# ALPHEUS

## Assessment of Loading with the P2Y12 inhibitor ticagrelor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting

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**on behalf of the ALPHEUS investigators**

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ClinicalTrials.gov number, NCT02617290.

# Disclosures

## DISCLOSURE STATEMENT OF FINANCIAL INTEREST

**Johanne SILVAIN MD, PhD**

**During the last two years I declare having received the following:**

- **Grant to Institution**: AstraZeneca France, ICAN
- **Consulting Fees or Lecture Fees**: AstraZeneca, Bayer HealthCare SAS, Boehringer Ingelheim France, BPI France , CSL Behring SA, Gilead Science, Sanofi-Aventis France and Zoll
- **Travel Support:** Abbott Medical France SAS, Terumo France SAS
- **Stockholder:** Pharmaseeds

# Background

- **PCI is a safe procedure** when performed in an **elective setting** in **stable coronary patients with <1% serious complications**
- However **PCI-related MI and myocardial injury** can be **frequently diagnosed after the PCI**
- **Studies have demonstrated** that patients have a **better prognosis in the absence** of such periprocedural myonecrosis

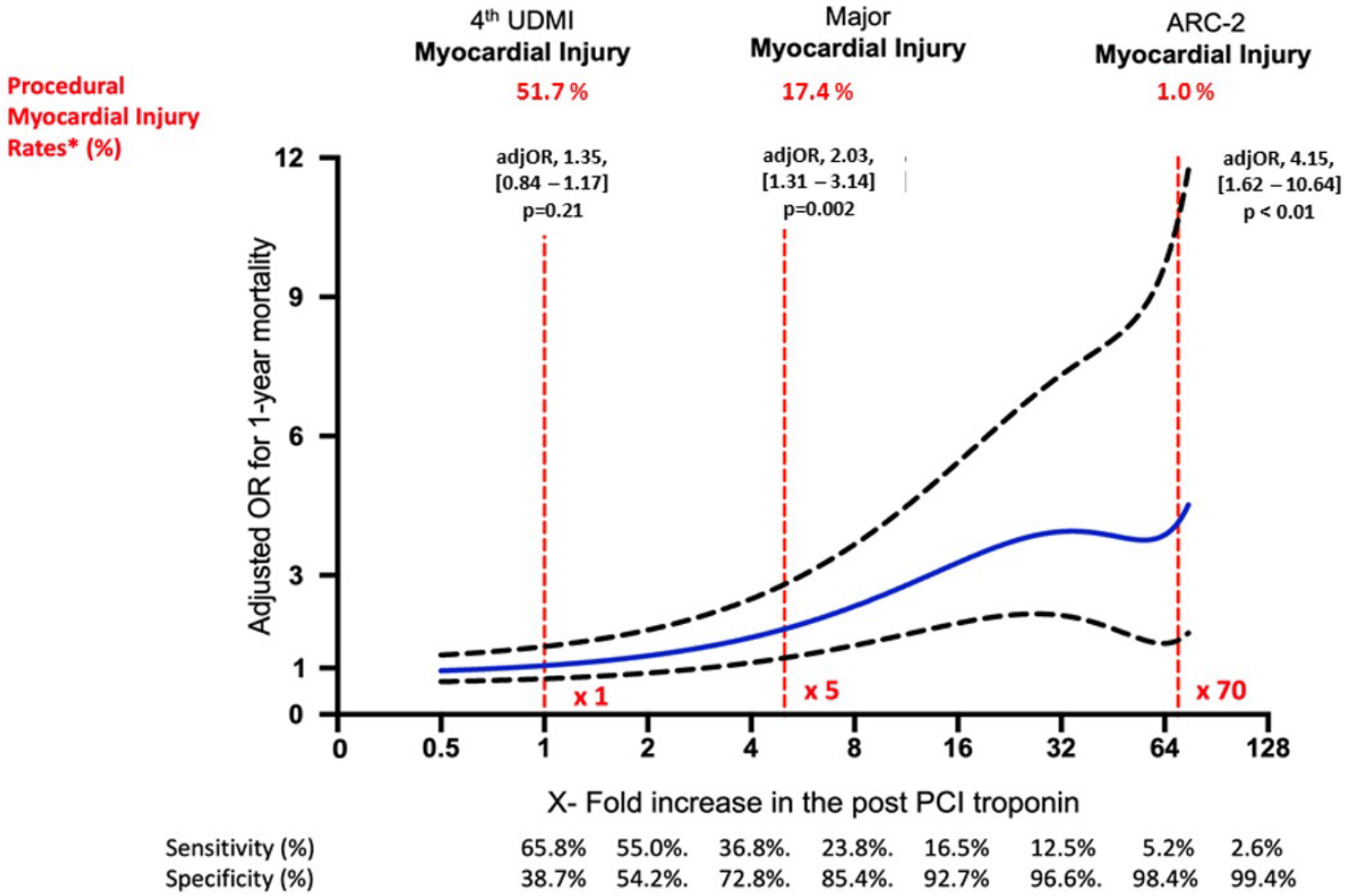
Zeitouni M et al. Eur Heart J 2018

Silvain J et al. Eur Heart J 2020

- **A stronger platelet inhibition could** potentially lower these events and **make the procedure safer**

# Association with Higher Mortality

N= 9092 Patient level data pooled analysis in CCS patients with normal troponin



# Study Objective

**To examine the effect of ticagrelor as compared with clopidogrel to reduce periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI.**

# Study organization

**Academic Research Organization**

- Pr Gilles MONTALESCOT (Scientific Director)
