Report Synopsis of Study Effects of clopidogrel vs prasugel vs ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting. A randomised, prospective study

Short Title: Endothelium, Stenting, and antiplatelet Therapy (EST) - Clopidogrel, Prasugrel, Ticagrelor study

EudraCT-Nr.: 2011-005305-73

Vorlage-Nr.: 4038158

1) **Name of Sponsor/Company:** University Medical Centre of the Johannes Gutenberg-University Mainz represented by the executive board of the University represented by the scientific member of the executive board Univ.-Prof. Dr. U. Förstermann delegated to the Director of II. Medizinische Klinik und Poliklinik Univ.-Prof Thomas Münzel	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** *Efient®, Brilique™, Clopidogrel ratiopharm*		
3) **Name of Active Substance:** *clopidogrel, prasugrel, ticagrelor*		

5) **Title of Study[2]:** Effects of clopidogrel vs prasugel vs ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting. A randomised, prospective study. The initial study protocol (version 1.2. dated 18-April-2012) was approve on 06-July-2012. The study initially randomized a total of 90 subjects to one of the 3 groups. After performing an interims analysis and evaluation of the results by an external advisory board, it was decided to continue with the recruitment of patients until a total of 36 patients per group complete the study. The recruitment of the first 90 patients needed for the interim analysis started in September 2012 and ended in November 2013. Interim analysis was perform in January 2014. The data were evaluate by the Data Safety and Monitoring Committee of the study. After review, it was decide to prolong the recruitment of patients. Due to the publication of a "rote hand Brief" by EMEAH on the use of prasugrel, the protocol needed an important change. It was recommend that the administration of Prasugrel (Efient) should only occur at the time of coronary angiography, and not before. This recommendation was respect for the future. This was involve two changes to the protocol: 1. randomization and dispense of the medication was occur at the time of catheterization, 2. there was no assessment of endothelial function at 2 hours after administration of the medication. The recruitment restarted after approval of the revised protocol (amended version 1.3 dated 24-February-2013, approved on 27-March-2014) in April 2014 and was to last until April 2015. On 24-Feb-2016 the sponsor notified the early termination of the trial due to slow recruitment.

6) **Principal Investigator(s):** Univ.-Prof. Dr. med. Thomas Münzel

7) **Study centre(s):** Zentrum für Kardiologie, Kardiologie I, Universitätsmedizin Mainz der Johannes Gutenberg-Universität Mainz, Langenbeckstraße 1, 55131 Mainz, Germany

8) **Publication (reference):**

Effects of clopidogrel, prasugrel and ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting for an acute coronary syndrome. A randomised, prospective, controlled study. Schnorbus B1, Daiber A, Jurk K, Warnke S, König J, Krahn U, Lackner K, Munzel T, Gori T; BMJ Open. 2014 May 6;4(5):e005268. doi: 10.1136/bmjopen-2014-005268.

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

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Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Münzel T, Gori T;Eur Heart J. 2020 Jan 3. pii: ehz917. doi: 10.1093/eurheartj/ehz917

9) **Studied period (years)**[3]:	10) **Phase of development:** IV
Date of first enrolment: 20.09.2012 *Date of last completed: 14.12.2015* *On 24-Feb-2016 the sponsor notified the early termination of the trial*	

11) **Objectives:** The primary objective of the trial is to investigate the impact of the three treatments under study on endothelial function as assessed by flow-mediated dilation (FMD) in patients who have undergone stenting

Secondary objectives:

- To investigate the changes in L-FMC and reactive hyperemia in the three groups at 1 day, 1 week, 1 month after stenting.
- To investigate the safety and tolerability of clopidogrel, prasugrel and ticagrelor

12) **Methodology:**

The effect of coronary artery stenting on endothelial function was tested. The parameters of endothelial function used for this purpose included flow-mediated dilation (FMD, primary endpoint) and flow-mediated constriction (FMC). For both outcomes FMD and FMC, linear mixed models were fitted to measurements taken on day 1, 6 and 28 after stenting that allowed for expected outcome to depend on measurement time independently in each treatment group. Dependency between repeated measurements was modelled with unstructured covariance structure. Separate models were fitted to compare Prasugrel with Clopidogrel and Ticagrelor with Clopidogrel. For the primary analysis, effects were allowed to vary with study period thus acknowledging the fact that treatment schedule had to be modified after period 1. Treatment effects were defined as averaged contrast (mean difference) over measurements on day 1, 6 and 28. The primary endpoint of the study was the mean difference in FMD on these three study visits among the three grous. One sided p-values obtained for each period were combined by the inverse normal method. Combined effect estimates were estimated by fitting a model to all data without considering study period as an effect. The smaller of the two combined one sided p values resulting from comparing Prasugrel and Ticagrelor to was referred to a Bonferroni adjusted critcal nominal alfa of 0.0125, which results in control of a global type I error of 0.025 for one sided hypotheses. If the first hypothesis was rejected, the second had to be tested against a critical alfa of 0.025.

13) **Number of patients (planned and analyzed):**

Planned: 216, analysed 125

This three armed trial was planned as an adaptive two stage design with maximally 72 patients per group and one interim analysis after 18 evaluable patients per group.

Interim analysis was undertaken after randomization of 30 patients per group with 57/90 patients having received a stent and 56 patients evaluable for the primary outcome. Based on the results, revised sample size was fixed to further 18 patients per group. Recruitment was then stopped after recruiting 36 further patients with one patient withdrawn before assignment of treatment.

Final analysis of primary outcome is based on 91 patients (Clopidogrel/ Prasugrel/ Ticagrelor: 31/ 17/ 33)

For comparison of the three treatment arms with respect to the average FMD over the three measurements after stenting, we used an ordered test strategy.

At first, prasugrel and ticagrelor were tested separately versus clopodigrel by a one-sided t-test for independent samples at a nominal level of 0.0125. This assures a multiple level of 0.025 by virtue of the Bonferroni correction method. By protocol, if at least

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

one of the two null hypotheses is rejected, the two treatments prasugrel and ticagrelor would be tested for difference by a two-sided t-test at a significance level of 0.05.

The preceding testing (prasugrel and ticagrelor separately versus clopodigrel) has in each case an adaptive design with an interim analysis. The weighted inverse normal combination method and an O'Brien-Fleming-design will be used with a binding stopping for futility. The interim analysis is planned after 18 patients for each treatment group have been randomized, have received a stent and have completed their 4 weeks follow-up with at least one evaluable FMD measurement after stent implantation. The first stage of each comparison is stopped for futility if the respective one-sided p value exceeds 0.7.

The sample size calculation was based on a simplified analysis applied to one pre-specified time point (e.g. 4 weeks) with the following assumptions:

Standard deviations in each group = 3%

Mean difference between groups = 2.6%

Power of 0.90.

Then a sample size of 18 patients in each group was needed for the interim analysis.

We assumed that 70% of the randomized patients would actually receive a stent and would be evaluable. Then a total of 78 patient would have to be randomized for the interim analysis. It was planned to continue randomization until 18 patients per group with stent and evaluable follow-up are available.

