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CASE SERIES
Coronary heart disease

Clinical experience with dual pathway inhibition therapy: case series and mini review

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Background Dual pathway inhibition (DPI) with rivaroxaban 2.5 mg twice daily plus aspirin has demonstrated reductions in major adverse cardiovascular and limb events in eligible patients with chronic coronary artery disease (CAD), peripheral artery disease, or both. Patients with polyvascular disease, heart failure, renal impairment, or diabetes can benefit particularly from this therapy. We present our clinical experience to elucidate practical issues regarding the selection of patients eligible for DPI and the timing of initiation.

Case summary The first patient was at high risk of recurrent cardiovascular events due to his history of multi-vessel CAD, myocardial infarction, heart failure, and diabetes. Following a period of post-myocardial infarction dual antiplatelet therapy, he was transitioned to DPI therapy. The second patient was at high risk of cardiovascular events due to his history of polyvascular disease, diffuse CAD, and diabetes. He was hospitalized for unstable angina, which was medically managed because no target lesion was identified. DPI was initiated a day after admission. The third patient was at high risk of cardiovascular events due to an extensive history of polyvascular disease, revascularization, and renal impairment. Although the patient was asymptomatic at routine follow-up, DPI was initiated to reduce the risk of further cardiovascular events.

Discussion In eligible patients who are at high risk of cardiovascular events, DPI therapy with low-dose rivaroxaban should be considered. Treatment can be started at various times, including at the end of dual antiplatelet therapy, at routine follow-up, or after new events or diagnoses.

Keywords dual pathway inhibition • antithrombotic therapy • rivaroxaban • coronary artery disease • peripheral artery disease • case report

ESC Curriculum 3.1 Coronary artery disease • 3.2 Acute coronary syndrome • 3.3 Chronic coronary syndrome • 9.3 Peripheral artery disease

Learning points

- DPI should be considered in eligible patients with a high risk for vascular events, especially in patients with specific risk factors (e.g. polyvascular disease, diabetes, heart failure, or renal impairment) and after exclusion of major bleeding risk.
- DPI therapy can reduce the risk of CV and limb events, including stroke and limb amputation.
- Logical times to initiate DPI therapy include after discontinuing dual antiplatelet therapy, after a CV event, or after the diagnosis of a new CV comorbidity.

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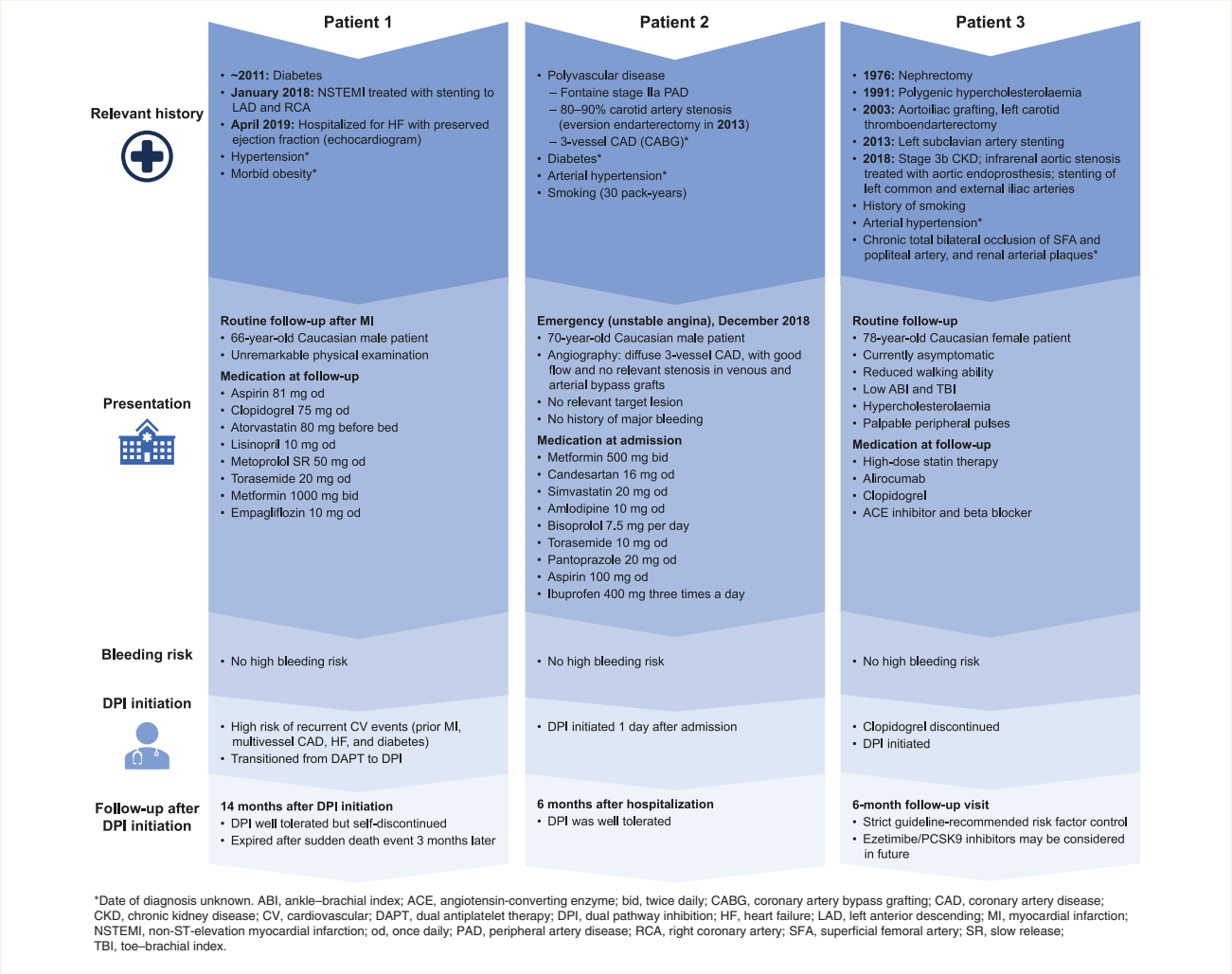
Introduction

