On-treatment platelet reactivity' under both high and low shear stress conditions and relationship with cerebral micro-embolic signals in asymptomatic and symptomatic carotid stenosis: Results from the HaEmostasis In carotid STenosis (HEIST) study

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Introduction

- Assessment of 'High on-Treatment Platelet Reactivity' (HTPR) may enhance understanding of pathogenesis of 1st or recurrent vascular events in carotid stenosis

Aims

- Assess Aspirin-HTPR status and its relationship with micro-emboli signals (MES) and shear stress using whole blood platelet function testing platforms in moderate-severe (50 – 99%) carotid stenosis patients

Methods

- Prospective, longitudinal observational, analytical study (Subgroup of HEIST)
- Compared Aspirin-HTPR status in:

Case-Case Study:

- **'Early Symptomatic'** 50-99% (≤ 4/52 after TIA / stroke; N = 42)
- **'Late Symptomatic'** 50-99% (≥ 3/12 after TIA / stroke, N = 36)

vs.

- **Asymptomatic** 50-99% Carotid Stenosis patients (N = 30)

Longitudinal Study:

- Matched Early *vs.* Late Symptomatic patients (N = 36)

- Whole Blood Platelet Function Testing on '**moderately-high shear** stress PFA-100® (Plaelet adhesion + aggregation) and '**low shear stress'** VerifyNow® + Multiplate® (Aggregation) **[Fig. 1]**
- **Definitions of 'Aspirin-HTPR':**
  - **PFA-100 C-EPI:** ≤ 176 s
  - **VerifyNow Aspirin:** ≥ 550 ARU
  - **Multiplate Aspirin**: > 40 Units
- 1-hour bilateral Transcranial Doppler (TCD) Ultrasound of MCAs classified patients as MES +ve or MES-ve

Results

Table 1: Degree of carotid stenosis at initial recruitment *, demographic and vascular risk factors & prescribed anti-platelet regimens in groups. P values refer to comparisons between Symptomatic and Asymptomatic patients. Values are means (±SD) or percentages (absolute values)

Characteristic	Early Symptomatic (N = 43)	P Value	Late Symptomatic (N = 37)	P Value	Asymptomatic (N=34)
Mean Age (Yrs)	65 (±8.5)	0.004	65.4 (±9)	0.017	71.9 (± 7.85)
Hyperlipidemia	76.7% (33)	0.06	82.35% (28)	0.048	94.1% (32)
Smoking initially	39.5% (17)	0.009	35.3% (20)	< 0.001	11.8% (4)
50-99% stenosis	34.9% (15)	0.25	29.7% (11) *	0.1	50% (17)
70-99% stenosis	65.1% (28)	0.25	70.3% (26) *	0.1	50% (17)
Aspirin Monotherapy	55.8% (24)	0.5	48.7% (18)	0.23	64.7% (22)
Aspirin-Dipyridamole	30.2% (13)	0.4	35.1% (13)	0.2	20.6% (7)
Clopidogrel Monotherapy	2.3% (1)	0.6	2.7% (1)	0.6	5.9% (2)
Aspirin-Clopidogrel	11.6% (5)	0.5	13.5% (5)	0.4	5.9% (2)
No Antiplatelet Rx	0% (0)	0.4	0% (0)	0.5	2.9% (1)
Median Daily Aspirin Dose (mg)	225 mg	<0.001	75 mg	0.6	75 mg

Table 2: Comparison of Prevalences of Aspirin-HTPR in Early and Late Symptomatic *vs.* Asymptomatic patients on Aspirin, alone or in combination with Dipyridamole or Clopidogrel. Values are percentages (absolute numbers)

	Early Symptomatic (N = 42) % HTPR (N)	Late Symptomatic (N = 36) % HTPR (N)	Asymptomatic (N = 30) % HTPR (N)
Median Daily Aspirin Dose	225 mg (P < 0.001)	75 mg (P = 0.62)	75 mg
PFA-100 C-EPI	28.6% (12)	38.9% (14)	56.7% (17)
P	0.028	0.2	
VerifyNow Aspirin (ARU)	9.5% (4)	13.9% (5)	23.3% (7)
P	0.2	0.5	
Multiplate ASP (U)	11.9% (5)	13.9% (5)	23.3% (7)
P	0.2	0.4	

