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Title: Impact of terminating reimbursement of symptomatic slow-acting drugs in osteoarthritis in France on volume and cost of drug deliveries, assessed with administrative databases

Authors:

Mari K(1), Rannou F(2), Guillemin F(3), Elegbede M(4), Gueyffier F(4), Badot G(5), Mistretta F(1).

1 : RCTs, Lyon

2 : INSERM UMR 1124, Laboratoire de Pharmacologie, Toxicologie et Signalisation Cellulaire, Faculté des Sciences Fondamentales et Biomédicales, UFR Biomédicale des Saints-Pères, Paris, France.

3 : INSERM CIC 1433 Clinical Epidemiology, CHRU de Nancy, Université de Lorraine, Nancy, France

4 : University of Lyon, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, CNRS, Claude Bernard University Lyon, Université de Lyon, F-69003, France

5 : Laboratoires Genevrier

3 : INSERM CIC 1433 Clinical Epidemiology, CHRU de Nancy, Université de Lorraine, Nancy, France

Abstract

With osteoarthritis (OA) as one of the leading causes of disability in adults worldwide, its toll on patients and its economic burden for payers are substantial. The issue of change in OA management with the evolution of reimbursement schemes needs to be addressed.

Objective: To assess the impact of terminating the reimbursement of symptomatic slow-acting drugs in OA (SYSADOAs) in France in terms of volume and cost, from a healthcare payer perspective.

Principal results: We obtained costs and volumes from French public national databases. We considered three exposure periods around cutoff dates according to decisions of decreased then terminated SYSADOA reimbursement. The periods included 19 345 (control), 20 066 (secondary), and 16 200 (primary) patients, respectively. Mean ages were 66.2 (± 11.8), 65.3 (± 11.6) and 64.6 (± 11.5) years and about 70% were women. The volume of nonsteroidal anti-inflammatory drug (NSAID) deliveries estimated by defined daily doses (DDDs) decreased during the periods from 40.5 (± 76.3) DDDs per patient in 2008 to 29.6 (± 66.4) in 2015. The volume of analgesic deliveries increased slowly over the three periods, from 70.2 (± 108.9) DDDs in 2008 to 76.9 (± 123.1) in 2015 for all patients.

Major conclusions: Our results did not show a measurable impact of terminating SYSADOA reimbursement on the delivery of NSAIDs and analgesics or on hospitalizations. However, neither do they allow for concluding that terminating SYSADOA reimbursement did not generate an increase in deliveries of non-reimbursed drugs, with their associated potential risks for public health.

Keywords: osteoarthritis, cost, reimbursement, NSAID, SYSADOA, hospitalization

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1. Introduction

Osteoarthritis (OA) is one of the leading causes of disability in adults worldwide. Indeed, OA was estimated to be the tenth leading cause of non-fatal burden in the world in 1990 ¹ and the eleventh highest contributor to global disability in 2010 ². Although non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are first-line therapies for OA ^{3 4}, the effect and efficiency of symptomatic slow-acting drugs in OA (SYSADOAs) have been largely studied in the last decade. The 2014 guidelines of OsteoArthritis Research Society International (OARSI) for the non-surgical management of knee OA ranked chondroitin and glucosamine at the fourth and fifth positions on a 100-point scale assessing the combination of benefits and no comorbidities for pharmaceutical treatments ³.

In France, the National Health Insurance (NHI) has set different levels of reimbursement for SYSADOAs (avocado/soybean unsaponifiables ⁵, glucosamine sulfate ⁶, diacerein ⁷ and chondroitin sulfate ⁸ in France), from 2011 (decrease from 35% to 15%) to 2015. Meanwhile, several studies and meta-studies were conducted to assess the efficacy of SYSADOAs, with results synthesized in European scientific society guidelines ⁹.

