

# Evaluating the Effectiveness of an Additional Risk Minimization Measure to Reduce the Risk of Prescribing Mirabegron to Patients with Severe Uncontrolled Hypertension in Four European Countries

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**Background:** Mirabegron, indicated for the treatment of overactive bladder, is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure  $\geq 180$  mm Hg and/or diastolic blood pressure  $\geq 110$  mm Hg). In September 2015, a Direct Healthcare Professional Communication (DHPC) letter was disseminated as an additional risk minimisation measure.

**Purpose:** To assess the effectiveness of the DHPC in reducing the proportions of patients with severe or non-severe uncontrolled hypertension at mirabegron initiation.

**Methods:** An observational multi-database cohort study was undertaken using routinely collected healthcare data (December 2012–December 2016) from the PHARMO Database Network (Netherlands), SIDIAP database (Spain), CPRD (United Kingdom, UK) and national healthcare registers and electronic medical records from Finland. DHPC effectiveness was evaluated using interrupted time series analyses comparing trends and changes in monthly proportions of severe or non-severe uncontrolled hypertensive mirabegron initiations relative to the timing of the DHPC dissemination.

**Results:** The study population comprised 52,078 patients. Prior to DHPC dissemination, across the four databases, 0.3–1.3% had severe uncontrolled hypertension. Estimated absolute changes (EAC) in proportions of severe uncontrolled hypertension post-DHPC indicated a tendency towards a lower proportion in the Netherlands (EAC  $-0.36\%$ ,  $p=0.053$ ), unchanged proportions in Spain and the UK and a higher proportion in Finland (EAC  $+0.73\%$ ,  $p=0.016$ ). For non-severe uncontrolled hypertension (13–16% pre-DHPC), post-DHPC proportions tended to be lower in the Netherlands (EAC  $-2.02\%$ ,  $p=0.038$ ) and Spain (EAC  $-1.04\%$ ,  $p=0.071$ ), and unchanged in the UK and Finland.

**Conclusion:** Severe uncontrolled hypertension prior to mirabegron initiation was uncommon in these four European countries even before DHPC dissemination. This suggests that other risk minimisation communications (prior to the DHPC dissemination) had worked adequately with respect to minimising mirabegron use among patients with severe uncontrolled hypertension. No strong and consistent evidence of further risk minimisation after the DHPC dissemination was observed in this study.

**Keywords:** drug utilisation study, direct healthcare professional communication, risk minimization, interrupted time series analysis

## Introduction

Mirabegron was introduced into the European market in 2012 for the treatment of overactive bladder. Although tolerability of mirabegron is generally acceptable with regard to side effects, including dry mouth, blurred vision, cognitive impairment and constipation,<sup>1,2</sup> there have been concerns regarding a possible increase in blood pressure. This resulted in a contraindication in the product label of mirabegron<sup>3</sup> for patients with severe uncontrolled high blood pressure (systolic  $\geq 180$  mm Hg and/or diastolic  $\geq 110$  mm Hg). In line with a request from the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee, a Direct Healthcare Professional Communication (DHPC) was disseminated on 7 September 2015 as a further risk minimisation activity. In accordance with the EMA Committee for Medicinal Products for Human Use guideline on good pharmacovigilance practices Module IX,<sup>4</sup> an effectiveness evaluation of this risk minimisation activity was performed in the form of a retrospective database study in four European countries.

The primary objective of the study was to assess the effectiveness of the DHPC as a risk minimisation measure in the participating countries by quantifying the proportions of mirabegron initiations with documented uncontrolled hypertension (severe and non-severe) before and after DHPC dissemination. The secondary objective was to assess the frequency of blood pressure recordings before and during mirabegron treatment among patients with documented hypertension before and after DHPC dissemination. In addition, methodological considerations for evaluation of the effectiveness of risk minimisation activities are discussed.

## Methods

The protocol for this study is available on the EU PAS Register under Number EUPAS15063.<sup>5</sup>

## Data Sources

Healthcare records from the PHARMO Database Network in the Netherlands, the SIDIAP database in Spain, the CPRD in the United Kingdom and all inhabitants of the capital region (cities of Helsinki, Espoo and Vantaa) in Finland were used. In Finland, data sources included the nationwide electronic e-Prescription Register (drug exposure data), Care Register for Health Care (in- and outpatient hospital care data), Register of Primary Health Care Visits (primary care data), Population Register

Centre (place of residence, migration information) and Causes of Death Registry (time of death).

Overactive bladder management primarily takes place in the primary care setting. General Practice (GP) records were used to collect hypertension and blood pressure information in all countries. Mirabegron use was based on GP prescriptions in the UK. In the Netherlands, Spain and Finland, mirabegron use was based on both GP prescribed and specialist prescribed mirabegron dispensed from outpatient pharmacies. Hereafter, both are referred to as "prescriptions".

