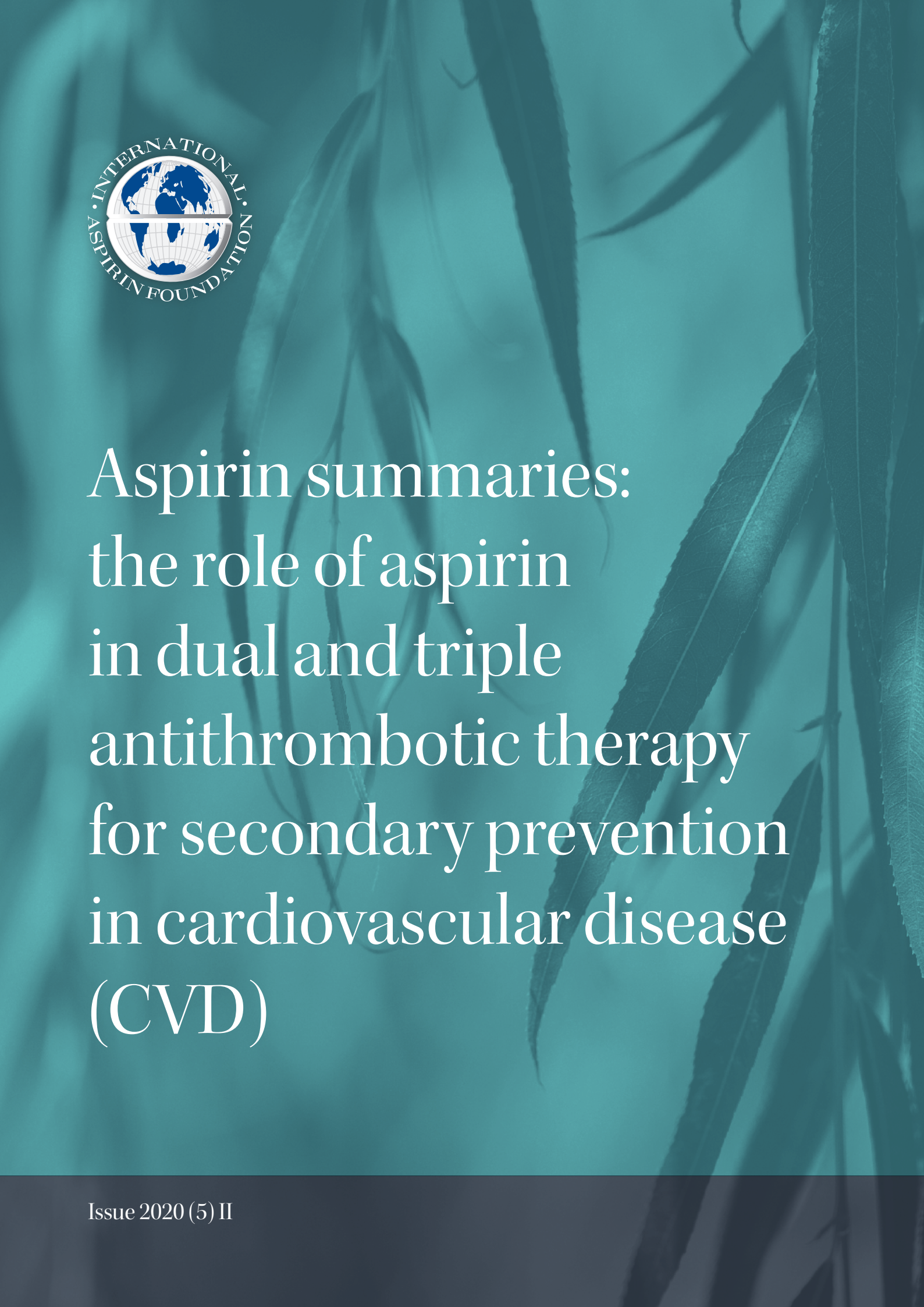

Aspirin summaries: the role of aspirin in dual and triple antithrombotic therapy for secondary prevention in cardiovascular disease (CVD)

Issue 2020 (5) II

Double versus triple antithrombotic therapy in people with atrial fibrillation who undergo percutaneous coronary intervention.

