Final Study Report

Study Title: Evaluation of the effects and plasma concentration of the potent platelet inhibitor ticagrelor, after crushed and non-crushed intake, after semi-urgent coronary bypass and in patients after cardiac arrest

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1. Introduction

Since the publication and evaluation of the PLATO study and the reimbursement of ticagrelor for patients with an acute coronary syndrome, the department of cardiology of UZ Ghent started the administration of ticagrelor in patients following an acute coronary syndrome.
Not all of these patients are fully awake and responsive, patients can be hospitalised in an intensive care unit following a cardiac arrest or following (semi-)urgent cardiac surgery. These patients will also receive ticagrelor, but the tablets need to be crushed and given by a nasogastric tube.

The efficacy of a crushed tablet has not yet been studied within this setting. The first aim of the study is to evaluate the platelet inhibition by a crushed tablet of ticagrelor. We will evaluate the platelet inhibition in patients when taking a crushed tablet, given through a nasogastric tube when they are sedated and secondly in the same patients after administration of intact tablets of ticagrelor, when fully awake. We will evaluate the effect of ticagrelor on platelet inhibition in patients who are sedated versus non-sedated patients. This will be evaluated in two separate clinical conditions of ACS.

The first group are patients after semi-urgent coronary bypass surgery.

The second group are patients after cardiac arrest.

This is a non-randomised design.

We will test the platelet inhibition by a Platelet Function Analyser (PFA) activated by Adenosine Di Phosphate. Results of the PFA give 'closure times' and are expresses in seconds.
A second test is a Platelet Aggregometry (Aggreguide A-100) that analyses and measures a patient's platelet function. Results will be expressed in Aggregation Units (Scale 0-10).

The second aim of the study is to determine plasma concentrations of ticagrelor and its main metabolite AR-C124910XX in these two patient populations after receiving 180mg or 90mg start-dose. Determination of plasma concentrations is done after protein precipitation, by using liquid chromatography with mass spectrometry detection[6]. The tests will be done by the Covance laboratory using fully validated analytical methods.

2. Objectives of the study

2.1 Primary objectives

The first aim of the study is to prove that after starting the therapy with crushed tablets, the platelet inhibition will be as expected after starting therapy with intact tablets. Gurbel et al. showed that 100% of the patients on ticagrelor treatment have a decrease from baseline platelet aggregation of >10% 4 hours after last maintenance dose.[1] So we expect

that after 3 days of treatment[2], all of our patients will have a closing time of more than 106seconds[3-5].
We will observe two different clinical conditions of Acute Coronary Syndrome. First after semi-urgent coronary bypass surgery, secondly in patients after cardiac arrest.
Both are clinical situations in which crushed tablets are needed to give.

2.2 Secondary objectives

The second objective is to determine plasma concentrations of Ticagrelor and AR-C124910XX in these two patient populations after receiving 180mg or 90mg start-dose. Determination of plasma concentrations is done after protein precipitation, by using liquid chromatography with mass spectrometry detection[6]. Measurements will be determined before intake (0h) and at 0,5; 1; 2; 4; 8; 24h and at day 4 +4h.[7] The first 24h this will be a crushed tablet and 4 hours after the first intake at day 4 of therapy, this will be a non crushed tablet.

3. Investigational Medicinal Product

Composition and dosing

The commercially available Brilique™ tablets of 90mg.
The active substance is ticagrelor. Each film-coated tablet contains 90 mg of ticagrelor.
The other ingredients are:
Tablet core: mannitol (E421), dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl-cellulose (E463), magnesium stearate (E470b)
Tablet film coating: hypromellose (E464), titanium dioxide (E171), talc, polyethylene-glycol 400, and ferric oxide yellow (E172).
Dosing: 90mg tablet, twice a day after a loading dose of 180mg 12hrs before.

Producer

Astra Zeneca AB, Södertalje, Sweden

Distributor

Astra Zeneca AB.
Commercially packs will be relabelled and distributed by MOVIANTO.

Packaging

Commercially available package is used for the normal oral and crushed administration of tablets.

