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Effect Of Stopping Antiplatelet Therapy On Stent Thrombosis In Patients With Coronary Stents

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1. Abstract

1.1. Background:
In recent years, the introduction of drug-eluting stents(DES) in PCIs (Percutaneous Coronary Interventions) for coronary revascularization has beenone of the major breakthroughs in interventional procedures since it addressed the issue of re-stenosis.However, late safety outcome of this is not wellestablished. Late and very late stent thrombosis is associated with major adverse cardiac events.

1.2. Methods:
This prospective and retrospective observational study with minimal exclusion criteria was conducted in a tertiary care centre in New Delhi, India with the aim to determine the incidence of possible coronary stent thrombosis in patients with coronary stents while he is off all antiplatelet therapy. Patients post PTCA (Percutaneous Transluminal Coronary Angioplasty), in whom antiplatelet therapy was withheld due to a cerebrovascular bleed or gastrointestinal bleed were included and observed for clinical symptoms, rise in cardiac enzymes, ECG and ECHO findings, if any, as indicators of possible stent thrombosis.

1.3. Results:
A total of 1971 consecutive patients, admitted with cerebrovascular/ gastrointestinal bleed from were screened. Out of these, 50 (2.5%) patients had undergone PTCA and were on antiplatelet agents. 4 (8%) patients had possible stent thrombosis; 1 with a bare metal stent (BMS), and 3 with DES. 3 cases were of very late stent thrombosis, i.e. >12 months, while one patient experienced late stent stenosis (>30 days). The mean duration from the time of stopping antiplatelet agents to development of stent thrombosis was 3.25 days; no one developed stent thrombosis after 5 days.

1.4. Conclusions:
The incidence of DES thrombosis is infrequent; case reports and observational studies describe an overall rate of <1.5%. However, in this subset, it was 8%. The high incidence of very late stent thrombosis is expected to extensively curb the use of DESs in routine clinical practice. However, more data needs to be collected and scrutinized and a revision of the guidelines of duration of antiplatelet therapy is in order.

2. Keywords:
DAPT (Dual Antiplatelet therapy), DES (Drug-eluting stents), LAST (Late Stent Thrombosis), VLST (Very late Stent thrombosis)

The use of drug-eluting stents (DES) can reduce restenosis and target vessel revascularization by >70% compared with bare metal stents (BMS). [1,2] However, the polymer coatings and other aspects of DES may result in increased thrombogenicity compared with BMS.[3] Late angiographic stent thrombosis (LAST >1 y) continues to occur with a drug-eluting stent, while it is exceedingly rare for a bare metal stent. The biggest factor contributing to stent thrombosis is interruption of antiplatelet therapy. Current guidelines recommend a minimum of 1 year of dual antiplatelet therapy for drug-eluting stents and a month for bare metal stents.[4] Drug-eluting stents take longer to endothelialize on the coronary vessel wall than bare metal stents and discontinuing dual antiplatelet therapy may expose these patients to an increased risk for stent thrombosis over time. The present study was conducted to determine the incidence of stent thrombosis in patients in whom antiplatelet therapy was stopped due to occurrence of intracranial or gastrointestinal hemorrhage.

3. Methods

3.1. Study Design
A purely observational study, it was conducted in Indraprastha Apollo hospital, a tertiary care hospital, located in New Delhi, India. It is both a retrospective and prospective study; retrospective from March 2005 and prospective from September 2008 upto June 2010.

3.2. Selection Of Study Patients
The medical records of serial patients above 18 yrs of age, hospitalized between March 2005 and June 2010 with intracranial or gastrointestinal hemorrhage were screened. Out of a total number of 1971 such patients

screened, 50 had prior history of PTCA and 39 were on DAPT. The latter was discontinued in all the patients by the treating physician/surgeon with the occurrence of bleed. Since this was an observational study, the author had no role in discontinuing the antiplatelet therapy.