- Pr Johanne SILVAIN (Principal Investigator)
- Pr Eric VICAUT (Méthodologist-statistician)
- Abdourahmane DIALLO (Independent Statistician)
- Karine BROCHARD (Project Manager)
- Martine TANKE (Project Manager)

**Steering Committee**

- Pr Johanne SILVAIN (Paris, France )
- Pr Gilles MONTALESCOT (Paris, France)
- Pr Eric VICAUT (Paris, France )
- Pr Guillaume CAYLA (Nîmes, France)
- Pr Farzin BEYGUI (Caen, France )
- Dr Grégoire RANGE (Chartres, France)
- Pr Zuzana MOTOVSKA (Prague, Czech Republic)

**Sponsor**

Assistance Publique des Hôpitaux de Paris

- Damien VANHOYE - DRCI

**Funding**

ACTION fonds and Astra Zeneca

**DSMB**

- Pr Philippe Gabriel STEG – Chair
- Pr Jean-Sébastien HULOT
- Pr Corinne ALBERTI

**Members of the Clinical Events Committee**

- Pr Grégory DUCROCQ
- Dr Mikael LAREDO
- Dr Raphaelle DUMAINE

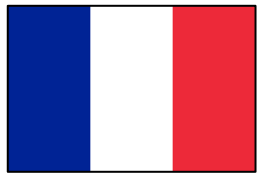
# Study design

**N= 1900 troponin negative* or modestly positive patients scheduled for PCI**

R

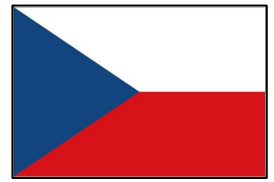
- **Ticagrelor 180 mg**
- **Clopidogrel LD***
  *300 or 600mg at physicians discretion

**PCI procedure**



44 French PCI Centers

**Troponin evaluation post PCI**



5 Czech Republic PCI Centers

***Primary end-point :*** **MI type 4a, 4b (stent thrombosis) or major myocardial injury *at 48 hours or discharge***

- **Ticagrelor MD**
  90mg x2/day
- **Clopidogrel MD**
  75 mg /day

**Follow up at 30days** for clinical secondary EP

# Incusion Criteria

- Male or non-pregnant female ≥ 18 years of age
- Undergoing **non-emergent PCI**
- Having **at least one high-risk feature**
- **Negative troponin** or moderatly positive and decreasing **before PCI**
- Informed consent obtained in writing at enrolment into the study