Administration way

Orally intake of the tablet is done with 30 ml of water.
Administration via nasogastric tube:
The tablets for nasogastric administration will be crushed at the bedside as small as possible, using a mortar and pestle. The crushed ticagrelor will be added, at the bedside of the patient, to 10ml water in a syringe, which perfectly fits the nasogastric tube. The syringe will be shaken until the crushed tablet is homogeneously mixed with the water. Immediately after adding the water the administration of ticagrelor takes place. Hereafter a flush of 20 ml of water will follow. The ICU nurse will do all this manipulations.

Labelling

Commercially available package with study specific labelling, including withdrawing of the commercially label for the "off"-label use tablets.

Storage conditions

Room temperature, in original package

4. Study Protocol Summary

Tracht de belangrijkste informatie uit het protocol beknopt weer te geven. Hieronder een aantal tussentitels als suggestie welke informatie hier kan vermeld worden. Dit is geen nieuwe informatie maar terug te vinden in het protocol.

4.1 Inclusion criteria

- Subject with an acute myocardial infarction with ST elevation
- Subject with an acute myocardial infarction without ST elevation
- Subject with unstable angina (progressive angina during past 2 weeks, negative cardiac markers, Trop T < 0,014µg/l
- First time of taking Brilique
- ≥ 18 years
- Possibility to take a blood sample before administration of Brilique
- Signed Informed Consent, signed by subject or authorized representative, able and willing to provide written informed consent for study participation

4.2 Exclusion criteria

- Active haemorrhage
- Moderate or severe liver failure with coagulopathy
- Pregnancy and lactation
- A history of an intra cerebral haemorrhage
- Patient is HIV positive and treated with Ritonavir and /or Atazanavir
- Patient treated with vitamin K antagonist or with a new oral anti coagulant
- Hypersensitivity to ticagrelor or any of the exipients

4.3 Primary endpoint

The first aim of the study is to prove that after starting the therapy with crushed tablets, the platelet inhibition will be as expected after starting therapy with intact tablets. So we expect that after 3 days of treatment, all of our patients will have a closing time of more than 106seconds.
We will observe two different clinical conditions of Acute Coronary Syndrome. First after semi-urgent coronary bypass surgery, secondly in patients after cardiac arrest.
Both are clinical situations in which crushed tablets are needed to give.

