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# Outcomes in post-myocardial infarction patients similar to those of the PEGASUS-TIMI 54 trial: A cohort study in the French national claims database sample EGB

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## Abstract

**Background:** The PEGASUS-TIMI-54 study found long-term benefits of ticagrelor in patients with a history of MI. However the external validity of such clinical trials remains to be demonstrated**. Objectives:** The present study aims to describe real-life outcomes in stable post-myocardial infarction (MI) patients. **Methods:** One-year event-free post-MI patients were identified in the French claims database representative 1/97 sample (EGB, 2005-2010) and followed up to 3 years. A PEGASUS-like (PL) population included patients with age 65 years, or age above 50 and diabetes, renal dysfunction or prior MI, without stroke, end-stage renal failure or oral anticoagulation. Outcomes were: a composite of all-cause death or hospital admission for MI or stroke; individual events; major bleeding. Analysis used fully adjusted multiple Cox proportional hazards models. Study registration: EUPAS 5816, European Medicines Agency, www.encepp.eu. **Results:** There were 1585 post-MI patients totalling 3926 person-years (PY) including 865 PL patients (2114 PY); 68% were male; mean age was 66 (SD 15) in post-MI, 74 (10) in PL. Outcomes per 100 PY [95%CI] were respectively in post-MI and PL 6.3 [5.6-7.1] and 7.8 [6.7-8.9] for the composite outcome; 5.1 [4.4-5.8] and 6.5 [5.5-7.6] for death; 1.0 [0.7-1.3] and 1.0 [0.6-1.4] for MI; 0.6 [0.4-0.9] and 0.9 [0.5-1.2] for stroke; 1.3 [0.9-1.6] and 1.4 [0.9-1.9] for major bleeding. Event rates were stable over the three study years. Placebo patients in the PEGASUS-TIMI 54 study were younger, more often male and had lower event rates, especially for all-cause death and major bleeding. **Conclusions:** Patients similar to those included in PEGASUS were older and had higher all-cause death and bleeding rates, but similar MI recurrence, indicating probable patient selection bias in the clinical trial.

## Conflict of Interest Statement

This study was supported by an unconditional grant from AstraZeneca, and supervised by an independent cardiologist expert. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi Platform, CIC Bordeaux CIC1401 of the Bordeaux University. This study was registered with the European Medicine agency's EUPAS registry (www.encepp.eu), under study number 5816. The funder assisted as an observer to all the meetings of the study. The funder did not have any role in study protocol, data acquisition, management or analysis.

## Background

- Antiplatelet agents such as clopidogrel or ticagrelor have demonstrated benefits during the first year post-myocardial infarction (MI).
- The PEGASUS-TIMI 54 trial (NCT01225562) showed a benefit of long-term use of ticagrelor in combination with aspirin in patients with a history of MI and additional risk factors compared with aspirin alone [1].

## Objectives

- To describe real-life outcomes in stable post-MI patients similar to those in the PEGASUS-TIMI 54 trial.

## Methods

- **Design:** cohort study of patients identified with stable MI in a representative French health insurance and hospitalisation claims database (EGB) with up to 3 years of follow-up until 31/12/2012 (Figure 1).

