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The effects of Repeated Medication Reinforcement on Dual-Antiplatlet Therapy and Cardiovascular Outcomes after Drug -stent placement: A randomized clinical trial.

A. Study Purpose and Rationale

Rationale: Dual anti-platelet therapy is recommended after placement of a drug-eluting stent to prevent the occurrence of in-stent re-thrombosis, a serious and potentially fatal complication. It has been shown that lapses of said medication can adversely affect mortality and re-hospitalization rates. Given the importance of this drug regimen we aim to study the effect of repeated medication reinforcement (RMR) on cardiac outcomes of patients in the first year after drug eluting stent (DES) stent placement.

Background:

In 2009 there were a recorded 484,530 hospital stays involving the placement of a DES. These stents elute a drug that retards neointimization of the vasculature after stent placement such as sirolimus or paclitaxel. This decreased neointimization results in a decrease in the need to re-vascularize the artery after stent placement without any change in mortality[i]. By preventing this neointimization of the vasculature, however, DES leave an exposed substrate that can act as a nidus for thrombosis formation and increase the risk of in-stent thrombosis[ii]. As a result, patients are put on dual anti-platelet therapy with aspirin and an ADP receptor antagonist such as a thienopyridine.

Studies have shown that patients who discontinue their thienopyridines at 30 days after placement of a drug eluding stent have a HR of 9.02 (95% CI 1.3 to 60.6, $P<0.02$) in all cause mortality[iii]. Other studies have shown that those who stop DAPT within 6 months have an increased risk of stent thrombosis with a hazard ratio of 13.74 (95% CI, 4.04 to 46.68; $P<0.001$) . In this study stent thrombosis resulted in death 39% of the time and MI 79% of the time. This represents a considerable effect of DAPT in effecting outcomes in those receiving DES. In this same study, the median timing from DAPT cessation to adverse events was calculated to be 13.5 days (interquartile range, 5.2 to 25.7 days) [iv]. These outcome studies relied on self-reporting of medication adherence, a modality that likely underestimates non-compliance in the control group. As a result the true effect of medication compliance may actually be actually higher than reported.

Economic pressures continue to push towards a decrease in hospital stay and a push in many centers for same-day PCI leaving for less time for patient education and less of an impact of the procedure in the patient's perception of his or her own health[v]. This leaves room for an outpatient follow-up reinforcing the importance of these medications and ensuring DAPT persistence.

In a study looking at the effects of telephone contact on DAPT adherence investigators made 5-10 minute phone calls at 7 days 1,6 and 9 months. They measured drug adherence by contacting pharmacies and dividing the number of pills used by the number of days in the trial (365). They found a median pill use of 99.2% and 99.3% for aspirin and clopidogrel respectfully in the treatment arm and 90.2% and 91.5% in the control group. They also looked at drug persistence which they defined as a period free of a 14 day lapse in clopidogrel determined by delayed refills. Those in the treatment arm had an 87.2% persistence vs. 43.1% in the control group [vi].

While some studies have looked at the effects of medication non-compliance on adverse outcomes on patients after DES placement and others have looked at the effect of telephone contact on medication compliance this will be the first study powered to look at the effects of patient reinforcement on outcomes. Given the relatively low cost of this intervention when compared to primary outcomes of this study we expect even a modest improvement in outcomes to be clinically relevant and have powered this study accordingly.

B. Study Design and Statistical Analysis

Goals: The purpose of the study is to determine the benefit with regards to patient education and reinforcement of medication compliance in cardiac outcomes.

Hypothesis: We hypothesize that there will be a reduction in primary endpoints with repeated medication reinforcement.

Study overview: This is a prospective, randomized, open-label, interventional, multi-center study during which we will assess the long term benefits or lack thereof of repeated medication reinforcement in patients after a coronary

thrombotic event receiving stent placement. The primary objective is to compare the effect of RMR on the mortality and other secondary clinical outcomes of patients in the year following stent placement.

Randomization: Randomization will be done before discharge after stent placement in a 1:1 fashion to either standard follow up or repeated medication reinforcement. Randomization will take place using blinded-envelopes at each study center to be opened after inclusion/exclusion criteria have been met and consent for the study has been obtained.

Study end points: The primary endpoint will be major adverse cardiac events (MACE) which includes all-cause death, MI and repeat revascularization. Revascularization will be classified as target lesion re-interventions including by-pass surgery or percutaneous coronary intervention inside the implanted stent or within 5mm of the target stent.

Masking: The study will be performed as an open-label comparison. Due to the nature of the study masking of the subjects would be impossible. All study staff and investigators will be masked as well as any physicians interacting with the patient.

Follow up:. Patients in the RMR group will be contacted at 7 days and in months 1, 2, 4 regarding the importance of medication compliance and possible issues preventing compliance but patients will not be surveyed with regards to outcomes until 6 months and then again at 1 year in both groups. Both groups will be allowed standard medical follow up in addition to any study considerations. Outcomes will be gathered from telephone contact after one year with regards to clinical status and interim occurrence of any adverse events. If there is any question of doubt or uncertainty referring cardiologists or general practitioners will be contacted for further information.

Statistical Analysis: The assumed primary end point rates for the two treatment groups are extrapolated using conservative data from articles in publication on DAPT compliance and outcomes. In powering the study for the primary endpoint, the following are the treatment effect size assumptions:

	Repeated Medication Reinforcement	Standard follow up
Primary Endpoint:	18.0%	16.0%
Effect Size:	2.0%	

Assuming 1:1 randomization with a chi-square test for 80% power and significance at $p<.05$ the number needed in each group is 5600 patients with at least 11,200 patients required for randomization. Assuming that 10% of patients initially enrolled will be lost to follow up or unable to fulfill the RMR protocol, the number needed to be enrolled at the time of stent placement is 12320.

