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The stent thrombosis in Belgium (STIB) scoring system reliability in Indonesia patients and the modified STIB scoring (M-STIB)

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Abstract

Introduction Clopidogrel is recommended as an alternative to Acetyl Salicylic Acid (ASA), the first-line drug for secondary stroke prevention. Clopidogrel resistance in Indonesia is reportedly 15.8%. The Stent Thrombosis in Belgium (STIB) is a scoring system proposed to assess clopidogrel resistance which has not been tested for the reliability in Indonesian population.

Objectives The objective of the study is to test the reliability of the STIB scoring and modified-STIB scoring system in Indonesian population.

Methods This study was conducted cross-sectionally in Dr. Cipto Mangunkusumo Hospital and Universitas Indonesia Hospital from January 2020 to December 2021. Laboratory examinations of human CYP450 concentration in blood plasma from 112 subjects were carried out using the ELISA method. The clopidogrel resistance test was carried out using the *VerifyNow* method.

Results Out of 112 ischemic stroke patients in this study, 14.3% of them did not respond to clopidogrel. Cross-tabulation between the STIB score and clopidogrel resistance showed significant results ($p < 0.05$) on the Hb variable and a combination of two or three factors involving Hb levels. Both Hb and CYP450 levels can be independent factors predicting clopidogrel resistance. Once combined, the Hb and CYP450 cutoff levels of 458.9 pg/mL had a sensitivity of 100% with a specificity of 30.2%.

Conclusions STIB scoring system did not prove to be reliable in screening for Clopidogrel resistance in Indonesian population. The modified STIB scoring system proposed in this study showed a promising result. Further research with larger population should be conducted.

Keywords STIB, Modified STIB, Clopidogrel resistance, CYP450, Stroke

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Introduction

The leading cause of disability and death worldwide is stroke [1]. In Indonesia, the 2013 Basic Health Research (Riskesdas) reported the prevalence of stroke was 7% and increased to 10.9% in 2018 [2].

A recurrent stroke is an acute vascular event after the stabilization of the previous stroke [3]. The rate of recurrent stroke ranges from 7 to 20% in the first year and increases after 5 years by 16–35% [4, 5]. The recurrent stroke rate in Indonesia was 19.9% [6]. To avoid stroke recurrence, adequate secondary preventive management is required, where oral antiplatelet drugs are recommended to be administered within the first 24–48 h after the first stroke onset [7, 8].

Acetyl Salicylic Acid (ASA) is recommended as the first-line drug to prevent recurrent stroke (secondary prevention) [9]. Clopidogrel is recommended as an alternative in cases of intolerance or contraindication to ASA [10]. Clopidogrel is a prodrug that will be converted into active metabolites by cytochrome P450 in the liver. The active metabolite of clopidogrel will inhibit platelet aggregation induced by Adenine diphosphate (ADP) [11]. ADP or its receptors may be affected by several factors that result in a decreased response to clopidogrel, which may alter the blockage of ADP receptors through several processes known as clopidogrel resistance [12]. Clopidogrel resistance in Chinese–Americans is reported to be relatively high (68–73%), which is thought to be because nearly 50% of Asians are missing an allele of genetic function that can reduce the response to clopidogrel [13].

VerifyNow is light transmission aggregometry which frequently utilized to test clopidogrel resistance. However, it is relatively expensive in Indonesia, costing roughly \$150. Stent Thrombosis in Belgium (STIB) is one of several scoring systems developed to measure clopidogrel resistance and is anticipated not to require a *VerifyNow* assessment. The STIB scoring system identifies a history of diabetes mellitus, a body mass index (BMI) of $> 28 \text{ kg/m}^2$, and hemoglobin (Hb) level below 13.9 g/dL as the three characteristics that predict clopidogrel resistance [14]. The presence of two or three risk factors correspond to 62.6% or 77.8% clopidogrel resistance, respectively. Clopidogrel monotherapy is not an option if the STIB score indicates resistance [14]. Due to the high expense of *VerifyNow* testing for clopidogrel resistance, the researchers conducted a study to measure the reliability of STIB scoring in Indonesian patients and attempted to modify the STIB scoring system.

