Long-term recovery of vascular function in chronic coronary total occlusion recanalization: a randomized clinical trial of ticagrelor vs. clopidogrel

Brief title: TIGER trial

Juan Jose Rodriguez, MD[1]; Josep Gomez-Lara, MD, PhD[2]; Juan Caballero, MD, PhD[3]; Luis Ortega-Paz, MD, PhD[1]; Luis Teruel, MD[2]; Rafael Romaguera, MD[2]; Vicente Alcalde Martinez, MD[3]; Eduardo Molina Navarro, MD[3]; Joan-Antoni Gomez-Hospital, MD, PhD[2]; Concepcion Correa Vilches, MD[3]; Angel Cequier, MD, PhD[2]; Manel Sabate, MD, PhD[1]; Salvatore Brugaletta, MD, PhD[1].

[1] Cardiovascular Institute, Hospital Clinic, IDIBAPS, Barcelona, Spain.

[2] Heart Disease Institute, Bellvitge University Hospital, University of Barcelona, IDIBELL

[3] Hospitales Universitarios San Cecilio y Virgen de las Nieves. Granada.

[4] Hospital Clinic, Barcelona, Spain.

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Address for correspondence

Salvatore Brugaletta, MD, PhD, FESC.

c/ Villarroel 170, 08036 Barcelona, Spain

Cardiovascular Institute, Cardiology department, University Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain.

Telephone: +34932279305 Fax: +34932279305

Email: sabrugaletta@gmail.com

ABSTRACT

Background: Coronary vascular function of a chronic coronary total occlusion (CTO) immediately after recanalization is known to be poor and to be slightly improved by ticagrelor vs. clopidogrel. It is unknown if this vascular dysfunction is maintained at long-term follow-up and still improved by ticagrelor after 1 year of dual antiplatelet therapy.

Methods: The TIGER is a prospective, double-randomized, open-label, two parallel-group controlled clinical trial, which 1:1 randomized patients undergoing CTO PCI with anterograde approach to receive ticagrelor vs. clopidogrel at least 3 days before PCI. Patients were maintained under aspirin 100 mg/daily plus the randomized antiplatelet drug during 1 year and were 1:1 randomized to receive angiographic follow-up at 1 vs. 3 years follow-up. At follow-up, coronary blood flow (CBF) under stepwise adenosine infusion was evaluated and compared between clopidogrel vs. ticagrelor groups.

Results Out of 50 patients included in the trial, 25 patients per group received ticagrelor vs. clopidogrel during 1-year after CTO PCI and were 1:1 randomized to 1 vs. 3 years angiographic follow-up. Twenty-three (92%) and 15 (60%) patients eventually received angiographic follow-up. Under stepwise adenosine infusion, ticagrelor group showed a significantly increased in the area under the curve of CBF vs. clopidogrel group without any influence of time of follow-up or interaction between time and drug. Whereas baseline increased ticagrelor-related CBF was maintained at follow-up without any change, the baseline clopidogrel-related CBF increased at follow-up as compared to baseline.

Conclusion: The TIGER trial showed that effect of ticagrelor on CBF in a recanalized CTO is maintained at follow-up, with still significant advantages over clopidogrel, despite a significant increase in CBF in clopidogrel patients at follow-up as compared to baseline. The clinical value of a higher coronary flow in this context should be evaluated in a larger group of patients.

Keywords: Clopidogrel, Ticagrelor, CTO.

Clinical Trial registration: https://clinicaltrials.gov/ct2/show/NCT02211066 (ClinicalTrials.gov number NCT02211066)

INTRODUCTION

Chronic coronary total occlusions (CTO) are one of the most complex forms of stable coronary artery disease. (1) Clinical data about the effectiveness of its percutaneous treatment for improving prognosis or symptoms are discordant, as PCI still exhibits higher rates of target lesion revascularization (TLR) as compared to conventional PCI (2-7) with controversial data about its relationship with a big and clear improvement in angina symptoms and health status. In the EUROCTO trial, for example, only 71% of CTO PCI patients reported a complete freedom from angina and a recent report found a gap between residual angina and CTO PCI procedural success. (8,9) A possible explanation of this gap may come from evidence that immediately after CTO-PCI there is a lack of a normal vascular function in the recanalized vessel. (10-13)

We have previously shown that ticagrelor loading dose before CTO-PCI may reduce this vascular dysfunction as compared with clopidogrel. (13) In addition to exerting more potent $P2Y_{12}$ inhibitory effects compared with clopidogrel, ticagrelor inhibits the equilibrative nucleoside transporter 1 which in turn leads to an increase of adenosine interstitial concentration, which may increase coronary blood flow and improve vascular function. (14-21) Long-term effect of 1-year dual antiplatelet therapy with ticagrelor vs. clopidogrel on coronary blood flow after CTO-PCI are however unknown.

