Efficacy of $P2Y_{12}$ receptor antagonists in patients with atrial fibrillation according to the CHA_2DS_2VASc score

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BACKGROUND I

- ⇨ 5.0–10.0% of the patients undergoing PCI have concomitant AF
- ⇨ AF is associated with a prothrombotic (hypercoagulable) state

  (higher amounts of the platelet microparticles and the soluble P-selectin, abnormalities of the coagulant factors (tissue factor, von Willebrand factor, factor IX and X, thrombin and fibrinogen)
- ⇨ Triple antitthrombotic therapy (DAPT + OA) is associated with high bleeding risk

BACKGROUND II

- Patients with AF who undergo PCI represent a group of patients where balancing between risks of thrombo-embolism and bleeding complications is accented.
- Only sparse data are currently available on the combination of OA with newer $P2Y_{12}$ inhibitors, which have been proven to reduce coronary endpoints, however, at the expense of more bleeding

PURPOSE

- to verify whether the presence of AF impacts the efficacy of $P2Y_{12}$ inhibitors in the group of patients after stent-PCI,
- to investigate whether there is a correlation between CHA2DS2VASc score and the efficacy of $P2Y_{12}$ inhibitors in this group of patients

METHODS

- The prospective LAPCOR (Laboratory AntiPlatelet efficacy and Clinical Outcome Registry; ClinicalTrials.gov Identifier: NCT02264912) registry was analyzed.
- Consecutive patients (N = 896)who underwent stent-PCI were included. No exclusion criteria were applied.
- The platelet reactivity was measured by phosphorylation of the protein VASP 24 ± 4 h after loading a dose of clopidogrel (600 mg), prasugrel (60 mg), ticagrelor (180 mg)
- The high on treatment platelet reactivity (HTPR) was defined by Platelet Reactivity Index ≥ 50.

METHODS

CHA_2DS_2-VASc score	
Stroke	2
Age ≥ 75 y	2
Hypertension	1
Diabetes mellitus	1
Congestive heart failure	1
Age 65–74 y.	1
Sex category, female	1
Vascular disease	1
Maximum total score	9

⇨ The univariate and multivariate logistic regression were used to test the correlation between CHA2DS2VASc score and the efficacy of $P2Y_{12}$ inhibitors

STUDY POPULATION

Baseline characteristics of the study population in relation to presence of AF

	Patients without AF *n=768* *N (%)*		*Patients with AF* *n=128* *N (%)*		*p (value)*
Age	65.6	(12.2)	74.6	(9.3)	<0.001
Sex (representation of male sex)	432	(67.2)	59	(51.8)	0.002
BMI	28.5	(4.5)	27.6	(4.7)	0.043
Acute coronary syndrome	468	(72.8)	69	(60.5)	0.010
Hypertension	436	(67.8)	92	(80.7)	0.006
Diabetes mellitus	210	(32.7)	36	(31.6)	0.914
Dyslipidemia	240	(37.3)	45	(39.5)	0.676
Previous myocardial infarction	157	(24.5)	36	(31.6)	0.129
Previous coronary artery bypass grafting	65	(10.1)	13	(11.4)	0.738
Chronic ischemic limb disease	47	(7.3)	15	(13.2)	0.042
Previous stroke	41	(6.4)	21	(18.4)	<0.001
Smoking	250	(39.7)	26	(23.0)	0.001
Renal dysfunction	73	(11.4)	18	(15.9)	0.209
GFR before PCI	73.6	(56.6-89.4)	58.5	(44.8-77.3)	<0.001
GFR after PCI	73.1	(54.8-89.4)	59.0	(40.4-69.2)	<0.001
White blood count	9.7	(7.6-12.5)	8.6	(6.8-10.9)	0.003
Red blood count	4.6	(4.2-4.9)	4.4	(4.1-4.7)	0.020
Hemoglobin	13.9	(12.7-14.9)	13.7	(12.5-14.7)	0.200
Platelet	227	(190-270)	209.5	(175-273)	0.014
INR	1.11	(1.05-1.21)	1.19	(1.10-1.27)	<0.001

Proportion of patients with atrial fibrillation				
	Patients without AF		*Patients with AF*	
⌘clopidogrel	535	83.72 %	104	16.28 %
prasugrel	129	94.85 %	7	5.15 %
ticagrelor	104	85.95 %	17	14.05 %
total	768	85.71%	128	14.29 %

⌘65.4% of patients underwent stent-PCI for ACS

RESULTS

The efficacy of $P2Y_{12}$ receptor antagonists in relation to the presence of atrial fibrillation in patients with an acute coronary syndrome

		mean	*median*	*IQR*	*P (value)*
Patients treated with clopidogrel n= 418	with AF n= 59	42.3	41.6	38.5	p= 0.429
	without AF n= 359	44.8	46.0	36.1	
Patients treated with prasugrel/ ticagrelor n= 252	with AF n=23	14.2	11.6	10.5	p= 0.195
	without AF n= 229	19.3	12.7	18.0	

