

Scrip magazine

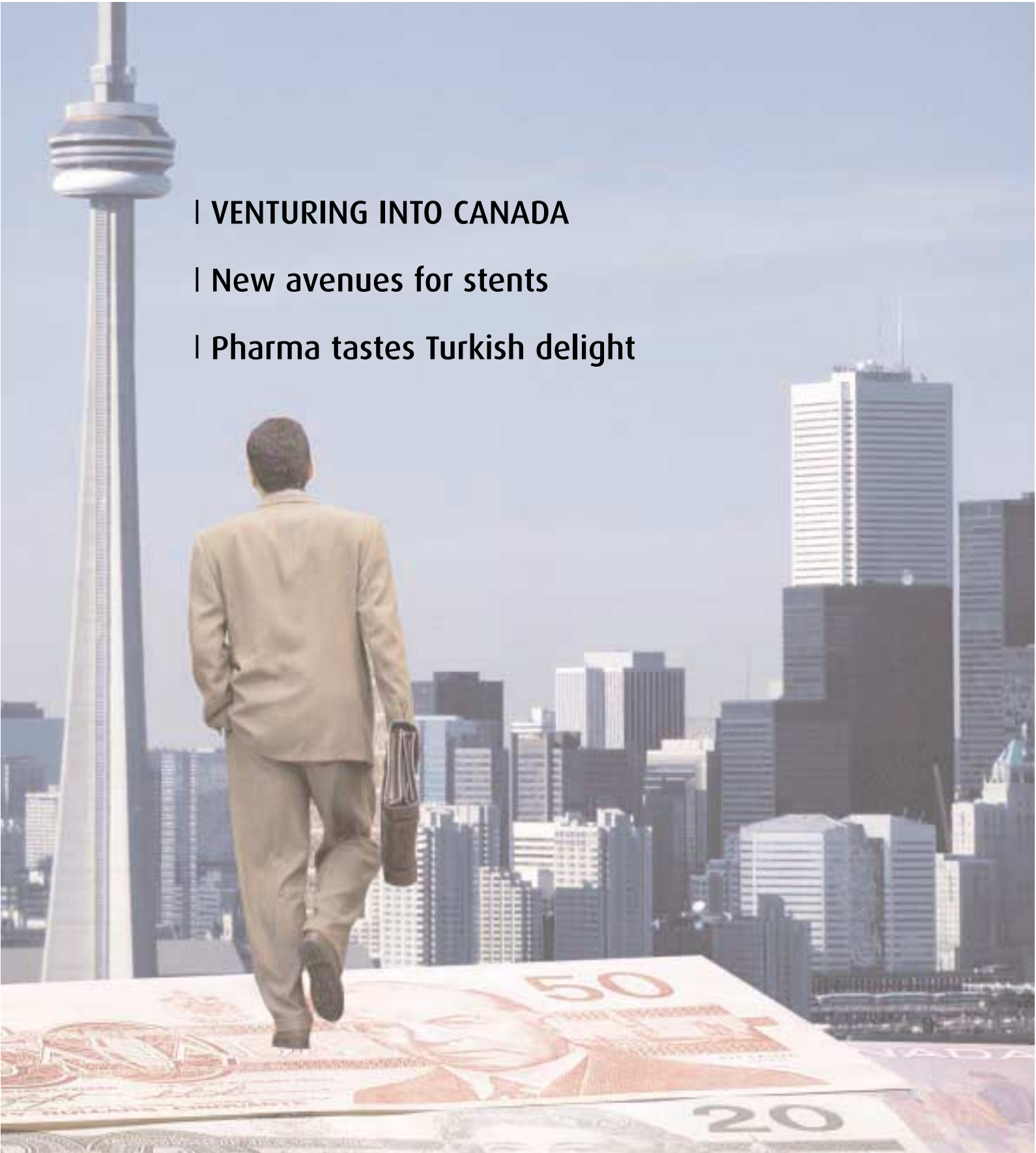
January 2006

Pharmaceutical issues in perspective

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| New avenues for stents

| Pharma tastes Turkish delight



The rise and rise of stents

Stenting techniques that restore blood flow to narrowed coronary arteries have been widely adopted in the last decade. Now, research is focusing on the next development steps – stent performance and adaptation, using alternative drug coatings, biodegradable materials and other emergent technologies. **Caroline Wright** explains

