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CLOPIDOGREL USE - ARE WE FOLLOWING THE GUIDE LINES?

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ABSTRACT

Objective: To see the prescription patterns of clopidogrel in the outpatient department of a tertiary care hospital.

Methodology: This descriptive cross-sectional study was conducted at Armed Forces Institute of Cardiology and National Institute of Heart Diseases Rawalpindi, from 1st February 2012 to April 2012, after approval from Ethical review board of the institute. A structured team of MBBS doctors was created to conduct the study. Data on clopidogrel prescriptions was collected from the pharmacy where their source notes were assessed and patients taking clopidogrel were identified.

Results: The study population consisted of 2263 patients. The age of patients ranged from 25 to 93 years with the mean of 60.45 years ± 9.969. The standard indications found for clopidogrel prescription included ST elevation MI (STEMI) in 582 (25.7%), Non-ST elevation MI (NSTEMI) in 130 (5.7%), percutaneous coronary interventions (PCI) in 703 (31.1 %), CABG in 300 (13.3%), stroke/TIA in 60 (2.6 %) and atrial fibrillation in 15 (0.66%). These standard indications constituted 79.09% of prescription. The duration of clopidogrel use ranged from 1 year to maximum of 10 years with mean of 3.38 ± 2.13 years. Patients who had suffered a NSTEMI 84.6%, and 84.3% who had suffered a STEMI more than 1 year ago were still receiving clopidogrel.

Conclusion: We concluded that indications for which clopidogrel were prescribed to most patients were according to recommended international guidelines. But duration of its use is not according to guideline directed medical therapy.

Key Words: Dual Antiplatelet Therapy, Aspirin, Clopidogrel

INTRODUCTION

Clopidogrel is an antiplatelet drug that irreversibly binds to the P2Y12 receptor (which is a completely different site of action from aspirin) on the platelet surface.[1] It causes significantly less bleeding as compared to aspirin.[2]

Clopidogrel is licensed for a limited number of indications. When clopidogrel is given in a loading dose of 600 mg it achieves maximum platelet inhibition within 2 hours of administration, this duration increases to 24 hours or more if only 300 mg is administered as a loading dose. In a prospective trial it was shown that double dose clopidogrel (loading dose of 600 mg followed by 150 mg/ day for 7 days) was superior to standard dosage protocol (loading dose of 300 mg followed by 75mg/ day) for PCI for ACS at 7 days.[3] The optimal duration of clopidogrel therapy to prevent stent thrombosis in patients who receive a drug eluting coronary stent (DES) is one year.[4] In acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI) it is prescribed in a loading dose with maintenance dose for a period of one year.[5,6]

For cerebrovascular events clopidogrel (in combination with aspirin, or alone if the patient is allergic to aspirin) is recommended as initial treatment in the management of TIA or stroke (to prevent further events). It is also recommended before and for at least 30 days after carotid artery stenting. The combination of aspirin and dipyridamole is preferred.[7]

Clopidogrel is currently not approved for post- coronary artery bypass graft surgery (CABG) therapy by the Food and Drug Agency (USA), and continues to be the subject of significant debate. However, as in all other scenarios, the standard indication of clopidogrel use in case of aspirin allergy holds. Animal studies have demonstrated a favorable effect of clopidogrel on intimal hyperplasia in vein grafts. Based on this evidence the aim of the CASCADE trial was to study the effects of clopidogrel on long term intimal hyperplasia in vein grafts. The trial concluded that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia 1 year after coronary artery bypass grafting.[8] A recent sub-analysis of the CASCADE trial shows that hypertension, SVG diameter, grafting to the right coronary artery, and low quality of the target vessel correlate with the development of SVG hyperplasia or occlusion by 1 year after CABG, whereas ß-blockers and statins are associated with less SVG disease.[9] A study has shown that the early venous graft patency rates are higher in patients who receive both aspirin and clopidogrel, however this evidence has been contested during peer review.[10] Clopidogrel is a safe alternative to aspirin if aspirin is not tolerated but there is no strong evidence that clopidogrel is superior to aspirin post CABG.[11] There is data to highlight the fact that bleeding risk and transfusion requirement increase after CABG in patients who have received clopidogrel with or without aspirin.[12-16] It is thus recommended that aspirin and clopidogrel should be discontinued 7 days and 5 days respectively before CABG surgery. The major side effect of clopidogrel is an increase in bleeding events.[17] Although the effects are due to a qualitative effect on platelet function, there have been case reports of significant thrombocytopenia attributable to clopidogrel.[18-22]

This study was conducted to determine the prescription patterns of clopidogrel in the outpatient department of a tertiary care hospital.