Dual pathway inhibition (DPI) with rivaroxaban 2.5 mg twice daily (bid) plus aspirin can be used to prevent atherothrombotic events in eligible patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD).[1,2] This is based on the Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) study, which showed that DPI significantly reduced the risk of major adverse cardiovascular (CV) and limb events versus aspirin alone in patients with chronic CAD, PAD, or both.[3,4] The risk of major bleeding, but not intracranial or fatal bleeding, was significantly increased with DPI versus aspirin alone.[3,4] The benefit–risk profile of DPI was favourable across subgroups in the COMPASS study, and those with the highest absolute risk of ischaemic events were shown to benefit most from DPI.[5] These high-benefit subgroups were patients with polyvascular disease, heart failure, renal impairment, or diabetes.[5]

Based on these data, numerous international organizations have adopted DPI into their guidelines. The updated European Society of Cardiology (ESC), European Society of Vascular Medicine (ESVM), and Global Vascular Guidelines included recommendations to consider DPI in a broad population of patients with chronic CAD or PAD.[6–10] This guidance was later repeated in the ESC guidelines on non-ST segment elevation (NSTE)-acute coronary syndrome (ACS).[11] The ESC guidelines on chronic coronary syndromes (CCS), diabetes, and heart failure recommend considering the addition of a second antithrombotic (clopidogrel, ticagrelor, prasugrel, or rivaroxaban 2.5 mg bid) to aspirin in patients with a moderate-to-high risk of ischaemic events and without a high risk of bleeding.[6–8] The ESVM guidelines on the management of PAD recommend that DPI should be considered in patients who have PAD without a high risk of bleeding or other contraindications.[9] The ESC guidelines on diabetes and the Global Vascular Guidelines include similar recommendations for patients with symptomatic lower-extremity PAD and diabetes and patients with chronic limb-threatening ischaemia, respectively.[7,10]

Despite these recommendations, physicians may still have practical questions about the use of DPI, such as which patients to prioritize for treatment and when to initiate DPI. Here, we aim to address these questions by discussing our practical experience with the use of DPI.

Timeline



*Date of diagnosis unknown. ABI, ankle–brachial index; ACE, angiotensin-converting enzyme; bid, twice daily; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; HF, heart failure; LAD, left anterior descending; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; od, once daily; PAD, peripheral artery disease; RCA, right coronary artery; SFA, superficial femoral artery; SR, slow release; TBI, toe–brachial index.

