

# Prevalence and risk factors of clopidogrel non-response among Saudi patients undergoing coronary angiography

Haitham I. Sakr, MD, Hussein S. Alamri, MD, Abdulrahman M. Almoghairi, MD, Ashraf A. Alkhubair, MD, Ali S. AlMasood, MD.

## ABSTRACT

**الأهداف:** تقدير نسبة انتشار عدم الاستجابة لعقار كلويدوجريل وتحديد عوامل خطر ذلك لدى المرضى السعوديين.

**الطريقة:** أُجريت هذه الدراسة المستعرضة في مركز الأمير سلطان للقلب، الرياض، المملكة العربية السعودية بين شهري يناير ويونيو 2013م، وذلك لتقييم درجة تثبيط الصفائح الدموية باستخدام فحص VerifyNow assay: Accumetrics, San Diego, CA, USA بعد تلقي جرعة تحميل كلويدوجريل  $\leq 15\%$  تثبيط الصفائح الدموية أو  $>213$  P2Y12 وحدة ردة فعل (PRU).

**النتائج:** شملت الدراسة 304 مريضاً. كان متوسط عمر المرضى  $60.3 \pm 11.4$  سنة، 73% منهم ذكور. كانت جرعات عقار كلويدوجريل (57%)، 600mg (27%)، و75mg (16%)، 300mg استخدم جميع المرضى الأسبيرين (81mg في 94%). أظهر ما يقارب 66% (200/304) عدم الاستجابة لعقار كلويدوجريل في المختبر أن 54% كان لديهم انخفاض في تثبيط الصفائح الدموية و61% منهم كان لديهم ارتفاع PRU بعد التحميل. باستخدام تحليل الإنحدار متعدد المتغيرات والذي شمل جميع الخصائص المهمة؛ ظل كلاً من مرض السكري (OR: 2.36, 95% CI: 1.30-4.27,  $p=0.005$ ) وارتفاع تحميل PRU (OR: 2.39, 95% CI: 1.40-4.11,  $p=0.002$ ) فقط مرتبطة بشكل كبير مع ارتفاع عدم التجاوب مع عقار كلويدوجريل، بينما ظل إحتماء عضلة القلب (OR: 0.34, 95% CI: 0.15-0.81,  $p=0.014$ ) مرتبطاً بشكل كبير مع انخفاض عدم استجابة عقار كلويدوجريل. قل ربط السمعة المرضية واستخدام مدرات البول مع ارتفاع عدم استجابة عقار كلويدوجريل.

**الخاتمة:** تشير النتائج التي توصلنا إليها إلى وجود نسبة عالية من عدم الاستجابة لعقار كلويدوجريل في المختبر بين المرضى السعوديين عند التصوير بالأشعة للأوعية التاجية.

**Objectives:** To estimate the prevalence of clopidogrel non-response and identify its risk factors among Saudi patients.

**Methods:** This cross-sectional study was conducted at Prince Sultan Cardiac Center, Riyadh, Kingdom of

Saudi Arabia between January and June 2013, to assess the degree of platelet inhibition using the VerifyNow assay (Accumetrics, San Diego, CA, USA) after receiving clopidogrel standard loading dose. Clopidogrel resistance was defined as  $\leq 15\%$  platelet inhibition or  $>213$  P2Y12 reaction units (PRU).

**Results:** Three hundred and four patients were included in the study. The mean age was  $60.3 \pm 11.4$  years, and 73% were males. Clopidogrel doses were 300 mg (57%), 600 mg (27%), and 75 mg (16%). All patients used aspirin (81 mg in 94%). Approximately 66% (200/304) showed in vitro clopidogrel non-response, 54% had low platelet inhibitions, and 61% had high post-loading PRU. Using multivariate regression analysis that included all significant characteristics; only diabetes (odds ratio [OR]: 2.36, 95% confidence interval [CI]: 1.30-4.27,  $p=0.005$ ) and higher preloading PRU (OR: 2.39, 95% CI: 1.40-4.11,  $p=0.002$ ) remained significantly associated with higher clopidogrel non-response while myocardial infarction (OR: 0.34, 95% CI: 0.15-0.81,  $p=0.014$ ) remained significantly associated with lower clopidogrel non-response. The associations of morbid obesity and diuretics use with higher clopidogrel non-response were slightly attenuated.