**Patient related**

Age > 75
Creat Clearance < 60ml/min
Diabetes Mellitus
BMI >30
History of ACS in the past 12 months
LVEF <40% and/or prior episode of HF

**Procedure related**

Multivessel disease
Multiple stents needed
Left main stenting
Bifurcation stenting
ACC/AHA type B2, C lesion
Venous or arterial coronary graft

**Key Exclusions:** ACS; need for chronic oral anticoagulation; other planned coronary revascularization within 30 days

# Sample Size Calculation

**Expected events rates :** 30% for the primary EP of MI-4/I at 48 hours in the clopidogrel arm

Zeitouni M et al. Eur Heart J 2018

**Expected relative risk :** 20 % reduction

**Power 80% , two-sided alpha level of 5%**
**856 patients/group required + 10% of dropout rate :** 1900 patients required

**An interim analysis** was performed with no necessary sample size adjustment


# 1910 patients underwent randomisation


**956** were assigned to the Ticagrelor group

13 did not have PCI
2 withdrew consent

**941** patients analyzed in the intention to treat and safety populations

**954** were assigned to the Clopidogrel group

9 did not have PCI
2 withdrew consent
1 was randomised twice

**942** patients analyzed in the intention to treat and safety populations

## Primary outcome at 48 hours

**15** patients didn't complete the Follow up at 30 days because of the following reasons:

- n= 2 Death
- n= 2 Decision of the investigator
- n= 4 Patient refuse to continue the study
- n= 1 Patient was lost to follow up
- n= 1 Patient released study for SAE
- n= 5 Other

**7** patients didn't complete the Follow at 30 days because of the following reasons:

- n= 0 Death
- n= 0 Decision of the investigator
- n= 1 Patient refuse to continue the study
- n= 3 Patient was lost to follow up
- n= 0 Patient released study for SAE
- n= 3 Other

