. Pharmacoepidemiol Drug Saf. 2012;21(5):553–9. https://doi.org/10.1002/pds.3224.
52. Fatuzzo P, Portale G, Scollo V, Zanoli L, Granata A. Proton pump inhibitors and symptomatic hypomagnesemic hypoparathyroidism. J Nephrol. 2017;30(2):297–301. https://doi.org/10.1007/s40620-016-0319-0.
53. Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56(1):112–6. https://doi.org/10.1053/j.ajkd.2009.11.019.
54. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: a new challenge. World J Nephrol. 2012;1(6):151–4. https://doi.org/10.5527/wjn.v1.i6.151.
55. Biyik M, Solak Y, Ucar R, Cifci S, Tekis D, Polat I, et al. Hypomagnesemia among outpatient long-term proton pump inhibitor users. Am J Ther. 2017;24(1):e52–5. https://doi.org/10.1097/MJT.0000000000000154.
56. Pasina L, Zanotta D, Puricelli S, Djignefa DC, Bonoldi G. Proton pump inhibitors and risk of hypomagnesemia. Eur J Intern Med. 2015;26(7):e25–6. https://doi.org/10.1016/j.ejim.2015.06.019.
57. Danziger J, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. Kidney Int. 2013;83(4):692–9. https://doi.org/10.1038/ki.2012.452.
58. Lindner G, Funk GC, Leichtle AB, Fiedler GM, Schwarz C, Eleftheriadis T, et al. Impact of proton pump inhibitor use on magnesium homoeostasis: a cross-sectional study in a tertiary emergency department. Int J Clin Pract. 2014;68(11):1352–7. https://doi.org/10.1111/ijcp.12469.
59. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail. 2015;37(7):1237–41. https://doi.org/10.3109/0886022X.2015.1057800.
60. Park CH, Kim EH, Roh YH, Kim HY, Lee SK. The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. PLoS ONE. 2014;9(11):e112558. https://doi.org/10.1371/journal.pone.0112558.
61. Koulouridis I, Alfayez M, Tighiouart H, Madias NE, Kent DM, Paulus JK, et al. Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case-control study. Am J Kidney Dis. 2013;62(4):730–7. https://doi.org/10.1053/j.ajkd.2013.02.373.
62. Gragossian A, Bashir K, Friede R. Hypomagnesemia. StatPearls. Treasure Island (FL). 2020.
63. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med. 2011;124(6):519–26. https://doi.org/10.1016/j.amjmed.2011.01.007.
64. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947–53. https://doi.org/10.1001/jama.296.24.2947.
65. US Food and Drug Administration (FDA). FDA Drug Safety Communication: ongoing review of Avandia (rosiglitazone) and cardiovascular safety. 2010. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-ongoing-review-avandia-rosiglitazone-and-cardiovascular-safety. Accessed 28 Aug 2019.
66. Pouwels KB, van Grootheest K. The rosiglitazone decision process at FDA and EMA. What should we learn? Int J

Risk Saf Med. 2012;24(2):73–80. https://doi.org/10.3233/JRS-2012-0559.
67. Nau R. Statistical forecasting: notes on regression and time series analysis. 2019. https://people.duke.edu/~rnau/411home.htm. Accessed 23 Aug 2019.
68. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–71. https://doi.org/10.1056/NEJMoa072761.
69. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007;298(10):1189–95. https://doi.org/10.1001/jama.298.10.1189.
70. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170(14):1191–201. https://doi.org/10.1001/archinternmed.2010.207.
71. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2008;10(12):1221–38. https://doi.org/10.1111/j.1463-1326.2008.00892.x.
72. Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013;166(2):240–9 e1. https://doi.org/10.1016/j.ahj.2013.05.004.
73. Pladevall M, Riera-Guardia N, Margulis AV, Varas-Lorenzo C, Calingaert B, Perez-Gutthann S. Cardiovascular risk associated with the use of glitazones, metformin and sufonylureas: meta-analysis of published observational studies. BMC Cardiovasc Disord. 2016;16:14. https://doi.org/10.1186/s12872-016-0187-5.
74. StatLine. Internet; toegang, gebruik en faciliteiten. 2019. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83429NED/table?dl=2F8AA. Accessed 9 Mar 2020.
75. Herdeiro MT, Soares S, Silva T, Roque F, Figueiras A. Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a countrywide study in Portugal. Fundam Clin Pharmacol. 2016;30(5):440–9. https://doi.org/10.1111/fcp.12207.
76. Ruiter R, Visser LE, van Herk-Sukel MP, Geelhoed-Duijvestijn PH, de Bie S, Straus SM, et al. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. Drug Saf. 2012;35(6):471–80. https://doi.org/10.2165/11596950-000000000-00000.
77. Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. BMJ. 2014;348:g3596.
78. Weatherburn CJ, Guthrie B, Dreischulte T, Morales DR. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: systematic review, time series analysis and meta-analysis. Br J Clin Pharmacol. 2020;86(4):698–710. https://doi.org/10.1111/bcp.14104.
79. Briesacher BA, Soumerai SB, Zhang F, Toh S, Andrade SE, Wagner JL, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. Pharmacoepidemiol Drug Saf. 2013;22(9):986–94.
80. Hawton K, Bergen H, Simkin S, Dodd S, Pocock P, Bernal W, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ. 2013;346:f403. https://doi.org/10.1136/bmj.f403.