We sought therefore to analyze the long-term coronary blood flow in CTO patients with a successful PCI who were randomly assigned to receive 1-year treatment with ticagrelor vs. clopidogrel.

METHODS

Patients and study design

The TIGER trial is a multi-center, prospective, double-randomized, open-label, two group-parallel controlled clinical trial to evaluate superiority of ticagrelor vs. clopidogrel in improving coronary blood flow in the coronary segment distal to CTO after PCI. Details about inclusion/exclusion criteria and patients enrollment have been already reported. (13,22)

All patients included in the trial were randomized 1:1 to one of two treatment arms: 1) loading dose of clopidogrel (600mg); or 2) loading dose of ticagrelor (180mg). Primary endpoint of the trial was coronary blood flow (CBF) immediately after CTO PCI and it has been already published. (13) At the time of this study design, bioresorbable vascular scaffold (BRS) were selected for use in the trial, as lack of a long-term metallic caging was thought to allow late lumen enlargement and normal biological response to shear stress, potentially improving vascular function. (23-26) Data showing lack of significant vasomotion in the scaffolded segment with a higher than expected risk of thrombosis (27) were still not available.

After CTO PCI, patients were maintained on the assigned antiplatelet treatment regimen for 12 months and were further randomized 1:1 to undergo angiographic follow-up at 1 or 3 years. (22) Patients were followed up by telephone/clinical visit at 30 days, 6 months, and yearly up to 3 years.

The TIGER BVS trial is investigator initiated and promoted by the “Fundacio Clinic per a la Recerca Biomedica” (FCRB, Barcelona, Spain). An unrestricted educational grant was provided by AstraZeneca for the conduct and analyses of the trial. The Clinical Trial Unit (CTU, Barcelona, Spain) was responsible for monitoring the trial. The TIGER BVS trial is registered with ClinicalTrials.gov number NCT02211066.

This trial was conducted in accordance with the Clinical Investigation Plan, the Declaration of Helsinki and the applicable local legislation. The conduct of the trial has been approved by local

ethical committee of each participating center. All participating subjects provided informed consent in accordance with the local requirements, using the approved informed consent forms.

Vasomotion evaluation

Coronary function study was performed as previously described. (10,28) Briefly, a Doppler wire (FlowWire, Volcano, Therapeutics Inc., Rancho Cordova, California) was advanced into the coronary artery of previous CTO-PCI, with the Doppler wire tip approximately in the same angiographic position as in the baseline, according to angiographic landmarks.

Subjects received multiple intravenous adenosine infusions with a stepwise dosing protocol (0, 50, 80, 110 and 140 μg/Kg/min) for a period of 2 minutes each to assess coronary flow. After a washout period of at least 5 minutes from the last dose, a nitroglycerin (NTG) bolus (200 μg) was administered through the guiding catheter to evaluate endothelium-independent vasomotion. Continuous average peak velocity (APV) Doppler traces (calculated as the time-averaged value of the instantaneous peak velocity over two consecutive cardiac cycles) and angiographic images of the studies artery were recorded at baseline and after each adenosine infusion and after nitroglycerin bolus). (22)

Mean lumen diameter (MLD) in the coronary segment distal to recanalized CTO at baseline (approximately at the same location of the flow sensor of the flow wire), after each adenosine infusion and after nitroglycerin bolus was analyzed offline using specific software for quantitative coronary angiography analysis (CASS, Pie Medical, the Netherlands) by an independent core laboratory (Barcelona Cardiac Imaging Core-laboratory; BARCICORE-Lab, Barcelona, Spain), blinded to randomization.

Coronary blood flow (CBF) was calculated from the product of corresponding peak APV values and QCA-derived coronary artery diameter/area (1/2 x APV x coronary cross-sectional area) at baseline and after each adenosine infusion and after NTG bolus. (10,22)

OCT analysis

After vascular function evaluation, all the patients received an optical coherence tomography evaluation of the treated segment. OCT analysis was also performed by a dedicated core laboratory (BARCICORE-lab) using specific software for analysis (LightLab Imaging, Westford, Massachusetts).

