SUPPLEMENTAL MATERIAL

Study population

Inclusion criteria:

1. Patients with a prior MI between 2 weeks and 24 months or with PAD*.
2. On DAPT with low-dose aspirin (81 mg od) and clopidogrel (75 mg od) as per standard-of-care for at least 14 days.
3. Age ≥ 18 years old.
4. Patients entering the DM cohort will need to have diagnosis of type 2 DM defined according to the WHO definition [1], on treatment with oral hypoglycemic agents and/or insulin for at least two months, without any changes in regimen.

*Patients meeting both MI and PAD criteria will be categorized as MI

Exclusion criteria:

1. History of ACS in the previous 2 weeks.
2. History of stroke, transient ischemic attack, or intracranial hemorrhage.
3. Active pathological bleeding, history of bleeding events or increased risk of bleeding.
4. Known severe hepatic impairment.
5. Type 2 DM on dietary control.
6. Use of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) or inducers (e.g., rifampin, carbamazepine, St. John's Wort and phenytoin).

7. On treatment with any oral anticoagulant (vitamin K antagonists, dabigatran, rivaroxaban, apixaban, edoxaban).
8. On treatment with any antiplatelet agent other than aspirin and clopidogrel in the past 14 days.
9. Creatinine clearance <30 mL/minute.
10. Platelet count $<80x10^6$/mL.
11. Hemoglobin <10g/dL.
12. Hemodynamic instability.
13. Pregnant females.

Description of laboratory assays

1) ***Light transmittance aggregometry (LTA)***: Platelet aggregation was performed using LTA according to standard protocols. Blood was collected in citrated (3.2%) tubes. LTA was assessed using platelet-rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown) as previously described [2,3]. Platelet agonists included AA (1 mM), collagen (3µg/ml), ADP (5 and 20 µM), TRAP (15 µM), and a combination of 2 µg/ml collagen-related peptide + 5 µM ADP + 15 µM TRAP (CAT). The reagent cocktail CAT allowed to assess the overall platelet response to a combination of agonists that leads to activation of multiple platelet pathways. PRP was obtained as a supernatant after centrifugation of citrated blood at 1000 rpm for 10 minutes. The isolated PRP was kept at 37° C before use. Platelet poor plasma (PPP) was obtained by a second centrifugation of the blood fraction at 2800 rpm for 10 minutes. Light transmission was adjusted to 0% with the PRP and to 100% for the PPP for each measurement. Curves were recorded for 6 minutes and platelet aggregation was determined as the maximal percent change (MPA) in light transmittance from baseline using PPP as a reference.

2) ***Whole blood vasodilator-stimulated phosphoprotein (VASP)***: VASP phosphorylation (VASP-P) is a marker of $P2Y_{12}$ receptor reactivity. VASP was assessed according to standard protocol using labeled monoclonal antibodies by flow cytometry with the Platelet VASP-FCM kit (Biocytex Inc., Marseille, France) as previously described [2]. PGE1 increases VASP-P levels by stimulation of adenylate cyclase. Binding of ADP to P2Y12 leads to Gi-coupled inhibition of adenylate cyclase. Therefore, the addition of ADP to PGE1-stimulated platelets reduces PGE1-induced VASP-P levels. If $P2Y_{12}$ receptors are successfully inhibited by inhibitors, addition of ADP will not reduce the PGE1-stimulated VASP-P levels. The platelet reactivity index (PRI)

was calculated after measuring VASP-P levels after stimulation with PGE1 (MFI PGE1) and also PGE1 + ADP (MFI PGE1 + ADP). The PRI = ([MFI PGE1] – [MFI PGE1 + ADP]/[MFI PGE1]) x 100%.

