Scope of Bare Metal Stent in the Era of a Potent Newer Anti-platelet Drug 'Ticagrelor'- Single Centre Observational Study (SOBEAT STUDY)

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2. Key words

1. Abstract

1.1. Background: Despite overwhelming data supporting the use of ticagrelor as an alternate potent antiplatelet agent in Percutaneous Intervention (PCI) with Drug Eluting Stent (DES), to the best of our knowledge there is no study which assessed safety and efficacy of ticagrelor in PCI with Bare Metal Stent (BMS). We aimed to study ticagrelor in cases of PCI with BMS in terms of primary (major adverse cardiac events composite of myocardial infarction, unplanned revascularization and stroke) and secondary (in-stent restenosis, re-hospitalisation, minor bleed and drug switch) end points.

1.2. Methodology: This is a prospective, single center, open label observational study conducted between Feb 2016 to July 2016 at post graduate department of cardiology JLN medical college, Ajmer in patients undergoing primary or elective PCI. Total 276 patients were included in the study. Ticagrelor was given in recommended doses with aspirin 75 mg once daily. Procedure was done by upper arm access.

1.3. Results: Major adverse cardiovascular events occurred at 6 month in 11 patients (0.05%). Quantitative angiography revealed the different values of BMS stented lesion as minimal luminal diameter (mm), before procedure, after procedure, and at 6 month were 0.94 ± 0.31, 2.43 ± 0.41, and 2.12 ± 0.49 respectively, in our study. The trial of the BMS with dual anti-platelets ticagrelor with aspirin reported an average late loss well below the expected historical range, where mean instant late loss is -0.31-/+0.33 mm which corresponded to a Binary angiographic restenosis rate of 8.8%. Total 78 (28.0%) patients switched out of 276 study persons. Switch was more common in people of low socio-economic status particularly in non-educated patients.

1.4. Conclusion

This study results offer more freedom to clinicians to select the either BMS or DES if patients economic status allow to use newer potent antiplatelet ticagrelor to be added on top of aspirin for patients with PCI.

3. Introduction

The rationale for the development of DES was the high rate of in-stent restenosis and target lesion revascularization associated with early bare metalstents [1,23]. In contrast, several recent drug-eluting stent (DES) trials have demonstrated a breakthrough in the reduction of late restenosis compared with bare metal stents, with a consistent incidence of BAR and TLR below 10%.[2]. DES have become the stents of choice, recommended in guidelines for almost all indications [3,23].

But in the current era, when a bucket of newer anti-platelets are available in the markets, still we are ignorant about the effect of newer antiplatelet on post deployment event of older bare metal stents. Still we arein search for answer of long term question,can newer anti-platelets have some different effect on older bare

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metal stents or not?

There are limited studies which compared BMS versus DES with the older dual anti-platelets but to the best of our knowledge, there is no any study till date has evaluated the restenosis rate with dual anti-platelets containing the latest antiplatelet 'Ticagrelor'. Ticagrelor is newer and relatively more potent but costly than the other available ADPri in market. So there are high chances of switching of ADPri after post deployment. In-hospital AD-Priswitching has been previously described [4,5], (t) but switching in the post stent deployment setting is not well characterized . Nevertheless, the safety of switching is not well studied, because randomized clinical trials typically involve blinded study treatments that continue for the duration of the study. Switching from Ticagrelor is known to occur for a variety of reasons including adverse events, cost, and patient or provider preference. So we also sought to describe the incidence and patterns of post-discharge ticagrelor switching among patients with post percutaneous coronary intervention. We also observed different adverse events and tabulated them during follow up of study.

Journey of angiographic restenosis following various angioplasty and there remedy in clinical cardiology has been traditionally complex since very early.