Two blinded analysts were requested to assess the following qualitative OCT findings in the entire pullback (0.2-mm intervals) according to previously published studies (14,15) in a qualitative fashion: neointima pattern at the cross-section with largest neointima area, the observation of cross-sections with a ratio of uncovered to total stent struts >o= 30%, strut malapposition, neoatherosclerosis and structural discontinuities.

Quantitative OCT data was also evaluated each 1-mm cross-section according to stan- dard core-laboratory procedures using the same offline specific software (LightLab Imaging) and included reference lumen area, scaffold length, lumen, stent, and neointima area, neointima obstruction and thickness and stenosis area. Supplementary appendix includes a more detailed description of the assessment.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, while categorical data are expressed as absolute numbers and percentages and were compared by chi-square or Anova test, as appropriate. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Analyses were done according to the intention-to-treat principle.

Comparison of MLD, APV and CBF in the vasomotor test between clopidogrel vs. ticagrelor at follow-up was estimated by means of mixed regression models for repeated measurements. In order

to avoid multiple comparisons between groups according to drug (ticagrelor vs. clopidogrel) or time of follow-up (1 vs. 3 years), main comparison was performed between ticagrelor vs. clopidogrel group, considering time of follow-up as in between-subject factor. Moreover, AUC for each variable was calculated using the trapezoidal rule and compared by a two-sample t-test.

To evaluate CBF between baseline and follow-up in clopidogrel vs. ticagrelor group, a linear mixed regression model was performed, using the repeated AUC of CBF at baseline and follow-up (within each patient), including time of follow-up (1 vs. 3 years) as in between-subject factor.

OCT strut level analysis was performed considering the clustering nature of the OCT data with generalized estimating equations. All struts were classified into the following types: apposed and covered, apposed and uncovered, malapposed and covered and malapposed and uncovered. Each strut type was introduced into the model as dependent variable using the binary logistic model. Each model was performed introducing drug (ticagrelor vs. clopidogrel) as covariate, time of follow-up as in between-subject factor and the patient identification as subject variable. Another model using time of follow-up as covariate was also performed.

A two-tailed level of $p < 0.05$ was considered statistically significant. Taking into account the large number of parameters with multiple comparisons, p values presented in this paper are exploratory only and should therefore be interpreted with caution. Commercially available computer software (SPSS version 20.0, SPSS Inc, Chicago, Illinois) was used for all analyses.

RESULTS

Baseline and procedural characteristics

Overall, 50 patients with a successful CTO-PCI were included in the study (25 patients per group). They were further randomized to angiographic follow-up at 1 or 3-year (25 patients per group). Baseline clinical characteristics of patients according to the drug randomized have been previously reported. (13) Table 1 shows baseline clinical characteristics according to the time of angiographic follow-up. Clinical follow-up was obtained in all patients. (**Figure 1**)

Coronary blood flow evaluation under adenosine infusion between ticagrelor and clopidogrel at follow-up

Coronary blood flow evaluation was obtained from a total of 38 patients, 23 patients at 1-year and 15 patients at 3-year follow-up. (**Figure 1**) During stepwise infusion of adenosine, no significant differences were found in MLD between the drug groups, without any effect of time of follow-up (1 vs. 3 years, p=0.849) or interaction between time and drug (p=0.483). No significant differences were also found in terms of APV between drug group, without any effect of time of follow-up (p=0.751) or interaction between time and drug (p=0.661). (Table 2)

A trend toward a higher CBF was found in Ticagrelor as compared to clopidogrel group (p=0.136), without any effect of time of follow-up (p=0.956) or interaction between time and drug (p=0.346). (**Figure 2**) The same trend was found considering AUC of CBF.

Comparing changes overtime of CBF between baseline and follow-up, whereas within clopidogrel patients, a significant increase in CBF was found between baseline and follow-up (p=0.039), within ticagrelor patients no changes in CBF was found (p=0.933). Nevertheless, AUC of repeated CBF was still higher in ticagrelor group as compared to clopidogrel group (p=0.032), without any effect of time of follow-up or any interaction between time and drug. (**Figure 2**)

Coronary blood flow evaluation under nitrate administration at follow-up

After NTG bolus administration, no differences were found in terms of MLD, APV or CBF changes inter- and intra- groups (Table 3).

