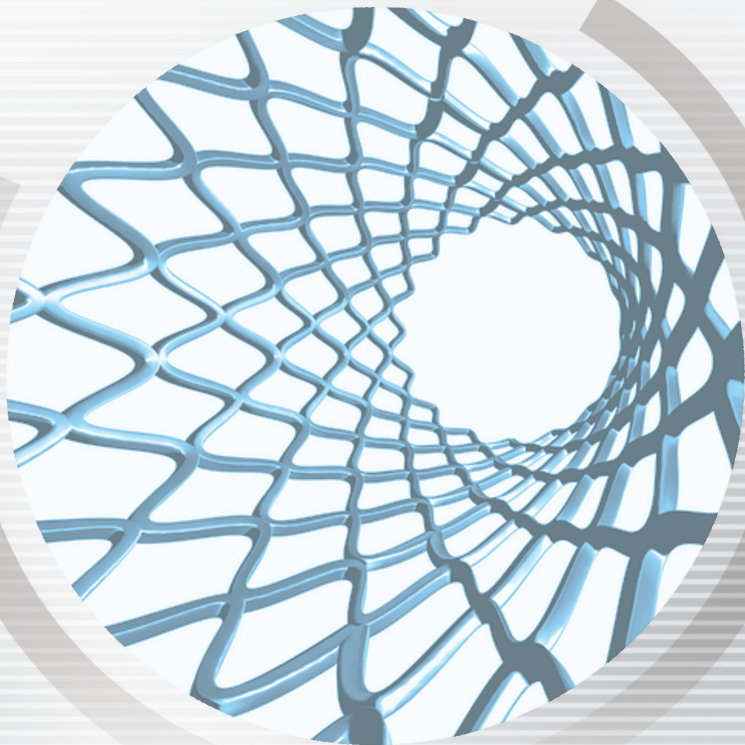


The rise of the balloon: drug eluting balloons show great promise in treating arterial disease



A market report by Cambridge Consultants

Recent advances in the field of intravascular medicine have seen the emergence of drug eluting balloon (DEB) technologies as a viable alternative for treating stenosed arterial vessels. The question is whether such technology will be disruptive to currently available treatments, including stents.

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DEBs - a viable alternative?

Recent advances in the field of intravascular medicine have seen the emergence of drug eluting balloon (DEB) technologies as a viable alternative for treating stenosed arterial vessels. The question is whether such technology will be disruptive to currently available treatments, including stents.

The concept of using a balloon catheter to deliver an anti-restenotic drug, such as paclitaxel, at the site of arterial disease was initiated by Scheller et al in 2003¹. Pre-clinical studies demonstrated effective inhibition of restenosis after PTCA with stent implantation. Subsequent clinical trials (PACCOATH^{®2}- ISR I and PACCOATH[®] - ISR II) successfully validated the efficacy of a paclitaxel coated balloon catheter to treat coronary in-stent restenosis after two years' follow-up³.

The evolution of DEB technologies started at about the same time drug eluting stents (DES) were being adopted in the US market. Within coronary applications, stents are expected to remain the 'gold standard' and it is unlikely that DEBs will be a disruptive technology in coronary beds, although niche applications exist, as detailed in Figure 1. Such application opportunities have been verified by Professor Bruno Scheller who, along with Professor Ulrich Speck, was instrumental in the development of DEB technologies: "DEBs will have great impact in coronary applications e.g. for the treatment of in-stent restenosis and bifurcation lesions. Furthermore, in combination with bare metal stents they may overcome some of the limitations of DES".

Tim Clay, who leads the Market Strategy Group at Cambridge Consultants, initiated the first market evaluation study to be performed on these products in 2005. At that time, interventionalists were conservative in their views on potential applications of DEBs in the coronary bed. As a result, our initial evaluations may be underestimates, particularly as DEBs are now seen as a real opportunity to provide an alternative treatment which circumvents many of the current safety concerns associated with DES placement. Additionally, subsequent clinical trial data for Paccocath has exceeded therapeutic expectations.