Methods

The Neurology Outpatient Clinic of Cipto Mangunkusumo Hospital (RSCM) and Universitas Indonesia Hospital (RSUI) hosted the cross-sectional study in 2020 and 2021. The researchers employed a sequential sampling approach to choose the participants. Patients who experienced either a primary or recurrent ischemic stroke and had been administered clopidogrel for at least 5 days qualified for inclusion in this study. Patients with a history of clopidogrel allergy, impaired renal function, blood coagulation disorders, and certain medications administration, including omeprazole, esomeprazole, and atorvastatin, were excluded from the study (Fig. 1). Statistical analyses were conducted using IBM SPSS Statistics (Version 26) and presented descriptively. Bivariate analysis was performed to determine the correlation between various variables and CYP resistance. Chi-square analysis was conducted and p value of < 0.05 was deemed significant.

Human CYP450 analysis was conducted in Pharmacology Laboratory in Universitas Indonesia by the standards of the Indonesian Ministry of Health. CYP450 concentration was measured using ELISA method, which has high sensitivity and specificity

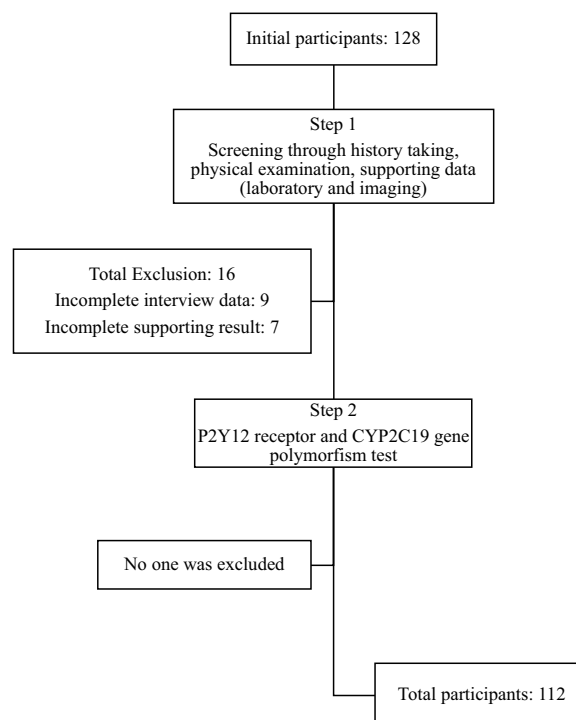


Fig. 1 Subject screening

to detect human CYP450 [15]. P2Y12 reaction units (PRU) with a cutoff of >208 was deemed inadequate response (resistant).

Results

Based on 112 subjects' epidemiological characteristics of the studied patients (Table 1), it was found that in this study, most of the subjects were men (58.9%), <68 years (88.4%), and with BMI <28 (76.8%). Adjusting to the participant characteristics of this study, the researchers made additional cutoffs for age of >57 years and BMI of >25.

The subjects were examined for clopidogrel resistance and laboratory and radiological examinations. According to the test results, 16 subjects (14.3%) did not react to clopidogrel (Table 2). The subjects with FBG 100 were $\geq 62.5\%$, total cholesterol ≥ 200 was 43.8%, HDL ≥ 60 was 71.4%, LDL ≥ 100 was 76.8%, and triglycerides ≥ 150 were 58.0% (Table 2).

The hemoglobin level, BMI, and history of diabetes were cross-tabulated on the clopidogrel resistance data to create the STIB score variable. The STIB score was included in the cross-tabulation component as the three factors crossed, two, and three factors combined. Significant correlations between clopidogrel resistance and Hb, Hb+BMI, and Hb+DM were found ($p < 0.05$) (Table 3).