OCT results

OCT data are shown in table 4 and table 5, according to patients or struts level. Overall 3-year follow-up show better healing as compared to 1-year follow-up. Ticagrelor group have larger lumen and stent area as compared to clopidogrel group.

Adverse events

No major bleeding events or major cardiac events were recorded in either treatment group during the follow-up period. Severe dyspnoea was observed in one patient while receiving ticagrelor at 3 months finally switching to Clopidogrel. Severe anemia was detected in one patient in the clopidogrel group and in one patient in the ticagrelor group at 6 months having to stop ticagrelor and switched to only clopidogrel treatment.

Conclusions

Our study shows that: 1) coronary blood flow, under incremental doses of adenosine, maintained to be enhanced by ticagrelor as compared to clopidogrel in a CTO vessel after 1-year of DAPT; 2) as compared with baseline, there is an increase of flow in clopidogrel patients, which nevertheless does not reduce the gap from ticagrelor patients, whose baseline higher flow is maintained at follow-up; 3) no differing effects on endothelial-independent vasomotion and flow changes with nitrates administration may be seen between ticagrelor vs. clopidogrel.

The clinical value of a maintained higher coronary flow in this context should be evaluated in a larger group of patients.

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TABLES

Table 1. Baseline Clinical and procedural characteristics according to time of follow-up

	All (n=50)	1-Year (n=25)	3-Year (n=25)	p-value
Age, y	62±10.73	61.92±10.68	62.08±11.00	0.930
Sex (male), n (%)	41 (82)	20 (80)	21 (84)	1.000
Coronary risk factors, n (%)				
Hypertension	36 (72)	18 (72)	18 (72)	1.000
Dyslipidemia	42 (84)	19 (76)	23 (92)	0.247
Diabetes	17 (34)	8 (32)	9 (36)	1.000
Smoke	10 (20)	7 (28)	3 (12)	0.490
Previous MI, n (%)	12 (24)	12 (48)	9 (36)	0.567
Ejection fraction LV, %	56.64±9.39	56.58±9.85	56.70±9.11	0.861
Location of previous MI, n (%)	29 (58)	13 (52)	16 (64)	0.691
• Anterior	14 (28)	8 (32)	6 (24)	
• Lateral	7 (14)	4 (16)	3 (12)	
• Inferior				
Previous PCI, n (%)	25 (50)	11 (44)	14 (56)	0.572
Renal Impairment, n (%)	1 (2)	0 (0)	1 (4)	0.490
Localization of CTO, n (%)				0.082
• LAD	16 (32)	10 (40)	6 (24)	
• LCx	4 (8)	0 (0)	4 (16)	
• RCA	30 (60)	15 (60)	15 (60)	
CTO length (mm)	17.8±8.8	17.6±6.5	18.0±10.9	0.875
J-CTO score value±SD	1.3±1.0	1.4±1.0	1.2±1.1	0.497
J-CTO score variables, n (%):				
Blunt entry shape	12 (24)	5 (20.0)	7 (28.0)	0.508
Calcification	20 (40)	12 (48.0)	8 (32.0)	0.248

Bending >45º	11 (22)	7 (28.0)	4 (16.0)	0.306
Occlusion length ≥ 20 mm	20 (40)	10 (40.0)	10 (40.0)	1.000
Re-entry lesion	0	0	0	NA
Micro-channel, n (%)	22 (44)	10 (40.0)	12 (48.0)	0.569
Bridging collaterals, n (%)	9 (18)	4 (16.0)	5 (20.0)	0.713

Continuous data are expressed as mean±SD; SD = standard deviation; LV = left ventricle; MI = myocardial infarction; NA = not applicable, ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; RVD = reference vessel diameter; BRS =Bioresorbable scaffold,

Table 2. Vascular function analysis under adenosine infusion at follow-up

	Group	Baseline	Adenosine 50	Adenosine 80	Adenosine 110	Adenosine 140	AUC	p-value*	p-value for AUC
MLD (mm)	Ticagrelor group	2.20±0.87	2.13±0.74	2.18±0.72	2.17±0.70	2.22±0.68	741.81±316.11	0.298	0.381
	Clopidogrel group	1.74±0.55	1.79±0.46	1.87±0.42	1.97±0.45	1.96±0.45	659.52±205.47		
APV (cm/s)	Ticagrelor group	26.55±11.02	34.05±13.43	41.9±16.68	53.25±17.31	57.11±20.34	16424.72±5976.44	0.301	0.248
	Clopidogrel group	22.69±7.38	26.4±7.59	40.4±15.45	47±10.04	50.29±8.83	14234.67±5012.49		
CBF (ml/min)	Ticagrelor group	51.31±38.92	63.69±49.16	84.04±59.80	107.23±74.11	126.13±96.36	34815.22±24206.06	0.136	0.071
	Clopidogrel group	28.80±20.05	36.12±22.45	62.19±43.82	76.46±47.75	76.77±32.45	22712.47±13768.95		

