Canadian Journal of Cardiology 30 (2014) 35–45

Review

The Evolution of Coronary Stents: A Brief Review

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ABSTRACT

Percutaneous coronary intervention is the most prevalent method for coronary artery revascularization. Initial interventions using balloon angioplasty had limited efficacy because coronary dissections, arterial recoil, and neointimal formation led to high rates of abrupt vessel closure and clinical restenosis. With the introduction of coronary stents, vascular dissections were stabilized and arterial recoil was eliminated, but neointimal accumulation remained problematic, resulting in the development of in-stent restenosis (ISR) in 20%-30% of cases. Drug-eluting stents (DESs) were developed to release antiproliferative agents at the site of arterial injury to attenuate neointimal formation. Although DESs have incrementally improved outcomes after percutaneous coronary intervention, delayed re-endothelialization and stent thrombosis remain important challenges. Herein we review the pathophysiology of ISR, stent thrombosis, and briefly summarize the clinical evidence behind first- and second-generation DESs. Moreover, we discuss advancements in our understanding of the pathogenesis of ISR and potential novel therapeutic strategies to improve clinical outcomes.

RÉSUMÉ

L'intervention coronarienne percutanée est la méthode de revascularisation coronarienne la plus répandue. Les interventions initiales au moyen de l'angioplastie par cathéter á ballonnet avaient limité l'efficacité puisque les dissections de l'artère coronaire, le recul de la paroi artérielle et la formation néointimale ont mené à des taux élevés de fermeture abrupte d'un vaisseau et de resténose clinique. Par l'introduction d'endoprothèses coronaires, les dissections vasculaires étaient stabilisées et le recul de la paroi artérielle était éliminé, cependant l'accumulation néointimale demeurait problématique, entraînant le développement de la resténose intrastent (RIS) dans 20 % à 30 % des cas. Les endoprothèses médicamentées (EM) étaient conçues pour libérer les agents antiprolifératifs au site de la lésion artérielle afin d'atténuer la formation néointimale. Bien que les EM aient progressivement amélioré les résultats après l'intervention coronarienne percutanée, le retard de réendothélialisation et la thrombose d'endoprothèse restent des enjeux importants. Ici, nous passons en revue la physiopathologie de la RIS, la thrombose d'endoprothèse, et nous résumons brièvement les données cliniques qui sous-tendent l'utilisation des EM de première et de deuxième génération. De plus, nous discutons des progrès dans notre compréhension de la pathogenèse de la RIS et des nouvelles stratégies thérapeutiques potentielles pour améliorer les résultats cliniques.

Percutaneous management of obstructive coronary artery disease (CAD) has expanded greatly since Gruentzig's first percutaneous transluminal coronary balloon angioplasty in 1977.[1] The procedure has since evolved to include the insertion of metallic scaffolds known as stents to prevent arterial recoil and restenosis (ie. renarrowing of the dilated segment) after balloon dilatation. Improvements in stent technology have contributed to the widespread adoption of percutaneous coronary intervention (PCI) for the treatment of an ever-expanding variety of CAD scenarios.[2] Since inception, stent design has undergone incessant refinement, including the development of drug-eluting stents (DESs) (Fig. 1). This review will highlight the evolution and future directions in stent design.

Bare-metal stents were the first devices used for coronary stenting. Interestingly, although these devices reduced rates of restenosis compared with balloon angioplasty, in-stent restenosis (ISR), narrowing within the stented segment, continued to develop in 20%-30% of lesions.[3,4] Although stent insertion prevents arterial recoil and stabilizes vascular dissections, ISR might still occur because of exuberant neointimal accumulation—much akin to "scar formation"—the mechanisms of which are discussed in detail herein.[5]

In addition to acting as a vascular scaffold, stents soon evolved to become drug delivery systems in the form of

Received for publication May 25, 2013. Accepted September 15, 2013.

