problems facing humanity whether they be in biomedicine or in agriculture and importantly to do that with an eye towards accessibility, sustainability, and affordability that will make the technology go from a lab tool to a standard of care some day in genetic disease or a way to create the kind of changes in agricultural products to meet the challenges of climate change, and so much more'.

The Nobel Prize was announced during an online ceremony in Stockholm. Claes Gustafsson reiterated the enormous implications—current and future of the discovery and said how it had revolutionized biomedical science and enabled the 'dream to cure' genetic diseases. He did, however, note with caution that the enormous power of this technology means it should be used with caution and great care must be taken regarding the ethical framework in which it is employed.

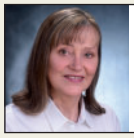
The two women share the prize fund of KR 10 000, a place in scientific history and will receive their awards at a future date as the traditional Nobel Week celebrations which take place in Stockholm in the December following the prize announcements have been cancelled for 2020 due to the ongoing CV19 pandemic.

Expert comment: Jeanette Erdmann PhD

Jeanette Erdmann is Professor of Cardiogenetics and Director of the Institute for Cardiogenetics (ICG) at the University of Lübeck, Germany and is known for her investigative work into the underlying genetic factors of cardiovascular disease and myocardial infarction to develop novel therapeutic targets.

'It's not only in cardiovascular research that CRISPR has opened up a whole new avenue of applications. Experimentally, we can now systematically interrogate the influence of non-coding variants we have identified in the past decade by genome-wide association studies, for example, by generating cell culture models into which we introduce the variant under investigation using CRISPR and then study whether this change is functionally effective. Importantly, these studies can also be done in a large-scale setting allowing us to study thousands of variants simultaneously. But CRISPR plays an even more important role when it comes to possible therapies. Firstly, CRISPR allows the establishment of urgently needed disease models necessary for the development of novel therapeutics approaches. And secondly, in the not so far future, we might use CRISPR to tackle other cardiovascular risk genes apart from PCSK9 to reduce cholesterol'.

Conflict of interest: none declared.



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Antiplatelet and direct oral anticoagulation management after coronary artery bypass graft surgery: the Cinderella of current cardiovascular trials, please show me (some) evidence

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Introduction

Even today, it remains unclear whether an intensification of platelet inhibition or anticoagulant therapy is beneficial when added to the standard therapy with acetylsalicylic acid (ASA) after coronary artery bypass graft (CABG) surgery.

The literature shows clear evidence supporting dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome (ACS), especially after coronary stent implantation or on medical treatment alone, as well as in patients with stable coronary artery disease (CAD) after coronary interventions, unless there is an indication for full-dose anticoagulation or an elevated bleeding risk. DAPT with ASA plus clopidogrel or ticagrelor after CABG surgery decreases the incidence of bypass graft failures and might protect against recurrent ischaemic events in off-pump surgical strategies or after coronary endarterectomy. Concerning graft patency, there is strong evidence that ASA prevents early occlusion and increases long-term graft survival. Based on some data from subgroup analyses of randomized controlled ACS