**Conclusion:** Our findings indicate a high rate of clopidogrel in-vitro non-response among Saudi patients undergoing coronary angiography.

*Saudi Med J 2016; Vol. 37 (2): 166-172  
doi: 10.15537/smj.2016.2.14263*

*From the Department of Adult Cardiology, Prince Sultan Cardiac Center, Riyadh, Kingdom of Saudi Arabia.*

*Received 3rd November 2015. Accepted 3rd December 2015.*

*Address correspondence and reprint request to: Dr. Ali AlMasood, Department of Adult Cardiology, Prince Sultan Cardiac Center, Riyadh, Kingdom of Saudi Arabia. E-mail: aalmasood@gmail.com*

Platelets play a critical role in the pathogenesis of atherothrombotic diseases such as coronary artery disease (CAD). The rupture of atherosclerotic plaques initiates a complex process of platelet adhesion, activation, and aggregation.<sup>1</sup> Recently, clopidogrel and aspirin were the cornerstones of oral antiplatelet therapy for preventing ischemic events of atherothrombotic disease such as myocardial infarction and stroke.<sup>2,3</sup> Clopidogrel was shown to be even more effective than aspirin in preventing such events of atherothrombotic disease.<sup>4</sup> Clopidogrel is a prodrug and the active metabolite is generated by the cytochrome P450 system.<sup>5</sup> The active metabolite acts by inhibiting platelet aggregation in response to adenosine diphosphate (ADP) through binding and blocking the platelet P2Y<sub>12</sub> receptors.<sup>5</sup> Variability in individual responsiveness to the antiplatelet effects of clopidogrel may lead to the occurrence of thromboembolic events despite regular antiplatelet therapy.<sup>6,7</sup> This may be clinically translated into poor procedural and long-term morbidity and mortality outcomes.<sup>8,9</sup> The prevalence of clopidogrel non-response (resistance) is highly variable in different studies and populations. A review<sup>10</sup> estimated the non-response rate to range from 4-30%. This variability is partly caused by the lack of standard definition and the different assessment methods of clopidogrel non-response.<sup>11,12</sup> A number of studies examined the patients characteristics associated with clopidogrel non-response but failed to identify any, probably due to small sample sizes and the presence of multiple confounding factors.<sup>13-15</sup> Although, approximately 84% of Saudi patients admitted with acute coronary syndrome are treated with clopidogrel,<sup>16</sup> there is lack of estimates of clopidogrel non-response and the associated risk factors in this population. The objective of the current study was to estimate the prevalence of clopidogrel non-response and to identify its risk factors among Saudi patients undergoing coronary angiography at a specialized cardiac center in Kingdom of Saudi Arabia (KSA).

**Methods.** This cross-sectional study was conducted at Prince Sultan Cardiac Center (PSCC), a 200-bed specialized cardiac center located in Riyadh that provides a substantial portion of diagnostic and therapeutic cardiac services in KSA. The study population consisted of 304 consecutive patients who

received a clopidogrel loading dose (300 or 600 mg) or were receiving clopidogrel maintenance treatment (75 mg) before undergoing coronary angiography between January 2013 and June 2013. Those on aspirin were not excluded. Those who had pretreatment or intention to treat with glycoprotein (GP) IIb IIIa inhibitors and those who were not preloaded prior to performing coronary angiography were excluded from the study.

The degree of platelet inhibition was assessed using the VerifyNow assay (Accumetrics, San Diego, CA, USA). Blood samples were drawn at 12-24 hours after the 300 or 600 mg clopidogrel loading dose. Since clopidogrel specifically blocks the P2Y<sub>12</sub> receptors involved in platelet aggregation, the VerifyNow assay is designed to measure P2Y<sub>12</sub> reaction units (PRU) and photometrically determines platelet inhibition percentage (surrogate of platelet P2Y<sub>12</sub> receptor blockade). The VerifyNow assay results are reported as the percentage change in the light transmittance of the assay reagent (adenosine-5-diphosphate/prostaglandin E1) compared with the baseline (thrombin receptor activating peptide-induced platelet aggregation). Clopidogrel non-response was defined as  $\leq 15\%$  platelet inhibition or  $>213$  PRU as suggested by Godino et al.<sup>17</sup> Patients charts were used to collect the following information; demographics (such as age, gender, body mass index), medical history of comorbidities and cardiovascular risk factors (such as hypertension, diabetes, hyperlipidemia, and smoking), concurrent medications (such as statins, antihypertensives, anticoagulants, and diabetic medications), and laboratory data (such as platelets count, hemoglobin level, hematocrit value, and serum creatinine). Anemia was defined as hemoglobin level less than 13 g/dL for males and less than 12 g/dL for females.