Case presentation

Patient 1

A 66-year-old Caucasian male patient presented for routine follow-up after NSTE-myocardial infarction (MI) with no new complaints. He had experienced an MI in January 2018 and was treated with stenting of the left anterior descending and right coronary arteries. He had several CV risk factors, including hypertension, diabetes, and morbid obesity, as well as hospitalization in April 2019 for heart failure with preserved ejection fraction (echocardiogram, *Figure 1*). His medications at follow-up were aspirin, clopidogrel, atorvastatin, lisinopril, metoprolol sustained release (SR), torasemide, metformin, and empagliflozin. His physical examination was unremarkable, with a blood pressure of 118/62 mmHg, a heart rate of 62 beats per minute, and a respiratory rate of 12 breaths per minute. The patient was considered to be at high risk of recurrent CV events due to his history of MI, multi-vessel CAD, heart failure with preserved ejection fraction[12] and diabetes.[13] Therefore, the decision was made to transition from dual antiplatelet therapy (DAPT) to DPI after exclusion of high bleeding risk. He did well for 14 months and then self-discontinued his DPI due to high insurance co-pay. He expired after an out-of-hospital cardiac arrest 3 months later.

Patient 2

A 70-year-old Caucasian male patient presented to the emergency department with unstable angina. His physical examination showed no abnormalities except for weak foot pulses. Electrocardiogram showed sinus rhythm without significant repolarization disturbances and a transthoracic echocardiogram showed good left ventricular function without relevant valvular heart disease. He had a history of polyvascular disease: he had Fontaine stage IIa PAD with diffuse moderate-degree stenosis in the femoral artery that was managed with non-interventional treatment, carotid artery stenosis (80–90%) treated with eversion endarterectomy in 2013, and three-vessel CAD recently treated with coronary artery bypass grafting (CABG) surgery. In addition, he had several CV risk factors, including arterial hypertension, a history of smoking (30 pack years), and diabetes. His medications at the time of presentation to the emergency department were metformin, candesartan, simvastatin, amlodipine, bisoprolol, torasemide, pantoprazole, and aspirin. The patient was also taking ibuprofen for pain caused by osteoarthritis. After admission, a coronary angiogram revealed diffuse three-vessel disease and multiple stenoses in the right and left coronary arteries with subtotal left main coronary artery stenosis, and venous and arterial bypass grafts showed good flow without any relevant stenosis (*Figure 2*).

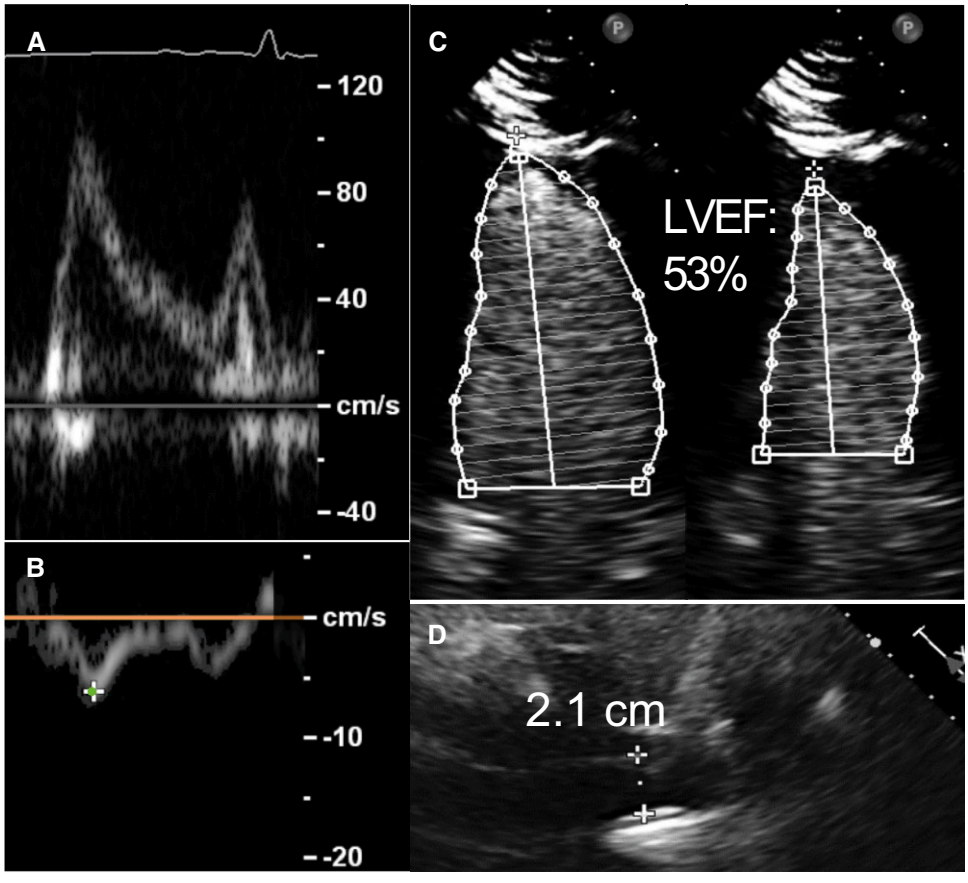


Figure 1 Patient hospitalized for heart failure. Echocardiogram showing (*A*) high E/A for age and (*B*) low medial e′, consistent with (*C*) elevated left ventricular filling pressures in the setting of preserved ejection fraction and (*D*) central venous pressure of 5–10 mmHg. LVEF, left ventricular ejection fraction.