## Study Design and Population

A multi-country post-authorisation safety study (PASS) was conducted,<sup>5</sup> using an observational retrospective study design. Patients starting mirabegron use (ATC G04BD12) between 20 December 2012 (first authorisation) and 31 December 2016 (end of data availability) were included. The index date was defined as the start of mirabegron treatment, after at least 12 months of recorded database history without mirabegron use. Patients aged  $<18$  years at index date were excluded. Patients were followed from 12 months before index date until the earliest of 1) end of mirabegron treatment (see below), 2) transfer out of the database (death or end of database follow-up/censoring) or 3) 31 December 2016.

## Mirabegron Exposure

Prescriptions of mirabegron from index date until the end of database follow-up were converted into treatment episodes of uninterrupted use. The number and dose of tablets prescribed divided by the prescribed daily dose (or, if not available, the number of doses reflecting 1 defined daily dose of 50 mg (1 tablet)<sup>6</sup>) were used to determine the duration of a prescription. Gaps between prescriptions of more than half the duration of the prior prescription were considered interruptions of treatment, according to the method described by Catalan.<sup>7</sup> The end date of total mirabegron treatment was defined as the end date of an episode after which no mirabegron exposure was observed for at least 12 months. For the secondary objective, all BP measurements up to the end of total mirabegron treatment were included. Patients who re-started mirabegron use after at least 12 months of non-use were included multiple times as independent initiations for both objectives.

## Hypertension Status Definitions

Information on hypertension diagnosis, antihypertensive treatment and the last recorded BP during the 6 months before the index date was combined to assign patients to five hypertension statuses: 1) Severe uncontrolled

hypertension: systolic BP (SBP)  $\geq 180$  mm Hg and/or diastolic BP (DBP)  $\geq 110$  mm Hg, 2) non-severe uncontrolled hypertension:  $140 \leq SBP < 180$  mm Hg and/or  $90 \leq DBP < 110$  mm Hg, 3) controlled hypertension: SBP  $< 140$  mm Hg and DBP  $< 90$  mm Hg during treatment for hypertension, 4) normal BP: SBP  $< 140$  mm Hg and DBP  $< 90$  mm Hg in the absence of treatment for hypertension, or no BP measurements and no diagnosis or treatment for hypertension, and 5) unconfirmed hypertension status: diagnosis or treatment for hypertension but no BP value, or a single measurement indicating elevated DBP and/or SBP in the absence of a diagnosis or treatment for hypertension.

For severe and non-severe uncontrolled hypertension, confirmation was needed by a second measurement in the same range, or a diagnosis or treatment for hypertension. In the absence of both a BP value and diagnosis of hypertension, the use of at least two classes of antihypertensive drugs was required to qualify as antihypertensive treatment.

The reference values for hypertension were based on the European product information,<sup>3</sup> local guidelines<sup>8-10</sup> and instructions for use<sup>11</sup> and were the same across participating countries.

## Study Endpoints

The primary endpoint was the change in the proportion of patients with severe uncontrolled hypertension among patients initiated on mirabegron from pre- to post-DHPC dissemination. The proportion with non-severe uncontrolled hypertension was included as a separate outcome in order to provide additional context. Secondary endpoints were the change in frequency of blood pressure recordings at initiation and during mirabegron treatment relative to DHPC dissemination.

## Statistical Analysis

All data were structured to a study-specific common data model in order to apply identical SAS analytical programs across databases. All analyses were done using SAS version 9.4 under Windows (SAS Institute Inc., Cary, NC, USA).

To estimate absolute changes in the proportion of patients with severe and non-severe uncontrolled hypertension after the dissemination of the DHPC, an interrupted time series (ITS) analysis was conducted.<sup>12,13</sup> A segmented regression model analysed monthly proportions of severe and non-severe uncontrolled hypertension pre-DHPC and post-DHPC. The pre-DHPC period spanned from the first month in which counts of mirabegron users allowed estimation of the proportions per blood pressure status, up to the intervention

month (September 2015). September 2015 was excluded from the analysis. The post-DHPC period ended at the end of data availability in December 2016 (Figure 1).