Since their introduction in the early 1990s, stents have revolutionised the treatment of coronary arterial stenosis, decreasing the incidence of restenosis (renarrowing of the artery) relative to standard balloon angioplasty by around 50%, and simultaneously reducing the need for more invasive cardiac surgery. With continuous improvements in design and drug delivery capabilities, the global stent market has grown to become a US\$6 billion business in ten years. The holy grail of stenting, namely the complete prevention of restenosis, has still not been achieved, and around 7% of procedures require secondary treatment. In addition, while the major driver for stent development is the US market in interventional cardiology, there remains a major unmet need for stenting in vessels throughout the body, including the oesophagus, ureter and peripheral arteries.

So what are the medical applications of stenting, including non-cardiac uses, and how will the design and development of different stents affect their future markets?

Reviewing coronary stents

The prevalence of ischaemic coronary heart disease (ICHD) has increased markedly over

the last 50 years, particularly in developed countries. However, in contrast with developing countries, incidence rates have now slowed in the West because of improved education related to smoking, diet and exercise. But the cost of treating the disease is still a major burden on healthcare budgets.

Until the mid-1990s, treatment of ICHD was based on coronary arterial bypass grafts (CABG). Although this method is still a viable option today, it has been largely replaced by percutaneous transluminal coronary angioplasty (PTCA) and stenting. CABG is a very intense procedure, requiring several hours of surgery under general anaesthetic, followed by days of hospitalisation and weeks of rehabilitation. PTCA and stenting, on the other hand, are non-surgical procedures that commonly take less than an hour, during which time the patient is conscious, and recovery may take just a few days. The huge impact of these procedures on hospital workflow is clear and, as a result, throughout the 1990s, these technologies led to increasing percutaneous coronary intervention (PCI) rates of 10–20% annually.

Although PTCA drove this change in

treatment, the technique has several drawbacks. Following removal of the balloon, positive intercoronary pressure causes elastic recoil of the arterial walls, resulting in a dynamic narrowing of the vessel. Furthermore, endothelial damage caused by the balloon itself leads to cell proliferation and restenosis in 30–50% of cases.

Coronary arterial stents were designed to overcome some of the shortfalls of angioplasty. An expandable wire mesh tube is collapsed over the balloon, and inserted using a catheter. Once in place, the stent is expanded by inflating the balloon and is then held in place by its own tension. The stent prevents arterial recoil by forming a permanent scaffold to hold the artery open. This simple ‘plumbing’ job reduced the restenosis rate to 15–20% and is now standard practice in over 80% of angioplasty procedures. In 2004, over 1.5 million PCIs were performed the US and Europe alone, 90% of them with stents, using an average of 1.3 (Europe) to 1.6 (US) stents per procedure.

Despite their successful prevention of elastic recoil, bare metal stents (BMS) still result in restenosis due to cell proliferation induced by ‘injury’ to the arterial wall. Arterial damage stimulates neointimal formation from vascular muscle cell proliferation and activation of the immune response causing inflammation. To address this problem, the first drug-eluting stent (DES) was introduced in 2002. Coated in a slow-release cytostatic drug to prevent cell growth, it halved the restenosis rate relative to BMS, reducing it to 5–7%. As a result, despite their significant cost relative to BMS, DES already dominate the US market (see Figure 1).