He had no history of major bleeding. No relevant target lesion was identified; therefore, the ACS was medically managed. DPI was initiated 1 day after admission to hospital after exclusion of high bleeding risk. Because limited data suggest that ibuprofen could attenuate the effect of low-dose aspirin if it is administered within 8 h before or 30 min after aspirin,[14] the patient was advised to take ibuprofen at least 30 min after aspirin. Intensification of secondary prevention, including intensive lipid-lowering and antidiabetic therapy to achieve the target values recommended by the ESC CCS guidelines, was considered.[6] DPI was well tolerated at the follow-up visit after 6 months.

Patient 3

A currently asymptomatic 78-year-old female Caucasian patient with polyvascular disease presented to the vascular specialist for routine follow-up. Physical examination revealed palpable peripheral pulses and was otherwise unremarkable except for the scars following nephrectomy, carotid endarterectomy and aortoiliac open surgery. She had several CV risk factors. In 1976, she underwent a nephrectomy due to pyelonephritic kidney cirrhosis, and by 2018 her estimated glomerular filtration rate was 46 mL/min (stage IIIb chronic kidney disease). In 1991, she was diagnosed with polygenic hypercholesterolaemia; in 2018, she had a total cholesterol level of 294 mg/dl, a high-density lipoprotein level of 73 mg/dl, and a LDL level of 192 mg/dl. The patient also had a history of smoking and arterial hypertension with frequent hypertensive crises. Furthermore, she had generalized atherosclerosis and an extensive history of revascularization (*Figure 3*). In 2003, she underwent aortoiliac grafting with open surgery and left carotid thromboendarterectomy. In 2013, a stent was implanted in her left subclavian artery. Following a diagnosis of infrarenal aortic stenosis using ankle-brachial index measurements, duplex sonography, treadmill and computed tomographic angiography, she underwent implantation of an aortic endoprosthesis in 2018. In the same year, she underwent stent implantation in the left common and external iliac arteries. The patient had chronic total bilateral occlusions of the superficial femoral and popliteal arteries, as well as renal arterial plaques. At her routine follow-up visit, she was asymptomatic, with no sign of ST segment abnormalities. Her maximum walking distance was 516 m on a treadmill at a 12% grade and a speed of 3.2 km/h. Low ankle–brachial index and toe–brachial index values were observed in both legs before and after the treadmill walking test. Her medication included high-dose statin therapy (atorvastatin), a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (alirocumab), a platelet aggregation inhibitor (clopidogrel) and antihypertensives (angiotensin-converting enzyme inhibitor and beta blocker). The decision was made to discontinue clopidogrel and introduce rivaroxaban 2.5 mg bid plus aspirin, after exclusion of high bleeding risk, by taking her history and checking her patient files. Because the patient still had high

