# TicagRelor Or Clopidogrel in severe or terminal chronic kidney patients Undergoing PERcutaneous coronary intervention for acute coronary syndrome: The TROUPER trial

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## Rationale and design

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**Abstract**

Chronic kidney disease (CKD) is associated with an increased risk of acute coronary syndrome (ACS) and cardiovascular death. CKD patients suffering from ACS are exposed to an increased risk of thrombotic recurrences and a higher bleeding rate than patients with normal renal function. However, CKD patients are excluded or underrepresented in clinical trials. Therefore, determining the optimal antiplatelet strategy in this population is of utmost importance. We designed the TicagRelor Or Clopidogrel in severe or terminal chronic kidney patients Undergoing PERcutaneous coronary intervention for acute coronary syndrome (TROUPER) trial: a prospective, controlled, multicenter, randomized trial to investigate the optimal P2Y12 antagonist in CKD patients with ACS. Patients with stage ≥3b CKD are eligible if the diagnosis of ACS is made and invasive strategy scheduled. Patients are randomized 1:1 between a control group with a 600 mg loading dose (LD) of clopidogrel followed by a 75 mg/day maintenance dose (MD) for one year and an experimental group with a 180 mg LD of ticagrelor followed by a 90 *bid* MD for the same duration. The primary endpoint is defined by the rate of major adverse cardiovascular events (MACE), including death, myocardial infarction, urgent revascularization and stroke at one year. Safety will be evaluated by the bleeding rate (BARC). To demonstrate the superiority of ticagrelor on MACE, we calculated that 508 patients are required. The aim of the TROUPER trial is to compare the efficacy of ticagrelor and clopidogrel in stage >3b CKD patients presenting with ACS and scheduled for an invasive strategy.

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**Keywords:** *Acute coronary syndrome, percutaneous coronary intervention, thrombosis, chronic kidney disease, P2Y12-ADP-receptor inhibitor*

## Highlights

- CKD patients are at high risk of bleeding and thrombotic events after ACS.
- CKD patients are underrepresented in clinical trials, especially in cardiology.
- The TROUPER trial will compare ticagrelor to clopidogrel in CKD patients with ACS.

## Introduction

Chronic kidney disease (CKD) is a major public health issue with a stable prevalence in developed countries of approximately 15% of the general population (1–3). This prevalence is increasing with age and reaches 30% in the elderly (4). CKD is associated with an increased risk of major adverse cardiovascular events (MACE), including cardiovascular death(5, 6). Moreover, CKD patients are more likely to die of cardiovascular events, including acute coronary syndrome (ACS), than to develop end-stage renal failure(6–8). In contrast, CKD is encountered in up to 40% of patients admitted for ACS. Furthermore, the prognosis is poor: the 1-year rate of MACE can reach 40% in CKD patients with ACS, while they have a threefold in-hospital mortality rate compared to patients with normal renal function (9–12). Thus, CKD patients comprise a very high-risk population regarding thrombotic events.

The rupture of an atherosclerotic plaque that leads to thrombosis of a coronary artery is the leading cause of ACS. Therefore, platelet inhibition is of the utmost importance to prevent recurrences. Dual antiplatelet therapy (DAPT) (which combines aspirin with a platelet P2Y12 ADP-receptor inhibitor) is the cornerstone of the therapeutic strategy for the management of patients with ACS undergoing PCI (13–15). Clopidogrel has major limitations: a mild level of platelet inhibition, delayed onset of action, particularly in ACS patients, and a wide interindividual variability in its biological efficacy, leading to a 40% rate of high on-treatment platelet reactivity (HTPR)(16). Of importance, CKD patients have a higher rate of HTPR than the general population. HTPR in CKD patients was shown to correlate with thrombotic events and CV death in those undergoing PCI (17, 18).