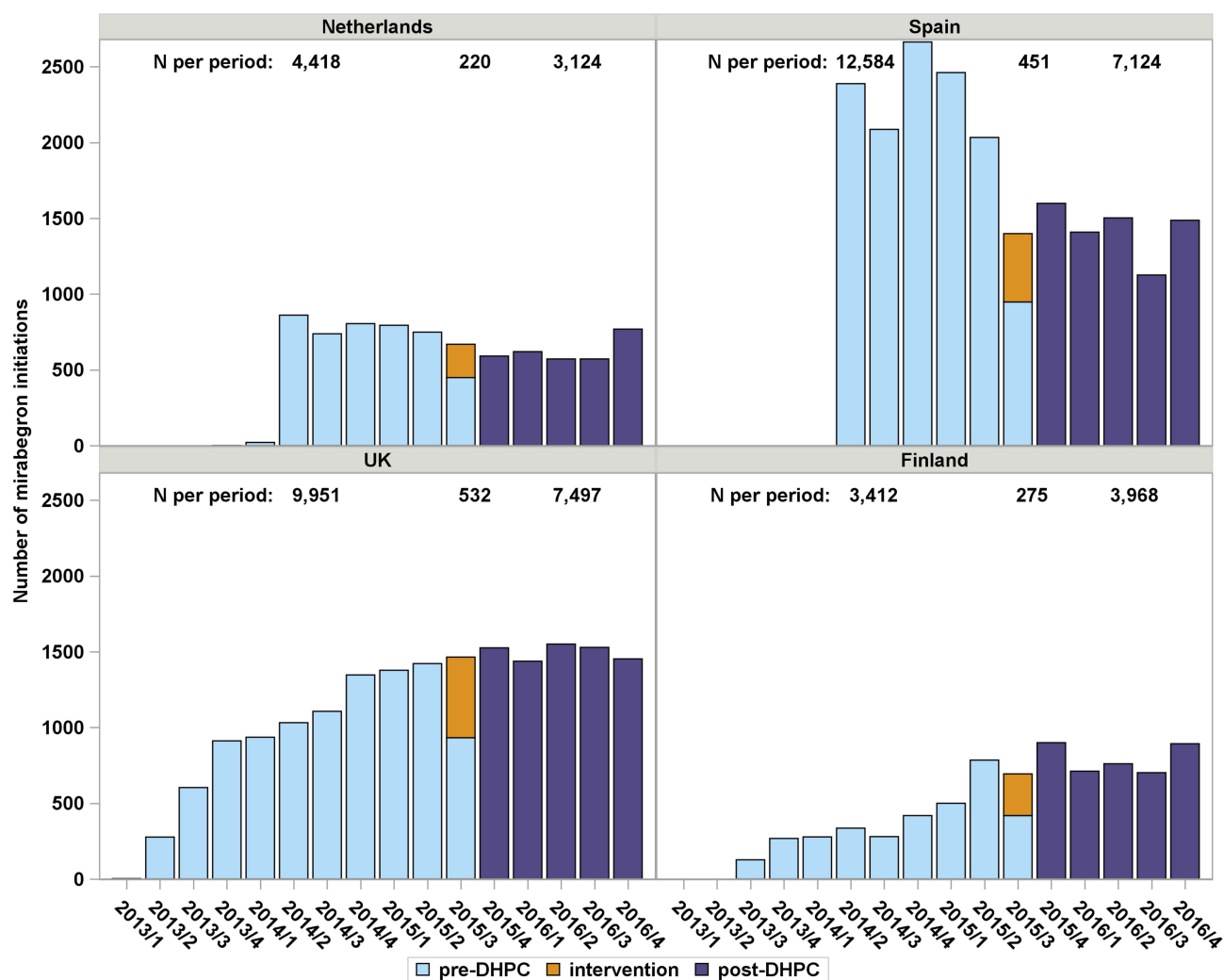
Three statistical models were fit to the data. Model one was the most extensive and included the change in level of the proportion from before to after DHPC dissemination, a trend (i.e. a slope indicating increase or decrease over time), and a change in trend after DHPC. Model two included only the change in level and an unchanged trend. Model three included only the change in level, but no trend. The best-fitting model was chosen based on the lowest AIC (Akaike Information Criterion), BIC (Bayesian Information Criterion) and statistical significance of the variables. The Durbin-Watson statistic was used to assess potential autocorrelation influencing the precision of the estimates.<sup>14</sup> Predicted proportions were calculated based on estimates from the best fit model. Pre-DHPC predicted values were projected in the post-DHPC period to produce counterfactual values (assuming no change in level and trend had occurred). The estimated absolute change (EAC) was calculated mid-period post-DHPC as the difference between counterfactual projected values and predicted values based on the best fit model.<sup>14,15</sup> The observed monthly proportions, together with predicted proportions and counterfactual proportions are represented graphically for both severe and non-severe hypertension (Figure 2).

Rates of BP measurements per person-quarter (3 month period) during mirabegron use were compared descriptively pre- and post-DHPC, overall and separately for patients with documented hypertension (controlled or uncontrolled).

## Results

Of 55,716 mirabegron users across all countries, 4% had insufficient database history prior to mirabegron initiation to be included in the study, leaving 53,559: 7762 from the Netherlands (276 (3%) excluded), 20,159 from Spain (38 (0.2%) excluded), 17,980 from the UK (1684 (9%) excluded) and 7655 from Finland (159 (2%) excluded). In each country, a small proportion of the patients were included with multiple treatment initiations: 108 (1.4%) in the Netherlands, 363 (1.8%) in Spain, 323 (1.8%) in the UK and 205 (2.7%) in Finland.

