Drug-eluting stents in the management of peripheral arterial disease

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Abstract: Since major meta-analyses of randomized controlled trials in interventional cardiology showed the potential of drug-eluting stents in decreasing restenosis and reintervention rates after coronary artery stenting, one of the next steps in the treatment of arterial occlusive disease is the transfer of the active coating technology towards peripheral arterial interventions. In this manuscript, we aim to provide a literature overview on available peripheral (lower limb, renal, and supra-aortic) drug-eluting stent applications, debate the cost implications, and give recommendations for future treatment strategies.

Keywords: critical limb ischemia, drug-eluting stent, below the knee, infrapopliteal, crural, limb salvage

Endovascular interventional techniques have been used to treat peripheral arterial occlusive disease (PAOD) since their conception and, despite many improvements, they remain the subject of continued modifications. Although percutaneous transluminal angioplasty (PTA) and stenting are now widely accepted and are even gradually replacing traditional open peripheral vascular surgical approaches, there remains one significant limiting factor: post-angioplasty and in-stent restenosis. Major meta-analyses of randomized controlled trials (RCT) from interventional cardiology show that in coronary artery disease, the use of drug-eluting stents (DES) has resulted in decreased restenosis and reintervention rates compared to bare metal stents (BMS) (Hill et al 2004; Mauri et al 2005; Roiron et al 2006). There is heterogeneity between outcomes depending on different drug coatings (sirolimus and its derivates versus paclitaxel and its derivates), suggesting higher efficacy with sirolimus-eluting stents. This manuscript reviews the literature for the available applications of DES in the management of PAOD and presents recommendations for future treatment strategies.

Methods

We reviewed publications listed in MEDLINE that presented applications of DES in noncoronary arterial disease from 1950 up to March 2007. The key word searched was "stent" combined with terms describing stent coating, "eluting, paclitaxel, sirolimus", and lesion location, "peripheral, infrapopliteal, below-the-knee, crural, femoral, iliac, renal, carotid, intravascular, extravascular". In addition, relevant abstracts and presentations from pertinent conferences (TCT, CIRSE, Charing Cross and Euro-PCR) were identified and the reference sections of retrieved articles were manually screened. Furthermore, ongoing unpublished trials were identified by accessing www.clinicaltrials.gov.

Results

Drug-eluting stents have been used to ameliorate outcomes in the treatment of atherosclerotic occlusive disease in various noncoronary locations. We believe that DES

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may influence outcomes depending on the vascular bed treated, thus, below are presented results subdivided into anatomic regions.

Lower limb arteries

Femoropopliteal vasculature

The investigators of the SIROCCO trial (SIROlimus Coated COrdis Self-expandable Stent), were the first to publish the outcomes following use of sirolimus-eluting (SES) stents in the infrainguinal vasculature. This double-blind RCT evaluated the efficacy of sirolimus-eluting self-expanding nitinol stents versus the same commercially available bare metal stents (SMART®, Cordis. Miami, FL, USA) in the superficial femoral artery (SFA) (Duda et al 2002, 2005, 2006). The study was performed in 2 phases. After interim analysis of SIROCCO I revealed a high fracture rate, it was decided to reduce the maximal allowed lesion length from 20 cm to 14.5 cm in order to decrease the number of stents implanted from 3 to 2 in an attempt to avoid stent fractures (Duda et al 2002). In total, 93 patients with occlusions or stenoses (average lesion length 8.3 cm) at the level of the SFA were included. The sirolimus-eluting SMART® stent was implanted in 47 and the bare SMART® nitinol stent in 46 patients. (Duda et al 2006) Both groups were followed for a mean of 24 months and no significant differences were observed in either the peak velocity ratios (PVR), nor ankle-brachial index (ABI). At 24 months, the in-stent restenosis rate as measured by duplex ultrasound was not significantly different between the sirolimus and the bare metal stent group, being 22.9% versus 21.1%, respectively. The target lesion revascularization (TLR) was 6% in the sirolimus group and 13% in the bare stent group. Higher values were found for target vessel revascularization (TVR): 13% and 22%, respectively. (Duda et al 2006) In both groups at 24 months, no amputations were performed as a result of complications from stenting. The SIROCCO-investigators concluded that the study provided objective evidence supporting the safety and efficacy of drug-eluting and bare metal self-expanding nitinol SMART® stents in patients with chronic limb ischemia (CLI) and TASC C SFA lesions. They stated that no significant difference could be found between the bare and the sirolimus-eluting SMART® stents, because the restenosis rate in the bare stent group was unexpectedly low (Duda et al 2002, 2005, 2006).

