The methodology in interventional cardiology has historically evolved from diagnostic coronary angiography to balloon angioplasty, to the use of bare metal stents (BMSs), to their refinement to drug-eluting stents with a durable polymer, and is now on the verge of drug-eluting stents with further developed drug delivery approaches such as reservoir technology and the use of biodegradable polymers. Two decades ago, coronary stents were stainless steel (316L) tubes designed to prevent the acute complication of balloon angioplasty – acute vessel closure. Ever since, efforts have been directed, not only to improve acute procedural outcomes, but also towards long-term outcomes and prognosis. Many lessons learned in the past are still relevant for stent design today and the future.

Lessons from the past
In the early days of coronary stents, development was focused on improvement of stent deliverability. Advances in this area included pre-mounted stents, self-expanding stents, reduced crossing profiles and improved flexibility. Modifications in stent design such as ‘rotating’ and ‘locking’ mechanisms afforded them higher flexibility when unexpanded and remarkable radial strength when expanded. When most issues of acute feasibility of stenting were resolved, long-term outcomes became the focus of attention, with in-stent restenosis presenting the major limitation of coronary stenting. It was recognised that neointimal formation and in-stent restenosis were related to patient-specific factors such as genetic predisposition or diabetes; to lesion-specific factors such as vessel caliber, lesion length or plaque burden, and to procedure-specific factors such as extent of vessel damage, residual dissections, stent length, or postprocedure minimal diameter or area.

Systematic investigations gave insights into mechanisms of stent action and vessel biology. Stent expansion principles (balloon- or self-expansion), geometry (number of intersections and inter-strut area), strut configuration and thickness and metal-to-artery ratio are all major determinants of stent profile, flexibility, radial strength and (elastic) expansion characteristics, polishing, ion implantation or coating as chemistry, charge, and texture.

In the late 1990s, radioactive stents were introduced based on the observation that radiation has inhibitory effects on smooth muscle cell growths. However, clinical results were disappointing. Another strategy to modify stent surface characteristics was the coating of metallic struts. However, polymer surfaces have shown conflicting results. While some have proven able to reduce protein deposition and platelet adhesion others provoked severe tissue responses. In clinical trials, a number of other coatings like inert polymer, phosphorylcholine or heparin were able to reduce (sub)acute stent thrombosis rates. However, these acute beneficial effects did not translate into a substantial decrease for in-stent restenosis rates. In response to this, the interest in coatings has shifted towards considering coatings as vehicles for local drug delivery. Local drug delivery was hypothesised as being able to overcome the repeated failure of clinical drug studies. It was a widely
accepted explanation that the failure of systemic agents to significantly impact restenosis was due to insufficient achievable drug levels at the arterial lesion site. Local drug administration allows higher tissue concentrations while systemic release is minimal and may reduce the risk of remote or systemic toxicity. Early studies with numerous anti-proliferative agents showed mixed results.\textsuperscript{21-26} It was concluded that it might not be sufficient to have an active drug and a metallic stent, but that a delivery vehicle must ensure drug release into the vessel in predictable concentrations and duration while being able to resist mechanical stress during stent expansion. This concept has proven successful in reducing in-stent restenosis in the landmark RA\textsuperscript{VEL}\textsuperscript{27} and the SIRIUS\textsuperscript{27} trials, employing sirolimus (rapamycin) eluting coronary stents (SES), followed by the TAXUS (paclitaxel eluting stent [PES]) trial family.\textsuperscript{29-31} The SIRIUS trial was the pivotal study evaluating SES for FDA approval. It compared SES with the Bx Velocity™ (Cordis Corporation, Bridgewater, NJ, USA) BMS in a total of 1,058 subjects. The primary endpoint, target vessel failure, was reached by 21% of BMS subjects versus 8.6% with SES (p<0.001). Long-term follow-up to 6 years has been completed and demonstrates preservation of clinical benefit related to reductions in target lesion failure of the SES over BMS and no differences in safety between the experimental or control arms with respect to stent thrombosis.

