CASE STUDY

# Clopidogrel Responsiveness in Patients Undergoing Percutaneous Coronary Intervention using Multiplate Analyzer: Frequency and Outcomes

Murad A. Khadim[1*], Hasan A. Farhan[1], Muthanna[2], Muthanna H. Al-Quraishi[3]

[1]*Imam Sadiq Hospital, Department of Interventional Cardiology, Babylon, Iraq.*
[2]*Baghdad heart center, Medical City, Iraqi scientific council of cardiology, Baghdad, Iraq.*
[3]*Ibn-AlBitar Cardiac Center, Baghdad, Iraq.*

***Received: 30th May, 2023; Revised: 16th July, 2023; Accepted: 14th August, 2023; Available Online: 25th September, 2023***

## ABSTRACT

**Objectives:** Over and under response to dual antiplatelet therapy (DAPT) can lead to bleeding and thrombotic events in patients undergoing coronary stent placement. The present study aimed to assess the platelet response to clopidogrel in patient undergoing percutaneous coronary intervention (PCI) using Multiplate Analyzer. The primary outcome in the present study was the short-term incidence of stent thrombosis and bleeding events.

**Background:** Multiple electrode aggregometry is a rapid and standardized tool to for diagnosis of platelet defects and monitoring response to DAPT.

**Methods:** A hospital-based, prospective study was conducted on 431 patients who underwent PCI from September 2016 to November 2017 and received clopidogrel therapy. The platelet aggregometry was done using a Multiplate analyzer (Dynabyte, Munich, Germany). Patients were followed for 30 days to assess the incidence of stent thrombosis and bleeding.

**Results:** The patients' mean age was 58 ± 6.7 years. A total of 40% of the patients were diabetic and 7.7% had chronic renal failure. The rate of clopidogrel non-responders was 10.7%, while clopidogrel over-responders were 18.3%. Patients with diabetes and chronic renal failure had significantly lower platelet responsiveness (40.1% with $p < 0.05$ and 7.7% with $p < 0.005$, respectively). Smoking was significantly associated with platelet over-responsiveness (39.4%, $p < 0.001$). Patients with low platelet responsiveness to clopidogrel were associated with an increased risk of definite stent thrombosis ($p < 0.005$), while increasing bleeding risk was significantly associated with over-responsiveness to patients to clopidogrel ($p < 0.001$).

**Conclusions:** Antiplatelet responsiveness showing individual variability with increased risk of stent thrombosis among the cases with no response to the effect of clopidogrel and high risk of bleeding with the over-responsiveness group.

**Keywords**: Antiplatelet therapy, Bleeding, Clopidogrel, Platelet aggregometry, Stent thrombosis.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.3.53

**How to cite this article:** Khadim MA, Farhan HA, Muthanna, Al-Quraishi MH. Clopidogrel Responsiveness in Patients Undergoing Percutaneous Coronary Intervention using Multiplate Analyzer: Frequency and Outcomes. International Journal of Drug Delivery Technology. 2023;13(3):1112-1116.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Globally, diabetes and cardiovascular disease are the major causes of morbidity and mortality; in its 2013 report, the World Health Organization (WHO) estimated that both myocardial infarction and stroke accounted for almost 22% of global mortality in 2004, which is expected to reach 26.3% of global mortality by 2030.[1] Aspirin is the most commonly prescribed drug for secondary prevention of ischemic cardiovascular diseases following percutaneous coronary intervention (PCI). However, stent thrombosis, a life-threatening complication with grave clinical consequences, is still a major concern with an estimated incidence ranging between 1 and 5%.[2,3] The recognition of the higher risk of stent thrombosis following PCI led to the recommendation of the use of dual antiplatelet therapy (DAPT), a combination of aspirin and antagonists of the platelet ADP receptor P2Y12.[4] Clopidogrel is a common component of DAPT that exhibited high efficacy in prevention stent thrombosis when administrated for 12 months after PCI.[5]

Nevertheless, the current body of published literature demonstrated that poor response to DAPT, usually indicated by platelet function tests, is associated with a significant increase in the risk of stent thrombosis.[6,7] On the other hand, over-response to clopidogrel is of clinical consequence as well; recent reports showed that enhanced response to clopidogrel carrying a higher risk for bleeding events.[8] Evidence exists that the occurrence of bleeding during or after PCI has a similar