To date, SIROCCO is the only completed RCT that has published results showing the utility of DES in the femoropopliteal (FP) vasculature. At the preparation of this manuscript, 2 further clinical trials investigating the efficacy of different types of DES for the treatment of FP atherosclerotic occlusive disease are in the process of completing patient enrollment. It is hoped that publication of these ongoing trials will clarify whether DES are in fact superior to bare metal stents (BMS) in the FP area.

The first trial from Abbott Vascular Inc (Santa Clara, CA, USA) has completed enrollment of 100 patients. Known as the STRIDES trial (SFA Treatment with Drug-Eluting Stents Study), this is a European prospective non-randomized controlled trial that aims to evaluate the safety and performance of the DYNALINK-E® Everolimus-Eluting Peripheral Stent System in above-knee (AK) FP de novo or restenotic lesions. The maximal length of lesion treated is 17 cm. The second trial, the ZILVER® PTX™ paclitaxel-eluting stent study from Cook Inc (Bloomington, IN, USA) is also completing enrollment. In this study, the safety and efficacy of the ZILVER® PTX™ stent is being evaluated in the AK FP vasculature for lesions up to 28 cm in length. This study has 2 components, the first being a randomized investigational device exemption (IDE) trial that compares 240 ZILVER® PTX™ patients with 240 control patients. The control patients undergo percutaneous transluminal angioplasty (PTA) followed by placement of ZILVER® BMS for procedural failures. The second phase is a Global Registry evaluating an extra 760 ZILVER® PTX™, thus, giving a total of 1000 patients who will have received the paclitaxel-coated ZILVER® stents for FP lesions. At the 2007 International Symposium on Endovascular Therapies (ISET) meeting in Miami (http://www.iset.org/), Michael Dake presented an interim report for the IDE-phase, on behalf of the ZILVER® PTX™ investigators. Data on the first 60 patients enrolled in the trial were presented. Twenty-eight patients were assigned to the ZILVER® PTX™ group and 32 to the PTA control group. The mean follow-up duration was 9 months (range 6–18 months). Based on this preliminary data set, Dake concluded that the use of DES in AK FP lesions did not result in any safety concerns. The event-free survival was 89% in the ZILVER® PTX™ versus 91% in the PTA groups. Stent safety at 6 months was evaluated by plain X-ray, which showed no stent fractures in any of the implanted stents, and IVUS which did not reveal aneurysm formation or strut malapposition. Taking into account acute treatment failure, the investigators found a higher 9-month primary patency rate in the patients assigned to the ZILVER® PTX™ treatment (90%) in comparison to the PTA control group (52%). Stent effectiveness as evaluated by preliminary results in this analysis leads us to anticipate an equally encouraging final trial outcome.

These 2 landmark DES trials are of utmost importance for the endovascular community because positive results could

facilitate implementation of broad changes in the treatment paradigm of PAOD.

Infrapopliteal vasculature

The diameter similarities between infrapopliteal and coronary vessels make the use of DES in the BK vascular bed an intuitive application. Feiring and colleagues (2004) were the first to demonstrate the safety and utility of using coronary DES in the tibial vessels and paved the way for a more widespread application of DES for treating infrapopliteal disease.