In Finland and the UK, uptake of mirabegron started in 2013, soon after market authorisation, and numbers of patients initiating treatment increased gradually up to the fourth quarter of 2015, after which uptake levelled off (Figure 1). In the Netherlands and Spain, uptake started only in 2014 after reimbursement was approved; numbers initiating treatment were relatively high and constant for



**Figure 1** Number of mirabegron initiations per quarter year between January 2013 and December 2016 per country. Total number of initiations are shown for the pre-DHPC period, the DHPC intervention month (September 2015), and for the post-DHPC period.

the first year, and then slightly decreased until the fourth quarter of 2015, after which numbers levelled off.

Patients starting mirabegron in the intervention month of September 2015 were excluded from the analyses (220 in the Netherlands, 451 in Spain, 532 in the UK and 275 in Finland), leaving 52,078 patients.

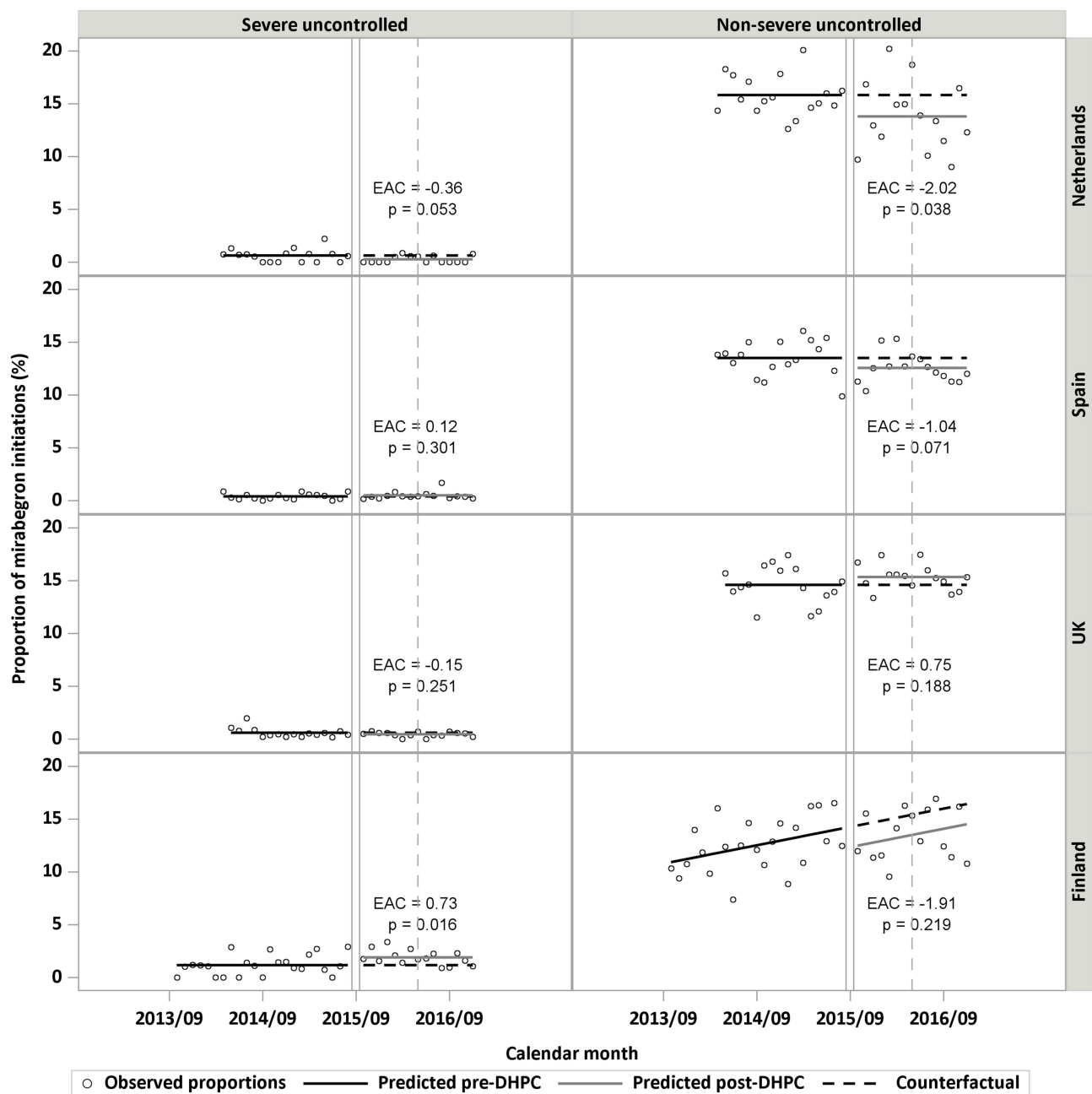
Patient characteristics (Table 1) did not differ appreciably between the pre- and post-DHPC periods within each country, but tended to vary across countries. Mean age varied from 66 years in the Netherlands to 71 in Finland. Patients in Finland had more cardiovascular comorbidities.