The Committee of transparency of the Haute Autorité de Santé (HAS) in France requested a study to document lowering NSAID consumption by patients receiving SYSADOAs, the results of which were integrated in HAS reports in 2013 ¹⁰. In the PEGASUS study, with results published only for glucosamine-exposed patients ¹¹, a significant proportion of patients did not take their prescribed SYSADOA (reaching 45% for one of these drugs), and the consumption of NSAIDs was not statistically different between patients receiving and not receiving SYSADOAs. The subgroup of patients with incident SYSADOAs showed a statistically significant reduction in NSAID consumption. However, because this was a post-hoc analysis of a subgroup of patients, it was disregarded by the HAS. Also taking into account the updating of available scientific data, which had shown a modest effect size of SYSADOAs, in November 2013, the HAS issued a conclusion of insufficient medical service and on March 1, 2015, the final decision to terminate reimbursement.

The main hypothesis of the present study was that reduced reimbursement of SYSADOAs would result in significant changes, both in reimbursed medications (especially NSAIDs and analgesics) and hospitalizations, in the management of OA. To assess these consequences, we analyzed the evolution of drug prescriptions and hospitalizations of interest around the dates of reimbursement changes based on a non-biased and representative reimbursement database. The goal was to assess the modifications in reimbursed treatments

and hospitalizations (from the perspective of the NHI), following the progressive reduction in reimbursement of SYSADOAs and the economic burden of these modifications.

2. Methods

2.1. Data sources

Data were provided by the Échantillon Généraliste de Bénéficiaires (EGB), a 1/97th random permanent representative sample of Système National d'Information Inter Régime de l'Assurance Maladie (SNIIRAM) ^{12 13} established to facilitate the building of patient cohorts for the most common diseases and planned to provide a 20-year follow-up of beneficiaries. SNIIRAM is an administrative health database merging anonymous information for all outpatient reimbursed health expenditures. It is linked to the Programme de Médicalisation des Systèmes d'Information (PMSI) ¹⁴, the national hospital-discharge summaries database system and to the national death registry. SNIIRAM now covers 98.8% of the French population. The database includes demographic data (age, sex, place of residence); reimbursements of healthcare provider encounters, medications, medical devices, and laboratory tests (without results); long-term diseases (the NHI diseases that involve prolonged treatment and more expensive therapies and induce the total coverage of costs for all disease-related expenditures); and the date (but until recently not the cause) of death. The PMSI contains all data from private and public hospitals for hospitalizations with International Classification of Diseases, 10th revision codes for primary, related and associated diagnoses, dates and duration of stay, as well as cost.

We conducted comparative analyses with data from Medic'AM and Groupement pour l'Élaboration et la Réalisation de Statistiques (GERS) ¹⁵ to compare drug consumption in the population with OA and the general population and to take into account over-the-counter (OTC) deliveries, respectively. The Medic'AM database presents monthly and annual data on medications reimbursed by the NHI. GERS is a group created by pharmaceutical companies that pooled their hospital and pharmacy sales data in order to understand and monitor their markets. Both sources could give additional information on the volumes of drug deliveries considered in the present study.

2.2. Exposure periods

Three exposure periods (primary, secondary and control periods) with an equal length of 2 years were considered, and all three were divided into two halves of 1 year around a cutoff date, to avoid any bias due to a possible seasonality effect on OA crisis and medication

consumption. The cutoff dates for the primary and secondary periods were defined according to two reimbursement decisions by the French health authorities: the dates of decreased reimbursement from 35% to 15% (December 1, 2011) of SYSADOAs in France and of terminated reimbursement (March 1, 2015). The control period was when no SYSADOA-related event was registered. Its cutoff period was arbitrarily set to March 1, 2009 to coincide with the seasonality of the primary period of interest.

Therefore, the control period was set from March 1, 2008 to February 28, 2010; the secondary period from December 1, 2010 to November 30, 2012; and the primary period from March 1, 2014 to February 29, 2016. These study periods are displayed in Figure 1.

2.3. Study population

To be included in the study, patients had to meet the following two criteria: at least one delivery of SYSADOAs (identified by their Anatomical-Therapeutic-Chemical [ATC] codes) during the 1-year pre-cutoff periods and > 40 years old at the time of inclusion.

The medication possession ratio (MPR) was used to measure the proportion of time patients were exposed to SYSADOAs. The MPR was calculated as total quantity delivered over the period/quantity first delivered x duration of follow-up. The duration of follow-up was the difference between the end date of each period (control: February 28, 2010, secondary: November 30, 2012, primary: February 29, 2016) and the patients' date of inclusion in these periods.