3) Thrombelastograph Coagulation Analyzer TEG 6s system: the TEG 6s system (Haemonetics Corporation, Braintree, MA, USA) was be used according to manufacture instructions [4]. In brief, the TEG 6s system is a new generation portable thromboelastography technology able to evaluate all phases of hemostasis, including time to clot formation, rate of clot formation, strength of clot and residual clot strength due to antiplatelet drugs, rate of clot lysis. Disposable assay cartridges contain all of the components necessary to allow the analyzer to prepare samples and perform hemostasis tests. The analyzer automatically draws the blood into the active area of the cartridge, meters the exact amount required for the test, and mixes it with the reagents spotted in the cartridge. The analyzer then monitors the harmonic motion of a pendant drop of blood in response to external vibration. As the sample transitions from a liquid state to a gel-like state during clotting, the modulus of elasticity and resonant frequency increase. The instrument measures these variations in resonant frequency during clotting and lysis. The results are displayed in a table and on a graphical tracing that reflects a hemostasis profile of clot formation. The resulting hemostasis profile is a measure of the time it takes for the first measurable clot to be formed, the kinetics of clot formation, the strength of the clot, and the breakdown of the clot, or fibrinolysis. The PlateletMapping Cartridge are used to assess platelet function in patients who have received platelet inhibiting drugs. The PlateletMapping assay consists of a set of agonists, ADP and ActivatorF, which can measure the inhibition of platelet function. This assay specifically determines the MA (Maximum Amplitude, a measure of clot strength) and the reduction in MA due to antiplatelet therapy and reports it as a percentage of reduction in clot

strength. The assay uses ADP agonist to generate test results that reflect the inhibiting effects of antiplatelet agents such as ADP $P2Y_{12}$ inhibitors (e.g., clopidogrel). Since thrombin (present in blood samples) is the primary and most potent activator of platelets, its activity must be inhibited with heparin so that the platelet activating effects of ADP can be measured. Since thrombin has been rendered inactive by heparin, activatorF is used to replace thrombin's role in the conversion of fibrinogen to fibrin and Factor XIII to Factor XIIIa. Thus, with this cross-linked fibrin network as the foundation, additional clot strength due to platelet-fibrin bonding related to ADP platelet receptor activation can be measured. The HKH reagent, a combination of kaolin and heparinase, generates test data for the uninhibited MA resulting from thrombin activation of the blood sample, while the heparinase neutralizes the effects of heparin. The HKH test provides measures of R (Reaction time; the amount of time between the start of the test and the beginning of coagulation), K (the speed of formation of the clot from R time to a specific clot strength), Angle (the speed of clot strengthening), LY30 (Percent lysis 30 minutes after MA is finalized) and MA parameters; the activatorF test provides only the corresponding MA parameter; the ADP test provides measures of MA, percent inhibition and percent aggregation.

