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Clopidogrel Adherence to AHA/ACC guideline in Patients with Open Heart Surgery in a Tertiary Heart Center

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Abstract

Background: Clopidogrel is an antiplatelet drug that is widely prescribed for cardiovascular disease. In cardiac surgery, it is used in patients after coronary artery bypass grafting (CABG) to prevent coagulation disorders. The irrational use of this drug can lead to bleeding and require surgical exploration along with increased therapeutic cost. Therefore, it is essential to study the pattern of clopidogrel use in hospitals.

Methods: This study was conducted for a 6-month period to evaluate clopidogrel adherence to American Heart Association/American College of Cardiology (AHA / ACC) Guidelines in patients after coronary artery bypass grafting (CABG) surgery. Patients' data were recorded in the pre-designed questionnaire, which included demographic data, past medical history, drug history along with the indications of clopidogrel use. Data analysis was performed by SPSS 16 software.

Results: A total of 120 patients with a mean age of 61.3 ± 8.9 years old were recruited in to this study. Male to female ratio was 3 times. The main risk factors in patients with ischemic heart disease were male gender (74.2%), hypertension (80%), and smoking (47.5%). In addition to clopidogrel, most of the patients received aspirin (95.8%), followed by heparin (31.7%), and warfarin (5%) or enoxaparin (2.5%). The clopidogrel indications were non ST-elevation myocardial infarction / unstable angina (33.3%), acute ST-elevation myocardial infarction (20.8%), recent myocardial infarction or stroke (3.3%), and CABG off-pump (30%). In 70.8% of cases, the administration of clopidogrel was consistent with AHA / ACC standard guidelines and most of the irrational cases belonged to the usage of the drug after on-pump CABG surgery.

24 **Conclusion:** The results showed that the rates of adherence to clopidogrel use with the AHA/ACC
25 guidelines for patients who underwent CABG surgery was relatively good, but required further
26 improvement.

27 **Key words:** clopidogrel, aspirin, coronary artery bypass grafting, guideline.
28

29 **Introduction**

30 Coronary artery bypass grafting (CABG) has become one of the most common cardiac procedures in
31 the United States and worldwide.^{1,2} Antiplatelet therapy after CABG has been confirmed to increase the
32 patency of vein graft and to decrease postoperative related adverse events.³ According to American
33 Heart Association and American College of Chest Physicians (AHA/ACCP) guidelines, patients who
34 are undergoing CABG and receiving aspirin should continue taking aspirin around the time of the
35 surgery, but clopidogrel and prasugrel should be stopped five days before the day of CABG surgery.⁴

36 Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by antagonizing the P2Y₁₂
37 platelet receptor.⁵ Clopidogrel decreases ischemic events and mortality in patients with cardiovascular
38 diseases and its clinical efficacy has been established in some clinical trials.⁶

39 AHA/ACC usually recommends clopidogrel for the following disorders: Unstable angina / non-ST-
40 elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), percutaneous
41 coronary intervention (PCI). The off-label uses of clopidogrel are: atrial fibrillation (AF), carotid artery
42 stenosis, CABG off-pump, coronary artery disease, recent myocardial infarction (MI), recent stroke,
43 established peripheral arterial disease (PAD), peripheral artery percutaneous transluminal angioplasty
44 (PTCA) with or without stenting or peripheral artery bypass graft surgery.⁷ This study was designed to
45 evaluate the rational use of clopidogrel in our heart center.

46 **Methods**

47 Setting and design

48 This descriptive **cross-sectional** drug utilization evaluation (DUE) study was done in Shahid Madani
49 Heart Centre (the largest referral hospital for cardiovascular disorders at the northwest of Iran) from
50 March to September 2017. The ethics committee of Tabriz University of Medical Sciences was approved
51 this study. All patients underwent CABG and were receiving clopidogrel after surgery was identified on
52 regular reviews of the patients' case records in the intensive care unit (ICU).

53 Study protocol

54 Patients' data were recorded in the pre-designed form, which included demographic data, past medical
55 history, drug history, indications of clopidogrel treatment, other antiplatelet and anticoagulant drugs,
56 and routine laboratory records (Platelet, Hemoglobin, Hematocrite, and Creatinine). Compliance with
57 standard recommendations was assessed by the AHA/ACCP guidelines for clopidogrel use.⁸

58 Statistical analysis

59 Collected data were analyzed using the SPSS version 16 (SPSS Inc, Chicago, IL, USA). For discrete
60 variables number and percentage and for continuous variables mean \pm standard deviation was provided.
61 Spearman correlation test was used to evaluate correlation between the study variables. A p value of less
62 than 0.05 was considered as the statistically significant.

63 **Results**

64 In total, 120 patients were included in this study. Mean age of patients was 61.3 ± 8.9 years, and average
65 body mass index (BMI) was 27.5 ± 4.4 **kg/m²** Male to female ratio was 3 times. Demographic and clinical
66 data are shown in Table 1.

67 The most important risk factors in patients with cardiovascular disease in this study were male gender
68 (74.2%), hypertension (80%), and smoking (47.5%). Only 19.2% of patients had a positive family
69 history of cardiovascular disease. In addition to hypertension, some of the patients had diabetes mellitus

70 (39.2%), hyperlipidemia (37.5%), and MI (15%). As a result, the usage of cardiovascular drugs and anti-
71 hyperlipidemic drugs had the highest frequency in patients' drug history. However, the most commonly
72 prescribed antiplatelet and anticoagulant drugs along with clopidogrel were aspirin (95.8%), heparin
73 (31.7%), warfarin (5%), and enoxaparin (2.5%). Indications of clopidogrel and antiplatelet/
74 anticoagulant prescribed drugs **have been** included in Table 2. Clopidogrel was prescribed in NSTEMI
75 / unstable angina (33.3%), acute STEMI (20.8%), recent MI or stroke (3.3%) and CABG off-pump
76 (30%). Clopidogrel consumption in 70.8% of cases was rational and complies with AHA/ACC
77 recommendations, while in 29.2% was irrational. The correct use of clopidogrel was in cases of CABG
78 off-pump, MI, PCI stenting, and balloon. Most of the irrational cases belonged to the usage of the drug
79 after on-pump CABG surgery. Models of correlation between data are **shown** in Table 3.