Ticagrelor, a platelet P2Y12 ADP-platelet receptor inhibitor, has been developed to overcome the limitations of clopidogrel. From a biological point of view, ticagrelor has a more rapid onset of action and induces a more potent and reproducible platelet inhibition than clopidogrel, including in CKD patients (19–22). Pharmacodynamic and pharmacokinetic studies have demonstrated that ticagrelor could be safely used in patients with kidney failure, including patients under dialysis (23, 24). In the PLATO trial, focused on ACS patients, ticagrelor demonstrated superiority over clopidogrel regarding ischemic recurrences and mortality. Although major bleedings were similar in the two study arms, there was a higher rate of non-CABG-related major bleeding in the ticagrelor group according to the study criteria (4.5% vs. 3.8%, p =0.03) and the TIMI criteria (2.8% vs. 2.2%, p =0.03)(25). However, a limited number of patients with stage >3b CKD (glomerular filtration rate (GFR) < 45 mL/min or dialysis) were included (21%), and dialysis patients were excluded. Moreover, CKD is associated with an increased rate of bleeding events; therefore, the particular ratio of thrombotic and bleeding risk in CKD patients is likely to differ from patients without CKD and remains to be determined(26–28). Frequently, CKD patients do not receive up-to-date management in relation to both therapeutic nihilism and the paucity of data regarding new therapies(29). To fill this gap in evidence, we designed the TicagRelor Or Clopidogrel in severe or terminal chronic kidney patients Undergoing PERcutaneous coronary intervention for acute coronary syndrome (TROUPER) trial to compare the efficacy of ticagrelor and clopidogrel in ACS patients with stage ≥3b CKD intended for an invasive strategy.

## Methods

## Study design

The TROUPER study is a prospective, multicenter, randomized, controlled, open-label, 2 parallel-group study. The study design was recorded in clinicaltrial.gov (database: NCT03357874). The overall study design is summarized in Figure 1. This study includes 20 centers in France.

Patients with ACS with or without ST segment elevation intended for an invasive strategy will be eligible. They will be included if all inclusion criteria are met and in the absence of non-inclusion criteria after an informed consent is signed. Following inclusion, patients will be randomized in a 1:1 ratio to receive clopidogrel or ticagrelor. In the control group, patients will receive a 600 mg loading dose of clopidogrel after randomization followed by a 75 mg od regimen for 1 year after PCI. In the ticagrelor group, patients will receive a 180 mg loading dose of ticagrelor after randomization followed by a 90 mg bid for 1 year. Treatment with a loading dose of the platelet P2Y12 ADP-receptor inhibitor could be administered as soon as the diagnosis of ACS is made, with randomization performed until the end of PCI. Patients already treated with a P2Y12 antagonist before randomization will receive a loading dose of the allocated treatment following the consensus recommendations on switching between oral P2Y12 inhibitors if required (30). Of note, patients undergoing coronary angiography and medically managed without PCI will also be included in the study. The study will be performed in accordance with ethical principles consistent with the Declaration of Helsinki. The final study protocol and informed consent have been reviewed and approved by the health authorities and institutional review boards for all participating sites.

### Participants

The aim of the TROUPER study is to include a representative population of CKD patients (stages 3b, 4 and 5). The glomerular filtration rate will be estimated with the Modification of Diet in Renal Disease (MDRD) formula. Only patients with a creatinine clearance <45 ml/kg/min will be eligible. Patients will be included if CKD is already known. Patients with acute kidney failure are not eligible.

Of importance, the delays of medical strategies will not be affected by the protocol. Information obtained as part of routine care will be reviewed to determine eligibility for enrollment, including 12 lead electrocardiograms (ECG) and a physical exam, cardiac biomarkers and all means considered necessary for the diagnosis of STE-ACS and intermediate, high-risk and very high-risk NSTE-ACS(13).

Patients must be intended for primary PCI for STE ACS or an invasive strategy in the case of NSTE ACS according to the ESC definition (13, 14) (Table 1). Non-inclusion criteria are listed Table 1. The only exclusion criterion is a subject wishing to interrupt his/her participation during the study. After delivery of oral information regarding the study (e.g., objectives, schedule, benefits and risks), written consent will be obtained from all patients before inclusion.

## Treatment protocol

### Coronary revascularization

In the 2 groups, PCI will be performed according to international guidelines and at the discretion of the operator. The use of a drug-eluting stent and state-of-the-art intervention will be encouraged in both groups. The anticoagulant used during PCI is left to the physician's discretion between the drugs listed in the guidelines(13, 14).

Culprit PCI is recommended during the initial procedure and in the case of multivessel PCI; non-culprit vessels could be treated in the same setting or in a staged fashion, according to the investigator's preferences.

The use of glycoprotein 2b/3a inhibitors will be left to the physician's decision; however, it must not be started before angiography.

**Other care management**

***Aspirin Therapy***

Adjunctive aspirin (ASA) is required for all patients. Aspirin (150 to 300 mg IV) can be administered as soon as the diagnosis is made. Daily maintenance therapy should be taken with 75 mg to 100 mg ASA (13, 14).

