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EVALUATION OF CLINICAL PRACTICE IN PRESCRIBING DUAL ANTIPLATELET THERAY FOLLOWING ACUTE CORONARY SYNDROME IN A TERITIARY CARE HOSPITAL

Introduction

Acute coronary syndrome (ACS) is a term referring to myocardial infarction (MI) with or without changes in ECG for ST- segment elevation (STEMI or NSTEMI) and unstable angina (UA). Dual antiplatelet therapy (DAPT) is used for management of ACS as standard therapy to ensure optimal anti-platelet action. This has been shown in clinical trials (CURE, PLATO, and TRILOGY ACS Trial) [1-3] to reduce incidence of major adverse cardiovascular events (MACE) in the immediate aftermath of an ACS. The term dual antiplatelet therapy (DAPT) refers to addition of P2Y12 inhibitor (thienopyridine - Clopidogrel or prasugrel) or (cyclopentyltriazolopyramidine or ticagrelol) to aspirin. DAPT includes aspirin 75mg QD with Clopidogrel 75mg QD or ticagrelol 90mg BiD or prasugrel 10mg QD in order to avoid complications of thrombosis after coronary stent implantation and prevent coronary atherothrombotic events [4-5]. Whilst DAPT is useful, the tradeoff is the increased risk of bleeding - particularly GI bleeding which is more pronounced in the elderly (over 80s). All the trials quoted above used DAPT for a period of 12 months and this has been incorporated in current international guidelines on the management of ACS. There is new emerging data suggesting that in a small subset of high risk individuals, prolonging the duration of some DAPT regimes (particularly using lower dose Ticagrelor) beyond the 12 month period may be beneficial but this has not yet been universally `accepted nor incorporated in guidelines [6-8]. Review of clinical practice indicates that, frequently patients are left on DAPT for much longer than the prescribed 12 months without review and end up on these drugs for a much longer period than originally intended, as a result of oversight. We designed this study to objectively evaluate current practice of DAPT prescription and to see if a rigorous scheme to ensure review of medications at 12 months completion will reduce the risk of inadvertent prolonged use of DAPT therapy.

Materials and methods

All Patients above 18yrs of age and are taking DAPT for prior ACS that was commenced minimum of 12 months prior to enrolment, excluding those Patients who were unwilling to take part in the study for a period of 6 months.

The patient consent is taken in PCF (patient consent form) following explanation about the project and its intention. A series of questions were asked to know about their disease status and about their dual antiplatelet use.

In addition to the above questions - other details such as laboratory values, other medications use was noted in a predefined data collection form (DCF). Hemoglobin count at the time of commencement of DAPT, and there after every six months until discontinuation of DAPT was noted to detect any internal bleeding that could lead to drop in Hb. Creatinine values were used to check kidney function since antiplatelet agents could cause kidney damage. Other medications that patient were taking for co-morbid conditions were checked to verify whether any of them, besides DAPT - is capable of causing bleeding.

These charts were also analyzed with the current prescription guidelines for DAPT according to AMA/AHA or ECC guidelines. Drug interactions capable of enhancing bleeding were verified by - Micromedex, Medscape, drugs.com, Reference books and original research articles were also used as a tool to review prescription and case charts.

Patient's history about adverse bleeding events like Gastro-intestinal irritation, GI bleed for which they had to undergo endoscopy, black stools, and other side effects were noted.

Sample size:

- Around 70-80% of patients commenced on DAPT tend to remain on the drug beyond 12-month period often without prescription review.
- Considering patient's availability and other aspects, we believe a sample size of 75 patients will provide a meaningful insight into this practice. The sample size was not calculated on any statistics but was considered ideally to recruit 100 patients based on availability of patients. But couldn't reach the target due to COVID-19 issues.

Results

TABLE 1: Patient age distribution and duration of DAPT use

SI NO	AGE	DIAGNOSIS	FOR1 YEAR	FOR > 1 YEAR
1	29-38	ACS, Hbs Ag +ve	1	0
2	39-48	ACS, HTN,DM,CVA,LRTI	4	11
3	49-58	ACS,HTN,DM	3	13
4	59-68	ACS,DM.HTN,CKD,COPD, BPH, OSA, ASTHAMA.	4	15
5	69-78	ACS,DM,HTN,AKI,RTA, HYPOTHYROIDISM	5	14
6.	79-88	ACS,DM,HTN,RV+ve	1	5
TOTAL			18	57

The main aim of the study was to determine whether DAPT guidelines are being followed or not, and the duration of DAPT therapy. All patients included in the study were asked about

