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Original Article

Effects of Non-Adherence to Clopidogrel in Patients Undergoing Primary Percutaneous Coronary Intervention

Running Title: Clopidogrel Non-Adherence in Primary Percutaneous Coronary Intervention

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Abstract

Aims: Adherence to clopidogrel therapy is crucial for achieving favorable outcomes in patients with ST-segment elevation myocardial infarction (STEMI) who undergo primary percutaneous coronary intervention (PCI). This prospective cohort study aimed to investigate the rates of clopidogrel adherence, factors associated with adherence, and clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: This study employed a prospective observational design involving patients diagnosed with myocardial infarction (MI) who were scheduled for percutaneous coronary intervention (PCI) and prescribed clopidogrel. Adherence to clopidogrel therapy was assessed, with follow-up visits scheduled at 30 days, 6 months, and 1 year post-intervention.

Results: The study included 268 participants with a mean age of 58.9±13.2 years, predominantly male (82%). Adherence rates to clopidogrel were 94.8% at 1 month, 93% at 6 months, and 90.5% at 12 months post-PCI. The patients were compared in terms of adherence to clopidogrel. There were no significant differences in the distribution of sexes between the groups (p = 0.567). However, a significant difference in education levels was observed (p=0.034), with lower education levels associated with non-adherence. The non-adherence group had a higher risk of death (HR: 7.8, 95% CI: 6-106.8, p=0.001), cerebrovascular accident (HR: 10, 95% CI: 0.08-1.3, p=0.043), and major adverse cardiac and cerebrovascular events (MACCE) (HR: 5.2, 95% CI: 1.2-22.2, p=0.000). The primary factors contributing to non-adherence were low income (52%) and low health literacy (32%) among patients.

Conclusion: Non-adherence to clopidogrel was associated with a heightened risk of adverse cardiovascular and cerebrovascular events in patients undergoing primary percutaneous coronary intervention for myocardial infarction.

Keywords: Clopidogrel, adherence, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention

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Introduction

Clopidogrel, commonly known as Plavix®, is an antiplatelet medication that is frequently prescribed to patients undergoing percutaneous coronary intervention (PCI) for the treatment of myocardial infarction (MI) (1). Its primary mechanism of action involves inhibiting platelet aggregation, thereby playing a crucial role in preventing recurrent cardiovascular events (2, 3). However, premature discontinuation of clopidogrel may increase the risk of adverse cardiovascular and cerebral events, collectively referred to as major adverse cardiac and cerebrovascular events (MACCE) (4). Despite recognizing the importance of clopidogrel adherence in this patient population, there is limited understanding regarding the impact of premature discontinuation on MACCE (5).

In the management of acute myocardial infarction (AMI), patients undergoing PCI heavily rely on the administration of clopidogrel. Although newer and more effective P2Y12 inhibitors like ticagrelor have emerged, their widespread use is hindered by their high cost and limited accessibility, particularly in developing countries such as Iran[6]. As a result, clopidogrel remains the preferred P2Y12 inhibitor for patients with acute coronary syndrome (ACS) in these regions. However, the extent to which patients adhere to clopidogrel during the treatment period and its critical role in preventing MACCE are areas of uncertainty that require further investigation.

The primary motivation for conducting this prospective cohort study is the lack of comprehensive knowledge regarding clopidogrel adherence rates, the factors associated with non-adherence, and their impact on clinical outcomes. The study aims to investigate the rates of clopidogrel adherence, identify factors contributing to non-adherence, and examine the clinical outcomes in patients undergoing primary PCI for treating AMI. By addressing these objectives, this research seeks to enhance our understanding of clopidogrel adherence and its implications in optimizing patient outcomes within this specific patient population.

Methods

Study Design

This study employed a prospective observational design to evaluate the impact of non-adherence to clopidogrel on major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Study Population

The study recruited patients diagnosed with acute myocardial infarction who were referred to the Afshar Hospital in Yazd between January and December 2017. The inclusion criteria comprised a diagnosis of MI, planned PCI, and clopidogrel prescription as part of the treatment regimen. Patients with contraindications to clopidogrel, a history of bleeding disorders or significant bleeding events, or those participating in other clinical trials were excluded from the study.