A DES generally has three basic components: the stent, the drug and a polymer coating. The stent is covered in a drug dissolved in a formulation such as phosphorlycholine or a bioabsorbable polymer. The coating must be biocompatible, suitable for sterilisation and

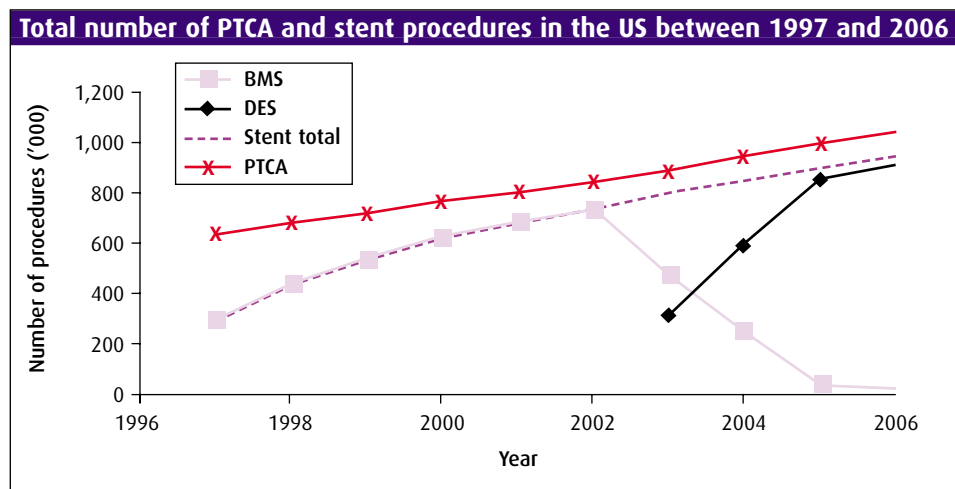


Figure 1: Introduced in the US in 2002, drug-eluting stents (DES) halved the incidence of restenosis compared with bare metal stents (BMS), encouraging swift and widespread uptake of the drug-eluting products.

resistant to mechanical expansion and abrasion. Once implanted, the drug should be released in a controlled and predictable way over an appropriate time period. Potential drug candidates include immunosuppressive, antithrombotic, anti-inflammatory and antiproliferative compounds. To date, there are only two DES approved for sale in the US – Cypher, from Cordis (Johnson & Johnson), and Taxus, from Boston Scientific. Cypher elutes sirolimus (rapamycin), a naturally occurring macrolide antibiotic that causes cell cycle arrest and immunosuppression by inhibiting T-cell activation. Taxus is coated with Taxol (paclitaxel), a popular anticancer drug that inhibits cell proliferation and migration by hyper-stabilising microtubules, thus preventing the cell from using them in a flexible manner. There are also various other drug candidates for DES, including additional immunosuppressive macrolide antibiotics such as everolimus and tacrolimus, as well as the anticoagulant heparin.

As an alternative to drug coating, radioactivity offers another potential strategy for preventing in-stent restenosis. Radiation inhibits the formation of scar tissue – a problem created when the heart's artery wall is damaged by angioplasty, and the resultant scar tissue narrows the lumen of the artery. Radioactive stents do prevent in-stent restenosis, but arterial narrowing is seen at the edges in nearly 50% of cases. Various strategies have been tried to counteract this 'candy-wrapper' phenomenon, such as making stents with 'hot ends' and using low-pressure balloon expansion to reduce arterial injury; but to no avail. As well as these technical problems, radioactive stents have to

contend with containment issues and the type of 'bad press' associated with any sources of radiation; unsurprisingly, when given the option, cardiologists and patients alike would rather avoid the hazard of radioactive contamination. These outstanding issues mean that radioactive stents, despite their success at preventing in-stent restenosis, have now largely been abandoned. However, vascular brachytherapy – a procedure whereby the inner layers of the arterial wall are irradiated – is still an alternative treatment for prevention of in-stent restenosis, and at least one US-based firm, Novoste, has developed a removable radioactive catheter specifically for this purpose.

A tale of two continents

More than US\$4 billion of the annual US\$6 billion global stent market is in the US and Europe. The US market for stents is very different from that observed elsewhere in the world, because of the disparity between reimbursement trends. In the US, healthcare plans pay differentially for alternative stents, so hospitals are not penalised for using the more expensive drug-eluting products. As a result, the DES market is forecast to grow with a compound annual growth rate (CAGR) of 36% between 2003 and 2008, while the BMS market has a declining CAGR of 35% over the same timescale (see Figure 2). But these large CAGRs mask the underlying market dynamics; annual growth rates in the US are levelling off and will soon plateau as the

number of procedures will saturate the market.

