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[Original article]

The STIB score: a simple clinical test to predict clopidogrel resistance

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Background High platelet reactivity (HPR) to clopidogrel is associated with an increased risk of ischaemic complications during and after coronary interventions and concerns up to 50% of patients undergoing PCI.

Aim of the study The aim of the study was to identify patients with HPR to clopidogrel using bedside clinical information obtained in the Stent Thrombosis In Belgium (STIB) trial.

Methods Data on platelet reactivity using the VerifyNow® point-of-care assay were obtained in 844 patients undergoing PCI for stable coronary artery disease 12 to 24 hours after a 600-mg loading dose of clopidogrel was given. Demographic, clinical and baseline routine biological tests were obtained and compared with P2Y12 reaction units (PRU). Patients with PRU > 230 (HPR) were considered as non-responders to clopidogrel.

Results HPR was observed in 424/844 pts. Age, weight, body mass index (BMI), HPR to aspirin, diabetes, renal failure (MDRD < 60 ml/min), haemoglobin (Hb), haematocrit, fibrinogen, glycaemia and glycated haemoglobin were associated with HPR to clopidogrel. In multivariate analysis, only Hb (OR: 0.77), BMI (OR: 1.06) and diabetes (OR: 1.62) emerged as independent risk factors. Hb < 13.9 g/dl, BMI > 28 kg/m^2 and presence of diabetes were equally associated to predict HPR and can be added to derive a simple score to predict clopidogrel resistance.

Although 38.5% of patients without a single clinical predictor still have HPR, 2/3 patients with 2 or 3 risk factors are resistant to clopidogrel.

Conclusions STIB HPR score allows identification of patients with a high probability of resistance to clopidogrel based on diabetes, Hb < 13.9 g/dl and BMI > 28 kg/m^2. This bedside clinical test could be useful for the identification of patients in whom another P2Y12 inhibitor should be recommended before and after PCI.

Keywords *Clopidogrel resistance – VerifyNow® – coronary disease – ischaemic events – bleeding.*

INTRODUCTION

Clopidogrel and acetylsalicylic acid are the cornerstone treatment of acute coronary syndromes and percutaneous coronary interventions (PCI). High platelet reactivity (HPR) after clopidogrel loading is defined as clopidogrel resistance and linked to adverse ischaemic events[1]. Although clinical value and impact of individually adjusted dosage according to platelet reactivity are still debated, treatment adaptations are proposed to overcome HPR to clopidogrel by doubling the current clopidogrel dosage or by switching to another more potent agent such as prasugrel or ticagrelor[2].This strategy is recommended for patients with unstable angina or non-ST-elevation myocardial infarction as a class IIb recommendation[3].

One-month results of the STIB trial showed that HPR was not predictive of early ischaemic events in patients with stable angina undergoing planned PCI, although HPR to clopidogrel was observed in 50% of these patients using the point-of-care VerifyNow® test[4]. These data contrast with the observations made in patients undergoing PCI for unstable coronary syndromes[5]. However, despite absence of early clinical benefit in the STIB trial, a late negative impact of HPR to clopidogrel on the development

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of stent thrombosis or recurrent ischaemic events has been documented[1]. Conversely, prescription of a drug with no significant biological effect may be questioned. Because real-life platelet reactivity testing is limited by test cost and availability, it is of paramount importance to easily identify patients unresponsive to clopidogrel at bedside. We therefore performed statistical analysis of baseline clinical and biological factors of the patients enrolled in the STIB trial in order to derive a simple clinical score associated with clopidogrel resistance.

METHODS

Study population

From March 2008 to October 2010, 891consecutive patients undergoing coronary angioplasty for stable angina pectoris were screened with platelet function testing from five sites in Belgium. All patients were treated with 500 mg acetylsalicylic acid and 600 mg clopidogrel, per os, 12 to 18 h before the intervention.