**Author for Correspondence: muradfatlawi@yahoo.com*

impact on the patient's mortality risk as compared with the occurrence of a post PCI myocardial infarction (MI).[9-11]

The prevalence of non-repose or over-response to clopidogrel varies substantially across the published literature. Recent findings suggest that, in 4 to 44% of patients, there is an insufficient inhibitory effect of clopidogrel on ADP-dependent platelet aggregation, which is called clopidogrel "resistance" or "non-response".[12-15] The prevalence of non-responders was reported to be notably higher among patients with chronic renal failure(CRF); impaired renal function has been characterized as a major predictor for arthero-thrombotic complications, including thrombotic stent occlusions as well as bleeding events.[16]

## PATIENTS AND METHODS

A prospective, interventional, hospital-based study was conducted from September 2016 to November 2017. The study was approved by the Research Ethics Committee of the Iraqi Board for Medical Specializations and performed according to the ethical standards of the declaration of Helsinki.

### Study Participant

The present study included consecutive patients who underwent PCI with drug-eluting stents deployments at Ibn Al-Bitar Hospital for Cardiac Surgery, Baghdad, Iraq. Patients were considered eligible for the study irrespective of the clinical presentation at the time point of the PCI. Therefore, patients with acute coronary syndrome, as well as patients with stable ischemic heart diseases were included in the study. All eligible patients were on clopidogrel (PLAVIX 75mg – SANOFI®) with full drug compliance. CRF was defined by the elevation of serum creatinine ≥2 mg/dl and evidence of clinical and radiological findings that suggest CRF.

We excluded patients with a history of administration of glycoprotein IIB/IIIA inhibitors in the last 10 days, thrombocytopenia, and/or contraindications to antiplatelet therapy.

All eligible patients underwent full history taking and clinical examination. The platelets' responsiveness was done using platelets aggregometry. Patients were followed for 30 days postoperatively.

### Multiplate Aggregometry

The platelets aggregometry was done using Multiplate Analyzer (Dynabyte, Munich, Germany). The reference cut-off values for both tests is the last published data from Roche Company 2013:[17]

| | |
|---|---|
| Over response group | <190 AU*min |
| Normal response group | 190–460 AU*min |
| Non-response group | >460 AU*min |

### Study Endpoints

The endpoints of this study were the cumulative incidences of definite stent thrombosis and bleeding. The stent thrombosis was defined according to the Academic Research Consortium criteria;[18] While the bleeding was defined in accordance with TIMI classification.[19]

### Statistical Analysis

Statistical analysis was carried out using SPSS version 21. Categorical variables were presented as frequencies and percentages. Data were expressed as means ± standard deviation (SD). ANOVA test was used to test the relationship between different parameters. Patients were divided into 3 groups according to the cut lines. A *p-value* of 0.05 or less was considered to be statistically significant. A binary regression model is used to assess covariates' independence in affecting clopidogrel antiplatelet responsiveness individually.

## RESULTS

From a total of 440 patients, 431 patients were included in the present study. The remaining patients were excluded due to thrombocytopenia (No. = 2) and history of intake of glycoprotein IIb/IIIa inhibitors (No. = 7). The majority of patients were females (51.8%) with a mean age of 58 ± 6.7 years. Forty percent of the patients were diabetic and 7.7% had CRF. In addition, 170 (39.4%) patients were smokers. At the end of follow-up. 10 (2.3%) patients had stent thrombosis and 32 (7.4%) had minimal-to-minor bleeding event (Table 1). Overall, 79 (18.3%) patients were over-responders to clopidogrel and 10.7% of the patients were non-responders (Figure 1).

Regarding the relationship between platelet responsiveness tertiles and diabetes, there was a statistically significant association between the prevalence of were non-responders and diabetes (Table 2); diabetic patients were more likely to be in 3rd tertile. Similarly, CRF patients were more likely to be in the 3rd tertile of the platelet responsiveness to the effect of clopidogrel (Table 3). On the other hand, smokers were more likely to be in the 1st tertile of the platelet responsiveness to the effect of clopidogrel (Table 4).