This trend is in stark contrast with Europe, where the cost of DES can be up to ten times more than BMS. The cost differentiation is unlikely to remain for long however, as DES are already undergoing a dramatic price erosion,

Biodegradable stents hold great promise as temporary drug delivery vehicles, and can be loaded with a cocktail of multiple drugs to treat a range of problems

like BMS before them, at an average annual rate of about 10%. In light of more fragmented health systems and wide discrepancies between funding models, acceptance and uptake of DES has been much slower in Europe, with a CAGR of 22% and a declining CAGR of 12% forecasted for BMS (see Figure 2) between 2003 and 2008. Reimbursement systems vary between countries and can strongly influence treatment choices. Under the current system in Germany, for example, hospitals are reimbursed a set sum per procedure, regardless of the type of stent and how many are used, providing a strong disincentive to use more expensive products.

Sophisticated products rewarded

The stent market is highly dynamic, as technological developments are paired with unmet medical needs. Revenue growth is tied into new, higher priced products of increasing sophistication. With so many products and

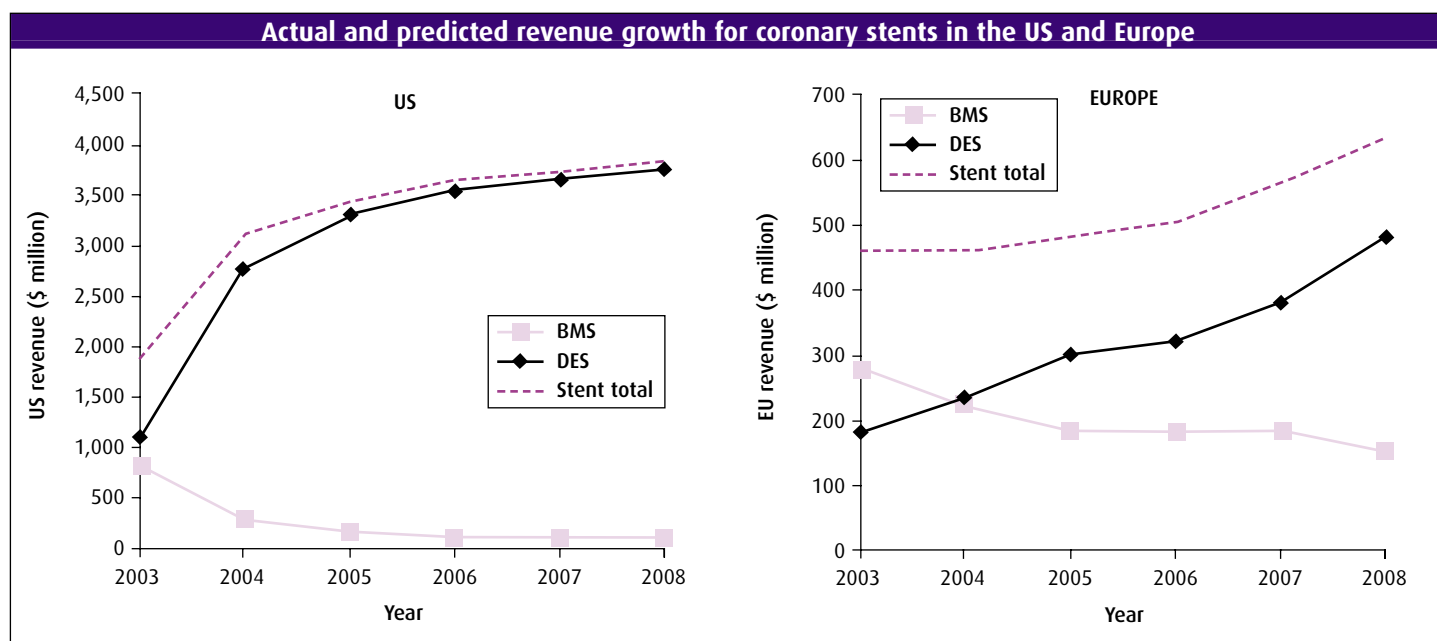


Figure 2: Predicted growth rates for DES and BMS products reflect the differing reimbursement practices of healthcare plans in the US and Europe.