If a treatment comparison of the interim analyses resulted in a p-value of 0.0007 or lower, the respective superior treatment arm may be excluded from further randomization.

14) **Diagnosis and main criteria for inclusion:**

- 18-75 years old consecutive patients undergoing coronary angiography and stenting at the University Medical Centre Mainz
- A coronary lesion (and patient) amenable to treatment with drug eluting stent
- Ability of subject to understand character and individual consequences of clinical trial
- Signed and dated informed consent of the subject must be available before start of any specific trial procedures.
- Negative pregnancy test of women with childbearing potential

15) **Test product, dose and mode of administration, batch number:**

Observer-blind randomization to one of 3 groups:

- Group A: Loading dose of 600 mg Clopidogrel, followed by Clopidogrel 75mg o.d. (morning) for 4 weeks
- Group B: Loading dose of 180mg Ticagrelor, followed by Ticagrelor 90mg b.i.d. (morning and evening) for 4 weeks
- Group C: Loading dose of 60mg Prasugrel, followed by Prasugrel 10mg o.d. (morning)

General information about investigational medicinal product (IMP)

General information about investigational medicinal product (IMP) - - clopidogrel

Drug code: clopidogrel

International nonproprietary name (INN): 113665-84-2

Formulation: tablets

Manufacturer: Ratiopharm

Dosage authorized: 75mg

Chargen-number: H05471, N46170, P50902, L55937, L68147, N05471,

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General information about investigational medicinal product (IMP) - prasugrel

Drug code: prasugrel

International nonproprietary name (INN): 274693-27-5

Formulation: tablets

Manufacturer: Ely-Lilly/Daiichi Sankyo

Dosage authorized: 10mg

Chargen-numbers: C260935, C146654, C085417, C124828, C305841, C305841, C371092, C436868, C028309, C085417

General information about investigational medicinal product (IMP) - ticagrelor

Drug code: ticagrelor

International nonproprietary name (INN): 113665-84-2

Formulation: tablets

Manufacturer: Astra Zeneca

Dosage authorized: 90mg

Chargen-numbers: RABA, TDDK, TDCL, RAAK, BAAF, TDAD, NM 146

After interims analysis no loading dose before catheterization were administered (based on the results of the ACCOAST trial: Gilles Montalescot, M.D. et al., N Engl J Med 2013; 369:999-1010September 12, 2013DOI: 10.1056/NEJMoa1308075)

All treatments were administered orally. The active treatments were prepared by the local pharmacy and were boxed in packages that look the same for the three treatments. The dosages selected here are those approved for treatment of patients undergoing coronary artery stenting and/or with acute coronary syndromes and according to the guideline of the European Society for Cardiology.

16) **Duration of treatment:** 28 days

17) **Reference therapy, dose and mode of administration, batch number:**

Ticagrelor is administered orally in a dosage of 90mg b.i.d. Prasugrel is administered orally in a dosage of 10mg o.d., and clopidogrel is administered orally in a dosage of 75mg o.d. The first administration of the drugs is given as a loading dose of respectively 180mg, 60mg, and 600mg for ticagrelor, prasugrel, clopidogrel. After interims analysis, no loading dose was administered. Regarding Chargen-number see 15).

18) **Criteria for evaluation:**

Efficacy:

Assessment of endothelial function

Among the many techniques that allow testing of endothelial function both invasively and non-invasively, the measurement of flow-mediated vasodilation (FMD) remains the most widely employed due to its simplicity, reproducibility, and, particularly, for its non-invasive nature. Along with FMD, our laboratory has recently developed and validated a new measure of endothelial function, which we termed "low-flow mediated constriction" or L-FMC. This method complements the information of FMD and provides a more detailed insight into endothelial homeostasis. The interpretation of these parameters is described in detail in previous papers from our group15, 68. In our laboratory, FMD and L-FMC are measured using a GE vivid 7 ultrasound machine with a 14 MHz matrix linear-array transducer and automatic analysis software15, 68. The analysis of endothelial function data will be performed off line by personnel blinded to the allocation group (also in the case of withdrawal of the patient from the study and/or from the study medication).

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Measurement of endothelial function using FMD: In the method originally developed by Celermajer et al, the radial (or brachial) artery is imaged at rest using high resolution ultrasound imaging. Subsequently, a pneumatic cuff is inflated at the forearm to cause a temporary (4.5-5') interruption of the blood flow. In response to this ischemia, peripheral resistances decrease dramatically. Immediately upon reperfusion, this results in a sudden increase in blood flow and shear stress that reaches 500-1000% of the baseline values (so-called reactive hyperaemia). This increase in shear stress is sensed by the endothelium of the brachial (or radial) arteries, resulting in a vasodilation that can be imaged and quantified by ultrasound techniques.

Measurement of flow-mediated constriction: When performing FMD measurements, the inflation of the pneumatic cuff leads to a progressive reduction in blood flow in the segment of the artery studied with ultrasounds. This reduction is associated with a parallel reduction in shear stress which in turn leads, in healthy volunteers, to a vasoconstriction of ca. 5-6% (in the radial artery). We hypothesized that this vasoconstriction, which we termed "low-flow-mediated constriction" (FMC), could represent a parameter of resting endothelial activity, i.e., a measure of basal (unstimulated) endothelial function. The implementation of FMC has two advantages: the first, that this method allows measuring resting endothelial activity (which complements FMD's "endothelial recruitability"). The second, that it is mediated by different biochemical pathways: while FMD is mainly a nitric oxide (NO)-dependent phenomenon, FMC is determined by release of endothelin-1, of the endothelium-derived hyperpolarization factor (EDHF) and of prostaglandins (PGs)68.

Assessment of reactive hyperemia: reactive hyperemia is the increase in blood flow in response to a prolonged ischemia. Reactive hyperemia can be calculated using a variety of non-invasive methods. In our laboratory, blood flow is assessed using Doppler ultrasounds and Laser Doppler. For Doppler Ultrasound, the procedures are exactly identical to those described above in the section endothelial function studies. Microvascular blood flow will also be measured with laser Doppler flowmetry (Perimed, Sweden). This device measures changes in microvascular blood flow by measuring changes in the frequency of a laser beam reflected from red blood cells. Both methods are absolutely non-invasive, and none of them is associated with any potential risk or discomfort for the patient.

During visits screening, 2, 4, 5 and 6 blood will be sampled for the assessment of cardiac markers and blood counts and other parameters as clinically indicated. An additional sample of 40ml will be sampled and frozen for assessment of cardiovascular biomarkers.

Safety:

Adverse Event (AE)

According to GCP, an adverse event (AE) is defined as any untoward medical occurrence in a subject treated with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not related to that product.

