Characterization of new users of cilostazol in the UK, Spain, Sweden, and Germany

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ABSTRACT

Purpose To describe the characteristics of new users of cilostazol in Europe with the aim to support the evaluation of its benefit/risk as used in regular clinical practice before the implementation of labeling changes recommended by the European Medicines Agency.

Methods New users of cilostazol were identified in populations enrolled in five European health automated databases in the UK (The Health Improvement Network [THIN]), Spain (EpiChron cohort and Information System for the Improvement of Research in Primary Care [SIDIAP]), Sweden (National Registers), and Germany (German Pharmacoepidemiological Research Database [GePaRD]) between 2002 and 2012. New users were characterized according to the prevalence of cardiovascular disease and other comorbidities, concurrent use of interacting medications, new contraindications, duration of use, and potential off-label prescribing.

Results We identified 22,593 new users of cilostazol. The median age was between 68.0 (THIN) and 73.7 (Sweden) years. More than 78% of users had comorbid cardiovascular disease, and between 78.8% (GePaRD) and 91.6% (THIN) were treated with interacting medications. Prevalence of new cardiovascular contraindications ranged from 1.5% (THIN) to 11.6% (GePaRD), and concurrent use of two or more antiplatelet drugs ranged from 6.3% (SIDIAP) to 13.5% (EpiChron cohort). Between 39.4% (Sweden) and 52.9% (THIN) of users discontinued cilostazol in the first 3 months. Between 41.0% (SIDIAP) and 93.4% (THIN) were considered to have received cilostazol according to the European Medicines Agency labeling.

Conclusions In this collaborative European study, most cilostazol users were elderly patients with a high prevalence of cardiovascular diseases and other comorbidity and concurrent use of interacting drugs, indicating that this is a vulnerable population at high risk of complications, especially cardiovascular events. © 2017 The Authors.

KEY WORDS cilostazol; intermittent claudication; drug utilization study; database study; pharmacoepidemiology; peripheral artery disease

INTRODUCTION

Cilostazol is a platelet aggregation inhibitor approved in Europe in 2002 to improve walking distances in patients with intermittent claudication. Cilostazol has been associated with spontaneous reports of cardiovascular adverse effects (heart attacks, angina, and arrhythmias) and serious bleeding. The European Medicines Agency (EMA) evaluated the benefits and risks of cilostazol in a referral and recommended labeling changes to include contraindications to patients with unstable angina pectoris, recent myocardial infarction, or recent coronary intervention (Table 1). The EMA also required a drug utilization study to support the benefit–risk evaluation of cilostazol before the implementation of labeling changes, which were introduced in 2013.

We present results of the drug utilization study conducted in the UK, Spain, Sweden, and Germany by using information from automated health...
databases. The main objectives were to describe the characteristics of new users of cilostazol, including comorbidity and comedications, to assess potential off-label prescribing and conduct a baseline assessment of the labeling changes recommended by the EMA.

METHODS

Data sources

New users of cilostazol were identified in five databases: The Health Improvement Network (THIN), UK; the EpiChron cohort from Aragon Health Sciences Institute, Aragon, Spain; the Information System for the Improvement of Research in Primary Care (SIDIAP), Catalonia, Spain; the Swedish National Registers; and the German Pharmacoepidemiological Research Database (GePaRD). Main characteristics of the study databases are presented in Table S1.

Study population

The study included all new users of cilostazol identified in the study databases because the date cilostazol was available in each country before the implementation in 2013 of labeling changes requested by the EMA. New users were defined as patients who received a first-ever prescription of cilostazol during the study period and had at least 6 months of continuous enrollment in the study databases before this first prescription (start date). New users were followed from the start date until the earliest of end of enrollment in the database, death, or end of the study period.

Exposure definition

We defined exposure to cilostazol as the number of days’ supply calculated from the quantity prescribed and dosage instructions or from a descriptive analysis of the time between consecutive prescriptions. An interval of 7 days was added to days’ supply to allow for delay in the start of treatment and incomplete adherence. Continuous use of cilostazol was defined as the total number of days covered by consecutive prescriptions, with a maximum gap of 60 days between the end of days’ supply of one prescription and the start of the next prescription. In THIN and the EpiChron cohort, daily dose was calculated from strength of product, package quantity, and dosage instructions. In the EpiChron cohort, daily dose information was available for 1052 patients (26.1%). In Sweden and GePaRD, daily dose was calculated by assuming a twice-daily dosage. In SIDIAP, evaluation of daily dose was not conducted as information on dosage instructions was not available.

