SUPPLEMENTAL MATERIAL

Data S1.

Study Population

Inclusion criteria:

1. Patients with a prior MI within the previous 2 weeks - 12 months.
2. On DAPT with low-dose aspirin (81mg od) and either prasugrel (10mg od) or ticagrelor (90mg bid) as per standard-of-care.
3. Free from bleeding and ischemic events after the index MI event.
4. Age between 18 and 75 years old.

Exclusion criteria:

1. History of stroke, transient ischemic attack, or intracranial hemorrhage.
2. Active pathological bleeding, history of bleeding events or increased risk of bleeding.
3. Known severe hepatic impairment.
4. Age >75 years.
5. Body weight <60 Kg.
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, prasugrel and ticagrelor 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 [women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study].

Description of laboratory assays

1) Light transmittance aggregometry (LTA): Platelet aggregation was performed using LTA according to standard protocols. Blood was collected in citrated (3.8%) 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 [14,16,17]. Platelet agonists included AA (1 mM), collagen (3µg/ml), ADP (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 (platelet-mediated thrombogenicity). 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 [14,16]. 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 ratio (PRI) was calculated after measuring VASP-P levels after stimulation with PGE1 (MFI PGE1) and also PGE1 + ADP (MFI PGE1 + ADP). The platelet reactivity index (PRI) = ([MFI PGE1] – [MFI PGE1 + ADP]/[MFI PGE1]) x 100%.

2) Thromboelastography (TEG) 6s Series system: the TEG 6s system (Haemonetics Corporation, Braintree, MA, USA) was used according to manufacture instructions [14]. In brief, the TEG 6s system is a new generation portable thrombelastography 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. In particular, the PlateletMapping Cartridge are used to assess platelet function in patients who have received platelet inhibiting drugs. The PlateletMapping assay consists of 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 agonists to generate test results that reflect the inhibiting effects of ADP $P2Y_{12}$ inhibitors. 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

the contribution of fibrin to the overall strength of the clot. The ADP test provide measures of MA, percent inhibition and percent aggregation.

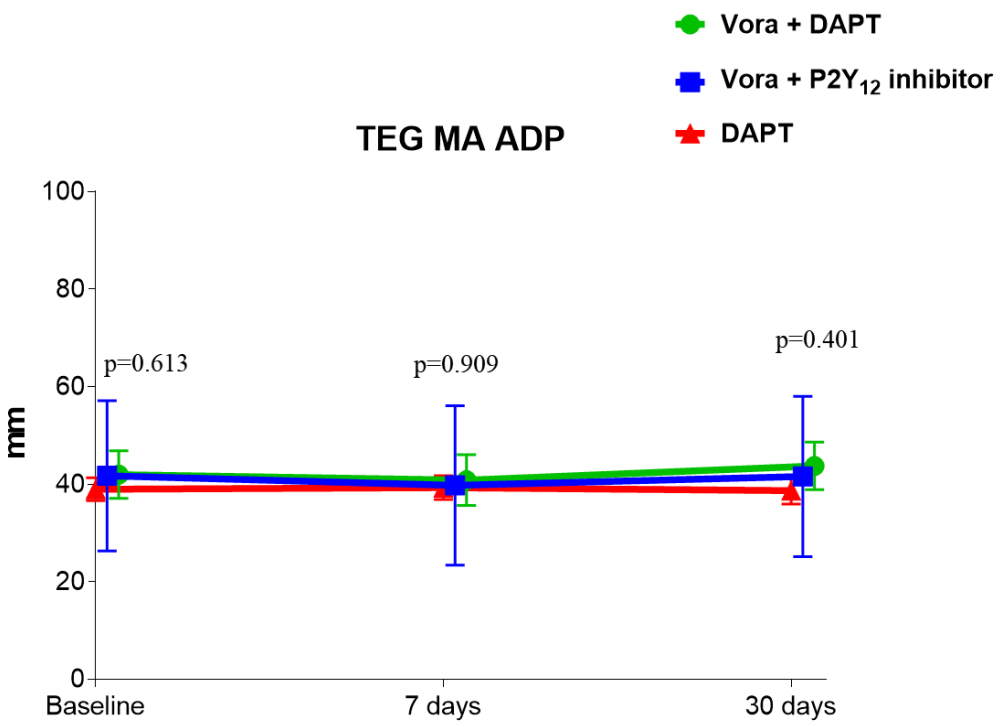
4) Serum thromboxane B_2: The concentration of serum thromboxane B2 (TXB_2) was measured by using the TXB_2 EIA kit (Cayman Chemical Company, Ann Arbor, MI) according to the instructions of the manufacturer, as previously described [15]. Briefly, samples were diluted with EIA buffer to bring their concentrations 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 1000 pg/mL and 7.8 pg/mL using EIA 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.