***Other permitted medications*** include, but are not limited to, histamine 2 receptor (H2) blockers; proton pump inhibitors (PPI); oral, sublingual, or intravenous nitrates; calcium channel blockers; beta blockers; angiotensin converting enzyme inhibitors (ACEIs); angiotensin receptor blockers (ARBs); 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins); anti-arrhythmic drugs; vasodilators; and intravenous vasopressor agents.

Subjects will be treated with concomitant long-term therapies according to current guideline recommendations(13, 14). The use of all concomitant medications will be recorded on the CRF. Concomitant medications will be summarized by the treatment cohort. Following PCI, there will be no difference between the 2 groups in the therapeutic strategy and medical care with the exception of the P2Y12-ADP-receptor inhibitor used. Blood sampling will be performed, including usual tests and troponin measures, at each recurrent chest pain during the hospital stay to detect ongoing necrosis and peri-procedural myocardial infarction (MI).

During the hospital stay, patients will be monitored for recurrent myocardial ischemia with ECG monitoring and daily clinical examination.

**Follow-up and study outcomes**

The primary endpoint is defined by the rate of MACE, including death, myocardial infarction, urgent revascularization and stroke, at the one-year follow-up (31). MI will be defined according to the universal definition, including type 1 to 3 MI(32). Urgent revascularization will be defined as all unplanned revascularization during follow-up by PCI or coronary artery bypass graft. Stroke, transient or definitive, as diagnosed by a neurologist will be based on the following:

- a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction;
- a definite stroke is defined by the occurrence of neurological dysfunction as diagnosed by a neurologist (>24 h duration) and/or the presence of acute infarction as demonstrated by imaging.

The secondary objectives are to assess the 2 strategies in terms of efficacy and tolerance through in-person visits at discharge, one month and one year. Secondary endpoints are listed in Table 2 and include bleeding events, dyspnea, requirement of hemodialysis and ischemic events.

For all events, the date of the occurrence will be obtained. The delay will be calculated from the randomization day and the date of the occurrence. A subject would be considered lost to follow-up if he or she fails to return or is unable to be contacted by the site for the 30-day and 12-month visits. Site staff are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit. Survival status will be obtained within legal and ethical boundaries for all randomized subjects, including those who did not receive study drug. The status of “lost to follow-up” should only be determined at the conclusion of the trial. A blinded clinical endpoint committee will review clinical events.

### Sample size

The sample size calculation was performed on the hypothesis formulated on the primary endpoint, *i.e.*, the one-year rate of major adverse cardiovascular events (MACE), including all-cause mortality, myocardial infarction, urgent revascularization and stroke.

According to the literature, ischemic recurrences are more frequent in CKD patients and increases when creatinine clearance decreases (33–41). Therefore, it is estimated that the rate of the primary endpoint (MACE) at 12 months will be 40% in the control group and 28% in the ticagrelor group (relative risk reduction of 30%)(34, 35, 37, 42–44).

Therefore, to show a significant difference with a power of 80% and an alpha risk of 5% between 40% and 28%, 244 patients are required in each group. With a 5% lost to follow-up rate, we plan to enroll 257 patients in each group. A 2-year inclusion period is scheduled. Recruitment began in November 2018, and 40 patients have been randomized.

### Randomization

Computer-generated randomized lists have been created using a permuted block design (stratified on center). Each center has a specific list.

### Statistical analysis

The data will be analyzed using SPSS version 17.0 software (IBM) or a later version. All tests will be two-sided. Statistical significance is defined as $p<0.05$. The methodology will be based on the Consolidated Standards of Reporting Trials

Statement(45). The full analysis population (including all subjects who will be at least evaluated at baseline and randomized) will be used in the primary analysis. In this intention-to-treat analysis, all patients will remain in the group to which they were allocated. The per-protocol population (including all subjects who will be randomized and will not have major protocol deviations) will be used in the secondary analysis to assess the robustness of the results. No interim analysis is planned. The time from randomization to the first occurrence of a MACE during the 1-year follow-up will be compared between the 2 groups using a two-sided log-rank test. The Kaplan-Meier method will be used to depict this comparison and estimate the median survival times and one-year event rates. A hazard ratio and its 95% confidence interval will be estimated using a Cox proportional-hazards model after determining that the treatment effect is not time-dependent. A secondary adjusted analysis will include prespecified baseline variables of prognostic value. A per-protocol analysis will then be conducted using the same procedure. The rates of the secondary endpoints will be compared between the 2 groups using the same procedure. Multivariate approaches will be performed according to the procedure described for the primary endpoint. If the exact date of some endpoints cannot be determined with sufficient confidence, one-month and one-year rates will be compared using $\chi^2$ tests and logistic regression models.