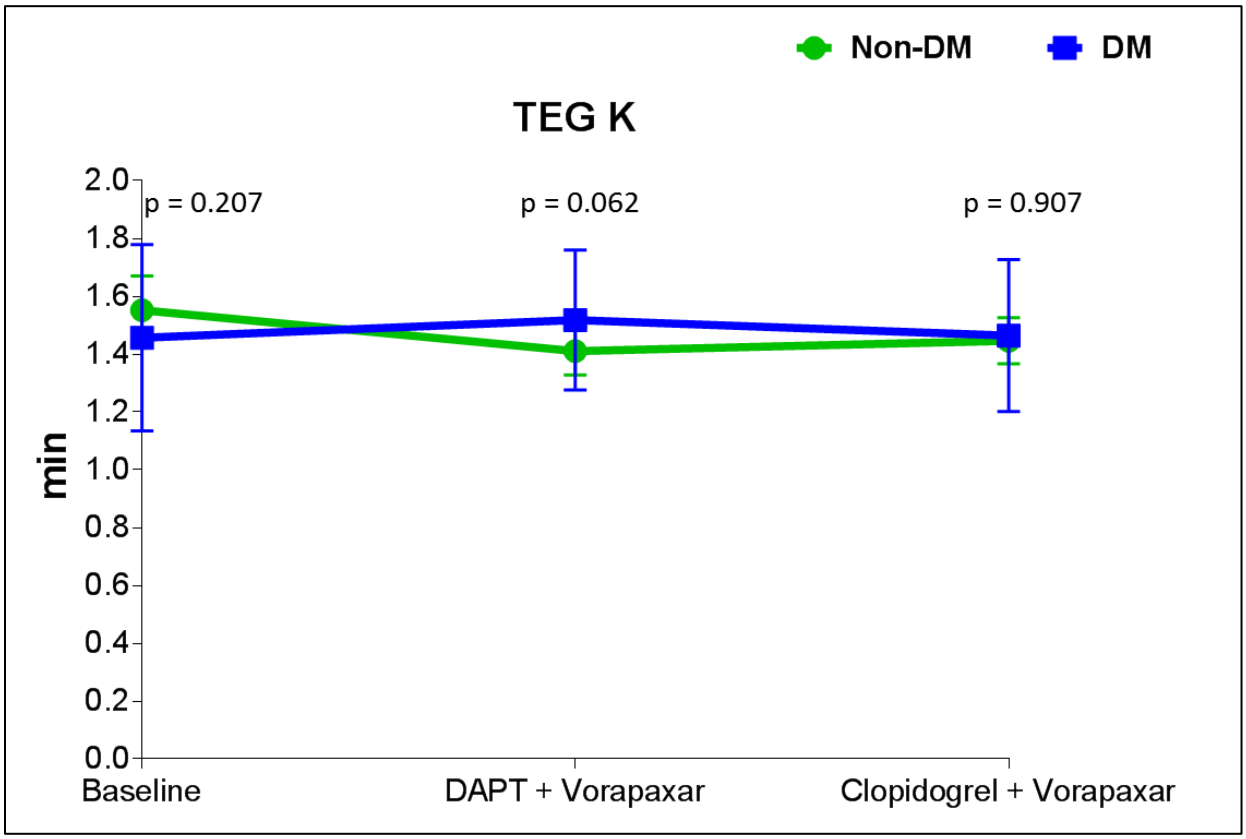
4) Serum thromboxane B_2: The concentration of serum thromboxane B_2 (TXB_2) was measured by using the TXB_2 ELISA kit (R & D Systems, Minneapolis, MN) according to the instructions of the manufacturer, as previously described [5]. Briefly, samples will be diluted with calibrator diluent RD5-57 to bring their concentrations within the range of the standard curve. No other purification was performed on any of the samples. A standard curve was established by serial dilution of TXB_2 between 20ng/mL and 0.313ng/mL using RD5-57 buffer as the matrix. The concentration of TXB_2 in the samples was calculated from a logistic 4-parameter fit of the standard concentrations versus percentage bound/maximum bound.

Non-bleeding adverse events

DM patients: diarrhea (n=1), hypotension (n=1), chest pain not requiring intervention (n=1), Bell's palsy (n=1), heart failure exacerbation (n=1), leg pain (n=1), urinary tract infection (n=1).

Non-DM patients: chest pain not requiring intervention (n=2), weakness (n=1), dyspnea (n=1).

Supplemental Figure 1. K (speed of thrombus formation) measured by TEG. P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.