Exploring ways to optimise antithrombotic therapy for the secondary prevention of CVD whilst reducing the risk of bleeding complications is an important and clinically relevant research question. This article describes a meta-analysis of four non-vitamin K antagonist oral anticoagulant (NOAC) randomised clinical trials in which the safety and efficacy of double versus triple antithrombotic therapy (DAT vs TAT) are compared in people with atrial fibrillation who require percutaneous coronary intervention (PCI).

Four trials (AUGUSTUS, ENTRUSTAF-PCI, Pioneer AF-PCI and RE-DUAL PCI) were included covering 10 234 patients. Major or clinically relevant non-major bleeding was found to be significantly lower for DAT when compared with TAT [risk ratio (RR) 0.66, 95% confidence interval (CI) 0.56-0.78; P<0.0001: I^2=69%] but this was balanced by a significantly increased risk of stent thrombosis [RR 1.59, 95% CI 1.01-2.50: P=0.04: I^2=0%] and a higher risk of MI in those taking DAT alone. In particular, NOAC based DAT in comparison with vitamin K antagonist TAT showed a significant reduction in intracranial haemorrhage.

One interesting clinically relevant finding from this meta-analysis is the fact that the bleeding benefit from using DAT appears to come with a cost of additional cardiac (but not cerebrovascular) ischaemic events.

The authors state that:

'This finding carries relevant clinical and pathophysiological implications and reinforces the notion that the upfront selection between TAT or DAT and/or the optimal timing for aspirin discontinuation after intervention or ACS should be individualized.'

Gargiulo et al 2019 Page 3765

For further information please see:

Gargiulo G., Goette A., Tijssen J., Eckardt L., Lewalter T., Vranckx P. and Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. European Heart Journal (2019) **40**, 3757-3767.

Aspirin in people with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI).

The authors in this correspondence article review the evidence for dual antithrombotic therapy (DAT) versus triple antithrombotic therapy (TAT). They look at some of the limitations in the four randomised clinical trials on which the DAT recommendations are based. These include:

- Open- label design
- Lack of power for efficacy outcomes
- Two of the four trials had efficacy outcomes that included non-thrombotic events
- Subsequent meta-analyses performed on these four trials share these limitations
- The prognostic impact of a bleeding event is not always equivalent to a non- fatal MI

After a careful discussion of this data the authors conclude:

"It is probably too soon to routinely drop aspirin immediately after PCI in patients with AF."

Galli M et al 2019

For further information please see:

Galli M., Andreotti F., Savarese G. et al. Dropping aspirin in patients with atrial fibrillation undergoing percutaneous coronary intervention: a jump with a weak parachute? European Heart Journals Cardiovascular Pharmacotherapy (2019) **5**, 55-56.

2018 Joint European Consensus document on antithrombotic therapy in people with atrial fibrillation (AF) presenting with acute coronary syndrome (ACS) and/or undergoing percutaneous cardiovascular interventions (PCI)

The Joint European consensus guidelines for antithrombotic therapy discuss recent TAT versus DAT trials for people with AF undergoing PCI and conclude that:

"An initial period of triple therapy should be used in most AF patients undergoing PCI depending on presentation (ACS vs elective), stroke vs bleeding risk, procedural considerations (e.g. disease severity) etc."

Lip et al 2019

They do however suggest dual therapy with an oral anticoagulant (OAC) plus one $P2Y_{12}$ inhibitor (e.g. clopidogrel) in people with excessive bleeding risk but a low thrombotic risk.

The authors state that some questions remain over the use of DAT e.g. NOAC plus clopidogrel as opposed to a TAT regimen that includes aspirin.

For further information please see:

Lip G.Y.H., Collet J.P., Haude M. et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of EHRA, EAPCI, ACCA, HRS, APHRS, LAHRS, CASSA. Europace (2019) **21** 192-193.

Dual versus triple antithrombotic therapy (DAT v TAT) after percutaneous coronary intervention (PCI) in people with atrial fibrillation (AF) – dual therapy brings a lower risk of bleeding events but increases the risk of ischemic events.

This article describes the importance of finding the optimum antithrombotic therapy for people with AF requiring PCI in order to prevent stroke [using an anticoagulant], myocardial infarction (MI) and stent thrombosis [using an anti-platelet].

In reviewing the literature, the authors explain the issue that whilst recent trials, carried out to help find the optimum regimen for this population, have shown that bleeding risk is lower in people taking DAT none of these randomized controlled trials (RCTs) were designed with the power to understand the impact of DAT versus TAT on ischemic events.