Characterization of users

New users of cilostazol were characterized at the start date according to age, sex, socioeconomic status, comorbidity and comedications, to assess potential off-label prescribing and conduct a baseline assessment of the labeling changes recommended by the EMA.

Baseline assessment of labeling changes

To assess the potential impact of the cilostazol labeling changes, we conducted a baseline assessment of the frequency of conditions included in the labeling recommended by the EMA (Table 1). Information on smoking was available in THIN, the EpiChron cohort, and SIDIAP. In Sweden, we evaluated smoking by using diagnosis codes for smoking-related disease
and use of smoking-cessation drugs. Information on smoking was not available in GePaRD. Monitoring of patients after 3 months was assessed by the number of patients who had at least one visit to a general practitioner (GP) or specialist (vascular surgery, cardiology, and diabetology) 2–4 months after the start date. In Sweden, evaluation of visits was restricted to the hospital setting. In GePaRD, diagnoses are recorded on a quarterly basis and visits were evaluated by the number of patients who had at least one diagnosis for intermittent claudication recorded in the 3 months following the quarter in which cilostazol was started. In THIN and SIDIAP, the reason for visits to GPs and specialists was assessed by clinically reviewing computerized information and free text for a random sample of 200 patients. Discontinuation of cilostazol after 3 months was evaluated for the first period of continuous use. New contraindications included in the revised label approved by the EMA were unstable angina pectoris, myocardial infarction or coronary intervention within 6 months before the start date, and concurrent use of cilostazol and two or more additional platelet aggregation inhibitors. Monitoring of patients at increased risk of serious cardiac events was evaluated by comparing rates of visits to GPs or specialists between patients with and without a history of arrhythmias, hypotension, or coronary heart disease. In GePaRD, monitoring was expressed as the number of diagnoses per patient-year of continuous use because only the first visit to the same physician is recorded during a quarter.

Potential off-label prescribing

In THIN and SIDIAP, potential off-label prescribing was evaluated through manual review of computerized clinical information and free text of a random sample of 200 patients. In other databases, indication was evaluated by using diagnostic codes and referrals. On-label prescribing was defined as any patient who had a recorded diagnosis of intermittent claudication or peripheral arterial disease recorded at any time before or after the start date or who had a referral to vascular surgery, cardiology, or diabetology within 1 month before and 1 month after the start date (28 days were used in Germany). In Germany, the period of ascertainment of diagnoses was the calendar quarter before and after the start date.

Analysis

The average annual prevalence of cilostazol use was calculated by using the age and sex distribution of the population in each database. The cumulative proportion of patients discontinuing cilostazol was calculated by using survival analysis. Rates of visits were calculated as the number of visits per 100 person-years of continuous use of cilostazol, except in GePaRD, where the number of diagnoses per patient-year was used. Crude incidence rate ratios and 95% confidence intervals were estimated to compare rates of visits between patients at high risk of cardiac complications and patients not at high risk.

At RTI Health Solutions (RTI-HS; THIN data), SIDIAP, Sweden, and GePaRD, analyses were conducted by using SAS version 9.3 or 9.4 (Cary, NC: SAS Institute Inc.). STATA v13.0 (StataCorp, 2013) was used in the EpiChron cohort. STATA v13.1 and R 3.1 (R Core Team, 2013) were also used in SIDIAP.

The protocol was approved by the EMA and posted in the EU PAS Register in March 2013 (EU PAS ID 3596).11

RESULTS

Prevalence and patterns of use

We included 22 593 new users of cilostazol. SIDIAP (Spain) contributed the largest proportion of users (44.9%; Table 2). The average annual prevalence of cilostazol use was higher in Spain than in the other countries. Between 52.3% (Sweden) and 77.3% (SIDIAP) of users were men. The median age ranged from 68.0 years in SIDIAP to 73.7 years in Sweden and was higher in women than in men in all study populations.

From 15.9% (SIDIAP) to 42.0% (Sweden) of users received only one prescription. Most users received a daily dose of 200 mg at the start date. The percentage of users discontinuing cilostazol in the first 6 months of treatment ranged from 50.4% in SIDIAP to 65.2% in Sweden. From 15.9% (SIDIAP) to 42.0% (Sweden) of users received only one prescription. Most users received a daily dose of 200 mg at the start date. The percentage of users discontinuing cilostazol in the first 6 months of treatment ranged from 50.4% in SIDIAP to 65.2% in Sweden. Information on socioeconomic status of new users of cilostazol is presented in Table S2.