This study proposed a modification of the STIB score by looking at several prognostic factors. The results of cross-tabulation of various prognostic variables against clopidogrel resistance with a p value of <0.25 can be seen in Table 4. Based on the result, it was also found that there was a significant correlation ($p < 0.05$) between clopidogrel resistance and hemoglobin levels and CYP450 concentrations with a cutoff of 458.9 pg/mL.

To determine the correlation between prognostic variables and clopidogrel resistance, multivariate analysis in the form of linear regression was subsequently conducted on the prognostic variables with p value of <0.25 (Table 4). Based on multivariate analysis, the hemoglobin ($p = 0.003$) and CYP450 cutoff of 458.9 pg/mL ($p = 0.004$) both had a significant correlation.

Between these two variables, each of them had the potential to independently predicts clopidogrel resistance. Hb 13.9 g/dL and CYP450 458.9 pg/mL were thus combined to test how the two variables performed as an assessment component in the modified STIB score (Table 5). The combined sensitivity and specificity of the Hb and CYP450 cutoff levels of 458.9 pg/mL were 100% and 30.2%, respectively.

Discussion

This study assessed clopidogrel resistance using *VerifyNow*. The mean and median yielded 115.2 PRU and 105.5 PRU, respectively. These results indicated that the subjects of this study have an excellent response to clopidogrel (85.7%), meaning that the Indonesian population is sensitive to clopidogrel administration. Only a few subjects (14.3%) did not respond to clopidogrel. Similar results were found in a preliminary study by Hidayat and colleagues [15] which the number of resistances was only found in 9 people (15.8%) [15]. These results differed from the two previous studies, the STIB study in Belgium and the GRAVITAS study in the United States (50.2% and 40.8%, respectively) perhaps due to the difference in baseline characteristics and genetic makeup [16].

Most subjects were male (58.9%) and under 68 years (88.4%), with the median and mean being 57.5 and 57.14 years, respectively. The age restriction for the STIB score was 68 years ($p = 0.05$), yet Belgium, the nation that created the STIB score, has an 81.75-year life expectancy. The mean age of this study was 57 years, while the average life expectancy in Indonesia was 71.2 years [2]. The study also found that the subjects were dominated by a BMI score of <28 kg/m² (76.8%).

It was found that 33% subjects in this study were diabetics. It was per the results of a previous study by Lau et al. [17], who reported that 1 in 3 stroke patients (24.7–56.2%) did not have diabetes. It contradicted the Indonesian registry data, where 24% of ischemic stroke patients have DM [18].

The BMI, Hb levels, and DM components comprised the STIB score. In other words, DM symptoms, BMI readings above 28 kg/m², and hemoglobin levels below 13.9 g/dL predicted an elevated risk of clopidogrel resistance. According to a recent study by Nie et al. [19], BMI scores did not significantly correlate with clopidogrel resistance ($p = 0.921$). The study by Legrand et al. [20]

Table 1 Epidemiological and clinical characteristics of the studied ischemic stroke patients

	n (%)	Mean (\pm SD)/median (min–max)
Gender		
Male/female	66 (58.9%)/46 (41.1%)	
Age (years)		57.1 (\pm 10.6)/57.5 (25–80)
>68/ \leq 68	13 (11.6%)/99 (88.4%)	
>57/ \leq 57	57 (50.9%)/55 (49.1%)	
BMI (kg/m ²)		24.9 (\pm 4.7)/24.3 (15.6–45.8)
>28/ \leq 28	26 (23.2%)/86 (76.8%)	
>25/ \leq 25	48 (42.9%)/64 (57.1%)	
History of DM		
Yes/no	37 (33.0%)/75 (67.0%)	

BMI body mass index, DM diabetes mellitus, SD standard deviation, min minimum, max maximum