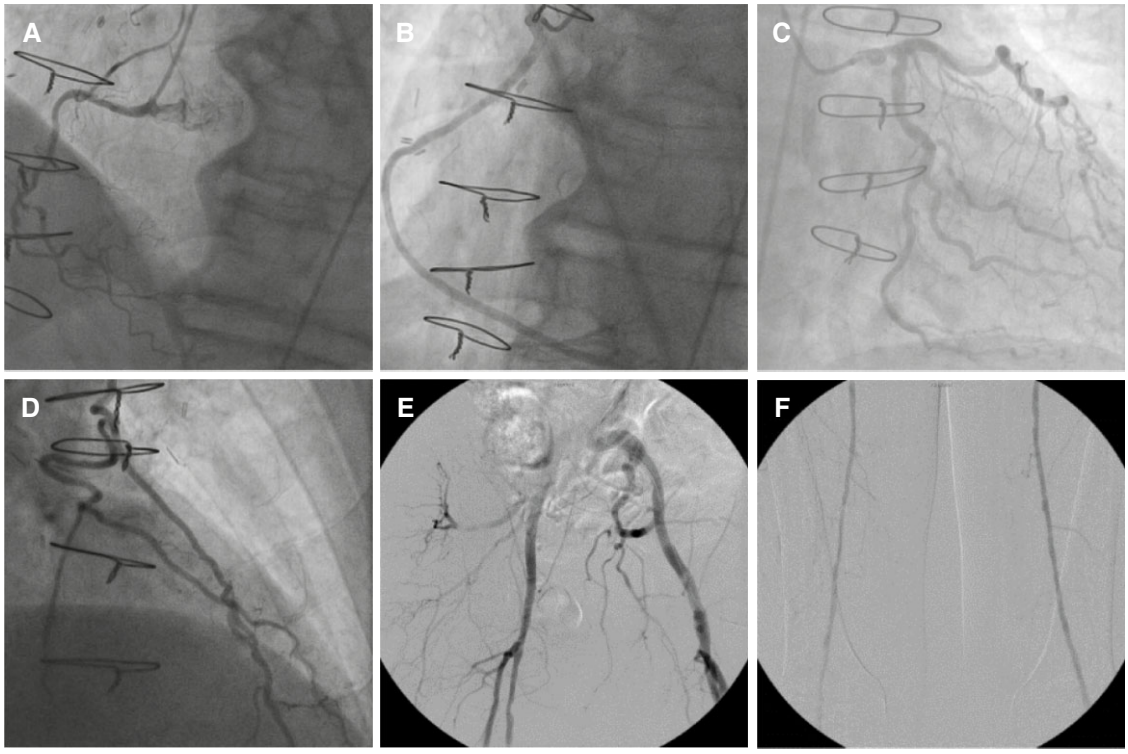


Figure 2 Coronary angiogram showing (*A*) diffuse disease in the right coronary artery with occlusion in the medial segment, (*B*) aortic coronary venous graft to the right coronary artery without relevant stenosis, (*C*) left coronary artery diffusely diseased with multiple stenoses and a high-degree left main stenosis, (*D*) sequential arterial bypass graft with the LIMA to the left anterior descending artery and right internal mammary internal artery connected to LIMA as a T-graft to left circumflex artery, (*E*) moderate plaque stenosis in the right common femoral artery and 70% degree stenosis in the right superficial femoral artery, and (*F*) diffuse atherosclerosis with moderate stenoses in both sided superficial arteries (tibial and fibular arteries not shown). LIMA, left internal mammary artery.

cholesterol levels (LDL 158 mg/dl), the addition of ezetimibe or PCSK9 inhibitors may be considered in the future, aiming for a level of <55 mg/dl according to current guidelines for high-risk atherosclerotic patients.[14] At the 6-month follow-up visit, the patient was still receiving strict risk factor control. Vascular follow-up was then planned for every 6 months, in addition to seeing an endocrinologist, nephrologist and cardiologist.

Discussion

DPI has the potential to reduce the risk of major adverse CV and limb outcomes in a broad population of patients with chronic atherosclerotic disease.[3,4] DPI with rivaroxaban is still underutilized due to various reasons, likely including relative unawareness, clinical inertia and reimbursement issues by national health insurance systems. Although DPI has been approved by many health regulatory agencies, including the US Food and Drug Administration and European Medicines Agency, it has only been approved by a few national health insurance systems, which may contribute to underutilization. We present our experience with DPI in clinical practice to raise awareness and illustrate which patients may be eligible for DPI, when treatment can be initiated, and how these decisions can be made. In addition to considering intensified antithrombotic therapy, it is important to ensure that the overall secondary prevention strategy is optimized in each patient. In all three cases, the patients were receiving a high standard of secondary prevention therapies. According to current guidelines, the duration of DPI was recommended long term under careful reconsideration of the indication and the net clinical benefit, which might be altered under changing disease conditions and bleeding risk over time.[6,9,11] The mean treatment time in the COMPASS trial was 23 months, and the benefit became increasingly favourable with longer treatment duration.[3,15] Therefore, we are of the opinion that there is no particular time limit for DPI once the patient has been identified as a potential candidate. The rivaroxaban label recommends that the duration of treatment should be assessed based on the risk of thrombotic and bleeding events in each individual patient over time.[1]