Baseline comorbidity

Cardiovascular disease other than peripheral vascular disease was the most frequent comorbidity in all study populations, affecting 62.8% (Sweden) to 95.7% (GePaRD) of users (Table 3). The most frequent cardiovascular condition was hypertension, ranging from 46.8% (Sweden) to 86.0% of users (GePaRD). Between 20.4% (Sweden) and 75.3% (GePaRD) of users had a recorded diagnosis of hyperlipidemia, and 20.5% (Sweden) to 41.1% (GePaRD) had .
diagnosis of diabetes. Use of comediations at the start date was consistent with the prevalence of comorbidity (Table S3). The most frequent comediations were antihypertensive drugs (63.6 to 80.6% of users), platelet aggregation inhibitors (33.8 to 73.1%), lipid-modifying agents (45.8 to 68.6%), and proton pump inhibitors (22.4 to 60.9%).

Concurrent use of interacting medications
Between 78.8% (GePaRD) and 91.6% (THIN) of users were concurrently treated with interacting medications (Table S4). The most frequent interacting medications were simvastatin, atorvastatin, amlodipine, omeprazole, and clopidogrel. The percentages of users treated with potent CYP3A4 or CYP2C19 inhibitors were 2.7% (Sweden), 3.8% (GePaRD), 7.3% (SIDIAP), 10.2% (EpiChron cohort), and 22.3% (THIN). Between 26.9% (GePaRD) and 69.0% (THIN) of users were concurrently treated with other platelet aggregation inhibitors. Among these users, 8.5% (SIDIAP) to 21.1% (GePaRD) discontinued platelet aggregation inhibitors after starting cilostazol.

Assessment of contraindications
The percentages of users with diagnoses suggestive of contraindications included in the label before the 2013 changes were 6.2% (EpiChron cohort), 10.0% (THIN), 12.2% (Sweden), 39.1% (SIDIAP), and 51.8% (GePaRD; Table 4). The prevalence of each individual contraindication, except heart failure, was higher in GePaRD than in other study populations. SIDIAP was the only database in which poorly controlled hypertension could be evaluated.

Baseline assessment of labeling changes
The baseline assessment of labeling changes is presented in Table 5. For databases with information from GPs, current smoking at the start date was found in 15.9% of users (EpiChron cohort), 30.4% (THIN), and 32.3% (SIDIAP). In these populations, 80.9–83.6% of users had a visit with a GP or specialist 2–4 months after starting cilostazol. Discontinuation within the first 3 months ranged from 39.4% (Sweden) to 52.9% (THIN) of users. Between 1.5% (THIN) and 11.6% (GePaRD) of users had new cardiovascular contraindications at the start date, and
6.3% (SIDIAP) to 13.5% (EpiChron cohort) were concurrently treated with two or more additional platelet aggregation inhibitors. In all databases, rates of visits with GPs or specialists were higher in users with increased risk of serious cardiovascular events than in users without such risk. Between 2.1% (Sweden) and 19.6% (THIN) of users had concurrent use of cilostazol 200 mg per day and potent CYP3A4 or CYP2C19 inhibitors. Among patients treated with a daily dose of 200 mg who started potent inhibitors during follow-up (n = 235), reduction of the cilostazol daily dose was found in one patient.

Off-label prescribing

Between 41.0% (SIDIAP) and 93.4% (THIN) of users had a recorded diagnosis compatible with the labelled indication (Table 6). Potential off-label prescribing ranged from 5.6% (THIN) to 24.5% (Sweden) of users. Between 1.0% (THIN) and 48.7% (SIDIAP) of users had recorded diagnoses not related to the potential on-label use of cilostazol or did not have any recorded diagnosis around the start date. Potential off-label cardiovascular indications of cilostazol were cerebrovascular disease (0.3%, EpiChron cohort and
DISCUSSION

In this study, we described the characteristics of 22,593 new users of cilostazol identified in the UK, Spain, Sweden, and Germany. Prevalence of use varied across study populations and countries, and it was higher in Spain than in the other countries. Most users were aged older than 60 years and had a high prevalence of comorbidity, especially cardiovascular disease and use of comedications. Concurrent use of cilostazol and potent CYP3A4 and CYP2C19 inhibitors ranged from 3 to 22% of users. The baseline assessment of labeling changes enabled estimation of the potential impact that could be achieved after the labeling changes were implemented in 2013. Up to one third of users were current smokers when initiating treatment; most patients were monitored after the start of treatment, up to 50% discontinued cilostazol in the first 3 months of therapy; and prevalence of new contraindications and concurrent use of cilostazol 200 mg daily and potent CYP3A4 and CYP2C19 inhibitors was low. On-label prescribing of cilostazol was variable, lower in Spain than in other countries, and variability was probably related to the extent to which diagnoses and free text were recorded in different databases.