Table S1. Adverse events.

	Vorapaxar + DAPT n=44	**Vorapaxar + $P2Y_{12}$ inhibitor** n=43	**DAPT** n=43
BARC I bleeding, n (%)	6 (13.6%)	1 (2.3%)	0 (0%)
Chest pain*, n (%)	0 (0%)	0 (0%)	4 (9%)
Diarrhea, n (%)	1 (2%)	2 (4%)	0 (0%)
Dizziness, n (%)	1 (2%)	2 (4%)	0 (0%)
Dyspnea, n (%)	1 (2%)	1 (2%)	0 (0%)

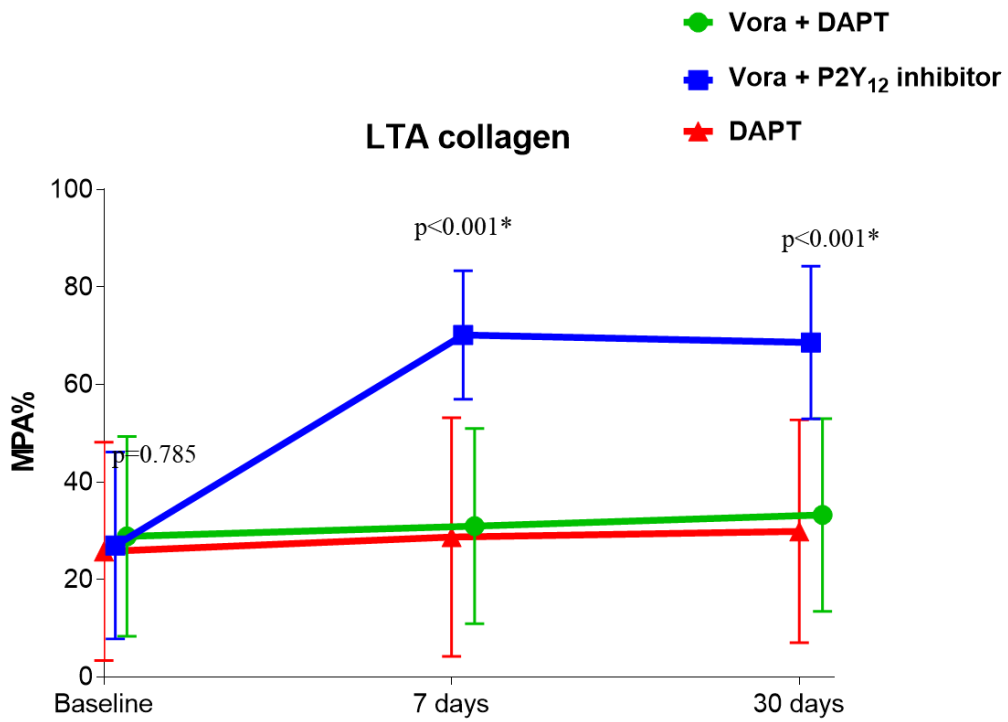
* No intervention was required

Figure S1. Clot strength (MA) measured by TEG platelet mapping using ADP as agonist.



Data are presented as mean, error bars represent standard deviation. P-values indicate the overall difference among the three groups at each time point. Offset between symbols and error bars is to improve readability.

Figure S2. Collage-induced maximal platelet aggregation (MPA%) measured by LTA.



* p<0.001 for Vora + P2Y12 inhibitor vs Vora + DAPT *and* Vora + P2Y12 inhibitor vs DAPT

Data are presented as mean, error bars represent standard deviation. P-values indicate the overall difference among the three groups at each time point. Offset between symbols and error bars is to improve readability.