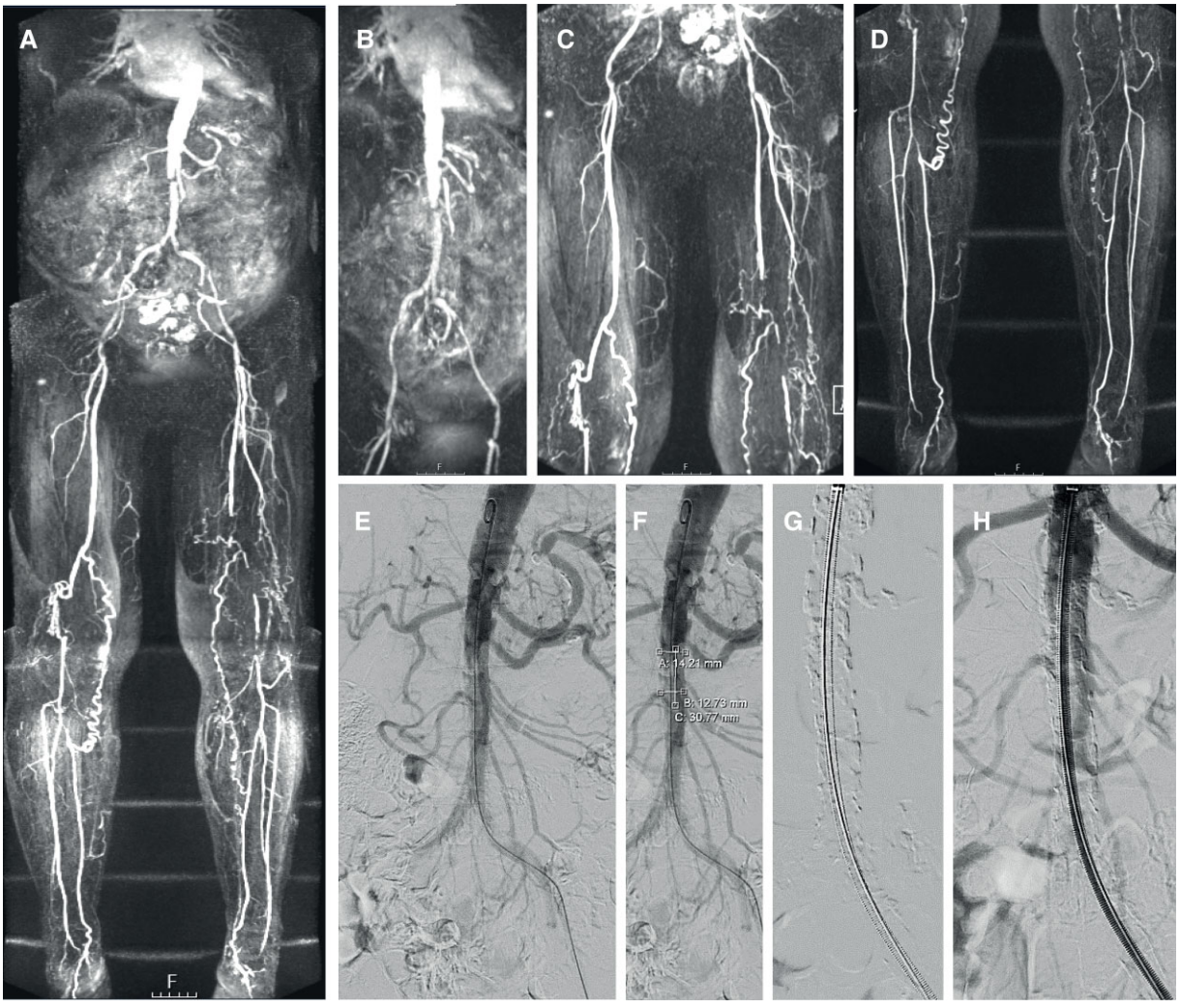


Figure 3 (*A*) Patient with widespread polyvascular disease, including (*B*) stenoses in the mesenteric, infrarenal aortic, and iliac arteries, (*C* and *D*) occlusions in the femoral and popliteal arteries (magnetic resonance angiography). (*E–H*) Stent implantation into the infrarenal aorta (digital subtraction angiography).

The first case showed that DPI could be initiated at routine follow-up after a period of DAPT following MI. The patient was at high risk of ischaemic events, according to the COMPASS study and the 2019 ESC CCS guidelines, but not at high risk of bleeding (*Figure 4*).[5,6] DAPT is another option for intensified antithrombotic therapy listed by the ESC CCS guidelines,[6] but DPI may be preferred when the overall vascular risk exceeds the risk associated with stenting or the acute coronary event.[16] This patient had several risk factors increasing his long-term risk of ischaemic events, including heart failure with preserved ejection fraction, which made him a more suitable candidate for DPI than DAPT.[5,12] In general, there may be several opportunities to consider the initiation of DPI, including when antiplatelet prescriptions are due to be renewed, after a recent CV event or revascularization, or upon identifying new atherosclerotic disease or symptoms.