Analyses of characteristics stratified by hypertension status are available in [Supplemental Table 1](#) online; the main findings are summarized below. In all countries, the normotensive patients were on average 12–14 years younger than

hypertensive patients. The proportion of men was around 35% in the UK and Finland, irrespective of hypertension status. In the Netherlands and Spain, the proportion of men was approximately 35% among normotensive patients and 50% among hypertensive patients. In all countries, diabetes was less common among normotensive patients (5–10%) than among hypertensive patients with documented blood pressure (approximately 25–35%) or among hypertensive patients without documented BP (10–20%). Similarly, cardiovascular comorbidities were more frequent among hypertensive patients than normotensive patients.

## Interrupted Time Series Analysis

No autocorrelation was detected in any of the models assessing changes over time in the proportion of patients



**Figure 2** Observed, predicted and counterfactual proportions of patients with severe or non-severe uncontrolled hypertension at mirabegron initiation, by country. EAC = Estimated absolute change, i.e. projected counterfactual proportion – predicted proportion based on the best fit model at mid-point of post-DHPC period (denoted with dashed vertical lines). The DHPC intervention month is denoted with solid vertical lines.

with severe or non-severe uncontrolled hypertension. The proportion of patients with severe uncontrolled hypertension was low in all databases, both before and after DHPC dissemination (Table 2). In some months, there were no patients with severe uncontrolled hypertension among mirabegron initiations (Figure 2). The best fit model was that without time trends (model three) in all countries. In the Netherlands, there was

a tendency towards a lower proportion of patients with severe uncontrolled hypertension post-DHPC (0.61% pre-DHPC, EAC:  $-0.36\%$  ( $p=0.053$ )). In Spain and the UK, pre- and post-DHPC proportions with severe uncontrolled hypertension were similar. In Finland, there was a small increase in the proportion of patients with severe uncontrolled hypertension (1.29% pre-DHPC, EAC:  $+0.73\%$  ( $p=0.016$ )).

**Table 1** Patient Characteristics

	Netherlands		Spain		UK		Finland	
	Pre-DHPC N = 4,418 n (%)	Post-DHPC N = 3,124 n (%)	Pre-DHPC N = 12,584 n (%)	Post-DHPC N = 7,124 n (%)	Pre-DHPC N = 9,951 n (%)	Post-DHPC N = 7,497 n (%)	Pre-DHPC N = 3,412 n (%)	Post-DHPC N = 3,968 n (%)
Age, mean ± SD	66 ± 15	66 ± 15	69 ± 13	69 ± 13	65 ± 15	67 ± 15	71 ± 14	70 ± 14
Gender, Male	1,912 (43)	1,420 (45)	5,498 (44)	3,168 (44)	3,071 (31)	2,625 (35)	1,129 (33)	1,343 (34)
Hypertension status								
Severe uncontrolled hypertension	27 (0.6)	8 (0.3)	42 (0.3)	30 (0.4)	46 (0.5)	33 (0.4)	44 (1.3)	74 (1.9)
Non-severe uncontrolled hypertension	700 (16)	431 (14)	1,578 (13)	811 (11)	1,488 (15)	1,173 (16)	442 (13)	534 (13)
Controlled hypertension	545 (12)	423 (14)	3,477 (28)	1,921 (27)	2,235 (22)	1,762 (24)	333 (10)	388 (10)
Normal blood pressure	1,836 (42)	1,274 (41)	4,623 (37)	2,686 (38)	4,202 (42)	2,971 (40)	1,190 (35)	1,325 (33)
Unconfirmed hypertension status	1,310 (30)	988 (32)	2,864 (23)	1,676 (24)	1,980 (20)	1,558 (21)	1,403 (41)	1,647 (42)
Comorbid conditions								
Acute myocardial infarction (MI) <sup>a</sup>	90 (2)	76 (2)	314 (2)	179 (3)	63 (1)	87 (1)	143 (4)	158 (4)
Ischemic heart diseases (excl. MI) <sup>a</sup>	208 (5)	158 (5)	911 (7)	506 (7)	320 (3)	360 (5)	517 (15)	647 (16)
Cardiac arrhythmias <sup>a</sup>	232 (5)	181 (6)	1,093 (9)	694 (10)	281 (3)	384 (5)	673 (20)	842 (21)
Congestive heart failure <sup>a</sup>	104 (2)	75 (2)	414 (3)	249 (3)	118 (1)	139 (2)	212 (6)	258 (7)
Cerebrovascular events <sup>a</sup>	267 (6)	204 (7)	1,209 (10)	699 (10)	489 (5)	542 (7)	558 (16)	587 (15)
Peripheral artery disease (PAD) <sup>a</sup>	170 (4)	124 (4)	552 (4)	330 (5)	80 (1)	87 (1)	164 (5)	196 (5)
Chronic kidney disease (CKD) <sup>a</sup>	230 (5)	209 (7)	965 (8)	615 (9)	682 (7)	666 (9)	79 (2)	101 (3)
Diabetes <sup>ab</sup>	598 (14)	409 (13)	2,692 (21)	1,483 (21)	1,486 (15)	1,276 (17)	566 (17)	770 (19)
Hyperlipidaemia <sup>ab</sup>	1,491 (34)	1,054 (34)	5,413 (43)	2,897 (41)	3,632 (36)	2,931 (39)	1,099 (32)	1,495 (38)
Chronic respiratory disease <sup>ab</sup>	664 (15)	490 (16)	1,867 (15)	989 (14)	2,173 (22)	1,557 (21)	422 (12)	564 (14)

Notes: <sup>a</sup>Any time before starting mirabegron; <sup>b</sup>based on treatment or diagnosis.