Data Collection

Baseline assessments were conducted to collect patient information, including demographic data, cardiac risk factors, medical history, medication history, laboratory test results, echocardiogram

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findings, and angiography results. Clopidogrel adherence was assessed based on patient-reported adherence. The non-adherent group consisted of patients who either altogether discontinued the medication or ceased taking it for a minimum of two weeks.

We assessed the health literacy levels of patients using a questionnaire consisting of ten questions, which categorized the participants into three groups:

- Low: 0-4 points
- Medium: 4.1-7 points
- High: 7.1-10 points

Follow-up

Patients were regularly followed up, including 30 days, 6 months, and 1 year after the PCI procedure. During these follow-up visits, clinical outcomes and adverse events, such as recurrent myocardial infarction, stroke, target vessel revascularization, and mortality, were recorded.

Adherence to clopidogrel therapy was evaluated through questioning, and a medication count was performed by counting the number of pills used during each visit. We utilized a questionnaire consisting of eight questions to assess medication adherence. Based on the scores obtained, patients were classified as follows:

- Non/Low adherence: <6
- Medium adherence: 6 - <8
- High adherence: ≥8.

Patients were also instructed to report any changes in medication usage, adverse events, or hospitalizations during the follow-up period.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 24 software (IBM SPSS Statistics 24, Chicago, IL, USA). Descriptive statistics, including mean and standard deviation(mean±SD), were used to summarize quantitative data, while frequency and percentage were used for qualitative data. The independent t-test was employed to analyze quantitative variables, while the Chi-square test and Fisher's exact test were utilized for qualitative variables. A p-value less than 0.05 was considered statistically significant. The primary analysis evaluated the association between premature discontinuation of clopidogrel and MACCE using Cox proportional hazards regression. Survival analysis was conducted to assess clopidogrel usage during the 12-month follow-up period.

Results

A total of 277 out of the initial 302 patients who underwent primary percutaneous coronary intervention (PCI) met the eligibility criteria and were included in the study. Nine patients declined to participate, resulting in a final study population of 268 participants. The mean age of the participants was 58.9±13.2 years, and the majority (82%) were male. Hypertension was the most prevalent risk factor for coronary artery disease (CAD), observed in 41.1% of the participants. The mean body mass index (BMI) was 27.6±5.3 kg/m^2(Table).

Table 1. Baseline characteristics of the patients

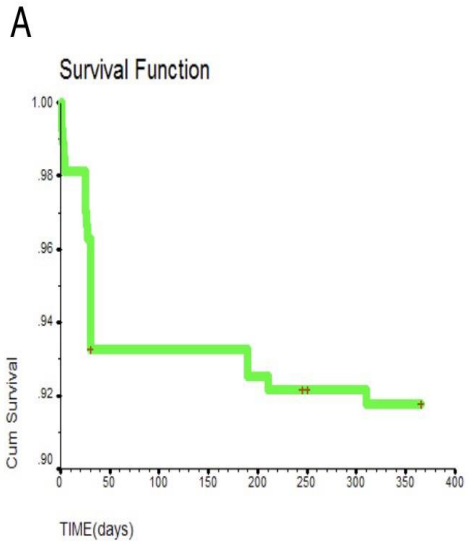
Character	Value (n(%)/mean±SD)
Age (year)	58.9±13.2
Sex -Male -Female	 220(82) 48(18)
CAD Risk factor -Hypertension -Hyperlipidemia -Diabetes mellitus -Smoking -Positive family history	 110(41.1) 85(31.8) 102(38.1) 103(38.2) 86(32.1)
-Body mass index (kg/ m^2)	27.6±5.3
Comorbidity -Prior coronary artery disease -Cerebrovascular accident -Chronic obstructive pulmonary disease -Chronic kidney disease	 50(18.8) 5(1.7) 3(1) 4(1.3)
Echocardiogram -LVEF (%)	 43.5±6.7
Lab tests -Hemoglubin (g/dl) -Blood sugar (mg/dl) -Creatinin(mg/dl) -LDL(mg/dl) -HDL(mg/dl) -uric acid(mg/dl)	 14.4±1.8 179±86 1.2±0.4 121±32.8 32.7±7.6 4.9±1.7
Angiography result One vessel disease Two vessel disease Three vessel disease	 96(35.9) 101(37.6) 71(26.5)
MI territory Anterior Non-anterior	 145(54) 123(46)
Stent -Diameter(mm) -Length (mm)	 2.99±0.44 32.1±15.2
Education level -Illiterate -undergraduate -Graduate -Postgraduate	 75(28) 101(38) 53(20) 39(14)