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See page 42 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2013.09.012

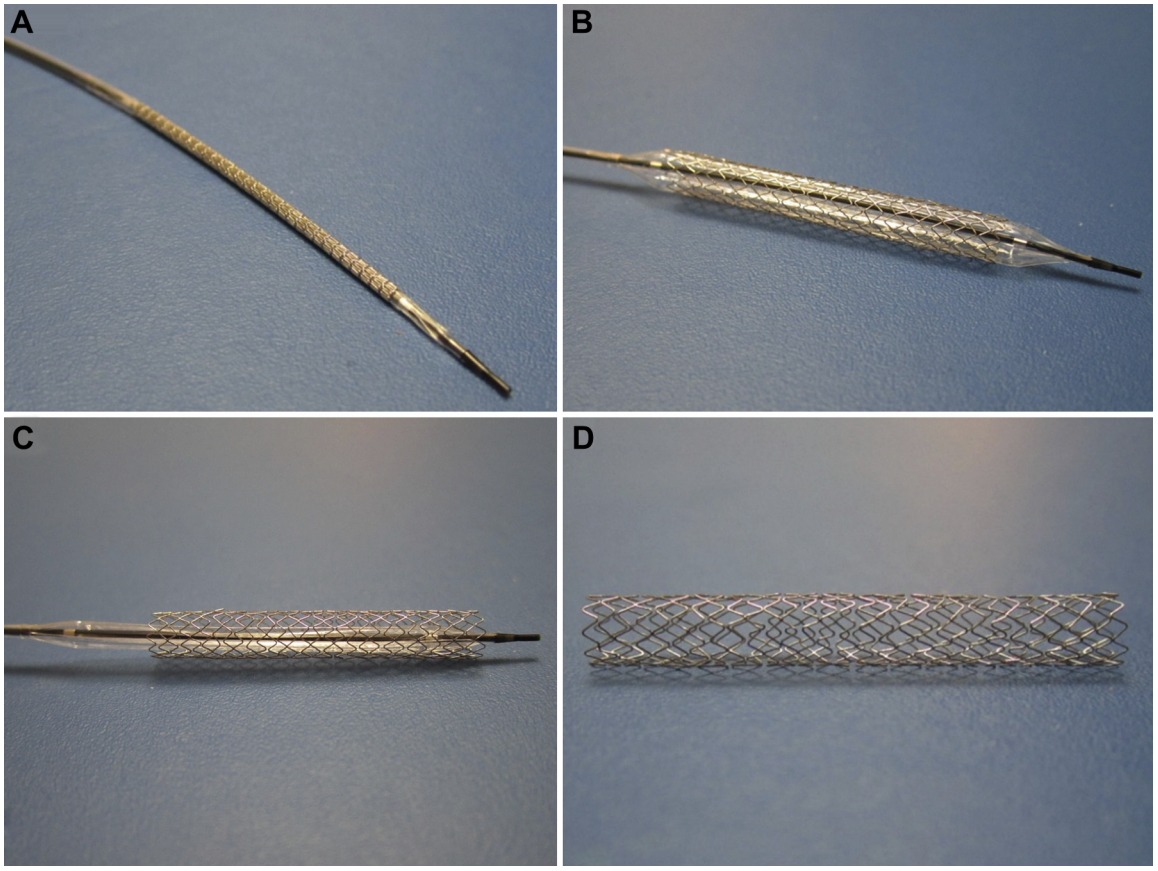

Figure 1. Zotarolimus (Endeavor)-eluting stent. (**A**) Undeployed stent attached to a balloon-tipped catheter for transarterial delivery. (**B**) Expanded stent after inflation of balloon tip on catheter assembly. (**C**) Removal of the deflated balloon-tipped catheter assembly from within the expanded stent. (**D**) Deployed stent.

modern day DESs. DESs are composed of a metallic stent, a polymer-based drug delivery platform, and a pharmacologic agent (typically an immunosuppressant and/or anti-proliferative compound). The goal of DES technology is to minimize PCI-related vascular inflammation and cellular proliferation thus reducing ISR. Indeed, early trials of the sirolimus (SES)- and paclitaxel-eluting (PES) stents demonstrated markedly reduced rates of ISR (5%-8%), heralding the DES revolution that followed.[6,7]

Challenges With Current Stents

Neointimal formation and ISR

The mechanisms underlying ISR after PCI remain incompletely understood. Indeed, the accepted pathogenesis of ISR is in flux as numerous animal models are used to attempt to mimic and explain the mechanisms leading to restenosis. These models and their implications for therapeutic intervention have recently been reviewed.[5] The most widely accepted model is an adaptation of the "response-to-injury" model proposed by Ross in 1976, whereby the mechanical disruption of the endothelial lining by PCI serves as an initiating factor.[8] Lack of endothelial coverage and the ensuing inflammatory response in the vessel wall are thought to stimulate a remodelling process with inward migration and proliferation of medial smooth muscle cells (SMCs). Neointimal growth is then further exacerbated as SMCs adopt a synthetic phenotype and deposit excess extracellular matrix (ECM) proteins that ultimately obstruct the vessel lumen (Fig. 2).