Three subgroups of patients were defined according to their MPR:

- Patients with persisting delivery: $MPR > 80\%$ during the period, which is the usual threshold to consider for good maintenance
- Patients with intermittent delivery: $MPR \leq 80\%$
- Patients with punctual delivery: a single delivery

The age of prescription was also derived to distinguish patients with longer adherence to treatment from patients with new treatment. It was estimated as the difference between the cutoff date for each period and the date of the first delivery of SYSADOAs registered in EGB, expressed in years. From this estimation, we also considered the following subgroups of patients:

- o Incident patients: with a date of first delivery included in the 1-year pre-cutoff

- Prevalent patients: with a date of first delivery before the pre-cutoff period and still on prescription at the time of observation.

2.4. Description of the events

The events were the deliveries of the drugs of interest (using their ATC codes to identify them) and the hospitalizations (identified using their Diagnosis-Related Group codes) for the included patients. They were measured during the study period by their volumes (defined daily doses [DDD]) of drug deliveries and number of hospitalizations and their cost of reimbursement.

The drugs of interest were SYSADOAs, NSAIDs, analgesics, corticosteroids, and proton pump inhibitors. Hospitalizations of interest were those for cardiovascular causes, OA surgery, gastrointestinal cause and renal insufficiency.

2.5. Statistical analysis

Group characteristics are presented as means (\pm SD) for quantitative data and as number (%) for categorical data. The drug deliveries are presented as volume estimated by DDDs and as variations in DDDs pre- and post-cutoff for subgroups of patients and overall. The subgroups were compared by using ANCOVA adjusted with the variables available in EGB: age, sex, department of residence in France and derived age of prescription. Total costs in the national health system perspective for all drug reimbursements and the cost of hospital stays are expressed per patient, in euros.

3. Results

3.1. Study populations

In total, 19 345, 20 066, and 16 200 patients were included in the control, secondary and primary periods, respectively (Figure 1). The mean age (\pm SD) of patients (at the beginning of the period) was 66.2 (\pm 11.8), 65.3 (\pm 11.6) and 64.6 (\pm 11.5), respectively. About 70% were women, and the age of prescription increased over the periods (Table 1).

A total of 4345 patients were present for all three periods. The incidence of prescription deliveries decreased between the secondary and primary periods (Figure 2).

3.2. Volume of NSAID and analgesic deliveries

The percentage of patients receiving SYSADOAs and with at least one NSAID delivery decreased over the three periods. In the control period, 41.6% of patients had at least one

NSAID delivery for both pre- and post-cutoff periods and 12.9% had at least one NSAID delivery only post-cutoff. For the secondary and primary periods, the percentages were 38.8% and 37.1%, respectively, with at least one NSAID delivery for both pre- and post-cutoff periods and 12.7% and 12.3% with at least one NSAID delivery only post-cutoff (see supplementary materials).

The proportion of patients receiving SYSADOAs and at least one analgesic delivery remained constant during the control, secondary and primary periods: 70.6%, 69.7% and 70.9% of patients, respectively, had at least one analgesic delivery during both pre-and post-cutoff periods and 9.1%, 9.4% and 8.8%, respectively, had at least one analgesic delivery only post-cutoff (see supplementary materials).

The number of NSAID deliveries estimated by DDDs decreased over the three periods (Figure 3. Panel A) for all types of patients [total of 40.5 (\pm 76.3) DDDs per patient in 2008, 29.6 (\pm 66.4) DDDs in 2015].

The total analgesic DDDs increased slowly over the three study periods; it was higher for patients with persisting delivery of SYSADOAs (Figure 3. Panel B): 86.9 (\pm 125.0) and 98.0 (\pm 146.5) DDDs in 2008 and 2015, respectively, versus 70.2 (\pm 108.9) and 76.9 (\pm 123.1) DDDs in 2008 and 2015, respectively, for all patients.

Using the ANCOVA model of adjusted post-pre variations in DDDs, we found that the decrease in NSAID DDDs between pre- and post-cutoff in the primary period was significantly lower for patients with persisting delivery than those with punctual delivery ($p=0.033$) and intermittent delivery ($p=0.006$). However, the same results were observed in both the control and secondary periods (Figure 3. Panel C).