Based on the outcome of 4 independent investigator-intiated studies, the sirolimus-eluting Cypher® stent (Cordis, Miami, FL, USA) have been CE-marked for the BK indication (Siablis et al 2005; Scheinert et al 2005; Bosiers et al 2006; Commeau et al 2006). Our own study (Bosiers et al 2006) evaluated the Cypher® stent for BK applications in 18 CLI patients (Rutherford 4 and 5) resulted in a 6-month limb salvage rate of 94.4% with an angiographic late lumen loss of only 0.38 mm in the surviving patients. Commeau and colleagues (2006) used SES to treat 30 consecutive patients with CLI (Rutherford category 3–6) and a minimum of 2 diseased infrapopliteal vessels. A limb salvage rate of 100% was achieved at a mean follow-up of 7.7 months, and all surviving patients treated with Cypher® stents had marked clinical improvement with 97% primary patency as measured by target lesion revascularization (Commeau et al 2006). Siablis and colleagues (2005) compared the outcome of 29 CLI patients treated with the sirolimus-eluting Cypher® stent with another 29 CLI patients receiving a BMS for infrapopliteal revascularization. The 6-month primary patency rate was significantly higher in the Cypher® group compared to the BMS group (92.0% and 68.1%, respectively, $p < 0.002$) (Siablis et al 2005). Angiographic follow-up 6-months post index intervention revealed a binary in-stent restenosis of only 4.0% after Cypher® stent implantation, while the rate was as high as 55.3% after BMS implantion ($p < 0.001$) (Siablis et al 2005). Siablis and colleagues (2007) also published their one-year follow-up results showing 86.4% primary patency in patients with DES, whereas patients with BMS had primary patency of 40.5% ($p < 0.001$). Likewise, the binary in-stent restenosis was better with DES, 36.7% in the Cypher® stent group, and 78.6% in the BMS group ($p < 0.001$). (Siablis et al 2007). The same highly significant difference in 6-month angiographic outcome between the Cypher® and the nondrug-eluting BX Sonic® stent (Cordis, Miami, FL, USA) was confirmed by Scheinert and colleagues (2006) in a nonrandomized controlled trial. The study evaluated 60 consecutive patients presenting with infrapopliteal lesions. The binary restenosis rate was found to be 0% in the Cypher® arm and 56.5% in the control BMS arm ($p < 0.001$) (Scheinert et al 2006).

Feiring and Wesolowski (2007) recently proposed a new technique for combining antegrade popliteal arterial access with tibial DES implantation in patients with occluded SFA occlusions. Five patients scheduled for BK amputations, successfully received overlapping infrapopliteal DES via this approach. After a mean follow-up period of 29 months, no deaths, no amputations, and no TLR were recorded. (Feiring and Wesolowski 2007).

The current generation DES used for BK interventions are balloon-expandable, which are known to be crushable. Stent crushing and fracturing may negatively influence stent performance and patient clinical outcome. To date, one case report of a fractured DES has been published (Scharzmaier-D'Assie et al 2007). The development of small vessel drug-eluting, self-expanding nitinol stents may improve the efficacy of the current generation of DES because self-expanding nitinol stents are less prone to fractures when compared with balloon-expandable stents. This can be important if longer infrapopliteal lesions will start to be treated. Our group recently reported the 12-month results using the commercially available non-drug-eluting Xpert® (Abbott Vascular, Santa Clara, CA, USA) nitinol stent system in BK interventions. With a 12-month primary patency rate of 76.3%, and a limb salvage rate of 95.9%, the clinical outcome after bare metal nitinol stent implantation was remarkable. Moreover, 12-month angiography with quantative vessel analysis (QVA) on the 73% of patients available for follow-up in the cohort revealed an angiographic binary restenosis rate of only 20.5%, which is comparable with well accepted coronary DES study outcomes. We attributed this optimal performance in the infrapopliteal arteries to the maintenance of flow dynamics because the stent was specifically designed for use in small vessels (Bosiers et al 2007). Although evidence currently indicates that the implantation of DES in the infrapopliteal vasculature leads to favorable outcomes with high mid-term primary patency and limb salvages rates, further support for the use of DES in patients with CLI and BK lesions will be gained from well-designed RCT. Such trials are about to start in conjunction with industry support.

Renal arteries

DES have also been applied for the treatment of renal artery stenosis, but as in the peripheral vascular bed, the number of publications remains sparse. Only 1 case report exists

on the use of DES for bilateral renal stenting, Granillo and colleagues (2005) described a single case receiving a paclitaxel-eluting stent in both renal arteries. In another case report, Kakkar and colleagues (2006) reported on the implantation of a paclitaxel-eluting stent (Scimed®, Boston Scientific, Maple Grove, MN, USA) in a patient with recurrent renal artery in-stent restenosis. Angiographic control 6 months after index intervention showed continued wide patency of the treated vessel (Kakkar et al 2006).