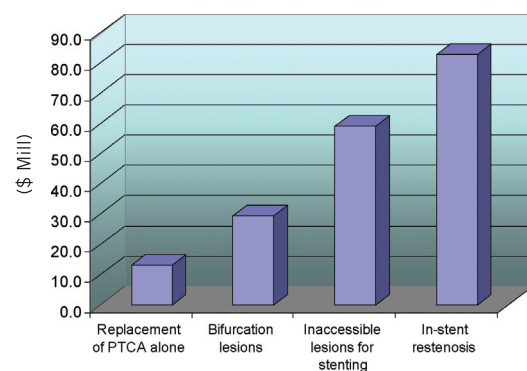


Figure 1 Estimated addressable US market for drug coated balloon catheters in coronary applications (Cambridge Consultants' valuations based on potential in 2012). The addressable market assumes DEBs to be available on the market. The data was based on potential usage rates of such products and pricing analysis.

¹ Scheller B. et al. 2004. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 110(7):810-4. ² PACCOATH is a registered trademark of Bayer Schering Pharma AG
³ Scheller B. et al. 2008. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 97(10):773-81

A fast changing market

Since these early investigations on the market potential for DEBs, the market dynamics have changed. A number of follow-up studies identified late stage thrombosis after DES placement; a serious clinical condition associated with major adverse cardiac events and high rates of mortality. These findings caused the once rapid penetration of DES in the US coronary market to decline by around 20% in 2006 resulting in a reverse of fortunes for bare metal stent (BMS) providers. Since then there has been some restoration in the balance of the coronary stent market. This was greatly assisted by the FDA's conclusion at the end of 2006 that, although DES were associated with a small increase in stent thrombosis compared with BMS, overall there was no increased risk of myocardial infarction or mortality.

However, because of such safety concerns, the market is more receptive to simpler and less invasive technologies. Cambridge Consultants believes that DEBs fulfil these requirements and that they could have a significant impact across the interventional landscape.

The situation with treating peripheral arterial disease (PAD) is very different. There is wider treatment potential, especially in femoral, popliteal and below the knee interventions. Current treatment regimes for these areas vary but overall use of stents is lower and restenosis rates are high. Similarly to coronary interventions, DEBs could also have a role in treating peripheral in-stent restenosis, as well as diffuse and small vessel disease. However, it is unlikely to replace the predominant use of stents in carotid and renal procedures. Indeed, according to Dr Thomas Zeller, Head Physician, Herz-Zentrum Bad Krozingen, Germany: "The device [DEB] might be indicated in all types of lesions and lesion locations where we have so far no durable alternative solution available: the femoro-popliteal axis and below the knee regardless of the type of lesion." The technology also has the potential to replace the use of standard PTA, either alone, or in combination with a BMS. In 2005, interventional radiologists believed that the opportunity for DEBs in PAD was greatest in the femoral popliteal axis. However, with high unmet needs in below knee applications and the existence of diffuse disease, DEBs could drive the markets in treating these more distal vessels. Indeed, studies are ongoing for such clinical proof, the first of which is the THUNDER trial in 2004 to evaluate the efficacy of Paccocath[®] in femoral and popliteal arteries. More recently, the Piccolo trial has been initiated using a Paclitaxel coated Amphirion[®] balloon catheter⁴, which is an academic study, led by Prof. Gunnar Tepe, based around a commercially available balloon catheter. It was not surprising therefore to hear of the launch of Invatec's IN.PACT Amphirion paclitaxel-eluting balloon catheter for infrapopliteal interventions during the LINC congress earlier this year.

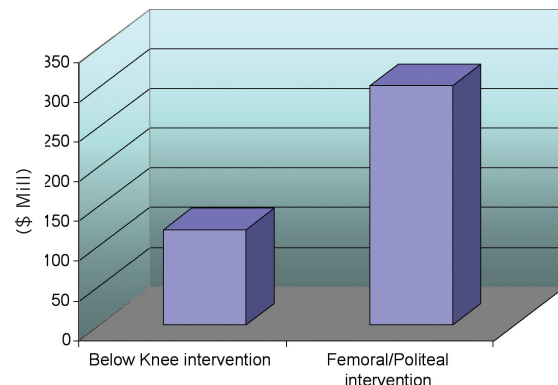


Figure 2 Estimated addressable US market for drug coated balloon catheters in peripheral applications (Cambridge Consultants' valuations based on potential in 2012). The addressable market assumes DEBs to be available on the market. The data was based on potential usage rates of such products and pricing analysis.

