Impact of Risk-Minimization Measures on the Use of Cilostazol in Europe

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DISCLOSURE

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BACKGROUND

- Cilostazol is indicated in Europe to improve walking distances in patients with intermittent claudication.
- Cilostazol has been associated with spontaneous reports of serious bleeding and cardiovascular effects, including heart attacks, angina, and arrhythmias.
- The EMA evaluated the benefits and risks of cilostazol, recommended risk-minimization measures, including labeling changes and communication to health care professionals in 2013,[1] and required two drug-utilization studies (DUS) to characterize users of cilostazol before (DUS1)[2] and after (DUS2) the implementation of these measures.

OBJECTIVE

- To evaluate the effectiveness of risk-minimization measures implemented for the use of cilostazol in Europe.

METHODS

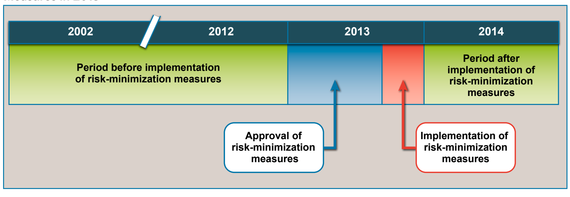
Study Population

- Observational study of new users of cilostazol in five European populations through automated health databases:
  - The Health Improvement Network (THIN), United Kingdom (UK)—led by RTI Health Solutions
  - EpiChron Cohort—led by IACS, Aragón, Spain
  - Information System for Research in Primary Care (SIDIAP)—led by IDIAP Jordi Gol, Catalonia, Spain
  - Swedish National Registers—led by the Centre for Pharmacoepidemiology, Karolinska Institutet, Sweden
  - German Pharmacoepidemiological Research Database (GePaRD), Germany—led by the Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany

Measures

- Frequency of conditions associated with labeling changes among new users of cilostazol were compared for the period before (2002-2012) and after (2014) the implementation of risk-minimization measures in 2013 (Figure 1).

Figure 1. Study Period for DUS1 and DUS2 in Relation to Implementation of Risk-Minimization Measures in 2013



Assessment of Labeling Changes

- Labeling changes evaluated are presented in Table 1.

Table 1. Cilostazol Labeling Changes, 2013

Indication	Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programs, 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, clopidogrel).
Warnings and precautions	Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate (e.g., 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.

- The study protocol is available in the EU PAS registry: EUPAS 3596.

RESULTS

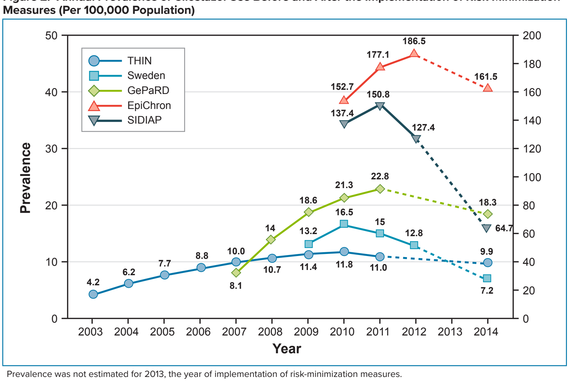
- **Study population**. The study included 22,593 and 1,821 new cilostazol users before and after implementation of risk-minimization measures, respectively. SIDIAP (Spain) contributed the largest proportion of users (Table 2).
- **Prevalence of use**. After labeling changes, the annual prevalence of cilostazol use decreased in all study populations: from 13% reduction in EpiChron to 57% reduction in SIDIAP (Figure 2).
- **Evaluation of labeling changes**. Frequency of conditions associated with labeling changes before and after the implementation of risk-minimization measures are presented in Table 3, and the overall assessment is provided in Figure 3.
  - Information on smoking was available in THIN, EpiChron, and SIDIAP. Current smoking at the start date decreased only in EpiChron.
  - Early monitoring increased in the UK, Spain (EpiChron), and Sweden.
  - Cardiovascular contraindications decreased in all study populations.
  - Use of ≥ 2 antiplatelet drugs decreased in the UK, Spain (EpiChron), and Sweden.
  - Monitoring of users at high cardiovascular risk, compared with users not at high risk, increased in Spain (SIDIAP), Sweden, and Germany (GePaRD).
  - Concurrent use of cilostazol 200 mg and potent inhibitors decreased in all study populations.

Table 2. Characteristics and Patterns of Use—New Users of Cilostazol Before and After the Implementation of Risk-Minimization Measures

Characteristic		THIN UK	EpiChron Aragón, Spain	SIDIAP Catalonia, Spain	Sweden	GePaRD Germany
Study period	Before	2002-2012	2009-2012	2009-2012	2008-2012	2007-2011
	After	2014	2014	2014	2014	2014
Number of users	Before	1,528	4,024	10,142	2,887	4,012
	After	104	367	771	149	430
Men (%)	Before	65.6	72.2	77.3	52.3	73.3
	After	66.3	85.6	78.5	58.4	70.9
Median age before/after (years)	Men	68.0/69.0	69.0/65.9	68.0/65.0	72.4/69.7	69.0/70.0
	Women	71.0/74.0	73.9/69.7	75.0/68.0	75.0/72.5	70.0/69.0
Daily dose 200 mg (%)	Before	85.7	77.3	NA	78.1	87.9
	After	31.7	7.1	NA	79.9	77.0
Discontinuation before/after (%)	< 1 month	28.7/38.5	33.9/25.5	22.2/20.5	38.3/43.0	39.4/40.7
	< 3 months	52.9/64.4	51.9/30.4	40.6/58.1	39.4/47.9	51.9/52.8
	< 6 months	62.2/70.3	60.5/35.2	50.4/77.3	65.2/70.6	64.9/68.6
	< 12 months	71.3/70.3	69.1/45.8	64.6/100.0	81.9/82.6	77.8/77.5

EpiChron = EpiChron cohort from the Aragon Health Sciences Institute (IACS); GePaRD = German Pharmacoepidemiological Research Database; NA = not available; SIDIAP = Information System for Research in Primary Care; THIN = The Health Improvement Network.