Study protocol

PR was measured in the catheterization laboratory before PCI by the Point-of-care VerifyNow test with P2Y12 cartridge to test the degree of platelet inhibition to clopidogrel and with the aspirin cartridge to assess degree of platelet inhibition to aspirin (Accumetrics Inc., San Diego, CA, USA). Measures of antiplatelet effect of clopidogrel are expressed as P2Y12 reaction units (PRU). High PR has been defined in numerous studies as > 230 PRU [6,7]. Measures of the antiplatelet effect of aspirin are expressed as aspirin reaction units (ARU). ARU values less than 550 indicate that platelets are inhibited by aspirin. Operators were blinded to the PRU and ARU measurements.

Among the 891 eligible patients, PRU was obtained in 882 and ARU in 852 patients. Both PRU and ARU values were available in 848 patients.

Baseline demographic and clinical data were prospectively recorded according to a standard data base[4]. Venous blood samples were collected in each patient at admission. Blood cells count, fibrinogen, us CRP, kidney function, glycaemia, glycated haemoglobin, creatine kinase and troponin were analysed. Complete data sets were available for 844 patients.

Statistical analysis

Continuous variables are presented as mean value ± standard deviation. Categorical data are reported as frequencies and percentages. Differences in continuous variables were compared by one-way analysis of variance. Comparisons of categorical variables were tested by the χ^2 test or Fisher's exact test, as appropriate. Multivariate stepwise logistic regression was used to identify independent predictors of the occurrence of HPR (PRU > 230 U or ARU > 550 U). The variables (demographic, clinical, and laboratory) entered in the model were selected using stepwise regression analysis with an entry criterion of $P < 0.10$. Variables significantly associated with HPR in multivariate analysis were used to build a logistic regression model. The β coefficient of each variable was determined and allows construction of a simple score. All analyses were performed with the SPSS software version 13.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The baseline characteristics of the 844 patients enrolled in the STIB trial with complete clinical and biological data are detailed in table 1.

We found that 50.2% (424/844) of the patients had clopidogrel resistance (PRU > 230) and 7% had aspirin resistance. Clinical and demographic characteristics, medications and laboratory findings of clopidogrel resistant patients are given in table 2.

Factors associated with HPR

Clinical factors significantly associated with HPR on clopidogrel are increasing age, weight and BMI, diabetes and renal failure.

Biological factors associated with clopidogrel resistance are anaemia (low haematocrit, low haemoglobin), fibrinogen, glycaemia, glycated haemoglobin, and resistance to aspirin (ARU ≥ 550).

In multivariate analysis, haemoglobin (OR: 0.77), BMI (OR: 1.06) and diabetes (OR: 1.62) remain significantly associated with clopidogrel resistance.

Resistance risk (PRU ≥ 230) was best correlated with diabetes: relative risk: 1.58 (1.27 to 1.98) (sensitivity: 61%, specificity: 54%), haemoglobin < 13.9 g/dl: relative risk: 1.45 (1.24 to 1.69) (sensitivity: 60%, specificity: 57%), and BMI > 28 kg/m^2: relative risk: 1.38 (1.17 to 1.63) (sensitivity: 59%, specificity: 55%).

No association was found between HPR and diabetes duration or the class of antidiabetic medication among the 239 diabetes patients.

Prediction of HPR to clopidogrel (clopidogrel resistance)

Anaemia, BMI and diabetes were significantly and equally associated with clopidogrel resistance (in logistic regression equation). As such, these three factors act as independent variables with similar weight to predict

clopidogrel resistance risk. Because of the similar diagnostic performance, they may be used to derive a simple prediction score of HPR to clopidogrel. Probability for HPR to clopidogrel is 77.8% in patients with diabetes, BMI >28 kg/m² and haemoglobin <13.9 g/dl (n = 56, 13%) and 62.6% of patients with at least 2 of these characteristics (n = 134, 31.6%). Conversely, probability of HPR is lower in patients without or with only one of these characteristics (38.5 and 44.1%, respectively) (figure 1).

DISCUSSION

The prospective multicentre STIB study helps us to identify simple clinical and biological factors associated with clopidogrel resistance in patients undergoing PCI for stable angina pectoris and pretreated according to current standard with 500 mg aspirin plus 600 mg clopidogrel at least 12 hours before the procedure.