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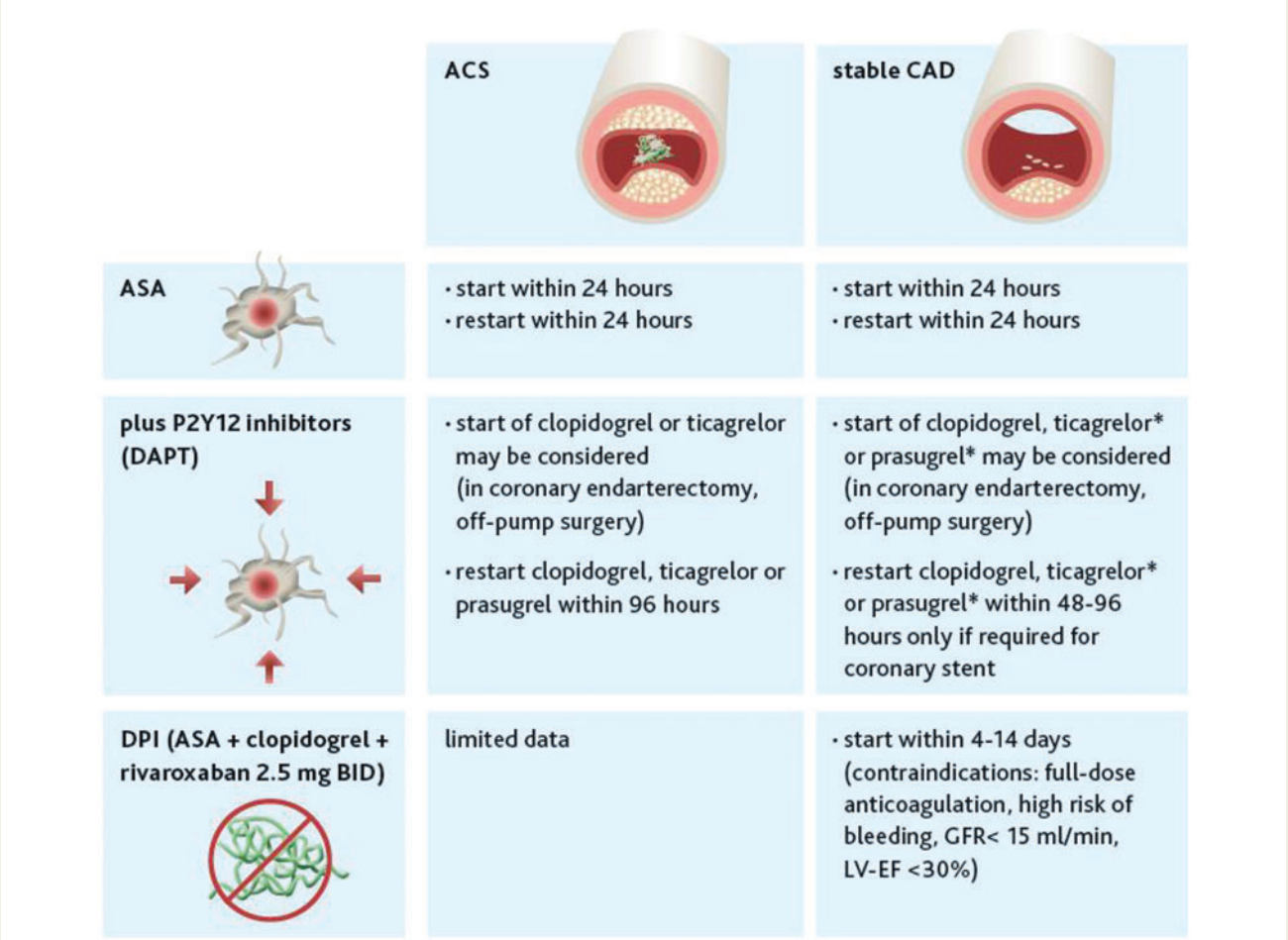

Figure 1 The current state of evidence on postoperative antiplatelet and anticoagulation therapy in coronary artery bypass graft surgery.[1,3] ACS, acute coronary syndrome; ASA, acetylsalicylic acid; b.i.d., twice daily; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; GFR, glomerular filtration rate; LV-EF, left ventricular ejection fraction. *Patients post-ACS and if DAPT was well tolerated for 12 months.

trials, DAPT is associated with reduced mortality and improved vein graft patency.[1,2]

For decades, anticoagulation with vitamin K antagonists (VKA) was the therapy of choice in patients with coexisting atrial fibrillation (AF) and stable CAD due to its beneficial stroke prevention and anti-ischaemic potential comparable to combination therapy with ASA and VKA, but with a significantly lower bleeding risk.[3] In recent years, an anticoagulation strategy with low-dose direct oral anticoagulants was tested in large-scale randomized trials, which confirmed that some patients with ACS or stable CAD benefit from dual pathway inhibition (DPI) by combining coagulation factor Xa inhibition and ASA (NCT00809965, NCT00831441, NCT01776424).

It remains an important clinical question whether this strategy is applicable in patients after CABG surgery, and if so, whether the benefits outweigh the increased risk of bleeding. Moreover, it is desirable to define the clinical setting in which patients may benefit the most, especially with regard to patients in whom DAPT is indicated, according to the aforementioned scenarios. Although the European Medicines Agency (EMA) has approved a DPI regimen in patients who are at high risk of a recurrent thrombotic event after ACS, evidence from trials addressing a surgical cohort is scarce (EMEA/H/C/005279).