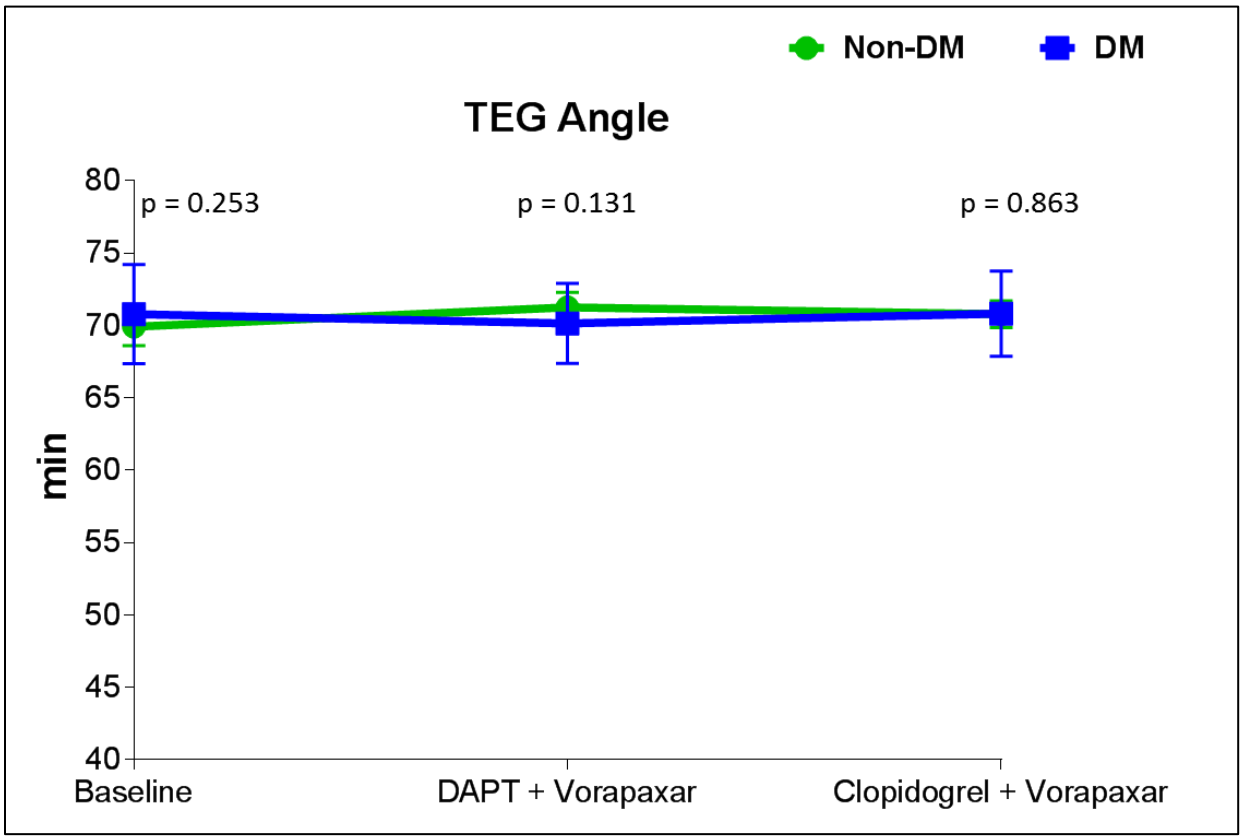


Intragroup comparisons

Non-DM: Baseline vs DAPT+Vorapaxar: p=0.013. Baseline vs Clopidogrel+Vorapaxar: p=0.099. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.503.

DM: Baseline vs DAPT+Vorapaxar: p=0.439. Baseline vs Clopidogrel+Vorapaxar: p=0.763. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.269.

Supplemental Figure 2. Angle (speed of clot strengthening) measured by TEG. P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.