Published information on cilostazol use in general practice is limited to a drug utilization study conducted in Spain by Cantabrian regional health service and the Spanish Medicines and Health Products Agency12; the results are published only in an abstract. The results from the EpiChron cohort and SIDIAP (Spain) in our study are in line with results from this study: Most cilostazol users were elderly, with a high prevalence of comorbidity and comedications, including those potentially interacting with cilostazol, and did not achieve 6 months of treatment. The high rates of discontinuation found in that study and in our study could be driven not only by a potential lack of effectiveness of cilostazol but also by intolerance or adverse effects. Our study was not designed to assess cause of discontinuation, and the clinical information evaluated (e.g., reasons for monitoring visits) did not provide further insight. In a large randomized clinical trial, the most frequent reasons for early termination were patient withdrawal of consent (16%), adverse events (18%), and other reasons (10%) (Hiatt et al., 2008). The high prevalence of comorbidity and concurrent use of multiple medications, many interacting with cilostazol, could also reduce the adherence to cilostazol treatment. For example, the concurrent use of statins

| Contraindication*                  | THIN, UK (n = 1528) | EpiChron Cohort, Aragon, Spain (n = 4024) | SIDAPI, Catalonia, Spain (n = 10,142) | Sweden (n = 2,887) | GePaRD, Germany (n = 4,012) |
|-----------------------------------|--------------------|--------------------------------------|-----------------------------------|-----------------|------------------------|
| Renal failure                     | 2.4 NA             | 7.9                                  | 2.8                               | 20.7            |
| Liver disease                     | 1.3 1.6            | 3.7                                  | 1.0                               | 25.4            |
| Heart failure                     | 4.8 2.9            | 3.7                                  | 3.0                               | 3.9             |
| Risk factors for bleeding         | 1.8 1.7            | 29.9                                 | 5.7                               | 16.3            |
| Active peptic ulcer               | 0.1 0.1            | 0.1                                  | 0.4                               | 3.9             |
| Recent cerebral hemorrhage        | 0.0 NA             | 0.2                                  | 0.1                               | 0.6             |
| Proliferative diabetic retinopathy** | 0.7 1.7         | 4.5                                  | 5.2                               | 12.4            |
| Poorly controlled hypertension*** | 1.0 NA             | 26.6                                 | NA                                | NA              |
| Arrhythmias                       | 0.7 0.2            | 0.03                                 | 1.4                               | 8.3             |
| Ventricular tachycardia           | 0.1 0.2            | 0.02                                 | 0.6                               | 1.5             |
| Ventricular fibrillation or multifocal ventricular ectopics | 0.5 NA | 0.01 | 0.8 | 7.3 |
| Prolongation of the QT interval   | 0.0 NA             | NA                                   | 0.1                               | NA              |
| Any contraindication              | 10.0 0.2           | 39.1                                 | 12.2                              | 51.8            |

GePaRD, German Pharmacoepidemiological Research Database, Germany; EpiChron, EpiChron cohort from Aragon Health Sciences Institute (IACS), Aragón, Spain; NA, not available; SIDIAP, Information System for the Improvement of Research in Primary Care, Catalonia, Spain; THIN, The Health Improvement Network, UK; UK, United Kingdom.

Note: Old contraindications refer to those already included in the labeling before the implementation of labeling changes in 2013.

*Contraindications were severe renal impairment, moderate-to-severe hepatic impairment, congestive heart failure, risk factors for bleeding (active peptic ulcer, hemorrhagic stroke within the prior 6 months, proliferative diabetic retinopathy, and poorly controlled hypertension), and history of arrhythmias.

**Refers to diabetic retinopathy.

***Poorly controlled hypertension was evaluated in THIN by using specific Read codes and in SIDIAP defined as any patient with a blood pressure value greater than 140/90 mmHg or diagnosed with hypertension without at least one control of blood pressure recorded in the last 12 months. Blood pressure values were not available in the rest of the study populations.