Efficacy = Platelet Reactivity Index; Effective inhibition of Platelet aggregation = PRI < 50%

RESULTS

- Clopidogrel - The HTPR (High on-treatment platelet reactivity) was assessed in 39.98% of the patients with AF and in 43.4% patients without AF (p= 0.572)
- Prasugrel or ticagrelor group - HTPR in 4.4% of patients with AF and 7.9% of patients without AF (p=1.000))

THE EFFECT OF CO-MEDICATION WITH OTHER ANTITHROMBOTICS

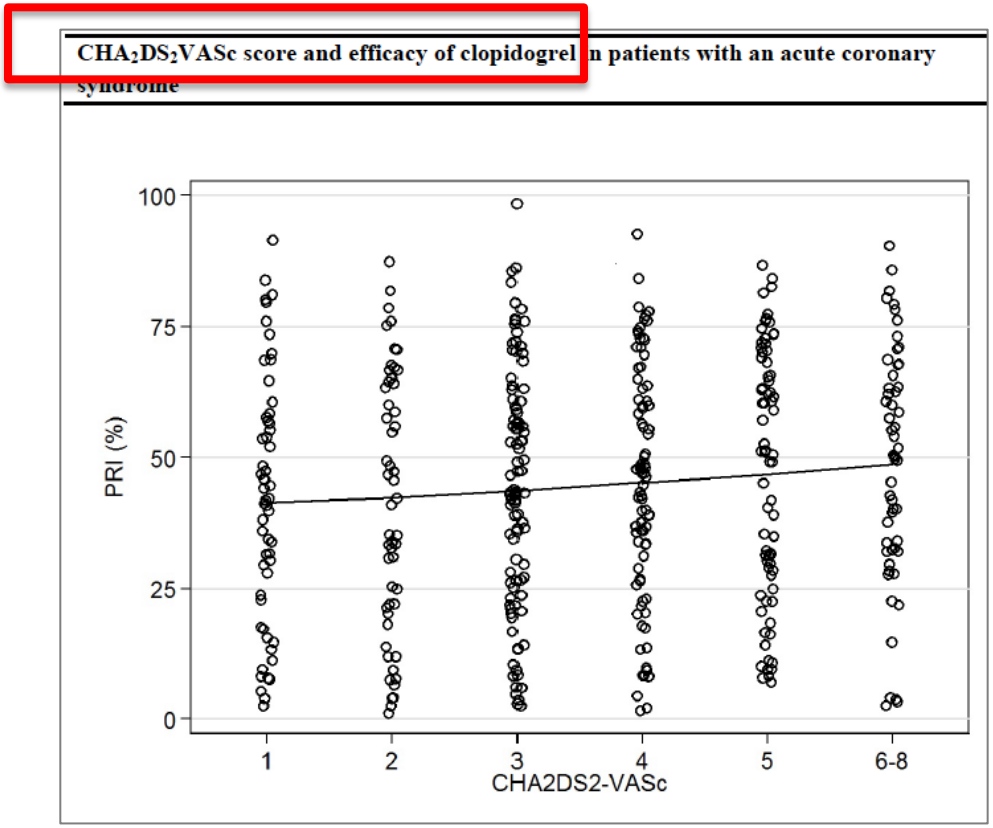
⇨Periprocedural administration of GP IIb/IIIa inhibitors was associated with significantly higher efficacy of $P2Y_{12}$ inhibitors:

Median PRI in patients with GP IIb/IIIa inhibitors = 23.3 (IQR 40.5) %;