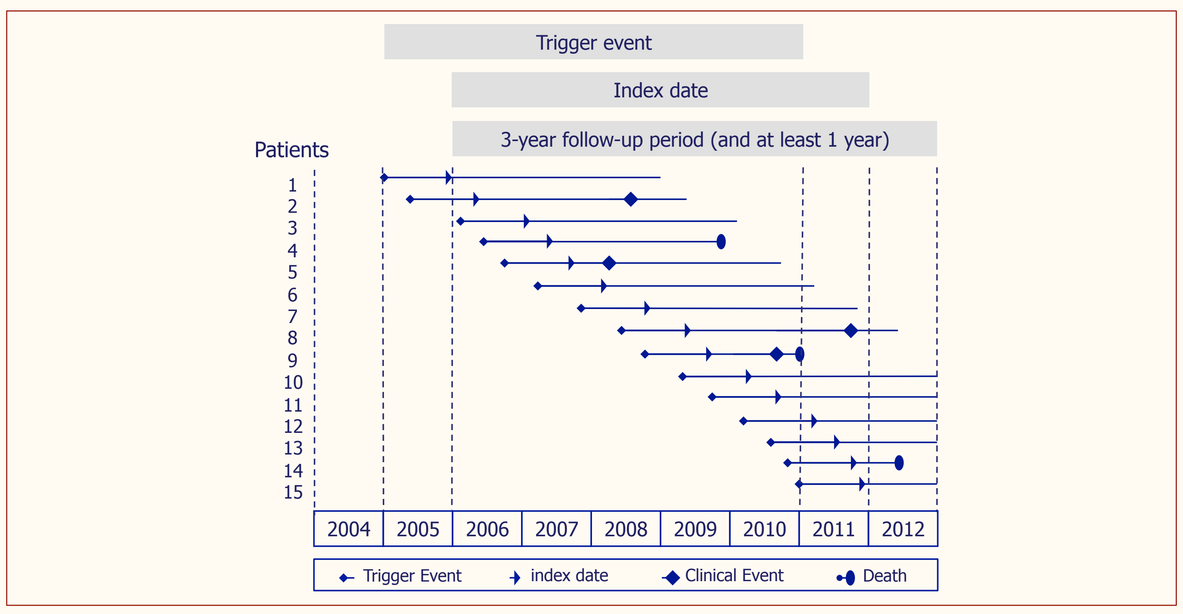


*Figure 1. Study design*

- **Data source:** EGB, *Echantillon Généraliste de Bénéficiaires*
  - Permanent 1/97 representative random sample of the national healthcare insurance database linked to the national hospital-discharge summary database, and the national death registry.
  - Includes approximately 780,000 persons.
  - Contains anonymised data on: demographic characteristics (gender, year of birth, month and year of death), long-term diseases (with full insurance coverage), reimbursed outpatient healthcare expenditures (visits, medical procedures, laboratory tests, dispensed drugs, medical devices), as well as hospital procedures and discharge summaries.
- **Populations:**
  - **Source population:** all adults with main hospital discharge diagnosis of MI between 01/01/2005 and 31/12/2010 (trigger event), with database follow-up data until death or 31/12/2012.
  - **Stable post-MI population:** patients of the source population alive and free of MI 1 year after trigger event. Index date for inclusion in the cohort was the 1st anniversary of admission for initial MI.
  - **PEGASUS-TIMI 54-like population (PL population):** patients of the stable post-MI population with ≥ 1 risk factor (≥ 65 years, diabetes, history of MI, renal disease), ≥ 50 years, without history of stroke, without dialysis, and without use of oral anticoagulant within 30 days of the index date.
- **Outcomes:** a composite of death (all-cause), hospitalisation for MI or stroke; each event separately; hospitalisation for major bleeding.
- **Statistical analysis:**
  - Estimation of incidence rate of outcomes (per 100 person-years [PY]).
  - Estimation of cumulative incidence of outcomes using Kaplan-Meier estimate.

[1] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, and al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. N Engl J Med. 2015 May 7;372:1791-800.

## Results

- Among the 2226 adults with an MI hospitalisation during the period 2005-2010:
  - **1585 patients** (71%) were included in the stable post-MI population, with 3926 PY of follow-up.
  - **865 patients** (39%) in the PL population, with 2114 PY.
- At the index date, 68% of patients were men in the post-MI population, and the mean age was 66 years. Patients in the PL population were older on average (74 years), and 61% were men. In the PEGASUS trial placebo arm, the mean age was 65 years and 76% were men (Table 1).
- The incidence rate of the composite criterion (death, hospitalisation for MI or stroke) was 6.3 per 100 PY (95% CI [5.6; 7.1]) for the post-MI population, and 7.8 per 100 PY [6.7; 9.0] for the PL population. In the PEGASUS trial, the composite event rate (including cardiovascular death) was 3.0% (Table 2, Figure 2).
- Death was the most frequent event for the post-MI and PL populations (5.1 and 6.5 per 100 PY, respectively). It was four times lower (1.7%) in the placebo arm of the PEGASUS trial (Table 2).
- The incidence of hospitalisation for bleeding was 1.3 and 1.4 per 100 PY for the post-MI and PL populations, respectively, and 0.4 in the placebo arm of PEGASUS (Table 2, Figure 2).