There were larger proportions of patients with non-severe uncontrolled hypertension. A slightly lower proportion of patients with non-severe uncontrolled hypertension was observed post-DHPC in the Netherlands (15.84% pre-DHPC, EAC:  $-2.02$  ( $p=0.038$ )). No trends over time were observed in the proportion of non-severe uncontrolled hypertension in the Netherlands, Spain or UK (model three provided the best fit, Table 2 and Figure 2). In Spain, a tendency towards a decrease in the proportion was observed post-DHPC dissemination (12.54% pre-DHPC, EAC:  $-1.04\%$  ( $p=0.071$ )). In the UK, no substantial change was observed. A trend of 0.14% increase per month ( $p=0.034$ ) was observed in the Finnish data, which persisted after the intervention (model two). This was off-set by a small overall decrease in the proportion of non-severe uncontrolled hypertension post-DHPC (EAC:  $-1.91\%$  ( $p=0.219$ ), see Figure 2).

## Blood Pressure Monitoring

The proportions of the study population with recorded BP measurements were similar pre- and post-DHPC dissemination in all databases: 40% and 39% in the Netherlands, 57% and 55% in Spain, 57% and 60% in the UK, and 33% and 34% in Finland (Table 3). By definition, all patients with documented hypertension (controlled or uncontrolled, excluding unconfirmed status) had a recorded BP measurement prior to index date. Pre-DHPC, person-time for calculation of BP measurement rates was censored in September 2015. During mirabegron treatment, the frequency of BP measurements was greater among the population with documented hypertension than in the overall study population; no clinically relevant change was observed after DHPC dissemination.

**Table 2** Proportion of Mirabegron Initiations with Severe and Non-Severe Uncontrolled Hypertension Relative to DHPC Dissemination

		Netherlands	Spain	UK	Finland
Severe uncontrolled hypertension	Pre-DHPC % (95% CI)	0.61 (0.40–0.89)	0.33 (0.24–0.45)	0.46 (0.34–0.62)	1.29 (0.94–1.73)
	Post-DHPC % (95% CI)	0.26 (0.11–0.50)	0.42 (0.28–0.60)	0.44 (0.30–0.62)	1.86 (1.47–2.34)
	Estimated absolute % change <sup>a</sup>	−0.36 ( <i>p</i> =0.053)	0.12 ( <i>p</i> =0.301)	−0.15 ( <i>p</i> =0.251)	0.73 ( <i>p</i> =0.016)
Non-severe uncontrolled hypertension	Pre-DHPC % (95% CI)	15.84 (14.78–16.95)	12.54 (11.97–13.13)	14.95 (14.26–15.67)	12.95 (11.84–14.13)
	Post-DHPC % (95% CI)	13.80 (12.61–15.06)	11.38 (10.66–12.14)	15.65 (14.83–16.49)	13.46 (12.41–14.56)
	Estimated absolute % change <sup>a</sup>	−2.02 ( <i>p</i> =0.038)	−1.04 ( <i>p</i> =0.071)	0.75 ( <i>p</i> =0.188)	−1.91 ( <i>p</i> =0.219) <sup>p</sup>

**Notes:** <sup>a</sup>Estimated absolute change is calculated as the projected counterfactual proportion – predicted proportion based on the best fit model at the mid-point of post-DHPC period (as indicated in Figure 2). <sup>b</sup>*p*-value pertains to change in level; time trend was retained in the model with *p*=0.034