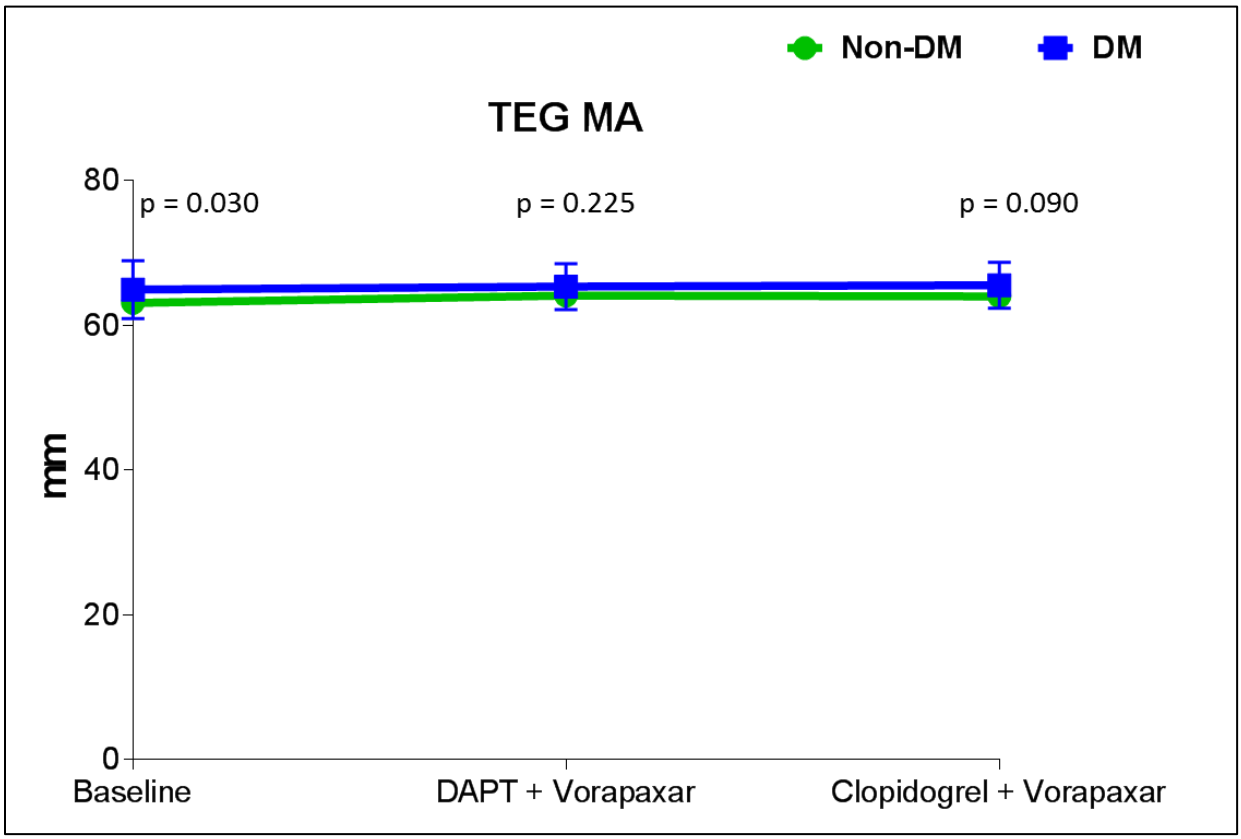
Intragroup comparisons

Non-DM: Baseline vs DAPT+Vorapaxar: p=0.036. Baseline vs Clopidogrel+Vorapaxar: p=0.173. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.476.

DM: Baseline vs DAPT+Vorapaxar: p=0.356. Baseline vs Clopidogrel+Vorapaxar: p=0.586. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.166.

Supplemental Figure 3. Clot strength (maximum amplitude, MA) measured by TEG.

P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.