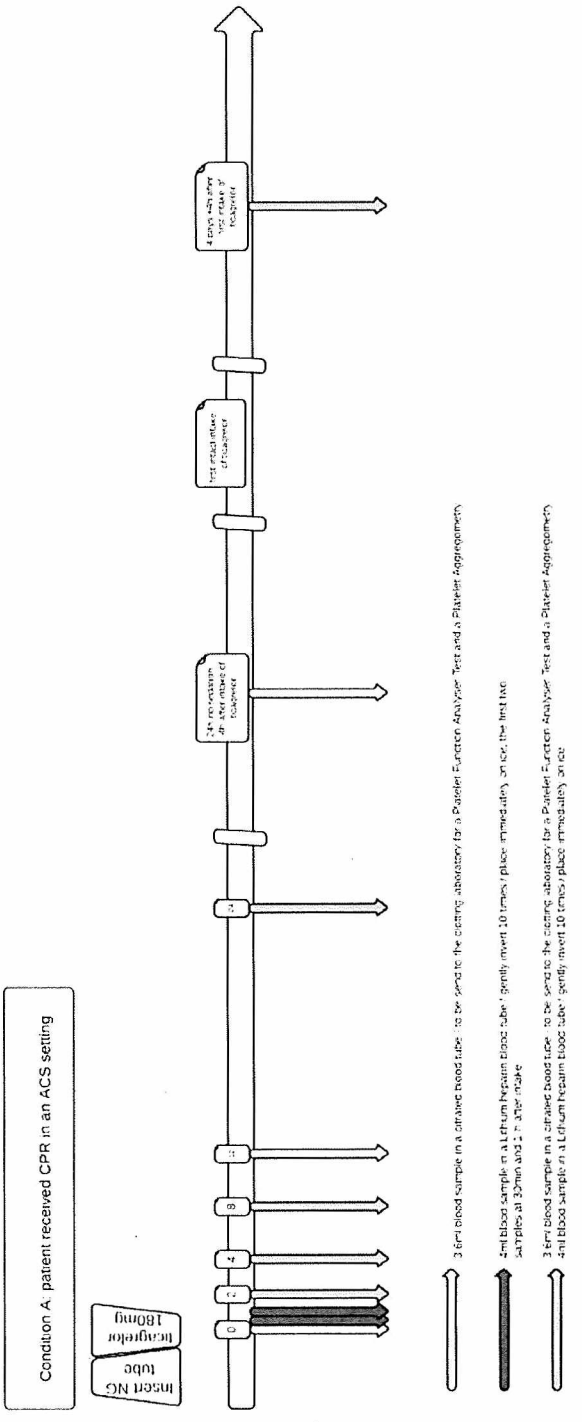
4.4 Secondary endpoints

The second objective is to determine plasma concentrations of Ticagrelor and AR-C124910XX in these two patient populations after receiving 180mg or 90mg start-dose. Measurements will be determined before intake (0h) and at 0,5; 1; 2; 4; 8; 24h and at day 4 +4h.[7] The first 24h this will be a crushed tablet and 4 hours after the first intake at day 4 of therapy, this will be a non crushed tablet.

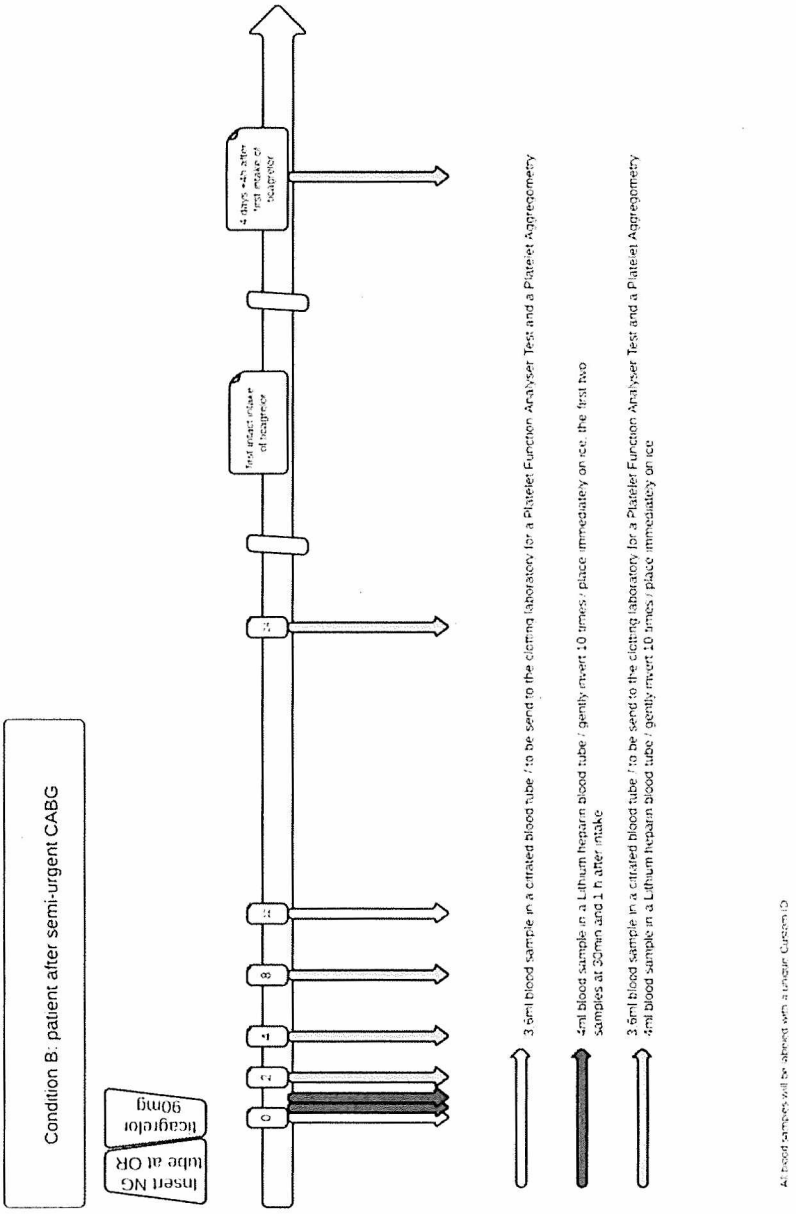
4.5 Procedures

50 patients of each condition :

Condition A: patient received CPR in an ACS setting



Condition B: patient in need of a semi-urgent CABG



For the clotting tests: The ICU nurse, following standard of care rules, takes a 3,6ml blood sample. The sample is taken in a citrated blood tube. The tube will be send to the clotting laboratory of UZ Ghent. Within a maximum of 4 hours after arrival, the laboratory staff will perform the Platelet Function Analyser test and the Platelet Aggregometry. The sample will be processed at ambient temperature. The sampling blood volume will equal the laboratory testing volume needed. The citrated blood tube and any remaining blood residuals will be destructed by incineration.