developers, the market share is extremely variable between years (see Figure 3). To date, two market leaders have emerged, Cypher and Taxus, which are the only DES currently approved for sale in the US. Cypher was launched in the EU in 2002, in the US in 2003 and in Japan in 2004, and immediately restored Johnson & Johnson's former position as leader in the stent market. Boston Scientific's Taxus was introduced in the EU in 2003, the US in 2004 and is due to be launched in Japan in 2006. Initially, it took significant market share from Cypher, as it was considered to be much easier to deploy. But this trend looks set to reverse since, in 2004, Boston Scientific was forced to recall nearly 100,000 now obsolete stents due to a manufacturing fault which caused the inflated balloon to become stuck to the inside of the stent, resulting in significant patient complications.

One of the difficulties faced by stent manufacturers is the extensive and lengthy clinical trials required to assess the long-term effects of a permanent, pharmacologically active implant. Clinical endpoints have included vessel revascularisation rates and major adverse cardiac events or event-free survival at one, six, and 12 months, and annually out to five years. Some companies have used surrogate endpoints to

Certain alloys exhibit super-elasticity and shape memory properties, making them ideal for use in peripheral arteries. Thermally activated NiTiNol stents become self-expanding inside the body, removing the need for a delivery balloon

shorten the trial length, as well as running parallel trials in different countries. DES clinical trials present a considerable barrier to market entry, and have left many stent companies playing catch-up.

Although only two DES are currently approved for sale in the US, many more are available elsewhere, including Sorin Biomedica's tacrolimus-eluting stent, Janus, which has already captured 5% of the market since its European launch in late 2004, and the recently CE-marked Axxion (Biosensors) and Endeavor (Medtronic). In India, where indigenously made stents are much cheaper than many imports, the use of unapproved or 'illegal' stents in cardiac patients has been reported. According to one interventional cardiologist, there are only small design differences between

FDA/CE approved and these unapproved stents. In response to the FDA's crusade against 'illegal' stents, objection has been raised as to why products need FDA approval if they are not intended for sale in the US. While this point seems reasonable, in the current environment where many countries simply cannot afford FDA-approved products, independent standards of safety and efficacy must be rigorously applied for the protection of the patient.

The market in BMS for coronary arteries is now mature and largely saturated. Currently, the big money is in coronary DES, but the growth phase is already starting to tail off and this market will also mature and saturate within the foreseeable future. The initially dizzy annual growth rate of nearly 90% for DES has now plateaued at around 5%, the same as the annual increase in PTCA procedures. Growth rates are unlikely to increase again as they are limited by the number and workflow of cardiologists, as well as the number of patients undergoing this procedure. With the current DES market dominated by a few big players who have a massive head start, both in terms of technology and clinical testing, it is a rather unattractive arena to consider entering at this stage.

The future market potential for stenting lies elsewhere, and the most obvious challenge in the battle for market supremacy is to develop a product with zero restenosis rate. This goal is most likely to be achieved by the development of more efficacious drugs and polymer coatings. However, there are various other directions open to exploitation, many of which are complementary to the existing DES market, rather than in competition with it.

The promise of peripheral stents

The major emerging area for growth in the stent market is the treatment of peripheral arterial disease (PAD), an extremely prevalent and serious disease that is rarely diagnosed and even less frequently treated. This situation is now changing, as physician awareness grows in parallel with developing technologies. PAD is a manifestation of systemic atherosclerosis causing significant morbidity and mortality; in 2003, 30 million people were estimated to be suffering from PAD, and the prevalence is predicted to increase by over 40% between 2004 and 2020. The combined European and

US peripheral vascular stent market for 2002 was valued at over US\$600 million, with a forecasted CAGR of 10% out to 2007.