**Abbreviations:** BP, blood pressure; IQR, interquartile range.

**Table 3** Frequency of Blood Pressure Recordings Before and During Mirabegron Treatment

	Netherlands		Spain		UK		Finland	
	Pre-DHPC	Post-DHPC	Pre-DHPC	Post-DHPC	Pre-DHPC	Post-DHPC	Pre-DHPC	Post-DHPC
All mirabegron initiations	N = 4,418	N = 3,124	N = 12,584	N = 7,124	N = 9,951	N = 7,497	N = 3,412	N = 3,968
n (%) with BP record before initiation	1,747 (40)	1,228 (39)	7,135 (57)	3,909 (55)	5,720 (57)	4,505 (60)	1,133 (33)	1,331 (34)
Duration (months) of total mirabegron treatment <sup>a</sup> , median (IQR)	5 (1–17)	2 (1–6)	8 (2–21)	3 (1–8)	10 (2–23)	4 (1–9)	8 (1–20)	3 (1–7)
Number of BP records per person-quarter year of treatment, median (IQR)	0.0 (0.0–0.4)	0.0 (0.0–0.4)	0.0 (0.0–0.9)	0.0 (0.0–0.9)	0.0 (0.0–0.6)	0.0 (0.0–0.7)	0.0 (0.0–0.2)	0.0 (0.0–0.2)
Documented hypertension at mirabegron initiation <sup>b</sup>	N = 1,272	N = 862	N = 5,097	N = 2,762	N = 3,769	N = 2,968	N = 819	N = 996
Duration (months) of total mirabegron treatment <sup>a</sup> , median (IQR)	6 (1–18)	2 (1–6)	10 (3–22)	3 (1–8)	11 (3–23)	4 (1–8)	9 (3–19)	4 (1–8)
Number of BP records/per person-quarter year of treatment, median (IQR)	0.4 (0.0–1.1)	0.3 (0.0–1.3)	0.5 (0.0–1.2)	0.4 (0.0–1.2)	0.4 (0.0–0.9)	0.4 (0.0–1.1)	0.0 (0.0–2.3)	0.0 (0.0–2.4)

**Notes:** <sup>a</sup>Mirabegron treatment including gaps < 12 months. <sup>b</sup>Excluding hypertension with unconfirmed blood pressure; Pre-DHPC person time was censored at DHPC dissemination date.

**Abbreviations:** BP, blood pressure; IQR, interquartile range.

## Discussion

The proportion of patients with severe uncontrolled hypertension initiated on mirabegron was low in all countries even before DHPC dissemination (0.33% - 1.29%). This was reassuring and may reflect the impact of the contra-indication specified in the summary of product characteristics (SmPC) since the launch of mirabegron. However, in the context of this study, these low proportions did not allow for substantial additional reductions (given the resulting floor effect). Nevertheless, in the Netherlands, a small non-significant absolute reduction was observed after DHPC dissemination (−0.36%; *p*=0.053). In Finland, there

was a small increase in the proportion (+0.73%, *p*=0.016) despite reiterating the contra-indication in the DHPC.

Pre-DHPC proportions for non-severe uncontrolled hypertension were considerably larger (13% - 16%) than those for severe uncontrolled hypertension. Reductions post-DHPC dissemination were observed in the Netherlands (−2.02%, *p*=0.038) and to a lesser extent Spain (−1.04%, *p*=0.071). In Finland, a small trend towards more non-severe uncontrolled hypertension persisted after DHPC dissemination, but this was somewhat counter-balanced by a drop in the level directly after DHPC dissemination.

With regard to the secondary endpoint of BP monitoring, we observed no increase post-DHPC in the rate of screening for severe uncontrolled hypertension prior to initiation of mirabegron, nor did we observe increased monitoring of BP during mirabegron treatment.

Data for the Vantaa region in Finland only became available after the initial study report was posted,<sup>5</sup> but conclusions remained unchanged.

No comparable published data are available to provide context for the results of this study. In this study, we faced multiple challenges. First, we needed to identify data sources across Europe in which mirabegron was widely used, BP readings were comprehensively captured and researchers were permitted to access the records. We identified four data sources, all of which were included in the final study.

Secondly, the ITS method using segmented regression analysis is a tool recognised for its ability to assess changes associated with health-care policies or risk minimisation measures, but it requires at least 10 data points prior to and after the intervention.<sup>14</sup> The limited time between market authorisation of mirabegron and the timing of the DHPC therefore necessitated the use of monthly (rather than longer) time intervals. Limited sample sizes per month increased variability and thus uncertainty around the parameter estimates in the segmented regression models, limiting the power to detect changes.<sup>16</sup> Interestingly, we did not observe changes in the UK and Spain, the databases with the larger sample sizes.

Thirdly, incomplete BP recordings in general practice may have led to information bias. Generally, patients with more healthcare encounters and/or chronic diseases are more likely to have their BP measured and recorded.<sup>17–20</sup> The incomplete information on blood pressure values in the electronic healthcare records in our study was consistent with other reports.<sup>21–24</sup> All four countries included in this study have guidelines recommending regular blood pressure measurements for chronic diseases such as diabetes and cardiovascular disease.<sup>9,10,22,25</sup> The Netherlands,<sup>26</sup> the UK<sup>27</sup> and Spain,<sup>28</sup> but not Finland, use monitoring of risk factors such as BP as indicators to monitor the quality of care for chronic diseases. This is consistent with the observed higher proportion of patients without recorded blood pressure measurements in Finland. The 40–60% lower proportion of diabetes patients among patients with unconfirmed hypertension status compared to those with documented hypertension ([Supplemental Table 1](#)) is also consistent with more frequent BP recording among patients with chronic disease. Among

normotensive patients or patients without chronic diseases, BP measurements may not be assessed as often, or may simply be recorded in inaccessible plain text fields in the electronic health records, rather than accessible fields used for the purpose of assessing the quality of care. In this study, patients without recorded BP, hypertension diagnosis or anti-hypertensive treatment were therefore assumed to be normotensive. This may have led to the potential misclassification of patients with unconfirmed hypertension to the group of normotensive patients. This does not impact our study findings, as these are based on patients with documented hypertension.