Adverse events (AEs) will be summarized by frequency and proportion. The characteristics of AEs, the maximum grade, the incidence of deaths and the primary cause of death will be summarized. The results of scheduled assessments will be described. An independent Clinical Endpoints Committee (CEC), blinded to the treatment, will adjudicate all death, recurrent ischemia, MI, stroke, recurrent and all BARC bleeds. Primary analyses will be conducted on CEC-adjudicated endpoints.

Safety monitoring will be conducted under the auspices of an independent, external data monitoring committee (DMC) assigned to this study. The primary endpoint analysis and all other key efficacy and safety analyses will be conducted using the two-sided log-rank test from a time-to-first event analysis, unless otherwise specified.

### Funding and conduct of the study

This academic study is entirely funded by the French Ministry of Health. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## Discussion

CKD patients have a high incidence of ACS with a worse outcome than the general population (9–12). These patients have a high thrombotic risk related to 3 main factors: i) alteration of the coagulation cascade; ii) endothelial injury; and iii) platelet alteration. Platelets play a key role in thrombotic events that affect CKD patients and in atherothrombotic events, thus emphasizing the importance of an adequate antiplatelet strategy in secondary prevention in this specific population. Platelet reactivity and platelet-leucocyte aggregation are stimulated due to increased fibrinogen receptor PAC-1 and P-selectin concentrations associated with higher platelet susceptibility to thrombin(46). This high thrombotic phenotype of platelets in CKD is critical to their higher risk of recurrent thrombotic events following ACS. However, at the same time, CKD is also associated with an increased bleeding risk(26–28). Of importance, bleedings are major adverse events associated with death in ACS patients(47). Various mechanisms come into play in CKD patients and can be responsible for altered platelet adhesion and aggregation leading to

hemorrhages: reduced ADP release, deregulation of arachidonic acid and prostaglandin metabolism, disturbance of alpha-granules, changes in intraplatelet calcium flux, and circulating fibrinogen fragments that interfere with glycoprotein IIb/IIIa(46). Furthermore, anemia that is common in CKD patients increases the NO level and therefore amplifies the alteration of platelet aggregation(48–50). The specific and complex alteration of platelet physiology are responsible for a particular risk profile of CKD patients suffering from ACS. This specific thrombotic and bleeding risk ratio may influence the optimal antiplatelet regimen particularly if PCI is performed(28).

There is a major gap in evidence regarding the optimal P2Y12 ADP-receptor antagonists in this clinical setting. While CKD affects 20-40% of ACS patients, this population is deeply underrepresented in major clinical trials. In the PLATO trial that recruited more than 18,000 patients, 21% of the patients had an estimated creatinine clearance < 60 mL/min, while only 214 patients had a calculated clearance < 30 mL/min(25, 42). According to the substudy dedicated to CKD patients, ticagrelor significantly reduced the rate of ischemic events and mortality without an increase in major bleedings(42). However, the limited sample of stage > 3 CKD patients included in the PLATO trial highlights the need for an adequately designed clinical trial that tests antiplatelet treatment in CKD patients with ACS. Similarly, the TRITON trial that compared prasugrel to clopidogrel in ACS included only 10.9% of patients with a creatinine clearance < 60 mL/min(51). Therefore, the benefit observed in the prasugrel group regarding ischemic events can hardly be extrapolated to the CKD population. Moreover, data are lacking in patients with a creatinine clearance less than 30 mL/min(46).

We recently performed a meta-analysis that compared potent P2Y12 ADP-receptor antagonists with clopidogrel in patients with CKD suffering from ACS. In patients treated by PCI, there seemed to be a benefit with ticagrelor, although the number of patients with a creatinine clearance less than 45 mL/min was limited(52). With regard to prasugrel, in a propensity adjustment of the PROMETHEUS registry, prasugrel did not appear to be superior to clopidogrel regarding ischemic events in CKD patients(53).