Important insights into the pathophysiology of human ISR are available from animal models and examination of post-mortem arteries and atherectomy tissue specimens from humans.[9,10] Indeed, re-endothelialization is thought to play a substantial role in neointimal formation, with studies reporting varied re-endothelialization patterns after coronary stent placement.[11,12] Regardless, even if sufficient re-endothelialization occurs, it remains uncertain if the endothelium that repopulates a stented arterial segment is functional.[13] In addition, studies of proliferation in human ISR tissue have yielded conflicting results, with variable proliferation rates being reported in ISR lesions.[10,14,15] In human coronary arteries where small changes in luminal mass can lead to significant changes in luminal diameter one would assume that sustained proliferation at these high rates would result in stent occlusion within weeks. Previously, we examined the proliferation profile of human coronary artery ISR tissue and found a virtual absence of proliferation.[16] Hence, although arterial cell proliferation likely occurs within and adjacent to the stent implantation site in the days to weeks after implantation, it is unclear if antiproliferative treatment strategies actually target the vessel wall proliferation or

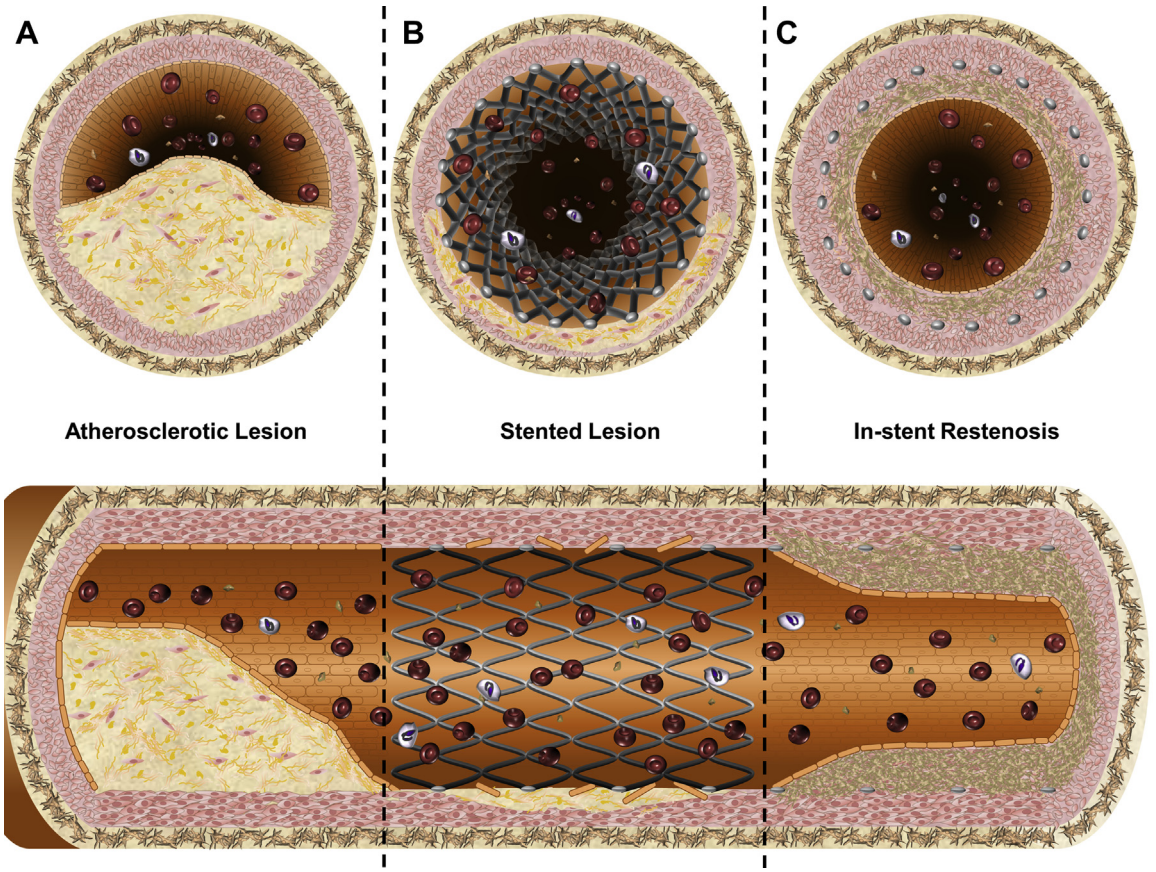

Figure 2. Progression of in-stent restenosis. Cross-sectional and longitudinal views of artery depicting chronological progression of in-stent restenosis. (**A**) Obstructive atheromatous plaque causing flow-limiting stenosis of the arterial lumen with reduced luminal diameter. (**B**) After percutaneous endoluminal stenting which restores the native vessel diameter by compressing the atheromatous plaque into the vessel wall with resultant denudation of the endothelial layer. (**C**) In-stent restenosis after inappropriate neointimal hyperplasia in response to percutaneous stent insertion resulting in recurrence of flow-limiting stenosis.