Fourthly, in order to detect a change in BP monitoring intensity during treatment, regular check-ups are required, but the duration of treatment is often limited. More than 50% of patients have been reported to have stopped treatment after 1 month<sup>29</sup> or after the first prescription<sup>30</sup> (i.e. non-persistence), and after 1 year the supplied amount of mirabegron has been reported to cover <60% of the period.<sup>29</sup> Alleviation of symptoms is a factor in non-persistence with treatment for overactive bladder, and intermittent treatment is often observed.<sup>29,30</sup> Therefore, we allowed mirabegron treatment to contain gaps of up to 12 months, with the aim of ensuring that duration of treatment was long enough to allow comparison of quarterly BP monitoring rates before and after DHPC dissemination. Multiple post-hoc sensitivity analyses with different periods of follow-up, including as short as 1 month, were performed to assess the impact on results, but none of the analyses yielded a difference in BP monitoring rates before and after the DHPC.<sup>5</sup>

Fifthly, up to March 2015, reimbursement of mirabegron in Finland was limited to patients who did not tolerate anticholinergic drugs. The time between March and September 2015 was too short to allow sensitivity analyses to assess if potential changes in patient characteristics since then may have impacted any conclusions.

Finally, because of the floor effect for the primary outcome of severe uncontrolled hypertension, and our approach to extend analyses to non-severe uncontrolled hypertension, our analysis did not only evaluate the outcome for which the additional risk minimisation measure was intended, and therefore conclusions related to this extended analysis need to be interpreted with caution. The floor effect for severe uncontrolled hypertension does raise the question whether studies to assess the effectiveness of risk minimisation measures should require certain conditions to be met (such as a minimum frequency of a contra-

indication), before committing to ITS analyses. Power calculation methods for ITS analyses have only become available after finalisation of our study.<sup>16</sup> However, these require estimates of the cumulative incidence of the outcome in the population being studied, which may only become available during execution of the study, as was the case in our study, or via a feasibility study.

Despite these uncertainties, many of which are common in studies using routinely collected healthcare data, we were able to incorporate large patient cohorts from four different countries into a study that offered the opportunity to evaluate the impact of the DHPC. The use of a common data model, and common programs ensuring identical analyses in each of the databases, made results across countries more comparable. The similarities in recorded population characteristics in the different countries were reassuring.

## Conclusion

The use of mirabegron by patients with severe uncontrolled hypertension was uncommon in our study even pre-DHPC dissemination, as reflected by the low prevalence in the population. This suggests that other risk minimisation communications (prior to the DHPC dissemination), such as the SmPC, may have generally worked with respect to minimising this particular potential risk. No strong or consistent evidence of further risk minimisation after the DHPC dissemination was observed in this study. Also, no evidence of increased monitoring of blood pressure in hypertensive patients was observed post-DHPC dissemination.

## Abbreviations

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BP, Blood pressure; DBP, Diastolic blood pressure; DHPC, Direct Healthcare Professional Communication; EAC, Estimated absolute change; EMA, European Medicines Agency; GP, General Practice; SBP, Systolic blood pressure; SD, Standard deviation; SmPC, Summary of product characteristics; UK, United Kingdom.

## Data Sharing Statement

The data used for this study were used under license for the current study, and so are not publicly available. The data can however be made available from each of the contributing database partners, upon reasonable request and with permission obtained through required ethics applications and applications to each data holder.

## Ethics and Consent Statement

No ethics approval is required for use of anonymized data from the PHARMO Database Network. Scientific approval was obtained from the SIDIAP Scientific Committee and ethical approval was granted by CEIC Idiap Jordi Gol (reference number P17/019). CPRD obtains annual research ethics approval from the UK's Health Research Authority (HRA) Research Ethics Committee (REC) (East Midlands – Derby, REC reference number 05/MRE04/87) for observational studies using CPRD data for public health research. In Finland, the study protocol was approved by the Coordinating Ethical Review Board of Helsinki University Hospital (Dnro HUS/618/2017). Patient informed consent was not required in any database as only anonymised retrospective data were used for this study.

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## Disclosure

Edith M. Heintjes, Irene D. Bezemer, Elisabeth Smits and Fernie J.A. Penning-van Beest performed this work as employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and pharmaceutical companies. Daniel Prieto-Alhambra leads the Pharmaco- and Device Epidemiology research group at the Centre for Statistics in Medicine, Oxford University. Daniel Prieto-Alhambra also reports that Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums, and Synapse

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