*Table 1. Baseline characteristics of patients in different populations*

| | Stable post-MI population n = 1585 | PL population n = 865 | PEGASUS-TIMI 54 trial placebo arm n = 7067 |
|---|---|---|---|
| **Men at index date, n (%)** | **1085 (68.5)** | **525 (60.7)** | **5350 (75.7)** |
| **Mean age at index date (in years) (± SD)** | **66.1 (14.5)** | **73.8 (10.2)** | **65.4 (8.3)** |
| **At least one of the following procedures during 1-year after trigger event, n (%)** | **211 (13.3)** | **116 (13.4)** | **/** |
| Angiography | 109 (6.9) | 63 (7.3) | |
| Percutaneous coronary intervention | 104 (6.6) | 59 (6.8) | |
| Coronary artery bypass graft | 31 (2.0) | 16 (1.8) | |
| **Drug exposure during 1-year after trigger event, n (%)** | | | |
| Coronary prevention treatment (ATC codes B01, C07, C09, C10) | 1556 (98.2) | 852 (98.5) | / |
| Statins | 1440 (90.9) | 781 (90.3) | 6583 (93.2) |
| Aspirin | 1402 (88.5) | 772 (89.2) | 7057 (99.9) |
| ß-blockers (ATC code C07) | 1364 (86.1) | 731 (84.5) | 5878 (83.2) |
| ACEi or ARB* (ATC code C09) | 1300 (82.0) | 719 (83.1) | 5697 (80.6) |

* ACEi : Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin II receptor antagonists
/: not indicated in the PEGASUS trial publication

*Table 2. Outcomes and incidence rates per 100 person-years during a 3-year follow-up after 1-year event-free survival post-MI in different populations*

| | Stable post-MI population n = 3926 PY | | PL population n = 2114 PY | | PEGASUS-TIMI 54 trial placebo arm per 100 PY* |
|---|---|---|---|---|---|
| **Composite criterion, n % [95% CI]** | **249** | **6.3 [5.6; 7.1]** | **165** | **7.8 [6.7; 9.0]** | **3.0**** |
| Death (all-cause) | 199 | 5.1 [4.4; 5.8] | 138 | 6.5 [5.5; 7.6] | 1.7 |
| Hospitalisation for MI | 40 | 1.0 [0.7; 1.3] | 21 | 1.0 [0.6; 1.4] | 1.8 |
| Hospitalisation for stroke | 24 | 0.6 [0.4; 0.9] | 18 | 0.9 [0.5; 1.2] | 0.7 |
| **Hospitalisation for bleeding, n % [95% CI]** | **49** | **1.3 [0.9; 1.6]** | **29** | **1.4 [0.9; 1.9]** | **0.4** |

* Data in PEGASUS are given as percent over 3 years, and have been recomputed to per 100 PY
** Cardiovascular death, MI or stroke

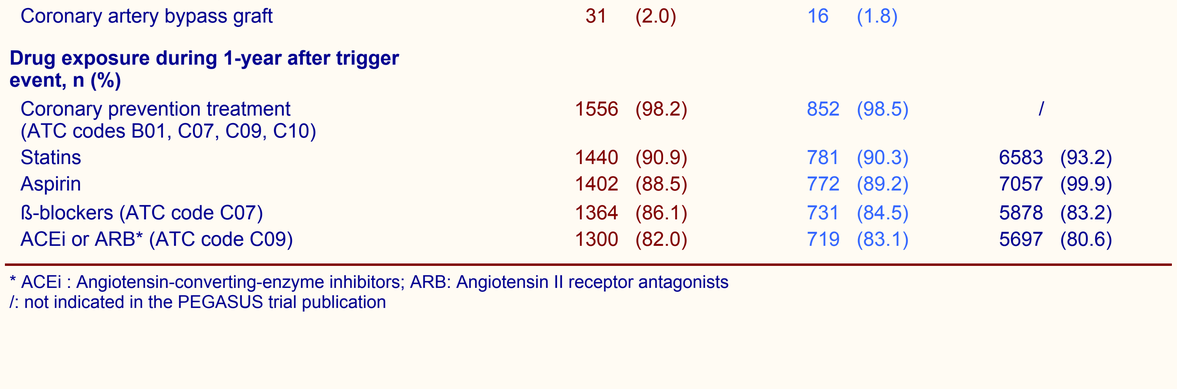


*Figure 2. Cumulative incidences of composite criterion and hospitalisation for bleeding in the stable post-MI and PL populations (Kaplan-Meier estimate)*

## Conclusions

- **Patients selected using the criteria described in the PEGASUS-TIMI 54 trial were older, resulting in higher all-cause death and bleeding rates, but similar MI recurrence.**

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