3.3. Follow-Up And Assessment Of End-Points

Data of the selected patients was collected, including date of stenting, make and characteristics of stent deployed and details of antiplatelet therapy. Note was made of any comorbid factors. Baseline ECG, ECHO and platelet count reports of each patient were noted. The patient was then followed-up for the time period during which the therapy was discontinued. The ARC criteria for stent thrombosis were used for diagnosis of possible stent thrombosis. The patient was observed for any clinical symptoms of CAD, viz. chest pain, palpitations or dyspnoea. If the patient was unable to report any of the above clinical symptoms or in the presence of any the above, any fresh ECG or ECHO change or rise in cardiac biomarkers (CK-MB, Trop T and Trop I) was taken as a criterion for possible stent thrombosis. Angiographic evidence was not considered as many patients were not in a general condition to undergo the same. After the patients were discharged, they were followed-up with telephonic conversations and interviews. The data was collected, tabulated and statistically evaluated, using Chi-square test and independent sample t-Test. It was analyzed for calculation of incidence and outcome of coronary stent thrombosis considering associated patient and stent characteristics. The author vouches for the accuracy and authenticity of the data and attests to the fidelity of the report to the study protocol.

4. Results

4.1. Demographical characteristics of the patients:

58% of the patients were admitted with a cerebrovascular bleed, while 42% had a gastrointestinal bleed. The average age of the patients was 66.3 years, with a minimum of 46 and maximum of 84 years. 37 patients (74%) were males and 13 patients (26%) were females. 90% of the patients were hypertensive, 46% were diabetic, and 16% had some degree of renal failure and/or were on dialysis. 20% had LV dysfunction (Table 1). Blood was transfused in 23 (46%) of the patients. The number of units transfused ranged from 1 to 5. No patient qualified for massive hemorrhage or massive transfusion. [6] However, 74% of the patients, including the patients who developed stent thrombosis received more than 2 units of blood; this was found to be statistically significant (p=0.008) (Table 1).

Table 1: Baseline characteristics of patients included (n=50)

Characteristic		No. of patients (%)
Type of bleed	Cerebrovascular	29 (58%)
	Gastrointestinal	21 (42%)
Age (yrs)	Mean	66.3
	Minimum	46
	Maximum	84
Male sex (% of patients)		37 (74%)
Risk factors (% of patients)		
- Hypertension		45 (90%)
- Diabetes		23 (46%)
- Dyslipidemia		03 (06%)
- LV dysfunction		10 (20%)
- Intraluminal clot		01 (02%)
- Renal failure		08 (16%)
Blood transfusion		23 (46%)
- < 2 units		06 (26%)
- ≥ 2 units		17 (74%)

Table 1: Baseline characteristics of patients included (n=50) (contd.)

Characteristic		No. of patients (%)
Antiplatelet therapy		
- Patients on DAPT		39 (78%)
- Patients on single APA		08 (16%)
- Patients not on APAs		03 (06%)
Vessels affected		
- Multivessel		09 (26%)
- Single vessel		29 (76%)
- LAD		16 (52%)
- LCx		06 (19%)
- RCA		09 (29%)
Time from stenting to bleed (when DAPT stopped) (months)		33.2
Duration for which DAPT stopped (days)	Mean	23.2
	Minimum	1
	Maximum	243

DAPT- Dual antiplatelet therapy, APA- Antiplatelet agent
LAD- Left anterior descending, LCx- Left circumflex artery, RCA- Right coronary artery

4.2. Antiplatelet therapy and Stent characteristics:

Of the 50 patients, 39 (78%) were on DAPT, 8 (16%) were on a single antiplatelet agent, while 3 (6%) were not on any antiplatelet therapy. The mean duration from the time of PTCA and stenting to the development of the bleed was 33.2 months. Antiplatelet therapy was withheld in the patients for a mean duration of 23 days; the minimum duration was 1 day and maximum was 243 days (Table 2).