Every treated lesion undergoes some degree of late loss but fortunately late loss usually negates only part (roughly less than half) of the acute gain,so that a long term net gain in lumen diameter results with alleviation of myocardial ischemia. In fact,there tends to be a roughly linearrelationship between the acute gain in lumen diameter caused by the interventions and late loss in lumen diameter (caused by the proliferative and fibrotic reaction of the artery during the healing phase) with a slope (the loss index) of roughly 0.5 for the most interventions. There has been a relentless search for drugs or procedural variations that could decrease the late loss index. Although manipulating procedure-related variables (such as duration of conventional balloon inflation) has been unrewarding and trials of numerous system drug regimens (aspirin, nifedipine, ticlopidine, steroids, prolonged heparin administration, fish oil ,mevinolin, ketanserin etc.) have been shown little or no beneficial effect against restenosis, two modalities (brachytherapy and drug eluting stents) have shown important benefits against late loss and consequently, restenosis [6].

Multiple questions were in our mind during planning of this study,are newer anti-plateletssufficientto prevent restenosis in BMS if yes, then how much and upto what extent?

4.Methods

4.1. Study Population

This isprospective, single canter open label observational pilot study in patients undergoing primary as well as elective PCI. Total 276 patients of stable angina or acute coronary syndromeincluded in the study. Ticagrelor was given in recommended doses inall study patients along with aspirin 75 mg once daily. Bare metal stents were deployed in every patients of study by default.

4.2. Data Collection

Baseline clinical characteristics, demographics, medical history, in-hospital medications, laboratory values, procedural data, and discharge medications were abstracted from the medical record or patient interviews into the study data collection from using standardized data elements and definitions. Data was screened upon entry; only those data meeting predetermined criteria for completeness and accuracy were entered in the database for analysis.

Patients who were discharged only on ticagrelor and aspirin with Bare metal stent deployment were included in our study. Cost of Bare metal stents deployed in patients were fully covered within the healthcare system of Rajasthan government.

4.3. Definitions

Major adverse cardiovascular events (MACE) were defined as a composite of MI, unplanned revascularization, or stroke. Stent thrombosis was defined according to Academic Research Consortium criteria [7]. Bleeding events were defined using the GUSTO criteria (moderate or severe). Late loss was defined as the MLD immediately after the procedure minus the MLD at 6-month follow-up. Percentage diameter stenos is was defined as [1-(MLD/reference vessel diameter) x 100]. BAR (binary angiographic restenosis) was defined as a>50% diameter stenosis at follow-up. Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by$\geq$20%. The target lesion was defined as the stented segment plus the 5-mm segments proximal and distal to the stented segment. Target lesion revascularisationdefined as clinically driven revascularization of the target lesion by 6 months of follow-up and was adjudicated by an independent Clinical Events Committee. A switch was defined as a change to a different ADPri categorized into groups (clopidogrel, or prasugrel,) based on their discharge medication.

The traditional angiographic variables, late MLD and percentage diameter stenosis, are powerful continuous measures, but late loss (post procedural MLD minus 6-month MLD) has the unique ability to distinguish the magnitude of late intimal re-narrowing from baseline and procedural variables (reference vessel diameter and residual stenosis).

4.4. Inclusion Criteria

1 .Patients between 18 and 75 years old.

2. Patients planned for PCIof intermediate or high-risk ACS (USA, NSTEMI and STEMI) and agreeing toparticipate in the study .

Informed written consent were taken from all patients participating in study**.** Both the drug given to thepatients1 to 8 hours before the procedure. Mobile number of patients werecollected for further information on urgent basis. PCI was done through the upper arm access (radial and ulnar) until contraindicated .

4.5. Exclusion Criteria

1. NSTEMI/STEMI medically managed or intended for surgery after PCI

2. Cardiogenic shock

3. Cardiac arrest

4. Contra indication to antiplatelet therapy

5. Treatment with a P2Y12-ADP antagonist <1 month

6.Platelet count <100 G/L 7.History of bleeding diathesis

8.History of haemorrhagic stroke

9.Recent surgery (<1 month)

10.Age75 years old

11.Haemodialysis

12. Treatment with a P2Y12-ADP receptor during the previous month,

13. Oral anticoagulant therapyand use of medication with known interference with ticagrelor and bradycardia.

Briefly, the study included ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI) patients treated with PCI and an ADPri (ticagrelor) during the index MI hospitalization. The only patients excluded were those who were unable to provide written informed consent for longitudinal follow-up and those who were participating in another research study that specified use of either an investigational or approved ADPri within the first 6 months post-MI. In accordance with the observational nature of the study, all treatment decisions were left to the discretion of the individual patient's care team.