For the plasma concentrations: The ICU nurse, following standard of care rules, takes a 4ml blood sample. The sample is withdrawn in a BD vacutainer tube, containing spray-dried Lithium Heparin. Following collection, the samples is gently inverted 10 times and immediately placed on ice. Within 30 minutes of blood collection, the sample is centrifuged at 1500g, at 4°C during 10 minutes. 2 aliquots of at least 1ml plasma are transferred into 2

x1,8ml screw-capped polypropylene tubes using a disposable polypropylene pipette. The plasma samples are stored at -20°C in an upright position within 30 minutes of plasma preparation and kept frozen at this temperature until shipment and during shipment to the BA laboratory.

Pre-printed labels with a unique Custom ID will be used on all sample and aliquot tubes. Information on PK labels: Study, Subject ID, Custom ID, Period, Visit, Time Nominal, Analyte and Biological Matrix. Information on clotting labels: Study, Subject ID, Custom ID, Period, Visit, Time Nominal.

Shipment Instructions

Ship the aliquots frozen on dry ice. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to **ensure they remain frozen for at least 72 hours.**

Samples should be placed in a courier box with a paper copy of the Sample Inventory. Samples should be boxed up with each subject's samples in profile order and listed in the same order on the Sample Inventory for ease of checking at the bioanalytical laboratory (BioA Lab).

Once the courier has collected the samples, the sample receiver at the BioA Lab should be notified via email of the courier name, airway bill number, expected delivery date/time and shipment contact. An electronic sample inventory (Excel format, Request file) should also be attached to this email. The CBioA PM should be copied on this correspondence.

4.6 Randomisation and blinding

No randomisation, no blinding

5. Study analysis

Sample size calculation

For the PFA tests:

With a sample size of 100 patients (50 in each condition), and an expected proportion of 99%, we have 92% power to show that the proportion of patients with a closing time of >106 seconds, is 93% or higher after 4 days of ticagrelor therapy.

For the PK tests:

For a coefficient of variation (CV) of 44%, a probability width of 0,8 0,8; a two-sided 95% confidence interval (CI) and a CI half width of 20%, a sample size of 22 in each condition will be needed.

Analysis of the samples

Platelet Function Analysis, done under supervision of K. Devreese, MD PhD. The Platelet Function Analyser is a system for analysing platelet function in which citrated whole blood is aspirated at high shear rates through disposable cartridges containing an aperture within a membrane coated with in this case collagen and ADP (CADP). A special cartridge (PFA P2Y) is used intended for the detection of platelet P2Y12-receptor blockade in patients undergoing therapy with a P2Y12-receptor antagonist. These agonists induce platelet adhesion, activation and aggregation leading to rapid occlusion of the aperture and cessation of blood flow termed the closure time (CT).

AggreGuide A-100-light scattering Platelet Aggregometry, done under supervision of K. Devreese, MD PhD. This blood test analyses and measures a patient's platelet function (stickiness). The AggreGuide can analyse and measure the response to anti platelet therapy including: aspirin and ADP inhibitors.

Pharmacokinetic analytic methods: Ticagrelor and AR-C124910XX (the predominant active metabolite of ticagrelor) plasma concentrations are determined after protein precipitation, by Covance laboratories, using liquid chromatography with mass spectrometry.

Statistical analysis

For the PFA tests: To detect differences in the mean of the closing time (PFA) at each sample time compared to the baseline, we will use the paired t-test.

To detect differences in the proportion of patients with a closing time >106 seconds between sample times, McNemar testing will be used.

The two patient cohorts will receive blood samples during 4 days, with this short period; the risk for dropouts is reduced.

Bonferroni correction was not calculated as the principle aim of the study is to prove that after 4 days of treatment 99% of the patients have a closing time > 106s.

