Relative clinical contraindications to the use of drug-eluting stents: what are the alternatives?

Advances in stent technology and medical therapy have improved patient outcomes following revascularisation by PCI. In particular, drug-eluting stents (DES) have been proven effective in nearly all clinical conditions and lesions treated; nevertheless, prolonged dual-antiplatelet therapy, required with the implantation of DES, has raised concerns for certain subsets of patients. In clinical practice, interventional cardiologists are faced with complex cases, such as patients who require non-cardiac surgery in the near term and must discontinue dual-antiplatelet therapy prematurely, that render long-term (≥3 months) use of dual-antiplatelet therapy undesirable, thus necessitating alternatives to DES. Several alternative stent technologies have been investigated to provide interventional cardiologists with safe and effective options for the treatment of patients with contraindications to DES. One such technology is the Genous™ stent (OrbusNeich), which is coated with CD34+ antibodies to capture circulating endothelial progenitor cells and accelerate the natural healing of the vessel wall after stent implantation. This article discusses relative contraindications to the use of DES and current alternatives to DES in these patients, with accompanying clinical support.

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INTRODUCTION

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Percutaneous coronary intervention (PCI) was first introduced into medical practice by Andreas Grüntzig in 1977, and today it is widely used for most coronary lesions. Since the early days, advances in stent technology and medical therapy have improved patient outcomes following revascularisation by PCI. In particular, drug eluting stents (DES) have proven to be more effective and at least as safe as bare metal stents in nearly all clinical conditions; this is, however, only true if prolonged dual antiplatelet therapy (DAPT), is prescribed after the implantation of DES.

The Guidelines on Myocardial Revascularization published in 2010 by the Task Force on Myocardial Revascularisation of the European Society of Cardiology (ESC) in consensus with the European Association for Cardio-Thoracic Surgery (EACTS) provided a recommendation of clinical situations where DES should not be used.[1] Although the optimal duration of DAPT is not known, data from two large, two-institutional cohort studies determining early and late coronary stent thrombosis with sirolimus- and paclitaxel-eluting stents recommend 6–12 months of DAPT for patients treated with DES.[1,2] The recommended duration of DAPT for patients with acute coronary syndromes (ACS) is 12 months.

In clinical practice, interventional cardiologists are faced with complex cases that render long-term use of DAPT undesirable, thus necessitating alternatives to DES. These patients include those who require non-cardiac surgery in the near term and therefore must discontinue DAPT prior to scheduled surgery, those with medical history difficult to obtain, especially in the setting of acute severe clinical conditions such as ST-segment elevation acute myocardial infarction (STEMI) and cardiogenic shock, those who are expected to have poor adherence with DAPT and patients with an increased risk of bleeding, a known allergy to acetylsalicylic acid (ASA), clopidogrel, prasugrel or ticagrelor, or an absolute indication for long-term anticoagulation.

Several alternative stent technologies have been investigated to provide interventional cardiologists with safe and effective options for the treatment of patients with contraindications to DES. One of these technologies is the Genous™ stent (OrbusNeich), which is coated with CD34$^+$ antibodies to capture circulating endothelial progenitor cells and accelerate the natural healing of the vessel wall after stent implantation. A study with patients undergoing coronary angiography demonstrated that the Genous stent increased the rate of endothelialisation and reduced thrombogenicity compared to a bare-metal stent (BMS). This *ex vivo* human arteriovenous shunt study showed an increase in strut coverage for the Genous stent *versus* BMS following exposure to human circulating blood; the cells captured by the Genous stent had increased expression of endothelial markers and decreased expression of prothrombogenic markers compared with BMS.[3]

We recently reported 12-month outcome data from the worldwide e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) registry, a multicentre, worldwide prospective clinical registry conducted at 144 centres in 31 countries outside of the USA that included 4,939 patients with at least one lesion suitable for non-urgent PCI and Genous stent implantation.[4] Both the rate of target vessel failure (8.4%) and the rate of clinically driven target lesion revascularisation (5.7%) were comparable with those associated with DES in similarly organised registries. The stent thrombosis rate was 1.1% at 12 months, and the recommended DAPT duration was 1 month.

