Characterization of New Users of Cilostazol in the United Kingdom, Spain, Sweden, and Germany

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

[1] RTI Health Solutions, Barcelona, Spain; [2] RTI Health Solutions, Research Triangle Park, NC, United States;
[3] EpiChron Research Group on Chronic Diseases, IIS Aragón, Aragón Health Sciences Institute (IACS), REDISSEC, Zaragoza, Spain;
[4] Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain and Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), 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 GmbH, Bremen, Germany

CONFLICT OF INTEREST

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BACKGROUND

- Cilostazol is indicated in Europe to improve walking distances in patients with intermittent claudication.
- The EMA evaluated the benefits and risks associated with cilostazol and recommended new contraindications in the labeling, including unstable angina, recent myocardial infarction, and recent coronary intervention.[1]
- The EMA also required a drug utilization study to support the benefit-risk evaluation of cilostazol.

OBJECTIVE

- To describe the characteristics of new users of cilostazol as used in regular clinical practice in Europe before the implementation of new contraindications.

METHODS

- We identified new users of cilostazol between 2002 and 2013 in five European automated health databases:
  - The Health Improvement Network (THIN), United Kingdom (UK); data analyzed by RTI Health Solutions
  - EpiChron Cohort, IACS, Aragón, Spain
  - Information System for the Improvement of Research in Primary Care (SIDIAP), Catalonia, Spain
  - Swedish National Registers; data analyzed by the Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden
  - German Pharmacoepidemiological Research Database (GePaRD), Germany; data analyzed by the Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany
- 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).
- We followed new users from the start date to the earliest of end of enrollment in the database, death, or end of the study period.
- New users were characterized at the start date according to age, sex, socioeconomic status, comorbidity at any time before the start date, use of medications including interacting drugs within 6 months before the start date, and current and new contraindications to the labeling.
- We evaluated labeling changes recommended by the EMA and the study variables used to ascertain them before they were implemented in 2013 (Table 4).
- The study and protocol are available in the EU PAS Register (ENCEPP/SDPP/3596).

RESULTS

- **Study population (Table 1):** 22,593 new users of cilostazol.
  - SIDIAP (Spain) contributed the largest proportion of users.
- **Comorbidities (Figure 1):** Cardiovascular disease other than peripheral vascular disease was most frequent in all study populations.
- **Comedications (Figure 2):** Most frequent comedications were antihypertensive drugs, platelet aggregation inhibitors, lipid-modifying agents, and proton pump inhibitors.
- **Concurrent use (Table 2):** Most users of cilostazol were concurrently treated with interacting medications, and between 2.7% and 22.3% were treated with potent CYP3A4 and/or CYP2C19 inhibitors.
- **Contraindications (Table 3):** Prevalence ranged from 6.2% to 51.8%.
- **Baseline evaluation of labeling changes in 2013 (Table 4):**
  - Current smoking at start date ranged from 15.9% to 32.3% of users; between 80.9% and 83.6% had a visit with a general practitioner (GP) or specialist 2 to 4 months after starting cilostazol. Discontinuation within the first 3 months ranged from 39.4% to 52.9% of users.
  - New cardiovascular contraindications at start date ranged from 1.5% to 11.6%. Between 6.3% and 13.5% of users were concurrently treated with two or more additional platelet aggregation inhibitors.
  - Visits with GPs or specialists were higher in users with increased risk of serious cardiovascular events than in users without such risk.
  - Among concurrent users of potent inhibitors, reduction of daily dose was found in only one patient in GePaRD.
  - Potential off-label prescribing of cilostazol ranged from 5.6% to 24.5%.

CONCLUSION

- This European multicenter study showed that most cilostazol users were elderly patients with a high prevalence of comorbidity, particularly of cardiovascular diseases; high concurrent use of interacting drugs; and high discontinuation rates in the first 3 months of treatment.

REFERENCES

1. European Medicines Agency (EMA). Rapporteurs' Joint Assessment Report. Cilostazol Article 31 referral. Pletal 50 mg/100 mg tablets. Ekistol 50 mg/100 mg tablets. EMEA/H/A-31/1306. Data on file. July 4, 2012.