Intragroup comparisons

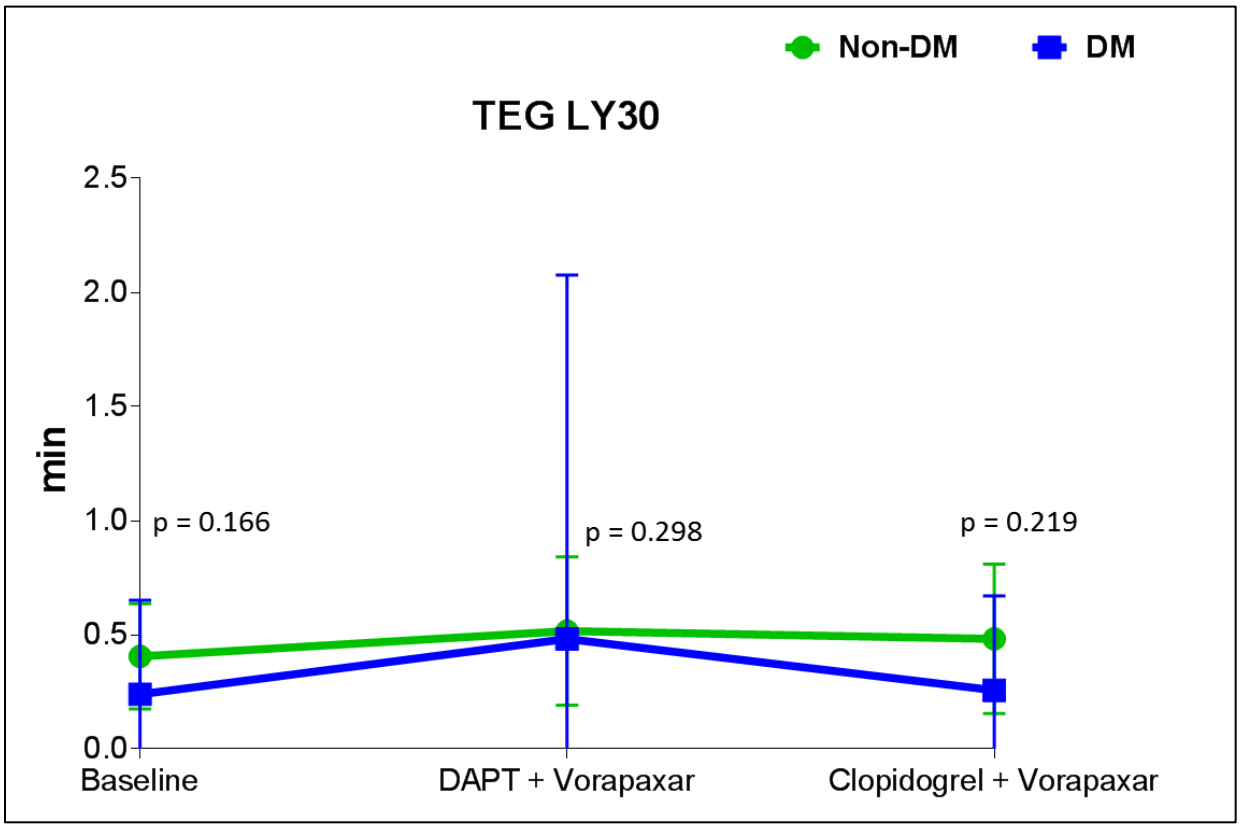
Non-DM: Baseline vs DAPT+Vorapaxar: p=0.069. Baseline vs Clopidogrel+Vorapaxar: p=0.083

DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.781.

DM: Baseline vs DAPT+Vorapaxar: p=0.412. Baseline vs Clopidogrel+Vorapaxar: p=0.136.

DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.527.

Supplemental Figure 4. LY30 (Percent lysis 30 minutes after MA is finalized) measured by TEG. P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.