An AE may be:

a new symptom or medical condition

a new diagnosis

a change in laboratory parameters

an intercurrent illness or accident

worsening of a medical condition/diseases existing before the start of the clinical trial

recurrence of a disease

an increase in frequency or intensity of episodic diseases.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

Change in laboratory parameters: The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial,

significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor

a) Risks for the patient connected with the participation to the clinical trial

Beyond the risks associated with the treatments under study (see above), we do not expect any additional risk. The diagnostic tests employed in the study are all non-invasive except blood collection and there are no risks connected to these methods. The assessment of endothelial function is associated with a mild discomfort when the pneumatic cuff is deflated but is per se not associated with any potential risk.

Serious adverse event (SAE)

A serious adverse event (SAE) is one that at any dose (including overdose):

- results in death

- is life-threatening (1)

- requires subject hospitalization or prolongation of existing hospitalization (2)

- results in persistent or significant disability/incapacity (3) or

- is a congenital anomaly/birth defect

- is an important medical event (4).

1 "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

2 If the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to start of the trial) or not associated with an adverse event (e.g., social hospitalisation for purpose) or results in a hospital stay less than 12 hours, the serious criterion "hospitalisation" is not fulfilled. However, it should be noted that invasive treatment during a hospitalisation may fulfil the criteria of "medically important" and may be reportable as a serious adverse event dependent on clinical judgement.

3 "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g., paresis, diabetes, cardiac arrhythmia) fulfils this criterion.

4 Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important.

Clarification of the difference in meaning between "serious" and "severe":

The terms "serious" and "severe" are not synonymous but are often used interchangeably. The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations."

Adverse Reaction (AR)

An adverse reaction is any noxious and unintended response to an investigational medicinal product (the causal relationship between the medicinal product and the adverse event is at least a reasonable possibility).

Serious Adverse Reaction (SAR)

If there is a causal relationship between a serious adverse event and trial medication then the event is called serious adverse reaction (SAR).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction which is unexpected.

An unexpected serious adverse reaction is any adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., the Investigator's Brochure or the current SmPC).

Assessment of AEs by investigator

Subjects must be carefully monitored for adverse events by the investigator. The intensity of the adverse events and the causal relation to trial medication and/or procedures are to be assessed.

Intensity/Severity

The intensity of an AE will be assessed by the investigator as follows:

- Mild: Temporary event which is tolerated well by the subject and does not interfere with normal daily activities.

- Moderate: Event which results in discomfort for the subject and impairs his/her normal activity.

- Severe: Event which results in substantial impairment of normal activities of subject.

Causal relation to trial medication/procedures

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

□ Factors to be considered in assessing the relationship of the adverse event to study drug include: The temporal sequence from drug administration

□ Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

□ Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

□ Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them maybe suspected to cause the event in question.

The investigator evaluated the causal relationship of each adverse event with the administration of the investigational product(s) and/or trial procedures according to modified criteria of WHO 1991.

Certain: A clinical event, including laboratory test abnormalities, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not related: A clinical event, including laboratory test abnormality, that does not follow a reasonable temporal sequence from trial participation and that is definitely caused by the subject's clinical state, other modes of therapy or other known etiology.

1 Period of observation

In this trial, the period of observation for collection of adverse events extends from the time the subject has signed the informed consent document up to the end of the 28 day follow-up visit.

If the investigator detects a serious adverse event in a trial subject after the end of the period of observation, and considers the event possibly related to the prior trial, he/she should contact the sponsor to determine how the adverse event should be

documented and reported.

Documentation of AEs and Follow up

All AEs reported by the subject or detected by the investigator will be documented on the appropriate pages of the case report form (CRF). AEs must also be documented in the subject's medical records.

The following approach will be taken for documentation:

All adverse events (whether serious or non-serious) must be documented on the "Adverse Event" page of the CRF.

If the adverse event is serious the investigator must complete, in addition to the "Adverse Event Page", a "Serious Adverse Event Form" at the time the serious adverse event is detected.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up, but no longer than 30 days after the end of the trial.

Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor.

Immediate reporting of SAEs by investigator

SAEs must immediately (within 24 hours of the investigator's awareness) be reported to:

IZKS Mainz, Langenbeckstr 2, 55131 Mainz, FAX 0049 6131/17-9916

The initial SAE Report should be as complete as possible including the essential details of subject's identification (screening number, random number), the serious adverse event (medical term, diagnosis), the trial medication and the assessment of the causal relationship between the event and the trial medication. The SAE report must be reviewed and signed by the investigator.

The investigator should provide related additional information on the clinical course and the outcome of each SAE as soon as possible via facsimile to IZKS Mainz using the SAE form (Follow up report).

The "Serious Adverse Event Form" is provided in the Investigator Site File.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfils the definition of "serious adverse event", it must be reported as such.

Immediate Reporting of pregnancy by investigator

Any pregnancy diagnosed in a female subject or in the female partner of a male subject during treatment with the investigational product must be reported immediately using the "Pregnancy Reporting Form" to:

IZKS Mainz, Langenbeckstr 2, 55131 Mainz, FAX 0049 6131/17-9916

Pregnancy occurring during the clinical trial, although not considered a SAE, must be reported within the same timelines as a serious adverse event. The outcome of a pregnancy should be followed up carefully and abnormal outcome of mother or child should be reported if any (Follow-up Pregnancy Reporting Form).

Safety evaluation and Reporting by sponsor

The sponsor will ensure that all legal reporting requirements are met. According to GCP the sponsor is responsible for the continuous safety evaluation of the investigational product(s) and the clinical trial.

On behalf of the sponsor, the IZKS Mainz will conduct the management of SAEs and the expedited reporting as required by German Drug Law (AMG) and GCP regulation (GCP-V). Suspected unexpected serious adverse reactions (SUSARs) and safety issues as defined by GCP-V are determined for expedited reporting: The competent authorities and the ethics committees should be notified as soon as possible but not later than 15 calendar days if the event is non-fatal and 7 calendar days if it was fatal.

All investigators will be informed too.

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During the clinical trial the sponsor will submit an annual safety report (development safety update report (DSUR)) to the ethics committee(s) and the competent authorities once a year.

Emergency procedures

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AEs including clinically significant laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Emergency treatment for overdose:

Platelet inhibition by clopidogrel and prasugrel is irreversible and will last for the life of the platelet. Overdose following administration of the study drugs may result in bleeding complications. Symptoms of acute toxicity may be vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals. Based on biological plausibility, platelet transfusion may restore clotting ability.

Emergency Unblinding:

If it is medically imperative to know what trial medication the subject is receiving, the investigator or authorized person should open the randomisation envelope. The investigator or the person who breaks the blind must record the date and the reasons for doing so in the CRF, in the subject's medical record and on the randomisation envelope. Whenever possible, the LKP should be contacted before the blind is broken.

Unblinding within the scope of emergency treatment by third parties

Not needed, emergency procedures are the same for all three drugs.

Other safety data

All observations pertinent to the safety of the study medication will be recorded in the eCRF and included in the final report.