In an editorial comment, Zeller and colleagues (2006) described the potential role of DES in the treatment of renal artery stenosis. They made reference to the GREAT trial (Palmaz Genesis peripheral stainless steel balloon expandable stent: comparing a sirolimus-coated vs.a bare stent in REnal Artery Treatment), the only trial which evaluates the efficacy of DES in renal artery disease. In this nonrandomized, nonblinded, prospective, multicenter observational study, the sirolimus-eluting Palmaz Genesis™ Peripheral Stent (Cordis, Miami, FL) is compared with its bare metal counterpart in 105 consecutive, patients with symptomatic renal artery disease. Sapoval and colleagues (2005) published beneficial results for the BMS arm of the study. Zähringer and colleagues (2007) published results from both arms of the study after 2 years of clinical follow-up. They reported that implantation of the sirolimus-eluting version led to an absolute reduction in the 6-month angiographic binary restenosis rate of 50% (BMS = 14.3%, DES = 6.7%; p = 0.30) After 1 year, the target lesion revascularization rate was 11.5% in the BMS group compared with 1.9% in the drug-eluting group (p = 0.21). Implantation of both BMS and DES led to significant improvements in blood pressure, but 4%–7% patients had deterioration in renal function as measured by changes in serum creatinine. Despite, a trend toward improved outcome with DES in renal vasculature, the authors stated that the small sample size (n = 53) did not allow for detection of statistical significance between groups. Zeller and colleagues (2006) conclude that DES might be beneficial for patients with small renal arteries and impaired renal function. They believe that conventional BMS stent technology may lead to further deterioration in renal function because the need for reintervention exposes patients to recurrent administration of contrast and potential risk of renal embolism. According to their commentary, DES do not need to be used in patients with renal artery diameters greater or equal to 6 mm because results of existing endovascular interventions are already associated with a low restenosis rate in renal vasculature of this size. They state that use of DES may be preferable in patients with small diameter renal vessels (≤5 mm), a single, functional kidney or bilateral renal artery stenosis with small vessels, where the tendency toward inferior outcomes may justify the added expense and the risk of intensified, prolonged antiplatelet therapy with acetylsalicylic acid and clopidogrel (Zeller et al 2006).

Supra-aortic arteries

Extracranial vasculature

Gupta and colleagues (2006) reported outcomes of DES in the extracranial circulation. They retrospectively reviewed data from 59 patients with either extra- (n = 36) or intracranial stenoses (n = 29) treated with Cypher® or Taxus® stents. The majority of the extracranial stents were implanted in the vertebral artery (n = 31) or the internal carotid artery (ICA) (n = 5). Most (95%) procedures were technically successful and the peri-procedural complication rate was 3% (one nonflow limiting dissection and one stroke). Follow-up angiography (n = 41) or computed tomography (n = 7) performed at a median of 4 months post implantation revealed a restenosis rate of 6% (Gupta et al 2006). Although these results are early and retrospective, they provide hope for patients with cerebrovascular atherosclerosis who have a 19% risk of ipsilateral stroke when medically treated (Kasner et al 2006).

Two other authors have published case reports describing their experience with DES implanted for single extracranial lesions. Ko and colleagues (2004) mention in their report of 25 extracranial vertebral artery stenosis treated with balloon-expandable stents, the placement of one DES. At 1-month post-implantation, no adverse neurological events were observed (Ko et al 2004). In another case report Nussbaumer-Ochsner and colleagues (2006) present a patient with pre-procedural complaints of impaired left ocular perfusion and amaurosis fugax. The patient had occlusion at the origin of bilateral ICAs, stenoses of bilateral ECAs, and restenosis of the distal left CCA following prior endarterectomy. A Cypher® DES was implanted in the left ECA followed by placement of a non-drug-eluting self-expanding nitinol stent (Precise, Cordis. Miami, FL, USA) in the left CCA. The procedure was uneventful, and the ocular symptoms resolved. At 6 months, the patient remained asymptomatic, with both stents being angiographically patent (Nussbaumer-Oschner et al 2006).

Intracranial vasculature

Abou-Chebl and colleagues (2005) collected data from 8 patients receiving a DES, 4 Cypher® and 4 Taxus® (Boston

Scientific, Maple Grove, MN, USA). Stents were placed in the following locations: 3 intracranial ICA, 2 middle cerebral, 2 basilar, and 1 vertebral artery stenosis. Patients had a significant reduction in the initial stenosis (84% to 2.5%). One patient had a retinal embolism during guide catheter removal and there was a post-stenting, nonflow-limiting, asymptomatic basilar artery dissection, which healed spontaneously during the follow-up period. No recurrence of cerebral ischemic events was observed during the follow-up period (mean 11.1 months). None of the angiographically studied patients (n = 5 of 8) developed significant restenosis, and none required target vessel revascularization (Abou-Chebl et al 2005).