Regarding the results of stent thrombosis, Figure 2 shows that the relation between platelets' non-responsiveness to the effect of clopidogrel and the incidence of stent thrombosis was statistically significant, with higher risk of stent thrombosis among non-responders. On the other hand, enhanced platelet responsiveness to the effect of clopidogrel was associated with an increased risk of bleeding events (Figure 3).

## DISCUSSION

### Frequency of Clopidogrel Non-responsiveness

The current study showed that the frequency of clopidogrel non-responsiveness was 10.7%. This finding is in agreement with a study by Yaseen IF *et al.*[20] It has been described that there is wide range for antiplatelet non-responsiveness worldwide,[13,21,22]

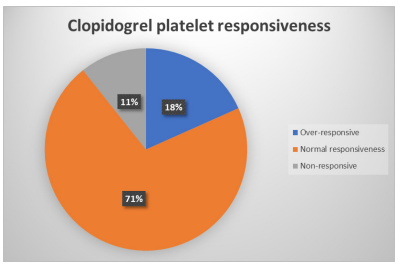


**Figure 1:** Distribution of clopidogrel platelets responsiveness

**Table 1:** Baseline patient characteristics

| | *Type of variable* | *Number No.* | *Percentage (%)* |
|---|---|---|---|
| Age Mean ± S.D (Years) | 1st tertile | 79 Mean (58.82) ± 6.4 S.D | (18.3) |
| | 2nd tertile | 306 Mean (58.59) ± 6.5 S.D | (71) |
| | 3rd tertile | 46 Mean (55.95) ± 7.8 S.D | (10.7) |
| Gender | Male | 208 | (48.3) |
| | Female | 223 | (51.7) |
| Diabetes | Diabetic | 173 | (40.1) |
| Smoking | Smoker | 170 | (39.4) |
| Chronic Renal Failure | CRF | 33 | (7.7) |
| Stent Thrombosis | Yes | 10 | (2.3) |
| | No | 421 | (97.7) |
| Bleeding | No bleeding | 399 | (92.6) |
| | Minimal Bleeding | 26 | (6) |
| | Minor bleeding | 6 | (1.4) |

the nature of reduced response is multifactorial and might comprise clinical, biological, pharmacological, and genetic elements,[23] and it ranged from (4–44%).[12-15]

## Risk Factors for Abnormal Platelet Responsiveness

Multiple contributing factors affect the platelets aggregation in vitro, which might be reflected on the clinical outcome of the patients. In our study, diabetes was a significant predictive factor for clopidogrel non-responsiveness. This findings is similar to other studies conducted in Switzerland, Germany, Italy, China and France.[24-28] While very few studies like a study conducted in Germany showed no statistically significant association.[29] The non-responsiveness was attributed to insufficient generation of the active metabolite of clopidogrel, rather than to alterations in P2Y12 receptor function; and although non-responsiveness to clopidogrel was not related to glycemic control, but appeared to be affected by a systemic inflammatory response, as reflected by increased levels of fibrinogen; or increased white blood cell count.[30] The impaired renal function was associated with reduced *in-vitro* responsiveness to DAPT in diabetic patients with coronary artery disease.[30]

The present study showed that smoking is more likely to be associated with over-response of platelets to clopidogrel. Such a finding is in agreement with the study of Ueno M *et al.,*[31] Gremmel T *et al.,*[32] and Jeong YH *et al.*[33] On the contrary, Dirk Sibbing *et al.*[28] showed a higher incidence of non-responders among smokers. This heterogeneity between the findings of our study and Dirk Sibbing *et al.*[28] study may be attributed to the impact of other factors on platelet responsiveness, such as patients' presentation, the presence of diabetes, and CRF. In addition, the smoking effect on platelet responsiveness is complicated and needs to be studied thoroughly in a future study to explain this variability in responsiveness.