Other safety variables are as follows changes in vital signs and in physical examination

Vital signs

- Blood pressure, Heart rate and temperature

(Blood pressure measurement should be performed in a consistent manner after the patient has been sitting for five minutes. A manual cuff should be used on the same arm each time blood pressure is measured)

Physical examination: assessment of the presence of bleeding (skin, eyes).

1 Other assessments

1 Prior and concomitant illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the case report form (CRF).

1 Prior and concomitant treatments

Relevant additional treatments administered to the subjects on entry to the trial or at any time during the trial are regarded as concomitant treatments und must be documented on the appropriate pages of the CRF.

19) **Statistical methods:**

For both outcomes FMD and FMC, linear mixed models were fitted to measurements taken on day 1, 6 and 28 after stenting that allowed for expected outcome to depend on measurement time independently in each treatment group. Dependency between repeated measurements was modelled with unstructured covariance structure. Separate models were fitted for comparing Prasugrel with Clopidogrel and Ticagrelor with Clopidogrel. For the primary analysis, effects were allowed to vary with study period thus acknowledging the fact that treatment schedule had to be modified after period 1. Treatment effects were defined as averaged contrast (mean difference) over measurements on day 1, 6 and 28. One sided p-values obtained for each period were combined by the inverse normal method. Combined effect estimates were estimated by fitting a model to all data without considering study period as an effect. The smaller of the two combined one sided p values resulting from comparing Prasugrel and Ticagrelor to was referred to a Bonferroni adjusted critcal nominal alfa of 0.0125, which results in control of a global type I error of 0.025 for one sided hypotheses. If the first hypothesis was rejected, the second had to be tested against a critical alfa of 0.025.

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20) **Summary – Conclusions:**

Efficacy results:

In accordance with the protocol, efficacy analysis was based on a modified intention to treat analysis set, containing all patients who received a stent and had at least one FMD measurement during follow up.

These were 90 patients:

- 56 interim patients with stent (C/P/T= 20 /15/21)

- 34 post-interim patients with stent (C/P/T= 11/12/11)

Table 1: Numbers of patients broken down by treatment, stenting and study period.

		Randomized Treatment				
		ND	*C*	*P*	*T*	*All*
Subgroup	*Stent*					
Interim patients	*Wrong medication on loading dose*	.	.	1	.	1
	No Stent	.	10	13	9	32
	Stented	.	20	16	21	57
	All	.	30	30	30	90
Post interim patients	*Stent*					
	No	1	.	.	.	1
	Yes	.	11	12	12	35
	All	1	11	12	12	36
All	*Stent*					
	NA	.	.	1	.	1
	No	1	10	13	9	33
	Yes	.	31	28	33	92
	All	1	41	42	42	126

C = Clopidogrel, P = Prasugrel, T = Ticagrelor, ND = not defined, NA = not available

Homogenity of treatment groups

Patient characteristics broken down by treatment group and study period are displayed in Table 2 for quantitative variables and in Table 3 for qualitative variables. Treatment groups are apparently comparable for the considered characteristics.

Table 2: Baseline characteristics, quantitative variables, efficacy analysis set, for all patients and broken down by study period. P values according to one way ANOVA F test.

All patients

Report Synopsis of Study Effects of clopidogrel vs prasugel vs ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting. A randomised, prospective study

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Vorlage-Nr.: 4038158

	Treatment group									
	Clopidogrel			Prasugrel			Ticagrelor			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	P value
age	31	62.2	10.3	27	60.6	7.8	33	60.5	9.0	0.7140
BMI	31	27.7	4.0	27	28.1	3.1	33	29.2	4.3	0.2956
CHOL	31	197.5	44.7	23	207.6	62.1	28	223.2	52.8	0.6225
HDL	30	44.9	11.3	23	44.5	9.6	28	44.6	11.9	0.4427
LDL	30	119.4	34.2	23	124.9	43.8	28	142.8	41.7	0.5658
TRIG	30	160.5	70.7	23	234.8	179.0	28	192.8	140.4	0.6688
Troponin	8	0.1	0.1	6	0.4	0.9	9	0.4	0.6	0.8101
Troponin sensitive	19	17.8	25.7	17	14.3	25.5	18	14.1	22.1	0.2692
CREAT	31	1.0	0.2	27	0.9	0.2	33	0.9	0.1	0.1801
HGB	31	15.2	1.4	27	15.1	1.3	33	14.8	1.1	0.9912
Troponin post Stent	8	0.1	0.1	8	1.1	2.7	10	2.0	4.5	0.0738
Troponin post Stent sensitive	20	16.8	24.7	19	11.1	19.9	22	20.9	29.1	0.1380
CREAT_postStent	29	0.9	0.2	27	0.9	0.2	33	0.9	0.2	0.4126
rrsys	31	136.8	16.2	27	135.8	18.7	33	140.7	21.9	0.8744
rrdia	31	80.6	8.8	27	82.3	13.1	33	83.2	12.5	0.4801
FMD	31	4.4	4.7	27	4.3	2.8	33	3.8	3.7	0.4617
FMC	31	-2.7	3.3	27	-4.3	3.1	33	-3.3	4.3	0.4659
Basediameter	20	0.3	0.1	15	0.3	0.1	21	0.3	0.1	0.6315

Interim patients

	Treatment group								
	Clopidogrel			Prasugrel			Ticagrelor		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
age	20	62.6	9.9	15	60.3	6.3	21	62.0	9.7
BMI	20	27.7	3.5	15	28.3	3.0	21	29.1	3.4
CHOL	20	195.7	36.9	13	205.5	73.8	17	218.0	40.4
HDL	20	46.3	10.9	13	46.8	10.8	17	43.8	9.9
LDL	20	119.6	30.7	13	121.1	45.9	17	139.1	37.7
TRIG	20	149.6	53.9	13	248.8	220.3	17	199.2	150.6
Troponin	8	0.1	0.1	6	0.4	0.9	9	0.4	0.6
Troponin sensitive	8	16.1	15.6	6	11.1	13.4	8	13.6	27.0
CREAT	20	0.9	0.1	15	0.9	0.2	21	0.9	0.2
HGB	20	15.3	1.2	15	15.3	1.3	21	14.6	1.1
Troponin post Stent	8	0.1	0.1	8	1.1	2.7	10	2.0	4.5
Troponin post Stent sensitive	9	8.9	12.5	7	22.0	29.5	11	15.9	23.3
CREAT_postStent	18	0.9	0.1	15	0.9	0.2	21	0.9	0.2
rrsys	20	135.0	16.8	15	134.1	19.8	21	140.0	23.1
rrdia	20	79.7	7.2	15	80.5	14.8	21	82.1	13.4
FMD	20	4.4	3.0	15	4.0	2.8	21	4.9	3.8
FMC	20	-2.0	2.7	15	-4.6	2.5	21	-2.7	4.3
Basediameter	20	0.3	0.1	15	0.3	0.1	21	0.3	0.1