The study was carried out according to the principles of the Helsinki declaration, and was approved by the PSCC research ethics committee.

Data were presented as frequencies and percentages for categorical variables and mean  $\pm$  standard deviation or median and inter-quartile range for continuous variables. Chi-square or Fisher, as appropriate, were used to evaluate significant differences of categorical characteristics (such as hypertension) between those who respond and those did not respond to clopidogrel treatment. Similarly, student t-test was used to detect significant differences of continuous characteristics (such as age). All significant characteristics were then entered in univariate and multivariate regression models to assess the crude and adjusted associations (odds ratios) with the study outcome (clopidogrel non-response). Backward stepwise elimination was

**Disclosure.** Authors have no conflict of interest, and the work was not supported or funded by any drug company.

used in the multivariate model. Variables with *p*-value of 0.10 or greater were removed from the models. All *p*-values were 2-tailed. *P*-value <0.05 was considered as significant. SPSS software (Version 20, SPSS Inc., Chicago, U.S.) was used for all statistical analyses.

**Results.** The demographic and clinical characteristics of the study patients are summarized in Tables 1-3. The mean age of the patients was 60.3 ± 11.4 years, with 73% males, and 50.2% obese. Clopidogrel doses were 300 mg (57%), 600 mg (27%), and 75 mg (16%).

**Table 1** - Demographic characteristics of 304 consecutive Saudi patients.

Demographic characteristics	Overall n (%)	Clopidogrel n (%)		<i>P</i> -value
		Responder	Non-responder	
<i>Age (years)</i>				
Mean±SD	60.3 ± 11.4	57.3 ± 12.1	61.9 ± 10.8	0.001
<45	22 (7.3)	10 (45.5)	12 (54.5)	0.021
45-64	164 (54.3)	65 (39.6)	99 (60.4)	
≥65	116 (38.4)	29 (25.0)	87 (75.0)	
<i>Gender</i>				
Male	222 (73.0)	88 (39.6)	134 (60.4)	0.001
Female	82 (27.0)	16 (19.5)	66 (80.5)	
Weight (mean±SD, kg)	80.8 ± 14.6	80.2 ± 14.5	81.2 ± 14.7	0.555
Height (mean±SD, cm)	162.5 ± 8.5	163.7 ± 8.3	161.9 ± 8.6	0.081
<i>Body mass index</i>				
Mean±SD	30.7 ± 5.0	29.8 ± 4.5	31.1 ± 5.2	0.036
Normal	33 (11.2)	13 (39.4)	20 (60.6)	0.172
Overweight	114 (38.6)	46 (40.4)	68 (59.6)	
Obese	148 (50.2)	44 (29.7)	104 (70.3)	