Table 2 Clopidogrel resistance results and laboratory examinations

	Normal reference	n (%)	Mean (± SD)/median (min–max)
VerifyNow (PRU)			115.2 (± 71.3)/105.5 (1–273)
No response	> 208	16 (14.3%)	244.5 (± 18.8)/241.5 (216.0–273.0)
Response	< 208	96 (85.7%)	93.7 (± 51.0)/98.0 (1.0–195.0)
STIB score			
1/2/3	–	16 (14.3%)/51 (45.5%)/45 (40.2%)	–
Haemoglobin (g/dL)			13.8 (± 1.6)/13.9 (7.9–18.4)
≤ 13.9/> 13.9	13.0–16.0	57 (50.9%)/55 (49.1%)	
HbA1c (%)			6.5 (± 2.3)/5.7 (4.0–15.0)
≥ 6.5/< 6.5	< 5.7: normal 5.7–6.4: at risk of D. melitus ≥ 6.5: diabetes melitus	37 (33.0%)/75 (67.0%)	
FBG (mg/dL)			129.7 (± 60.8)/109.5 (73–449)
≥ 100/< 100	< 100	70 (62.5%)/42 (37.5%)	
Total cholesterol (mg/dL)			191.8 (± 50.9)/189.5 (93–379)
≥ 200/< 200	< 200	49 (43.8%)/63 (56.3%)	
HDL (mg/dL)			52.2 (± 14.9)/52.2 (22–102)
≥ 60/< 60	40–59	32 (28.6%)/80 (71.4%)	
LDL (mg/dL)			127.0 (± 40.6)/125 (38–269)
≥ 100/< 100	< 100	86 (76.8%)/26 (23.2%)	
Triglyceride (mg/dL)			159.8 (± 85.7)/140 (43–552)
≥ 150/< 150	< 150	47 (42.0%)/65 (58.0%)	
AST (IU/L)			22.2 (± 20.7)/19 (8–220)
≥ 34/< 34	5–34	8 (7.1%)/104 (92.9%)	
ALT (IU/L)			25.2 (± 23.7)/20 (6–205)
≥ 55/< 55	0–55	5 (4.5%)/107 (95.5%)	
Ureum (mg/dL)			30.0 (± 17.3)/26.5 (0.7–168.4)
≥ 40/< 40	19–44	22 (19.6%)/90 (80.4%)	
Creatinine (mg/dL)			1.7 (± 1.6)/1.0 (0.48–17.8)
≥ 1/< 1	0.70–1.20	58 (51.8%)/54 (48.2%)	
Uric acid (mg/dL)			5.9 (± 2.0)/5.7 (2.8–13.6)
≥ 5.7/< 5.7	3.4–7.0	57 (50.9%)/55 (49.1%)	

HbA1c hemoglobin A1c, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *SD* standard deviation, *min* minimum, *max* maximum

and Price et al. [21], which revealed a significant correlation, was distinct from the study. In contrast to the Indonesian population, which had a lower BMI, they obtained the mean BMI of the non-resistant group at 27 kg/m², the unresponsive group at 28 kg/m², the median score of the non-resistant group at 29 kg/m², and the unresponsive group at 31 kg/m². There was a difference that reached 3–4 kg/m² with the Indonesian population which might affect the BMI variable in the Indonesian population to not be a factor that affects clopidogrel resistance.

According to this study, the Hb level was an independent factor that could raise the risk of clopidogrel resistance by 19 times if it was ≤ 13.9 g/dL ($p=0.003$). Previous findings confirmed that the average Hb level in the clopidogrel resistance group was 13.6 g/dL ($p=0.001$) [20].

Our findings on the correlation of DM comorbidity and HbA1c level with clopidogrel resistance were in line with Liu et al. [22] and Nie et al. [19], who also found no significant correlation between the two variables ($p>0.05$). The studies by Legrand and colleagues [14] and Price et al. [20], which demonstrated a significant correlation ($p=0.05$), had different results. It was assumed that variations in the mean scores caused variance in the result. In this study, the non-resistant and resistant groups had mean HbA1C values of 6.6% and 6.3%, respectively, compared to 6.0% and 6.3% in previous study [14, 20].