have other cellular targets—for instance, circulating progenitor cell populations.[17] Experiments using impermeable Dacron graft implants demonstrate that endothelial cells and myo/fibroblasts might collect within the grafts and appear to be of blood-borne origin.[18] Indeed, subsequent experiments involving more elaborate cell tracking methodologies suggest that circulating progenitor cells populate the subintimal space and differentiate into a mature SMC phenotype[19-21]—a finding in keeping with the growing, yet controversial concept that at least some fraction of the neointima is derived from circulatory sources.[21]

What about the ECM of ISR lesions? It is clear that proteoglycans occupy most of the ECM and might play important roles in human ISR lesions.[22] First, the abundant matrix creates a "space-occupying" lesion that contributes to luminal narrowing. Second, this matrix might facilitate cell migration and/or proliferation of SMCs. For example, the phenotype and behaviour of SMCs are influenced by interactions between ECM receptors on the surface of SMCs and specific ECM ligands.[23] Finally, the nature of this tissue might at least in part explain the poor results of repeat angioplasty for ISR. Dilating a tissue mass that consists primarily of proteoglycans (and therefore with a consistency similar to that of rubber) might result in only a transient enlargement of the lumen area because tissue recoil occurs shortly after removing the balloon catheter.[24]

Stent thrombosis

Although DESs reduce ISR, this comes with the increased risk of stent thrombosis (ST). Interestingly, the pathophysiology of ISR and ST appear to be diametrically opposed. In simple terms, ISR is related to an overzealous response of the vessel to injury whereas ST arises because of impaired or delayed healing resulting in acute thrombotic events. Consequently, although DESs provide improved outcomes from an ISR perspective, they increase the risk of abrupt, thrombotic vessel closure that can lead to a myocardial infarction (MI) and/or significant morbidity, concerns which led to dedicated analyses of ISR/ST in DESs.[25,26]

In brief, ST is thought to stem from mechanical and biologic risk factors. For instance, incomplete stent apposition (ISA) to the vessel wall likely plays a significant role and might occur for several reasons. First, the insertion of a stent with a nominal diameter smaller than that of the vessel wall can leave struts that are not apposed to the vessel wall. The true dimensions of the artery can be difficult to ascertain using angiography—particularly if the vessel thrombus burden is