Incidence of clopidogrel hypo-responders (50.2%) found in the STIB trial is slightly higher than in the multicentre GRAVITAS trial (40.6%) using the same hypo-responsiveness definition[7]. Platelet reactivity was assessed before PCI in the STIB trial, while it was measured 12 to 24 h post PCI in the GRAVITAS trial. The higher HPR found in the STIB study may be related to the pharmacokinetics of clopidogrel which is a prodrug that may require more than 12 h in some patients to be transformed into an active metabolite.

In this population of patients with stable angina pectoris, we found that response to clopidogrel diminishes with advancing age, increasing body mass index, renal failure, diabetes, poor glycaemic control, low haemoglobin, high fibrinogen values and HPR to aspirin. Numerous studies have shown that responsiveness to clopidogrel is influenced, not only by pharmacogenetic factors linked to CYP enzymes, but also by clinical factors such as age, diabetes, renal failure, obesity, anaemia or elevated fibrinogen[8,9].

Results of trials conducted in patients with stable angina pectoris diverge from those reported in studies performed among patients presenting with acute and unstable coronary disease which showed an association between clopidogrel resistance and adverse ischaemic events. Lack of association between HPR to clopidogrel and clinical outcomes in stable coronary disease, highlight a lower need for optimal platelet inhibition in low risk patients[10]. This conclusion is reinforced by the absence of incremental protection with more potent platelet inhibition (through higher clopidogrel doses or prasugrel)[11] or with the extension of dual antiplatelet therapy beyond one year after stenting in stable conditions[12]. In these patients, adverse events are more likely

Table 1 Demographic features, platelets reactivity, cardiovascular risk factors, medication use, laboratory findings in global population

Age	66 ± 10
Male sex, n (%)	638 (75)
BMI, kg/m²	27 ± 4
PRU value (unit)	221 ± 101
ARU value (unit)	434 ± 70
HPR on clopidogrel, PRU > 230 U, n (%)	424 (50)
HPR on aspirin, ARU > 550 U, n (%)	57 (7)
HPR on clopidogrel and aspirin, n (%)	34 (4)
Hypertensive (PA ≥ 140/90 mmHg), n (%)	547 (65)
LDL ≥ 135 mg/dl, n (%)	614 (73)
GFR (MDRD formula) < 60 ml/min), n (%)	176 (21)
Diabetes, n (%)	239 (28)
Diabetes with insulin, n (%)	42 (18)
with OAD, n (%)	169 (71)
on diet, n (%)	5 (2)
Unknown diabete (Hba1c ≥ 6.5%), n (%)	23 (10)
Diabete duration (years)	11
Smoking, n (%)	459 (54)
active, n (%)	192 (23)
previous, n (%)	267 (32)
Ischaemic cardiopathy, n (%)	528 (63)
Stable coronary disease, n (%)	85 (10)
Myocardial infarction, n (%)	213 (25)
Heart failure, n (%)	8 (1)
Percutaneous coronary intervention, n (%)	338 (40)
Stroke, n (%)	46 (5)
Coronary bypass, n (%)	88 (10)
Peripheral arterial disease n (%)	94 (11)
Valvulopathy, n (%)	30 (4)
Haemoglobin, g/dl	13.92 ± 1.60
Haematocrit, %	41 ± 4
Leukocyte count, $10^3/mm^3$	7769 ± 2211
Platelet count, $10^3/mm^3$	246 ± 77
Fibrinogen, mg/dl	360 ± 102
uCRP, mg/dl	2.87 ± 6.14
Glycaemia, mg/dl	109 ± 39
Hba1c, %	6.1 ± 0.9
Creatinin, mg/dl	1.01 ± 0.42
Aspirin on chronic treatment, n (%)	745 (88)
Thienopyridin on chronic treatment, n (%)	327 (39)
AVK, n (%)	5 (0.6)
Beta blocker, n (%)	513 (61)
ACE-i, n (%)	306 (36)
ARB, n (%)	116 (14)
Statin, n (%)	581 (69)
Fibrate, n (%)	39 (5)

Abbreviations: BMI: body mass index, PRU: P2Y12 reaction unit, ARU: aspirin reaction unit, HPR: high platelet reactivity, LDL: low-density lipoprotein, GFR: glomerular filtration rate, OAD: oral antidiabetic, HbA1c: haemoglobin A1c, u CRP: ultrasensitive C reactive protein, AVK: antivitamin K, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker.