Median PRI in patients without GP IIb/IIIa inhibitors = 35.3 (IQR 42.6) %

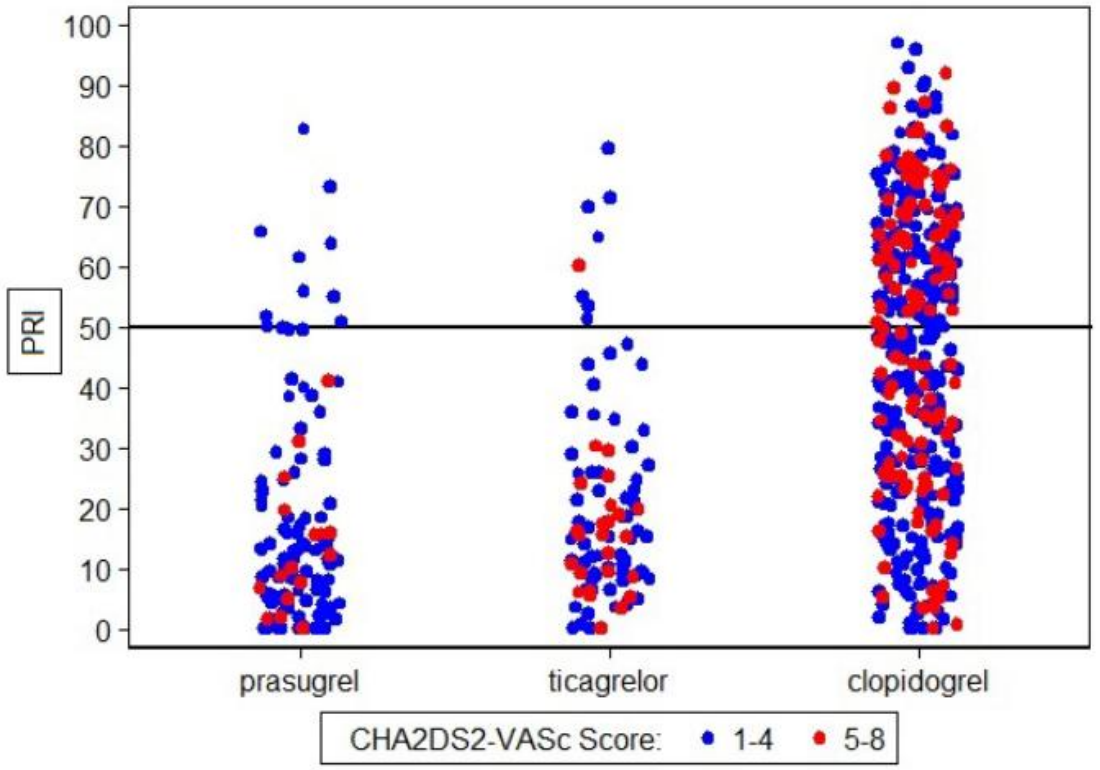
(p= 0.008).

THE EFFICACY OF $P2Y_{12}$ INHIBITORS AND CHA2DS2VASC SCORE



Using univariate analysis, CHA2DS2VASc score was recognized as a significant predictor of the HTPR in clopidogrel group of patients with ACS (p=0.015). Primarily if CHA2DS2VASc score was ≥5 (odds ratio 1.72 [95%CI 1.13 to 2.63, p=0.011])

CHA_2DS_2VASc score and efficacy of $P2Y_{12}$ receptor antagonists in patients with an acute coronary syndrome



There was also no significant correlation between the efficacy of prasugrel and ticagrelol and CHA2DS2VASc score (p=0.879). Multivariate analysis underscored these results

CONCLUSION

The presence of AF does not impact the efficacy of prasugrel or ticagrelor. In patients with AF and the high risk of thrombotic events and low bleeding risk, who were undergoing stent implantation because of ACS, replacing clopidogrel with one of prasugrel or ticagrelor should be considered. Periprocedural administration of GPIIb/IIIa inhibitors in this high risk population increases efficacy of clopidogrel.

Circulation Research

REVIEW

Purinergic Signaling in the Cardiovascular System

Geoffrey Burnstock

AMISTAD clinical trials (Acute Myocardial Infarction Studyof Adenosine) showed that the infusion of adenosine for 3 hours resulted in a striking reduction in infarct size.[130,131] Protection against myocardial infarction is mediated by A_1 and probably A_3 receptors in the rabbit heart. Adenosine reduces the incidence of postoperative atrial fibrillation (AF). Upregulation of A_{2A} receptors is linked to abnormal calcium handling in AF. Prevention of A_{2A} receptor activation may be a novel way to maintain uniform beat-to-beat responses at higher beating frequencies in patients with AF.[132] Adenosine-guided pulmonary vein isolation has been recommended, after a randomized clinical trial, for the treatment of paroxysmal AF,[133] but this has been questioned in a more recent clinical trial.[134] The clinical significance of ATP-induced AF has been investigated.[135] The presence of AF does not affect the efficacy of the $P2Y_{12}$ antagonists prasugrel and ticagrelor.[136] Articles discussing the role of adenosine in atrial arrhythmias and fibrillation have been
the role of ATP.[138] ATP was used for acute therapy of paroxysmal su
tachycardia in the late 1940s and later utilized by others. Bolus injec
(Adenocard) is being used clinically to slow conduction time through
the reentry pathways through the AV node in patients with paroxysmal supraventricular tachycardia. The treatment of paroxysmal supraventricular tachycardia by ATP and adenosine has been discussed in a recent review.[139] Adenosine and ATP have been used in conjunction with the head-up tilt table test to provoke vasovagal reaction in syncope patients.[140]

Ondrakova M, Knot J, Ulman J, Maly M, Motovska Z. Efficacy of P2Y12 receptor antagonists in patients with atrial fibrillation according to the CHA2DS2VASc score. *Int J Cardiol*. 2016;**207**:84–86. doi: 10.1016/j.ijcard.2016.01.039.
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Circulation Research (IF 11.551). 2017;120:207-228