The cases of CRF were more prone to have impaired platelet responsiveness to the effect of clopidogrel, which agrees with the study by Park SH *et al.*[34] and study by H Patrik *et al.*[16]

## Study Outcomes

Early definite stent thrombosis events were significantly higher in the non-responsiveness group in the present study. This finding is similar to other studies conducted in Switzerland, France, USA, Germany and China.[26,35-40] The bleeding events obviously to be more with the over-responsiveness group and is statistically significant, which agrees with Dirk Sibbing *et al.,*[28] Patti *et al.,*[41] and Stone *et al.*[42]

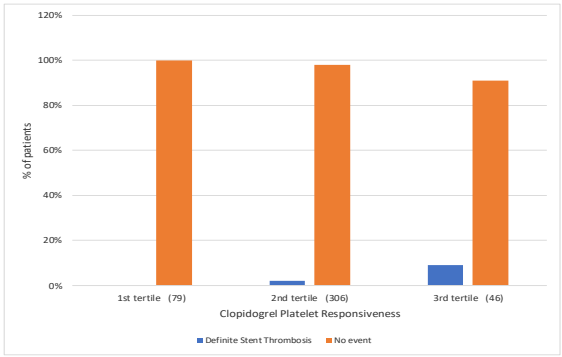


**Figure 2:** Distribution of stent thrombosis according to clopidogrel platelets responsiveness

**Table 2:** Distribution of clopidogrel platelets responsiveness in DM patients

| *Clopidogrel Platelet Responsiveness* | *Non-Diabetic* | | *Diabetic* | | *p-value* |
|---|---|---|---|---|---|
| | *No.* | *Percentage* | *No.* | *Percentage* | |
| 1st tertile (79) | 49 | 62 | 30 | 38 | < 0.05 |
| 2nd tertile (306) | 190 | 62.1 | 116 | 38 | |
| 3rd tertile (46) | 19 | 41.3 | 27 | 58.7 | |
| Total (431) | 258 | 59.9 | 173 | 40.1 | - |

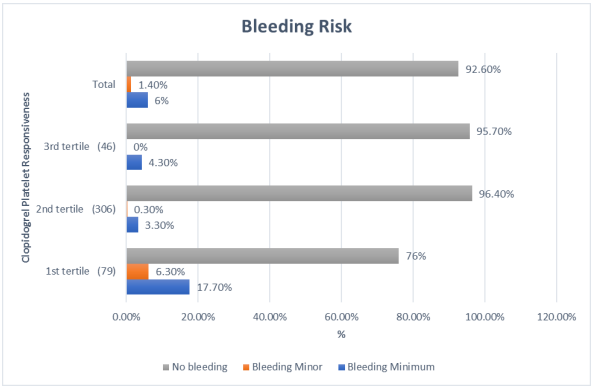


**Figure 3:** Distribution of bleeding events according to clopidogrel platelets responsiveness

**Table 3:** Association between clopidogrel platelets responsiveness and history of CRF

| *Clopidogrel platelet responsiveness* | *Chronic renal failure* | | *Normal renal function* | | *p-value* |
|---|---|---|---|---|---|
| | *No.* | *Percentage* | *No.* | *Percentage* | |
| 1st tertile (79) | 4 | 5 | 75 | 95 | < 0.005 |
| 2nd tertile (306) | 20 | 6.5 | 286 | 93.5 | |
| 3rd tertile (46) | 9 | 19.6 | 37 | 80.4 | |
| Total (431) | 33 | 7.7 | 398 | 92.3 | |

**Table 4:** Association of clopidogrel platelets responsiveness and smoking

| *Clopidogrel platelet responsiveness* | *Non-smoker* | | *Smoker* | | *p-value* |
|---|---|---|---|---|---|
| | *No.* | *Percentage* | *No.* | *Percentage* | |
| 1st tertile (79) | 32 | 40.5 | 47 | 59.5 | < 0.001 |
| 2nd tertile (306) | 197 | 64.4 | 109 | 35.6 | |
| 3rd tertile (46) | 32 | 69.6 | 14 | 30.4 | |
| Total (431) | 261 | 60.6 | 170 | 39.4 | - |

## CONCLUSION AND RECOMMENDATION

Platelets aggregometry is an important, widely available, and strong predictor of adverse in-hospital outcomes for patients who have undergone PCI whether they presented in stable ischemic heart disease or ACS presentation with a higher risk of stent thrombosis in the non-responsiveness group. Diabetes and CRF were associated with reduced platelet responsiveness in general, exposing these patients to more risk of adverse outcomes. Although over-responsiveness carries more risk of bleeding events, under responsiveness seems to be protective against this adverse outcome.