Post interim patients

	Treatment group								
	Clopidogrel			Prasugrel			Ticagrelor		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
age	11	61.6	11.4	12	61.0	9.8	12	58.0	7.3
BMI	11	27.8	4.9	12	27.8	3.5	12	29.3	5.7
CHOL	11	200.9	58.3	10	210.2	46.4	11	231.3	69.3
HDL	10	42.2	12.0	10	41.5	7.2	11	45.8	14.9
LDL	10	119.0	42.1	10	129.9	42.7	11	148.5	48.4
TRIG	10	182.3	95.9	10	216.6	113.9	11	182.7	129.2

Troponin	0	.	.	0	.	.	0	.	.
Troponin sensitive	11	19.0	31.8	11	16.0	30.6	10	14.5	18.8
CREAT	11	1.0	0.2	12	1.0	0.2	12	0.9	0.1
HGB	11	15.0	1.9	12	14.8	1.2	12	15.2	1.2
Troponin post Stent	0	.	.	0	.	.	0	.	.
Troponin post Stent sensitive	11	23.3	30.6	12	4.7	7.4	11	25.9	34.4
CREAT_postStent	11	1.0	0.2	12	1.0	0.2	12	0.8	0.1
rrsys	11	140.0	15.3	12	137.9	18.0	12	142.0	20.6
rrdia	11	82.4	11.4	12	84.6	10.8	12	85.1	11.2
FMD	11	4.4	7.0	12	4.7	3.0	12	2.0	2.8
FMC	11	-4.0	4.0	12	-3.9	3.9	12	-4.3	4.3
Basediameter	0	.	.	0	.	.	0	.	.

Table 3: Baseline characteristics, binary variables, efficacy analysis set, for all patients and broken down by study period. P values according to Fisher's exact test.

All

	Treatment group						
	Clopidogrel		*Prasugrel*		*Ticagrelor*		
	N	*Proportion*	*N*	*Proportion*	*N*	*Proportion*	*P value*
male	28	0.90	25	0.93	28	0.85	0.7009
Diabetes	5	0.16	5	0.19	12	0.36	0.1329
Hyperchol	15	0.48	18	0.67	18	0.55	0.4003
Hypertension	13	0.42	14	0.52	19	0.58	0.4714

Interim patients

	Treatment group					
	Clopidogrel		*Prasugrel*		*Ticagrelor*	
	N	*Proportion*	*N*	*Proportion*	*N*	*Proportion*
male	18	0.90	13	0.87	18	0.86
Diabetes	2	0.10	1	0.07	6	0.29
Hyperchol	11	0.55	8	0.53	11	0.52
Hypertension	8	0.40	7	0.47	12	0.57

Post interim patients

	Treatment group					
	Clopidogrel		*Prasugrel*		*Ticagrelor*	
	N	*Proportion*	*N*	*Proportion*	*N*	*Proportion*
male	10	0.91	12	1.00	10	0.83
Diabetes	3	0.27	4	0.33	6	0.50
Hyperchol	4	0.36	10	0.83	7	0.58
Hypertension	5	0.45	7	0.58	7	0.58

Efficacy

Treatment effects on FMD and FMC are displayed in Table 1, Table 2, and Table 3. In Table 1, means and standard errors are displayed for each treatment and each measurement time for both outcomes, at first for the whole study group and then broken down by study period. In Table 2 corresponding pairwise treatment comparisons are presented.

For the outcome FMD, Prasugrel is shown to be statistically significantly superior to Clopidogrel (Mean difference 2.13, 95% CI 0.68-3.58, p=0.0047) and to Ticagrelor (Mean difference 1.57, 95% CI 0.31-2.83 p=0.0155). Ticagrelor was not significantly superior to Clopidogrel (Mean difference 0.55, 95% CI -0.73 - +1.82 p=0.39). Broken down by study period, the effects show up even more

pronounced before interim analysis but disappear afterwards (see Table 3).

Table 4: Outcome parameters FMD and FMC. Means and standard errors stratified by treatment group, visit and study period (pre post interim analysis. Missing measurements are adjusted for by fitting linear mixed models for longitudinal data.

FMD [%]

	Treatment group					
	Clopidogrel (n=31)		*Prasugrel (n=27)*		*Ticagrelor (n=33)*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Measurement time						
Screening	4.40	0.69	4.29	0.74	3.81	0.67
2 h after first dose	5.91	0.62	5.33	0.70	6.37	0.62
1 day	2.34	0.60	4.56	0.64	2.89	0.59
6 days	3.19	0.65	4.99	0.67	3.07	0.64
28 days post stenting	2.78	0.63	5.11	0.67	3.98	0.65

FMC [%]

	Treatment group					
	Clopidogrel (n=31)		*Prasugrel (n=27)*		*Ticagrelor (n=33)*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Measurement time						
Screening	-2.71	0.66	-4.26	0.70	-3.26	0.64
2 h after first dose	-3.59	0.65	-5.22	0.74	-2.33	0.65
1 day	-4.08	0.57	-4.67	0.61	-4.87	0.56
6 days	-3.93	0.62	-3.50	0.65	-3.42	0.61
28 days post stenting	-3.89	0.54	-3.29	0.57	-4.91	0.55

FMD [%]

	Interim patients						*Post interim patients*					
	Treatment group						*Treatment group*					
	Clopidogrel (n=20)		*Prasugrel (n=15)*		*Ticagrelor (n=21)*		*Clopidogrel (n=11)*		*Prasugrel (n=12)*		*Ticagrelor (n=12)*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*
Measurement time												
Screening	4.40	0.86	3.99	0.99	4.87	0.83	4.41	1.15	4.66	1.10	1.95	1.10

2 h after first dose	5.86	0.65	5.71	0.75	6.73	0.64	.	.	.	.	.	.
1 day	1.48	0.74	5.23	0.85	2.84	0.72	3.90	1.00	3.73	0.95	3.04	0.99
6 days	3.09	0.78	6.75	0.87	3.09	0.75	3.39	1.06	2.80	0.97	2.96	1.10
28 days post stenting	2.34	0.77	5.73	0.89	4.59	0.80	3.62	1.09	4.34	1.00	2.89	1.08

FMC [%]

	Interim patients						*Post interim patients*					
	Treatment group						*Treatment group*					
	Clopidogrel (n=20)		*Prasugrel (n=15)*		*Ticagrelor (n=21)*		*Clopidogrel (n=11)*		*Prasugrel (n=12)*		*Ticagrelor (n=12)*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*
Measurement time												
Screening	4.40	0.86	3.99	0.99	4.87	0.83	4.41	1.15	4.66	1.10	1.95	1.1
2 h after first dose	5.86	0.65	5.71	0.75	6.73	0.64	.	.	.	.	.	
1 day	1.48	0.74	5.23	0.85	2.84	0.72	3.90	1.00	3.73	0.95	3.04	0.9
6 days	3.09	0.78	6.75	0.87	3.09	0.75	3.39	1.06	2.80	0.97	2.96	1.1
28 days post stenting	2.34	0.77	5.73	0.89	4.59	0.80	3.62	1.09	4.34	1.00	2.89	1.0

Table 5: Treatment effect estimates for the outcomes FMD and FMC. Model based estimates of the mean effect over measurements taken on day 1, 6, and 28. For each pair of treatments a separate linear mixed model for longitudinal data was fitted for three measurements taken after stenting and allowing for an unstructured covariance structure.

