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# Cost-effectiveness of rivaroxaban plus aspirin (dual pathway inhibition) for prevention of ischaemic events in patients with cardiovascular disease: on top optimisation of secondary prevention medication in the context of COVID-19 pandemia

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## History of progress in dual pathway inhibition in cardiovascular disease

In an attempt to optimise long-term prevention against adverse events in patients with cardiovascular disease (CVD) several antithrombotic regimens have been tested as potential alternatives to single medication with low dose aspirin, but initially a convincing improvement of the benefit–risk ratio has not been achieved.[1–5] In the ATLAS ACS 2–TIMI 51 trial ("Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome -thrombolysis in myocardial infarction 51"), however, the addition of low dose rivaroxaban (2.5 mg twice daily) to standard medication in patients after surviving an acute coronary syndrome (ACS) was associated with a significant reduction of mortality along a mean treatment period of 13.3 months.[6]

A beneficial effect of rivaroxaban $2 \times 2.5$ mg daily in combination with aspirin (100 mg daily; dual pathway inhibition; DPI) thereafter was confirmed by the COMPASS trial ("Cardiovascular Outcomes for People Using Anticoagulation Strategies") evaluating clinically stable patients with coronary artery disease (CAD)[7] as well as patients with stable peripheral artery disease (PAD) or carotid artery disease.[8] In stable CAD as well as in PAD patients, DPI was associated with a significantly reduced occurrence of the primary endpoint defined as a composite of cardiovascular death, myocardial infarction or stroke.[7,8] Moreover, in PAD patients the additional primary endpoint defined as 'major adverse limb events including major amputation' was also significantly reduced by DPI.[8]

## Benefit risk analysis of DPI

Notably, in CAD as well as in PAD patients the beneficial effect of DPI was demonstrated in a considerable number of subgroups including high-risk patients with diabetes and/or current smokers.[7,8] Not surprisingly, however, these cardiovascular benefits were accompanied by a significant increase of 'major bleeding' events, but fortunately not of 'fatal bleeding' or 'critical organ bleeding'.[7,8]

These data exemplify the conflict between the benefit and potential harm of therapeutic interventions, demanding high standards in clinical routine and daily medical practice, and including a thorough evaluation of each single patient with regard to the individual risk, compliance and treatment adherence. These ideal conditions are usually guaranteed in high standard prospective randomised trials but not necessarily in all day care. Therefore, additional checks of new regimens on top of well-established therapies on their effectiveness and added benefit are warranted. Well performed prospective registries reflecting clinical

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practice and professionally performed cost-effectiveness evaluations may provide this important additional information relevant for decision-making in all day care.

## Cost-effectiveness analysis, benefit and limitations of DPI

Against this background and based on data from the COMPASS trial[7,8] and a willingness to pay of €50,000, Petersohn et al. tested the cost effectiveness of DPI compared to aspirin alone in CAD, and clopidogrel alone in PAD patients following a sophisticated state transition model thereby including cardiovascular, ischaemic limb and bleeding events.[9] The cost-effectiveness probability of DPI was 92% in CAD patients, but only 56% in patients with PAD. DPI was especially cost-effective in young CAD patients and in PAD patients with existing comorbidities. In contrast, DPI was neither cost-effective in patients with carotid artery disease nor in older CAD patients more than 75 years of age.[9] This ambitious cost-effectiveness evaluation therefore confirms the baseline beneficial prognostic impact of DPI in patients with stable CAD and stable PAD, but also demonstrates well-defined limitations of this therapeutic regimen to be considered in clinical all day care and future research.

## Cost-effectiveness of DPI and clinical all day care reality

The cost-effectiveness of DPI in patients with stable CAD and stable PAD is based on the well-defined population of the COMPASS trial being followed for 21 (median) or 23 (mean) months.[7,8] The majority of the study population received guideline-adjusted medication for secondary prevention. However, approximately 27% (PAD) and 21% (CAD) of the participating patients were still current smokers.[7,8] Smoking, however, augments platelet activation/aggregation and supports activation of the endothelial-coagulative system.[10–13] This special risk group of current smokers therefore might especially benefit from DPI, but the preferred way would be simply to quit smoking life long, thereby favourably shifting cost-effectiveness evaluations.

These considerations cast light on a still unsolved major problem. Neither in primary nor in secondary prevention have lifestyle adaption and guideline-adjusted medication been followed to a sufficient degree for decades.[14,15] This problem is underscored by the observation that a large proportion of CAD patients in Europe do not achieve recommended treatment targets due to incomplete medication intake.[16] These considerable baseline deficits in prevention may therefore counteract sophisticated 'on top' improvements in drug regimen, and thereby also affect cost-effectiveness measures. On the other hand, the consequent utilisation of well-structured and supervised prevention and rehabilitation programmes will help to enforce prevention strategies and thereby also help to introduce innovative therapies sustainably in clinical all day care.[17–19]

## 'From the top back to baseline'

When writing this editorial COVID-19 threatens every country all over the world. At this time neither effective vaccination nor targeted therapeutic options are available, but patients with CVD and/or diabetes are known to be of special risk of dying from Sars-CoV-2 infection.[20,21] This situation may even be aggravated by the fact that new antiviral drugs being developed to treat Sars-CoV-2 infection need to be tested against potentially negative interactions with current cardioprotective medication, including antiplatelet drugs and novel anticoagulants.[22] This exceptional situation greatly interfering with our social and personal lives therefore strongly reminds us to do everything needed for disease prevention, and to do this in time. Disease prevention will thereby be the most cost-effective approach to save our lives and social living sustainably.

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