The presence of 10% non-response in Iraqi people with the availability of such test makes it rational to recommend the test for the high-risk group and complex interventional cases (including LMS) to prevent fatal outcome such as stent thrombosis. Gene study is recommended for people with non-response to understand the highly variable rate of no-response all over the world.

## REFERENCES


1. (2013) WHO | World Health Statistics 2013. WHO
2. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. Journal of the American College of Cardiology. 2005 Mar 15;45(6):947-53.
3. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza Jr JP, Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation. 2001 Apr 17;103(15):1967-71.
4. Ziada KM, Moliterno DJ. Dual antiplatelet therapy: is it time to cut the cord with aspirin?. JAMA. 2019 Jun 25;321(24):2409-11.
5. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circulation research. 2007 May 11;100(9):1261-75.
6. Geisler T, Langer H, Wydymus M, Göhring K, Zürn C, Bigalke B, Stellos K, May AE, Gawaz M. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. European heart journal. 2006 Oct 1;27(20):2420-5.
7. Chen WH, Cheng X, Lee PY, Ng W, Kwok JY, Tse HF, Lau CP. Aspirin resistance and adverse clinical events in patients with coronary artery disease. The American journal of medicine. 2007 Jul 1;120(7):631-5.
8. Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, Schömig A, Von Beckerath N, Kastrati A. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. Journal of Thrombosis and Haemostasis. 2010 Feb 1;8(2):250-6.
9. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schömig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. Journal of the American College of Cardiology. 2008 Feb 19;51(7):690-7.
10. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, Manoukian SV, Nikolsky E, Lansky AJ, Kirtane A, White HD. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. European heart journal. 2009 Jun 1;30(12):1457-66.
11. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006 Aug 22;114(8):774-82.
12. Steinhubl SR, Berger PB, Mann JT. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. Acc Current Journal Review. 2003;2(12):78-9.
13. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, Costa MA. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. Journal of the American College of Cardiology. 2007 Apr 10;49(14):1505-16.
14. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. Journal of the American College of Cardiology. 2005 Jan 18;45(2):246-51.
15. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003;107:2908–2913.
16. Htun P, Fateh-Moghadam S, Bischofs C, Banya W, Müller K, Bigalke B, Stellos K, May AE, Flather M, Gawaz M, Geisler T. Low responsiveness to clopidogrel increases risk among CKD patients undergoing coronary intervention. Journal of the American Society of Nephrology: JASN. 2011 Apr;22(4):627.
17. Kim J, Cho CH, Jung BK, Nam J, Seo HS, Shin S, Lim CS. Comparative evaluation of Plateletworks, Multiplate analyzer and Platelet function analyzer-200 in cardiology patients. Clinical Hemorheology and Microcirculation. 2018 Jan 1;70(3):257-65.
18. Cutlip DE, Windecker S, Mehran R. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation. 2007;115: 2344–2351
19. Libby P, Bonow RO, Zipes DP, Mann DL. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 2007. 8th ed.
20. Yaseen IF, Farhan HA, Abbas HM. Clopidogrel non-