"DEBs will allow procedures in the periphery to occur that are currently not possible. Overall procedure numbers will increase as a result", commented Prof. Ulrich Speck, who was responsible for the pharmaceutical development of the Paccocath[®] technology. Dr Dennis Wahr, Co-Founder, President and CEO of Lutonix, Inc. also noted that "DEBs could be used where long term anti-platelet therapy is problematic. This could represent around 10% of [coronary and peripheral] patients."

Compared to standard PTCA/PTA and stent technologies a number of advantages for DEB exist:

- Lower restenosis rates than standard PTCA/PTA treatments
- May avoid the need for a permanent implant i.e. stent placement
- Can be used on its own or in combination with a BMS of choice
- No increase in device or procedural complexity to use of a standard PTCA/PTA balloon catheter
- Immediate drug release without the use of a polymer that can cause inflammatory reactions with certain DES stents
- Potential decrease in anti-platelet therapy
- Potential for homogenous drug delivery to the vessel wall, unlike DES

"The strength of the technology is the ease of use", notes Dr Thomas Zeller. As a consequence, the technology is currently gaining huge momentum in the market.

⁴ Amphirion is a registered trademark of Invatec

Competition is heating up

Since the initial research undertaken by Scheller et al, many companies are attempting to commercialise a DEB. Paclitaxel is the drug of choice currently (Table 1) due to its tried and tested ability to reduce restenosis rates in coronary arterial disease, with typical dosage being $3\mu\text{g}/\text{mm}^2$ balloon surface. Cook Medical notes, "Paclitaxel is a wonderful drug because it will stay and inhibit cell proliferation for the duration of a cell's life."

Table 1: Key players active in developing DEB technologies

Company	DCB Name	Drug formulation
Aachen Resonance GmbH (distributed by Biotronik AG in UK, Switzerland, Benelux, Italy and Ireland).	ELUTAX®	Formulated with a matrix of pure Paclitaxel
B. Braun Melsungen AG	SeQuant® Please	Paclitaxel with ioprimde formulation (Paccocath® technology)
Bayer AG (MEDRAD, Inc.)	Cotavance™ with Paccocath® coating technology	Paclitaxel with ioprimde formulation (Paccocath® technology)
Caliber Therapeutics, Inc.	TADD (Targeted Angioplasty Drug Delivery)	Rapalog-based with unknown formulation
Cook Group, Inc.	Advance® 18PTX®	Paclitaxel with unknown additive-based formulation
Eurocor AG	DIOR®	Paclitaxel without any formulation. (Opto Circuits Ltd. also developing rapamycin-based technology)
Invatec s.r.l.	IN.PACT™ Amphirion	Paclitaxel with FreePac™ hydrophilic formulation
Lutonix, Inc.	Unknown	Paclitaxel with unknown formulation

The second critical factor enabling successful drug transfer is the formulation used to coat the balloon. Current products range from those with no formulation, to those applied in conjunction with standard contrast agents or other beneficial additives. A number of companies have undertaken extensive research into this issue and believe that the formulation will be critical to successful product performance and adoption. To date, a number of DEB technologies are already sold in Europe and Asia and some products are being applied on compassionate grounds in the US.

The regulatory paradox

There is a great regulatory paradox, however, for these products. Some of the competitors in this market have found it difficult to obtain CE marking, even though they can demonstrate clear clinical outcomes for the technology. This suggests an inconsistency among Notified Bodies with regard to the requirements for awarding CE Marking. The medical profession are naturally concerned with this paradox. “In view of the results of preclinical and clinical trials, physicians should discriminate between different DEB technologies”, warn Prof. Speck and Prof. Scheller. An overview of the status of competing products is given in Table 2.