The cross-tabulation of the STIB score variable with clopidogrel resistance in this study showed that only Hb levels had a significant correlation ($p<0.001$). In this study, the highest sensitivity was obtained by Hb levels

Table 3 Cross tabulation results between STIB score and resistance variables

	Resistant n (%)	Non-resistant n (%)	p (95% CI)	Sensitivity (%)	Specificity (%)
Hemoglobin (g/dL)			< 0.001 (2.448–151.924)* [†]	93.8	57.4
≤ 13.9	14 (24.6%)	43 (75.4%)			
> 13.9	1 (1.6%)	54 (98.4%)			
BMI (kg/m ²)			0.648 (0.192–2.797)*	18.8	76.0
> 28	3 (11.5%)	23 (88.5%)			
≤ 28	13 (15.1)	73 (84.9%)			
History of DM			0.460 (0.190–2.129)*	25.0	65.6
Yes	4 (10.8%)	33 (89.2%)			
No	12 (16.0%)	63 (84.0%)			
HB+BMI			0.008 (1.302–80.913)* [†]	93.8	40.6
Yes	15 (20.8%)	57 (79.2%)			
No	1 (2.5%)	39 (97.5%)			
HB+DM			0.012 (1.192–74.216)* [†]	93.8	38.5
Yes	15 (20.3%)	59 (79.7%)			
No	1 (2.6%)	37 (97.4%)			
BMI+DM			0.699 (0.279–2.354)*	43.8	51.0
Yes	7 (13.0%)	47 (87.0%)			
No	9 (15.5%)	49 (84.5%)			
HB+BMI+DM			0.053 (0.778–49.002)*	93.8	29.2
Yes	15 (18.1%)	68 (81.9%)			
No	1 (3.4%)	28 (96.6%)			

BMI body mass index, Hb hemoglobin, DM diabetes mellitus, CI confidence interval

*Chi-square; [†]p < 0.05**Table 4** Cross tabulation results between prognostic variables and clopidogrel resistance with p value < 0.25

	Resistant n (%)	Non-resistant n (%)	p	OR (95% CI)
Gender			0.06*	2.8 (0.931–8.288)
Female	10 (21.7%)	36 (78.3%)		
Male	6 (9.1%)	60 (90.9%)		
Haemoglobin (g/dL)			< 0.001* [†]	19.29 (2.448–0151.924)
≤ 13.9	15 (93.8%)	46 (42.6%)		
> 13.9	1 (6.2%)	62 (57.4%)		
FBG (mg/dL)			0.094*	0.407 (0.139–1.192)
≥ 100	7 (10.0%)	63 (90.0%)		
< 100	9 (21.4%)	33 (78.6%)		
AST (IU/L)			0.231*	1.182 (1.089–1.283)
≥ 34	0 (0.0%)	8 (100.0%)		
< 34	16 (15.4%)	88 (84.6%)		
Creatinine (mg/dL)			0.076*	0.369 (0.119–1.143)
≥ 1	5 (8.6%)	53 (91.4%)		
< 1	11 (20.4%)	43 (79.6%)		
CYP450 (pg/mL)			0.008* [†]	4.579 (1.375–15.252)
≥ 458.9	12 (24.0%)	38 (76.0%)		
< 458.9	4 (6.5%)	58 (93.5%)		

FBG fasting blood glucose, AST aspartate aminotransferase, CYP450 cytochrome P450, OR odd ratio, CI confidence interval

* Chi-square; [†]p < 0.05

Table 5 Relationship between independent prognostic variables on clopidogrel resistance

	Resistant n (%)	Non-resistant n (%)	p (95% CI)	Sensitivity (%)	Specificity (%)
Hb (g/dL)					
≤ 13.9	15 (24.6%)	46 (75.4%)	< 0.001 (2.448–151.924)*†	93.8	57.4
> 13.9	1 (1.6%)	62 (98.4%)			
CYP450 cut off 458.9 pg/mL					
≥ 458.9	12 (24.0%)	38 (76.0%)	0.008*† (1.375–15.252)	28.8	44.7
< 458.9	4 (6.5%)	58 (93.5%)			
Hb+CYP450 cut off 458.9 pg/mL					
Yes	16 (19.3%)	67 (80.7%)	0.011 (0.727–0.897)*†	100	30.2
No	0 (0.0%)	29 (100.0%)			