T adherence rate to clopidogrel therapy was 94.8% at 1 month, 93% at 6 months, and 90.5% at 12 months post-PCI. There was no statistically significant difference in age distribution between the adherence and non-adherence groups (p=0.866) [Table 2]. The distribution of male and female participants did not differ significantly between the adherence and non-adherence groups(p= 0.567). However, there was a statistically significant difference in the distribution of education levels between the two groups (p=0.034) **Figure 1**.

Table 2. Mean survival time on the use of clopidogrel across demographic variables

Variable	Adherence group N=243 Value N (%)	Non-adherence group N=25 Value N (%)	Survival time (mean)	SE	95%CI	P-value
Age(year) 34-54 55-69 70-91	79(91.9) 110(90.2) 54(90)	7(8.1) 12(9.8) 6(10)	346.1 335.7 339.1	8.1 8.6 11.4	330.1-362 319.9-352.5 316.9-361.4	0.866
Sex -Male -Female	201(91.4) 42(87.5)	19 (8.6) 6 (12.5)	341.2 333.3	5.8 13.7	329.9-352.5 306.4-360.3	0.567
Education level -Illiterate -undergraduate -Graduate -Postgraduate	64(85.3) 97(96) 45(85) 37(94.9)	11(14.7) 4(4) 8(15) 2(5.1)	323.9 354.8 327.8 347.8	12.5 5.8 14.2 11.8	299.4-348.3 343.4-366.2 300.1-355.6 324.6-371	0.034

Figure 1. Kaplan-Meier Survival Curves for clopidogrel consumption (A) Overall and according to (B) Age, (C) Gender, (D) Education Level.



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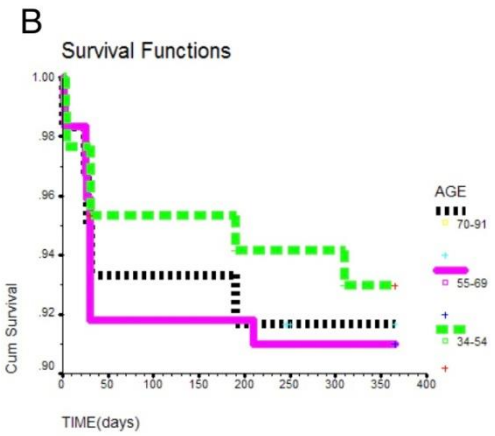