After results are collected, primary endpoints will be assessed with Kaplan Meier curves. Chi-squared and t-test analysis will be performed on the baseline characteristics between each groups to ensure effective randomization and homogeneity between the two groups

C. Study Procedure.

Patients will be enrolled in the study after cardiac catheterization and stent placement as per the standard of care. They will be randomized on a 1:1 basis to either standard follow up or RMR. Patients in the RMR group will receive one phone call at 7 days and at months 1, 2 and 4 where in they will be reminded the importance of their medication, the purpose of their DAPT and will be asked if there is any reason they are unable to take their medication. Anticipated phone call duration is 5-10 minutes. There will be no additional resources in terms of financial support for the RMR group . Both groups will be allowed standard follow-up with their PMD or Cardiologist who will not be informed of the patients randomization in the study.

At the six month and one year point, patients will be polled with regards to their cardiac outcomes. If patients are unable to describe cardiac outcomes their primary physician or cardiologist will be contacted.

D. Study Drugs

All patients will receive aspirin (81-325mg) PO daily with dosage determined by their primary physician or cardiologist. Additionally, all patients will receive an approved second antiplatelet agent which may include clopidogrel, prasgurel, ticagrelor or another FDA-approved antiplatelet agent. Choice of antiplatelet agent and dose will be made by the cardiologist or PMD per their discretion as per the standard of care.

E. Medical Device.*
There are no medical devices being followed in the study. All cardiac stents are per the managing team based on standards of care before enrollment in the study.

F. Study Questionnaires
Study questionnaires are still being developed. Topics covered in the questionnaire will focus on basic demographic risk factors as well as risk factors for medication non-compliance to ensure effective matching between groups.

G. Study Subjects

Population:
Study subjects with coronary artery disease who receive a drug eluding stent are eligible for study enrollment. This study will look at patients who receive a stent both for an acute coronary intervention during a thrombotic (ST-elevation or non-ST elevation MI) or for the treatment of stable coronary artery disease.

Inclusion/Exclusion Criteria at time of study: To enroll in the study, subjects must be greater than 18 years of age, had a drug-eluting stent placed and must be able to provide consent.

Patients will be excluded from the trial if they have an allergy or reaction that prevents taking of Aspirin or ADP receptor antagonist or any platelet dysfunction or risk of bleed that would otherwise serve as a contraindication to DAT. Patients will be excluded from the study if they have any planned surgeries at the time of the enrollment that would require cessation of anti-platelet therapy.

H. Recruitment of Subjects
Subjects will be recruited to the study prior to discharge after placement of their drug-eluting stent as an inpatient in the hospital. The study will be offered to all patients regardless of their prior history of medication compliance or past medical history.

I. Confidentially of Study Data
Patient data will be maintained confidentially at all times as outlined by HIPAA standards. No personnel that are not directly involved with the study will be allowed access to study information.

J. Potential Conflict of Interest
There are no potential conflicts of interest in this study.

K. Location of the Study
The study will be performed remotely using telephone and database access. No study activities will take place with patient involvement on CPMC campus. Other clinical sites will obtain IRB approval from their respective institutions.

L. Potential Risks
There are no potential risks of this study beyond standard dual-anti platelet therapy if adhered to at the recommended dosages.

M. Potential Benefits
You may or may not benefit as a result of your participation in this study. Potential benefits may include increased compliance of medications and decreased rate of cardiovascular events.

N. Alternative Therapies
The alternative to participation in this study is standard follow up with their primary medical doctor.

0. Compensation to Subjects
There is no compensation to subjects for participation in this studies.

P. Costs to Subjects
Patients may occur additional costs as a result of the study in the form of phone bills but these costs are predicted to be nominal.

Q. Minors as Research Subjects
This study does not involve minors.

R. Radiation or Radioactive Substances

There is no radiation or radioactive substances involved in this study more than that as standard management per the medical team

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[i] De Luca, Giuseppe, Maurits Dirksen, et al. "Drug-Eluting Vs Bare-metal stents in Primary Angioplasty."*Archives of Internal Medicine*. 172.8 (2012): 611-621

[ii] Dangas, George D., Adriano Caixeta, et al. "Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in ACute Myocardial Infarction." *Circulation*. 123. (2011): 1745-1756.

[iii] Spertus, John A., Richard KettleKamp, et al. "Prevalence, Predictors, and Outcomes of Premature Discontinuation of Thienopyridine Therapy AFter Drug-Eluting Stent Placement." *Circulation*. 113. (2006): 2803-2809.

[iv] Flavio , Airoldi, Antonio Colombo, et al. "Incidence and Predictors of Drug-Eluting Stent Thrombosis During and After Discontinuation of Thienopyridine Treatment ." *Circulation*. 116. (2007): 745-754.

[v] Heyde, Gerlind , Karel Koch, et al. "Randomized Trial Comparing Same-Day Discharge With overnight Hospital Stay After Percutaneous Coronary Intervnetion." *Interventional Cardiology*. 115. (2007): 2299-2306.

[vi] Rinfret, Stephane, Josep Rodes-Cabau, et al. "Telephone contact to imrpove adherence to dual antiplatelet therapy after drug-eluting stent implantation." *Heart*. 99.8 (2013): 562-569.