The second case illustrated that DPI can be initiated in medically managed patients with ACS who have no clear indication for DAPT and continued long term in eligible patients. DPI as initial antithrombotic therapy in the post-ACS phase should not be advocated as first-line therapy, and DAPT for 6 to 12 months should be generally favoured, according to current guidelines,[11] even though DPI may be used with or without clopidogrel in the post-ACS phase, according to the German and European rivaroxaban labels.[1] Nevertheless, in this particular patient presenting with thoracic pain of uncertain aetiology (the alternative diagnosis was post-sternotomy pain syndrome after recent CABG surgery) and without a clearly identifiable angiographic target lesion, based on our clinical experience we felt that this was an exception to the guideline recommendations, with several arguments for early DPI. First, this was a patient with polyvascular disease with a history of vascular interventions (cerebral and PAD) and multiple risk factors, ideally fitting in the COMPASS CAD/PAD risk cohort.[5,6] Second, the patient recently underwent CABG and, although there is a disagreement and no strong evidence regarding the benefit of more potent antithrombotic/antiplatelet therapy on graft patency,[17] patients with a recent CABG benefitted from DPI with respect to efficacy and safety, as in the overall COMPASS population.[18] Third, given that prasugrel should not be used in medically managed ACS patients,[19] the benefit of ticagrelor in post-CABG patients is debatable, and compliance issues regarding dyspnoea were expected in this patient. Furthermore, given the beneficial effect of combination therapy with very low dose rivaroxaban compared with aspirin, with or without clopidogrel, in the post-ACS setting,[20,21] we decided to choose DPI as the initial approach.[1,18,20]

The third case illustrated that asymptomatic patients can be good candidates for DPI when they are at high risk of CV events. This patient met the criteria for intensified antithrombotic therapy according to the ESC CCS and ESVM PAD guidelines.[6,9] In addition to her other CV risk factors, this patient had polyvascular disease and renal impairment, characteristics associated with a higher absolute benefit with DPI in COMPASS.[5] Furthermore, she had an extensive history of revascularization, which is known to increase the risk of ischaemic events.[22] As shown in the VOYAGER PAD study, DPI also reduced the risk of major adverse vascular events in the period immediately after peripheral revascularization in patients with symptomatic PAD, with no significant increase in the risk of the primary safety endpoint of Thrombolysis In Myocardial Infarction (TIMI) major bleeding.[23] This patient was also treated with a PCSK9, due to her extensive hypercholesterolaemia, another therapy that reduces the risk of CV events.[24] Potential synergistic effects between these therapies still require investigation.

There are key learning points from each patient case, and from the case series overall. Case 1: DPI could be initiated at routine follow-up, after a period of DAPT following MI, in a patient with persistent high risk of vascular events. Case 2: DPI could be initiated in patients with polyvascular disease hospitalized for an acute event, when there is no clear indication for DAPT. Case 3: asymptomatic patients can be good candidates for DPI when they are at high risk of CV events. For all cases: DPI should be initiated after exclusion of a high bleeding risk; the duration of DPI is long term without principal time restriction, but indication and changes in benefit–risk profile (e.g. by incidence of bleeding events, changes in bleeding risk profile, and/or