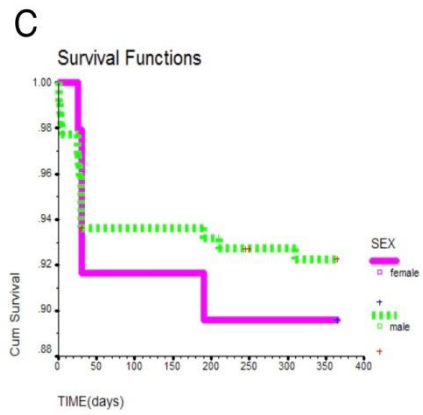

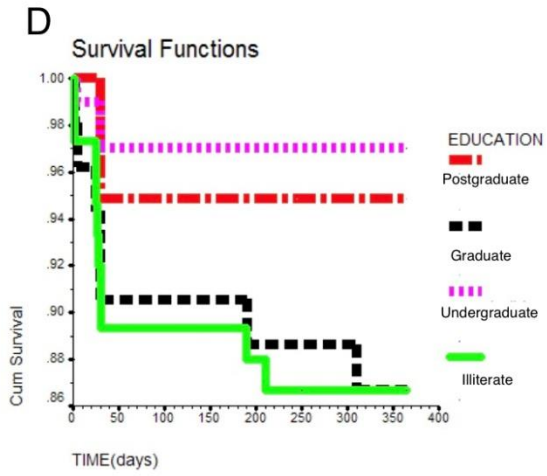

T non-adherence group exhibited a significantly higher risk of death (HR: 7.8, 95% CI: 6-106.8, p=0.001), cerebrovascular accident (HR: 10, 95% CI: 0.08-1.3, p=0.043), and total major adverse cardiovascular events (MACCE) (HR: 5.2, 95% CI: 1.2-22.2, p=0.000) compared to the adherence group. However, there were no significant differences between the groups regarding non-fatal myocardial infarction (MI) and repeat revascularization Table 3. The primary factors contributing to non-adherence were low income (28%) and low health literacy of patients (20%) **Table 4.**

Table 3. Comparison of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) between Adherent and Non-Adherent groups.

Event	Non-Adherent group N=25(%)	Adherent group N=243(%)	HR	95%CI	P value
Death	3(12)	4(1.6)	7.8	0.6-106.8	0.001
Nonfatal MI	0(0)	2(0.8)	0.0	0-0	0.648
Repeat revascularization	3(12)	13(5.3)	2.4	0.4-13.7	0.155
CVA	1(4)	1(0.4)	10.0	0.08-1.3	0.043
Total (%)	8(32)	20(8.1)	5.2	1.2 -22.2	0.0000

MI: myocardial infarction, **PCI:** percutaneous coronary intervention, **CVA:** cerebrovascular accident, **HR:** hazard ratio

Table 4. Variables contributing to clopidogrel discontinuation over one year

Variable	During the first 30 days n(%)	During 31-180 days n(%)	During 181-365 days N(%)	Total (%)
Low income	7(28)	3(12)	3(12)	13(52)
Low Health literacy	5(20)	1(4)	2(8)	8(32)
Drug intolerance	2(8)	1(4)	1(4)	4(16)
Total (%)	14(56)	5(20)	6(24)	25(100)

Discussion

Despite the introduction of more potent P2Y12 inhibitor medications as the preferred treatment for

patients with acute coronary syndrome (ACS), clopidogrel remains a significant option in managing these patients. Its use is particularly favored in cases where patients are at high risk of bleeding, have intolerance to newer and more potent antiplatelet drugs, cannot afford expensive alternatives, or present with comorbidities. This preference is attributable to clopidogrel's lower cost than newer agents such as ticagrelor and prasugrel and its reduced bleeding risk (7,8).

Our findings align with previous studies, underscoring the relationship between clopidogrel adherence and clinical outcomes in this patient population (9). Prior research has indicated clopidogrel discontinuation rates within 12 months ranging from 14% in the first month to 4%-38% by the end of the year (10). Zhu et al. reported an adherence rate of 66.8% (11). In our study, we observed a high adherence rate to clopidogrel therapy among patients with post-percutaneous coronary intervention (PCI) for myocardial infarction (MI), with adherence rates of 94.8% at 1 month, 93% at 6 months, and 90.5% at 12 months. These findings highlight the firm adherence to clopidogrel among this patient cohort, indicating that most patients recognized the importance of ongoing treatment.

Participants reported various reasons for non-adherence, including low income, inadequate health literacy, and intolerance to clopidogrel. Age-related differences in non-adherence to P2Y12 inhibitors have been documented in observational studies (12-14). However, our analysis did not reveal a statistically significant difference in age distribution between adherence and non-adherence groups.

Regarding gender, our study found no significant differences between the adherence and non-adherence groups, suggesting that sex did not influence clopidogrel adherence in our population. This contrasts with findings by Dehghani et al., who noted that females exhibited higher non-adherence rates to P2Y12 inhibitors (15).

Concerning education levels, our analysis revealed a significant difference between adherence and non-adherence groups, with a higher proportion of non-adherence observed among individuals with lower education levels. This suggests that educational interventions aimed at patients with lower educational attainment may enhance adherence to clopidogrel therapy (16).

Financial constraints significantly impacted medication adherence; the high cost of drugs, including clopidogrel, can lead to delayed treatment, inability to procure necessary medications, or improper use, ultimately resulting in severe cardiovascular events (17). This was identified as the most common reason for discontinuation in our study.