Dual pathway inhibition pathophysiology

The concept of combined antiplatelet and anticoagulant therapy was derived from molecular and cellular models of coronary atherogenesis. An atherosclerotic plaque rupture triggers platelet activation and an exposure of tissue factor, which is known to activate the coagulation cascade. Both mechanisms of arterial thrombus formation are medically addressed by the DPI strategy: ASA irreversibly inactivates the cyclooxygenase enzymes, leading to a reduced production of the prothrombotic thromboxane A2 and hereby inhibiting platelet activation, and the direct coagulation factor Xa inhibitor interrupts the coagulation cascade, consequently blocking thrombin and fibrin formation.[4]

Dual pathway inhibition trials

In the ATLAS ACS2-TIMI51 trial, 15 526 patients received the direct factor Xa inhibitor rivaroxaban [2.5 or 5 mg twice daily (b.i.d.)] or placebo in addition to standard therapy with ASA alone (7%) or as add-on to a combination of ASA and clopidogrel (93%) within 1 week after ACS. None of the participants received a more potent P2Y12 inhibitor

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(ticagrelor, prasugrel) in a DAPT or DPI regimen. In the combined rivaroxaban groups, the composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, and stroke, was reduced by 16% ($P = 0.008$) at the cost of an increase in major bleeding, but with no increase in fatal bleeding compared to placebo. The very low rivaroxaban dose (2.5 mg b.i.d.) also showed reduced mortality rates ($P = 0.002$) (NCT00809965).

Approximately 60% of ACS patients underwent revascularization by either percutaneous coronary intervention (PCI) or CABG surgery. The proportion of patients with CABG surgery has not been published and no subgroup analysis addressing the efficacy of DPI in preventing primary graft failure has been performed yet. In the case of non-emergency indications and randomization before revascularization, the study drug (rivaroxaban or placebo) was stopped 12 h before CABG surgery and was restarted after postoperative recovery, when no ongoing bleeding risk was assumed.[5]

A previous, similar trial underlined the importance of administering a low dose of the anticoagulant in the DPI regimen: The direct factor Xa inhibitor apixaban at a full therapeutic dose of 5 mg b.i.d., as given in AF, led to excessive major bleeding including intracranial haemorrhage when combined with ASA in an early post-ACS cohort. The participants were mainly treated by medical therapy only (55.6%) or by PCI (43.8%). The trial was terminated early for safety reasons. There was no reduction in MACE or mortality in the 7392 participants recruited (NCT00831441).

The combination of full-dose anticoagulation and a highly potent P2Y12 inhibitor (ticagrelor, prasugrel) has been studied in patients with AF undergoing PCI; dual or triple antithrombotic strategies with a vitamin K antagonist have been associated with significantly higher rates of clinically relevant haemorrhagic complications and should therefore be avoided according to the current guidelines.[6] The combination of rivaroxaban and ticagrelor is currently under investigation (CAPITOL PCI AF trial, NCT03331484).

In the COMPASS trial, more than 27 000 patients with stable cardiovascular diseases were randomized to ASA alone, rivaroxaban 5 mg b.i.d. alone, or rivaroxaban 2.5 mg b.i.d. combined with ASA. Compared to ASA alone, DPI was associated with a reduction in the composite of MACE by 24% (4.1% vs. 5.4%; $P < 0.001$) and a reduction in mortality (3.4% vs. 4.1%; $P = 0.01$) at the cost of an increase in major bleeding, defined as any bleeding that led to presentation to an acute care facility or to hospitalization (3.1% vs. 1.9%; $P < 0.001$). Fatal or critical organ bleeding was not increased (NCT01776424). Patients with a left ventricular ejection fraction (LV-EF) of less than 30% or New York Heart Association (NYHA) functional class III or IV symptoms were excluded from the investigation on the basis of the results of the COMMANDER-HF trial.[7] Here, a very low dose of rivaroxaban (2.5 mg b.i.d.) in addition to standard antiplatelet therapy (ASA or DAPT) was not superior to placebo at preventing MACE (25.0% vs. 26.2%; $P = 0.27$) or mortality in 5022 patients with CAD and chronic heart failure (LV-EF $\leq$ 40%) who had not undergone concurrent revascularization (NCT01877915).

A pre-planned sub-study of the COMPASS trial analysed whether DPI is effective in preventing graft failure and MACE after CABG surgery. A total of 1448 patients were randomized within 4–14 days after implantation of at least two bypass grafts. Compared to ASA alone the combined therapy reduced the composite of MACE (2.4% vs. 3.5%; $P = 0.34$) non-significantly, but in line with the results of the larger COMPASS trial. DPI failed to reduce graft failures (9.1% vs. 8.0%; odds ratio 1.13; 95% confidence interval 0.82–1.57; $P = 0.45$), which were diagnosed by a computed tomography angiogram (CTA) 1 year after surgery (NCT01776424). The authors discussed that this might be due to the low power of the sub-study, since the COMPASS trial was stopped early and not all patients underwent CTA. In concordance with these results, in a previous study from 1997, anticoagulation with low-dose warfarin (mean international normalized ratio 1.4) failed to reduce long-term graft failure.[8]

