BACKGROUND – THE STUDY QUESTION?	
Background	· Evidence has proven that drug-eluting stents are superior to bare-metal stents in high bleeding risks patients receiving dual antiplatelet therapy (DAPT). · DAPT after stent implantation has shown to improve morbidity and mortality by reducing ischemic events but increases bleeding risks. · A shorter course of DAPT therapy following drug-eluting stent implantation may be effective in patients that are at a higher risk of bleeding.
Previous Trials	· STOPDAPT-2 – when compared to 12 months of DAPT, 1 month of DAPT followed by clopidogrel monotherapy, resulted in lower risk of cardiovascular and bleeding events. · GLOBAL LEADERS – when compared to 1 month of DAPT followed by ticagrelor for 23 months, DAPT followed by aspirin monotherapy, resulted in no difference in lower all-cause mortality or lower incidence of new Q-wave MI. · ISAR-TRIPLE – compared 6 weeks vs 6 months of clopidogrel with aspirin in patients following drug-eluting stent implantation and found no significant difference in regards to composite outcome of death, MI, stroke, stent thrombosis or major bleeding.
Why this Study?	· Previous trials have not addressed appropriate duration of DAPT in patients with high bleeding risks post drug-eluting stent implantation. · Some of the studies were not randomized, did not include high risk bleeding patients, or patients with low ischemic risk were included. · There is evidence to indicate DAPT may not be needed for extended periods of time but the evidence is lacking in patients at high bleeding or ischemic event risk.
GENERAL STUDY OVERVIEW	
Title/Citation	· Valgimigli, M., Frigoli, E., Heg, D., Tijssen, J., Jüni, P., Vranckx, P., Ozaki, Y., Morice, M.-C., Chevalier, B., Onuma, Y., Windecker, S., Tonino, P. A. L., Roffi, M., Lesiak, M., Mahfoud, F., Bartunek, J., Hildick-Smith, D., Colombo, A., Stanković, G., … Smits, P. C. (2021). Dual antiplatelet therapy after PCI in patients at high bleeding risk. New England Journal of Medicine. https://doi.org/10.1056/nejmoa2108749
Funding	· The European Cardiovascular Research Institute was the sponsor and received grant support from Terumo. · Terumo is a medical device and service manufacturer which was founded in Tokyo, Japan. They expanded to North American in 1972.
Null Hypothesis	· 1 month of DAPT after implantation of a biodegradable-polymer sirolimus-eluting stent will be non-inferior on net adverse clinical events (NACE), major adverse cardiac/cerebral events (MACCE), and major or clinically relevant non-major bleeding events (MCB) when compared to a longer course of DAPT.
Trial Design	· Investigator-initiated, multicenter, randomized, open-label in 140 sites in 30 countries.
Objectives	· To determine in a high bleeding risk patient population undergoing PCI under standardized treatment, whether abbreviated DAPT is non-inferior to prolonged DAPT regimen in terms of NACE, MACCE and MCB within 12 months.
Enrollment	· 4,579 patients · 2,295 patients in abbreviated DAPT · 2,284 patients in standard DAPT
METHODS	

Inclusion Criteria	There were two sets of inclusion criteria: after index PCI implantation and at randomization visit one month after implantation. After index PCI implantation: · Meet at least one of the high bleeding risk criteria (treatment with oral anticoagulants for at least 12 months, age >75 years old, stroke in the last 6 months, chronic treatment with steroids or NSAIDs, to name a few) · All lesions successfully treated with Utlimaster stent in context of routine clinical care · Free from any flow-limiting angiographic complications · All stage of PCI complete and no further PCI planned At randomization visit, one month after PCI implantation:

	· Fulfillment of at least one of the high bleeding risks criteria or bleeding requiring medical attention that was not at the access site. · Uneventful 30-day clinical course · If not on an oral anticoagulant: on DAPT regimen of aspirin and P2Y12 inhibitor and the P2Y12 inhibitor must be the same for at least 7 days. · If on oral anticoagulant: on the same OAC for the last 7 days and also on clopidogrel for the last 7 days.
Exclusion Criteria	· Treated with stents other than Ultimaster stent within 6 months prior to index procedure · Treated for in-stent restenosis or stent thrombosis at index PCI or within 6 months before · Treated with bioresorbable scaffold at any time prior to index procedure · Active bleeding requiring medical attention on randomization visit · Hypersensitivity to aspirin, clopidogrel, ticagrelor, prasugrel, cobalt chromium or sirolimus · Pregnant or breast feeding women
Interventions	Abbreviated antiplatelet therapy · Aspirin and a P2Y12 inhibitor for 1 month post stent implantation, then single antiplatelet agent continued for 11 months. Standard antiplatelet therapy · Aspirin and P2Y12 inhibitor; P2Y12 inhibitor continued for 5-11 months post randomization and aspirin continued for 11 months.