Health literacy is critical for promoting individual and public health. It empowers individuals to engage in preventive health behaviors, manage chronic conditions, adhere to treatment plans, and make informed health decisions. Adequate health literacy correlates with improved health outcomes, reduced healthcare costs, and enhanced patient-provider communication (18, 19). In our study, inadequate health literacy was the second most frequent reason for clopidogrel discontinuation.

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Intolerance to clopidogrel, characterized by adverse drug reactions, is another significant factor influencing adherence. Accurate diagnosis of such reactions is essential for patient safety and optimizing treatment quality (20,21). Regrettably, many patients discontinued their medication without consulting healthcare professionals or identifying suitable alternatives, accounting for 16% of cases.

These factors underscore the necessity for interventions aimed at improving medication affordability and enhancing patient education and health literacy to foster adherence to clopidogrel therapy.

Stent thrombosis represents a catastrophic complication that can result in sudden cardiac death. The risk is exceptionally high in the months immediately following stent placement but can occur at any time. Discontinuation or non-adherence to clopidogrel is a strong predictor of stent thrombosis. Our comparison of adherence groups revealed significant differences in cardiovascular events, particularly regarding sudden cardiac death and stroke, which were attributed to acute thrombosis following clopidogrel discontinuation. Notably, these events were more prevalent within the first month after stent placement, emphasizing the critical need for adherence to clopidogrel therapy to mitigate the risk of adverse cardiovascular and cerebrovascular events in post-PCI patients with MI (22-25).

The study's limitations include its observational design, which restricts the ability to establish causality between premature clopidogrel discontinuation and clinical outcomes. Additionally, adherence was assessed through self-reported measures, which may be prone to recall or social desirability bias. Future studies employing objective measures of adherence are warranted. Furthermore, our study population consisted exclusively of patients undergoing PCI for MI, which may limit the generalizability of our findings to other patient groups.

Conclusion:

This study provides valuable insights into the impact of premature clopidogrel discontinuation on clinical outcomes in patients post-PCI for MI. While overall adherence to clopidogrel therapy was high, non-adherence was associated with an increased risk of adverse events. To optimize patient outcomes, strategies to improve adherence, particularly among patients with lower education levels, should be prioritized. Future research should focus on identifying approaches to address factors contributing to non-adherence, such as medication cost and health literacy, to enhance patient adherence further and improve clinical outcomes in this population.

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Ethical considerations: The Ethics Review Board of Islamic Azad University, Yazd Branch, reviewed and approved the study protocol. Before enrollment, written informed consent was obtained from all participants, ensuring their autonomy and comprehension of the study's objectives and procedures. Patient confidentiality and data protection were strictly upheld throughout the study to safeguard the participants' privacy and anonymity.

Authors' contribution: Abbas Andishmand contributed to the conception and design, drafted the manuscript, gave final approval, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Mahdiah Sadat Namayandah contributed to analysis and interpretation, drafted the manuscript, critically revised it, gave final approval, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Masha Sadat Mahdavi contributed to the acquisition, drafted the manuscript, and prepared and revised the manuscript.

References

1Faridi KF, Garratt KN, Kennedy KF, Maddox TM, Secemsky EA, Butala NM, et al. Physician and Hospital Utilization of P2Y12 Inhibitors in ST-Segment–Elevation Myocardial Infarction in the United States: A Study From the National Cardiovascular Data Registry's Research to Practice Initiative. Circulation: Cardiovascular Quality and Outcomes. 2020;13(3):e006275.

2. Wang TH, Bhatt DL, Topol EJ. Aspirin and clopidogrel resistance: an emerging clinical entity. European Heart Journal. 2006;27(6):647-54.

3. Patti G, Micieli G, Cimminiello C, Bolognese L. The role of clopidogrel in 2020: a reappraisal. Cardiovascular therapeutics. 2020;2020(1):8703627.

4. Piccolo R, Feres F, Abizaid A, Gilard M, Morice M-C, Hong M-K, et al. Risk of early adverse events after clopidogrel discontinuation in patients undergoing short-term dual antiplatelet therapy: an individual participant data analysis. JACC: Cardiovascular Interventions. 2017;10(16):1621-30.