Both SES and PES limited in-stent restenosis impressively and minimised the impact of patient- and lesion-specific factors.\textsuperscript{32} Therefore, many lesions that had shown disappointing results when treated interventionally, such as small vessels or chronic total occlusions, were suddenly candidates for percutaneous revascularisation therapy in the beginning of the new millennium. However, soon a new enemy emerged: late-stent thrombosis.\textsuperscript{33,34}

Today, we are facing the second generation of drug-eluting stents with improved deliverability and safety likely (Figure 1). Most of them still follow the concept of metallic stent structure for vessel scaffolding, coating as a delivery vehicle and a drug as antiproliferative agent. Only recently, however, reducing the risk for late-stent thrombosis by further developed drug delivery approaches, such as the reservoir technology or the use of bioresorbable polymers,\textsuperscript{35-38} have been identified as an additional goal. The reduction of polymer exposure to the vessel wall might improve vascular healing and lower the rate of undesirable side effects, such as stent thrombosis, especially in the long term once the drug is completely eluted. To date, a number of non-inferiority trials employing drug-eluting stents with different drug and coating principles are ongoing.

Future developments:

\textbf{technological breakthroughs}

Even with current drug-eluting technologies accompanied by modern pharmacological interventions, restenosis as well as late-stent thrombosis have not vanished as the most significant long-term limitations, especially in high-risk populations (i.e. insulin-dependent diabetics). In addition to the never-ending

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Stent generations}
\end{figure}
challenge of improving deliverability, future developments will, therefore, aim to eliminate the risk of late-stent thrombosis and restenosis. Research is directed toward further sophistication in coating and drug delivery technology, but also toward dramatic improvement of BMSs, taking into account numerous engineering lessons from the past as well as advanced material sciences, leading to innovative materials, finally resulting in very thin struts for example. Another target for the future is the simplification of the stenting procedure with the goal of further reducing the acute risk of adverse events in high-risk patients, decreasing radiation dose to the operator and patient, and decreasing procedural time and cost. An example is the Stent-on-a-Wire™ (SOaW; Svelte Medical Systems, New Providence, NJ, USA) coronary stent system, consisting of a delivery system using a fixed-wire catheter platform and a cobalt chromium stent. The system has a 0.012” lesion entry profile. Currently, a prospective study is being conducted to evaluate the safety and performance of the SOaW stent. Other examples include specialised stents dedicated for different lesion subsets, such as bifurcations, very long or ostial lesions.

A fundamentally different strategy is seen in creating a temporary vessel prosthesis, which would scaffold the vessel wall in the acute setting to allow for adequate lumen gain, in order to alleviate angina and myocardial ischaemia. Furthermore, a system that would support the biological healing process and would disappear when vascular healing has been accomplished (as stents exert their beneficial clinical effect within a relatively narrow time frame) is another opportunity.

Research into bioabsorbable technologies for stents began more than 20 years ago with the pioneering work done at Duke University. Back then, the first polylactic acid or PLA-based bioabsorbable stent was a braided, self-expanding stent. Five years later, the first balloon-expandable PLA stent was also developed at Duke. Around this time, metallic stents were being developed at an accelerated rate because they solved the problem of abrupt closure with balloon angioplasty. Hence, bioabsorbable stents were put on the back burner for a while as metallic stents gained rapid acceptance and proved efficacious.