Table 4. Percentage of new users of cilostazol with old contraindications

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### Table 5. Baseline assessment of cilostazol labeling changes

| Labeling changes | Study variable | THIN, UK (n = 1528) | EpiChron cohort, Aragon, Spain (n = 4024) | SIDIAP, Catalonia, Spain (n = 10 142) | Sweden (n = 2887) | GePaRD, Germany (n = 4012) |
|------------------|----------------|----------------------|-------------------------------------------|----------------------------------------|-------------------|--------------------------|
| **Indication**   | Smoking cessation | Current smoking at the start date | 30.4% | 15.9% | 32.3% | 3.2%* | NA |
| **Physician reassessment of patients after 3 months** | Visit to GP or specialist** between 2 and 4 months after the start date | 80.9%*** | 83.6% | 82.0%*** | 8.6%† | NA |
| **Contraindications** | Visit related to intermittent claudication | 49.6%*** | 21.3% | 53.5%*** | 8.5%† | 62.2% |
| **Concomitant treatment with two or more additional platelet aggregation inhibitors** | Discontinuation before 3 months of treatment | 52.9% | 51.9% | 40.6% | 39.4% | 51.9% |
| **Rate of visits to GP or specialist per 100 person-years (95%CI)** | Recorded diagnosis codes for contraindications | 1.5% | 1.7% | 3.0% | 5.2% | 11.6% |
| **Concomitant treatment with two or more additional platelet aggregation inhibitors** | Recorded drug codes for platelet aggregation inhibitors | 9.8% | 13.5% | 6.3% | 8.4% | 7.5% |
| **Close monitoring of patients at increased risk for serious cardiac adverse events§** | Rate ratio increased/no increased risk (95%CI) | 1457 (1430–1485) | 3390 (3348–3432) | 566 (556–575) | 923 (901–944)† | 2.75 (2.68–2.82)¶ |
| **Posology** | Concurrent use of cilostazol 200 mg per day and CYP3A4 or CYP2C19 potent inhibitorsa | 19.6% | 10.0%b | NA | 2.1% | 3.4% |
| | Reduction of daily dose to 100 mg in patients receiving medicines strongly interacting with CYP3A4 or CYP2C19 enzymes | At the start date | 9.9% | 6.8%b | NA | 1.0% | 1.5% |
| | | During follow-upc | 9.7% | 3.1%b | NA | 1.1% | 2.1% |
| | | Dose reduction after start of a CYP3A4 or CYP2C19 potent inhibitord during follow-up | 0.0% | 0.0%b | NA | 0.0% | 12.2% |

CI, confidence interval; GePaRD, German Pharmacoepidemiological Research Database, Germany; GP, general practitioner; EpiChron, EpiChron cohort from Aragon Health Sciences Institute (IACS), Aragón, Spain; NA, not available; RR, rate ratio; SIDIAP, Information System for the Improvement of Research in Primary Care, Catalonia, Spain; THIN, The Health Improvement Network, UK; UK, United Kingdom.

Note: baseline assessment refers to evaluation of labeling changes before they were implemented during 2013.

*In Sweden, smoking at the start date was evaluated through smoking-related diagnosis and dispensings for smoking-cessation drugs only.

**Specialties were vascular surgery, cardiology, or diabetology.

***Based on the review of patient profiles and free text of a random sample of 200 users in THIN and 200 users in SIDIAP.

†Hospital inpatient and outpatient visits. Information on GP visits was not available in Sweden.

§Increased risk of serious cardiac events as a result of increased heart rate, for example, patients with stable coronary disease or a history of tachyarrhythmias.

¶Number of diagnoses per patient-year during continuous use of cilostazol.

aCYP3A4 or CYP2C19 potent inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mifepristone, ketoconazole, and itraconazole.

bBased on 1052 (26.1%) patients with available information on daily dose.

cNumber of users treated with a daily dose of 200 mg who started potent inhibitors during follow-up: 85 in THIN, 33 in the EpiChron cohort, 32 in Sweden, and 85 in Germany.
A lack of efficacy could precipitate or aggravate leg pain, which could be attributed to other diagnoses.

A total of 14 patients (7.2%) had other diagnoses, and 81 (41.5%) did not have any recorded diagnosis.

Based on clinical review of patient profiles and free text of a random sample of users.