With the same ANCOVA model, we found that the decrease in analgesic DDDs between the pre-and post-cutoff in the primary period was significantly lower for patients with persisting delivery versus punctual delivery ($p=0.027$) and intermittent delivery ($p=0.042$). However, during the control and secondary periods, there was an increase in analgesic DDDs between pre- and post-cutoff for patients with persisting delivery but a decrease with punctual and intermittent delivery (Figure 3. Panel D).

On quantitative analyses of both raw DDDs and adjusted ANCOVA models, modifying the reimbursement of SYSADOAs did not have a significant impact on deliveries of NSAIDs or

analgesics, overall and by patient subgroup. Also, analysis of deliveries of corticosteroids and proton pump inhibitors did not show any significant results (data provided upon request).

We compared the previous results with two external sources of data to capture what occurred in the general population (using Medic'AM) and for OTC deliveries (using GERS). Both sources showed a decrease of 60.2% in SYSADOA sales after reimbursement was terminated. Longer trends observed previously were also reflected in these external sources: we found a slow decrease in NSAIDs over the years in terms of both sales and deliveries; for analgesics too, the comparisons mirrored the trend found in the analysis of EGB data: a constant increase followed by a slight decrease after 2015 (see supplementary materials).

3.3. Description of costs of deliveries and hospitalizations

For costs, we analyzed the amount reimbursed by NHI for all deliveries and found an overall decrease over the three study periods, which was accentuated during the primary period. This finding was confirmed with the ANCOVA model of adjusted post-/pre-cutoff variations (Figure 4. Panels A and C).

The amount reimbursed by NHI for hospitalizations in the disease-related groups of interest (cardiovascular cause, OA surgery, gastrointestinal cause and renal insufficiency) showed an overall decrease in hospitalization expenditures for patients receiving SYSADOAs (Figure 4. Panel B). Using the ANCOVA model of adjusted post-/pre-cutoff variations in reimbursed amount confirmed this overall decrease in hospitalization expenditures (Figure 4. Panel D).

4. Discussion

Consumers of SYSADOAs were of the same age as what was expected: mean 64.6 years in 2008-2009, 65.3 years in 2010-2011 and 66.2 years in 2014-2015. A population-based survey in France found that the mean age for prevalent cases of symptomatic knee OA was 61 years¹⁵. Patients were mostly women, which can be explained by the fact that SYSADOAs are mainly prescribed for knee OA, mostly found in women¹⁶. The flow chart of the incidence and persistence of patients in the study shows a decrease in incidence (new patients) before the termination of SYSADOA reimbursement.

We found no increase in the proportion of patients with at least one NSAID in the post-cutoff period during the three study periods and even an overall decrease, which could be explained by the recently increased awareness of NSAID-related secondary effects^{17 18 19}.

Almost all patients had at least one delivery of analgesics whatever the study period. This finding raises the question of painful relapses, which may not be sufficiently well treated.

Over time, the number of DDDs of prescribed NSAIDs decreased constantly, which is consistent with the changes in NSAID indications and physician practices. This was the probable effect of 2010 OARSI recommendations for NSAIDs as short term and at the lowest dose possible²⁰. Since then, there has been a continuous decrease in the prescription of long-term NSAIDs.

The number of analgesic DDDs increased constantly over the three study periods. The variation in number between pre- and post-cutoff periods was similar for the control and secondary periods for the three subgroups of patients: a lower consumption for punctual- and intermittent-delivery patients and a greater consumption for persisting-delivery patients. During the primary period, all categories of patients receiving SYSADOAs consumed fewer analgesics after termination of reimbursement than before. This can be explained by the messages about the toxicity of paracetamol and the lack of effect of analgesics on OA.

The same analyses were performed on the subgroups of patients classified as prevalent and incident (data not shown here) and the conclusions remained identical. We also considered the 4345 patients who were present during all three study periods and obtained similar results.