Until now, a variety of biodegradable or bioabsorbable materials have been investigated, with mixed clinical results. In the late 1990s, the Igaki-Tamai™ stent (Kyoto Medical Planning Ltd., Kyoto, Japan) was a self-expanding coil stent made of a poly-L-lactic (PLLA) monofilament that took between 18–24 months to fully biodegrade. Clinically it showed remarkable results with both restenosis and a target lesion revascularisation rate of 10.5% at 6 months. Today, very promising results are available from a clinical, first-in-man trial out to 2 years with an everolimus-eluting, bioabsorbable stent (BVS, Figure 2). Thirty patients with a single de-novo coronary artery lesion were followed up for 2 years clinically and with multiple imaging methods: multislice computed tomography (CT), angiography, intravascular ultrasound, derived morphology parameters (virtual histology, palmpography, and echogenicity), and optical coherence tomography (OCT). At 2 years, the stent was completely absorbed as demonstrated by intravascular ultrasound and OCT; had vasomotion restored and restenosis prevented; and was clinically safe without cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses. Metallic stents using mainly magnesium as a compound have also been used and evaluated in clinical trials with promising results (AMS stent, Figure 2).
Further conceptual advancements will challenge the ‘one size fits all’ philosophy of nearly all stents currently used in clinical practice. Dedicated stents for specific anatomic specifications (i.e. bifurcations or long lesions) are already in clinical use. In the near future, however, specific stents will also be available to address different clinical situations (i.e. acute coronary syndrome, diabetes) with specific restenosis and/or stent thrombosis risks and resulting requirements (i.e. high vs. low antiproliferative capacity). These will be likely accomplished by stents with multi-drug delivery and drug-specific elution characteristics as already used in clinical trials (i.e. NEVO™ stent system [Cordis Corporation, Bridgewater, NJ, USA]; Figure 2). Further promising approaches include the combination of innovative BMS concepts (i.e. continuous sinusoid technology) with non-polymeric drug elution controlled by organic diffusion physics (‘drug-filled stent’ [DFS] system; [Medtronic Inc, Minneapolis, MN, USA]; Figure 2).

How will the patient benefit?
How will changes in coronary stent design as discussed above translate into a measurable clinical benefit for the patient? In other words, what are we accomplishing with percutaneous coronary interventions at present and what kind of progress in stent technology would lead to further significant and measurable clinical improvements?

Clearly, the elementary advances in stent design (i.e. reduction of strut thickness, drug delivery) have mainly improved efficacy (reduction of restenosis) and deliverability of stents. Only recently, new developments in drug elution and polymer composition have addressed safety aspects, i.e. reduction of stent thrombosis. In the meantime, procedural aspects (i.e. high pressure implantation) and new pharmacological concepts (temporary dual-antiplatelet therapy) have significantly improved both, efficacy and safety (reduction of stent thrombosis rates) of coronary stents. As a result of 20 years in stent development, the use of stents has led to a reduction in mortality and morbidity in patients with acute coronary syndromes and to a more symptomatic and less prognostic improvement in lower-risk patients with stable coronary artery disease. These differences in treatment aims can be described as the ‘gradient of benefit’.

Completely degrading polymeric or metallic stents, however, will likely represent one of the next breakthrough technologies affecting the ‘gradient of benefit’ towards prognostic implications, even for stable patients if they
are able to match the high standards set forth for safety, efficacy and deliverability by existing stents. Degradation and polymer use are, therefore, pivotal characteristics for current and future stent generations and allow classification of stents in a simplified matrix (Figure 3).

The advances of future generation stents will be potentially mediated by the ease for re-interventions or re-operations, the ability for non-invasive follow-up studies using imaging technologies like coronary CT and/or magnetic resonance imaging (MRI), as well as the restoration of physiology/vascular adaptive processes (i.e. positive remodelling) and functionality (vasomotion; Figure 1).

Summary

Interventional cardiology has historically evolved from diagnostic coronary angiography to balloon angioplasty, from the short-term solutions through the use of BMIs to the improvement of longer-term outcomes by their refinement of drug-eluting stents. The field of percutaneous coronary interventions using stents is now set to shift the paradigm from angioplasty to vascular restoration by individualised absorbable/degradable stent technologies. Dramatic improvements in stent design will very likely translate into even better symptomatic and prognostic improvements in patients with stable or unstable coronary disease as compared to current clinical practice.

REFERENCES


DISCLAMER: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. EI and PP have no relevant disclosure. The authors have no competing interests and therefore, they have nothing to disclose.