4.6. Study End Points

The primary clinical end point of the study was a composite of major cardiac events, (myocardial infarction, unplanned revascularisation and stroke,) stent thrombosis and bleeding event sat7 days, 30 days, 3 months and 6 months after the index pro-

cedure. Secondaryclinical end point is incidence and patterns of switch of antiplatelet from ticagrelor to either clopidogrel or prasugrel due to various causes andto assess the clinical and cost factors associated with switching.Switchwere discussed at four specific time intervalsaccording to the interviews of participating population.

The primary angiographic end point was in-stent luminal late loss, as determined by quantitative angiography. Secondary angiography end points included the percentage of in-stent stenosis of the luminal diameter, the rate of restenosis (luminal narrowing of 50 percentor more), and the minimal luminal diameter of the stented segment and of the 5-mm segments proximal and distal to the stent at six months.

The end points were adjudicated by an independent clinical events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

4.7. Follow-up

During follow-up, interviews of patients were done on personal contact during routine medical check-ups as well by telephonic conversations at 1 month, 3 months and 6 months including intensive interrogation of symptoms and complication. They were asked specific questions about the interim developmentof angina, according to the Canadian Cardiovascular Society classification of stable angina [8] and the Braunwald's classification of unstable angina [9]. The patients were also monitored for major cardiac events and for the need for additional revascularization of the index target lesion. An electrocardiogram was obtained at each visit, and an angiographic study was performed at a mean (±SD) of 180±30 days. Details of individual's signs and symptoms like nausea, vomiting, hematemesis, haemoptysis, breathlessness, stent thrombosis were also observational nature assessed. Other studies and tests were performed at the discretion of the investigators. Because of the of the study, the decision to perform further revascularization of the target lesion or vessel after the six-month angiographic study was also left to the investigators' discretions**.**

4.8. Quantitative Coronary Angiographic Evaluation

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analyses of all angiographic data before, during, and after the procedure were performed by our catheterisation laboratory (Post graduate department of cardiology ,Ajmer) with the use of edge-detection techniques. The luminal diameter of the coronary artery and the degree of stenosis were measured before dilation, at the end of

the procedure, and at six months.

4.9. Intravascular Ultrasound Substudy

At the six-month visit, intravascular ultrasound examinations were performed by in subgroups of 48 patients who had received an bare metal stents.

4.10. Statistical Analysis

Ordinal variables are expressed as frequencies, and continuous variables are expressed as mean SD. Binary variables were compared with chai-sqaure analysis, and continuous variables were evaluated with the Student's *t* test. A 2-sided probability value <0.05 was considered significant. Statistical analyses were performed in SAS (version 8.2) unless otherwise noted.

5. Results

The demographic and Baseline Patient clinical characteristics of patients are presented in (Table 2). Sample size of 356 patients were decided for the study among which 70 patients didnot give written consent, so they were excluded from study. The study prematurely terminated due to withdrawal of bare metal stent supply by government scheme, so only 276 patients included in study. Total 78 patients switched to other ADPri along with death of 5 patients. Total 193 patients remained in study for follow up for 6th month.

Total 78 (28.0%) patients switched out of 276 study persons. Total Switch occurred among patients discharged on ticagrelor to clopidogrel (30/276, 10.0%) or prasugrel (48/276,17.0%). Switchwere discussed at four specific point of time according to the interviews of participating patients. Twelve (4.3%) patients switched within first week. Twentyfour (8.6%) patients switched in between first week to first month whereas 22 patients (7.9%) switched between first month to third month that were not statically different to each other. Total 20 (7.2%) patients switched in between third month to sixth month. Switch in first week were almost all due to acute breathlessness developed as side effect of ticagrelor, cost was not prohibiting factor during this period.