Table 2: Stent characteristics of patients included (n=38)

Type of stent	Polymer in stent	No. of patients (%)
Multivessel	--	09 (24)
Singlevessel	--	29 (76)
BMS	--	14 (33)

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DES	--	28 (67)
- Sirolimus		14 (50)
--Cypher	Fixed (PEVA, PBMA)	10
--ProNOVA	Fixed (Biocompatible)	4
--Yukon	Nil	3
- Paclitaxel		04 (14.3)
--Taxcor	Biodegradable	2
--Infinnium	Biodegradable	1
--Axxion	Biodegradable	1
- Everolimus		01 (03.6)
--Xience	Fixed (PBMA, PVDF-HFP)	1
- Zotarolimus		04 (14.3)
--Endeavor	Fixed (Phosphorylcholine)	1
- Mycophenolic Acid		01 (03.6)
--Duraflex	Fixed (Biocompatible)	1

BMS- Bare-metal stent, DES- Drug-eluting stent
PEVA- Polyethylene-co-vinyl acetate, PBMA- Poly n-butyl methacrylate, PVDF-HFP- Poly-vinylidene fluoride and hexafluoropropylene

Of the 39 patients who were on DAPT prior to onset of bleed, only 13 patients were re-started on it by the treating physician/surgeon. A single antiplatelet agent was re-started in 11 patients. 7 patients succumbed to their illness and 8 patients did not re-start any kind of antiplatelet agents. Stent characteristics were available in 38 patients. 29 (76%) of these had single vessel disease, while 9 (24%) had stenting to multiple vessels. 14 patients had Bare-metal stents (BMS) and 42 had DESs. Of the latter, 14 were Sirolimus-eluting (Cypher, ProNOVA), 3 were Sirolimus-coated (Yukon), 4 each were Paclitaxel (Infinnium, Taxcor and Axxion) and Zotarolimus-eluting (Endeavor), and 1 each were Everolimus(Xience) and Mycophenolic acid-eluting (Duraflex) (Table 3).

Table 3: Characteristics of patients who developed Stent thrombosis (n=4)

Characteristic	**No. of patients (%)**	
Type of bleed	Cerebrovascular	0
Gastrointestinal		04 (100%)
Age (yrs)	Mean	68
	Minimum	55
	Maximum	78
Male sex (% of patients)	03 (75%)	
Risk factors (% of patients)		
- Hypertension	03 (75%)	
- Diabetes	03 (75%)	
- Dyslipidemia	0	
- LV dysfunction	02 (50%)	
- Intraluminal clot	0	
- Renal failure	01 (25%)	
Blood transfusion	04 (100%)	
- < 2 units	0	
- ≥ 2 units	04 (100%)	

4.3. Stent thrombosis:

4 of the 50 (8%) patients were observed to have features of possible stent thrombosis. 3 patients were admitted with upper GI bleed and 1 with lower GI bleed; 3 patients were hypertensive, 2 had LV dysfunction, 2 were diabetic, and 1 was on hemodialysis for End-stage renal disease. 3 of the 4 patient were on DAPT prior to the onset of bleed, while one patient was on a single antiplatelet agent (Table 4).

Table 4: Characteristics of patients who developed Stent thrombosis (n=4)

Characteristic		**No. of patients / % of patients**
Antiplatelet therapy		
- Patients on DAPT		03 (75%)
- Patients on single APA		01 (25%)
Vessels affected		
- Multivessel		02 (50%)
- Single vessel		02 (50%)
- LAD		03 (75%)
- LCx		02 (50%)
- RCA		01 (25%)
Average time from stenting to bleed (when DAPT stopped) (months)		54
Time from stopping DAPT and development of Stent thrombosis (days)	Mean	3.25
	Minimum	2
	Maximum	5
Duration for which APA stopped (days)	Mean	23
	Minimum	1
	Maximum	67

DAPT- Dual antiplatelet therapy, APA- Antiplatelet agent
LAD- Left anterior descending, LCx- Left circumflex artery, RCA- Right coronary artery

2 patients had multivessel disease and multivessel stenting. 1 patient had a BMS in situ; the rest had 1 stent each Sirolimus-eluting (ProNOVA), Paclitaxel-eluting (Infinnium) and Everolimus-eluting (Xience). The mean duration from the time of stenting of the positive cases was 54.5 months. Thus 3 cases were of very late stent thrombosis, i.e. >12 months, while one patient experienced late stent stenosis (>30 days). Interestingly, the patient with BMS had VLST. The mean duration of development of stent thrombosis from the time of stopping therapy was 3.25 days; the

maximum duration was 5 days (Table 5).