The comparative analysis with the NHI data (Medic'AM aggregated data for the number of reimbursed boxes) and GERS confirmed what was observed for the populations extracted from EGB, namely:

- A decrease in number of reimbursed NSAID boxes in France in 2008-2015 for all reimbursement schemes
- An increase in number of reimbursed analgesic boxes in France in 2008-2015 for all schemes combined
- A decrease in number of reimbursed SYSADOA boxes in France in 2008-2015 for all schemes combined

The fact that sales of SYSADOAs were maintained in 2015 at 39.2% of the 2014 figures leads to two remarks: the first is that terminating SYSADOA reimbursement had an obvious impact on sales and by proxy on the number of patients receiving SYSADOAs, but this decrease in sales was not as dramatic as expected. The effect of terminating SYSADOA reimbursement

on SYSADOAs themselves was quite limited. The effect on co-medications might also be limited and would thus be difficult to assess.

Besides, in our study populations, around 39% of patients had persisting delivery (40.6% in the control period, 38.8% in the secondary period and 38.3% in the primary period) and the maintenance of SYSADOAs between pre- and post-cutoff periods was largely driven by those patients. One can only wonder whether the maintenance in SYSADOAs sales was not due to the subgroup of patients with persisting delivery who kept taking SYSADOAs regardless of their reimbursement and whether the other patients followed the usual medication turnover regardless of the reimbursement status. This assumption can neither be confirmed nor denied and is perhaps one of the limitations of using administrative health databases, which are relevant to reimbursed health expenditures.

Our study has various limitations. It is by nature a post-hoc analysis, conducted by retrospectively interrogating an administrative database. It does not allow for mastering the various potential confusion biases associated with its observational nature. The French database gives information on drug dispensation and contains no data on prescription of or compliance with delivered prescriptions; it does not contain any information on important individual characteristics such as diagnoses or important biological (e.g., cholesterol, diabetes) or behavioral risk factors (e.g. smoking). Some of these characteristics can be obtained by studying hospitalizations or prescriptions or some specific traits of social insurance such as disease registrations opening a full-care reimbursement, but this was not relevant for our objectives. It does not deal with OTC drugs, only reimbursed drugs. It is built from a sampling procedure, with some delay of about 1 year in the availability of updated data. It is not an ad-hoc cohort but rather an administrative claims database, with limited power to address the hospitalizations linked to the disease of interest, OA.

The EGB database has advantages: it is produced by a sampling mechanism ensuring its representativeness, including non-drug-consuming individuals; its size allows for powerful analyses of drug deliveries; and it has collected data from the principal social security insurance since 2013 and thus offers time-depth data appropriate for answering our research question. To reduce the biases associated with the retrospective nature of our work, we used the control period as a negative control.

5. Conclusion

The present study aimed to measure the impact of terminating SYSADOA reimbursement on the delivery of other reimbursed medications that have a higher risk profile (NSAIDs and analgesics). Administrative databases (EGB and PMSI) were used and provided an adequate tool to address our initial assumption. As such, our results did not show a measurable impact of terminating reimbursement on the delivery of NSAIDs and analgesics or on hospitalizations.

However, the purpose of our study was not to answer whether the decision by the French health authorities to terminate SYSADOA reimbursement had an impact in terms of public health. Indeed, NSAIDs and analgesics can be delivered OTC, without prescription and without reimbursement by the NHI. Consequently, we cannot deduce from our results that terminating SYSADOA reimbursement did not generate an increase in delivery of non-reimbursed NSAIDs or analgesics, with the associated potential risks of adverse events. We could not identify nor measure whether terminating SYSADOA reimbursement affected the consumption of these treatments.

Disclosure/Conflict of Interest statement

G Badot was in the staff of Genevrier laboratory involved in the study. F Mistretta's institution received fees from Genevrier laboratory. F Rannou received fees for relevant activities outside of the submitted work from Pierre Fabre, Sanofi Aventis, Pfizer, Bayer, and Expansciences. No conflict of interest was reported by other authors.

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Table 1: Demographic characteristics of the population according to persistence of delivery.