Hb hemoglobin, CYP450 cytochrome P450

* Chi-square; †p < 0.05

(93.8%), but the highest specificity was BMI > 28 kg/m² (76%). These results indicated that the reliability of the STIB study was not justified, because only Hb levels obtained a high sensitivity score. Low haemoglobin levels, a high body mass index, and a history of diabetes revealed an insignificant correlation ($p=0.053$) but had a high sensitivity value (93.85%). This demonstrated that the STIB scoring was only consistently reliable for Hb and inconsistent for the other variables. This demonstrated that clopidogrel resistance in the Indonesian population could not be determined only based on the STIB score.

The STIB score was adjusted in this study to become the modified-STIB score (mSTIB) by adding CYP450 level as one of the components. Except for CYP450, which was determined to be involved in drug metabolism, none of the evaluated risk factors demonstrated a significant correlation with clopidogrel resistance. According to the results of the genetic analysis, the median score of CYP450 was 407.63 pg/mL, and the mean score was 874.5 pg/mL in the group with a normal response to clopidogrel. The synthesis of modified STIB may have been affected by CYP450 levels in this study ($p=0.005$). The modification of Hb+CYP450 displayed a very high sensitivity in the STIB test. When paired with the Hb value, this study discovered a cutoff CYP450 concentration of 458.9 pg/mL with a sensitivity value of 100% and a specificity value of 30.2%. Given that CYP450 testing was reasonably inexpensive, these findings suggested that it can be recommended as one of the prognostic tests for clopidogrel users. However, the number of the subject was not adequate enough to conclude CYP450 as one of the factors to predict CPG resistance.

Conclusion

The STIB score was not reliable to screen for CPG resistance in Indonesian population. The STIB score was not advised for Indonesian patients with poor resistance rate unless they had a history of recurrent stroke, were taking medications regularly, and had no hematological or cardiac abnormalities. This study attempted to suggest a modified STIB scoring by adding CYP450 level of ≥ 458.9 pg/mL and showed a promising result. Further research should be conducted with larger number of subjects.

Abbreviations

ADP	Adenosine diphosphate
ALT	Alanine aminotransferase
ASA	Acetyl salicylic acid
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CYP450	Cytochrome P450
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
FBG	Fasting blood glucose
GRAVITAS	Gauging Responsiveness with a VerifyNow P2Y12 Assay, Impact on Thrombosis and Safety
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
Max	Maximum
Min	Minimum
M-STIB	Modified Stent Thrombosis in Belgium Scoring
OR	Odd ratio
PRU	P2Y12 reaction units
Riskesdas	Riset Kesehatan Dasar (Basic Health Research)
RSCM	Rumah Sakit Dr. Cipto Mangunkusumo (Dr. Cipto Mangunkusumo Hospital)
RSUI	Rumah Sakit Universitas Indonesia (Universitas Indonesia Hospital)
SD	Standard deviation
STIB	Stent Thrombosis in Belgium

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Author contributions

RH contributed to the drafting of the manuscript and its revision. Other authors contributed to providing guidance on the conception and design of the study. All authors participated in the analysis and interpretation of the data. All authors agree to take responsibility for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are properly investigated and resolved.

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Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to institutional limitations, yet they are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ethical aspect of this study has been approved by the Research Ethics Committee Faculty of Medicine Universitas Indonesia No. KET-658/UN2/F1/ETIK/PPM.00.02/2020 and has been granted permission for execution by Cipto Mangunkusumo Hospital. Written informed consent has been obtained from all subjects that are included in this study.

Consent for publication

Not applicable.

Competing interests

All authors report no conflict of interest and are alone responsible for the content and the writing of the article.

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