Table 2

Characteristics	Clopidogrel sensitive PRU ≤ 230 (n = 420) Mean, standard deviation	Clopidogrel resistant PRU > 230 (n = 424) Mean, standard deviation	*P* value
Age, years	64 ± 11	68 ± 11	0.001
Male sex, n (%)	327 (51)	311 (49)	0.12
BMI, kg/m^2	27 ± 4	28 ± 4	0.001
PRU value (unit)	137 ± 64	304 ± 55	0.001
ARU value (unit)	422 ± 64	446 ± 75	0.001
Aspirin resistant, ARU ≥ 550 U	23 (5)	34 (8)	0.14
Hypertensive (PA ≥ 140/90 mmHg), n (%)	267 (64)	280 (66)	0.453
LDL ≥ 135 mg/dl, n (%)	310 (74)	304 (72)	0.491
GFR (MDRD formula) < 60 ml/min), n (%)	76 (18)	100 (24)	0.05
Diabetes, n (%)	92 (22)	147 (35)	0.001
Diabetes with insulin, n (%)	23 (43)	31 (57)	0.48
with OAD, n (%)	59 (36)	106 (64)	0.194
on diet, n (%)	43 (34)	84 (66)	0.11
Diabete duration (years)	10 ± 8	12 ± 9	0.43
Smoking, n (%)	232 (55)	227 (54)	0.372
Ischaemic cardiopathy, n (%)	274 (65)	254 (60)	0.109
Stable coronary disease, n (%)	39 (9)	46 (11)	0.451
Myocardial infarction, n (%)	117 (28)	96 (23)	0.81
Heart failure, n (%)	2 (0.5)	6 (1)	0.159
Percutaneous coronary intervention, n (%)	183 (44)	155 (37)	0.38
Stroke, n (%)	23 (5)	23 (5)	0.974
Coronary bypass, n (%)	39 (9)	49 (12)	0.28
Peripheral arterial disease n (%)	42 (10)	52 (12)	0.296
Valvulopathy, n (%)	12 (3)	18 (4)	0.276
Haemoglobin, g/dl	14.25 ± 1.50	13.59 ± 1.64	0.001
Haematocrit, %	42 ± 4	40 ± 4	0.001
Leukocyte count, 10^3/mm^3)	7744 ± 2160	7794 ± 2263	0.75
Platelet count, 10^3/mm^3	248 ± 84	244 ± 69	0.49
Fibrinogen, mg/dl	325 ± 97	369 ± 103	0.029
uCRP, mg/dl	2.91 ± 7.05	2.8 ± 5.12	0.87
Glycaemia, mg/dl	105 ± 36	114 ± 43	0.006
Hba1c, %	6.00 ± 0.81	6.29 ± 1.00	0.001
Creatinin, mg/dl	1.02 ± 0.48	1.01 ± 0.366	0.95
GFR, ml/min	70 ± 23	67 ± 22	0.93
Aspirin on chronic treatment, n (%)	365 (89)	363 (87)	0.325
Thienopyridin on chronic treatment, n (%)	164 (40)	156 (37)	0.427
AVK, n (%)	1 (0)	4 (1)	0.186
Beta blocker, n (%)	255 (62)	246 (59)	0.322
ACE-i, n (%)	152 (37)	147 (35)	0.567
ARB, n (%)	49 (12)	64 (15)	0.163
Statin, n (%)	282 (69)	286 (69)	0.909
Fibrate, n (%)	20 (5)	18 (4)	0.688

Abbreviations: BMI: body mass index, PRU: P2Y12 reaction unit, ARU: aspirin reaction unit, HPR: high platelet reactivity, LDL: low-density lipoprotein, GFR: glomerular filtration rate, OAD: oral antidiabetic, HbA1c: haemoglobin A1c, u CRP: ultrasensitive C reactive protein, AVK: antivitamin K, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker.