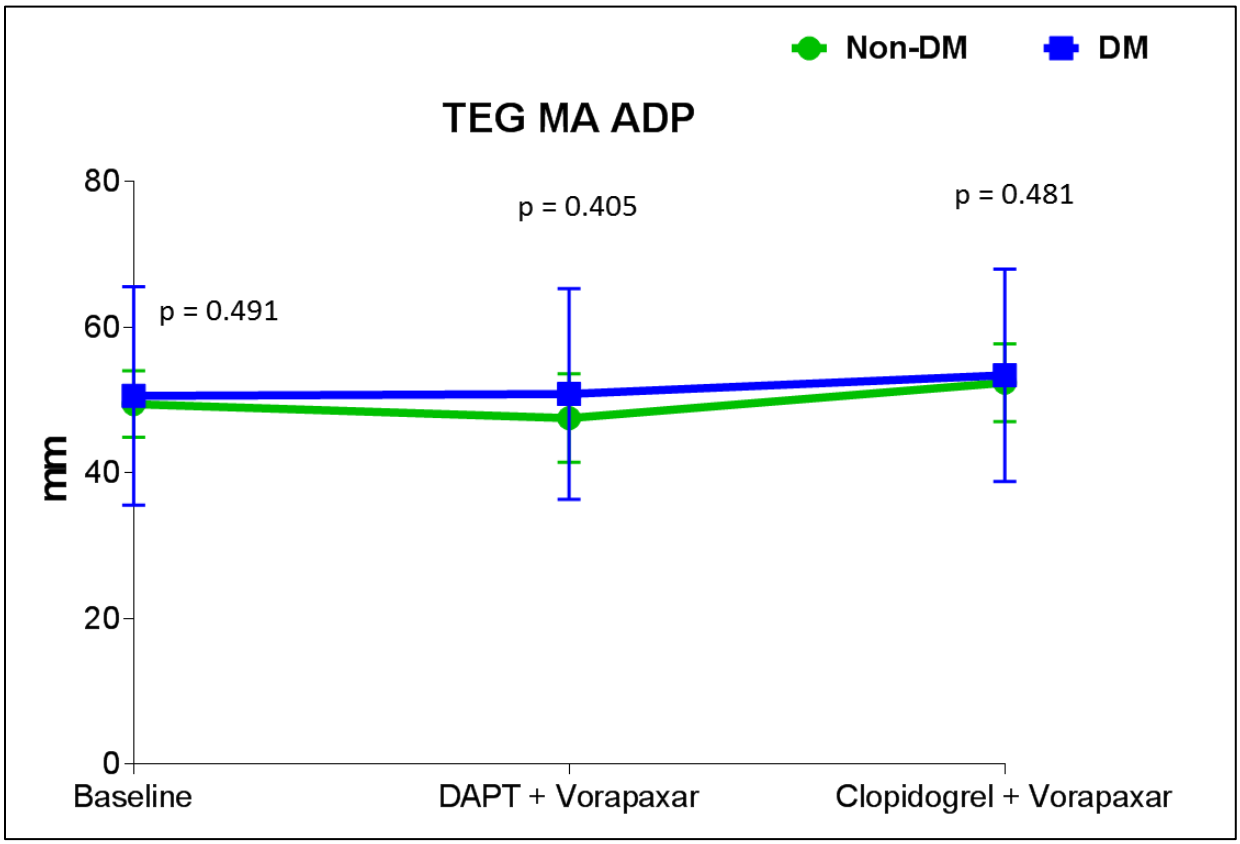


Intragroup comparisons

Non-DM: Baseline vs DAPT+Vorapaxar: p=0.098. Baseline vs Clopidogrel+Vorapaxar: p=0.175. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.418.

DM: Baseline vs DAPT+Vorapaxar: p=0.156. Baseline vs Clopidogrel+Vorapaxar: p=0.389. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.538.

Supplemental Figure 5. Clot strength (maximum amplitude, MA_{ADP}) measured by PlateletMapping TEG using ADP as agonist. P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.