MLD =mean lumen diameter; APV = average peak velocity; CBF = coronary blood flow; CFR = coronary flow reserve; NA = not applicable.
* p-value were calculated by mixed-ANOVA model for between-subject effect

Table 3. Vascular function analysis after nitrates administration at follow-up

	Group	Baseline	Nitrates	p-value*
MLD (mm)	Ticagrelor group	2.20±0.87	2.30±0.72	0.207
	Clopidogrel group	1.74±0.55	1.97±0.44	
APV (cm/s)	Ticagrelor group	26.55±11.02	41.47±17.68	0.134
	Clopidogrelgroup	22.69±7.38	35.79±8.95	
CBF (ml/min)	Ticagrelor group	51.31±38.92	82.21±53.56	0.141
	Clopidogrelgroup	28.80±20.05	59.71±41.44	

MLD =mean lumen diameter; APV = average peak velocity; CBF = coronary blood flow.
* p-value were calculated by mixed-ANOVA model for between-subject effect

Table 4. OCT data (patient level)

	All (n=38)	Clopidogrel Group (n=17)	Ticagrelor Group (n=21)	p-value	1Y FU (n=23)	3Y FU (n=15)	p-value
Qualitative data:							
Neointima pattern, n(%):				0.193			0.250
Absent neointima							
Homogeneous	7 (18.4)	2 (11.8)	5 (23.8)		6 (26.1)	1 (6.7)	
Heterogeneous	27 (71.1)	13 (76.4)	14 (66.7)		14 (60.9)	13 (86.7)	
Layered	2 (5.3)	2 (11.8)	0		2 (8.7)	0	
	2 (5.3)	0	2 (9.5)		1 (4.3)	1 (6.7)	
Lack of tissue coverage, n (%):							
Any uncovered strut							
>5% uncovered struts	32 (84.2)	15 (88.2)	17 (81)	0.672	21 (91.3	11 (73.3)	0.138
RUTTS, 30%	15 (39.5)	4 (23.5)	11 (52.4)	0.100	12 (52.2)	3 (20.0)	0.047
	15 (39.5)	5 (29.4)	10 (47.6)	0.326	11 (47.8)	4 (26.7)	0.192
Malapposition, n (%)							
Any malapposed strut	14 (36.8)	6 (35.3)	9 (42.9)	0.823	10 (43.5)	4 (26.7)	0.294
>5% malapposed struts	4 (10.8)	1 (5.9)	3 (14.3)	0.435	2 (9.1)	2 (13.3)	0.683
Neoatherosclerosis, n (%)	11 (28.9)	7 (41.2)	4 (19)	0.167	5 (21.7)	6 (40.0)	0.225
Scaffold discontinuities, n (%)							
Any strut discontinuity	17 (44.7)	6 (35.3)	11 (52.4)	0.342	10 (43.5)	7 (46.7)	0.847
Intraluminal strut dismantling	7 (18.4)	2 (11.8)	5 (23.8)	0.427	4 (17.4)	3 (20.0)	0.839