Some of the trial work has also indicated that people with other risk factors, such as diabetes and acute coronary syndrome (ACS), have an increased the risk of having an MI or a stent thrombosis while on DAT, making an individualised approach important.

The authors performed a meta-analysis on five RCTs with data from 9931 patients and this showed that DAT compared with TAT lowers the risk of bleeding events. However, they also found a numerically higher number of ischemic events in the DAT group but this was not statistically significant.

The authors estimate that the currently available trial data does not provide enough patient numbers to perform a meta-analysis that will answer the question as to whether the benefit of less bleeding events comes at a cost of increased ischemic events in this group of people. They estimate that a meta-analysis with 31,290 patients for ischemic events, 39,106 patients for MI and 20,016 patients for stent thrombosis would be required to achieve a study with 80% power and 5% significance.

For further information please see:

Gupta K., Prejean S.P. Vaduganathan M. et al. Does dual vs. triple antithrombotic therapy after percutaneous coronary intervention in patients with atrial fibrillation lower the risk of bleeding at the cost of increased risk of ischemic events? IJC Heart and Vasculature (2019) **24**, 100404.

Extracts from the 2019 International Aspirin Foundation Scientific Conference, Rome, 2019: benefits and risks of antithrombotic therapy for cardiovascular disease prevention

Antithrombotic therapy in secondary cardiovascular disease (CVD) prevention was one of the many topics discussed during our Scientific Conference, where international experts gathered to discuss and debate 'Dropping aspirin from dual antithrombotic therapy (DAT) and triple antithrombotic therapy (TAT)'.

Below are the speaker biographies and their extract from the conference report.

Professor Marco Cattaneo

Professor Marco Cattaneo is Professor of Internal Medicine at Università degli Studi di Milano. He has been Post-Doctoral Fellow at McMaster University, Hamilton (Ontario), Guest or Visiting Scientist at McMaster University, Temple University, Philadelphia (PA), The Scripps Research Institute, La Jolla (CA). In 2001 he was awarded the International Society on Thrombosis and Haemostasis (ISTH) 10th Biennial Award for Contributions to Haemostasis and Thrombosis. Editor/Associate Editor/ member of Editorial Board/Advisory Board for high-tier journals, including Jornal of Thrombosis and Haemostasis, Thrombosis Research, Haematologica, Platelets, Thrombosis and Haemostasis, Arteriosclerosis, Thrombosis and Vascular Biology. Professor Marco Cattaneo is also Chair of the Working Party on Platelet Aggregation, Chair of the Scientific Subcommittee on Platelet Physiology, Scientific and Standardization Committee (ISTH). Member of the ISTH Council 2010-2016. President-Elect, President and Past-President of SISET, the Italian Society on thrombosis and hemostasis, 2002-2008. Main research interests: pathophysiology of primary haemostasis, pharmacology of antiplatelet agents, risk factors for thromboembolism.

Current affiliation: Medicina 2, ASST Santi Paolo e Carlo, Milan, Italy – Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

Extract from Conference Report
Dropping aspirin from DAT or TAT

Prof. Marco Cattaneo (University of Milan, Italy) presented experimental, mechanistic data to see if there is evidence that DAPT with aspirin and a P2Y12 antagonist and monotherapy with a P2Y12 antagonist alone had a similar inhibitory effect on platelet function. He showed that whilst pharmacological inhibition of the platelet P2Y12 receptors for adenosine diphosphate (ADP) significantly inhibits platelet aggregation and the platelet production of thromboxane A2 (TxA2) [thromboxaneB2 (TxB2)], the data also showed that four patients with severe inherited defects of P2Y12 had normal serum TxB2 levels and one patient with inherited dysfunctional P2Y12 also had normal levels of serum TxB2.

He explored whether the inhibitory effect of P2Y12 antagonists on platelet TxA2 production that has been demonstrated in other studies was due to effects such as methodological differences. It is thought that platelet aggregation leads to thromboxane synthesis, which stimulates the release of ADP from the platelet granules. The ADP interacts with its receptors thus amplifying the platelet response and thromboxane production. In order to confirm this hypothesis, platelet aggregation induced by collagen in healthy subjects was tested in stirring conditions. Results showed that in the presence of all P2Y12 antagonists, platelet aggregation is reduced compared to the vehicle. TxB2 production was measured in the same samples and found to be reduced with all P2Y12 antagonists compared to the vehicle. However, when no stirring conditions were used, thromboxane production was not reduced in the presence of the P2Y12 antagonists when compared to the vehicle. Therefore, it is the inhibition of platelet aggregation in vitro by P2Y12 antagonists that is responsible for the observed partial inhibition of TxA2 production by platelets.