Figure 2. Annual Prevalence of Cilostazol Use Before and After the Implementation of Risk-Minimization Measures (Per 100,000 Population)



Prevalence was not estimated for 2013, the year of implementation of risk-minimization measures.

Table 3. Assessment of Labeling Changes Before and After the Implementation of Risk-Minimization Measures

Labeling Change		THIN UK	EpiChron Aragón, Spain	SIDIAP Catalonia, Spain	Sweden	GePaRD Germany
Number of users	Before	1,528	4,024	10,142	2,887	4,012
	After	104	367	771	149	430
Current smoking (%)[a]	Before	30.4	15.9	32.3	3.2	NA
	After	37.5	8.2	45.5	4.0	NA
Early monitoring (%)[b]	Before	49.6	21.3	53.5	8.5	62.2
	After	69.2	24.2	10.8	13.0	63.0
Early discontinuation (%)[c]	Before	52.9	51.9	40.6	39.4	50.3
	After	64.4	30.4	58.1	47.9	52.8
New cardiovascular contraindications (%)[d]	Before	1.5	1.7	3.0	5.2	11.6
	After	1.0	0.3	0.9	2.7	10.7
Concurrent treatment with ≥ 2 antiplatelet agents (%)	Before	9.8	13.5	6.3	8.4	7.5
	After	2.9	7.4	6.7	6.7	7.7
Monitoring of patients at high risk of cardiac events (RR, 95% CI)[e]	Before	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)
	After	0.88 (0.71-1.09)	0.97 (0.90-1.05)	1.75 (1.63-1.88)	2.08 (1.65-2.64)	1.24 (0.99-1.56)
Concurrent use of cilostazol 200 mg + interacting medications (%)	Before	78.7	76.9	NA	67.5	69.4
	After	27.9	3.6	NA	63.8	61.6
Concurrent use of cilostazol 200 mg + potent CYP3A4 or CYP2C19 inhibitors (%)[f]	Before	19.6	10.0	NA	2.1	3.6
	After	5.8	0.0	NA	0.7	1.9

CI = confidence interval; NA = dose not available; RR = rate ratio.

[a] Currently smoking at the start date. In Sweden, smoking was evaluated only through smoking-related diagnoses and dispensings for smoking-cessation drugs.

[b] Percentage of users with at least one visit to a specialist (vascular surgery, cardiology, diabetology) 2-4 months after the start date.

[c] Discontinuation of cilostazol within the first 3 months of treatment.

[d] Unstable angina pectoris and myocardial infarction or coronary intervention within the last 6 months.

[e] RR of visits to the general practitioner or specialist between users with and without increased risk of serious cardiac events (arrhythmias, hypotension, or coronary heart disease). In GePaRD, visits were 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.

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

Figure 3. Overall Assessment of Labeling Changes Before and After the Implementation of Risk-Minimization Measures

Characteristic	THIN UK	EpiChron Aragón, Spain	SIDIAP Catalonia, Spain	Sweden	GePaRD Germany
Smoking at the start date	⊘	●	⊘	⊘	NA
Visit related to intermittent claudication	●	●	⊘	●	◉
Discontinuation before 3 months of treatment	●	⊘	●	●	●
New cardiovascular contraindications	●	●	●	●	●
Concomitant treatment with two or more additional antiplatelet agents	●	●	⊘	●	◉
Monitoring of patients at high risk of cardiac events	⊘	⊘	●	●	●
Concurrent use of cilostazol 200 mg per day and interacting medications	●	●	NA	●	●
Concurrent use of cilostazol 200 mg per day and potent inhibitors	●	●	NA	●	●

Classification was based on a 5% change from before to after the implementation of risk-minimization measures. Values below 5% were considered to represent no change.

Simple green circle = improvement after the SmPC changes; red crossed circle = worsening after the SmPC changes; bold orange circle = no changes after the SmPC changes.

DISCUSSION

- In this collaborative study, we evaluated the effectiveness of risk-minimization measures for the use of cilostazol in the UK, Spain, Sweden, and Germany.
- The study addressed the concerns raised during the EMA Article 31 cilostazol referral and the requirement to evaluate the risk-minimization measures through DUS.
- In general, the risk-minimization measures were effective in all the study populations, as indicated by the marked decrease in the prevalence of cilostazol use, the decrease of use in the presence of new cardiovascular contraindications, and the lower concurrent use of cilostazol and interacting medications, including CYP2C19 and CYP3A4 potent inhibitors. Other parameters improved in some but not all study populations. Current smoking at the time of initiating treatment with cilostazol improved only in one of the three databases where information on smoking was available.

CONCLUSIONS

- Results from this European multi-database study indicate that the risk-minimization measures implemented for the use of cilostazol were effective in all study populations. Smoking cessation before initiating cilostazol remains an area of improvement.

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