Total 46 patients switched in period between first week to third month of which 40 patients (86.95%) patients switched due to cost factor, 11patients (3.9%) patients switched due to minor bleed (recurrent epistaxis, hematemesis, and haemoptysis). We observed that switch was more common in people of low socioeconomic status particularly in non-educated patients. Switch was less prevalent in people of upper strata .

Outcomes of interest as primary clinical event included post discharge major adverse cardiovascular events (MACEs), stent thrombosis, and bleeding events and there result are as follows.

Major adverse cardiovascular events occurred at six month in

11patients (0.05%). One patient died (0.36%) within 7 days due to acute stent thrombosis, 2 patients died in between 1 month to 3 month ,one due to acute myocardial infarction with cardiogenic shock and other due to acute cerebrovascular accident and late stent thrombosis developed in 2 patients between 3 month to 6 months. Twopersons admitted with ischemic stroke in 8th week after procedure. Only one case of intra-cerebral significant major bleed was observed with ticagrelor which culminated into death during first month. Other symptoms and events profile of all participants were as mentioned in (table 3). All 193 patients under went repeat coronary angiography during follow up period of ½year of dual anti-platelets therapy, observation after the end of study showed the late lumen loss comparable to previous study which deployed DES. Binary angiographic restenosis (diameter loss more than >50%) developed in 17 patients (8.8%) that was statically significant compared to older study of BMS but was comparable to previous DES study. All of these events, including timing relative to ADPri switching, were independently adjudicated by study physicians via review of relevant medical records and angiographic films using protocol specified end point definitions.

*Plus–minus values are means ±SD. There were no significant differences between the treatment groups except for male sex (P=0.05). †Unstable angina was defined according to the Braunwald classification, 14 and stable angina accordingto the classification of the Canadian Cardiovascular Society. 13‡LAD denotes left anterior descending coronary artery, RCA right coronary artery, and LCX leftcircumflex artery§The classification of the American College of Cardiology–American Heart Association was used.

5.1 Clinical Events

The incidence of MACEs,(myocardial infarction, unplanned revascularisationand stroke),stent thrombosis, and GUSTO-moderate/severe bleeding events in the 30 days were [3,1 ,0(4)] respectively whereas in 6 month follow up period [11, 3, 1(15)] respectively .

Only onesignificant NON-CABG major bleed as intra cerebral bleed was observed with ticagrelor during whole follow up period of 6 month in contrast to result of PLATO trial where NON-CABG major bleed was 3.9% and fatal intracranial haemorrhage 0.3%. Two cases of recurrent epistaxis,5 cases of haemoptysis and 4 cases of hematemesis were recorded as minor bleed that was (5.6%). Finally, we assessed that in our study the incidence of both major and minor bleed are significantly lower than the landmark ticagrelor PLATO trial [10] .

5.2. Late Loss and its Skewed Distribution for BMS

Late loss was initially developed as a tool to compare the mechanisms of restenosis between different coronary interventions such as balloon angioplasty, stenting, and atherectomy.

Previous various Bare metal stent trials and registries have demonstrated mean late losses varying from -0.6 to -1.2 mm [5,11,17,18]. Even in the standard bare metal stent arm of the RAVEL randomized trial reported an average late loss in its own control arm (-0.80 mm), which corresponded to a BAR rate of 26% [12].

The SOBEAT trial of the bare metal stent with dual anti-platelets ticagrelor with aspirin is the first randomized trial to report a stent with an average late loss well below the expected historical range, where mean in-stent late loss is-0.31-/+0.33 mm which corresponded to a BAR (Binary angiographic restenosis) rate of 8.8%. As the positive mean of any normal distribution is reduced enough so that its spread becomes significantly bounded by zero, it becomes right-skewed.