The limited available data in CKD patients leave practitioners helpless and jeopardize patient outcomes. Therefore, it is of the utmost importance to investigate the potential of ticagrelor compared to clopidogrel in CKD patients. The primary goal of the TROUPER trial is to test the hypothesis that ticagrelor is superior to clopidogrel regarding ischemic recurrences in stage 3a, 4 and 5 CKD patients (or patients undergoing chronic dialysis) suffering from ACS(31). The primary endpoint was chosen considering the fact that MACE are the typical endpoint in trials focusing on ACS because of their major clinical interest.

Furthermore, due to the higher bleeding rate in CKD patients, the safety of potent P2Y12 ADP-receptor inhibitors, such as ticagrelor, should be carefully assessed and monitored(28, 54, 55). The TROUPER study will help to unveil the potential interest of ticagrelor in CKD patients and analyze safety issues, including bleedings. The net clinical benefit (combining ischemic and bleeding events) will be assessed.
The determination of the optimal P2Y12-ADP receptor inhibitor in ACS patients with stage 3b, 4 and 5 CKD or under chronic hemodialysis is critical to improve their clinical outcome. The TROUPER trial will provide critical data in this regard, which

could help physicians decide the optimal therapy in this population and update the guidelines.

**Challenges and limitations of the study design**

We acknowledge that the open nature of the TROUPER study is a limitation. However, the content of the primary endpoint (major adverse cardiovascular events, including death, myocardial infarction, urgent revascularization and stroke at one-year follow-up) tends to reduce this bias given the low subjectivity in its adjudication. In addition, all events will be adjudicated by a committee not involved in the study and blinded regarding the group assignment.

## Conclusion

The TROUPER trial is a prospective, multicenter, randomized, controlled and open label study comparing the efficacy of ticagrelor with clopidogrel in stage 3b, 4 or 5 chronic kidney disease patients presenting with acute coronary syndrome and scheduled for an invasive strategy. The primary endpoint will be the rate of major adverse cardiovascular events, including death, myocardial infarction, urgent revascularization and stroke, at the one-year follow-up. Bleedings will also be recorded. The aim of this trial is to determine the optimal antiplatelet regimen in this very high-risk population that has been poorly studied in previous clinical trials.

## References

1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80:17–

28.
2. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J. Am. Soc. Nephrol. 2006;17:2275–2284.
3. Murphy D, McCulloch CE, Lin F, et al. Trends in Prevalence of Chronic Kidney Disease in the United States. Ann. Intern. Med. 2016;165:473–481.
4. Stengel B, Metzger M, Froissart M, et al. Epidemiology and prognostic significance of chronic kidney disease in the elderly--the Three-City prospective cohort study. Nephrol. Dial. Transplant. 2011;26:3286–3295.
5. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050–1065.
6. Foster MC, Rawlings AM, Marrett E, et al. Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States. Am. Heart J. 2013;166:150–156.
7. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch. Intern. Med. 2004;164:659–663.
8. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. Hypertension 1989;13:I80-93.
9. Parikh PB, Jeremias A, Naidu SS, et al. Impact of severity of renal dysfunction on determinants of in-hospital mortality among patients undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv 2012;80:352–357.
10. Lin T-H, Hsin H-T, Wang C-L, et al. Impact of impaired glomerular filtration rate and revascularization strategy on one-year cardiovascular events in acute coronary syndrome: data from Taiwan acute coronary syndrome full spectrum registry. BMC Nephrol 2014;15:66.
11. Wong JA, Goodman SG, Yan RT, et al. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. Eur. Heart J. 2009;30:549–557.
12. Fox CS, Muntner P, Chen AY, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation 2010;121:357–365.
13. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur. Heart J. 2017.
14. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevationTask Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.
15. Mehta S, Yusuf S, Peters R, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. The Lancet 2001;358:527–533.
16. Bonello L, Tantry US, Marcucci R, et al. Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate. Journal of