For the PK tests: Pharmacokinetic parameters are descriptively summarized. Geometric mean and corresponding 95% interval of the maximum plasma concentrations (Cmax) and the median time to reach this maximum plasma concentration (tmax) will be calculated.

6. Independent Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 7, dd. 30/09/2014* - *ICF version dd. 03/10/2014* - *Protocol summary 1 dd. 17/09/2013* - *Document A version 30/09/2014* - *Investigators brochure dd. 03/06/2013*	***Approval date Central EC:*** *25 NOV 2014*	***Approval date FAMPH:*** *17 NOV 2014*

7. Results

7.1 Subject enrollment and demographics

ARM 1:

First inclusion at 18 March 2015, last Inclusion at 31 December 2017, last visit follow up visit at 4 January 2015. We included 20 patients after semi-urgent coronary bypass surgery. Ticagrelor was stopped in patients at least 72h before surgery, or was started for the first time after the surgery. From the first postoperative day, the patients received twice-daily 90mg. The first one or two tablets administered, were crushed, given through a nasogastric tube. The next tablets were mostly swallowed with water. Measurements for Platelet Function Analysis were done at 0h, 2h, 4h, 8h, 12h, 24h and at day 4+ 4h. Platelet inhibition was tested with Platelet Function Analyser (PFA) activated by Adenosine Di Phosphate (ADP). When testing platelet inhibition by ticagrelor, an ADP cartridge is used and the CT should be longer than 113 seconds. Plasma concentrations were determined at 30min, 1h, 2h, 4h, 8h, 24h and day 4+4h. Plasma concentrations were measured after protein precipitation, by using liquid chromatography with mass spectrometry detection.

ARM 2:

First inclusion at 8 April 2015, last inclusion at 5 December 2019, last follow up visit at 9 December 2019. We included 20 patients after successful resuscitation for cardiac arrest of acute ischaemic origin (16 STEMI + 4 NSTEMI). Only 1 patient was treated conservatively, 2 patients underwent an

urgent CABG, the remainder were treated with PCI. All patients received a loading dose of ticagrelor before starting daily therapy. As patients were not able to swallow, tablets were crushed and given through a nasogastric tube. Measurements for PFA were done at 0h, 2h, 4h, 8h, 12h, 24h and at day 4 + 4h. Platelet inhibition was tested with PFA activated by 20µg Adenosine Di Phosphate (ADP). PFA CT > 113 seconds was used as reference range for a ticagrelor effect. Plasma concentration were determined at 30min, 1h, 2h, 4h, 8h, 24h and day 4 + 4h. Plasma concentrations were measured after protein precipitation, by using liquid chromatography with mass spectrometry detection.