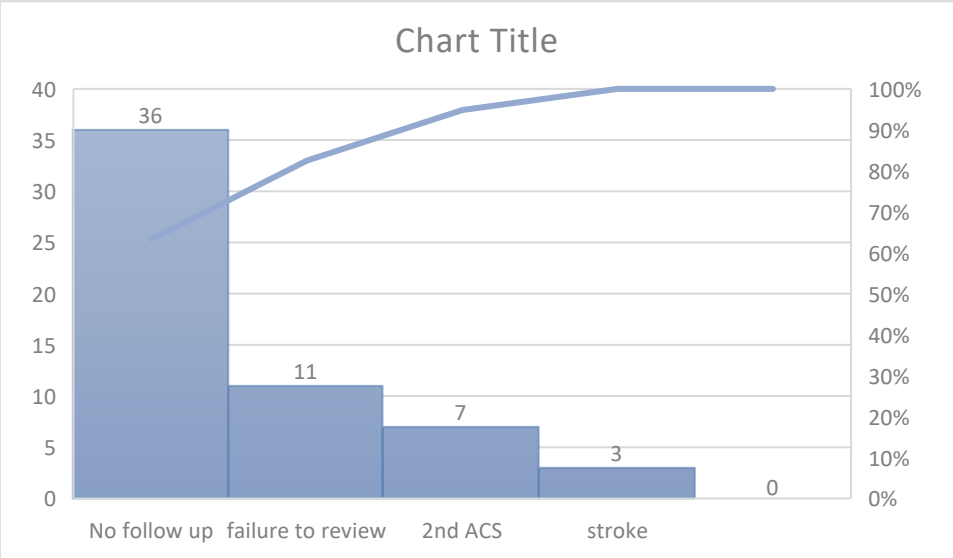
the duration they have been taking dual antiplatelet therapy, and were divided into two groups - patients taking DAPT for 1 year and those who have taken more than 1 year, based on their age group. Out of 75 patients -18 patients had taken for 1 year of duration whereas rest 57 had taken it for more than 1 year.

Patients who took DAPT for more than 1 year were further categorized into 4 groups as mentioned in graph number 1.

- patients who had stroke
- patients who had 2nd episode of ACS
- patients who did not come for follow up regularly
- Clinician's failure to review the prescription

Patients who were left on prolonged therapy for various reasons were further divided into four different subgroups. According to the guidelines patients remain on prolonged duration of DAPT for following reasons only – patients who had second episode of ACS within a year or had a stroke (needing DAPT for anticoagulation management) or any other medical needs besides those specified.

Figure 1: Distribution into sub groups and number of patients who took DAPT for More than one year



The main objective of the study was to check whether adherence to guidelines on prescription of DAPT following ACS is being followed or not. Data like number of patients who took DAPT for 1 year, patients who had taken prolonged therapy due to underlined definable reasons and their follow up were considered and evaluated to check for guidelines adherence. Data revealed that so far out of 75 prescriptions only 23 patients prescriptions met the guidelines.

Dual antiplatelet is combination of aspirin with other P2Y12 inhibitors like (Clopidogrel, ticagrelor, and prasugrel). In this study - it was noticed that aspirin in combination with Clopidogrel was used more frequently (57 patients) when compared to aspirin with ticagrelor (7 patients) and aspirin with prasugrel (11 patient). As Clopidogrel is

known to have more adverse effects compared to the other two drugs, it would have been preferable to choose prasugrel and ticagrelor for better therapeutic outcome. Clopidogrel is cheaper and one of the oldest drugs. Some prescribers do not want to change the practice as many believe that it works well.

Figure 2: Total percentage of cases who followed guidelines and who did not follow guidelines

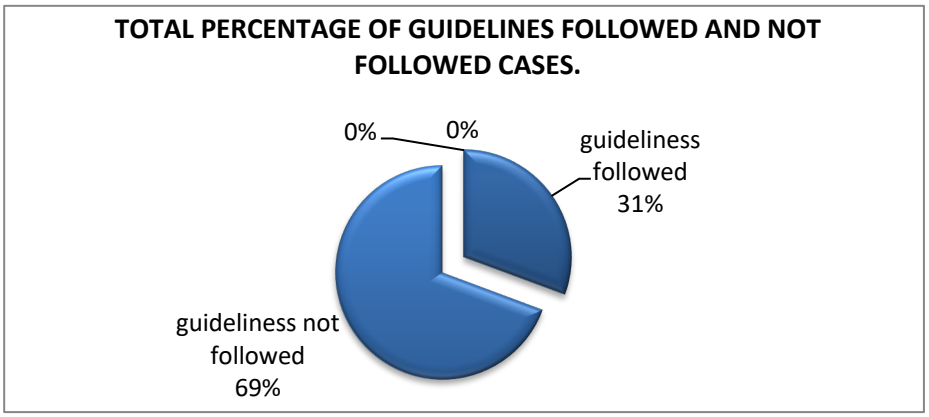


TABLE 2: Number of patients who experienced ADR in each group

Adherence (No of patients)		Non – Adherence (No of patients)		
Took Medication Regularly	Experienced Adverse Effect	Irregular To Medications		Experienced Adverse Effects
		Irregular	Discontinued	
55	16	16	9	4

While answering the secondary objective of the study, checking for bleeding episodes – we found that many patients had stopped taking the drugs on their own because of severe GI problem caused by these agents. Hence, data on adherence to medication was collected to determine the extent of severe GI problems - such as GI irritation, black colored stools experienced by these patients and others who discontinued the drug without any specific reason.