80 **Discussion**

81 This study was conducted in order to evaluate and improve the rate of appropriate use of clopidogrel, as
82 a potent antiplatelet agent. The AHA and ACC have set guidelines for medical secondary prevention in
83 patients with cardiovascular disease, which contain detailed drug recommendations, diabetes and
84 hypertension management and lifestyle modifications such as sport and smoking cessation. In The
85 secondary prevention after coronary bypass, a Get with the Guidelines (GWTG) study, the adherence to
86 AHA and ACC guidelines was between 10% and 90%. Lack of awareness, information overload, and
87 incomplete documentation are some reasons for **incomplete** adherence to guidelines. The results of this
88 study showed that the compliance rate of aspirin (75 to 325 mg daily), and warfarin (with therapeutic
89 INR range 2 - 3) were between 56% and 84 %. It was between 17% and 73% for beta-blockers (in post
90 MI and ischemic syndrome patients), and it was 24% for angiotensin-converting-enzyme inhibitors
91 (ACEI) (in post MI, congestive heart failure, and all vascular patients).⁹ The study by Sørensen et al.
92 was about patients who underwent CABG following a recent MI. It assessed the benefits of postoperative
93 clopidogrel usage. Just 27% of 3545 patients received clopidogrel treatment after CABG, and they had
94 a lower risk of death or recurrent MI. ¹⁰ Another study by Robert F. et al. showed that the adherence to
95 secondary prevention guidelines in STEMI patients who underwent CABG was lesser than patients who
96 underwent PCI. Patients who received the more appropriate regimen of standard medical therapies were
97 PCI patients. Compliance rates have been improved between the 2 groups. In 2006, it reached 85.6% for
98 CABG group and 87.6% for PCI group.¹¹our findings showed that compliance rate in our study were
99 70.8%. **In the study performed by Farahzadi M the use of clopidogrel in primary management of patients
100 with NSTEMI and its adherence to ACC/AHA guidelines was investigated. Adherence to ACC/AHA
101 guideline for the management of NSTEMI in patients who presented to a tertiary health-care center was
102 in a high degree (95%)¹² .** But in our study all indications of clopidogrel such as non ST-elevation
103 myocardial infarction / unstable angina, acute ST-elevation myocardial infarction, recent myocardial
104 infarction or stroke, and CABG off-pump and their adherence to guideline was assessed. In 70.8% of
105 cases, the administration of clopidogrel was consistent with AHA / ACC standard guidelines and most
106 of the irrational cases belonged to the usage of the drug after on-pump CABG surgery.

107

108 In the study of Abhinav G. et al. the use of beta-blockers, ACE inhibitors, or angiotensin receptor
109 blockers, antiplatelet and antihyperlipidemic agents in patients after CABG surgery were evaluated after
110 hospital discharge and at one year. Antiplatelet and antihyperlipidemic drugs were used extremely, but
111 other drugs' usage was suboptimal. Patients who take all recommended secondary prevention
112 medications after CABG have fewer rates of two years death or MI.¹³

113 In this study only indication of clopidogrel was evaluated but no other indexes and aspects usage such
114 as loading as well as maintenance doses. Time duration that clopidogrel have been stopped before
115 CABG was not available in this study.

116 Other limitations include small sample size and partially short study period. More studies with large
117 sample size are needed to periodically evaluate the use of critical drugs in hospitals to improve treatment
118 outcome and save of therapeutic cost.

119 **Conclusion**

120 According to the results of this study, the current prescription of clopidogrel in patients after CABG
121 surgery is acceptable in our centre.

122 **Conflict of interest**

123 None

124 **Founding**

125 None

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Table 1. Demographic information of the study population

Gender, n (%)	Male	89 (74.2%)
	Female	31 (25.8%)
Age, mean± SD* (Year)		61.3 ± 8.9
Body Mass Index, mean± SD (kg/m²)		27.5 ± 4.4
Disease history, n (%)	Hypertension	96 (80%)
	Diabetes Mellitus	47 (39.2%)
	Hyperlipidemia	45 (37.5%)
	Myocardial Infraction	18 (15%)
Drug history, n (%)	Cardiovascular drugs	107 (89.2%)
	Anti-hyperlipidemic drugs	71 (59.2%)
	Anti-diabetic drugs	26 (21.7%)
	Others	28 (23.3%)

SD: standard deviation

	Non-STEMI / Unstable Angina	40 (33.3%)
Clopidogrel indications	Acute STEMI disease	25 (20.8%)
	Recent MI or Stroke	4 (3.3%)
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Off-label indications	CABG on-pump	80 (66.7%)
	CABG off-pump	36 (30%)
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Antiplatelet / anticoagulant drugs	Aspirin	115 (95.8%)
	Heparin	38 (31.7%)
	Warfarin	6 (5%)
	Enoxaparin	3 (2.5%)
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CABG: coronary artery bypass grafting, MI: myocardial infarction, STEMI: ST – elevation of myocardial infarction		
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Table 3. Correlation between

	Correlation Coefficient (r)	P-value
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Acute STEMI	0.257	0.019
Non-STEMI / Unstable angina	0.384	0.001
CABG Method (on or off-pump)	0.441	0.001