**A total of 1541 patients (38.3%) had other diagnoses, and 11 (0.3%) did not have any recorded diagnosis.

* A total of 14 patients (7.2%) had other diagnoses, and 81 (41.5%) did not have any recorded diagnosis.

Table 6. Potential off-label prescribing of cilostazol

| Diagnosis                        | THIN, UK (n = 1528)* | EpiChron Cohort, Aragon, Spain (n = 4024) | SIDIAP, Catalonia, Spain (n = 10 142)* | Sweden (n = 2887) | GePaRD, Germany (n = 4012) |
|---------------------------------|----------------------|-------------------------------------------|----------------------------------------|-------------------|--------------------------|
| On-label prescribing            | 93.4%                | 53.6%                                     | 41.0%                                  | 70.2%             | 81.6%                    |
| Potential off-label prescribing | 5.6%                 | 7.9%                                      | 10.3%                                  | 24.5%             | 17.0%                    |
| Varices, phlebitis, and thrombophlebitis | 0.0%              | 2.0%                                      | 2.1%                                   | 2.3%              | 3.9%                     |
| Leg and foot pain, symptoms, and complains | 3.6%            | 1.5%                                      | 2.1%                                   | 1.3%              | 0.0%                     |
| Musculoskeletal disorders        | 0.0%                 | 1.2%                                      | 0.0%                                   | 3.7%              | 4.6%                     |
| Cerebrovascular disease          | 1.0%                 | 0.3%                                      | 2.1%                                   | 0.3%              | 4.8%                     |
| Ischemic heart disease           | 0.5%                 | 0.3%                                      | 1.0%                                   | 0.6%              | 7.0%                     |
| Other cardiovascular disease     | 0.0%                 | 1.6%                                      | 0.0%                                   | 16.2%             | 15.0%                    |
| Peripheral neuritis and neuropathy | 1.0%              | 0.02%                                     | 0.0%                                   | 0.0%              | 0.0%                     |
| Other diagnoses/no diagnoses recorded | 1.0%            | 38.5%**                                   | 48.7%***                               | 5.4%              | 1.5%                     |

GePaRD, German Pharmacoepidemiological Research Database, Germany; GP, general practitioner; EpiChron, EpiChron cohort from Aragon Health Sciences Institute (IACS), Aragón, Spain; SIDIAP, Information System for the Improvement of Research in Primary Care, Catalonia, Spain; THIN, The Health Improvement Network, UK; UK, United Kingdom.

*Based on clinical review of patient profiles and free text of a random sample of users.

**A total of 1541 patients (38.3%) had other diagnoses, and 11 (0.3%) did not have any recorded diagnosis.

***A total of 14 patients (7.2%) had other diagnoses, and 81 (41.5%) did not have any recorded diagnosis.

(41.8–66.8% of new users) could precipitate or aggravate leg pain, which could be attributed to lack of efficacy of cilostazol and lead to discontinuation of treatment.

A strength of our study is the use of automated health databases, which typically capture information from routine health care without modifying regular clinical practice. This allowed identification and characterization of long-term baseline medication and comorbidity history of a large number of cilostazol new users in several European populations—all of Sweden and with good representation of the overall country populations for other countries. The availability of prescription and dispensing records allowed a detailed evaluation of coprescription patterns over long periods of time.

A limitation of the use of databases is the heterogeneity of the data available for each population, which may explain part of the variability of the prevalence of comorbidity and contraindications (e.g., renal failure and liver disease) in the different study populations. The different health systems in each country or region also contribute to the heterogeneity between databases.

Information recorded in THIN and GePaRD is based on primary care, specialists, and hospital discharge diagnoses. In the EpiChron cohort and SIDIAP, information was restricted to primary care diagnoses and in Sweden was limited to inpatient and outpatient clinic hospital diagnoses.

Availability and specificity of some diagnoses used to assess comorbidity and contraindications varied between databases. Specific codes for renal failure and cerebral hemorrhage were not available in the EpiChron cohort. The diagnosis of proliferative diabetic retinopathy was available in THIN only and was approximated in the other databases by using the broader term of diabetic retinopathy; poorly controlled hypertension was evaluated in SIDIAP through recorded values of blood pressure and in THIN through Read codes. Also, to assess contraindications associated with disease severity (e.g., moderate-to-severe hepatic impairment), which is not captured in the study databases, we used broad diagnostic terms (e.g., liver disease) that could lead to misclassification and overestimation of the prevalence of these conditions.