Outcome=FMD [%]

Contrast	*Effect estimate*	*SE*	*95% confidence*	*interval*	*P value*
P vs C	2.13	0.72	0.68	3.58	0.0047
T vs C	0.55	0.64	-0.73	1.82	0.3934
P vs T	1.57	0.63	0.31	2.83	0.0155

Outcome=FMC [%]

Contrast	*Effect estimate*	*SE*	*95% confidence*	*interval*	*P value*
P vs C	0.13	0.54	-0.96	1.22	0.8130
T vs C	-0.43	0.57	-1.58	0.71	0.4511
P vs T	0.59	0.58	-0.57	1.75	0.3117

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Table 6: Treatment effect estimates for the outcomes FMD and FMC stratified for study period. Model based estimates of the mean effect over measurements taken on day 1, 6, and 28. For each pair of treatments a separate linear mixed model for longitudinal data was fitted for three measurements taken after stenting and allowing for an unstructured covariance structure. Effect estimates are presented for each study period. Then the difference between these estimates is displayed under the label 'post vs. pre'

Outcome=FMD [%]

Contrast	*Effect estimate*	*SE*	*95% confidence*	*interval*	*P value*
P vs C pre interim	3.61	0.90	1.81	5.40	0.0002
P vs C post interim	-0.00	1.11	-2.22	2.21	0.9979
P vs C : post vs. pre	-3.61	1.42	-6.46	-0.76	0.0140
T vs C pre interim	1.21	0.79	-0.37	2.79	0.1301
T vs C post interim	-0.67	1.08	-2.83	1.49	0.5370
T vs C : post vs. pre	-1.88	1.34	-4.55	0.79	0.1646
P vs T pre interim	2.38	0.78	0.81	3.94	0.0036
P vs T post interim	0.65	0.97	-1.28	2.59	0.5031
P vs T : post vs. pre	-1.73	1.24	-4.22	0.76	0.1697

Outcome=FMC [%]

Contrast	*Effect estimate*	*SE*	*95% confidence*	*interval*	*P value*
P vs C pre interim	0.22	0.70	-1.18	1.62	0.7517
P vs C post interim	-0.19	0.86	-1.90	1.53	0.8266
P vs C : post vs. pre	-0.41	1.10	-2.62	1.80	0.7116
T vs C pre interim	-0.16	0.71	-1.58	1.26	0.8195
T vs C post interim	-0.93	0.98	-2.88	1.03	0.3480
T vs C : post vs. pre	-0.76	1.21	-3.18	1.65	0.5299
P vs T pre interim	0.41	0.76	-1.11	1.93	0.5872
P vs T post interim	0.75	0.94	-1.13	2.63	0.4266
P vs T : post vs. pre	0.34	1.21	-2.08	2.75	0.7807

Interim-Analysis and Sample Size Reassessment for the Study CTH-C1 EST

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Interim Analysis

Patients

Ninety patients were randomized (Clopidogrel (C) 30, Prasugrel (P) 30, Ticagrelor (T) 30). A stent was implanted in 57 patients (C+P+T=20+16+21). One patient randomized to P stopped study medication before stenting and was not measured FMD

afterwards. The remaining 56 patients (C+P+T=20+15+21) are evaluable for the primary outcome (at least one FMD on day 2,7,28 after Stenting) . Two patients in group C and three patients in group T have missing observations on day 7 or 28 (six missing values in total).

Efficacy

Means and standard errors of FMD are for all treatment groups and all post stent visits are presented in Table 1. Calculation is based on linear mixed model with unspecified homogeneous covariance structure, in order to cope with missing values. All pairwise comparisons with unadjusted one-sided p-values are presented in Table 2. As specified in the SAP (see below), for the comparison P vs. C a linear mixed model was fitted to the data of groups C and P only, and similarly so for the other comparisons.

The one-sided p-values for comparison P:C is 0.00032, for comparison T:C it is 0.0588, for comparison P:T it is 0.0033. The time course of FMD before and after stent implantation is depicted in Figure 1.

Table 7: Primary efficacy analysis. FMD [%] after stent implantation. Means for all treatment groups and visits.

	Visit					
Group	*Day 2*		*Day 7*		*Day 28*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Clopidogrel	1.51	0.77	3.06	0.79	2.28	0.78
Prasugrel	5.23	0.76	6.75	0.85	5.73	0.93
Ticagrelor	2.84	0.64	3.08	0.74	4.64	0.82

Table 8: Primary efficacy analysis. FMD [%] after stent implantation. Statistical tests.

Comparison	*Mean difference*	*SE*	*95% Confidence interval*		*One-sided p-value*
P vs C	3.60	0.95	1.65	5.54	0.0003
T vs C	1.20	0.75	-0.32	2.72	0.0588
P vs T	2.38	0.82	0.71	4.05	0.0033

Safety

Non-serious and serious adverse events are listed in Table 3 and 4, respectively. Note, that one patient of group T died (Subject 39, see table 4).

Table 9: Primary efficacy analysis. FMD [%] after stent implantation. Means for all treatment groups and visits.

	Visit					
Group	*Day 2*		*Day 7*		*Day 28*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*
Clopidogrel	1.51	0.77	3.06	0.79	2.28	0.78
Prasugrel	5.23	0.76	6.75	0.85	5.73	0.93
Ticagrelor	2.84	0.64	3.08	0.74	4.64	0.82

Table 10: Primary efficacy analysis. FMD [%] after stent implantation. Statistical tests.

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Comparison	*Mean difference*	*SE*	*95% Confidence interval*		*One-sided p-value*
P vs C	3.60	0.95	1.65	5.54	0.0003
T vs C	1.20	0.75	-0.32	2.72	0.0588
P vs T	2.38	0.82	0.71	4.05	0.0033

Sample Size Reassessment

According to the study protocol, the study may proceed with all three treatments (option 1) or with the treatments Clopidogrel and Ticagrelor (option 2). The control of the multiple type one error is also possible after proceeding with Ticagrelor and Prasugrel only (option 3), or after fully stopping the trial (option 4).

The primary objective of the adaptive design was to reconsider sample size calculation on the basis of data based estimation of the standard deviation. The standard deviation for the mean of FMD over the visits ,day 2, day 7, and day 28 is 2.44 when pooling over all treatment groups. It is 2.62, 2.78, and 1.90 within groups C, P, and T respectively, which is roughly in accordance with the assumption of homogeneous variances. Therefore a standard deviation of 2.44 is assumed for all groups.

Option 1: Three groups of equal size for the second stage of the study.