This article discusses relative contraindications to the use of DES from the Guidelines on Myocardial Revascularization (Table 1)[1] and current alternatives to DES in these patients, with accompanying clinical support.

CLINICAL HISTORY DIFFICULT TO OBTAIN

By HC Tan MBBS, of the National University Hospital in Singapore

Approximately 30% of patients with ACS present with STEMI, with most cases of STEMI the result of thrombotic occlusion of a coronary artery caused by a ruptured

atherothrombotic plaque. Consequently, STEMI patients remain a challenge for interventional cardiologists.

A meta-analysis has suggested that DES in STEMI might improve outcomes,[5] but other studies have raised concerns regarding the use of DES in this clinical setting because of very late stent thrombosis.[6,7] In a prospective observational study, we enrolled 321 patients with acute STEMI (mean age 54.6±11.6 years; 81% male) and implanted 357 Genous stents. The cumulative major adverse cardiac event (MACE) rate was 8.1% at 30 days, 10% at 6 months and 12.2% at 1 year, with a low target vessel revascularisation rate of 4.4% at 1 year. There was no incidence of late stent thrombosis, despite an abbreviated 1-month course of DAPT. One case of acute thrombosis was observed, in addition to two cases of subacute stent thrombosis. Three-year follow-up data from this study are currently being prepared for publication.

In our experience, the Genous stent shows favourable late clinical outcomes for patients with STEMI, including a low rate of target vessel revascularisation and no incidences of late stent thrombosis.[8]

EXPECTED POOR ADHERENCE TO DAPT

By A Iniguez MD, of the Hospital Universitario de Vigo in Vigo, Spain

Elderly patients represent a high-risk patient group for complications after PCI, given the complexity of their conditions. DES have been shown to reduce in-stent restenosis in general, but the incidence of comorbidities in the elderly, in addition to their increased need for non-cardiovascular interventions and medications and their frequent low therapeutic adherence, lends itself to premature discontinuation of DAPT. Significantly, early discontinuation of DAPT is a major predictor for the occurrence of ST[9]; however, a shorter duration of DAPT use in this patient population is only desirable if safety is not compromised because of an increased risk of stent thrombosis.

A subset analysis of the e-HEALING registry with data from 2,651 patients aged 65 years and older showed that the Genous stent provides a safe and effective alternative for elderly patients. The 12-month follow-up data showed no significant difference in stent thrombosis between elderly (age 65 years or older) and younger patients, with late definite or probable stent thrombosis rates of 0.2% for patients younger than 65 years and those between 65 and 74 years, and a late stent thrombosis rate of 0.5% for patients aged 75 years and older. The target lesion revascularisation rate was not significantly higher with increasing age. The main outcome of the study, target vessel failure, occurred in 11.7% of patients over the age of 75 years, 8.8% of patients between the ages of 65 and 74 years and 7% of patients younger than 65 years. The increased rate of target vessel failure in elderly patients was driven mainly by increased mortality.[10]

Table 1: Reproduced with permission from Wijns W, Kolh P, Danchin N, *et al.*; for the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31: 2501–2555.

Table 1. Relative clinical contraindications to the use of drug-eluting stents

✓	• Clinical history difficult to obtain, epecially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock).
✓	• Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy.
✓	• Non-elective surgery required in the short term that would require interruption of DAPT.
✓	• Increased risk of bleeding.
✓	• Known allery to ASA or clopidogrel/prasugrel/ticagrelor.
✓	• Absolute indication for long-term anticoagulation.

ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction.