	Control period				Secondary period				Primary period			
	Patients with punctual delivery (N=4158)	Patients with intermittent delivery (N=7333)	Patients with persisting delivery (N=7854)	Total (N=19345)	Patients with punctual delivery (N=4539)	Patients with intermittent delivery (N=7734)	Patients with persisting delivery (N=7793)	Total (N=20066)	Patients with punctual delivery (N=3673)	Patients with intermittent delivery (N=6328)	Patients with persisting delivery (N=6199)	Total (N=16200)
Age of the beneficiary (at period start) (years)												
Mean (± SD)	60.8 (±11.9)	63.9 (±11.5)	67.1 (±10.8)	64.6 (±11.5)	61.7 (±12.1)	64.9 (±11.4)	67.7 (±10.9)	65.3 (±11.6)	62.3 (±12.1)	66.0 (±11.6)	68.7 (±11.1)	66.2 (±11.8)
Sex of the beneficiary - N (%)												
Male	1356 (32.6%)	1992 (27.2%)	2135 (27.2%)	5483 (28.3%)	1436 (31.6%)	2302 (29.8%)	2271 (29.1%)	6009 (29.9%)	1204 (32.8%)	1884 (29.8%)	1883 (30.4%)	4971 (30.7%)
Female	2802 (67.4%)	5341 (72.8%)	5719 (72.8%)	13862 (71.7%)	3103 (68.4%)	5432 (70.2%)	5522 (70.9%)	14057 (70.1%)	2469 (67.2%)	4444 (70.2%)	4316 (69.6%)	11229 (69.3%)
Age of prescription (years)												
Mean (± SD)	2.2 (±2.1)	3.3 (±2.1)	4.1 (±2.1)	3.4 (±2.2)	3.0 (±3.1)	4.3 (±3.2)	5.0 (±3.2)	4.3 (±3.3)	4.3 (±4.3)	6.0 (±4.2)	7.0 (±4.1)	6.0 (±4.3)