Fig. 1: Whole Blood Platelet Function Testing Platforms

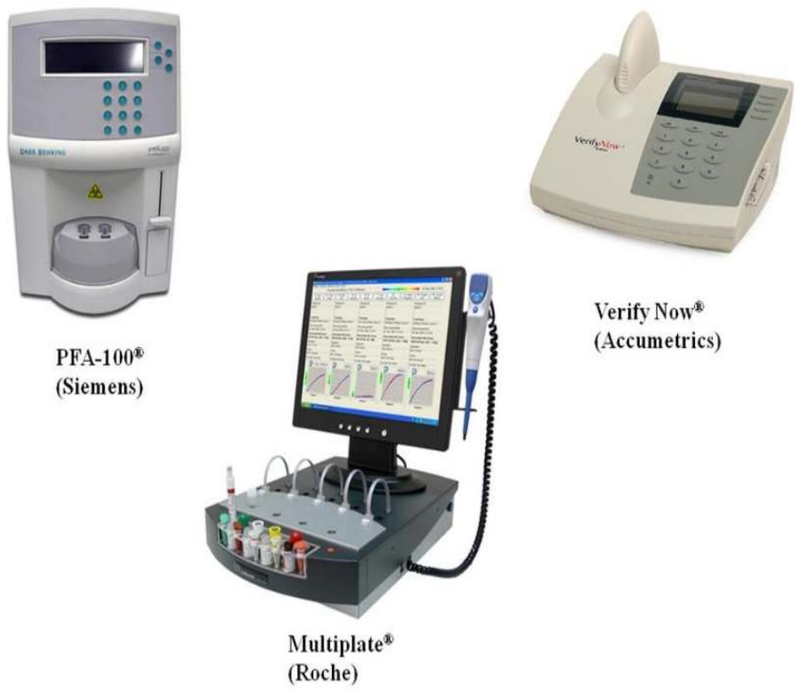

Table 3: Contingency table showing higher prevalence of Aspirin-HTPR % (N) on PFA-100 *vs.* VerifyNow (P= 0.049) but not *vs.* Multiplate (P = 0.1) in Early Symptomatic patients

Testing Platform	No HTPR	HTPR	Total
PFA-100 C-EPI	71.4% (30)	28.6 % (12)	100% (42)
Verify Now Aspirin	90.5% (38)	9.5% (4)	100% (42)
Multiplate Aspirin	88.1% (37)	11.9% (5)	100% (42)
Overall P for comparisons	0.038		

Figure 2A: Case-Case Study in entire group - MES Positivity:

7.1% Asymptomatic patients MES +ve (N = 2 / 28)

- 28.5 % Early Symptomatic (N = 10 / 35) **P = 0.049**
- 6.7% Late Symptomatic (N = 2 / 30) P = 0.996

Figure 2B: Longitudinal 'Matched' Study - MES Positivity:

33.3 % Early Symptomatic (N = 10 / 30); **P = 0.021** *vs.* 6.7% Late Symptomatic (N = 2 / 30)

- No significant difference in the prevalence of Aspirin-HTPR between MES+ve *vs.* MES-ve patients overall, regardless of symptomatic status (P > 0.05)

Discussion

- Important proportion of both Symptomatic and Asymptomatic patients have Aspirin-HTPR
- Lower prevalence of Aspirin-HTPR in Early Symptomatic *vs.* Asymptomatic patients on PFA-100, likely due to higher aspirin doses **(Table 2)**
- Prevalence of *ex vivo* antiplatelet-HTPR positively influenced by higher shear stress rates **(Table 3)**, but not associated with MES status (P > 0.05)
- 'Cross-sectional' HTPR definitions do not account for higher risk of recurrent cerebrovascular events in recently symptomatic patients
- Larger longitudinal studies using both 'cross-sectional' and 'longitudinal' HTPR definitions warranted to assess value of HTPR status at predicting the risk of recurrent vascular events in this patient population

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