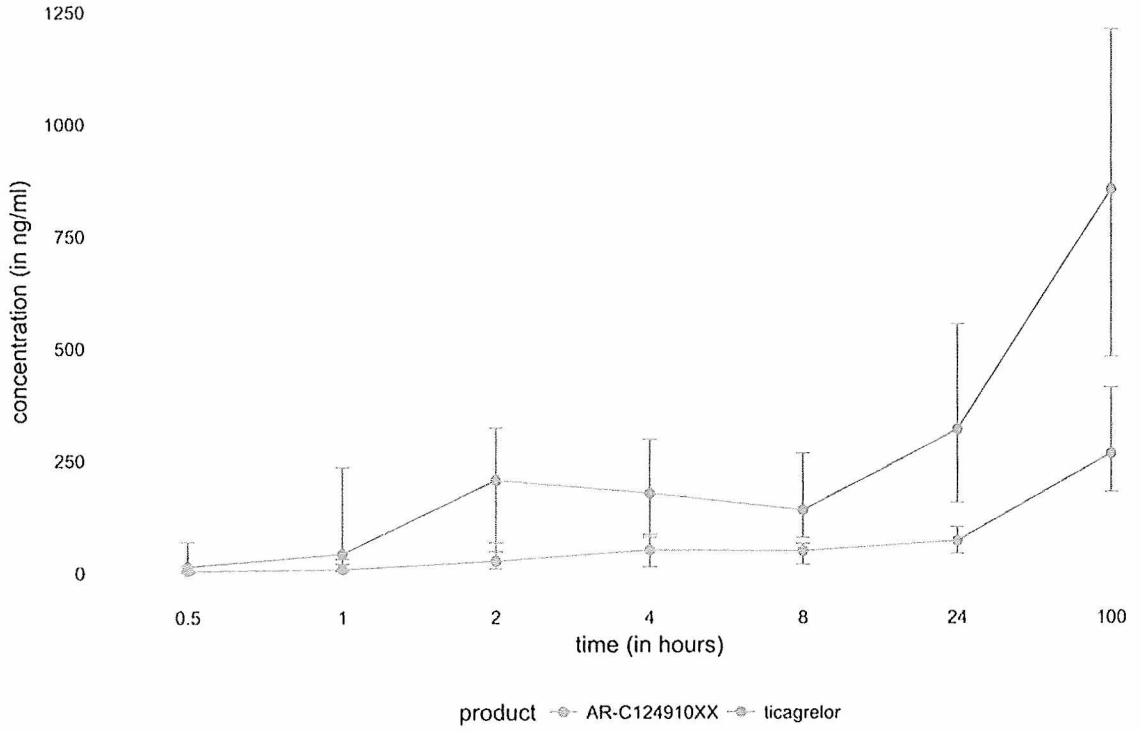
7.2 Study specific results

ARM 1:

We included 20 patients after ***semi-urgent coronary bypass surgery***. Ticagrelor was stopped in patients at least 72h before surgery, or was started for the first time after the surgery. From the first postoperative day, the patients received twice-daily 90mg. The first one or two tablets administered, were crushed, given through a nasogastric tube. The next tablets were mostly swallowed with water. Measurements for Platelet Function Analysis were done at 0h, 2h, 4h, 8h, 12h, 24h and at day 4+ 4h. Platelet inhibition was tested with Platelet Function Analyser (PFA) activated by Adenosine Di Phosphate (ADP). When testing platelet inhibition by ticagrelor, an ADP cartridge is used and the CT should be longer than 113 seconds. Plasma concentrations were determined at 30min, 1h, 2h, 4h, 8h, 24h and day 4+4h. Plasma concentrations were measured after protein precipitation, by using liquid chromatography with mass spectrometry detection

	Median [IQR]	Geometric mean (95% CI)
Ticagrelor		
Tmax (h)	100 [100;100]	
Cmax (ng/mL)	857.0 [496.8; 1157.5]	810.0 (631.2 – 1039.4)
AR-C124910XX		
Tmax (h)	100 [43;100]	
Cmax (ng/mL)	251.0 [173.0; 396.5]	243.5 (185.0 - 320.6)

	PFA 0h	PFA 2h	PFA 4h	PFA 8h	PFA 12h	PFA 24h	PFA 4d+4h
%pts with PFA> 113s	26.3% (5/19)	70% (14/20)	80% (16/20)	75% (15/20)	75% (15/20)	85% (17/20)	84% (16/20)
p		0.030	0.006	0.024	0.012	0.006	0.012