Typically, the major treatments for PAD include angioplasty and, more recently, stenting. There are various differences between coronary stents and peripheral stents. Firstly, the PAD market is divided into four discernible segments: ileac, renal, carotid and femoral-popliteal stents. Therefore, a larger range of sizes and shapes is required to fit the different vessels. Secondly, elastic recoil is not a problem in the periphery, as vessels are generally thinner and less muscular than coronary arteries, so strength can be sacrificed in favour of flexibility to allow increased musculo-skeletal movement, especially in the femoral and popliteal areas.

In fact, stents can be used in any vessel, tube or duct to re-open it and keep it open. Recently, they have been used in the oesophagus and trachea, which can both become blocked due to cancerous growths or severe trauma, resulting in the patient having difficulty swallowing or breathing respectively. Stents can be used to stabilise a reconstructive effort, or simply to prevent lumen collapse and ease the passage of fluid. However, the FDA recently issued a Public Health Notification warning that metallic tracheal stents should only be used for cancer patients as a last resort, due to complications such as stent fracture leading to infection and stenosis. Stents have also been used in the ureter and bowel, to treat malignant obstructions, and in the superior vena cava to relieve some of the symptoms of lung cancer.

Another area where there is still room for development is in the design of the stent itself. Already, different shapes and sizes are available, ranging from a hollow tube to a wire mesh and including bifurcated stents for treating lesions at arterial or bronchial branch points and double-pigtail stents which are commonly used in urology. The design of the wire mesh itself is critical; stents with fewer and thinner linkages have reduced restenosis rates. Research also suggests that surface 'nano-bumps' (around 100nm wide) encourage around three times as much endothelial cell coverage. One recent innovation, from US-based vascular drug delivery specialist Conor Medsystems, is a stent specifically designed for drug delivery. Rather than coating the surface in a drug-polymer matrix, the stent is manufactured with tiny reservoirs in the struts, into which different drug-polymer compositions can be loaded. The company believes this will enable a wider range of drug

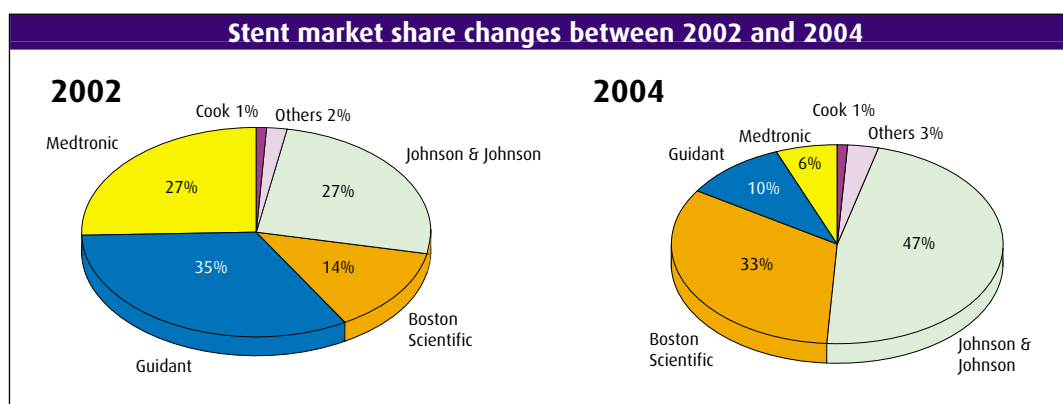


Figure 3: The dynamic nature of the stent market over the past few years is the result of developers grabbing market share with new and increasingly sophisticated products.

therapies with different release kinetics and dose capacities.

Although the first stents were made from stainless steel, various other materials are now available with suitable properties – resistance to fatigue and corrosion, radiopacity and, crucially, biocompatibility. The next generation of DES from Guidant and Medtronic will use a cobalt chromium alloy, which is both stronger and more radiopaque than stainless steel, allowing much thinner struts to be used without reducing strength or visibility.