**Table 2** - Anticoagulant therapy and platelet inhibition of 304 consecutive patients.

Variables	Overall* n (%)	Clopidogrel n (%)		<i>P</i> -value
		Responder	Non-responder	
<i>Clopidogrel dose (mg)</i>				
Mean±SD	345.6 ± 175.4	387.3 ± 170.5	324.0 ± 174.4	0.548
75	49 (16.1)	9 (18.4)	40 (81.6)	0.009
300	172 (56.6)	58 (33.7)	114 (66.3)	
600	83 (27.3)	37 (44.6)	46 (55.4)	
<i>Aspirin dose (mg)</i>				
Mean±SD	94.4 ± 55.2	97.2 ± 60.6	93.0 ± 52.3	0.527
81	287 (94.4)	97 (33.8)	190 (66.2)	0.806
300	3 (1.0)	1 (33.3)	2 (66.7)	
325	14 (4.6)	6 (42.9)	8 (57.1)	
<i>Platelets</i>				
Mean±SD, 1000/ml	267.1 ± 78.3	258.8 ± 80.4	271.3 ± 77.1	0.196
Low	12 (4.1)	6 (50.0)	6 (50.0)	0.332
Normal	266 (90.8)	87 (32.7)	179 (67.3)	
Higher	15 (5.1)	6 (40.0)	9 (60.0)	
<i>Platelet inhibition (%)</i>				
Median (IQR)	13.0 (0.0-33.8)	43.5 (31.3-57.8)	4.0 (0.0-12.0)	<0.001
Low (≤15%)	165 (54.3)	0 (0.0)	165 (100.0)	<0.001
High (≥15%)	139 (45.7)	104 (74.8)	35 (25.2)	
<i>Pre-loading PRU</i>				
Mean±SD	274.5 ± 58.6	253.3 ± 47.8	285.5 ± 60.7	<0.001
<i>Post-loading PRU</i>				
Mean±SD	228.0 ± 89.2	131.5 ± 55.4	278.1 ± 56.1	<0.001
Low (≤213)	119 (39.1)	104 (87.4)	15 (12.6)	<0.001
High (>213)	185 (60.9)	0 (0.0)	185 (100.0)	

PRU, P2Y12 Reaction Units, IQR - inter-quartile range

The average aspirin dose was  $94.4 \pm 55.2$  mg with approximately 94% taking an aspirin dose 81 mg. The average platelet level was  $267.1 \pm 78.3$  thousands per mL; 4% of the patients lower platelet levels (<150 thousands), and 5% had higher platelets level (>400 thousands). The median platelet inhibition was 13% (inter-quartile range; 0%-34%); 54% of the patients had low platelet inhibition ( $\leq 15\%$ ). The average pre-loading PRU was  $274.5 \pm 58.6$ . The average post-loading PRU was  $228.0 \pm 89.2$ ; approximately 61% of the patients had high post-loading PRU (>213). The medical history of comorbidities and cardiovascular risk factors are summarized in Table 3.

Out of the 304 patients, 200 (66%) were categorized as clopidogrel non-responders. Tables 1-3 compare demographic and clinical characteristics of the study patients by the response to clopidogrel. Those who

had clopidogrel non-response had significantly lower platelet inhibition (4% versus 43.5%,  $p < 0.001$ ), higher pre-loading ( $285.5 \pm 60.7$  versus  $253.3 \pm 47.8$ ,  $p < 0.001$ ), and post-loading PRU ( $278.1 \pm 56.1$  versus  $131.5 \pm 55.4$ ,  $p < 0.001$ ). Clopidogrel non-response was significantly associated with older age, female gender, and higher body mass index. For example, clopidogrel non-response was 54.5% among those aged <45 years, 60.4% age 45-64 years, and 75% age  $\geq 65$  years ( $p = 0.021$ ). It was also observed in 80.5% of females compared with 60.4% of males ( $p < 0.001$ ). Clopidogrel non-response was higher (81.6%) among those on clopidogrel maintenance dose (75 mg) as compared with those received regular loading doses of 300 mg or 600 mg (average 63%,  $p = 0.009$ ). Clopidogrel non-response was not associated with aspirin dose ( $p = 0.806$ ) nor baseline platelet level ( $p = 0.196$ ). History of morbid obesity (90.5%,  $p = 0.013$ ), diabetes (73.0%,  $p < 0.001$ ),

**Table 3** - Clinical characteristics of 304 consecutive Saudi patients who received clopidogrel loading dose (300 or 600 mg) or on clopidogrel maintenance treatment (75 mg) before undergoing coronary angiography.