Study Endpoints	Primary · Net adverse clinical endpoints defined as composite of all-cause death, myocardial infarction, stroke and bleeding events defined as Bleeding Academic Research Consortium (BARC) 3 or 5. · Major adverse cardiac or cerebral events defined as all cause death, myocardial infarction and stroke · Major or clinically relevant non-major bleeding depending as type 2,3 and 5 BARC bleeding events. Secondary · All cause death · Death from cardiovascular causes · Myocardial infarction · Stroke · Bleeding events · Definite or probable stent thrombosis · Any target vessel revascularization · Urgent or clinically indicated target/non target vessel revascularization · Transfusion rates both in patients with and/or without clinically detected overt bleeding BARC Bleeding Types · **Type 1:** bleeding that is not actionable and does not cause patients to seek treatment · **Type 2:** any overt, actionable sign of hemorrhage that does not fit in type 3, 4 or 5 but does meet one of the following: requiring nonsurgical, medical intervention, leads to hospitalization or increase care, or prompts evaluation · **Type 3a:** overt bleeding plus hemoglobin drop of 3-5 g/dL · **Type 3b:** overt bleeding plus hemoglobin drop of 5 g/dL; cardiac tamponade; bleeding requiring surgical intervention for control or bleeding requiring intravenous vasoactive agents · **Type 3c**: intracranial hemorrhage; subcategories confirmed by autopsy or imaging or lumbar puncture; intraocular bleeding compromising vision · **Type 4:** coronary artery bypass grafting-related bleeding · **Type 5a:** probable fatal bleeding; no autopsy or imaging confirmation but clinical suspicions · **Type 5b:** definite fatal bleeding, overt bleeding or autopsy or imaging confirmation
Statistical Analyses	· 90% power to show non-inferiority with regard to NACE; assumed cumulative incidence of 12.0% in each group · Differences in cumulative incidents at 335 days and P values calculated used Com-Nogue method · Kaplan-Meir method used for first two primary outcomes · Kaplan- Meir method, cause specific, used for third primary outcome

RESULTS	
Enrollment	· February 2017-Decemebr 2019 · 4,579 were randomly assigned · Abbreviated arm: 2,295 patient included in intention-to-treat population and 2,204 included in per-protocol population · Standard arm: 2,284 included in intention-to-treat population and 2,230 included in per protocol population
Baseline Characteristics	· Table 1 · Baseline characteristics and clinical presentation did not differ significantly between groups.
Monitoring	· Randomization visit at 30 to 44 days after the index procedure · Follow up visits at 60, 150 and 335 days after randomization. · Follow up at 60 and 150 days did not have to be on-site but it was preferred

	· Follow up at 335 days had to be an on-site visit.
Main Study Endpoint Results	· NACE Abbreviated arm: 7.5% (165 patients) Standard arm: 7.7% (172 patients) · MACCE Abbreviated arm: 6.1% (133 patients) Standard arm: 5.9% (132 patients) · MBE Abbreviated arm: 6.5% (148 patients) Standard arm: 9.4% (211 patients)
Subgroup Study Endpoint Results	· Kaplan-Meier cumulative incidence of death from any cause was similar between both groups (3.3% and 3.6%) · Cumulative incidence of bleeding of type 3, 4 or 5 was similar in both groups (2.3% and 2.6%)

AUTHOR'S CONCLUSIONS

· Discontinuation of DAPT at a median of 34 days after PCI was non-inferior to continuing DAPT for a median of 193 days · The lower risk of bleeding in the abbreviated therapy group was mostly due to the lower incidence of clinically relevant non major bleeding events.

GENERALIZABILITY/CRITIQUE/DISCUSSION

· Randomized, multicenter
· Baseline Characteristics: BMI of population lower than average in Arkansas, lower percentage of patients having diabetes, coronary artery disease, and heart failure than typical patient population in Arkansas.
· Non-inferiority was found for primary endpoints in regards to net clinical events, major adverse cardiac and cerebral events and non-major bleeding (BARC bleeding type 2 or less)
· Of note, the cumulative incidence of bleeding types 3, 4 or 5 was similar between groups showing there was no difference in major bleeding between them. (2.3 vs 2.6%)
· Some characteristics defined as high bleeding risk are questionable: this study used age greater than 75 as a high bleeding risk, although increased age does put patients at a risk of bleeding this does not necessarily mean they are high risk and this could be the only criteria some participants had as only one criteria had to be met.
· Cumulative incidence of bleeding of type 3, 4 or 5 was similar in both groups (2.3% and 2.6%); bleeding type 3, 4 and 5 are the most serious types of bleeding.
· Bleeding events when using Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) were also similar among both groups.
· Therapy in abbreviated treatment group varied, due to open-label
· This data set it limited only to those patients receiving a Temuro produced Ultimaster stent

Reviewed by Rachell Eaker, PharmD