Quantitative data:							
Reference lumen area, mm^2±SD	8.8±3.7	6.92±2.82	10.42±3.66	0.007	8.9±4.0	8.7±3.4	0.879
Scaffold length, mm±SD	48.6±18.0	50.71±18.72	46.90±17.70	0.491	48.7±16.8	48.4±20.4	0.956
Lumen area, mm^2±SD:							
Minimal	4.2±2.2	3.42±2.08	4.82±2.08	0.027	4.5±2.2	3.7±2.1	0.268
Mean	7.3±2.6	6.13±2.13	8.20±2.61	0.003	7.4±2.9	7.1±2.2	0.777
Stent area, mm^2±SD:							
Minimal	5.5±2.1	4.71±2.15	6.22±1.83	0.010	5.6±2.2	5.5±2.1	0.949
Mean	8.4±2.5	7.40±2.17	9.26±2.44	0.008	8.3±2.7	8.6±2.2	0.685
Neointima area, mm^2±SD:							
Mean							
Maximal	1.3±0.6	1.32±0.644	1.26±0.57	0.973	1.1±0.5	1.6±0.6	0.001
	3.0±1.6	2.95±1.59	3.07±1.68	0.765	2.6±1.2	3.6±1.9	0.011
Neointima obstruction, %±SD							
Mean							
Maximal	16.5±8.4	19.00±9.51	14.36±6.99	0.164	14.2±7.9	19.5±8.5	0.067
	37.5±19.4	41.19±20.44	34.47±18.38	0.304	33.7± 18.6	42.6±19.8	0.187
Area stenosis, mm^2±SD	51.5±16.8	50.31±18.51	52.46±15.48	0.809	48.1±15.5	55.7±17.8	0.196
Mean neointima thickness, µm±SD	129.0±65.6	136.54±73.40	122.65±59.60	0.666	110.4 ±54.8	153.7±72.4	0.052

Table 5. OCT table: Strut lesion data

	All (n=14,268)	**Clopidogrel Group (n=8967)**	**Ticagrelor Group (n=5301)**	**p-value**	**1Y FU (n=8,098)**	**3Y FU (n=6,170)**	**p-value**
Strut type, n (%):				0.142			p<0.001
Apposed and covered	13,391 (93.9)	8576 (96.6)	4815 (90.8)		7339 (90.6)	6052 (98.1)	
Apposed and uncovered	737 (5.1)	326 (3.6)	411 (7.8)		645 (8.0)	92 (1.5)	
Malapposed and uncovered	101 (0.7)	41 (0.5)	60 (1.1)		78 (1.0)	23 (0.4)	
Malapposed and covered	39 (0.3)	24 (0.3)	15 (0.3)		36 (0.4)	3 (0.0)	
Uncovered struts, n (%):	838 (5.9)	367(4.1)	471(8.9)	0.122	723 (8.9)	115 (1.9)	p<0.001
Malapposed struts, n (%)	140 (1.0)	65(0.7)	75(1.4)	0.399	114 (1.4)	26 (0.4)	p=0.215
Neointima thickness, μm ± SD	138.8 ± 128.5	146.66±129.73	125.47±125.20	0.291	117.1 ± 118.0	167.2 ± 135.9	p=0.019