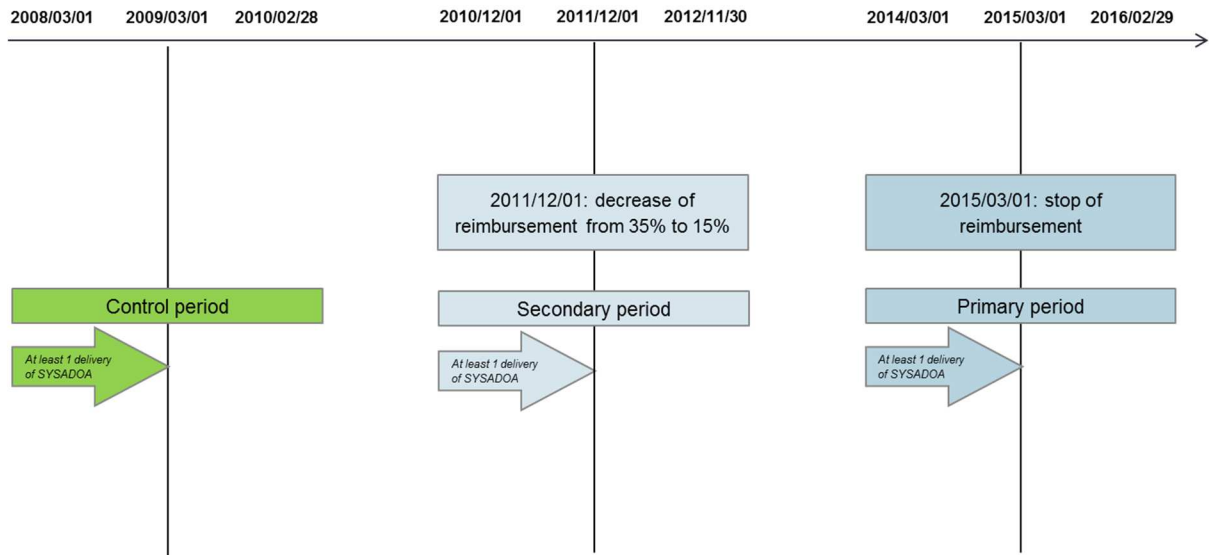


Figure 1: Description of study periods

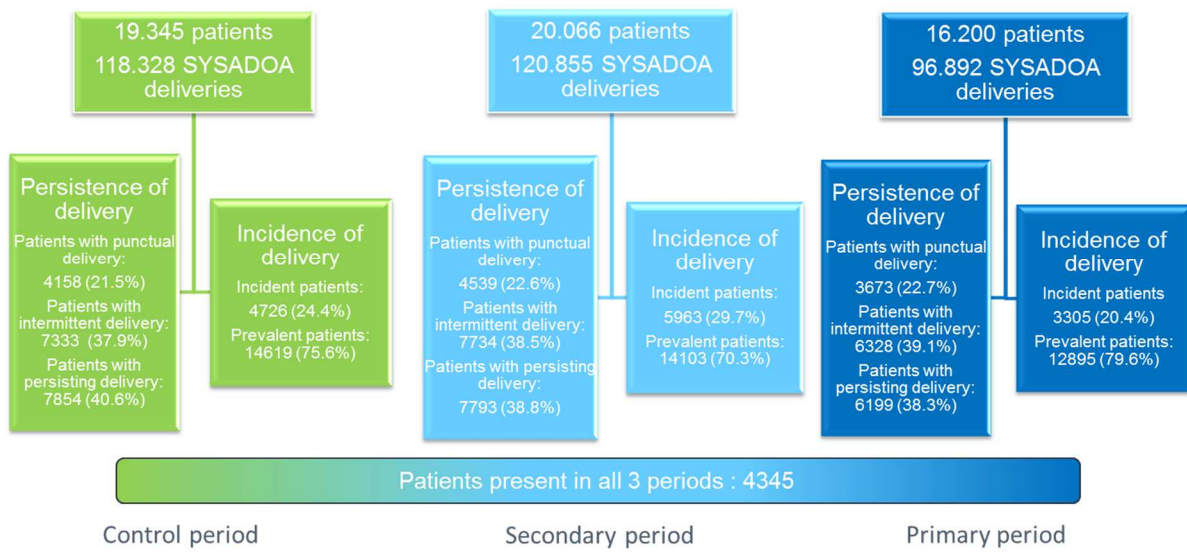


Figure 2: Flow chart of patient inclusion in the study.