responsiveness in patients undergoing percutaneous coronary intervention using the VerifyNow test: frequency and predictors. European Journal of Hospital Pharmacy. 2019 Mar 1;26(2):113-6.
21. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, Bhatt DL, Cattaneo M, Collet JP, Cuisset T, Gachet C. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. Journal of the American College of Cardiology. 2010 Sep 14;56(12):919-33.
22. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. The American journal of cardiology. 2009 Feb 2;103(3):27A-34A.
23. Würtz M, Grove EL, Wulff LN, Kaltoft AK, Tilsted HH, Jensen LO, Hvas AM, Kristensen SD. Patients with previous definite stent thrombosis have a reduced antiplatelet effect of aspirin and a larger fraction of immature platelets. JACC: Cardiovascular Interventions. 2010 Aug;3(8):828-35.
24. Fontana P, Berdagué P, Castelli C, Nolli S, Barazer I, Fabbro-Peray P, Schved JF, Bounameaux H, Mach F, De Moerloose P, Reny JL. Clinical predictors of dual aspirin and clopidogrel poor responsiveness in stable cardiovascular patients from the ADRIE study. Journal of Thrombosis and Haemostasis. 2010 Dec 1;8(12):2614-23.
25. Mangiacapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, D'Ambrosio A, Muller O, Barbato E, Di Sciascio G. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. The American journal of cardiology. 2010 Sep 1;106(5):619-23.
26. Lei L, Li HY, Rui Q, Yu HY, Hui Z, Wei G, Zhang J. Predictive value of antiplatelet resistance on early stent thrombosis in patients with acute coronary syndrome. Chinese medical journal. 2013 Feb 20;126(4):626-33.
27. Cayla G, Hulot JS, O'Connor SA, Pathak A, Scott SA, Gruel Y, Silvain J, Vignalou JB, Huerre Y, de la Briolle A, Allanic F. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. Jama. 2011 Oct 26;306(16):1765-74.
28. Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. Journal of the American College of Cardiology. 2009 Mar 10;53(10):849-56.
29. Sibbing D, Morath T, Braun S, Stegherr J, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N. Clopidogrel response status assessed with Multiplate point-of-care analysis and the incidence and timing of stent thrombosis over six months following coronary stenting. Thrombosis and haemostasis. 2010;103(01):151-9.
30. Hennekens CH, Cutlip D, Zehnder JL. Nonresponse and resistance to aspirin and clopidogrel.2010: 1–29
31. Ueno M, Ferreiro JL, Desai B, Tomasello SD, Tello-Montoliu A, Capodanno D, Capranzano P, Kodali M, Dharmashankar K, Charlton RK, Bass TA. Cigarette smoking is associated with a dose-response effect in clopidogrel-treated patients with diabetes mellitus and coronary artery disease: results of a pharmacodynamic study. JACC: Cardiovascular Interventions. 2012 Mar;5(3):293-300.
32. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Smoking promotes clopidogrel-mediated platelet inhibition in patients receiving dual antiplatelet therapy. Thrombosis research. 2009 Nov 1;124(5):588-91.
33. Jeong YH, Cho JH, Kang MK, Koh JS, Kim IS, Park Y, Hwang SJ, Kwak CH, Hwang JY. Smoking at least 10 cigarettes per day increases platelet inhibition by clopidogrel in patients with ST-segment-elevation myocardial infarction. Thrombosis research. 2010 Oct 1;126(4):e334-8.
34. Park SH, Kim W, Park CS, Kang WY, Hwang SH, Kim W. A comparison of clopidogrel responsiveness in patients with versus without chronic renal failure. The American journal of cardiology. 2009 Nov 1;104(9):1292-5.
35. Eshtehardi P, Windecker S, Cook S, Billinger M, Togni M, Garachemani A, Meier B, Hess OM, Wenaweser P. Dual low response to acetylsalicylic acid and clopidogrel is associated with myonecrosis and stent thrombosis after coronary stent implantation. American heart journal. 2010 May 1;159(5):891-8.
36. Frere C, Cuisset T, Quilici J, Camoin L, Carvajal J, Morange PE, Lambert M, Juhan-Vague I, Bonnet JL, Alessi MC. ADP-induced platelet aggregation and platelet reactivity index VASP are good predictive markers for clinical outcomes in non-ST elevation acute coronary syndrome. Thrombosis and haemostasis. 2007;98(10):838-43.
37. Brar SS, Ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, Patti G, Breet NJ, DiSciascio G, Cuisset T, Dangas G. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention: a collaborative meta-analysis of individual participant data. Journal of the American College of Cardiology. 2011 Nov 1;58(19):1945-54.
38. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Büttner HJ, Neumann FJ. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. Journal of the American College of Cardiology. 2006 Nov 7;48(9):1742-50.
39. Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissha MZ, Tantry US. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. Journal of the American College of Cardiology. 2005 Nov 15;46(10):1827-32.
40. Geisler T, Zürn C, Simonenko R, Rapin M, Kraibooj H, Kilias A, Bigalke B, Stellos K, Schwab M, May AE, Herdeg C. Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. European heart journal. 2010 Jan 1;31(1):59-66.
41. Patti G, Pasceri V, Vizzi V, Ricottini E, Di Sciascio G. Usefulness of platelet response to clopidogrel by point-of-care testing to predict bleeding outcomes in patients undergoing percutaneous coronary intervention (from the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study). The American journal of cardiology. 2011 Apr 1;107(7):995-1000.
42. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. The Lancet. 2013 Aug 17;382(9892):614-23.