# Demographics

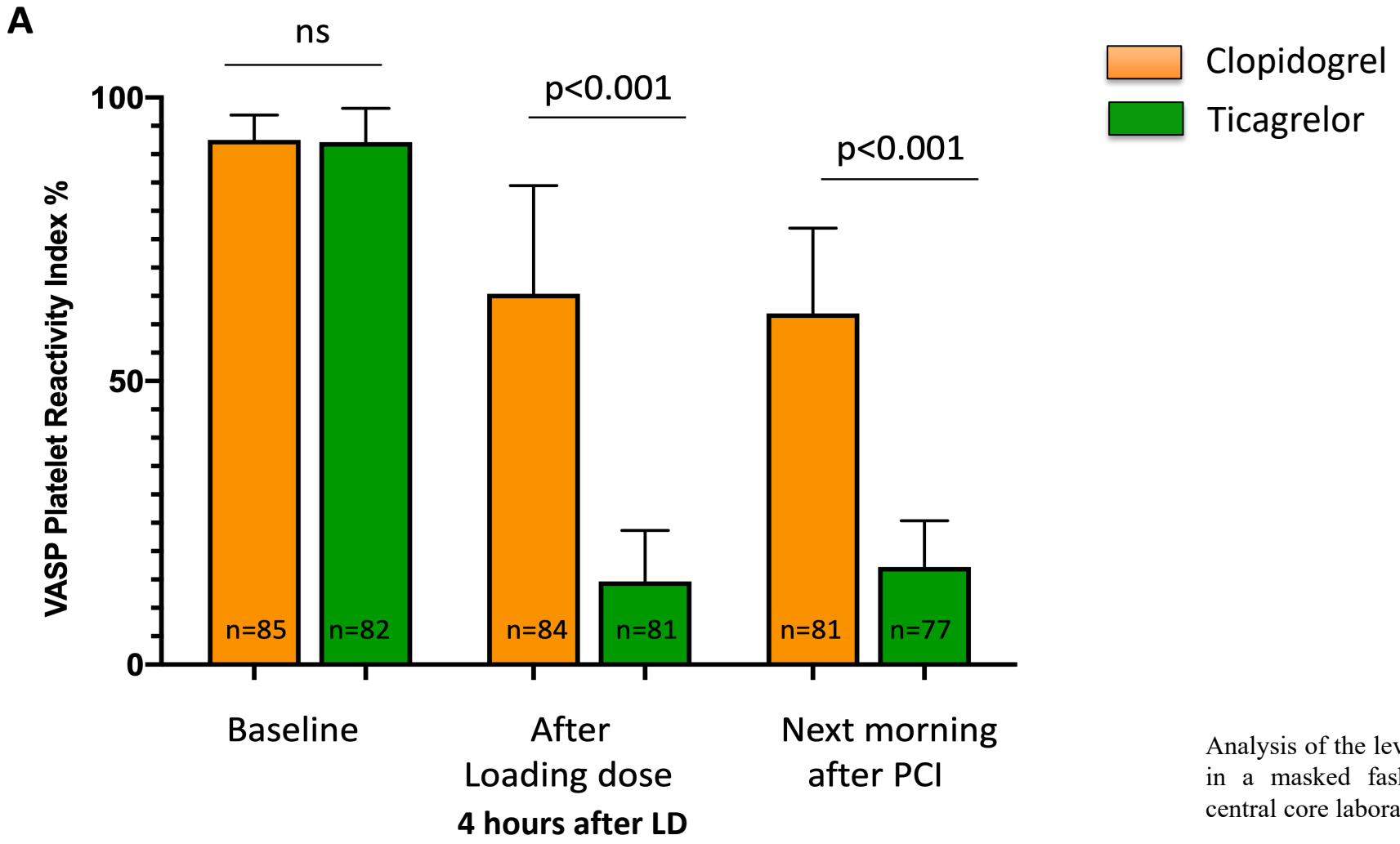
| | Ticagrelor n= 941 | Clopidogrel n= 942 |
|---|---|---|
| **Characteristics** | | |
| **Age – years** | **66 ± 9·2** | **66·6 ± 9·7** |
| Female sex – no. (%) | 177 (18·8) | 207 (22·0) |
| Body mass index – kg/m$^2$ | 27·8 ± 4·5 | 27·6 ± 4·9 |
| Current Smoker – no. (%) | 166 (17·6) | 171 (18·2) |
| Hypertension – no. (%) | 594 (63·1) | 607 (64·4) |
| **Diabetes – no. (%)** | **328 (34·9)** | **352 (37·4)** |
| Dyslipidemia – no. (%) | 581 (61·7) | 570 (60·5) |
| Renal Insufficiency (Crea Cl < 60ml/min) | 89 (9·5) | 98 (10·4) |
| **Past Medical History**- no. (%) | | |
| **History of ACS** | **51 (5·4)** | **50 (5·3)** |
| Prior CABG | 62 (6·6) | 60 (6·4) |
| **Prior PCI** | **339 (36·1)** | **362 (38·4)** |
| Peripheral vascular disease | 121 (12·9) | 115 (12·2) |
| Prior Stroke or Transient Ischemic Attack | 43 (4·6) | 49 (5·2) |
| LVEF < 40% and/or prior episode of HF | 46 (4·9) | 49 (5·2) |

*"the baseline cTn was negative in 93·2% of the patients with no differences between the groups"*

| | Ticagrelor n= 941 | Clopidogrel n= 942 |
|---|---|---|
| **Treatment on admission** | | |
| Aspirin | 814 (86·5) | 804 (85·4) |
| **Clopidogrel** | **388 (41·3)** | **417 (44·3)** |
| **Procedural Characteristics** | | |
| **Number of high-risk feature** | **3·2 ± 1·4** | **3·2 ± 1.5** |
| **Radial/Ulnar approach** | **891 (94·9)** | **895 (94·9)** |
| **Multivessel Disease** | **575 (61·1)** | **586 (62·2)** |
| Number of stents implanted per patient | 1·8 ± 1·0 | 1·8 ± 1·0 |
| Total stent length per patient – mm | 38·4 ± 24·5 | 38·9 ± 24·8 |