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CONTACT INFORMATION

Jordi Castellsague, MD, MPH
Senior Director, Epidemiology

RTI Health Solutions
Travessera de Gràcia 56, Àtic 1
08006 Barcelona, Spain

Phone: +34.93.241.7763
E-mail: castellsague@rti.org

Table 1. Study Period, Number of Users, Prevalence of Use, and Age and Sex Distribution of New Users of Cilostazol

Characteristic	THIN, UK	EpiChron Cohort, IACS, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Base population (million)	3.7	1.3	5.8	9.7	9.0
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	1,528	4,024	10,142	2,887	4,012
Average annual use prevalence (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)					
All users	69.0	70.1	68.0	73.7	68.0
Men	68.0	69.0	68.0	72.4	67.8
Women	71.0	73.9	75.0	75.0	68.7
Age > 60 years	79.9%	77.5%	79.2%	90.0%	78.7%

Figure 1. Percentage of Most Frequent Baseline Comorbidities
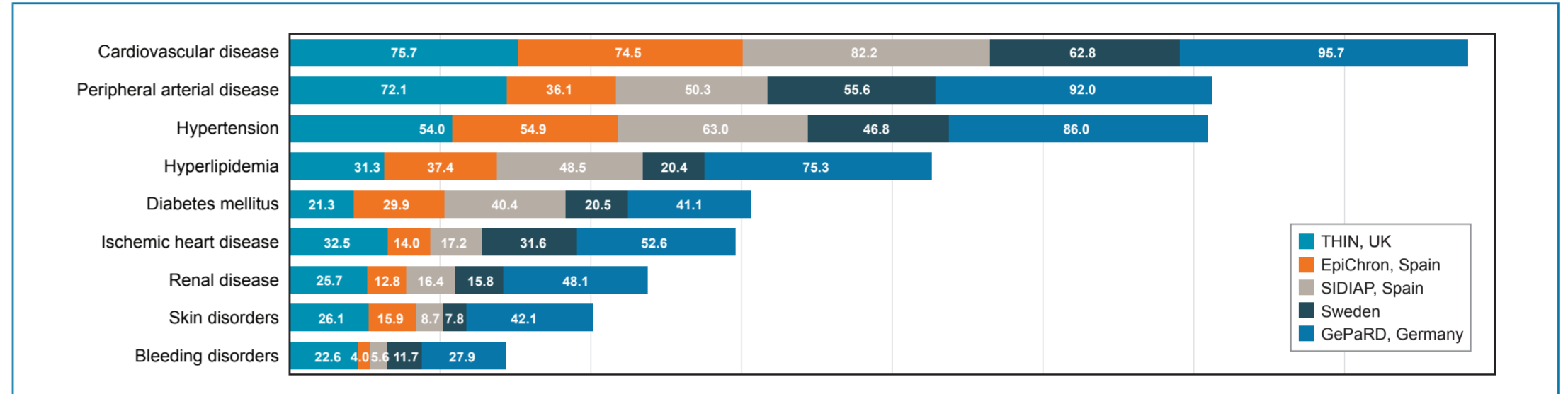
Cardiovascular diseases: hypertension, ischemic heart disease, hyperlipidemia, cerebrovascular diseases, arrhythmias, heart failure, hypotension, conduction disorders, cardiac arrest, and other cardiovascular diseases. Excludes peripheral arterial disease.

Figure 2. Percentage of Most Frequent Baseline Comedications
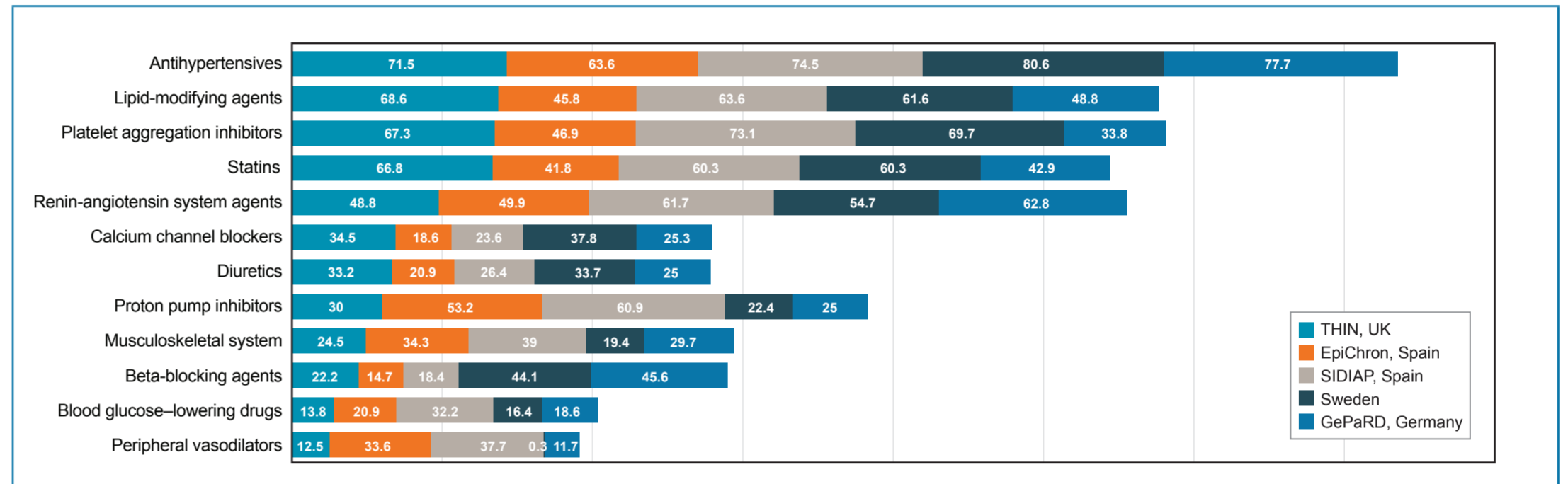
Antihypertensives: renin-angiotensin system agents, calcium channel blockers, diuretics, beta-blocking agents, and other antihypertensives (antiadrenergic agents, agents acting on arteriolar smooth muscle, antihypertensives and diuretics in combination, and other antihypertensives and combinations). Lipid-modifying agents: statins, fibrates, bile acid sequestrants, nicotinic acid and derivatives, and other lipid-modifying agents. Platelet aggregation inhibitors: excludes cilostazol.