In their retrospective analysis of patients treated with DES for both extra- and intracranial lesions, Gupta and colleagues (2006) described 29 intracranial cases treated with either Cypher® or Taxus® stents. In 19 cases, the lesions were in the intracranial vertebral or basilar artery, while the remaining 10 were in the intracranial ICA. Technically successful stent implantation was achieved in 90% (26/29) of cases: the stent could not be deployed in 2 intracranial ICAs and 1 vertebral. Two peri-procedural complications were observed: 1 non-flow limiting dissection in an intracranial ICA and 1 disabling stroke 12 hours after placement of a basilar artery stent. There were no new restenotic lesions seen in 20 stents that were followed with repeat angiography or computed tomography at least 3 months after implantation (Gupta et al 2006).

Qureshi and colleagues (2006) retrospectively analysed 18 patients stented with DES for symptomatic lesions located in the intracranial ICA (6), the proximal middle cerebral artery (4), the vertebral artery (4), the vertebrobasilar junction (2), or the basilar artery (2). A Cypher® stent was used in 14 cases and the remaining 4 received Taxus® stents. It was attempted to perform stenting in 3 more patients, but the procedure was unsuccessful, resulting in technical success rate of 85.7%. During the first month after the intervention, no patients died and 1 patient experienced a major stroke. Cerebral angiography was performed in 7 patients at 6 months follow-up and revealed a binary restenosis rate of 14% (Qureshi et al 2006).

In our service, we performed a single Cypher® DES implantation in a 63-years old female patient presenting with a symptomatic high-grade stenosis situated in the intracranial segment of the ICA. Primary stenting was performed using a 3.5 mm diameter stent of 33 mm in length. The procedure was successfully completed without residual stenosis, or clinical complaints. To date, 2 years after the intervention, the patient is alive and has not experienced any further neurological events.

Discussion

At present, DES exist only on a balloon-mounted platform, which is expensive and potentially prone to crush injury. The expected superiority of DES for infrapopliteal and intracranial interventions in comparison to BMS is theoretical at present and extrapolated from outcomes seen in the coronary literature (Holmes et al 2004; Stone et al 2004). The need for performance of randomized controlled trials cannot be emphasized enough. The treatment of CLI, is one indication where use of DES may have a major impact. If treated strictly medically, only 50% of the patients with CLI will be alive without a major amputation after 1 year. Approximately 25% will have died and 25% will have had a major amputation (Norgren et al 2007; Siablis et al 2007). These patients lack conduit, have unsuitable target vessels for revascularization and significant comorbidities that preclude open surgical intervention. The paradigm has shifted to minimally invasive revascularization using PTA and stenting, but, although this approach has modified outcomes, the present 30%–50% restenosis rate at one year after PTA and implantation of BMS in the below-knee location warrants further improvement (Siablis et al 2005; Scheinert et al 2005; Commeau et al 2006).

There is also definitely room for improvement in the intracranial circulation. The compelling stroke rate seen in the WASID study, where patients with greater than 70% intracranial stenosis treated medically had a 23% stroke rate at one year, and, the 35% documented angiographic restenosis seen in the SSYLVIA trial, where the bare metal, balloon-expandable Neurolink® stent (Advanced Cardiovascular Inc., Guidant, Indianapolis, IN) was implanted, both highlight the limitations of existing treatment strategies (SSYLVIA Investigators 2004; Chimowitz et al 2005). Despite the high angiographic restenosis rate seen after BMS implantion in the SSYLVIA trial, only 40% of these restenosis led to neurologic complaints. It is therefore unclear, whether the potential for symptomatic restenosis reduction that might be provided with DES implants in this location outweighs the risk of early thombotic occlusion attributed to DES.