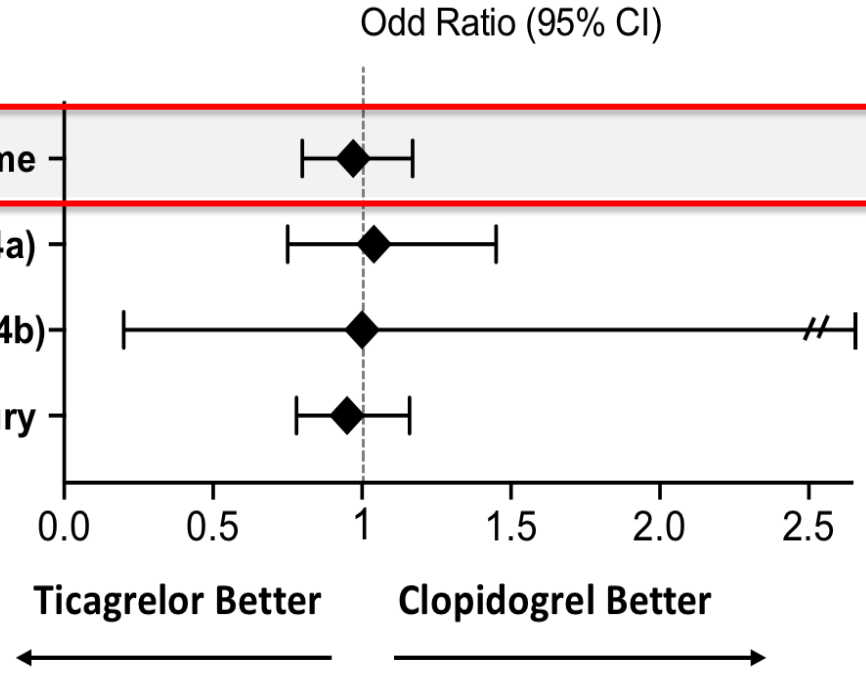
# Biological study

Bio-ALPHEUS ancillary PD study performed in 5 centers n= 167 patients




Analysis of the level of P2Y12 inhibition in a masked fashion at the ACTION central core laboratory (Paris, France)