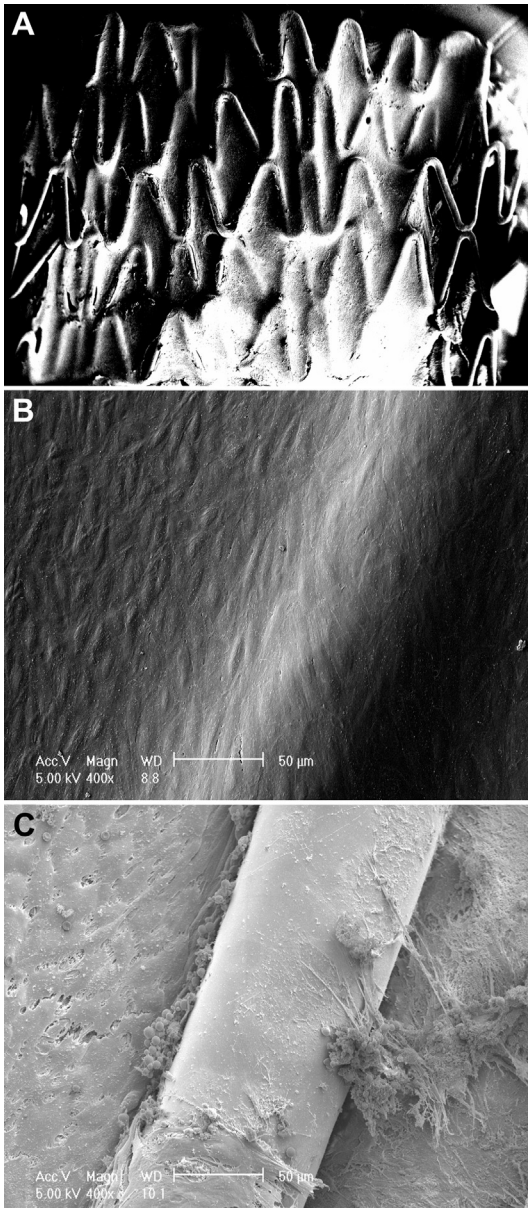

Figure 3. Stent re-endothelialization. (**A**) Overview of embedded stent displaying areas of completely re-endothelialized stent and exposed struts. (**B**) Completely re-endothelialized segment. (**C**) Close-up of single stent strut displaying partial re-endothelialization.

high (eg, during an acute MI). Second, ISA might occur with the insertion of a stent with a maximum diameter that is less than that of the vessel wall. For example, stenting of the left main coronary artery might be problematic because the vessel diameter can be more than 5.0 mm.[27] Considering that most conventional coronary stents are not made to expand to this degree, other strategies need to be considered, including the deployment of noncoronary (eg, renal) stents.[28] Third, when the vessel wall is heavily calcified and irregular it might prove difficult to deploy a stent that perfectly adheres to the "hill and valley" contour of the vessel. As a result, some sections of the stented segment might be perfectly apposed, while others might exhibit major gaps between the stent and artery wall. Finally, ISA might occur when the vessel wall undergoes late positive remodelling with expansion of the vessel diameter months or years after the initial deployment of certain DESs.[29] The precise cause of this phenomenon is unknown, but might be due to a local proinflammatory reaction that occurs in the stented segment likely due to a reaction of the vessel wall with the drug and/or polymer coating on the DES.[30-32] Taken in isolation or combined, these factors can certainly contribute to ISA and the subsequent risk of ST.

In addition, ST might arise from incomplete re-endothelialization of the stented vessel wall leading to exposed stent struts (Fig. 3).[33] Incomplete re-endothelialization might occur because of an intrinsic relative deficiency of vascular progenitor cells which is associated with poor clinical outcomes.[34,35] As well, the toxic effect of either the stent drug and/or polymer might result in the attenuation of the normal endothelial healing response. Indeed, autopsy studies confirm that DESs delay arterial healing, thereby complicating post-PCI antiplatelet management, especially in anticoagulated patients.[36,37] Although bare-metal stents (BMSs) exhibit complete re-endothelialization by 6-7 months, first generation DESs fail to fully re-endothelialize even at 40 months.[30] In addition, paclitaxel has been shown to inhibit endothelial cell migration more readily than sirolimus. This differential toxicity to cellular subtypes might explain greater delayed re-endothelialization and subsequent increased risk of ST with PESs.[38,39] As well, the polymer itself has garnered considerable attention because polymer-induced inflammation can lead to positive remodelling and impaired arterial healing and re-endothelialization.[30,32] In fact, second-generation stents demonstrate superior re-endothelialization performance and reduced ST rates when compared with their less biocompatible, first-generation counterparts.[40,41] Hence, there is considerable interest in improving polymer design to attenuate these effects.