The initial enthusiasm for DES stems from their efficacy in reducing in-stent restenosis and neointimal hyperplasia from 30% to approximately 5% (Holmes et al 2004; Stone et al 2004). Although direct arterial toxicity from the eluted drugs is unfounded, there are late thromboses secondary to delayed endothelialization that necessitate prolonged

dual antiplatelet therapy and should temper nonchalant use of DES (Levy et al 2004; Moreno et al 2005). Unlike in animal models, use of DES in human atherosclerotic arteries results in delayed endothelialazation around the stent struts and thus makes the stent more susceptible to thrombosis. In coronary DES trials, the increased incidence of thrombosis with DES is small, in the order of 0.6% per annum, but, the accompanying 31%–45% mortality rate from the resultant myocardial infarction is of great concern (Harper 2004). Despite the fact that DES thrombosis in the peripheral circulation is not as lethal as in coronaries, dual antiplatelet therapy after DES is also warranted for PAOD to guarantee optimal stent performance and patient clinical well-being. Nevertheless, the use of dual antiplatelet therapy is related with an increased incidence (1%–2% per annum) of major bleeding complications and is expensive (Diener et al 2004; Eisenstein et al 2007). One year of clopidogrel costs approximately US$1000.00. This expense is in addition to the cost already incurred by using a DES, which is usually fourfold greater than the bare metal equivalent; one coronary BMS costs US$800.00 while one DES costs up to US$2500.00 (Harper 2004). The duration of treatment with dual antiplatelet therapy after both coronary and peripheral implantation of DES remains a subject of ongoing debate. Based on emerging evidence, many cardiologists are recommending a minimum of 12 months of aspirin and clopidogrel, but, some are advocating indefinite use of dual antiplatelet therapy after DES implantation (Waksman 2006).

To overcome some of the shortcomings of the current generation of DES, further modifications in already existing stent technology need to be pursued, especially for infrapopliteal interventions. As CLI patients most often present with long, diffuse BK lesions, longer stents need to be manufactured to make use of DES more cost-effective in the BK vasculature. Especially for these longer lesions, there might be need for the development of specific infrapopliteal, drug-eluting, self-expanding nitinol stents to help circumvent potential crushing and strut fractures seen with the balloon-expandable platform (Scharzmaier-D'Assie et al 2007). One option involves development of drug-eluting bioabsorbable stents (Waksman 2006). The limitation of bioabsorbable stents has been the inflammatory response that is elicited after implantation. Modification of this response through local elution of anti-inflammatory, antiproliferative drugs should minimize restenosis, as well as inhibit injury-induced neointimal hyperplasia. As the requirement for vessel scaffolding provided by the stent is only needed temporarily, subsequent absorption of the stent should, in turn, allow endothelialazation, thus, precluding the need for ongoing antiplatelet therapy. (Waksman 2006) Another approach involves development of stents with inherent antithrombotic properties, such as stents coated with monoclonal antibodies capable of capturing circulating endothelial progenitor cells. (Harper 2004).

Conclusion

At present, the use of DES for noncoronary applications is investigational. Although there are good indications and some publications supporting the use of DES in several noncoronary vascular beds, more data and long-term follow-up are needed. The results from nonrandomized, controlled trials such as the ZILVER® PTX™ and STRIDES trials are eagerly anticipated, but, ultimately, randomized controlled trials comparing DES with BMS implantation need to be performed to determine DES superiority. Until these results are available, review of the literature prompts us to make the following recommendations:

1. DES in the SFA provide no added benefit to the current generation of nitinol BMS, except, in complex lesions (long stenoses or occlusions). Additionally, in these type of complex lesions it will need to be investigated whether the potential improved patency and quality adjusted life year (QALY), outweigh the increased cost of (multiple) DES and the need for prolonged dual-antiplatelet therapy.
2. DES in the infrapopliteal vasculature of patients with CLI have the greatest potential benefit because the one-year restenosis after implantation of BMS stents in this location is high (50%) (Bosiers et al 2006). From a financial standpoint, there is existing coronary drug-eluting technology that can also be used in the infrapopliteal vasculature thus making this a more cost-effective undertaking. Preliminary results using DES in the infrapopliteal vasculature from single center studies are encouraging with low amputation rates ($<$5% vs $>$50% for untreated patients with CLI) (Siablis et al 2005; Bosiers et al 2006; Commeau et al 2006). There is need for RCTs and there are plans to perform these in conjuction with industry.
3. DES in renal interventions provides no added benefit to the current generation of balloon-expandable stents, except potentially in patients with solitary functional kidneys, where treatment failure has more compelling implications, or in patients with small renal arteries ($\leq$5 mm) where outcomes are less favourable. Confirmation with RCTs is required.
4. Due to lack of evidence, DES in the intracranial and extracranial cerebrovascular vasculature is currently not supported.

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