Analysis of these data revealed some interesting facts - out of 75 patients, 20 patients who had experienced ADR, only 2 had taken DAPT for 1 year & the rest 18 had taken DAPT for >1 year. Of the 55 patients who had taken medication as directed, 16 patients experienced ADR. While out of other 25 patients - 16 were irregular and 9 had discontinued, in this population 4 patients had adverse effect.

No bleeding events recorded in the age groups between 18-38. In patient's reporting adverse

events, main adverse events included - GI bleed, GI irritation, Gastritis, and black stools. When investigating underlying reasons behind them - poor adherence to medication, unnecessary usage of medication and co – morbid condition contributed to bleeding events.

Discussion

It is a retrospective observational study, dedicated to compare short (12months) versus long duration (>12months) of dual antiplatelet therapy (DAPT) after primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI), to non ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA).

Current guidelines recommend DAPT for at least 12 months for patients with acute coronary syndrome and for 6 months after implantation of stent in patients with stable ischemic heart disease [9-10].

Our primary investigation was between DAPT duration and long-term clinical outcomes in patients undergoing PCI diagnosed as ACS. Preceded by index procedure, long term DAPT (>12 months) was associated with increased risk of MI, stroke and other thrombosis problems with DAPT <12 months. Although it is observational study, this is the one report that specifically addressed the issue of DAPT duration in patients undergoing PCI [11].

Significant and meaningful numerical differences was observed with endpoints like all-cause mortality, any myocardial infarction, any, stent thrombosis, stroke, or thrombolysis in myocardial infarction[12]. It showed high risk of event occurrence in long term DAPT, but patients who took DAPT for 12 months remain at a low risk for further events and remained event free, whereas 14 patients out of 75 had further ischemic and cardiovascular events when taking this medication for longer duration. Our findings are in line with those of other randomised studies which compared 12 versus long term of DAPT [12-13].

The issue about duration of DAPT is of major reasonable clinical importance to be studied, as there are increase number of case/patients with bifurcation lesions who need PCI and take DAPT. We investigated whether long term DAPT was associated with improved long-term clinical outcomes accordingly [11]. We could prove the fact that risk is higher in long term DAPT use but extent of risk and percentage of risk needs to be calculated.

Major bleeding is an adverse event that is strongly related to mortality [14]. Recent studies have even shown that bleeding is a stronger predictor of non-cardiovascular mortality than thromboembolic and ischaemic event [14]. Prolonged DAPT not only had shown impact on mortality in the Pegasus and OPTIDUAL trials, [15-16] but also it is associated with a higher all-cause mortality in the DAPT trial. [17]

The major secondary objective of the study is to check for bleeding events, and our study shows that prolonged duration of DAPT >12 months is associated with major adverse bleeding events when compared to <12 months of DAPT. The bleeding episodes observed are GI bleed, RUT positive, gastritis, black stools from which haemoglobin count declined in many patients and altered creatinine levels.

One more observation from the study was longer duration of DAPT not only increases drug costs by unnecessary drug intake also increased expenditure for endoscopy, and treatment of bleeding episodes. Our study is line with other CT (clinical trials) done so far [15-18].

Patient education plays a key role in both patient's physical and mental health behaviour. 90% of patients with ACS have co morbid conditions like DM, HTN and hence counselling patient about their disease and their drugs becomes even more important. A good and comprehensive counselling not only educates the patient but also enhances communication between patients and educator which makes patient more comfortable to clarify their doubts.[19,20] In our study we have educated patients about their current disease status, drugs that they have been taking, its uses, side effects, and doses and how to take drugs and most importantly the intention of giving two antiplatelet and importance of discontinuing one of it for their benefit for which follow up is a must.

Conclusion

For more than ten years DAPT is being studied opening opportunities for a thorough and evidence based treatment, yet in department of cardiology it is still in the stage of debate for optimal duration of DAPT after coronary stenting.

The interpretation of the current evidence suggest that, while longer DAPT duration is associated with a reduction of non-fatal ischemic events, but in turn it increases the adverse event of major bleeding at the same time. Though guidelines specify 12-months of duration, some patients require longer duration - like in case of 'stroke' or any other ACS events and even shorter duration (6-months) is recommended in case of accompanying bleeding events. For that reason, DAPT duration should be individualized for each individual patient, taking into account the baseline ischemic and bleeding risk status. Therefore, risk profile may change for each patient during every follow up and risk score may be helpful in decision making process. Hence, an individualized approach is mandatory when deciding optimal duration of DAPT for each patient so as to get the maximum benefits with minimum adverse effects.

Limitations

- Time period considerations:

1. In context to follow up – 6-8 months of follow up is considered as 6 month.
2. Time period of 8 months to 14 months is considered as 1 year follow up.

- This study is particularly limited to bleeding events and neither bleeding risk nor has any scale to measure risk is used.
- Since the study is retrospective observational, data about adherence to medication was that reported by the patient. So chances of bias could not be eliminated.

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