Studies on the impact of vasoconstrictors on the risk of myocardial infarction and stroke (VASO)

A ''Case CrossOver'' Study

using The PGRx Observational System

STUDY CONDUCTED BY LASER

EXECUTIVE SUMMARY

Rationale and background

The ANSM (French Medicines Agency) issued an alert on the cardiovascular effects of VC drugs for ENT use and therefore required the marketing authorization holders (MAHs) of VCs to conduct a study to determine whether exposure to vasoconstrictors was associated with an increased risk of occurrence of stroke and / or of myocardial infarction (MI). The interested MAH regrouped and decided to use the data collected in the PGRx System to conduct such a study. They also asked the Laser team to define the protocol, ensure the quality of the data used for the study, perform the analysis and produce the report. An independent scientific board was assembled by the MAHs to supervise the conduct of the study.

Research question and objectives

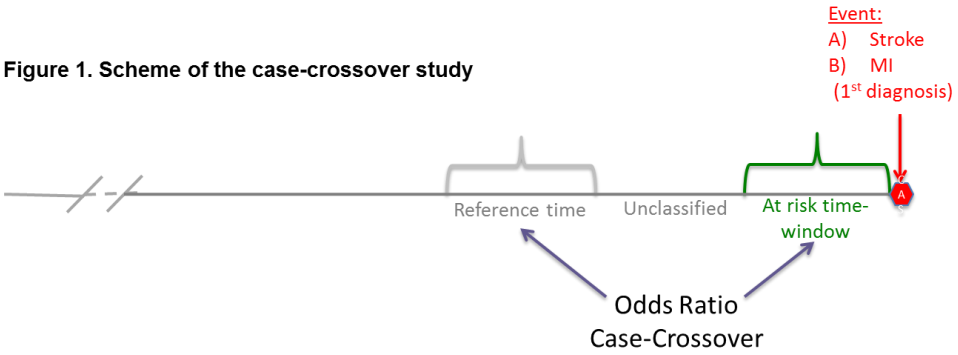
The main objective of the study was to determine whether exposure to vasoconstrictors was associated with an increased risk of occurrence of stroke and/or MI, as a composite endpoint.

Other objectives were to determine separately if the exposure to vasoconstrictors was associated with an increased risk of MI; and if the exposure to vasoconstrictors was associated with an increased risk of stroke.

Study design

The study design was a case-crossover study of patients with MI or stroke. The 'at risk' time-period was defined as the week preceding immediately the event of interest. The onset date of the event was the index date. The main control time window chosen for this study was the third week preceding the event. With this design, the proportion of exposure in the risk period was compared to the proportion of exposure in the reference period(s).

Figure 1. Scheme of the case-crossover study



General eligibility criteria

Using the PGRx framework, the following general criteria were used to include patients in the study:

General inclusion criteria applied to all subjects of the study:

- Male or female patients
- Age: ≥18 y.o
    - Until May 26, 2014, no upper limit was applied
    - From February-May 26, 2014 to December 31, 2015, age was restricted to ≤ 65 y.o
    - From January 2016 to 22 March 2016, age was restricted to ≤ 70 y.o
- Living in France
- Agreed to participate
- Had an interview on OTC use of drugs (either the patient or a proxy)

Seasons

Patients could be included in the study all over the year in PGRx. However only cases recruited with an index date from September to June were included in this study, as this represented exposure in the fall, winter and spring, with a higher likelihood of use of vasoconstrictor drugs.

Clinical eligibility criteria

The following clinical criteria were applied for the selection of patient cases in the PGRx Datasets for this study of vasoconstrictors' risks:

For MI cases:

Inclusion criteria: First diagnosed MI (incident cases) within 45 days prior to inclusion, diagnosis made by board-certified cardiologists.

Exclusion criteria: History of angioplasty, coronary bypass surgery or hospitalisation or diagnosis of MI prior to the current MI,

Clinical definition: MI non-fatal and resuscitated episodes were identified by cardiologists according to the following algorithm: at least two of the following criteria [Characteristic pain, Characteristic electrical abnormalities, cardiologic enzymes increase] or increased troponin.

For stroke cases:

Inclusion criteria: First haemorrhagic or ischemic stroke within 45 days prior to inclusion, documented by CT scan or MRI, and diagnosis made by a specialist (neurologist, cardiologist, internal medicine physician).

Exclusion criteria: Past history of documented stroke or TIA prior to the index date, subdural bleeding, aneurysms and vascular malformations or a recent severe cranial trauma.

Clinical definition: Stroke was defined as cerebral infarction or intraparenchymal or intraventricular or subarachnoid haemorrhagic stroke not related to a brain trauma or a vascular malformation or aneurysm rupture, and with no previous history of stroke or documented TIA.