the American College of Cardiology 2010;56:919–933.
17. Angiolillo DJ, Bernardo E, Capodanno D, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J. Am. Coll. Cardiol. 2010;55:1139–1146.
18. Barragan P, Bouvier J-L, Roquebert P-O, et al. Resistance to thienopyridines: Clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. Catheterization and Cardiovascular Interventions 2003;59:295–302.
19. Husted SE, Storey RF, Bliden K, et al. Pharmacokinetics and pharmacodynamics of ticagrelor in patients with stable coronary artery disease: results from the ONSET-OFFSET and RESPOND studies. Clin Pharmacokinet 2012;51:397–409.
20. Bliden KP, Tantry US, Storey RF, et al. The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: Combined analysis of the ONSET/OFFSET and RESPOND studies. American Heart Journal 2011;162:160–165.
21. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;120:2577–2585.
22. Laine M, Toesca R, Berbis J, et al. Platelet reactivity evaluated with the VASP assay following ticagrelor loading dose in acute coronary syndrome patients undergoing percutaneous coronary intervention. Thrombosis Research 2013;132:e15–e18.
23. Butler K, Teng R. Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with severe renal impairment. J Clin Pharmacol 2012;52:1388–1398.
24. Jeong KH, Cho JH, Woo JS, et al. Platelet reactivity after receiving clopidogrel compared with ticagrelor in patients with kidney failure treated with hemodialysis: a randomized crossover study. Am. J. Kidney Dis. 2015;65:916–924.
25. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine 2009;361:1045–1057.
26. Herzog CA, Shroff GR. Atherosclerotic versus nonatherosclerotic evaluation: the Yin and Yang of cardiovascular imaging in advanced chronic kidney disease. JACC Cardiovasc Imaging 2014;7:729–732.
27. Desai RJ, Spoendlin J, Mogun H, Gagne JJ. Contemporary Time Trends in Use of Antiplatelet Agents Among Patients with Acute Coronary Syndrome and Comorbid Diabetes Mellitus or Chronic Kidney Disease. Pharmacotherapy 2017;37:1322–1327.
28. Ocak G, Rookmaaker MB, Algra A, et al. Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study. J. Thromb. Haemost. 2018;16:65–73.
29. Rhee J-W, Wiviott SD, Scirica BM, et al. Clinical features, use of evidence-based therapies, and cardiovascular outcomes among patients with chronic kidney disease following non-ST-elevation acute coronary syndrome. Clin Cardiol 2014;37:350–356.
30. Angiolillo DJ, Rollini F, Storey RF, et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. Circulation 2017;136:1955–1975.
31. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J. Am. Coll. Cardiol. 2015;66:403–469.
32. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation 2018;138:e618–e651.
33. Lee JM, Kang J, Lee E, et al. Chronic Kidney Disease in the Second-Generation Drug-Eluting Stent Era: Pooled Analysis of the Korean Multicenter Drug-Eluting Stent Registry.

JACC Cardiovasc Interv 2016;9:2097–2109.
34. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N. Engl. J. Med. 2004;351:1296–1305.
35. Natanzon SS, Matetzky S, Beigel R, et al. Statin therapy among chronic kidney disease patients presenting with acute coronary syndrome. Atherosclerosis 2019;286:14–19.
36. Cardi T, Kayali A, Trimaille A, et al. Prognostic Value of Incomplete Revascularization after Percutaneous Coronary Intervention Following Acute Coronary Syndrome: Focus on CKD Patients. J Clin Med 2019;8.
37. Gowdak LHW, de Paula FJ, César LAM, et al. Screening for significant coronary artery disease in high-risk renal transplant candidates. Coron. Artery Dis. 2007;18:553–558.
38. Scholz SS, Lauder L, Ewen S, et al. One-year clinical outcomes in patients with renal insufficiency after contemporary PCI: data from a multicenter registry. Clin Res Cardiol 2019.
39. Sato T, Hatada K, Kishi S, et al. Comparison of clinical outcomes of coronary artery stent implantation in patients with end-stage chronic kidney disease including hemodialysis for three everolimus eluting (EES) stent designs: Bioresorbable polymer-EES, platinum chromium-EES, and cobalt chrome-EES. J Interv Cardiol 2018;31:170–176.
40. Edfors R, Sahlén A, Szummer K, et al. Outcomes in patients treated with ticagrelor versus clopidogrel after acute myocardial infarction stratified by renal function. Heart 2018;104:1575–1582.
41. Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Circulation 2009;120:851–858.
42. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 2010;122:1056–1067.
43. Saltzman AJ, Stone GW, Claessen BE, et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. JACC Cardiovasc Interv 2011;4:1011–1019.
44. Morel O, Muller C, Jesel L, Moulin B, Hannedouche T. Impaired platelet P2Y12 inhibition by thienopyridines in chronic kidney disease: mechanisms, clinical relevance and pharmacological options. Nephrol. Dial. Transplant. 2013;28:1994–2002.
45. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7:e1000251.
46. Bonello L, Angiolillo DJ, Aradi D, Sibbing D. P2Y12-ADP Receptor Blockade in Chronic Kidney Disease Patients With Acute Coronary Syndromes. Circulation 2018;138:1582–1596.
47. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KAA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–782.
48. Viganò G, Gotti E, Comberti E, Giangrande A, Trevisan R, Remuzzi G. Hyperparathyroidism does not influence the abnormal primary haemostasis in patients with chronic renal failure. Nephrol. Dial. Transplant. 1989;4:971–974.
49. Moal V, Brunet P, Dou L, Morange S, Sampol J, Berland Y. Impaired expression of glycoproteins on resting and stimulated platelets in uraemic patients. Nephrol. Dial.