Quantitative angiography revealed the different values of BMS stented lesion as minimal luminal diameter (mm), before procedure, after procedure, and at 6 month were 0.94±0.31 ,2.43±0.41, and 2.12±0.49 respectively ,in our study. Introduction of on-line QCA and IVUS guidance are potentially responsible for this improvement.

In this ticagrelor supported bare metal stent study, however, for which the mean late loss has ranged between -0.01 and -0.64 mm, the late-loss distributions studied are markedly deviated from normal and skewed to the right. In such skewed distributions, the variance, as estimated from the sample SD, no longer accurately denotes the deviation from the mean.

6. Discussion

To the best of our knowledge, this is the first contemporary pilot study in Indiato study scope of bare metal stent in the era of a potent newer antiplatelet drug 'Ticagrelor'.

This study was also unique in analysis patterns of and patient-reported reasons for postdischarge drug switching and restenosis rate 6 month study period.Switch was a major issue with ticagrelor in our study and the patient-reported reasons for switching ADPri are presented in (**Table 1**). Post-discharge ADPri switching occurred mostly within the first 3 months post-procedure and uncommonly was associated with MACEs or bleeding events. Switching occurred at a median of 70+/-10 days post-discharge which discharged on ticagrelor (78/276; 28 %).

Table 1: Time period of drug switch

Drug switch	< 7 days	1 month	3 month	6 month
Ticagrelor to prasugrel	8	14	15	12
Ticagrelor to clopidogrel	4	10	7	8
	12 (4.3 %)	24 (8.6%)	22 (7.9%)	20 (7.2%)

Table 2: The demographic and Baseline Patient clinical characteristics of patients

Age (yr)	60.7±10.4
Male sex (%)	76
Previous myocardial infarction (%)	36
Diabetes mellitus (%)	19
Treated hypercholesterolemia (%)	45
Treated hypertension	60
Current smoker (%)	36
Angina pectoris †	89
Unstable	50
Stable	39
Myocardial infarction	187
NSTEMI	97
STEMI (thrombolysis)	90
Done	55
Not done	35
Silent ischemia (%)	11
Target coronary artery (%)‡	
LAD	46
RCA	34
LCX	30
Lesion type (%)§	
A	6
B1	37
B2	57
Reference diameter of the vessel (mm)	2.62±0.53
Length of lesion (mm)	9.58±3.25
Previous CABG (%)	4
Educational level of patients (%)	49
Non educated	51
Post graduated level	10

Table 3: Symptoms and events profile of all participants.

Events	Patients no	percent
Nausea	12	4.30%
Vomiting / ghabrahat	5	1.80%
SOB (BREATHLESSNESS)	60	31.00%
Hemoptysis	5	2.50%
Hematemesis	4	0.02%
CVA	4	
Ischemic	3	1.50%
Hemorrhagic	1	0.50%
DEATH	5	1.80%
Myocardial infarction	4	0.02%
Stent thrombosis	3	1.50%
Restenosis(BAR)	17	8.80%
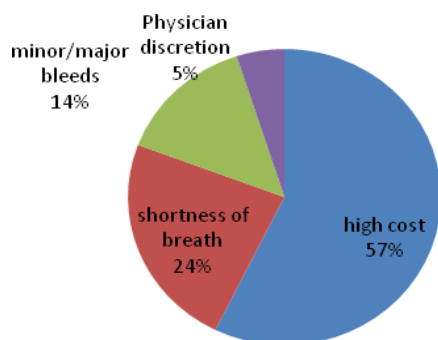
Figure 1: Pie chart given above illustrates the different cause of drug switch.

As far as possible,the treating physicians were instructed to switch the patients primarily on prasugrel because both prasugrel and ticagrelor had similar safety and efficacy revealed in results of PRAGUE-18, the first randomised trial, head-to-head comparison of the both drugs. However, some patients were switched to clopidogrel because of the relatively lower cost.