Clinical characteristics	Overall n (%)	Clopidogrel n (%)		P-value
		Responder	Non-responder	
<i>History</i>				
Cardiovascular accidents	10 (3.3)	2 (20.0)	8 (80.0)	0.503
Transient ischemic attacks	1 (0.3)	1 (100.0)	0 (0.0)	0.342
Myocardial infarction	48 (15.8)	24 (50.0)	24 (50.0)	0.012
Coronary artery bypass surgery	33 (10.9)	9 (27.3)	24 (72.7)	0.374
Percutaneous coronary intervention	82 (27.0)	32 (39.0)	50 (61.0)	0.282
Family History	5 (1.6)	1 (20.0)	4 (80.0)	0.664
Diabetes mellitus	201 (66.1)	54 (26.9)	147 (73.1)	<0.001
Hypertension	200 (65.8)	55 (27.5)	145 (72.5)	0.001
Morbid obesity	21 (6.9)	2 (9.5)	19 (90.5)	0.013
Dyslipidemia	128 (42.1)	45 (35.2)	83 (64.8)	0.767
Smoking	44 (14.5)	23 (52.3)	21 (47.7)	0.006
<i>Concurrent medications</i>				
Heparin	24 (7.9)	7 (29.2)	17 (70.8)	0.587
Warfarin	4 (1.3)	0 (0.0)	4 (100.0)	0.303
ACEI/ARB	223 (73.4)	71 (31.8)	152 (68.2)	0.148
Beta blockers	236 (77.6)	86 (36.4)	150 (63.6)	0.127
Statins	279 (91.8)	97 (34.8)	182 (65.2)	0.494
Nitroglycerin	160 (52.6)	55 (34.4)	105 (65.6)	0.949
Diuretics	82 (27.0)	17 (20.7)	65 (79.3)	0.003
Proton pump inhibitors	169 (55.6)	53 (31.4)	116 (68.6)	0.241
H2 blocker (Zantac)	22 (7.2)	11 (50.0)	11 (50.0)	0.105
B2 agonists	17 (5.6)	6 (35.3)	11 (64.7)	0.923
Insulin	51 (16.8)	15 (29.4)	36 (70.6)	0.428
Oral hypoglycemic agents	134 (44.1)	43 (32.1)	91 (67.9)	0.489
Thyroxin medications	26 (8.6)	4 (15.4)	22 (84.6)	0.023
<i>Laboratory tests</i>				
Hemoglobin (mean $\pm$ SD, g/dl)	13.7 $\pm$ 1.7	14.4 $\pm$ 1.5	13.4 $\pm$ 1.7	<0.001
Anemia	58 (19.2)	12 (20.7)	46 (79.3)	0.014
Hematocrit (mean $\pm$ SD, %)	41.6 $\pm$ 4.3	43.0 $\pm$ 4.1	40.8 $\pm$ 4.3	<0.001
Serum creatinine (mean $\pm$ SD, mg/dl)	0.90 $\pm$ 0.60	0.92 $\pm$ 0.78	0.90 $\pm$ 0.47	0.802

ACEI/ARB - angiotensin converting enzyme inhibitors/angiotensin receptor blocker

**Table 4** - Potential risk factors for clopidogrel non-response using univariate and multivariate regression analysis among Saudi patients undergoing .

Parameters	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.04 (1.02-1.06)	0.001		
Gender (male vs female)	0.37 (0.20-0.68)	0.001		
Body mass index	1.06 (1.00-1.11)	0.038		
Clopidogrel dose (300 mg vs 75 mg)	0.44 (0.20-0.97)	0.043		
Clopidogrel dose (600 mg vs 75 mg)	0.28 (0.12-0.65)	0.003		
Preloading PRU (in 100s)	2.69 (1.71-4.24)	<0.001	2.39 (1.40-4.11)	0.002
Diabetes	2.57 (1.56-4.22)	<0.001	2.36 (1.30-4.27)	0.005
Hypertension	2.35 (1.43-3.85)	0.001		
Morbid obesity	5.35 (1.22-23.45)	0.026	4.19 (0.85-20.57)	0.078
Myocardial infarction	0.46 (0.24-0.85)	0.013	0.34 (0.15-0.81)	0.014
Smoking	0.41 (0.22-0.79)	0.007		
Using diuretics	2.46 (1.36-4.48)	0.003	1.93 (0.95-3.94)	0.071
Using thyroxin	3.09 (1.04-9.22)	0.043		
Hemoglobin level (g/dl)	0.67 (0.57-0.80)	<0.001		
Hematocrit (%)	0.88 (0.82-0.94)	<0.001		