# Primary Outcome

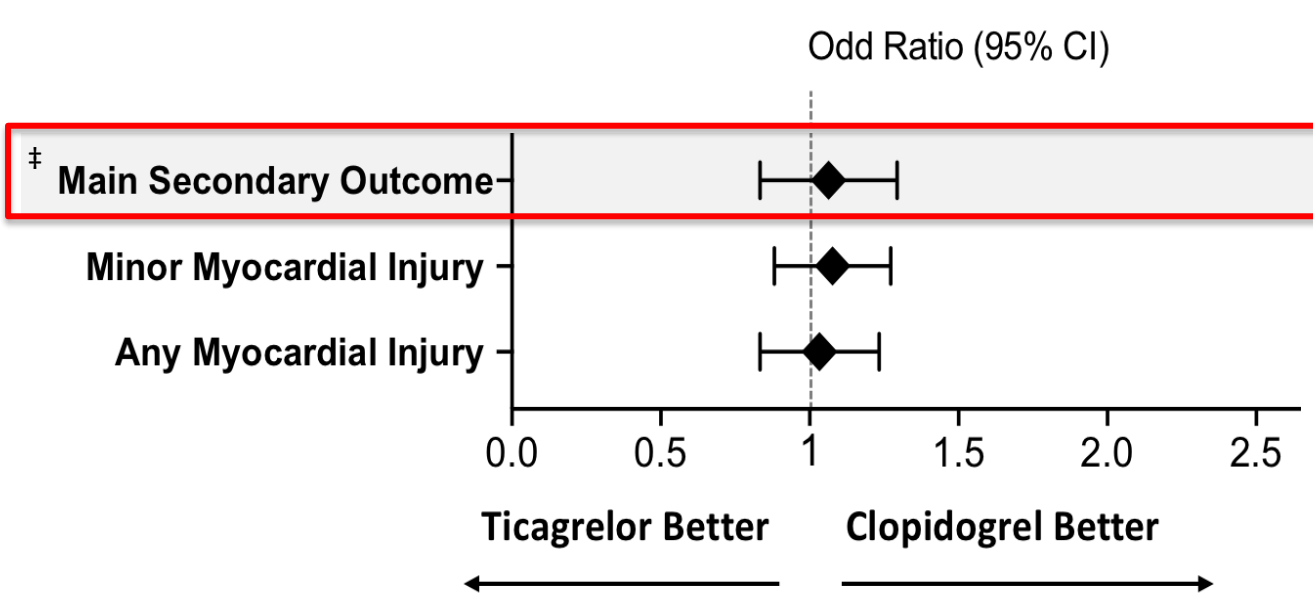



| | N events (%) Ticagrelor | N events (%) Clopidogrel | OR (95% CI) | p value |
|---|---|---|---|---|
| † Primary Outcome | 334/941 (35·5%) | 341/942 (36·2%) | 0·97 (0·80-1·17) | 0·75 |
| Myocardial Infarction (4a) | 80/941 (8·5%) | 77/942 (8·2%) | 1·03 (0·63-1·68) | 0·79 |
| Stent Thrombosis (4b) | 3/941 (0·3%) | 3/942 (0·3%) | 1·00 (0·20-4·97) | 1·00 |
| Major myocardial injury | 251/941 (26·7%) | 261/942 (27·7%) | 0·95 (0·78-1·17) | 0·61 |