NON-ELECTIVE SURGERY IN THE SHORT-TERM THAT REQUIRES INTERRUPTION OF DAPT

By P Scacciatella MD, PhD, of the Molinette Hospital in Turin, Italy

The optimal treatment strategy for patients in need of PCI with stent implantation prior to an undeferrable, non-cardiac surgery is still unknown and remains a challenge for clinicians because of the increased risk for MACE related to stent thrombosis and intraoperative bleeding. Therefore, these patients require a cardiac intervention that will not interfere with the planned surgery while addressing their revascularisation needs. DES require 6 months to 1 year of DAPT and are often prescribed indefinitely. For BMS, the duration of DAPT after implantation is at least 1 month; however, BMS are associated with a high incidence of late stent restenosis with repeated intervention in 12–30% of patients, peaking at 3–6 months.[11,12]

Several studies have demonstrated that the Genous stent allows the early and safe discontinuation of DAPT and provides a treatment option for this challenging patient group, without a major delay of non-cardiac surgery. A single-centre study investigated 26 high-risk patients who underwent PCI and received a Genous stent, 20 patients of whom subsequently underwent non-cardiac surgery.[13] Many of the patients were high risk, including 50% with ACS. In addition, 23.1% were diabetic, 46.2% had multivessel disease, 15.4% had proximal vessel disease and 3.8% presented with heart failure. DAPT was discontinued between 21 and 30 days following PCI. The investigators reported no stent thrombosis and no cases of perioperative MACE. After a mean follow-up of 15.4±10.3 months, two cases of cardiac death were recorded, but no ischaemia-driven target lesion revascularisation was detected. Importantly, no stent thrombosis was reported.

These data indicate that the Genous stent could allow early and safe discontinuation of DAPT in high-risk patients who require undeferrable non-cardiac surgery.[13] In another study, Piscione and colleagues treated 30 consecutive patients with the Genous stent prior to upcoming endovascular or surgical procedures that required early interruption of DAPT. DAPT was stopped after 12.2±3.9 days, and no cardiac events, thrombosis or bleeding episodes were observed during the perioperative period or at 30 days' follow-up.[14]

INCREASED RISK OF BLEEDING

By D Smith MD, of the Regional Cardiac Centre at Morriston Hospital in Swansea, Wales

Patients with ACS, including patients with STEMI, NSTEMI or unstable angina, represent a major patient population that now exceeds stable angina by volume within the group of patients who require revascularisation. Upon admission to hospital, ACS patients immediately receive DAPT, antithrombotic therapy, antianginal therapy and statins (unless contraindicated). This pharmacological cocktail, in patients who often have comorbid medical problems, leads to a relative increase in bleeding risk in the short, medium and long term. It must be noted that a major bleed following PCI is associated with an increased mortality risk at 1

year similar to the mortality risk of recurrent myocardial infarction. Thus, the evaluation of patients with ACS includes the assessment of risk for a future cardiac ischaemic event, as well as the risk of a bleeding complication from intensive medical therapy or an invasive cardiac procedure.

The optimal treatment for patients with ACS requires a combination of medical therapy, coronary angiography and revascularisation, tailored to the individual's risk of an ischaemic cardiac event or treatment-related complications.[15] The Genous stent has the potential to provide a better balance between the efficacy needed to prevent further coronary events and safety for patients at risk for bleeding. GATEWAY is an ongoing investigator-led, multicentre registry in the UK. A total of 137 patients are currently enrolled, with expected enrolment totalling 170 patients at eight sites. For the study, patients with ACS undergoing PCI who are at high risk of postprocedural bleeding will be treated with a Genous stent. The study protocol recommends that instead of receiving the 12 months of DAPT associated with DES, these patients receive DAPT for 3 months or less following stent implantation. The primary endpoint of GATEWAY is the occurrence of net adverse clinical events at 30 days and 1 year of follow-up, with net adverse clinical events defined as a composite of major postprocedural bleeding and MACE consisting of death, myocardial reinfarction, ischaemic target vessel revascularisation or stroke. We expect the data to show that the Genous stent offers clinical outcomes similar to those of DES, while providing a better balance for patients at risk for severe bleeding.