Certain alloys, such as NiTiinol (51% nickel and 49% titanium), exhibit super-elasticity and shape memory properties, making them ideal for use in the periphery. Thermally activated NiTiinol stents become self-expanding inside the body, removing the need for a delivery balloon. The stent is collapsed onto a catheter and stored below a critical temperature; when deployed in the body, it springs back to a pre-defined size. Premature expansion is prevented using a retractable sheath, which is removed once the stent is in place. The major limitation of self-expanding stents is that they do not allow for multiple expansions to adjust the diameter; consequently, conventional balloon-expandable stents are still used in around 90% of peripheral stenting procedures.

The long-term effects of permanent metal stents are still currently unknown, though poor positioning can lead to arterial rupture and reocclusion. Meanwhile, stents made from plastics and polymers such as silicone and polyethylene and are being investigated. Biodegradable stents are the most probable for use in the peripheral vascular system as well as the coronary arteries once the problem of elastic recoil has been overcome. These stents are designed to be stable for three to six months and to disappear within two years, during which time they can act as drug delivery vehicles. Biodegradable stents also

hold great promise as temporary drug delivery vehicles and can be loaded with a cocktail of multiple drugs to treat a range of problems. Potential bioabsorbable stent materials include poly-L-lactic acid (PLLA) and magnesium, currently under development from Biotronik. There are still numerous problems to be ironed out before biodegradable stents become viable, including uneven absorption across the structure and mechanical strength. However, the potential hazards and costs associated with re-stenting, which can require implanting another stent inside the first ('stent-in-stent'), would be greatly reduced with biodegradable stents, as would the permanence of the implant, making them much more desirable for the patient.

Given the remarkable market penetration of stents, their ease of use and the number of specialist catheterisation laboratories now set up around the world, stents offer a unique opportunity to provide a platform for future technologies. Julio Palmaz, an Argentinian doctor and the inventor of stents, believes that the future of stents is in combination with nanotechnology to interrogate internal problems. Nanodevices for diagnostics, imaging and treatment could be attached to a stent and placed in any vessel in the body to monitor disease onset and progression while supplying responsive and targeted drug delivery.

Alternative futures

It is possible that the future of cardiology may be one in which stents do not feature at all, or at least play a much reduced role. Following their meteoric 15 year rise, the stent market is likely to see a somewhat less illustrious fall over the next 15 years, as stents are increasingly replaced by new technologies. For all their successes, there are still many disadvantages to stents; aside from the obvious expense and possibility of restenosis or arterial

rupture, patients are left with a permanent metal implant, which interferes with standard imaging procedures such as MRI. This problem can, and probably will, be solved by using biodegradable stents, which no doubt will enter the market in a similarly ostentatious manner to the drug-eluting products.

However, new techniques are already being developed that will most likely supersede any breed of stent. Cryoplasty, a form of balloon angioplasty, re-opens arteries by

cooling and dilating them. One peripheral dilatation procedure, the PolarCath balloon system (developed by CryoVascular Systems), is filled with nitrous oxide, which evaporates on entering the balloon, cooling it to subzero temperatures. This cooling causes the arterial plaque to freeze and crack, allowing for uniform opening of the vessel, and also prompts apoptosis, thus minimising new tissue growth that might lead to restenosis. Other innovations in angioplasty are the development of a drug-coated balloon, recently announced by US-based medical product developer B Braun, and an injection catheter. Clinical and preclinical trial data suggest these techniques will result in less arterial damage than stenting and potentially lower restenosis rates.

The billion-dollar market

Originally postulated in 1978 by Palmaz while training in the US, the first coronary stent entered the market in 1993. Within just a few years of their US launch, stents had achieved over 80% penetration of all percutaneous coronary interventions and concurrently created a billion-dollar market.

In the near future, it is unlikely that the dominance of stents will be significantly challenged. However, as the need for interventional cardiology increases, less invasive techniques that are easier to use, faster to perform and cheaper to run will surely prevail, offering benefits to both medical professionals and patients alike. In the meantime, stents will continue to provide a reliable option for interventional cardiologists whilst simultaneously offering a lucrative and dynamic market for developers.



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