Percutaneous coronary therapies have generally been compared on the basis of their restenosis propensities. The restenos is rate of 8.8% percent in the standard BMS stent group is comparable to contemporary Drug eluting stents <5%. However, on the basisof a linear regression model derived from the Stent Restenos is Study and the Benestent I and II studies (unpublished data), the predicted rate of restenosisfor our patient cohort was approximately 28 percent.

The evaluation of restenosis in the DES era is more complex. In the SIRIUS and TAXUS experience, binary angiographic and clinical restenosis rates are below 10% [13] which makes comparisons between competing DES treatments more difficult with sample sizes below 1000 to 2000 subjects. With these robust features, in-stent late loss is a sensitive indicator of restenosis propensity.

The results of this (SOBEAT) study appear surprising at first glance. As a specialty, we take for granted the benefit of a DES over a BMS. But in reality,the reduction in revascularization with DES is small and with no impact on mortality or quality of life. Having nearly become extinct in many catheterization laboratories, bare metal stents will come back into focus with this study.

Lower restenosis rate compared to previous BMS study and equivalent to DES established the pleotropic effect of ticagrelor other than antiplatelet effect in reducing the influx of mononuclear cells,inhibiting monocyte and macrophage function, and influencing VSMC proliferation, [14].

As we know that the smooth muscle cell are vital to the healing process after arterial injury [15] because of its ability to migrate, proliferate and synthesize extra cellular matrix(ECM) upon stimulation [16], as it is known that growth factors released from platelets, leukocytes and Vascular smooth muscle cell (VSMC) stimulate a granulation or cellular proliferation phase. Smooth muscle cell (SMC)from the media and adventitia migrate into the intimal layer. The platelet-derived growth factor (PDGF) is a potent promoter of this SMC migration. So, ticagrelor being potent anti-platelet drug, it inhibit the PDGF release and its proliferating effect.

Late lumen loss in BMS is comparable to late lumen loss of DES [17], signify the role of ticagrelor as strong anti -inflammatory inhibiting the restenosis. We also hypothesize ticagrelor has anti-cytokines on different cytokines as well as inhibitor of PDGF which mediates neo-hyperplasia at stent deployment site producing re-stenosis.

The benefit of DES have often been overstated, or perhaps the danger of BMS. The purpose of DES was to overcome in-stent restenosis, not to reduce rates of death or myocardial infarction. The DES reduced in-stent restenosis, as expected, very effectively. However, the results of this trial provide confidence when delivering contemporary BMS if the indication dictates. There is no need to fear that the patient is receiving an inferior product, or that this choice will negatively impact on prognosis.

Overall, NORSTENT also reminds us that bare metal stents have — like drug-eluting stents—evolved over time and are now associated with impressively low risks for restenosis (about 10% over six years) and stent thrombosis (around 1% over six years).

7. Conclusion

These study results offer more freedom to clinicians to select either the DES or BMS if ticagreloradded on top of aspirin for patients of PCI who receive dual antiplatelet therapy.Patients discharged on a higher-potency AD Priticagrelor switched on either clopidogrel or prasugrel and citedcost as a reason for the switch. So, there is need of reduction of market price of this novel newer anti-platelet at global level .

Newer generation drug-eluting stents seem to be both very effective and very safe, and they should stay the first choice for most patients. However, the performance of bare metal stents have also improved over time and may be an effective and safe option for certain subsets of patients—such as those at higher bleeding risk, with planned major surgery and those with anticipated poor compliance to DAPT, especially if their restenosis risk is limited (larger diameter arteries, non-diabetics, short lesions).

8. Limitations

There were few limitations of study.

1. It was pilot study participating lesser no of patients, soa larger trial would be needed to conduct to definitely support the results born from this study.

2. Cost-effectiveness analysis proved it less economical, due to higher market price of ticagrelor .

3. Switching from ticagrelor was major issue ,making lesser no of patients available for repeat angiography to evaluate restenosis rate.