Study conduct

The study has benefited from the systematic recruitment already made in the PGRx system used for several studies. It used cases from the ***PGRx-ACS database*** (Acute Coronary Syndrome) comprised of patients with a recent ACS included by board certified cardiologist from different types of centres, including university hospitals, general hospitals, private clinics, private practice, and mixed based practice; and from the ***PGRx-Stroke database*** comprised of patients with a recent stroke included by board certified neurologists, cardiologists or other specialists in a unit that manages at least 50 strokes per year. The stroke recruiting physicians were academic and general hospitals, mainly stroke units.

PGRx databases are based on the systematic recruitment by participating centres of all cases of interest, independently of any reference to their exposure to VCs agents.

Study setting

Study was conducted in cardiology and neurology centres in France. Overall, 151 cardiology centres and 78 neurology centres recruited at least 1 eligible patient for the study. The database cut-off lock for the VASO study was May 11, 2016. The PGRx database counted more than 12,000 patients with acute coronary syndrome, or stroke at the time of the database cut-off, among whom: 7,525 patients with MI (3,809) or Stroke (3,716) with their index date in 2013-2016. Out of these patients, a total of 2,797 (37.6%) patients met the inclusion criteria for the VASO study (1,394 MI and 1,403 Strokes). They corresponded to the sample size targeted by the VASO protocol (1,350 patients for each disorder).

Variables and data sources

Medical information is entered by cardiologists and neurovascular specialists in the PGRx system. Drug exposure is obtained from patients through standardized and validated telephone interviews by independent and trained interviewers.

Statistical analysis

All analyses were performed using conditional logistic regression models with the risk-time window/control-time window status as dependant variable. All analyses were performed employing SAS software version 9.2 (SAS Institute, Inc. NC, USA).

Analyses followed that of a case-crossover study using a conditional logistic regression. Descriptive, univariate and multivariate analyses have been conducted.

Explanatory variable (Exposure to VC) was defined according to the characterisation of the timing of use during each time window:

A. 'Definite Non-Use of VC': patient was affirmative that no VC had been taken within a concerned time-window (one by one from week-1 to week-6)
B. 'Definite VC Use': precise dates of use were reported by the patients and each time-window was characterised accordingly, or patient was affirmative that a VC has been taken within a concerned time-window (one by one from week-1 to week-6)
C. 'Possible use:' the patient could not report precise dates of use or precise week of use but was affirmative about a use in one of the time-windows of interest (TW-1 and/or TW-3)

A 3-category exposure variable was built for each week using these ABC categories.

In the primary risk analysis, the first model used definite+possible VC use as explanatory category, the second used ''strictly definite exposure'' (i.e. when at least 1 'definite VC use' was identified within the 6 weeks, possible use in other time-windows were not retained for the patient), and the third model used 'patients with definite use only' (only patients that were ''definite'' for VC use or non-use in both time windows -1 and -3 were included in this analysis)).

Results

Primary risk analysis

No increase in the risk of MI and/or stroke (as a composite outcome) after VC use in the week before, was observed (Crude OR 0.63 [95% CI 0.36-1.09]; adjusted OR 0.62 [95% CI 0.36-1.09]). The same result was found in both univariate and adjusted models, whether considering definite and possible exposure together, 'strictly definite' exposure, or among patients with definite use only:

- Considering 'strictly definite' exposure: crude OR 0.88 [95% CI 0.50-1.56]; adjusted OR 0.90 [95% CI 0.51-1.61]
- Among patients with definite use only: crude OR 0.83 [95% CI 0.45-1.52]; adjusted OR 0.84 [0.46-1.54]

Secondary, sensitivity and exploratory risk analysis

When analysing separately MI and stroke patients, no significant association was observed between exposure to VC in the week before event and occurrence of MI or stroke compared, respectively, to no VC use. Similar findings were observed both in univariate or adjusted models, and whether considering definite and possible exposure together; 'strictly definite' exposure or among patients with definite use only.

When analysing separately by age strata (< 66 y.o. / ≥ 66 y.o.), despite OR estimated at 2.13 [0.53 - 8.58] and 1.83 [0.43 - 7.79] using the strictly definite exposure in the oldest population (≥ 66 y.o), the

wide confidence interval allowed no statistical conclusion and no significant association was observable between exposure to VC and occurrence of MI and/or stroke (as a composite outcome) compared to no VC use. This relationship (no association) holds both in univariate or adjusted multivariate models, and whether considering definite and possible exposure together; 'strictly definite' exposure or among definite patients only:
Other sensitivity analyses did not reveal any observable association.

Conclusion

In the principal analysis, no increase in risk of myocardial infarction and/or stroke (composite outcome) was observable as associated with the exposure to vasoconstrictors, considered altogether, in the conditions explored in the present study reflecting the conditions of use of these drugs in France.
In a secondary analysis, no increase in risk of myocardial infarction on the one hand and no increase in risk of stroke on the other hand, were observable as associated with exposure to vasoconstrictors, considered altogether, in the conditions explored in the present study reflecting the conditions of use of these drugs in France.

Exploratory analyses of subcategories of outcomes (type of myocardial infarction or type of stroke, such as haemorrhagic stroke) were limited in power due to the low prevalence of use, the study being not designed to draw conclusions on subpopulation analysis.