Schering AG (now part of Bayer AG) and B. Braun Melsungen AG appeared first on the scene by co-licensing Scheller et al’s DEB coating technology and process. Schering AG licensed the Paccocath® technology in 2005, gaining rights to develop and market the technology worldwide, for both coronary and peripheral applications. The company co-sponsored the THUNDER (Local Taxan with Short Time Exposure for Reduction of Restenosis in Distal Arteries) clinical trial in 2004 to assess the efficacy of the DEB technology for preventing restenosis in the superficial femoral and popliteal arteries. Trial results concluded that the Paccocath® DEB technology showed a significant reduction in late lumen loss and target-lesion revascularisation compared to standard PTA.



Table 2: Key players active in developing DEB technologies

Company	Trial activity	Development/launch status
Aachen Resonance GmbH (distributed by Biotronik AG in UK, Switzerland, Benelux, Italy and Ireland).	Trial data submitted based on DEBIUT trial	EU launch with CE approval
B. Braun Melsungen AG	PEPCAD I and PEPCAD II trials completed assessing treatment of coronary de novo lesions and in-stent restenosis. Further trials underway	Initial launch in Malaysia. CE application filed
Bayer AG (MEDRAD, Inc.)	Pre-clinical. Plans for clinical testing outside of the US for coronary applications	Late stage development
Caliber Therapeutics, Inc.	Clinical trial initiated to assess efficacy in peripheral applications	Early stage development
Cook Group, Inc.	Clinical trials initiated to assess efficacy in coronary applications	Late stage development
Eurocor AG	Pre-clinical testing undertaken. Clinical trial planned in 2009 to assess efficacy in peripheral applications (2nd generation device)	EU launch with CE approval
Invatec s.r.l.	Efficacy tested in porcine model. Clinical trial activity planned for both coronary and peripheral applications	EU launch with CE approval
Lutonix, Inc.	Pre-clinical testing undertaken	Early stage development

A second randomised trial was also undertaken by MEDRAD, a Bayer Healthcare affiliate, which concluded that the Paccocath[®] DEB technology was also able to inhibit restenosis and reduce target-lesion revascularisation in femoropopliteal arteries.

B. Braun Melsungen AG and the Charité Hospital also signed a licensing agreement for the Paccocath[®] DEB technology whereby B. Braun gained non-exclusive rights to develop and market the technology in coronary applications outside of the US. Under the name SeQuent[®] Please, the company tested the efficacy of the technology in two trials, PEPCAD (Paclitaxel-Eluting PTCA Balloon Catheter in Coronary Artery Disease) I and II for the treatment of small vessel de novo lesions and in-stent restenosis in coronary arteries respectively. Six month follow-up data demonstrated binary restenosis rates of less than 6% for treating small vessel de novo lesions and a significant reduction in binary restenosis compared to the use of the Taxus[™] paclitaxel-eluting coronary stent for treating in-stent restenosis. We understand that the product has recently been granted CE approval.

The company also has further plans to test its DEB technology in combination with a stent for the treatment of de novo lesions in diabetic patients, as well as the treatment of bifurcation lesions and chronic total occlusions. In addition, the company has recently completed enrolment for its PEPCAD III trial to assess the safety and effectiveness of its Coroflex[™] DEBlue platform (which utilises the SeQuent[®] Please DEB technology with a thin-strut CoCr stent) for the treatment of advanced coronary artery disease.

As a result of these initial DEB studies, a number of other companies have developed alternative drug coating technologies in order to gain a presence in the market.

Eurocor GmbH launched its DEB version, the DIOR[®] paclitaxel-eluting coronary balloon dilatation catheter, in Europe in 2007. The technology is indicated for the treatment of coronary de novo and bifurcation lesions, as well as in-stent restenosis. Initial six month follow-up data from the company's DIOR ISR registry indicates the use of DIOR[®] to treat DES in-stent restenosis is comparable to the use of a further DES based on target lesion revascularisation data.

Eurocor is currently expanding its distribution network and its parent company, Opto Circuits Ltd., also has plans to launch the technology in the US. The company is also actively pursuing peripheral applications with its FREEWAY[®] paclitaxel-eluting peripheral dilatation catheter. Opto Circuits Ltd and its new subsidiary, Maxcor Inc., has formed a collaboration with Micell Technologies, Inc. to develop possible next generation rapamycin (sirolimus)-based DES and DEB technologies to build upon its current offerings. Interestingly, this collaboration enables Maxcor to utilise Micell's proprietary coating technology.