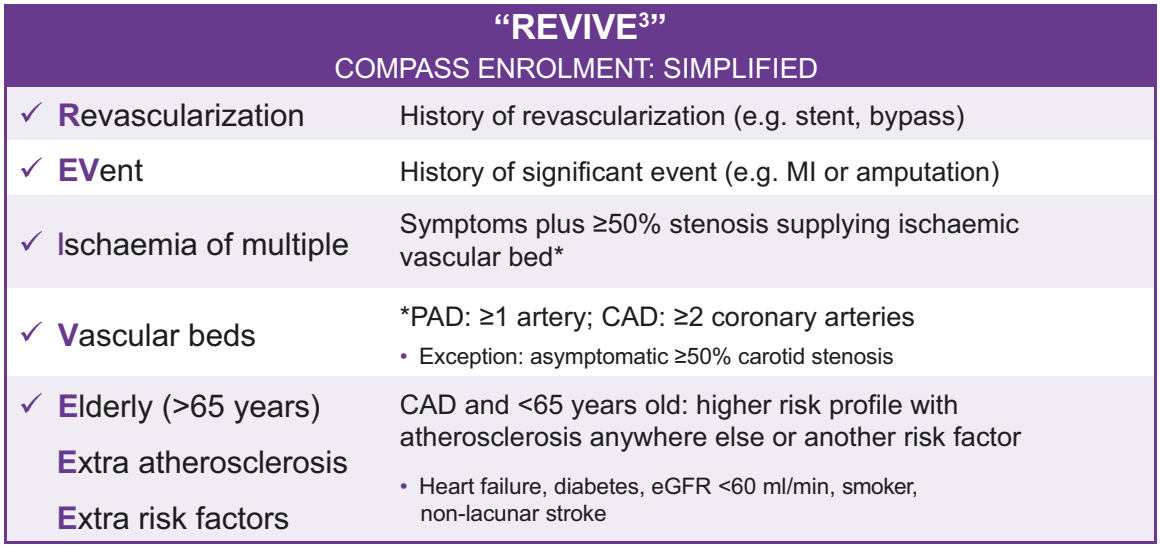


Figure 4 The REVIVE[3] acronym can be used to support the identification of patients eligible for dual pathway inhibition.[3] CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease.

necessity of coronary intervention or occurrence of new atrial fibrillation, requiring modification of antithrombotic therapy) should be re-evaluated on a regular basis (e.g. every 6–12 months).

Conclusions

Patients at high residual risk for CV events who are started on DPI have been shown to benefit from a reduced risk of major adverse CV and limb events.[3,5] However, the identification of patients who will benefit most and the optimal timing of DPI initiation remain challenging. These cases illustrate patients who are likely to benefit particularly from DPI because they have high-risk features (polyvascular disease, heart failure with ejection fraction >40%, diabetes, or renal dysfunction). It is important to carefully assess bleeding risk prior to initiation of DPI. In the present cases, high bleeding risk was excluded mainly using the Academic Research Consortium (ARC) bleeding risk assessment, which was developed and validated for patients on DAPT after percutaneous coronary intervention (PCI).[25] The PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy (PRECISE-DAPT) and ARC-High Bleeding Risk (HBR) models have been recommended to assess bleeding risk in patients receiving DAPT,[11,26,27] but have not been validated for DPI. Alternative tools to estimate lifetime risk based on the net clinical benefit under DPI, with integration of ischaemic versus bleeding risk factors, are warranted in the future.[28] Recently, de-escalation strategies trying to avoid aspirin after coronary revascularization were shown to be beneficial in a number of clinical trials and potentially preclude the use of DPI.[29] However, in our opinion, these strategies should only apply to patients undergoing PCI in whom bleeding risk exceeds the ischaemic risk, as recommended by recent guidelines (e.g. 2020 NSTE-ACS guidelines).[11] In contrast, DPI should be mainly applied to non-PCI patients in whom the atherothrombotic risk exceeds the bleeding risk.

Logical times to start therapy include when changing therapies, such as discontinuing DAPT, and after new CV events or diagnoses (such as with new arterial atheroma or peripheral revascularization). Every patient with CAD or PAD needs an optimized secondary prevention strategy that includes control of diabetes, lipids, and heart failure, where needed, and the most suitable antithrombotic therapy, according to their benefit–risk profile.

Lead author biography

Tobias Geisler is Professor of Cardiology at Eberhard-Karls-University Tübingen. He worked as senior research fellow at the Royal Brompton Hospital/Imperial College in London. Since 2015, he has been Vice Head of the Department of Cardiology at the German Heart Competence Center Tübingen. He leads the cardiovascular clinical research unit and is member of the steering board of the Collaborative Research Consortium TR240 'Platelets – Molecular, cellular and systemic functions in health and disease'. His main research interests include platelet biology, pharmacogenomics of antiplatelet and antithrombotic therapies, platelet-mediated inflammation, stroke, translational medicine, clinical trials, and structural heart interventions including TAVR.

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Consent: Written consent for publication of images and associated text has been obtained from two of the patients in this case series. Patient 1 reported in this case series is deceased. Despite the best efforts of the author, he has been unable to contact the patient's next-of-kin to obtain consent for publication. Every effort has been made to anonymize the case. This situation has been discussed with the editors.

Conflict of interest: T.G. has received personal fees from AstraZeneca, Boehringer Ingelheim, Ferrer and Pfizer, as well as grants and personal fees from Bayer, Daiichi Sankyo, Eli Lilly, Medtronic and Pfizer/BMS. K.B. has received grants from Kestra and Eli Lilly, non-financial support from Sana, personal fees from Janssen, and grants and personal fees from Bayer. S.N. has received speaker fees and honoraria from Bayer as a steering committee member and participated in the COMPASS study as PI.

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Data availability

No new data were generated or analysed in support of this research.

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