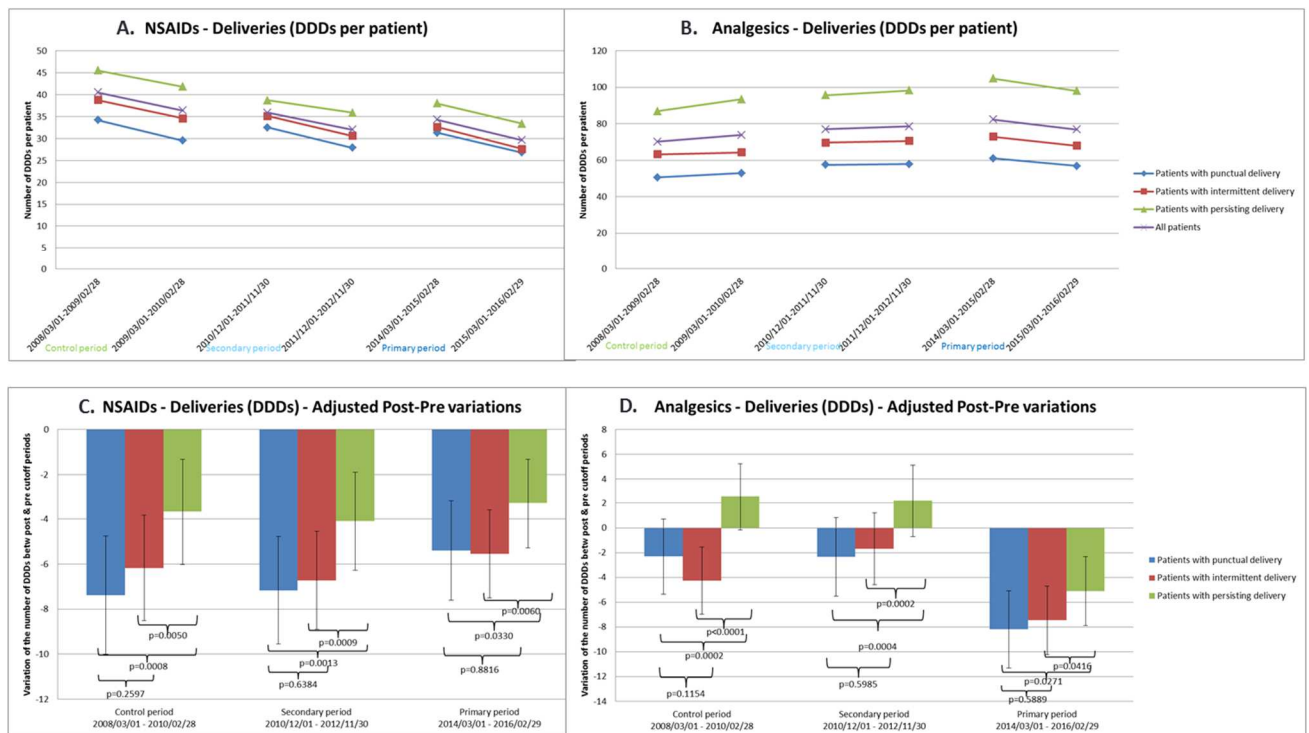


Figure 3: NSAID and analgesic deliveries estimated by DDDs: Evolution over the three study periods and variations between pre- and post-cutoff dates, according to persistence of delivery.

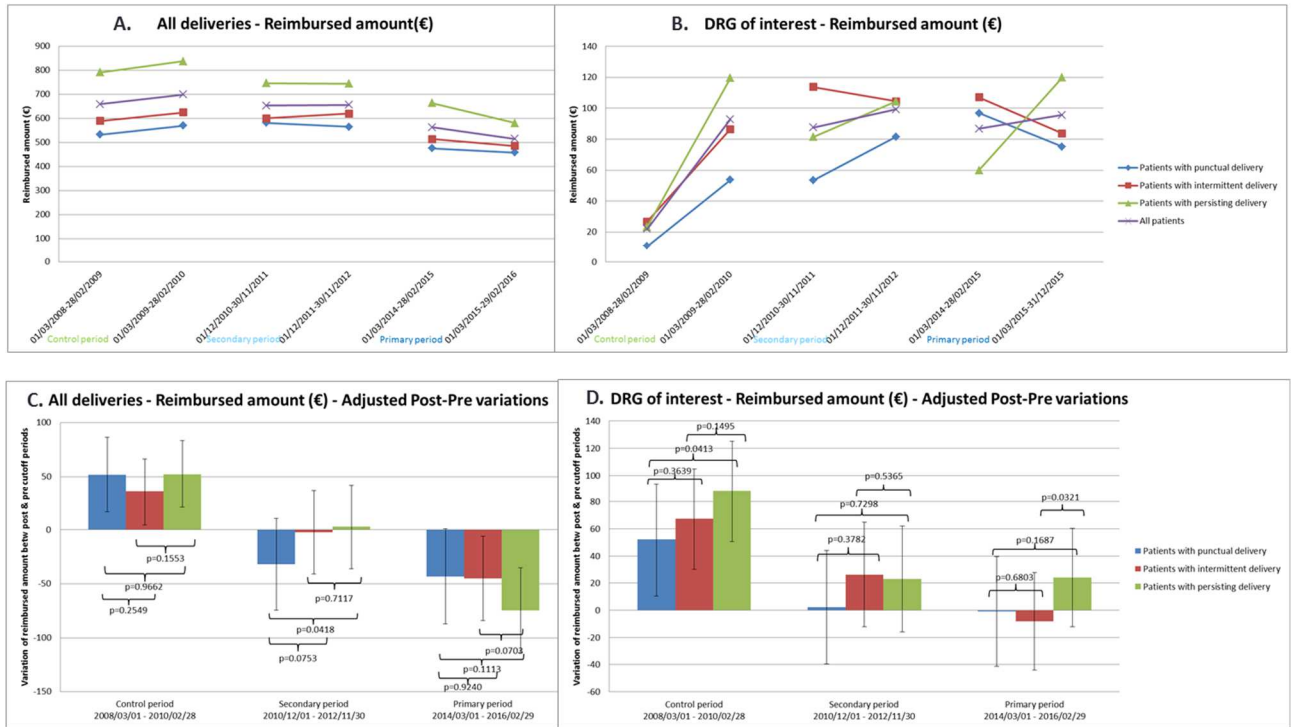


Figure 4: Amount reimbursed by NHI: Evolution over the three study periods and variation between pre- and post-cutoff dates for all deliveries and for hospitalizations, according to persistence of delivery. DRG, disease-related group