Finally, stent architecture is also thought to play a role in the re-endothelialization of stented arteries, with studies suggesting thinner stent struts reduce late luminal loss.[42] Second-generation DESs now use thinner struts than their first-generation counterparts. Indeed, the Endeavor Optical Coherence Tomography trial has demonstrated that the thinner second-generation stent profile reduces stent malapposition and facilitates re-endothelialization and stent coverage via optical coherence tomography, thereby reducing the risk of subsequent ST.[33,43] Overall, the newest-generation stents aim to optimize polymer compatibility, drug elution, toxicity profiles, and stent design to optimize re-endothelialization with the aim of improving clinical outcomes.

DESs

First-generation DESs

Although revolutionary at the time of their development, first-generation DESs are considered rudimentary by today's standards. They are comprised of a metallic stent platform (typically stainless steel) and coated with a polymer that elutes antiproliferative and/or anti-inflammatory therapeutic agents (ie, sirolimus or paclitaxel).

SESs. Sirolimus (also known as rapamycin) was originally designed as an antifungal agent but its early clinical use was

limited as a result of unintended immunosuppressive properties. Its mechanism of action stems from impedance of cell cycle progression by blocking G1 to S phase transition, thereby suppressing neointimal formation.[44] In 2001, the "first-in-man" experience with an SES showed promising results, leading to development of the commercial Cypher stent.[45] Subsequent large trials demonstrated its efficacy in preventing ISR (ie, the **Ra**ndomized Study With the Sirolimus-Eluting Bx **V**elocity Balloon-**E**xpandable Stent in the Treatment of Patients With De Novo Native Coronary Artery **L**esions [RAVEL] trial,[46] and **Sir**ol**im**u**s**-Eluting Stent in De Novo Native Coronary Lesions [SIRIUS] trials).[6,47,48] These trials demonstrated that elution of cytostatic compounds from a stent could effectively reduce the rate of ISR and improve target vessel revascularization (TVR) rates in patients undergoing PCI. Subsequent studies further broadened the clinical indications demonstrating that SESs reduced ISR in diabetic and unstable plaques.[49,50]

PESs. The Taxus Express PES was a contemporary of the SES. Paclitaxel was initially approved for the treatment of ovarian cancer, but its potent cytostatic properties made it a candidate compound for DESs. Paclitaxel stabilizes longer microtubules during mitosis causing cell cycle arrest, thereby halting cellular proliferation and leading to inhibition of SMC proliferation and neointimal formation in animal studies.[51] This work provided the impetus for randomized studies known as the TAXUS trials.[7,52] In particular, TAXUS V and VI demonstrated long-term efficacy of PESs in high risk, real world patients with complex coronary lesions.[53,54] The subsequent Taxus Liberté, featured a more deliverable stainless steel platform and despite being deployed in more complex lesions in the Polymer-Based, Paclitaxel-Eluting TAXUS Liberté Stent in De Novo Lesions (TAXUS-ATLAS) trial still demonstrated noninferiority to the existing Express system.[55]

PESs vs SESs. When superiority of the drug-eluting strategy was established, studies then focused on comparing outcomes between the first-generation platforms. Early data from randomized clinical trials suggested superiority of the SES over PES because of reductions in major adverse clinical events (MACE)—predominately driven by diminished TVR at relatively short-term follow-up (9 months).[56] Interestingly, although early outcomes favoured SES, late follow-up to 5 years actually yielded similar clinical outcomes, restenosis profiles, and very late ST rates between SES and PES, suggesting that a "catch-up" phenomenon might occur with SESs.[57] Conclusive evidence was derived from 2 systematic reviews and meta-analyses, which reported superiority of SES with diminished rates of ISR and TVR, coupled with a trend toward increased MIs in the PES cohort.[58,59] Nonetheless, despite representing a significant advance in our treatment of obstructive CAD, first-generation DESs have been largely replaced by more sophisticated stent systems.

Second-generation DESs

Second-generation DESs offer numerous improvements over their first-generation counterparts. Namely, second-generation devices have decreased strut thickness, improved flexibility/deliverability, enhanced polymer biocompatibility/drug elution profiles, and superior re-endothelialization kinetics. In contemporary practice, second-generation devices are now the predominant coronary stents implanted worldwide.