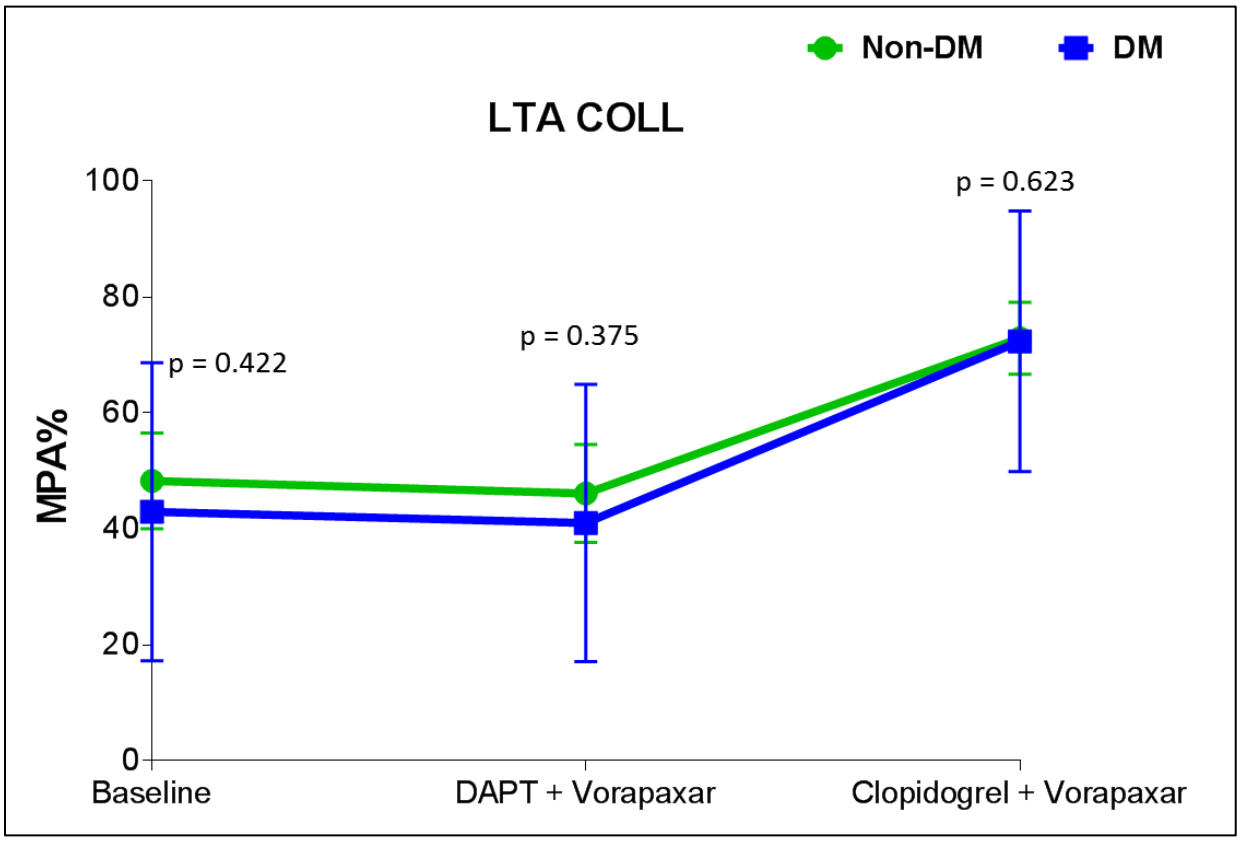


Intragroup comparisons

Non-DM: Baseline vs DAPT+Vorapaxar: p=0.206. Baseline vs Clopidogrel+Vorapaxar: p=0.013. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.016.

DM: Baseline vs DAPT+Vorapaxar: p=0.792. Baseline vs Clopidogrel+Vorapaxar: p=0.090. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p=0.268.

Supplemental Figure 6. Collagen-induced maximal platelet aggregation measured by LTA. P-values represent the comparisons between the 2 groups at each time point. Error bars indicate standard deviation.



Intragroup comparisons

Non-DM: Baseline vs DAPT+Vorapaxar: p=0.597. Baseline vs Clopidogrel+Vorapaxar: p<0.001. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p<0.001.

DM: Baseline vs DAPT+Vorapaxar: p=0.574. Baseline vs Clopidogrel+Vorapaxar: p<0.001. DAPT+Vorapaxar vs Clopidogrel+Vorapaxar: p<0.001.

References

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5. Capodanno D, Patel A, Dharmashankar K, Ferreiro JL, Ueno M, Kodali M, Tomasello SD, Capranzano P, Seecheran N, Darlington A, Tello-Montoliu A, Desai B, Bass TA, Angiolillo DJ. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. Circ Cardiovasc Interv. 2011;4:180-7.