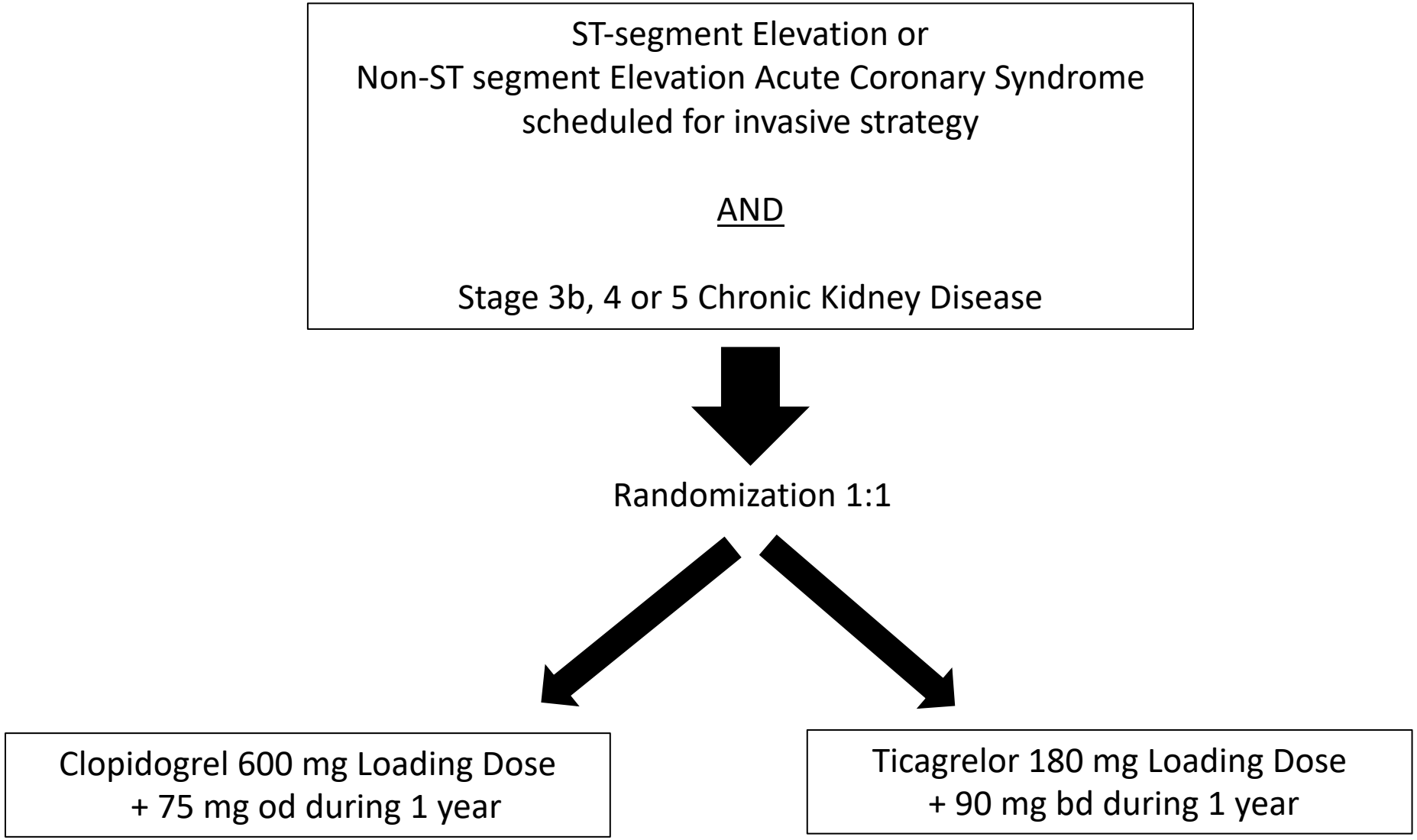
Transplant. 2003;18:1834–1841.
50. Benigni A, Boccardo P, Galbusera M, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. Am. J. Kidney Dis. 1993;22:668–676.
51. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine 2007;357:2001–2015.
52. Bonello L, Laine M, Lemesle G, et al. Meta-Analysis of Potent P2Y12-ADP Receptor Antagonist Therapy Compared to Clopidogrel Therapy in Acute Coronary Syndrome Patients with Chronic Kidney Disease. Thromb Haemost 2018;118:1839–1846.
53. Baber U, Chandrasekhar J, Sartori S, et al. Associations Between Chronic Kidney Disease and Outcomes With Use of Prasugrel Versus Clopidogrel in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: A Report From the PROMETHEUS Study. JACC Cardiovasc Interv 2017;10:2017–2025.
54. Bonello L, De Labriolle A, Roy P, et al. Impact of optimal medical therapy and revascularization on outcome of patients with chronic kidney disease and on dialysis who presented with acute coronary syndrome. Am. J. Cardiol. 2008;102:535–540.
55. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009;119:1873–1882.