†3rd Universal definition of MI

Thygesen K et al. Eur Heart J 2012

# Main Secondary Outcome

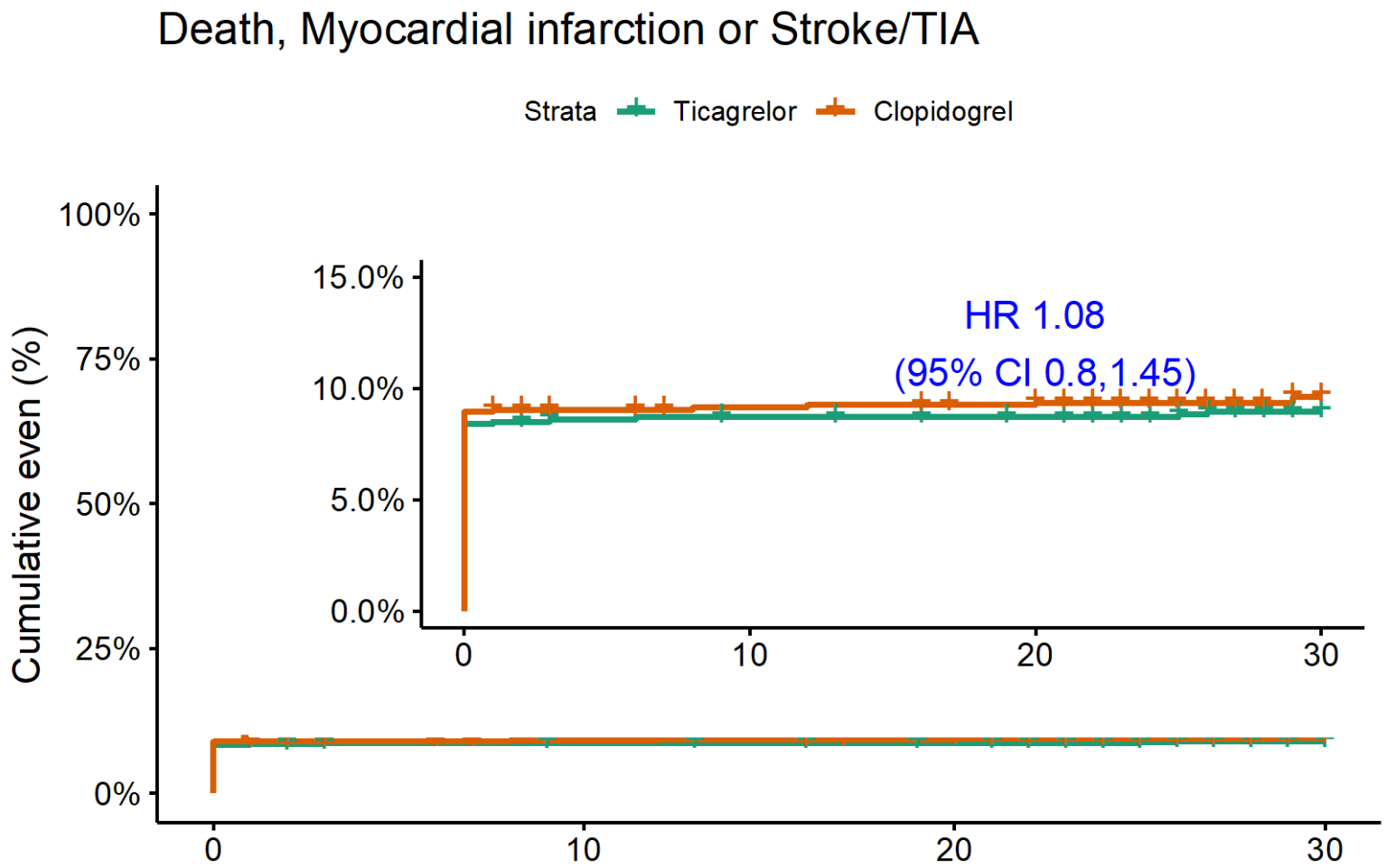



| | N events (%) Ticagrelor | N events (%) Clopidogrel | OR (95% CI) | p value |
|---|---|---|---|---|
| ‡ Main Secondary Outcome | 730/941 (77·6.%) | 723/942 (76·8%) | 1·05 (0·84-1·30) | 0·67 |
| Minor Myocardial Injury | 396/941 (42·1.%) | 382/942 (40·6%) | 1·07 (0·89-1·28) | 0·50 |
| Any Myocardial Injury | 647/941 (68·8.%) | 643/942 (68·3%) | 1·02 (0·84-1·24) | 0·82 |

‡4th Universal definition of MI

Thygesen K et al. Eur Heart J 2018

# Clinical Outcomes at 30 days




*"**death and stroke/TIA were rare events** (0·2% vs 0% and 0·2% vs 0·1%) in the ticagrelor and clopidogrel group respectively "*

# Safety

| | Ticagrelor N=941 | Clopidogrel N= 942 | OR 95% CI | P value |
|---|---|---|---|---|
| **At 48 hours** | | | | |
| Major Bleeding Events (BARC 3 or 5) | 1 (0·1%) | 0 (0·0%) | - | 0·50 |
| Nuisance or Minor bleeding (BARC 1 or 2) | 63 (6·7%) | 50 (5·3%) | 1·28 (0·87 – 1·88) | 0·20 |
| Any Bleeding (BARC 1 to 5) | 64 (6·8%) | 50 (5·3%) | 1·30 (0·89-1·91) | 0·17 |
| **At 30 days** | | | | |
| Major Bleeding Events (BARC 3 or 5) | 5 (0·5%) | 2 (0·2%) | 2·51 (0·49-13·0) | 0·29 |
| **Nuisance or Minor bleeding (BARC 1 or 2)** | **105 (11·2%)** | **71(7·5%)** | **1·54 (1·12-2·11)** | **0·007** |
| **Any Bleeding (BARC 1 to 5)** | **110 (11·7%)** | **73 (7·7%)** | **1·58 (1·15-2·15)** | **0·0039** |

*Dyspnea was more frequent in the ticagrelor group (11.2%) as compared with the clopidogrel group (0.5%) and lead to more frequent discontinuation of the study drug (2.2% vs. 0.4%) for each group respectively.*

# Limitations

- Open label trial
- Sensitive endpoint (periprocedural MI and myocardial injury)
- Patients under chronic clopidogrel therapy included
- All troponin assays authorized to reflect real-life