5. Sohail M, Patel P, Midha S, Shukla S, Dhamija D, Bello AO, et al. Identifying the Incidence, predictors, outcomes, and prevention of stent thrombosis (st) in post-percutaneous coronary revascularization patients with drug-eluting stents (des): A systematic review. Cureus. 2023;15(9).

6.James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, Becker R, Wallentin L. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2009 Apr;157(4):599-605. doi: 10.1016/j.ahj.2009.01.003. PMID: 19332184.

7. Pradhan A, Tiwari A, Caminiti G, Salimei C, Muscoli S, Sethi R, et al. Ideal P2Y12 inhibitor in acute coronary syndrome: a review and current status. International Journal of Environmental Research and Public Health. 2022;19(15):8977.

8. Abubakar M, Raza S, Hassan KM, Javed I, Hassan KM, Farrukh F, et al. Efficacy, safety, and role of antiplatelet drugs in the management of acute coronary syndrome: a comprehensive review of the literature. Cureus. 2023;15(3).

9. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. Jama. 2007;297(2):159-68.

10. Thim T, Johansen MB, Chisholm GE, Schmidt M, Kaltoft A, Sørensen HT, et al. Clopidogrel discontinuation within the first year after coronary drug-eluting stent implantation: an observational study. BMC cardiovascular disorders. 2014;14:1-8.

11. Zhu B, Zhao Z, McCollam P, Anderson J, Bae JP, Fu H, et al. Factors associated with clopidogrel use, adherence, and persistence in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Current medical research and opinion. 2011;27(3):633-41.

12. Johnston N, Weinman J, Ashworth L, Smethurst P, El Khoury J, Moloney C. Systematic reviews: causes of non-adherence to P2Y12 inhibitors in acute coronary syndromes and response to intervention. Open heart. 2016;3(2):e000479.

  DOI: https://doi.org/10.18502/aptj.v5i1.18134

13. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;117(8):1028-36.
14. Roth GA, Morden NE, Zhou W, Malenka DJ, Skinner J. Clopidogrel use and early outcomes among older patients receiving a drug-eluting coronary artery stent. Circulation: Cardiovascular Quality and Outcomes. 2012;5(1):103-12.
15. Dehghani P, Chopra V, Bell A, Kelly S, Zulyniak L, Booker J, et al. Southern Saskatchewan ticagrelor registry experience. Patient preference and adherence. 2014:1427-35.
16. Al-Tarawneh F, Ali T, Al-Tarawneh A, Altwalbeh D, Gogazeh E, Bdair O, et al. Study of adherence level and the relationship between treatment adherence, and superstitious thinking related to health issues among chronic disease patients in southern Jordan: cross-sectional study. Patient preference and adherence. 2023:605-14.
17. Momary KM, Kimble LP. Factors associated with clopidogrel adherence in community-dwelling patients. Journal of Cardiovascular Nursing. 2016;31(5):452-6.
18. Liu C, Wang D, Liu C, Jiang J, Wang X, Chen H, et al. What is the meaning of health literacy? A systematic review and qualitative synthesis. Family medicine and community health. 2020;8(2).
19. Coughlin SS, Vernon M, Hatzigeorgiou C, George V. Health literacy, social determinants of health, and disease prevention and control. Journal of environment and health sciences. 2020;6(1).
20. Jiang H, Lin Y, Ren W, Fang Z, Liu Y, Tan X, et al. Adverse drug reactions and correlations with drug-drug interactions: A retrospective study of reports from 2011 to 2020. Frontiers in pharmacology. 2022;13:923939.
21. Coleman JJ, Pontefract SK. Adverse drug reactions. Clinical Medicine. 2016;16(5):481-5.
22. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2-year results from a prospective observational study. The Lancet. 2013;382(9906):1714-22.
23. Weaver JM. Caution: maintain antiplatelet therapy in patients with coronary artery stents. Anesthesia Progress. 2007;54(4):161-2.
24. Ullrich H, Muenzel T, Gori T. Coronary stent thrombosis—predictors and prevention. Deutsches Ärzteblatt International. 2020;117(18):320.
25. Naidu SS, Krucoff MW, Rutledge DR, Mao VW, Zhao W, Zheng Q, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation: results from the 8,061-patient XIENCE V United States study. JACC: Cardiovascular Interventions. 2012;5(6):626-35.