Conclusions

The data on DPI after CABG surgery in patients with ACS or with stable CAD are limited: The size of the ACS cohort managed by surgical revascularization remained undefined and the time of starting or re-starting DPI after surgery was presumably too late to prevent early graft failures, since these commonly occur within the first days to weeks after surgery.[9,10] Additionally, DPI has never been compared to a DAPT strategy with a more potent P2Y12 inhibitor than clopidogrel in either an ACS cohort or a stable CAD cohort. Furthermore, DPI after elective CABG surgery has not been investigated in patients with a reduced LV-EF <30% or NYHA functional class III or IV symptoms. *Figure 1* summarizes the current state of evidence on DPI after cardiac surgery.

Taking the available evidence, with all its limitations for a surgical cohort, and the promising underlying pathophysiological concept into account, we suggest carefully considering DPI treatment in patients after elective CABG surgery with an LV-EF >35%. This is valid under the assumption that the bleeding risk is low and the risk of recurrent ischaemic events is elevated, especially in patients with more severe atherosclerosis and diabetes. Overall, further in-depth research assessing the adequate and safe time of DPI initialization after CABG surgery and its potential to prevent early graft failure is urgently needed.

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Introduction to the Department of Cardiology in West China Hospital of Sichuan University

History and current status of West China Hospital

The history of West China Hospital (WCH), situated at the city of Chengdu and affiliated with Sichuan University, can be traced back to the Renji and Cunren Hospital founded by missionaries from America and Canada in 1892. It became an epicentre for thriving of academic excellence and nurturing of medical talents in China during World War II, when renowned universities and colleges in war-afflicted area moved to take cover in the west. WCH has now become a leading medical centre in China, with 4300 beds and 5.7 million outpatient visits annually (*Figure 1*). WCH ranks No. 2 in the Best Hospital in China Rankings (2009–2019), and ranks No. 1 in the Science and Technology Evaluation Metrics (STEM) Rankings for Chinese Hospitals (2014–2019).

The Department of Cardiology, founded by Professor Luo Decheng in 1954, is now designated as a state key clinical specialty and the only state-qualified training centre for cardiac interventional therapeutics in Sichuan Province. The Department has 185 beds, one coronary care unit, and nine Cath Labs. The Department performs many percutaneous procedures to treat patients in need. Acknowledging the great potential of transcatheter valve interventions, the Department was devoted to promoting the technique in China during the past decade. Currently, the Department has developed as a leading centre of transcatheter aortic valve implantation (TAVI) in China, in terms of both quality of care and academic reputation.

The heart valve team

The multidisciplinary heart valve team of WCH strives to provide patient-oriented care (*Figure 2*). The team was founded by Professor Mao Chen in 2012, when TAVI had gained worldwide acceptance. However, promoting TAVI in China was encountered with enormous challenges, primarily due to the different aortic valve anatomy and the lack of commercially available devices. Approximately 40% of TAVI candidates in China have a bicuspid aortic valve (BAV) and 10~20% have non-calcific leaflets, both had been considered as relative contraindications for TAVI. Besides, many patients in China are in critical status when sought care, making the procedure even more challenging. By cooperating with leading valve centres and domestic manufacturers, the team was able to help solve some key problems that had impeded TAVI development in China.

Clinical research on transcatheter aortic valve implantation in bicuspid anatomy

BAV is frequently associated with eccentric annulus, 'volcano-shaped' leaflet configuration, and asymmetrical valve calcification. These unfavourable anatomical features pose significant challenges for TAVI, with increased risk of elliptical deployment and prosthetic valve dysfunction. However, given the high incidence, BAV is an inevitable problem for TAVI implanters in China. To date, the team has treated approximately 500 patients with BAV by TAVI. Incorporating their preliminary experience, the team comprehensively reviewed the safety and efficacy of TAVI in BAV in a paper published in *Nature Reviews Cardiology* in 2014. The paper proposed technical strategies for optimal outcomes and pointed out the knowledge gap for future research.

To optimize patient selection, the team cooperated with Professor Hasan Jilaihawi from NYU Langone Medical Center and proposed a simplified and novel classification of BAV for TAVI which categorized BAV as tricommissural, bicommissural raphe type, and bicommissural non-raphe type. Such classification better reflects the interaction between prosthesis and the aortic-valvular complex and provides informative guidance for procedural workup.

Another tricky issue was prosthetic valve sizing for BAV. The team proposed a novel sizing technique widely known as supra-annular sizing along with Professor Nicolo Piazza from McGill University Health Center, Canada. The concept derived from an observation of the

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