METHODOLOGY

This descriptive cross-sectional study was conducted at Armed Forces institute of Cardiology and National Institute of Heart Diseases Rawalpindi from 1st February 2012 to April 2012, after approval from Ethical review board of the institute. A structured team of MBBS doctors was created to conduct the study.

Over a period of three months data on clopidogrel prescriptions was collected from the pharmacy where their source notes were assessed and patients taking clopidogrel were identified. These patients were informed about the study and that it would have no bearing on the management of their disease and not affect their privacy status. Only patients who consented were processed further. A doctor (MBBS) looked through the source notes of the patients as they reached the pharmacy and then filled in a data form. The indications of clopidogrel use were also confirmed from the patient's source notes as well as from the electronic records on the hospital management information system (HMIS). Enquiry about major bleeding events was made from the patients in person and their source notes. Then electronic pharmacy records of these patients were accessed on the HMIS. The duration of prescription of clopidogrel was confirmed from the HMIS pharmacy records. The duration of use of clopidogrel was divided into two groups of less than or equal to 1 yr and more than 1 year.

The data form contained the medical registration (MR) number of the patient which could be accessed on the hospital information management system (HIMS) and further details about the prescriptions could be accessed. This MR no constituted the unique identification number for every patient. The data collection forms were regularly checked and forms incomplete in any respect were excluded if the information could not be obtained from the HMIS.

The Statistical analysis was done using SPSS version 19. Once data was entered the first step was to eliminate any patients being entered repetitively. This was done by elimination of duplicate MR numbers from the SPSS database. Descriptive statistics were used to describe the

Table 1: Age and Duration of Clopidogril Use

Variables	Minimum	Maximum	Mean	Std. Deviation
Age(Years)	25	93	60.45	9.96
Duration of clopidorel Use(years)	1	10	3.88	2.13

data i.e, mean and standard deviation (SD) for quantitative variables while frequency along with percentages for qualitative variables.

RESULTS

The study population consisted of 2263 patients. The age of patients ranged from 25 to 93 years with the mean of 60.45 years ± 9.969 as shown in Table 1.

Out of total 31% were females and rest 69% males. The standard indications found for clopidogrel prescription included ST elevation MI (STEMI) in 582 (25.7%), Non-ST elevation MI (NSTEMI) in 130 (5.7%), percutaneous coronary interventions (PCI) in 703 (31.1 %), coronary artery bypass graft surgery (CABG) in 300 (13.3%), stroke/TIA in 60 (2.6 %) and atrial fibrillation (AF) in 15 (0.66%). The above standard indications constituted an indication for prescription in 79.09% of the studied population. The remaining had no indication for clopidogrel prescription. The detail for these is given in table 2.

The duration of clopidogrel use ranged from 1 year to maximum of 10years and mean of 3.38 years ± (SD) 2.13. One hundred and ten patients (84.6%) had suffered an NSTEMI more than one year ago, and 491(84.3%) who had suffered an STEMI more than one year ago were still receiving clopidogrel. In PCI group of 703 patients, 583 (82.9%) had suffered an STEMI more than one year ago were still receiving clopidogrel. Where as in CABG out of 300 patients 86.3% (n= 259), in Stroke and TIA group 85% (n=51) all whereas all patients with AF were on clopidogrel

Table 2: Indications for Clopidogrel Use

Indications	No of Patients	Percentage
STEMI	582	25.71%
NSTEMI	130	5.74%
PCI	703	31.06%
CABG	300	13.25%
Stroke/TIA	60	2.65%
Atrial Fibrilation	15	0.663%
No indication	473	20.9%
Total	2263	100%

Table 3: Clopidogrel Duration of Use in Different Indications

	Less than 1 year	More than 1 year	Total
NSTEMI	110(84.6%)	20(15.4%)	130
STEMI	491(84.3%)	91(15.7%)	582
PCI	583(82.9%)	20(17.1%)	703
CABG	90(81.2%)	30(18.8%)	110
Endartectomy	161(84.7%)	29(15.3 %)	190
Stroke	32(84.2%)	6(15.78%)	38
TIA	19(86.3%)	3(13.6%)	22
AF	15(100%)	0	15
No Indication	267(56.4%)	206(43.5%)	473

for more than 2 years.

DISCUSSION

The study population was derived from the outpatients departments in AFIC-NIHD. The objective of the study was to determine the appropriateness of clopidogrel prescriptions in the light of the current available evidence. The appropriateness was assessed in terms of the indications of clopidogrel use and the appropriate duration of use of the drug. The data collection details have already been described in detail in the methods section.