FIGURES

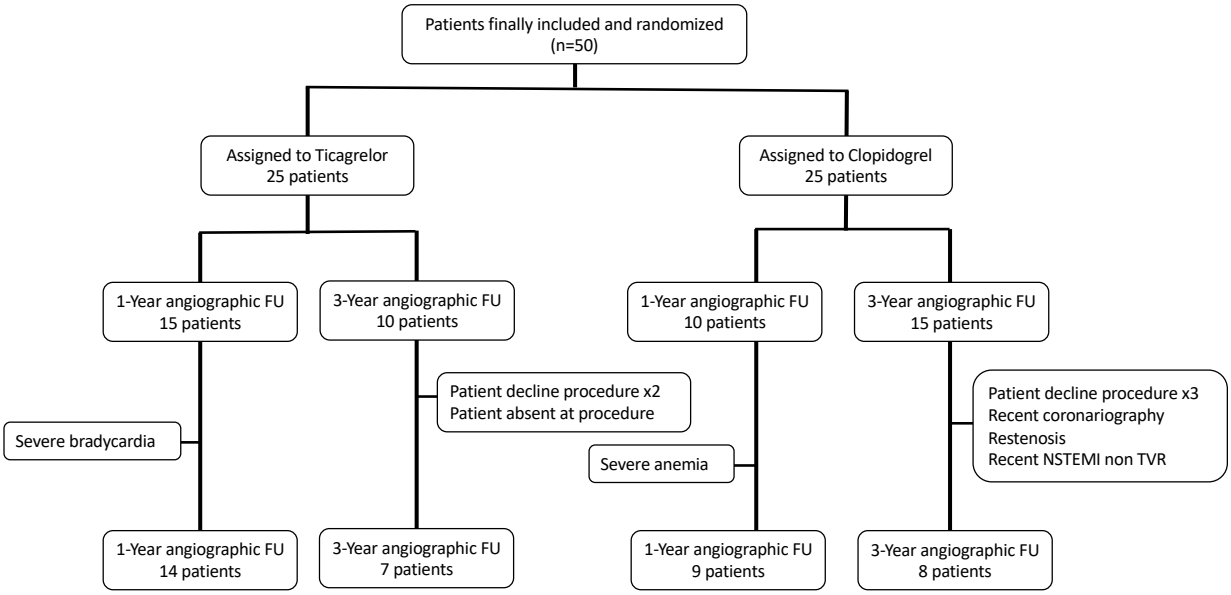

Figure 1. Flow chart of the study

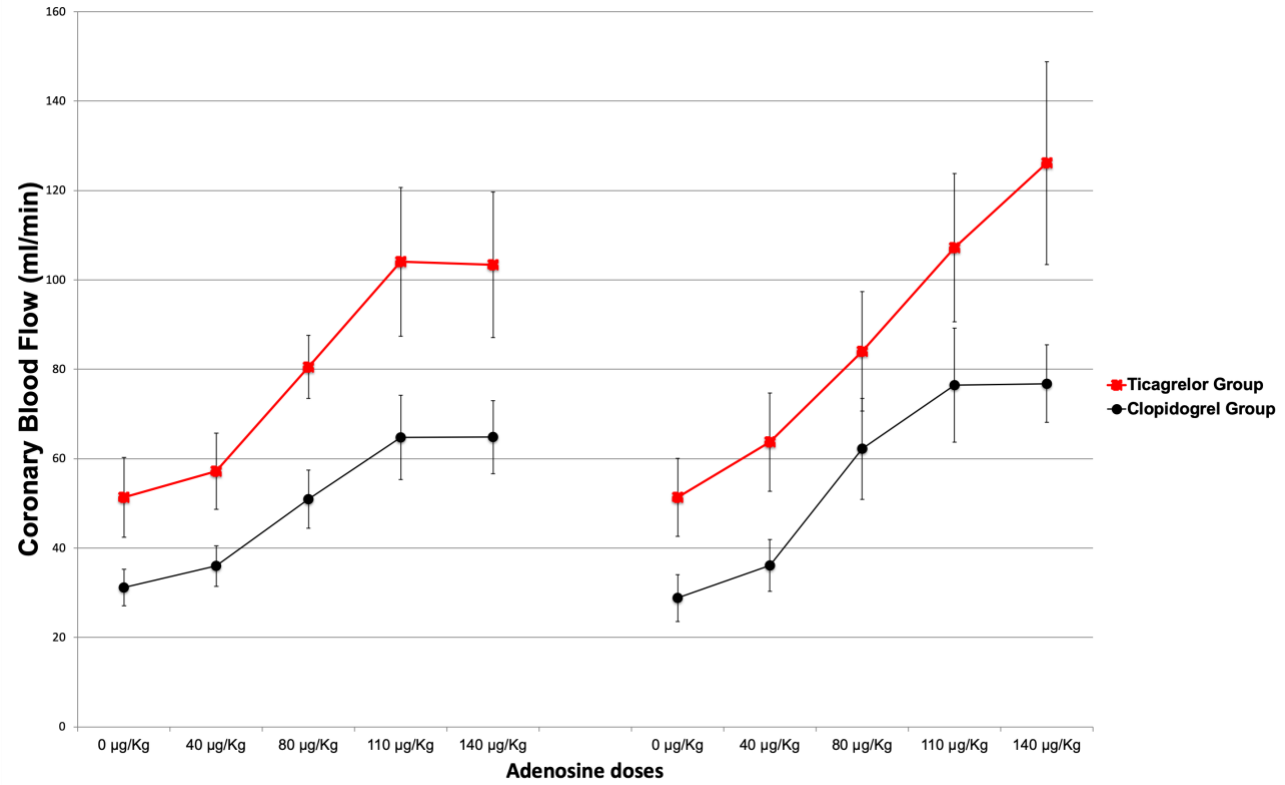

Figure 2. Coronary blood flow evaluation in CTO at baseline and follow-up.

Ticagrelor pre-treatment of CTO patients enables increase of coronary blood flow of the CTO vessel immediately after its PCI recanalization vs. clopidogrel pre-treatment (left hand-side). The same trend is maintained at follow-up (right hand-side). Graphs show paired patients at baseline and follow-up. CTO = chronic coronary total occlusion. PCI = percutaneous coronary intervention.