The completeness of recorded information may differ between databases. Information on medications can be considered complete in all databases as it is based on the automatic recording of prescriptions (THIN) or pharmacy dispensings (EpiChron cohort, SIDIAP, Sweden, and GePaRD). However, a first specialist prescription may be missed in GP databases (THIN and SIDIAP), which could overestimate discontinuation of cilostazol. Also, relevant over-the-counter medications, such as aspirin, are not recorded in any of the study data sources. Information on smoking was available in THIN and SIDIAP but for only 48% of users in the EpiChron cohort. Recording of diagnoses in THIN can be considered reliable; estimates of the prevalence of chronic and frequent disease are consistent with those reported in national health statistics in the UK (Blak et al., 2011). Recording of diagnoses for administrative hospital requirements (Sweden) or for insurance billing purposes (GePaRD) can also be considered reasonably complete. The lower prevalence of comorbidity in the EpiChron cohort than in SIDIAP (e.g., diabetes, 29.9 vs. 40.4% respectively; hypertension, 54.9 vs. 63.0%; hyperlipidemia, 37.4 vs. 48.5%) could be related to some underrecording of
diagnoses in the EpiChron cohort. Conversely, the lower percentages of patients in the EpiChron cohort treated with antihypertensives (63.6% vs. 74.5%, SIDIAP), blood glucose-lowering drugs (20.9% vs. 32.2%), and insulin (11.8% vs. 15.5%) suggest that these differences could be due to different characteristics of cilostazol users (e.g., more severe patients in SIDIAP) or to different patterns of use of health services, which are organized and managed at the regional level.

The frequency of on-label prescribing of cilostazol varied between the study databases and was lower in Spain than in the other countries. This variability could reflect not only differences in the recording of diagnoses between databases but also differences in the prescribing patterns of each country or region. Evaluation of off-label use was based on the absence of recorded diagnoses for intermittent claudication or peripheral arterial disease. Thus, the absence of recorded information does not exclude that the diagnosis may have occurred but may not have been recorded. This may have led to overestimating off-label prescribing in these populations.

CONCLUSIONS

This study indicates that the prevalence of cilostazol use varied by country and was higher in Spain than in the UK, Sweden, and Germany, and in men than in women. Among cilostazol users, the high prevalences of risk factors, comorbidity, and concurrent use of medications including interacting drugs suggest that this is a vulnerable population at increased risk of complications and especially cardiovascular events.

CONFLICT OF INTEREST

Jordi Castellsague, Susana Perez-Gutthann, Brian Calingaert, Christine Bui, Cristina Varas-Lorenzo, and Alejandro Arana are employees of RTI-HS and work on projects funded by pharmaceutical companies. As employees of RTI-HS, Susana Perez-Gutthann and Cristina Varas-Lorenzo also participate in scientific advisory boards (for studies and medications) that are funded by pharmaceutical companies.

Alexandra Prados-Torres, Beatriz Poblador-Plou, and Francisca Gonzalez-Rubio are members of the EpiChron Research Group on Chronic Diseases of the Aragon Health Sciences Institute, ascribed to IIS Aragón, and do not have any conflict of interest with this project.

Maria Giner-Soriano and Albert Roso-Llorach declare that they do not have conflicts of interest.

Marie Linder and Anna Citarella are employees at the Centre for Pharmacoepidemiology, Karolinska Institutet, who receive grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies.

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Edeltraut Garbe was an employee of BIPS at the time of conducting this study. Edeltraut Garbe has been a consultant to Bayer-Schering, Nycomed, Teva, GSK, Takeda, Astellas, and Novartis in the past.

KEY POINTS

- The study evaluated the characteristics of 22 593 new users of cilostazol in the UK, Spain, Sweden, and Germany.
- The average annual prevalence per 100 000 population of cilostazol use ranged from 8.9 users in the UK to 162.4 users in Spain.
- Most cilostazol users were elderly patients with high comorbidity, especially cardiovascular diseases, and a high prevalence of concurrent use of interacting medications.
- Up to half of cilostazol users discontinued the treatment within the first 3 months.

ETHICS STATEMENT

The study protocol was approved by the RTI International Institutional Review Board; ethics committees in THIN, EpiChron cohort, SIDIAP, and Sweden; Statistics Sweden and the National Board of Health and Welfare in Sweden; and the SHIs and German Federal Insurance Authority in Germany.
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