PLATELET ADP REACTIVITY AND BLEEDING RISK IN LONG-TERM DOUBLE ANTIPLATELET THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

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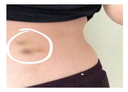
Background



- **Most studies assessing the dual antiplatelet therapy (DAPT) paid attention on major bleedings as events with negative prognosis impact**
- **In contrast, the minor (so called *nuisance)* bleedings are the most frequent but under recognized and under reported in patients with antiplatelet treatment***
- **Nuisance bleedings are related to the premature discontinuation of antiplatelet therapy therefore may impact negatively on clinical outcomes**
- **Clinical and laboratory variables associated with nuisance bleedings are mostly unknown**

* - Ben-Dor I, Torguson R, Scheinowitz M et al. Incidence, correlates, and clinical impact of nuisance bleeding after antiplatelet therapy for patients with drug-eluting stents. Am Heart J 2010;159:871-875

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Aim of the study

To assess the association between on-treatment platelet reactivity to ADP, CYP2C19 genotype and bleedings after elective percutaneous coronary intervention (PCI)

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Study Design

Study population

- ≥ 18 yrs eligible for elective PCI with planned use of ≥ 1 DES
- on medical treatment: statins, β-blockers and ACE inhibitors/ AR blockers (if needed)

DAPT for 12 months, **n = 188**

Methods

ASA 75-100 mg/d + Clopidogrel 75 mg/d, **n = 179**

ASA 75-100 mg/d + Clopidogrel 150 mg/d, **n = 9**

Genetic testing CYP 2C19, n = 185

Platelet reactivity VerifyNow P_2Y_{12}, n = 115

Mean follow-up 1,1 ± 0,3 years

End points

Ischemic events: - target vessel revascularization due to restenosis
- stent thrombosis: definite/probable (ARC criteria)

Bleedings: - BARC definition

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BARC bleeding definition*

- **Type 0:** no bleeding
- **Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional**
- **Type 2:** any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- **Type 3**
  - **Type 3a**: - Overt bleeding plus hemoglobin drop of 3 to 5 g/dL (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - **Type 3b**: - Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed)
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
    - Bleeding requiring intravenous vasoactive drugs
  - **Type 3c**: - Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)
    - Subcategories; confirmed by autopsy or imaging or lumbar puncture
    - Intra-ocular bleed compromising vision
- **Type 4:** - CABG-related bleeding
  - Perioperative intracranial bleeding within 48 h
  - Reoperation following closure of sternotomy for the purpose of controlling bleeding
  - Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period
  - Chest tube output ≥ 2 L within a 24 h period
  - If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event
- **Type 5:** - Fatal bleeding
  - **Type 5a**
    - Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
  - **Type 5b**
    - Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

* - Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the BARC, Circulation, 2011

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Study population

Gender (male/female)	188 (143/45)
Age (year), M ± SD	61.4 ± 10.7
Arterial hypertension, n (%)	172 (91.4)
Diabetes mellitus, n (%)	40 (21.3)
Total cholesterol, mmol/L (M ± SD)	4.7 ± 1.2
Smoking history (%):	
- active, n (%)	44 (23.4)
- former, n (%)	61 (32.4)
Obesity (BMI> 30 kg/m^2), n (%)	80 (42.6)
Renal impairment (GFR < 60 ml/min), n (%)	20 (10.6)
Previous CABG/PCI, n (%)	21 (11.2)/47 (24.9)
History of ACS, n (%)	128 (68.1)
Previous restenosis/stent thrombosis, n (%)	13 (6.9)/1 (0.5)
Frequency of CYP2C19 *1/*2, *2/*2, *1/*3, *3/*3	42 (22.7)
CYP2C19 *1/*17, *17/*17	59 (31.9)

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Bleeding and ischemic events

(mean follow-up period – 1.1 years)

End point	No of events
Patients with bleedings (BARC), of which:	**100* (53.2%)**
- type 1, n (%)	**96 (96.0%)**
- premature discontinuation of DAPT, n (%)	**15 (15.6%)**
- type 2, n (%)	17 (17.0%)
- types 3-5, n (%)	6 (6.0%)
Patients with ischemic events, n (%)	11 (5.9%)
- definite/probable stent thrombosis, n (%)	5 (2.7%)/1 (0.5%)
- target vessel revascularization, n (%)	5 (2.7%)

* - one patient may have more than one type of bleeding

- **A total of 100 patients on chronic DAPT had any bleedings (incidence 53.2%) of which 96% were nuisance**
- **Rate of DAPT discontinuation in the nuisance bleeding group was 15%**