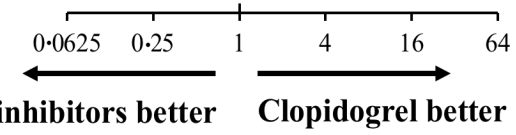
# Pooled Analysis n=2654 patients

# SASSICAIA trial (Prasugrel) – ALPHEUS trial (Ticagrelor)

781 patients

1883 patients

| | Ticagrelor or Prasugrel (n/N) | Clopidogrel (n/N) | Event rates (%) | | Odds ratio | 95% CI | P value |
|---|---|---|---|---|---|---|---|
| Death, MI, ST or stroke | 156/1323 | 158/1341 | 11·8 | 11·8 | 1·01 | 0·80 – 1·28 | 0·94 |
| Death | 3/1323 | 0/1341 | 0·23 | 0 | 4·09 | 0·46 – 36·70 | 0·21 |
| Any MI | 148/1323 | 154/1341 | 11·2 | 11·5 | 0·98 | 0·77 – 1·24 | 0·85 |
| Stent Thrombosis | 7/1323 | 4/1341 | 0·53 | 0·30 | 1·77 | 0·52 – 6·07 | 0·36 |
| Stroke | 4/1323 | 4/1341 | 0·30 | 0·30 | 1·03 | 0·26 – 4·13 | 0·97 |
| Urgent vessel revascularization | 5/1323 | 10/1341 | 0·38 | 0·75 | 0·51 | 0·17 – 1·48 | 0·21 |
| BARC ≥ 2 | 48/1323 | 37/1341 | 3·6 | 2·8 | 1·34 | 0·86 - 2·07 | 0·19 |
| BARC ≥ 3 | 12/1323 | 8/1341 | 0·91 | 0·60 | 1·55 | 0·63 - 3·82 | 0·34 |




SASSICAIA - Mehilli J. Circulation: Cardiovascular Interventions. 2020

# Conclusion

- **Higher level of platelet inhibition** obtained with ticagrelor, **does not translate into a reduction of periprocedural MI or myocardial injury** within 48 hours of high-risk PCI performed in stable coronary patients.

- None of the clinical outcomes differed between groups at 30-day follow-up.

- **Ticagrelor use for 30 days did not translate in increased major bleeding rate** but there was an excess of minor bleeding and dyspnea.

# Thanks all ALPHEUS Investigators and supporting team

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Julien | ADJEDJ | Nassim | BRAIK | Nicolas | DELARCHE | Petr | JERABEK | Thibault | MANIGOLD | Etienne | PUYMIRAT | Jean Richard | VI-FANE |
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| Aimé | AMONCHOT | Erwan | BRESSOLLETTE | Thibault | DEMICHELI | Petr | KALA | Marco | MENNUNI | Jack | RAVISY | Wael | YAFI |
| Yann | ANCEDY | Clément | BRIET | François | DERIMAY | Jan | KANOVSKÝ | Antoine | MERLET | Olivier | RESSENCOURT | Michel | ZEITOUNI |
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| Dominique | BOULMIER | Pierre | DEHARO | Laurent | JACQ | Luc | MAILLARD | Emmanuel | POULIDAKIS | Aurelie | VEUGEOIS | | |

THE LANCET

# Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial

*Johanne Silvain, Benoit Lattuca, Farzin Beygui, Grégoire Rangé, Zuzana Motovska, Jean-Guillaume Dillinger, Ziad Boueri, Philippe Brunel, Thibault Lhermusier, Christophe Pouillot, Elisa Larrieu-Ardilouze, Franck Boccara, Jean-Noël Labeque, Paul Guedeney, Mohamad El Kasty, Mikael Laredo, Raphaëlle Dumaine, Grégory Ducrocq, Jean-Philippe Collet, Guillaume Cayla, Katrien Blanchart, Petr Kala, Eric Vicaut, Gilles Montalescot, on behalf of the ALPHEUS investigators**

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ClinicalTrials.gov number, NCT02617290.