KNOWN ALLERGY TO ACETYLSALICYLIC ACID OR CLOPIDOGREL, PRASUGREL OR TICAGRELOR

By M Kutryk MD, PhD, of St. Michael's Hospital in Toronto, Ontario, Canada

Standard DAPT includes ASA and clopidogrel, prasugrel or ticagrelor, and current guidelines recommend at least 6 months to 1 year of DAPT for DES and a minimum of 1 month of DAPT for BMS. Patients undergoing PCI who have a known allergy or intolerance to any one of the drugs comprised within DAPT have limited options when faced with mandatory postprocedure medical therapy.

A recent study investigated 20 patients with ASA or clopidogrel intolerance, bleeding issues or patients who require urgent surgery. These patients underwent PCI with transplantation of a Genous stent for stable angina (45%), unstable angina/NSTEMI (45%) and recent STEMI (10%).[16] After PCI, patients were maintained on single-antiplatelet therapy with either enteric-coated ASA or clopidogrel daily indefinitely, or DAPT therapy with enteric-coated ASA indefinitely and clopidogrel for 1 month. The clinical follow-up at 24 months demonstrated that the implantation of a Genous stent is favourable for patients who are allergic to or intolerant of ASA, clopidogrel, prasugrel or ticagrelor. No acute, subacute or late stent thrombosis was observed, and the MACE rate was 10%, as reported at the Kiev Course on Coronary Revascularization in 2010.[16] It is noteworthy that 40% of the patient population had diabetes and, of the lesions treated, 60% were type B2/C.

ABSOLUTE INDICATION FOR LONG-TERM ANTICOAGULATION

By S Brugaletta MD, of the University Hospital Clinic in Barcelona, Spain

Prolonged DAPT is also problematic for patients receiving long-term anti-vitamin K therapy, a group that includes the older population with comorbidities, a high risk for bleeding and cardiovascular events. It is known that the incidence of MACE after PCI is high in this patient population, and while the interventional cardiologist may consider the use of DES, it is important to weigh the risk of haemorrhagic complications: the combination of anti-vitamin K and DAPT increases bleeding risk, but the discontinuation of DAPT may be associated with a higher incidence of thrombo-ischaemic events.

A recent study explored long-term outcomes with the Genous stent as an alternative treatment option.[17] The single-centre registry included 78 consecutive patients with a mean age of 72 years who were receiving chronic anti-vitamin K treatment and who underwent PCI with Genous stent implantation accompanied by 1 month of DAPT. Overall, 89% of the patients had a high comorbidity index and 30% had diabetes. MACE included cardiac death, acute myocardial infarction or target lesion revascularisation, and the incidence of stent thrombosis and rate of haemorrhagic events were also recorded. At 14±8 months the cumulative rate of MACE was 22%, with no acute myocardial infarctions (AMI) or definite/probable stent thrombosis. Importantly, the rate of haemorrhagic events was 5.2%, lower than described in other studies (9.2–18.2%). Taken together, these data validate our belief that the Genous stent may provide a safe and effective alternative for patients who need short-term DAPT when undergoing chronic anti-vitamin K treatment.

CONCLUSION

By S Silber MD, PhD, of Cardiology Practice and Hospital, Munich, Germany

In the large, multicentre e-HEALING registry and other clinical studies, the Genous stent has demonstrated good clinical outcomes in real-world use in more than 7,000 patients. One of the most notable trends is the low incidence of stent thrombosis in even the most complex and highest risk patient populations when accompanied by courses of DAPT significantly shorter than that required for DES and often even with BMS. These data validate the safety and efficacy of the prohealing Genous stent and support its use as an alternative to DES in the challenging patient groups where prolonged DAPT is not an option.

CONFLICTS OF INTEREST

Dave Smith: Received study sponsorship for a clinical trial and a speaker fee from OrbusNeich
Paolo Scacciatella: No conflicts of interest
Andres Iñiguez: No conflicts of interest
Huay Cheem Tan: Received a modest research grant from OrbusNeich
Salvatore Brugaletta: No conflicts of interest
Michael Kutryk: Consultant for OrbusNeich
Sigmund Silber: Received a research grant from OrbusNeich for the e-HEALING registry

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