OR - odds ratio, 95% CI - 95% confidence interval, PRU, P2Y12 - reaction units, vs - versus

and hypertension (72.5%,  $p=0.001$ ) was significantly associated with higher clopidogrel non-response while smokers (48%,  $p=0.006$ ) and those who had history of myocardial infarction (50%,  $p=0.012$ ) had significantly lower clopidogrel non-response. None of the concurrent medications was significantly associated with clopidogrel non-response with exception of those on thyroxin medications (84.6%,  $p=0.023$ ), and diuretics (79.3%,  $p=0.003$ ) who had higher clopidogrel non-response. Those who had clopidogrel non-response had significantly lower hemoglobin level and hematocrit value ( $p<0.001$  each). The above demographic and clinical characteristics that were significantly associated with clopidogrel non-response were similarly replicated in univariate logistic regression models (Table 4). Using multivariate regression model including all significant characteristics; only history of diabetes and higher preloading PRU measured in 100 units remained significantly associated with higher clopidogrel non-response while history of myocardial infarction remained significantly associated with lower clopidogrel non-response. The associations of morbid obesity and diuretics use with higher clopidogrel non-response were slightly attenuated (Table 4).

**Discussion.** We report a high rate of clopidogrel non-response in a Saudi population. Two-thirds of our patients undergoing coronary angiography were clopidogrel non-responders. The high rate of clopidogrel non-response was also reported in several international studies.<sup>18</sup> For example, the prevalence of clopidogrel non-response among patients undergoing percutaneous coronary intervention (PCI) with

stenting was estimated in a systematic review of 25 studies at 27% (95% confidence between 9-44%).<sup>18</sup> Estimated the clopidogrel non-response between 4% and 30%.<sup>10</sup> Light transmission aggregometry (LTA) was used in most of the studies<sup>18</sup> to assess platelet inhibition (defined as <10%) within or at 24 hours of loading clopidogrel dose. More recent study<sup>8</sup> which used the VerifyNow machine reported generally higher rates of clopidogrel non-response. For example, clopidogrel non-response (defined as platelet inhibition <40%) was diagnosed in 62% of the patients undergoing coronary artery angiography and PCI procedures 2-6 hours after a loading clopidogrel dose.<sup>8</sup> Additionally, Clopidogrel non-response (defined as platelet inhibition <20%) was diagnosed in 29-39% of patients with CAD or ischemic cerebrovascular disease on clopidogrel treatment for at least one week to a month before enrollment.<sup>13,19</sup>

Although making fair comparison of the rates of clopidogrel non-response in different studies is a difficult task due to variable populations, different technologies, measurement timing, definitions, and loading dose, the higher rate in our study compared with the previous studies may be partially explained by a number of reasons; our cut-off of platelet inhibition was 15%, while it was 10% in most of the studies that used an LTA methodology. Our assessment was carried out 12-24 hours after the intake of clopidogrel, which is shorter than recorded in many of these reports.<sup>13,18,19</sup> Approximately, three-fourth of our patients were either on clopidogrel 300 mg or a maintenance dose, which is reported to be associated with a higher non-response rate compared with clopidogrel 600 mg.<sup>18,20</sup>

Unlike several studies<sup>13-15</sup> that failed to identify patients characteristics associated with clopidogrel non-response, the current study identified a number of predictors of no response. For example, diabetes in the previous study was independently associated with clopidogrel non-response.<sup>21</sup> Diabetes is known for its enhanced platelet reactivity, and the higher risk of atherothrombotic events and prevalence of diabetes is estimated at 30% among the Saudi population according to the latest WHO announcement.<sup>21,22</sup> Morbid obesity and diuretic use were associated with clopidogrel non-response in univariate analysis, but slightly attenuated in multivariate analysis. The association of BMI and clopidogrel non-response was also seen in other studies that suggests the need to adjust clopidogrel dose in obese patients.<sup>23,24</sup> The association of diuretics use and clopidogrel non-response may indirectly indicate controlled hypertensive patients. Hypertension was associated with clopidogrel non-response in the univariate analysis of the current study and previous studies.<sup>25</sup> It is difficult to explain the relative protection of those who had myocardial infarction against clopidogrel non-response. However, this may point to the relatively better anti platelet care they were receiving and using multiple agents that can guard against the development of clopidogrel non-response. Several mechanisms of failure to respond to clopidogrel treatment have been described in the literature. These include patient non-compliance, inadequate bioavailability, drug interactions, and genetic polymorphism of the P2Y12 receptor.<sup>5,26</sup>