Table 5: Stent characteristics of patients who developed Stent thrombosis (n=4)

Type of stent	Polymer in stent	No. of patients (%)
Multivessel	--	02 (50)
Singlevessel	--	02 (50)
BMS	--	01 (25)
DES	--	03 (75)
- Sirolimus		01 (33.3)
--ProNOVA	Fixed (Biocompatible)	1
- Paclitaxel		01 (33.3)
--Infinnium	Biodegradable	1
- Everolimus		01 (33.3)
--Xience	Fixed (PBMA, PVDF-HFP)	01 (33.3)

BMS- Bare-metal stent, DES- Drug-eluting stent
PBMA- Poly n-butyl methacrylate, PVDF-HFP- Poly-vinylidene fluoride and hexafluoropropylene

5. Discussion

Aspirin or acetylsalicylic acid is the most widely prescribed antiplatelet drug since the first randomized trial showed a link between aspirin and reduced risk of myocardial infarction. [7] However, 10% to 20% of patients treated with aspirin following an arterial thrombotic event subsequently have a further arterial thrombotic event. [8,9] Over the past decade, a large body of evidence has established the usefulness of clopidogrel in a number of clinical settings. Since the mechanisms of action of these two groups of drugs are complementary, the combination may decrease clot formation over either agent alone. Furthermore, resistance to the effects of each agent has been well reported, but resistance to both agents in a given patient should be less frequent.[10] Despite the initial enthusiasm, some complications were clearly associated with Percutaneous coronary intervention; restenosis and thrombosis being the major problems to deal with. In the early nineties, bare metal stents (BMS) were introduced to avoid the so called “elastic recoil of the artery” leading to restenosis. Stent implantation, inherently a thrombogenic procedure, initiates a complex interaction between the blood components and the metal surface of the stent, which includes the deposition of protein; the activation of platelets, the complement system, and coagulation factors; and the eventual propagation of thrombi over the surface of the stent11 and the establishment of a confluent endothelial monolayer. Drug-eluting stents have been extensively tested in a wide spectrum of coronary lesions, all of which have demonstrated significant reductions in restenosis and target lesion revascularization rates when compared with bare metal stents. DES implantation resulted in a rate of restenosis below 10% (compared to 30% observed after bare metal stents implantation)[11,12], with a similar rate of instent thrombosis. [13,14] However some initial warns were raised by few groups suggesting that DES do not undergo a complete re-endothelization.[15,16] The introduction of DAPT, further decreased the rate of stent thrombosis, being currently a rare complication occurring in less than 1% of the procedures.[17]

In September 2006, surfaced the reports of the unexpected high rate of late (>30 days after stent deployment) and especially very late in-stent thrombosis (> 12 months from stent implantation) in DES compared to bare metal stents.[18,19] Further cause for concern came from the Basel Stent Cost-effectiveness Trial-Late Thrombotic Events (BASKET-LATE) data, which showed that among 746 DES or BMS patients who had dual antiplatelet therapy discontinued after the first six months, the rate of cardiac death or non-fatal MI over the following year was higher in patients with DES than BMS (4.9% versus 1.3%; $p = 0.01$), and that this was likely to be related to late stent thrombosis, which presented as death or MI in 88% of cases.[20]The new definition for stent thrombosis presented by the Academic Research Consortium (ARC) at the TCT (Transcatheter Cardiovascular Therapeutics) in October 2006 was designed to eliminate variability in the definitions across various drug-eluting-stent trials, where it has previously been difficult, if not impossible, to compare the true rates of late stent thrombosis across different trials. [21] Stent thrombosis was categorized as acute (within 24 hours after the procedure), subacute (1 to 30 days post procedure) or late (>30 days) thrombotic event. It is thus now apparent that late thrombosis seems to be associated more frequently with DES, and events have been reported to occur up to 4 years after initial stent deployment. Various comparative studies between BMSs and DESs and between the 4 types of DESs in use now, viz the sirolimus-eluting stent (SES) (Cypher), the paclitaxel-eluting stent (PES) (Taxus), and the newer generation zotarolimus-eluting stent (ZES) (Endeavor) and everolimus-eluting stent (EES) (Xience V), have been done and new data has come to light.