The power is controlled for the comparison T vs C. A sample size of 12 per group is needed for the second stage in order to achieve an unconditional power of 0.90 for this comparison, in order to detect the pre-specified effect of delta = 2.6%. With these sample sizes, a true difference in means of delta = 2.1 % between the groups P and T can be detected with probability 0.90, at the two-sided multiple level 0.05.

Option 2: Proceeding with Clopidogrel and Ticagrelor only

Under this design, the comparisons P:C and P:T are decided on the basis of the interim data alone. The power to detect a superiority of T over C at the multiple one sided level of 0.025 is 0.90, if 12 patients are randomized to C and T respectively (by virtue of the same arguments as for option 1).

Option 3: Proceeding with Prasugrel and Ticagrelor only

No further patients are needed for this option. It allows to accept the alternative hypothesis of superiority of P over C and of P over T at a multiple one-sided level of 0.025. The comparison between C and T remains undecided.

Option 4: Stopping the study

As under option 3, superiority of P over C and P over T can be affirmed at the multiple one sided level 0.025 and the comparison T versus C remains undecided.

Statistical Analysis Plan for Interim Analysis and Sample Size Reassessment for the Study CTH C1 EST

According to the study protocol, after 18 patients per treatment group are randomized, an interim analysis has to be carried out. Actually, the sample size of evaluable patients (at least one FMD on day 2,7,28 after Stenting) is 20, 15, 21 for groups Clopidogrel, Prasugrel, and Ticagrelor, respectively.

In this interim analysis Prasugrel and Ticagrelor will be tested separately versus clopodigrel by a one-sided t-test for independent samples comparing the FMD measurements. This will be done by testing the treatment effects in two independent mixed models in which the dependency between the three repeated measurements after stenting are incorporated by an unstructured covariance matrix. The denominator degrees of freedom for the tests of fixed effects will be computed by the Satterthwaite method.

If one of both one-sided p values exceeds 0.7, the first stage of the respective comparison will be stopped for futility. If both p values exceed 0.7, the trial stops with the acceptance of the null hypotheses. If a treatment comparison results in a p value of 0.0007 or less, then – as specified in the study protocol – the respective superior treatment arm may be excluded from further randomization.

The final analysis is planned as follows. Both, Prasugrel and Ticagrelor are compared to the reference Clopidogrel at a local one-sided level of alpha = 0.0125, which corresponds to a global two-sided level of alpha = 0.05, by virtue of Bonferroni adjustment. If one of both tests is significant, the other comparison and the comparison Ticagrelor vs. Prasugrel are performed at the one-sided level 0.025 (corresponding to a two-sided level of 0.05). For both comparisons vs. the reference Clopidogrel a two armed adaptive design is set up to control one-sided level of alpha = 0.0125, as described in the preceding paragraph.

In the case that in at least one comparison the stop criteria are not met, the sample size for the second stage will be planed

adaptively. Therefore, the standard deviation for FMD in further investigated treatment groups is calculated empirically regarding all three measurements after stenting based on the covariance matrix of the corresponding fitted mixed model. As for the first stage the assumption for the mean difference of 2.6% between groups is also used for the sample size recalculation. The significance level for the second stage will be determined depending on the p value of the first stage by the conditional error function. The power will be chosen depending on the spent power in the first stage in such a way that totally a power of 90% is reached.

A blinded assessment of the data has shown that only six observations of 168 expected are missing. These missing values are observed after 1 week or 1 month after stenting. All measurements 1 day after stenting are existent.

Safety results:

The safety analysis set comprised all 125 patients that have been offered study medication.

All AEs were documented on the appropriate pages of the eCRF and coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0.

The relatedness between each event and the intake of study medication was judged by the investigators according to modified WHO criteria. AEs assessed with "certain", "probable" or "possible" causal relationship to study treatment were graded as adverse drug reactions, assessed as "unlikely" or "none" were considered as not related to study treatment.

Seriousness was defined according to the Seriousness Criteria of Good Clinical Practice Guideline (GCP). The following table shows an overview of the reported AEs:

Table 11: Overview of reported AEs

	Clopidogrel		Prasugrel		Ticagrelor		Total	
Subjects with	N=41	nAE=12	N=42	nAE=8	N=42	nAE=17	N=125	nAE=37
Any AE	11	12	8	8	13	17	32	37
Related AE	0	0	0	0	1	1	1	1
Serious AE	4	4	1	1	6	7	11	12
Serious Related AE	0	0	0	0	0	0	0	0

Adverse Events:
25.6% of all patients reported at least one AE. A total of 37 AEs were reported (0.3 per pat.). Thereof, 12 AEs (32.4%, 0.3 per pat.) occurred in the Clopidogrel group, 8 AEs (21.6%, 0.2 per pat.) in the Prasugrel group and 17 AEs (45.9%, 0.4 per pat.) in the Ticagrelor group.

Adverse Events considered as related to study medication (ADRs):
In only one (2.7%) of all AEs a possible causal relation was assessed between the occurrence of the AE and the administration of study medication (MedDRA preferred term: Dyspnoea). This adverse drug reaction (ADR) occurred in the Ticagrelor group. The MedDRA systems organ class (SOC), in which the ADR occurred was Respiratory, thoracic and mediastinal disorders.
Causal relation was assessed as not evaluable for one adverse event in the Prasugrel group by the investigator (MedDRA preferred term: Circumstance or information capable of leading to medication error).

Severity of Adverse Events:
16 (43.2%) of all AEs were judged as mild, 15 (40.5%) as moderate and 6 (16.2%) as severe. 2 (33.3%, 0.05 per pat.) of the 6 severe AEs occurred in the Clopidogrel group and 4 (66.7%, 0.1 per pat.) in the Ticagrelor group.

Seriousness of Adverse Events:
In summary, 12 (32.4%, 0.1 per pat.) AEs were judged as serious according to the definition in the study protocol, none of these 12 SAEs was assessed as related (SAR) to the investigational medicinal product. Therefore no suspected unexpected serious adverse reaction (SUSAR) had to be reported to the competent authority, ethics committee and all investigators.

4 (33.3%, 0.1 per pat.) of the 12 total SAEs occurred in the Clopidogrel group, 1 (8.3%, 0.02 per pat.) in the Prasugrel group and 7 (58.3%, 0.2 per pat.) in the Ticagrelor group.

The SOC with most SAEs (5) was Cardiac disorders. The following table shows the number of SAEs allocated to MedDRA system organ classes (SOC) and treatment group.

Table 12: SAEs allocated to MedDRA system organ classes (SOC)

Report Synopsis of Study Effects of clopidogrel vs prasugel vs ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting. A randomised, prospective study

Short Title: Endothelium, Stenting, and antiplatelet Therapy (EST) - Clopidogrel, Prasugrel, Ticagrelor study

EudraCT-Nr.: 2011-005305-73

Vorlage-Nr.: 4038158

	Clopidogrel	Prasugrel	Ticagrelor	Total
System Organ Class (SOC)				
Cardiac disorders	1	0	4	5
Ear and labyrinth disorders	0	1	0	1
Gastrointestinal disorders	0	0	1	1
General disorders and administration site conditions	1	0	0	1
Injury, poisoning and procedural complications	1	0	0	1
Nervous system disorders	1	0	0	1
Surgical and medical procedures	0	0	1	1
Vascular disorders	0	0	1	1

Deaths:
In this clinical trial one SAE with outcome death was reported: According to the autopsy report the 72 year old male patient died of a coronary stent thrombosis resulting in anteroseptal myocardial infarction resulting in a cardiac tamponade. Investigator and sponsor judged causality between the event and the IMP (Ticagrelor) as unlikely.