Paclitaxel. The Taxus Element is a further advancement based on the early PES designs, using the same paclitaxel agent, but with a unique polymer designed to maximize early release so that most of the drug is eluted by 12 weeks. In addition, this system uses a novel platinum chromium strut system, providing thinner struts and enhanced radio-opacity over its precursors.[60] The Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System (PERSEUS) Workhorse trial, a noninferiority study that compared the Element with Taxus Express, noted similar outcomes between both stents up to 12 months.[61] Similarly, the PERSEUS small vessel trial, a superiority trial designed to compare the Element with historical BMS controls in small vessels, demonstrated improved late lumen loss but no differences in MACE or ST at 12 months.[62] Though preliminary trials show noninferiority to previous PESs and BMSs, trials comparing the Taxus Element with other second generation DESs are needed.

Zotarolimus. The zotarolimus-eluting stent (ZES; Endeavor) is a second-generation stent based on a stronger cobalt chromium stent platform, with improved flexibility and decreased stent strut size. In addition, the ZES uses a novel phosphorylcholine polymer coating—a stable, lipid membrane analogue designed to maximize biocompatibility and minimize inflammation associated with previous polymers. As well, the polymer was engineered to shorten the drug elution time such that most of the drug is eluted during the initial injury phase, leaving little drug on the stent thereafter to allow for normal arterial repair to occur. Zotarolimus is a sirolimus analogue with similar immunosuppressant properties but enhanced lipophilic properties. This key difference was to enhance vessel wall localization and minimize dispersion into the circulation.[63] Indeed, preliminary animal models supported the potential benefits of this novel stenting system, resulting in less local inflammation and improved re-endothelialization compared with SESs and PESs.[64]

Clinically, the ENDEAVOR I trial was the first to demonstrate safety and efficacy of ZESs in humans.[65] The ENDEAVOR II trial compared the ZES with the Driver BMS, showing improved ISR/target lesion revascularization/MACE at 2 years.[66] The subsequent ENDEAVOR III trial then compared ZES with SES, with the ZES paradoxically showing greater late lumen loss and ISR (11.7% vs 4.3%) but less MACE (0.6% vs 3.5%).[67] Long-term follow-up to 5 years displayed a "catch up" phenomenon whereby rates of ISR increased in SES patients to levels comparable with ZESs.[68] Similar in design, the ENDEAVOR IV trial compared ZES with PES and again found higher rates of ISR in the ZES group.[69] These findings persisted out to 3 years but clinical outcomes, mainly because of fewer MIs ostensibly from very late ST, were less common with the ZES, thereby suggesting a potential benefit with regard to vascular healing.[70] However, these trials were underpowered to adequately determine

differences in ST. The **P**atient **R**elated **Out**comes With **E**ndeavor vs **C**ypher S**t**enting (PROTECT) trial specifically addressed the incidence of ST in a randomized study of ZESs vs SESs in more than 8700 patients followed up to 3 years and failed to demonstrate a difference in definite or probable ST rates between Endeavor and Cypher stents.[71]

The Endeavor Resolute represents a refinement of the Endeavor stent, using the same cobalt chromium (Driver) stent platform and zotarolimus agent but with a novel trilayered polymer. Similarly, the newer Resolute Integrity (sometimes classed as a third-generation DES), uses the same drug and novel trilayered polymer, but is based on the new Integrity stent platform providing improved deliverability. This novel trilayered polymer is composed of 3 main components: a hydrophilic polymer for biocompatibility, a hydrophobic polymer for drug elution control, and a polyvinyl polymer which rapidly releases an initial surge of drug immediately after implantation. The net effect is suppression of the initial inflammatory response, followed by most of the drug being eluted over the next 60 days in an attempt to improve the late healing characteristics.