The effects of the platelet aggregation and level of TxB2 after stimulation by high concentrations of collagen in the presence of a P2Y12 antagonist (cangrelor) and aspirin, both were explored independently and individually. Results showed the combination

therapy of cangrelor and aspirin is better able to inhibit platelet aggregation. The combination therapy produced significant inhibition under experimental conditions.

Prof. Cattaneo explained that P2Y12 antagonists, therefore, do not inhibit the platelet production of TxA2 and that DAPT with aspirin and a P2Y12 antagonist is more effective in inhibiting platelet aggregation than either drug alone, and there is no pharmacological evidence that aspirin is dispensable in high-risk patients who are generally treated with DAPT.

Having established the need for DAPT, Prof. Cattaneo presented further data to help the audience understand how to dose aspirin in DAPT and showed that the effect is best with low-dose aspirin. He concluded that this is probably the lowest dose that causes >95% inhibition of platelet TxA2 production, potentially around 30 mg daily.

Professor Marco Valgimigli

Marco Valgimigli is associate professor cardiology and senior interventional cardiologist at the Inselspital Universitätsspital Bern. He obtained his medical degree, summa cum laude, from the University of Bologna, and completed his training in internal medicine at the same university. He received a degree in cardiological sciences at the University of Ferrara and a PhD in interventional cardiology at Erasmus Medical Center in Rotterdam.

Prof Valgimigli's areas of research are wide ranging and include high-risk percutaneous interventions (PCI); invasive treatment of myocardial ischaemia (MI); reparative medicine with adult stem cells during MI and heart failure; antithrombotic therapy during and after PCI; and prognostic stratification during acute coronary syndromes and MI.

He serves as national coordinator on numerous clinical trials, including MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study), 3T/2R (Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel), PRODIGY (Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia Study), EXCEL, ZEUS, MATRIX and ODYSSEY.

Prof Valgimigli is a fellow of the European Society of Cardiology, and has been widely published in international journals such as the European Heart Journal, American Heart Journal, Circulation, The Lancet, Journal of the American Medical Association, and The New England Journal of Medicine.

Prof. Marco Valgimigli (University of Bern, Switzerland) presented the clinical data for removing aspirin from DAT or TAT:

A recent meta-analysis of randomised clinical trials (RCTs) examined the safety and efficacy of DAT compared to TAT in patients with atrial fibrillation (AF) following percutaneous coronary intervention (PCI) [1]. This meta-analysis demonstrated that DAT is better than TAT when looking at bleeding events and comparable for TAT for efficacy outcomes suggesting DAT is the best regimen for the vast majority of patients.

Prof. Valgimigli explored if it was the triple therapy itself or its composition and duration that was the true culprit for the excess bleeding events. He found some issues related to choice of anticoagulant: for instance, warfarin causes more bleeding than a direct oral anticoagulant (DOAC) making this an unfair comparison. In addition, the duration of TAT was often prolonged for longer than the protocol indicated e.g. beyond 6 months which again influenced the results.

The Augustus trial [2, 3] gave important clarification around stroke risk and raised new concerns about stent thrombosis risk where aspirin was dropped from the regimen. The Augustus study showed that dropping aspirin early on was associated with less bleeding but a numerical increase in stent thrombosis events.

In the Augustus study, only patients who actually received a stent were included in the randomisation which is a better measure as in some trials around 50% of patients randomised do not actually receive a stent, which means the risk of a stent getting occluded is non-existent.

'GLOBAL LEADERS' [4] is a complex study in which low-dose aspirin (75–100 mg/day) taken for 1 month in patients with either acute coronary syndrome (ACS) or stable angina was followed by 23 months of monotherapy with ticagrelor 90-mg bid. The reference strategy arm received low-dose aspirin for 24 months and the patients with ACS including unstable angina without the cardiac biomarkers, NSTEMI and STEMI received ticagrelor during the first 12 months, whereas the patients with stable angina received clopidogrel 70 mg/day for the first 12 months. This trial had an all-comers design and recruited almost 16,000 patients in a 1:1 randomisation ratio in an open-label design in 130 centres worldwide. GLASSY, a sub set study from GLOBAL LEADERS, showed that 1 month of DAPT was non-inferior to 12 months DAPT when looking at preventing death, myocardial infarction (MI) stroke or urgent target vessel revascularisation.