The current study design cannot identify the exact mechanism. The high clopidogrel non-response in our patients may warrant the need for an improved local strategy to reduce the incidence of clopidogrel non-response and consequently its associated adverse effects. Several strategies have been suggested to guard against clopidogrel non-response. These include increasing the loading dose of clopidogrel, use of alternative medications, use of multiple antiplatelet medications, avoiding unwanted drug interactions, improving patient compliance, and personalizing treatment through screening for clopidogrel non-response in high risk patients.<sup>27-29</sup> Among the newer antiplatelet agents that have the potential to overcome the clopidogrel resistance are prasugrel and ticagrelor, which received more attention recently and have been recently approved for clinical use.<sup>30</sup> Prasugrel is a third generation thienopyridine that requires only one step hepatic metabolism; thus, active metabolites are generated more rapidly and effectively, translating into better pharmacodynamic effect.<sup>31</sup> Ticagrelor is the first

non-thienopyridine direct P2Y12 inhibitor. It exerts its effects through reversible binding of the P2Y12 receptor, acting as a non-competitive ADP antagonist.<sup>30</sup>

**Study limitations.** The current study had many advantages including bridging local lack of data, adequate sample size, studying both prevalence and risk factors that included a wide range of potential demographics, clinical, and medication factors; however, the study design being cross-sectional cannot prove-causal or temporal relationship between clopidogrel non-response and examined risk factor. Being a single center study, the current finding should be cautiously generalized to Saudi patients undergoing coronary angiography. Another limitation of the study is the lack of assessment of CYP 2 C19 loss-of-function polymorphism, which is related to clopidogrel non-responsiveness. Therefore, it is unclear whether the higher prevalence of non-responsiveness to clopidogrel in Saudi patients is related to the genetics (higher prevalence of CYP 2C19 loss-of-function polymorphism or to other factors). Additionally, in patients with CYP 2C19 loss-of-function polymorphism, clopidogrel non-responsiveness might increase over time, which requires multiple measurements. The responsiveness to clopidogrel was measured only once in the study. However, it has been documented that response to clopidogrel may change overtime.<sup>31</sup>

In conclusion, we report a high rate (66%) of clopidogrel non-response among Saudi patients undergoing coronary angiography. Diabetes, and to a lesser extent, morbid obesity and diuretics use were independently associated with clopidogrel non-response. The high clopidogrel non-response in our patients may warrant the need for an improved local strategy to reduce the incidence of clopidogrel non-responses specially among high-risk patients.

## References

1. Patrono C, Renda G. Platelet activation and inhibition in unstable coronary syndromes. *Am J Cardiol* 1997; 80: 17E-20E.
2. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 1994; 308: 81-106.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation. *N Engl J Med* 2001; 345: 494-502.
4. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (caprie). Caprie Steering Committee. *Lancet* 1996; 348: 1329-1339.
5. Sweeny JM, Gorog DA, Fuster V. Antiplatelet drug 'resistance'. Part 1: Mechanisms and clinical measurements. *Nat Rev Cardiol* 2009; 6: 273-282

6. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. *Am J Cardiol* 2009; 103 (3 Suppl): 27A-34A.
7. Jung HJ, Sir JJ. Recurrent myocardial infarction due to one subacute and two very late thrombotic events of drug-eluting stent associated with clopidogrel resistance. *J Invasive Cardiol* 2011; 23: E15-E18.
8. Campo G, Fileti L, de Cesare N, Meliga E, Furgieri A, Russo F, et al. Long-term clinical outcome based on aspirin and clopidogrel responsiveness status after elective percutaneous coronary intervention: A 3t/2r (tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel) trial substudy. *J Am Coll Cardiol* 2010; 56: 1447-1455.
9. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006; 48: 1742-1750.
10. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: A review of the evidence. *J Am Coll Cardiol* 2005; 45: 1157-1164.
11. Celik T, Iyisoy A, Gul H, Isik E. Clopidogrel resistance: A diagnostic challenge. *Int J Cardiol* 2009; 131: 267-268.
12. Harrison P, Frelinger AL 3rd, Furman MI, Michelson AD. Measuring antiplatelet drug effects in the laboratory. *Thromb Res* 2007; 120: 323-336.
13. Kim H, Lee HK, Han K, Jeon HK. Prevalence and risk factors for aspirin and clopidogrel resistance in patients with coronary artery disease or ischemic cerebrovascular disease. *Ann Clin Lab Sci* 2009; 39: 289-294.
14. Kar R, Meena A, Yadav BK, Yadav R, Kar SS, Saxena R. Clopidogrel resistance in north indian patients of coronary artery disease and lack of its association with platelet adp receptors p2y1 and p2y12 gene polymorphisms. *Platelets* 2013; 24: 297-302.
15. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Barrera-Ramirez C, Sabate M, et al. Identification of low responders to a 300-mg clopidogrel loading dose in patients undergoing coronary stenting. *Thromb Res* 2005; 115: 101-108.
16. Alhabib KF, Hersi A, Alfaleh H, Alnemer K, Alsaif S, Taraben A, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients with acute coronary syndromes: Results of the Saudi project for assessment of coronary events (space) registry. *J Saudi Heart Assoc* 2011; 23: 233-239.
17. Godino C, Mendolicchio L, Figini F, Latib A, Sharp AS, Cosgrave J, et al. Comparison of VerifyNow-p2y12 test and flow cytometry for monitoring individual platelet response to clopidogrel. What is the cut-off value for identifying patients who are low responders to clopidogrel therapy? *Thromb J* 2009; 7: 4.
18. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: A systematic review and meta-analysis. *Am Heart J* 2007; 154: 221-231.
19. Maruyama H, Takeda H, Dembo T, Nagoya H, Kato Y, Fukuoka T, et al. Clopidogrel resistance and the effect of combination cilostazol in patients with ischemic stroke or carotid artery stenting using the VerifyNow p2y12 assay. *Intern Med* 2011; 50: 695-698.
20. Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Carvajal J, et al. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-st-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 2006; 48: 1339-1345.
21. Hall HM, Banerjee S, McGuire DK. Variability of clopidogrel response in patients with type 2 diabetes mellitus. *Diab Vasc Dis Res* 2011; 8: 245-253.
22. Angiolillo DJ, Suryadevara S. Aspirin and clopidogrel: Efficacy and resistance in diabetes mellitus. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 375-388.
23. Angiolillo DJ, Fernández-Ortiz A, Bernardo E, Barrera Ramírez C, Sabaté M, Fernandez C, et al. Platelet aggregation according to body mass index in patients undergoing coronary stenting: Should clopidogrel loading-dose be weight adjusted? *J Invasive Cardiol* 2004; 16: 169-174.
24. Feher G, Koltai K, Alkonyi B, Papp E, Keszthelyi Z, Kesmarky G, Toth K. Clopidogrel resistance: Role of body mass and concomitant medications. *Int J Cardiol* 2007; 120: 188-192.
25. Akturk IF, Caglar FN, Erturk M, Tuncer N, Yalcin AA, Surgit O, et al. Hypertension as a risk factor for aspirin and clopidogrel resistance in patients with stable coronary artery disease. *Clin Appl Thromb Hemost* 2014; 20: 749-754.
26. Musallam KM, Charafeddine K, Bitar A, Khoury M, Assaad S, Beresian J, et al. Resistance to aspirin and clopidogrel therapy. *Int J Lab Hematol* 2011; 33: 1-18.
27. Qureshi Z, Hobson AR. Clopidogrel "resistance": Where are we now? *Cardiovasc Ther* 2013; 31: 3-11.
28. Uchiyama S. Clopidogrel resistance: Identifying and overcoming a barrier to effective antiplatelet treatment. *Cardiovasc Ther* 2011; 29: e100-e111.
29. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the amyda-pro (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Platelet Reactivity Predicts Outcome) study. *J Am Coll Cardiol* 2008; 52: 1128-1133.
30. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 64: e139-e228.
31. Gajos G, Zalewski J, Nessler J, Zmudka K, Undas A, Piwowarska W. Polyunsaturated omega-3 fatty acids improve responsiveness to clopidogrel after percutaneous coronary intervention in patients with cytochrome P450 2C19 loss-of-function polymorphism. *Kardiol Pol* 2012; 70: 439-445.