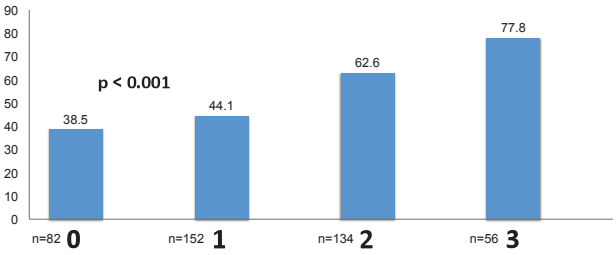

Fig. 1 HPR prevalence according to numbers of risk factors associated with HPR (BMI > 28 kg/m^2, diabetes, Hb < 13.9 g/dl).

linked to procedural and clinical conditions (stent length, kidney disease, diabetes, and leukocytosis).

Dual antiplatelet therapy remains the main medical therapy for optimizing stent-related outcomes after PCI and stent placement. It consists of aspirin plus a P2Y12 inhibitor. Selection of P2Y12 inhibitor depends on the patient's first clinical presentation. ACS patients should be treated with ticagrelor or prasugrel, both of which provide superior efficacy compared with clopidogrel but are also associated with increased risk of bleeding. Non-ACS patients may be treated with clopidogrel[13].

Our observations highlight that HPR to clopidogrel is present in 50% of this population, however. Therefore, it may be considered to lower the risk of early and late ischaemic events in those patients using a more potent P2Y12 inhibitor when risk of bleeding complications is low. Our results suggest that a simple clinical evaluation may help identify individuals with a high probability of HPR to clopidogrel who may benefit from a more potent P2Y12 inhibitor.

Data derived from the STIB trial indeed reveal that combination of three simple parameters (Hb < 13.9 g/dl, BMI > 28 and diabetes), the so-called STIB score, allows an excellent risk stratification for HPR to clopidogrel in non-ACS patients. This simple approach may replace routine platelet function or genetic testing which is currently not recommended to tailor antiplatelet therapy after PCI.

Recent data reveal that identification of HPR to clopidogrel may justify treatment adaptation post PCI of non-ACS patients. Post hoc analyses of the GRAVITAS trial data show that the lack of late clinical benefit of a higher clopidogrel dosage is linked to the persistence of clopidogrel resistance in 40% of the patients. Indeed, subgroup analysis of patients who became sensitive with higher clopidogrel dosages showed improved clinical outcome. Recent studies and registries do not erase the doubt, however. Two recent studies showed a lower rate of adverse events with step-by-step dose or drug adjustments[14,15] while the ARTIC trial, a study designed to mitigate weaknesses of the GRAVITAS trial, demonstrated no benefit[16].

Thanks to the "STIB score" we may simply enhance our capacity to improve identification of patients with a high risk of clopidogrel resistance (STIB score of 3 = HPR in 78% of patient) without any additional costs in whom an alternative P2Y12 inhibitor could be given. Conversely, it seems reasonable to consider clopidogrel as clinically and economically attractive in patients requiring dual antiplatelet therapy when the STIB score is of 0 or 1.

Specifically, our study confirms that clopidogrel monotherapy could be non-protective in most obese diabetic patients. Therefore in these patients, either a monotherapy with aspirin or a dual antiplatelet therapy with aspirin plus ticagrelor or prasugrel should be recommended according to the clinical situation and specifically the bleeding risk.

Conversely, patients with STIB score 2 or 3 can be considered as resistant to clopidogrel with a lower risk of bleeding when urgent surgery is planned. This finding could also influence the management of these patient before surgery.

CONCLUSION

Personalized antiplatelet therapy in non-ACS patients following PCI is an attractive strategy. We first proposed a simple clinical and biological score to predict clopidogrel resistance at bedside, avoiding the use of routine platelet function testing. The STIB score is based on the addition of three parameters: BMI > 28 kg/m^2, Hb < 13.9 g/dl and diabetes. Probability of HPR to clopidogrel ranges between 38.5 and 77.8% according to the presence of one, two or three cumulative factors. It may thus identify patients with high probability of resistance to clopidogrel.

CONFLICT OF INTEREST: none.

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