Data from SMART CHOICE [5] and STOP DAPT-2 [6] were also presented. They showed that dropping aspirin immediately after PCI when used as part of triple therapy cuts the bleeding risk but increases the risk of stent events and dropping aspirin 1–3 months after PCI in the context of dual therapy reduces bleeding risk without a higher ischaemic event risk.

Following the presentations, discussion took place around the types of bleeding events included and how having an MI is often not equivalent to a bleeding event unless this is an intracranial bleed.

Reference

Cattaneo Marco, Badimon Lina, Agnelli Giancarlo, Chan Andrew T, Lanas Angel, Rocca Bianca, Rothwell Peter, Patrignani Paola, Langley Ruth, Vilahur Gemma, Cosentino Francesco (2020) Highlights from the 2019 International Aspirin Foundation Scientific Conference, Rome, 28 June 2019: benefits and risks of antithrombotic therapy for cardiovascular disease prevention ecancer 14 998

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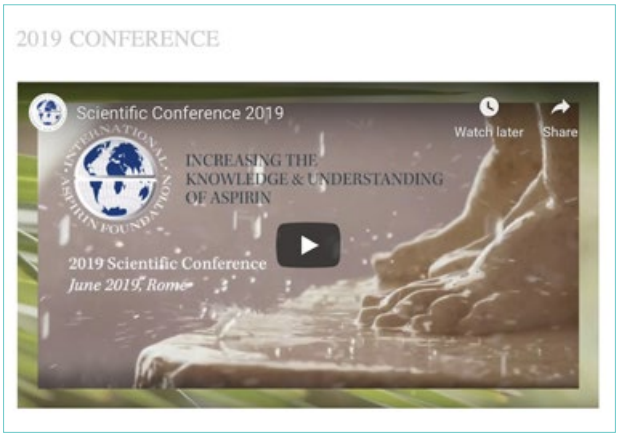
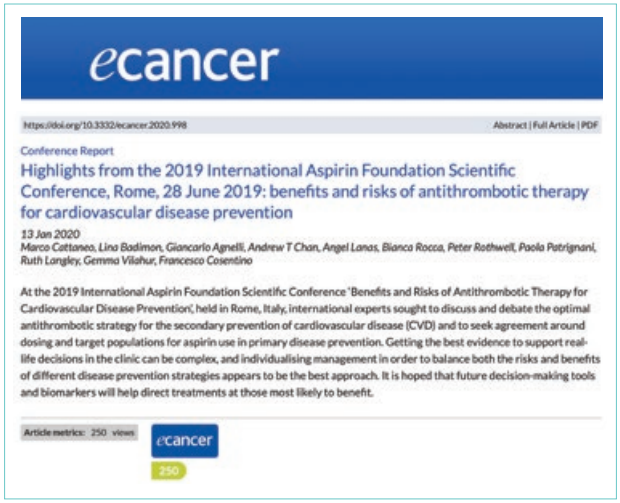


And read the conference report:

https://ecancer.org/en/journal/article/998-highlights-from-the-2019-international-aspirin-foundation-scientific-conference-rome-28-june-2019-benefits-and-risks-of-antithrombotic-therapy-for-cardiovascular-disease-prevention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Conference Report

Highlights from the 2019 International Aspirin Foundation Scientific Conference, Rome, 28 June 2019: benefits and risks of antithrombotic therapy for cardiovascular disease prevention

13 Jan 2020

Marco Cattaneo, Lina Badimon, Giancarlo Agnelli, Andrew T Chan, Angel Lanas, Bianca Rocca, Peter Rothwell, Paola Patrignani, Ruth Langley, Gemma Vilahur, Francesco Cosentino

At the 2019 International Aspirin Foundation Scientific Conference 'Benefits and Risks of Antithrombotic Therapy for Cardiovascular Disease Prevention', held in Rome, Italy, international experts sought to discuss and debate the optimal antithrombotic strategy for the secondary prevention of cardiovascular disease (CVD) and to seek agreement around dosing and target populations for aspirin use in primary disease prevention. Getting the best evidence to support real-life decisions in the clinic can be complex, and individualising management in order to balance both the risks and benefits of different disease prevention strategies appears to be the best approach. It is hoped that future decision-making tools and biomarkers will help direct treatments at those most likely to benefit.

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