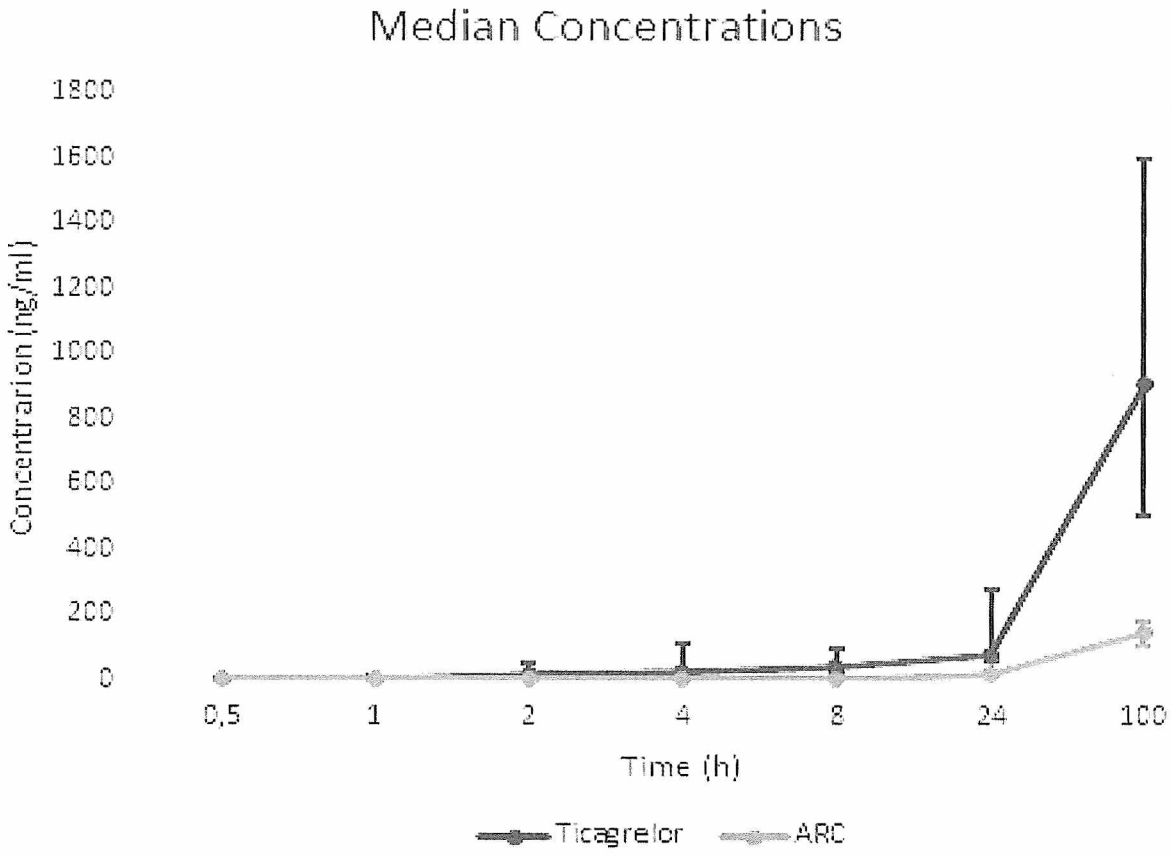


ARM 2:

Out of 20 ***resuscitated patients*** enlisted in this study, 13 were still alive at day 4. At 24h, more than 80% of the survivors showed platelet inhibition as proven by a CT >113s. In 92% of the survivors, the PFA showed platelet inhibition at day 4 with a median CT of > 300s. For ticagrelor, the median time to peak plasma concentration (Tmax) was 100h [8; 100] for a median Cmax of 615.5 ng/ml [217.5; 1385.0]. The geometric mean was 467 ng/ml (248.5; 877.4). For AR-C124910XX, median Tmax was 100h [8; 100] for a Cmax of 131.0 ng/ml [52.1; 177.7]. The geometric mean for the metabolite was 69.5 ng/ml (32.4; 149.0).

	Median [IQR]	Geometric Mean [CI 95%]
Ticagrelor		
Tmax (h)	100 [8; 100]	
Cmax (ng/ml)	615.50 [217.50; 1385.00]	466.98 [248.54; 877.40]
AR-C124910XX		
Tmax (h)	100 [8; 100]	
Cmax (ng/ml)	131.00 [52.10; 177.75]	69.49 [32.40; 149.00]

	PFA 0h	PFA 2h	PFA 4u	PFA 8h	PFA 12h	PFA 24h	PFA 4d+4h
% pts with PFA>113s	33% (1/3)	28% (5/18)	53% (9/17)	63% (12/19)	67% (12/18)	89% (17/19)	92% (12/13)
p	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05



8. Safety

As we have not seen adverse events and as all patients received ticagrelor for good indications, we can conclude that no extra risks were taken.

9. Protocol deviations

No protocol deviations

10. Discussion and overall conclusions

ARM 1:

At day four of therapy 84% of the patients showed a CT longer than 113s, meaning full platelet inhibition by ticagrelor.

At day 4 all patients reached the peak plasma concentration. These findings are comparable to pharmacokinetic studies with ticagrelor in healthy volunteers.

ARM 2:

At day 4 of therapy, 92% of the survivors showed a CT longer than 113s, meaning platelet inhibition by ticagrelor. In more than 80%, this was even the case at 24h.

The median time to reach peak concentrations was 4 days, which is comparable to pharmacokinetic studies with ticagrelor in healthy volunteers. It should be noted that the dispersion in achieving Cmax is wide and can be reached earlier than at 4 days.

11. References

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