Aachen Resonance has also gained CE approval for its ELUTAX[®] paclitaxel-eluting balloon catheter. Unlike other players, Aachen Resonance has coated the balloon with 2µg/mm² paclitaxel and it is understood that no additives are used to ensure drug attachment. Biotronik AG, a well established European cardiovascular company, has a known interest in DEB technology. In 2009, it was announced that Aachen Resonance and Biotronik had entered into a distribution agreement with Aachen's products, including ELUTAX[®].

The IN.PACT[™] Amphirion paclitaxel-eluting PTA balloon catheter, was launched by Invatec s.r.l. in January this year, for the treatment of peripheral arterial disease, specifically disease below the knee⁵. The company claims its FreePac[™] hydrophilic coating facilitates absorption of the drug to the vessel wall. Preclinical bioequivalence data for the product has recently been published by the company, highlighting the performance of the FreePac coating technology after stent implantation in porcine coronary arteries. It is understood that the company plans to launch a randomised trial, the IN.PACT DEEP study, in the first half of this year.

Also in January this year, Cook Medical unveiled its Advance[®] 18PTX[®] DEB for the treatment of peripheral vascular disease⁶. The technology is currently undergoing a randomised clinical assessment to study its safety and effectiveness in treating lesions in the superficial femoral and popliteal arteries.

Other DEB technologies are in earlier stages of development. A number of companies are investigating the use of alternative anti-restenotic drugs, such as a genistein-coated balloon catheter from Sahajanand Medical Technologies Pvt. Ltd., which has demonstrated anti-inflammatory properties in porcine coronary arteries, and Caliber Therapeutics, Inc.'s rapalog-based DEB technology which is being developed in combination with DSM Biomedical. Another direction being investigated is the optimisation of the drug eluting formulation to prevent premature release of the drug prior to balloon placement and to maximise rapid uptake of the drug into the vessel wall upon inflation. One example of this is Lutonix Inc.'s paclitaxel-eluting balloon technology which has undergone significant in vitro and in vivo testing to define the optimal formulation for drug release.

Major cardiovascular players are not ignoring the rapid interest in DEB technology either. Several are known to have initiated their own DEB research programmes and therefore greater market activity and competition can be expected over the next few years.

⁵ Invatec launches first drug eluting balloon designed to treat atherosclerosis below the knee. Invatec press release January 2009

⁶ Cook Medical unveils the Advance Drug Eluting Balloon and other cutting edge devices to advance leg therapy at the ISET 2009 International Symposium on Endovascular Therapy. January 2009

Future of treating vascular disease with DEBs

From its inception, DEB technology sparked widespread interest from both interventional cardiologists and interventional radiologists seeking improvements in procedural success and a reduction in lesion restenosis rates. Although the most promising applications for the technology appear to be niche, especially for coronary applications, it is highly feasible that utilisation could easily spread with DEB technologies becoming a mainstream tool in the interventionalist's repertoire, particularly for the treatment of PAD.

Indeed, its potential is highlighted by the number of companies known to be competing in this area, ranging from leading global players to small, highly specialised companies. Currently, only a handful of companies have gained market approval for their products but, with the level of pre-clinical and clinical activity reported here, many more can be expected to enter the market in the near future.

Although the technology appears to hold such promise, there is still a strong need for further clinical evidence of each product's capability, efficacy, and safety. The criteria for gaining market acceptance must be clear as the DEB holds much promise for the treatment of life-threatening vascular disease. It is imperative to allow this technology the potential for adoption by having safe and efficacious products developed within a fairly regulated environment.

About Cambridge Consultants

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With a team of 300 engineers, scientists and consultants at offices in Cambridge (UK) and Boston (USA), we are able to offer solutions across a diverse range of industries including medical technology, industrial and consumer products, transport, energy, cleantech and wireless communications.

This report was produced by the company's Market Strategy team, a group of industry specialists who formulate unique selling points for first in class products and build credible market models based on predicting future market performance of leading edge technologies.

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