Table 2. Concurrent Use of Cilostazol and Most Frequent Potentially Interacting Medications

Potentially Interacting Medication	THIN, UK	EpiChron Cohort, IACS, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Any potentially interacting medication	91.6%	82.5%	90.0%	84.4%	78.8%
Medications interacting with CYP3A4	85.1%	57.2%	73.2%	78.2%	66.0%
Simvastatin	44.0%	17.6%	38.0%	55.7%	48.9%
Atorvastatin	29.3%	26.8%	26.7%	10.1%	0.9%
Amlodipine	22.2%	7.7%	16.7%	18.5%	19.8%
Medications interacting with CYP2C19 any	55.3%	71.7%	75.3%	37.4%	47.8%
Omeprazole	22.4%	47.7%	59.3%	23.6%	17.2%
Clopidogrel	18.2%	23.4%	22.5%	11.7%	21.4%
Potent inhibitors of CYP3A4 or CYP2C19 enzymes[a]	22.3%	10.2%	7.3%	2.7%	3.8%

[a] Lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

Table 3. Percentage of New Users of Cilostazol With Contraindications Before Labeling Changes in 2013

Contraindication	THIN, UK	EpiChron Cohort, IACS, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Renal failure	2.4%	n/a	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%	n/a	0.2%	0.1%	0.6%
Proliferative diabetic retinopathy	0.7%	1.7%	4.5%	5.2%	12.4%
Poorly controlled hypertension[a]	1.0%	n/a	26.6%	n/a	n/a
Arrhythmias	0.7%	0.2%	0.03%	1.4%	8.3%
Any contraindication	10.0%	6.2%	39.1%	12.2%	51.8%

[a] Poorly controlled hypertension was evaluated in THIN using specific Read codes; in SIDIAP, it was 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.

Table 4. Baseline Assessment of Characteristics Related to Labeling Changes in 2013

Labeling Changes	Study Variable	THIN, UK	EpiChron Cohort, IACS, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Indication						
• Smoking cessation	• Current smoking at the start date	30.4%	15.9%	32.3%	3.2%[a]	n/a
• Physician reassessment of patients after 3 months	• Visit to GP or specialist[b] 2-4 months after start date	80.9%[c]	83.6%	82.0%[c]	8.6%[d]	n/a
	• Visit related to intermittent claudication	49.6%[c]	21.3%	53.5%[c]	8.5%[d]	62.2%
	• Discontinuation before 3 months of treatment	52.9%	51.9%	40.6%	39.4%	50.3%
Contraindications						
• Unstable angina pectoris, myocardial infarction,[e] coronary intervention[e]	• 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[f]	• Visits 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[g]					
	– At the start date	9.9%	6.8%[h]	n/a	1.0%	1.5%
	– During follow-up	9.7%	3.1%[h]	n/a	1.1%	2.1%
	• Dose reduction after start of a CYP3A4 or CYP2C19 potent inhibitor[g] during follow-up	0.0%	0.0%[h]	n/a	0.0%	1.2%

n/a = not available.

[a] In Sweden, smoking at the start date was evaluated through smoking-related diagnosis and dispensings for smoking-cessation drugs only.
[b] Specialties were vascular surgery, cardiology, or diabetology.
[c] Based on the review of patient profiles and free text of a random sample of users.
[d] Based on hospital inpatient and outpatient visits only. Primary care visits were not available.
[e] Within the last 6 months.
[f] Increased risk of serious cardiac events as a result of increased heart rate (e.g., patients with stable coronary disease or a history of tachyarrhythmias).
[g] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.
[h] Based on 1,052 (26.1%) patients with available information on daily dose.