Clopidogrel is licensed for a limited number of indications. When clopidogrel is given in a loading dose of 600 mg it achieves maximum platelet inhibition within 2 hours of administration, this duration increases to 24 hours or more if only 300 mg is administered as a loading dose. In a prospective trial it was shown that double dose clopidogrel (loading dose of 600 mg followed by 150 mg/ day for 7 days) was superior to standard dosage protocol (loading dose of 300 mg followed by 75mg/ day) for PCI for ACS at 7 days. The optimal duration of clopidogrel therapy to prevent stent thrombosis in patients who receive a drug eluting coronary stent (DES) is one year. In acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI) it is prescribed in a loading dose with maintenance dose for a period of one year.

In our study NSTEMI cases constituted 5.7 % of the study population. As per the current evidence base patients in this group should have clopidogrel for only 1 year, whether they have had PCI or not, depending on the timing of the index event, whichever one is later. Of this population of 130 patients 110 (84.6%) had suffered an NSTEMI more than one year ago, but were still receiving clopidogrel.

STEMI cases constituted 25.7% of the patients under

consideration. According to the current evidence base patients in this group should have clopidogrel for only 1 year, whether they have had PCI or not, depending on the timing of the index event, whichever one is later. Of this population of 582 patients 491(84.3%) had suffered an STEMI more than one year ago, but were still receiving clopidogrel.

A total 31.1% of the patients were receiving clopidogrel after having undergone PCI. According to the current evidence base patients in this group should have clopidogrel for only 1 year, whether they have had PCI or not, depending on the timing of the index event, whichever one is later. Of this population of 703 patients 583 (82.9%) had suffered an STEMI more than one year ago, but were still receiving clopidogrel.

For cerebrovascular events clopidogrel (in combination with aspirin, or alone if the patient is allergic to aspirin) is recommended as initial treatment in the management of TIA or stroke (to prevent further events). It is also recommended before and for at least 30 days after carotid artery stenting. The combination of aspirin and dipyridamole is preferred. In our study patients with AF all 15 patients were receiving Clopidogrel for more than a year. In Stroke and TIA group 85% (n=51) out of total 60 were receiving Clopidogrel after one year. In further break up in patients with Stroke 32 (82.05%) out of 38 where as in TIA 19 (86.36%) out of 22 patients were on Clopidogrel after a year.

Clopidogrel is currently not approved for post- coronary artery bypass graft surgery (CABG) therapy by the Food and Drug Agency (USA), and continues to be the subject of significant debate. However, as in all other scenarios, the standard indication of clopidogrel use in case of aspirin allergy holds. Animal studies have demonstrated a favorable effect of clopidogrel on intimal hyperplasia in vein grafts. Based on this evidence the aim of the CASCADE trial was to study the effects of clopidogrel on long term intimal hyperplasia in vein grafts. The trial concluded that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia 1 year after coronary artery bypass grafting.A recent sub-analysis of the CASCADE trial shows that hypertension, SVG diameter, grafting to the right coronary artery, and low quality of the target vessel correlate with the development of SVG hyperplasia or occlusion by 1 year after CABG, whereas ß-blockers and statins are associated with less SVG disease. A study has shown that the early venous graft patency rates are higher in patients who receive both aspirin and clopidogrel, however this evidence has been contested during peer review. Clopidogrel is a safe alternative to aspirin if aspirin is not tolerated but there is no strong evidence that clopidogrel is superior to aspirin post CABG. There is data to highlight the fact that bleeding risk and transfusion requirement increase after CABG in patients who have received clopidogrel with or without aspirin. It is thus recommended that aspirin and clopidogrel be discontinued 7 days and 5 days respectively before CABG surgery. The major side effect of clopidogrel is an increase in bleeding events. Although the effects are due to a qualitative effect on platelet function, there have been case reports of significant thrombocytopenia attributable to clopidogrel

In total of 300 patients who had CABG 86.3% (n= 259) were having clopidogrel for more than a year. In further break up of type of surgery 90 (81.2 %) out of 110 and 161 (84.73%) out of 190 were found to be receiving the drug for more than a year.

Although this was not a subject of our study however, one of the common reasons for prescription of clopidogrel appears to be the health care professional's fear of future cardiac or cerebrovascular events. These include but are not limited to stent thrombosis and vein graft occlusion, or recurrent stroke and MI.

The discussion above clearly shows that clopidogrel prescription has to be judicious otherwise it can lead to an increase in bleeding events and worsen outcomes.Our audit showed results not in congruence with the current international guidelines regarding duration of clopidogrel use.

LIMITATIONS

In our study we did not have the data on patients who had bleeding events, this would have added greatly to the strength of the study.

CONCLUSION

Our study results show that indications for which clopidogrel prescribed to most patients were according to recommended international guidelines. But duration of its used is not according to guideline directed medical therapy. The reasons of this deviation were not the subject of this study.

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