For example, when data were pooled from eight pivotal randomized trials of sirolimus-eluting stents (RAVEL, SIRIUS, E-SIRIUS, and CSIRIUS) and paclitaxel-eluting stents (TAXUS II, IV, V and VI), there were no significant differences between the 9-month incidences of stent thrombosis associated with DESs and BMSs. [22] Beyond 9 months, however, and with follow-up extended to 3 years, stent thrombosis continues to occur in patients treated with a DES, such that the overall long-term incidence is twice that associated with BMSs (1.2% versus 0.6%).[23,24] Studies comparing sirolimus-eluting stents and paclitaxel-eluting stents reported no significant difference in the the rates of angiographic restenosis and incidence of adverse cardiac events between the two devices and, more important, the need for reintervention in the treated lesion.[25,26]The two-center Randomized Comparison of Sirolimus with Paclitaxel Eluting Stents for Coronary Revascularization of All Comers (SIRTAX)[27] reported better outcomes with sirolimus-eluting stents than with paclitaxel-eluting stents; 6.2 percent of major adverse cardiac events at nine months in the sirolimus-stent group and 10.8 percent in the paclitaxel-stent group. The newer generation zotarolimus-eluting stent and everolimus-eluting stent have improved deliverability, thinner struts, thinner polymer layer, and may have clinical advantages over sirolimus-eluting and paclitaxel-eluting stents. At 13 months, no differences in efficacy and safety between

the two types of stents on the basis of prospectively adjudicated end points endorsed by the Food and Drug Administration were noted.[28]

The results of our observational study do not conform to the trend shown by any of the available series in the recent or remote past. We had a very well-defined high-risk subset of patients and observed them for a well-defined time period. Stent thrombosis in this specific study population (with cerebrovascular and/or gastrointestinal bleeds) has not been studied before and the rate (8%) is much higher than in any other series. We also report the incidence of VLST (165 months after stenting), in a patient with BMS. Initial analyses had suggested that late bare metal stent thrombosis is very infrequent on aspirin monotherapy.[29,30] Subsequently, some studies revealed that individuals with bare metal stents on chronic aspirin therapy are still at risk for late thrombotic events when total antiplatelet therapy is discontinued.[31,32] In our study as well, stopping antiplatelet therapy was the key; however, it is important to note that no patient developed stent thrombosis after 5 days of stopping therapy. Similarly, patients who were not on APA prior to onset of bleed or in whom the therapy was interrupted for more than 5 days also did not develop stent thrombosis. What kind of factors, whether the development of bleed, presence of multivessel stents and comorbidities like Type 2 diabetes and renal failure alter the thrombogenicity and due to an interplay of inflammatory biomarkers lead to stent thrombosis is not known. Although no patient qualified for massive bleed or transfusion, and there was no evidence of any coagulopathy or platelet dysfunction, the significance of thrombosis developing in those receiving more than two units of blood cannot be overlooked.

Further research on a molecular level needs to be carried out in this regard to determine the presence of any reversible factors for future practices and therapies. Even though endothelialization of the stent has been documented to occur in a fixed time period, antiplatelet therapy needs to be continued indefinitely, since hitherto unknown factors might be associated with impaired endothelial function. Our findings suggest that there may not be a safe period for drug-eluting stents after which clopidogrel can safely be stopped. Conversely, 6% of the patients who were observed in our study were not on any antiplatelet agents. Should these patients be re-started on antiplatelets once it has indefinitely been stopped, especially if they have no evidence of stent thrombosis? The criteria for stopping of antiplatelets prior to elective surgery also needs to be revised, and maybe decreased to 5days, instead of 7 days, as is the general practice.The inability to document definite stent thrombosis due to the presence of overt bleed and poor general condition of the patients was a drawback of this study. The DES represents an exciting area of breakthrough technology, which has generated an enormous literature in parallel with widespread use in a short period of time. Interaction of innovative stent platforms, polymers, and molecular entities, as well as pharmaceutical adjuncts such as dual antiplatelet therapy, present a unique degree of complexity for systematic ongoing evaluation of these devices, their optimal use, and their real safety and performance results. The acceptance of drug-eluting stents has followed the same course as all newly introduced techniques, with the initial period of overblown enthusiasm quickly followed by a period of intellectual reproach. The development of bioabsorbable stents and polymers is the new direction, towards which this new era is headed.

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