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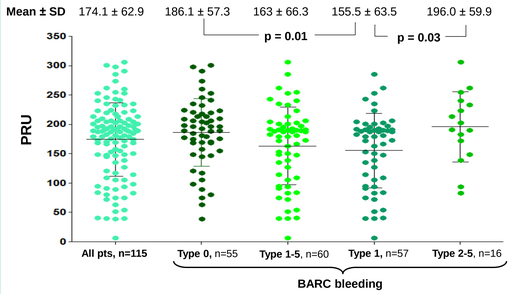
On-treatment platelet reactivity to ADP and bleedings



- **Only BARC type 1 bleedings were associated with the lowest on-treatment platelet reactivity to ADP**

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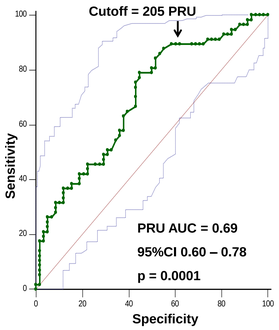
Platelet reactivity cutoff associated with BARC 1 bleedings

ROC curve analysis



- The cutoff point for minor bleedings was 205 PRU
- **PRU < 205 increased risk of BARC type 1 bleedings – OR 7.8, (95 %CI: 2.6 - 23.3, p=0.002)**
- High platelet reactivity (PRU > 205) was not related with ischemic events

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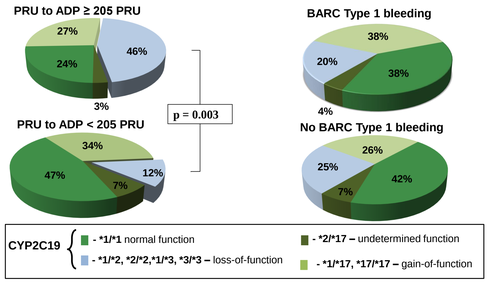
CYP2C19 distribution according to platelet reactivity and incidence of BARC Type 1 bleedings



- **The prevalence of loss-of-function CYP2C19 alleles was significantly higher in patients with platelet reactivity ≥ 205 PRU**
- **No significant relationship was found between CYP2C19 and BARC Type 1 bleedings**

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Relation of clinical and genetic variables to platelet reactivity > 205PRU

Stepwise selection procedure

Variable	OR	95% CI	p
Female sex	4.0	1.2 – 13.6	0.02
Age > 65 years	2.1	0.7 – 6.1	0.1
Diabetes mellitus	5.3	1.6-17.0	0.005
Genetic polymorphisms CYP2C19 *1/*2 + *2/*2	6.1	2.1 – 16.9	0.0006
Double-dose clopidogrel	0.13	0.006 – 2.7	0.2

- **Female sex, diabetes mellitus, loss-of-function CYP2C19 genotype were independently associated with platelet ADP reactivity > 205 PRU**

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BARC Type 1 Bleeding:

the relations to ischemic events and clinically significant bleedings (BARC Type 2-5)

Patients characteristics	BARC Type 1 **yes,** n=96 (1)	BARC Type 1 **no,** n=92 (2)	p_{1-2}
	% of patients		
Definite/probable stent thrombosis, (n=6)	0	6.52	0.02
TVR + Definite/probable stent thrombosis, (n=11)	2.08 %	9.78 %	0.02
Bleeding BARC Type 3-5, (n=6)	3.13 %	3.26 %	0.9
Bleeding BARC Type 2, (n=17)	11.46%	6.52%	0.24
Bleeding BARC Type 2-5, (n=22)	14.58%	8.7%	0.21

- **There was no association between clinically significant and non-significant bleedings**
- **The incidence of ischemic events was lower in patients with BARC type 1 bleedings (2.08% vs 9.78%, p=0.02)**

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Conclusion

- During 1.1 year DAPT the incidence of any bleedings was 53.2% of which 96% were nuisance. Rate of DAPT discontinuation in patients with nuisance bleedings was 15%
- BARC type 1 bleedings were associated with platelet ADP reactivity < 205 PRU (OR 7.8, 95%CI: 2.6 - 23.3, p=0.002)
- Female sex, diabetes mellitus, loss-of-function CYP2C19 genotype were independently associated with platelet ADP reactivity > 205 PRU
- BARC Type 1 bleedings were associated with low rate of ischemic events and may be reflect effective double antiplatelet therapy

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Conflict of interest disclosure statement: «We have no potential conflicts of interest to report»