4. The major use of IVUS in coronary intervention is to guide interventional strategies and assess optimal stent deployment but was not used during stents deployment in our study due to cost constrainment.

5. SOBEAT was an observational study and, consequently, is subject to unmeasured confounding and bias.

9. Acknowledgment

References

1. Bonaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygard O, et al. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. N Engl J Med 2016.

2. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, et al. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am CollCardiol. 2015; 65(23): 2496-507.

3. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med. 2013; 368(3): 254-65.

4. Bagai A, Peterson ED, Honeycutt E, et al. In-hospital switching between adenosine diphosphate receptor inhibitors in patients with acute myocardial infarction treated with percutaneous coronary intervention: insights into contemporary practice from the TRANSLATE-ACS study. Eur Heart J Acute Cardiovasc Care. 2015; 4: 499-508.

5. Bagai A, Wang Y, Wang TY, et al. In-hospital switching between clopidogrel and prasugrel among patients with acute myocardial infarction treated with percutaneous coronary intervention: insights into contemporary practice from the national cardiovascular data registry. CircCardiovascInterv. 2014; 7: 585-93.

6. Mauro Moscucci 8thedition, section VII, page 650-653.

7. Mehran R, RaoSV, BhattDL, etal. Standardized bleeding definitions for cardiovascular clinical trials:a consensus report from the bleeding Academic Research Consortium. Circulation 2011; 123: 2736.

8. Campeau L. Grading for angina pectoris. Circulation. 1976; 54: 522-3.

9. Braunwald E. Unstable angina: a classification. Circulation. 1989; 80: 410-4.

10. Mahaffey KW, WojdylDM, CarrollK,et al. Ticagrelor compared with clopidogrel by geographic region in the platelet inhibition and patient outcomes(PLATO)trial. circulation. 2011; 124: 544-554.

11. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987; 316: 701-6.

12. MoriceMC, SerruysPW, SousaJE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. NEng J Med. 2002; 346: 1773-1780.

13. WaughJ, WagstaffAJ. The paclitaxel (TAXUS)-eluting stent: a review of its use in the management of de novo coronary artery lesions. Am J Cardiovasc Drugs. 2004; 4: 257-268.

14. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am CollCardiol. 2011; 58(24): e44-122.

15. Berk BC, GordonJB, Alexander RW. Pharmacologic roles of heparin and glucocorticoids to prevent restenosis after coronary angioplasty. J Am CollCardiol. 1991; 17: 1117B-11B.

16. Murray M , Schrodt GR , Berg HG. Role of smooth muscle cells in healing of injured arteries. Arch Pathol. 1996; 82: 138-146.

17. ThybergJ, HedinU, Sjolund M et al. Regulation of differentiated properties and proliferation of arterial smooth muscle cells. Arteriosclerosis. 1990; 10: 966-990.

18. Hong MK, Lee CW, Kim JH, et al. Impact of various intravascular ultrasound criteria for stent optimization on the six month angiographic restenosis. Catheter CardiovascInterv. 2002; 56: 178-183.

19. Albiero R, Rau T, Schlüter M, et al. Comparison of immediate and intermediate-term results of intravascular ultrasound versus angiography-guided Palmaz-Schatz stent implantation in matched lesions. Circulation. 1997; 96: 2997-3005.

20. Hoffmann R, Mintz GS, Mehran R, et al. Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents. J Am CollCardiol. 1998; 31: 43-49.

21. Kasaoka S, Tobis JM, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am CollCardiol. 1998; 32: 1630-1635.

22. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mecha-

nisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation. 1996; 94: 1247-54.

23. Moussa I, Moses J, Di Mario C, et al. Does the specific intravascular ultrasound criterion used to optimize stent expansionhave an impact on the probability of stent restenosis? Am J Cardiol. 1999; 83: 1012-1017.

24. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am CollCardiol. 2011; 58(24): e44-122.