**Figure 1. Study protocol**

**Table 1. Inclusion and non-inclusion criteria**

**Table 2. Secondary endpoints**

ARC: Academic Research Consortium
BARC: Bleeding Academic Research Consortium
MACE: Major Adverse Cardiovascular Events




**Primary endpoint**: **MACE,** including all cause death, myocardial infarction, urgent revascularization and stroke at 1 year

| Inclusion Criteria | Noninclusion Criteria |
|---|---|
| - Man or woman ≥18 years old and <90<br>- Must not be of child-bearing potential (1 year postmenopausal, contraceptive or surgically sterile).<br>- Non ST-segment elevation ACS defined by the presence of at least 2 of the following criteria: (1) symptoms of myocardial ischemia, (2) electrocardiographic ST-segment abnormalities (depression or transient elevation of at least 0.1 mV) or T-wave inversion in at least 2 contiguous leads, or (3) an elevated cardiac troponin value (above the upper limit of normal) or ST segment elevation ACS scheduled for primary PCI defined as a history of chest discomfort or ischemic symptoms of > 20 minutes duration at rest ≤ 14 days prior to entry into the study with one of the following present on at least one ECG prior to randomization:<br>a) ST-segment elevation ≥1 mm in two or more contiguous ECG leads. | - Minors and pregnant or breast-feeding women<br>- Subject under chronic anticoagulant<br>- Subject with thrombolytic therapy during the preceding 24 hours<br>- Subject with bleeding diathesis<br>- Subject participating in another research protocol<br>- Subject does not agree to participate<br>- Subject with contraindication to clopidogrel or ticagrelor<br>- Severe hepatic failure<br>- Ischemic stroke within one month or a history of hemorrhagic stroke<br>- Bradycardia<br>- Platelet count <100 000/$mm^3$<br>- Major surgery or trauma within 10 days<br>- Life expectancy <1 year<br>- Known significant bleeding risk according to physician judgment |

| | |
|---|---|
| b) New or presumably new left bundle branch block (LBBB).<br>c) ST-segment depression ≥1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction.<br>- Subject intended for an invasive strategy if NSTE-ACS or primary PCI if STE-ACS according to guidelines<br>- Subject with CKD stage 3b, 4 and 5 (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 $m^2$ by (MDRD formula)) or undergoing chronic dialysis<br>- Must be enrolled at a cardiac catheterization laboratory hospital or a hospital/ambulance service affiliated with a cardiac catheterization laboratory hospital<br>- Subject affiliated with or beneficiary of a social security system | |

| Efficacy endpoints | Tolerance endpoints | Biological endpoints |
|---|---|---|
| - Net clinical benefit (MACE + BARC bleedings ≥ 3)<br>- MACE<br>- All-cause death<br>- Cardiovascular death<br>- Myocardial infarction<br>- Urgent revascularization<br>- Stroke<br>- Probable and definite stent thrombosis (ARC definition)<br>- Type 4a and type 5 myocardial infarction<br>- Hospital re-admission after discharge | -Bleedings using the BARC definition, BARC≥3<br>-the rate of BARC< 3 bleedings<br>- the course of creatinin clearance between ticagrelor and clopidogrel during one-year follow-up including the requirement for hemodialysis<br>Also, tolerance will be compared between the two groups:<br>- dyspnea at one month and one year<br>- compliance to P2Y12 ADP-receptor inhibitor at one month and one year | |