Subgroup analysis of adverse events:
Subgroups were organized in three strata: interim patients without documented stenting (33 pts), interim patients with stent (57 pts) and post-interim patients with stent (35 pts).
In the group of interim patients without documented stenting 2 AEs were reported: 1 AE in the Prasugrel group and 1 AE (serious) in the Clopidogrel group. In interim patients with stent 19 AEs were reported: 7 AEs (1 serious) in the Clopidogrel group, 5 AEs (1 serious) in the Prasugrel group and 7 AE (4 serious) in the Ticagrelor group. In post-interim collective with stent 16 AEs were reported: 4 AEs (2 serious) in the Clopidogrel group, 2 AEs in the Prasugrel group and 10 AE (3 serious) in the Ticagrelor group.
The SOC with most AEs (8) was Cardiac disorders. The following table shows the number of AEs allocated to MedDRA system organ classes (SOC) and treatment group.

Table 13: AEs allocated to MedDRA system organ classes (SOC) according to interim and post-interim strata

	Clopidogrel		Prasugrel		Ticagrelor		Total	
System Organ Class (SOC)	I*	PI**	I*	PI**	I*	PI**	I*	PI**
Cardiac disorders	2	1	0	0	3	2	5	3
Ear and labyrinth disorders	0	0	1	0	0	0	1	0
Gastrointestinal disorders	0	0	1	0	1	0	2	0
General disorders and administration site conditions	2	1	0	0	0	1	2	2
Infections and infestations	0	1	0	0	0	0	0	1
Injury, poisoning and procedural complications	0	1	1	1	0	3	1	5
Investigations	2	0	1	1	1	0	4	1

Metabolism and nutrition disorders	0	0	0	0	1	0	1	0
Nervous system disorders	1	0	1	0	0	0	2	0
Psychiatric disorders	0	0	0	0	1	0	1	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	1	0	1
Surgical and medical procedures	0	0	0	0	0	1	0	1
Vascular disorders	1	0	1	0	0	2	2	2

* Interim patients with and without stent
** Post-interim patients

Summary concerning safety:
In summary, in this clinical trial only 0.3 (0.05 severe) adverse events (AE) per patient, 0.1 serious adverse events (SAE) per patient and no serious adverse drug reaction (SAR) were reported to the sponsor. The frequency of SAEs in the Ticagrelor group was higher than in the Clopidogrel and higher than in the Prasugrel group (0.2; 0.1 and 0.02 per pat.). The same applies to the frequency of AEs. There was only one adverse drug reaction (ADR) which occurred in the Ticagrelor group.

Conclusion:

Efficacy

Primary outcome FMD [%]:

At Screening, means(standard errors) for Clopidogrel/Prasugrel/Ticagrelor were 4.40(0.86)/ 3.99(0.99)/4.87(0.83) in period 1 and 4.41(1.15)/ 4.66 (1.10)/ 1.95 (1.10) in the second study period.

2 h after first dose, means(standard errors) for Clopidogrel/Prasugrel/Ticagrelor were 5.86(0.65) 5.71 (0.75) 6.73 (0.64) in the first period and have not been assessed during the second study period.

On day one, means(standard errors) for Clopidogrel/Prasugrel/Ticagrelor were 1.48(0.74)/ 5.23(0.85)/ 2.84 (0.72) in the first study period and 3.90(1.00)/ 3.73 (0.95)/ 3.04(0.99) in the second study period.

On day six, means(standard errors) for Clopidogrel/Prasugrel/Ticagrelor were 3.09(0.78)/ 6.75(0.87)/ 3.09 (0.75) in the first study period and 3.39(1.06)/ 2.80(0.97)/ 2.96(1.10) in the second study period.

28 days post stenting, means(standard errors) for Clopidogrel/Prasugrel/Ticagrelor were 2.34(0.77)/ 5.73(0.89)/ 4.59 (0.80) in the first study period and 3.62 (1.09)/ 4.34 (1.00)/ 2.89 (1.08) in the second study period.

The model bases estimate of the difference between Prasugrel and Clopidogrel averaged over measurements on days 1, 6, and 28 after stenting was 3.61% (95% confidence interval 1.81-5.40, 2-sided p value 0.0002) in the first study period and 0.00 (95% confidence interval -2.22 - 2.21, 2-sided p value 0.998) in the second study period. The pre-planned test combining both periods' results according to the inverse normal method yielded a one sided p-value of 0.0045. This result is statistically significant according to the pre-planned Bonferroni adjustment at multiple level alpha = 0.025 for the one sided hypothesis of superiority (nominal alfa 0.0125). The combined effect estimate was 2.13 % (95% confidence interval 0.68-3.58).

The model bases estimate of the difference between Ticagrelor and Clopidogrel averaged over measurements on days 1, 6, and 28 after stenting was 1.21% (95% confidence interval -0.37 – 2.79, 2-sided p value 0.130) in the first study period and -0.67 (95% confidence interval -2.83 - 1.49, 2-sided p value 0.537) in the second study period. The pre-planned test combining both periods' results according to the inverse normal method yielded a one sided p-value of 0.263. The combined effect estimate was 0.55 % (95% confidence interval -0.73-1.82).

The combined effect estimate is 0.55 % (95% confidence interval -0.73-1.82).

Secondary outcome FMC[%]:

The model bases estimate of the difference between Prasugrel and Clopidogrel averaged over measurements on days 1, 6, and 28 after stenting was 0.22% (95% confidence interval -1.18 - 1.62, 2-sided p value 0.752) in the first study period and -0.19 (95% confidence interval -1.90 - 1.53, 2-sided p value 0.827) in the second study period. The pre-planned test combining both periods' results according to the inverse normal method yielded a one sided p-value of 0.395. The combined effect estimate was 0.13 %

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(95% confidence interval -0.96-1.22).

The model bases estimate of the difference between Ticagrelor and Clopidogrel averaged over measurements on days 1, 6, and 28 after stenting was -0.16% (95% confidence interval -1.58 – 1.26, 2-sided p value 0.820) in the first study period and -0.93 (95% confidence interval -2.88 - 1.03, 2-sided p value 0.348) in the second study period. The pre-planned test combining both periods' results according to the inverse normal method yielded a one sided p-value of 0.826. The combined effect estimate was -0.43 % (95% confidence interval -1.58-0.71).

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 19-02-2020

Print Name:Dr rer nat Silke Warnke (IZKS Mainz, Universitätsmedizin Mainz)

Signature: