PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 615–624
Published online 30 January 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4167

ORIGINAL REPORT

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

Jordi Castellsague[1]*, Susana Perez-Gutthann[1], Brian Calingaert[2], Christine Bui[2], Cristina Varas-Lorenzo[1], Alejandro Arana[1], Alexandra Prados-Torres[3], Beatriz Poblador-Plou[3], Francisca Gonzalez-Rubio[3], Maria Giner-Soriano[4], Albert Roso-Llorach[4], Marie Linder[5], Anna Citarella[5], Oliver Scholle[6], Tilo Blenk[6] and Edeltraut Garbe[6]

[1] *Department of Epidemiology, RTI Health Solutions, Barcelona, Spain*
[2] *Department of Epidemiology, RTI Health Solutions, Durham, NC, USA*
[3] *EpiChron Research Group on Chronic Diseases, IIS Aragón, Aragon Health Sciences Institute (IACS), REDISSEC, Zaragoza, Spain*
[4] *Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain*
[5] *Centre for Pharmacoepidemiology, Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden*
[6] *Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany*

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 concomitant 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. *Pharmacoepidemiology and Drug Safety* Published by John Wiley & Sons Ltd.

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

Received 16 March 2016; Revised 19 October 2016; Accepted 16 December 2016

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).[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

*Correspondence to: J. Castellsague, RTI Health Solutions, Av. Diagonal, 605, 9-1, 08028 Barcelona, Spain. Email: castellsague@rti.org

Table 1. Changes to the cilostazol summary of product characteristics, 2013

Indication	Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms.
	Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol where an inadequate effect is observed
Contraindications	Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months
	Concomitant treatment with two or more additional antiplatelet agents (e.g., aspirin and clopidogrel)
Warnings and precautions	Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, for example, patients with stable coronary disease or a history of tachyarrhythmias
Posology	Reduction of the dose to 50 mg twice daily in patients receiving medicines that strongly inhibit CYP3A4 or CYP2C19

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[2–4]; the EpiChron cohort from Aragon Health Sciences Institute, Aragon, Spain; the Information System for the Improvement of Research in Primary Care (SIDIAP), Catalonia, Spain[5]; the Swedish National Registers[6,7]; and the German Pharmacoepidemiological Research Database (GePaRD).[8] 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, concurrent use of interacting medications, and contraindications before and after the EMA-requested labeling changes.

Interacting medications evaluated were those interacting with cytochrome P-450 (CYP) enzymes, particularly CYP3A4 and CYP2C19, including potent CYP3A4 and CYP2C19 inhibitors.[9,10]

Old cilostazol contraindications evaluated were severe renal impairment, moderate-to-severe hepatic impairment, congestive heart failure, predisposing factors for bleeding (active peptic ulcer, hemorrhagic stroke within the prior 6 months, proliferative diabetic retinopathy, and poorly controlled hypertension), and history of specific arrhythmia.

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

DOI: 10.1002/pds

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. 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 a

DOI: 10.1002/pds

Table 2. Study period, number of new users, age and sex distribution, and patterns of use of cilostazol

Characteristic	THIN, UK	EpiChron Cohort, Aragon, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Study period	29 Jul 2002–14 Sep 2012	1 Jun 2009–31 Dec 2012	1 Jun 2009–31 Dec 2012	1 Jan 2008–31 Dec 2012	1 Jan 2007–31 Dec 2011
Number of users	1528	4024	10 142	2887	4012
Average annual prevalence of use (per 100 000)	8.9	162.4	133.5	13.3	17.0
Men	65.6%	72.2%	77.3%	52.3%	73.3%
Median age (years)					
Men	68.0	69.0	68.0	72.4	67.8
Women	71.0	73.9	75.0	75.0	68.7
Total number of prescriptions	21 513	35 719	47 205	11 295	23 478
Total number of DDDs	715 716	1 133 944	3 738 812	613 897	982 846
Total number of prescriptions per user					
1	28.6%	31.1%	15.9%	42.0%	32.9%
2–4	22.8%	20.4%	18.9%	29.2%	28.9%
5+	48.6%	48.5%	65.2%	28.8%	38.2%
Number of users of 50-mg strength	25.8%	NA*	NA*	23.4%	14.5%
Number of users of 10-mg strength	82.1%	100%	100%	81.0%	91.7%
Daily dose of 200 mg at start date	85.7%	77.3%	NA**	78.1%	87.9%
Discontinuation of use					
<1 month	28.7%	33.9%	22.2%	38.2%***	–
<3 months	52.9%	51.9%	40.6%	39.4%	51.9%
<6 months	62.2%	60.5%	50.4%	65.2%	64.9%
<12 months	71.3%	69.1%	64.6%	81.9%	77.8%
<24 months	79.8%	77.8%	82.0%	92.1%	87.5%

GePaRD, German Pharmacoepidemiological Research Database, Germany; 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.
*Strength of 50 mg was not available in Spain.
**Information on daily dose not available in SIDIAP.
***Refers to first 2 months of treatment.

diagnosis of diabetes. Use of comedications at the start date was consistent with the prevalence of comorbidity (Table S3). The most frequent comedications 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

DOI: 10.1002/pds

Table 3. Comorbidity among new users of cilostazol*

Disease description	THIN, UK (*n* = 1528)		EpiChron Cohort, Aragon, Spain (*n* = 4024)		SIDIAP, Catalonia, Spain (*n* = 10 142)		Sweden (*n* = 2887)		GePaRD, Germany (*n* = 4012)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Cardiovascular diseases and procedures	1399	91.6	3251	80.8	9027	89.0	2290	79.3	3972	99.0
Diseases of arteries, arterioles, and capillaries	1101	72.1	1453	36.1	5097	50.3	1605	55.6	3690	92.0
Intermittent claudication	808	52.9	1453	36.1	4268	42.1	1043	36.1	3151	78.5
Other peripheral arterial disease	652	42.7	1453	36.1	499	4.9	1003	34.7	3149	78.5
Revascularization procedures	164	10.7	0	0.0	4	0.0	525	18.2	1349	33.6
Cardiovascular disease excluding diseases of arteries, arterioles, and capillaries	1157	75.7	2997	74.5	8338	82.2	1812	62.8	3838	95.7
Ischemic heart disease	497	32.5	563	14.0	1746	17.2	912	31.6	2111	52.6
Acute myocardial infarction	194	12.7	274	6.8	674	6.6	399	13.8	631	15.7
Unstable angina pectoris	60	3.9	229	5.7	114	1.1	264	9.1	408	10.2
Angina pectoris	301	19.7	229	5.7	161	1.6	609	21.1	750	18.7
Coronary reperfusion and procedures	189	12.4	0	0.0	48	0.5	531	18.4	518	12.9
Arrhythmias	138	9.0	157	3.9	629	6.2	338	11.7	1199	29.9
Paroxysmal tachycardia	6	0.4	9	0.2	47	0.5	47	1.6	167	4.2
Atrial fibrillation and flutter	97	6.3	133	3.3	475	4.7	260	9.0	535	13.3
Heart failure	73	4.8	118	2.9	406	4.0	266	9.2	983	24.5
Cerebrovascular disease	189	12.4	313	7.8	971	9.6	339	11.7	1815	45.2
Hypertension	825	54.0	2209	54.9	6388	63.0	1352	46.8	3451	86.0
Hypotension	37	2.4	14	0.4	27	0.3	25	0.9	264	6.6
Disorders of lipoprotein metabolism	478	31.3	1503	37.4	4915	48.5	589	20.4	3021	75.3
Bleeding disorders	346	22.6	160	4.0	568	5.6	338	11.7	1120	27.9
Cerebral hemorrhage	8	0.5	0	0.0	30	0.3	20	0.7	62	1.5
Gastrointestinal bleeding	169	11.1	44	1.1	230	2.3	142	4.9	504	12.6
Gastroduodenal bleeding	61	4.0	18	0.5	94	0.9	102	3.5	299	7.5
Lower gastrointestinal bleeding	114	7.5	26	0.7	135	1.3	38	1.3	190	4.7
Genitourinary	133	8.7	87	2.2	213	2.1	122	4.2	451	11.2
Other site	90	5.9	33	0.8	152	1.5	77	2.7	276	6.9
Blood dyscrasias	97	6.3	203	5.0	378	3.7	162	5.6	923	23.0
Peptic ulcer disease	136	8.9	83	2.1	549	5.4	101	3.5	354	8.8
Liver disease	20	1.3	63	1.6	396	3.9	30	1.0	1021	25.4
Renal failure	37	2.4	0	0.0	830	8.2	80	2.8	830	20.7
Skin disorders	399	26.1	641	15.9	882	8.7	225	7.8	1691	42.1
Diabetes mellitus	326	21.3	1201	29.9	4102	40.4	593	20.5	1648	41.1
Chronic obstructive pulmonary disease	194	12.7	694	17.3	1823	18.0	247	8.6	1727	43.0
Asthma	215	14.1	115	2.9	206	2.0	106	3.7	395	9.8
Rheumatoid arthritis	30	2.0	198	4.9	666	6.6	144	5.0	921	23.0
Malignancy	197	12.9	316	7.9	1107	10.9	481	16.7	1002	25.0

COPD, chronic obstructive pulmonary disease; GePaRD, German Pharmacoepidemiological Research Database, Germany; GP, general practitioner; 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.
*Comorbidity was evaluated for any time before the start date.

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

DOI: 10.1002/pds

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

Contraindication*	THIN, UK (n = 1528) %	EpiChron Cohort, Aragon, Spain (n = 4024) %	SIDIAP, Catalonia, Spain (n = 10 142) %	Sweden (n = 2887) %	GePaRD, Germany (n = 4012) %
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	6.2	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.

Sweden; 4.8%, GePaRD) and ischemic heart disease (0.3%, EpiChron cohort; 7.0%, GePaRD).

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 Agency[12]; 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

DOI: 10.1002/pds

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
	Visit related to intermittent claudication	49.6%***	21.3%	53.5%***	8.5%[†]	62.2%
	Discontinuation before 3 months of treatment	52.9%	51.9%	40.6%	39.4%	51.9%
Contraindications						
Unstable angina pectoris, myocardial infarction,[‡] and coronary intervention[‡]	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%
Warnings and precautions						
Close monitoring of patients at increased risk for serious cardiac adverse events[§]	Rate of visits to GP or specialist per 100 person-years (95%CI)					
	Rates (95%CI) in patients at increased risk	1457 (1430–1485)	3390 (3348–3432)	566 (556–575)	923 (901–944)[†]	2.75 (2.68–2.82)[¶]
	Rates (95%CI) in patient not at increased risk	1354 (1335–1373)	3032 (3013–3052)	475 (470–480)	485[†] (473–497)	2.66 (2.58–2.75)[¶]
	Rate ratio increased/no increased risk (95%CI)	1.08 (1.05–1.10)	1.12 (1.10–1.13)	1.19 (1.17–1.22)	1.90 (1.84–1.97)	1.03 (0.99–1.08)
Posology						
Reduction of daily dose to 100 mg in patients receiving medicines strongly interacting with CYP3A4 or CYP2C19 enzymes	Concurrent use of cilostazol 200 mg per day and CYP3A4 or CYP2C19 potent inhibitors[a]	19.6%	10.0%[b]	NA	2.1%	3.4%
	At the start date	9.9%	6.8%[b]	NA	1.0%	1.5%
	During follow-up[c]	9.7%	3.1%[b]	NA	1.1%	2.1%
	Dose reduction after start of a CYP3A4 or CYP2C19 potent inhibitor[a] during follow-up	0.0%	0.0%[b]	NA	0.0%	1.2%

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.

[‡]Within the last 6 months.

[§]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.

[a]CYP3A4 or CYP2C19 potent inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

[b]Based on 1052 (26.1%) patients with available information on daily dose.

[c]Number 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.

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%
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

DOI: 10.1002/pds

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.

Oliver Scholle and Tilo Blenk are employees of the nonprofit scientific organization Leibniz Institute for Prevention Research and Epidemiology—BIPS GmbH, who are conducting studies financed by pharmaceutical companies based on data provided by German statutory health insurance agencies. The pharmaceutical companies include Mundipharma, Bayer, Stada, Sanofi-Aventis, Sanofi-Pasteur, Novartis, Purdue, Celgene, Otsuka, and GSK.

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.

ACKNOWLEDGEMENTS

The authors would like to thank the GPs contributing information to THIN, Dr. Josep María Elorza from IDIAP for his contribution to the analysis of SIDIAP data, the German statutory health insurances TK and AOK Bremen/Bremerhaven for their data, and the Health Department and Aragón Health Service (SALUD) for providing the data for the study.

The study was funded by the Otsuka Pharmaceutical Europe Ltd and Gallions, Wexham Springs Framewood Road, Wexham SL3 6PJ, UK. The contract provides the research team independent publication rights. The sponsor had no role in the data collection or analysis and was not involved in the interpretation of results or the decision to submit the manuscript; however, in line with the *Guideline on Good Pharmacovigilance Practices* (*GVP*): *Module VIII — Post-authorisation Safety Studies of the EMA*, the sponsor had the opportunity to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

REFERENCES

1. EMA. *Assessment Report for Cilostazol Containing Medicinal Products*. European Medicines Agency: London, 24 June2013 .http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Cilostazol_31/WC500148976.pdf (accessed 13 September 2016).
2. IMS Health. *About Us*. Author, London; 2015. http://csdmruk.cegedim.com/our-data/our-data.shtml (accessed 13 Septebmer 2016).
3. Blak BT, Thompson M, Dattani H, *et al.* Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; **19**: 251–255.
4. Denburg MR, Haynes K, Shults J, *et al.* Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 2011; **20**: 1138–1149. doi:10.1002/pds.2203.
5. Bolibar B, Fina Aviles F, Morros R, *et al.* [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research] in Spanish. *Med Clin (Barc)* 2012; **138**: 617–621. doi:10.1016/j.medcli.2012.01.020.
6. Ludvigsson JF, Andersson E, Ekbom A, *et al.* External review and validation of the Swedish National Inpatient Register. *BMC Public Health* 2011; **11**: 450. doi:10.1186/1471-2458-11-450.
7. Wettermark B, Hammar N, Fored CM, *et al.* The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; **16**: 726–735. doi:10.1002/pds.1294.
8. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. *Pharmacoepidemiol Drug Saf* 2008; **17**: 215–223. doi:10.1002/pds.1545.
9. The Trustees of Indiana University. P450 drug interactions. Abbreviated "clinically relevant" table. Substrates. Indiana University School of Medicine, Indianapolis, IN; 2016. http://medicine.iupui.edu/clinpharm/ddis/clinical-table/ (accessed 29 October 2015).
10. FDA. Drug development and drug interactions. Food and Drug Administration, Silver Spring, MD; 30 June 2015. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm (accessed 14 September 2016).
11. ENCePP. *The European Union Electronic Register of Post-authorisation Studies (EU PAS Register)*. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance: London, July2016 .http://www.encepp.eu/encepp_studies/indexRegister.shtml (accessed 14 September 2016).
12. González-Ruíz A, Cuaresma-Lasheras M, Blanco-Ramos I, *et al.* Cilostazol: from spontaneous reports of cardiovascular and haemorrhagic reactions to a thorough benefit–risk evaluation in Europe. A signal generation. Oral abstract #14 in Abstracts for the XXIV Conference of the Spanish Society of Clinical Pharmacology. *Basic Clin Pharmacol Toxicol* 2011; **109**: 32–40. doi:10.1111/j.1742-7843.2011.00777.x.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.