The RESOLUTE trial was the first clinical study to evaluate the Endeavor Resolute and enrolled patients with simple de novo lesions in a prospective, single-arm, nonrandomized trial demonstrating clinical outcomes similar to its predecessors with no cases of ST.[72] The RESOLUTE All-Comers trial then compared the Resolute with the Xience V (everolimus-eluting stent [EES]). This study population contained greater lesion complexity and demonstrated noninferiority of the Resolute system in terms of target lesion failure (cardiac death, target vessel MI, ischemia-driven target lesion revascularization).[73] As for the newer Resolute Integrity, we are eagerly awaiting results from the first randomized trials assessing its safety and efficacy in comparison with the Promus Element.[74]

Everolimus. Everolimus, a derivative of sirolimus, is also a cell cycle inhibitor. First described in 1997, everolimus was designed in an attempt to overcome the physicochemical properties that rendered the oral administration of sirolimus difficult.[75] Similar to its predecessor, everolimus inhibits SMC proliferation in vitro and inhibits vascular intimal thickening in animal transplant models.[76] Its cytostatic properties rendered it a potentially valuable addition to the evolving arsenal against ISR, prompting the development of the Xience-V/Promus CoCr EES in parallel to the ZES as another second-generation DES.

In 2004, Grube et al. published the prospective, randomized, single-centre, **F**irst **U**se **t**o **U**nderscore Restenosis **R**eduction With **E**verolimus (FUTURE I) feasibility trial, demonstrating safety and improved late loss (ie, narrowing of the stented segment) over BMSs at 12 months.[77] This was followed by the Clinical Evaluation of the Xience V Everolimus-Eluting Coronary Stent System (SPIRIT FIRST) trial demonstrating similar results with EES vs BMS in de novo coronary lesions.[78] Later, the SPIRIT II demonstrated improvements in late lumen loss, and neointimal volumes over the Taxus PES.[79] Similarly, the SPIRIT III trial compared the Xience-V and Taxus Express demonstrating improvements in late lumen loss and lower MACE rates largely because of fewer MIs.[80] The subsequent Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice (COMPARE) trial demonstrated improved stent and clinical outcomes in a "real world" experience, providing further support for the superiority of second-generation EES over their PES counterparts.[81] Finally, the **E**fficacy of **X**ience/Promus Versus **C**ypher in **R**educing **L**ate **L**oss After St**ent**ing (EXCELLENT) trial demonstrated noninferiority of EES to SES in inhibiting late loss at 9 months and clinical events at 12 months.[82] The newer Promus Element has the identical drug/polymer profile of the Xience-V/Promus, but offers improved deliverability with a novel platinum chromium scaffold, demonstrating noninferiority to the Xience-V/Promus in de novo lesions.[83]

Summary of DESs

First-generation SESs and PESs provided major advances in the treatment of obstructive CAD with marked reductions in ISR. Second-generation stents appear to be safe, efficacious, and provide a modest improvement in outcomes compared with their first-generation counterparts. This difference in outcomes was recently emphasized in a large (n = 94,384 patients) observational study. Compared with the first generation DESs and BMSs, second-generation devices are associated with a lower risk of ISR, ST, and mortality.[84] Thus, these new stent platforms represent the state of the art in DES design and form the cornerstone of modern PCI.

Novel Approaches to Stent Development

Although current DES technology focuses on mitigating ISR formation predominately by antiproliferative mechanisms, other novel approaches are presently being studied. Based on our expanding understanding of the pathophysiology of neointimal formation and ST, elution agents with diverse mechanisms of action are being developed.

Endothelial progenitor cells

First described by Asahara and Murohara,[85] endothelial progenitor cells (EPCs) are a subset of circulating cells that have been implicated in vascular homeostasis and endothelial repair,[34,86-88] thereby raising their profile in a host of vascular diseases.[20,89] EPCs are thought to enhance vascular re-endothelialization by homing to areas of injury and differentiating into mature endothelial cells and/or influencing mature endothelial cells via paracrine signalling. Indeed, increased cardiovascular risk has been linked to reduced numbers of circulating EPCs[35] and impaired EPC function has been linked to the development of ISR.[20,90] This intrinsic repair mechanism has therefore begun to be targeted in the development of certain emerging stent therapeutic agents.

The first foray into applying our understanding of EPC biology in the field of stent design was the development of the CD34 antibody-coated Genous stent. In a marked departure from its drug-eluting contemporaries, its aim was not to inhibit cell proliferation but rather to bind circulating EPCs via their hematopoietic marker[19,91] in an effort to enhance stent re-endothelialization. In its first-in-man registry, the Genous stent was deployed in 16 patients with 1 case of TVR noted at 9 months.[92] Subsequent studies in ST-elevation MI[93] and high-risk patients[94] found acceptable safety and

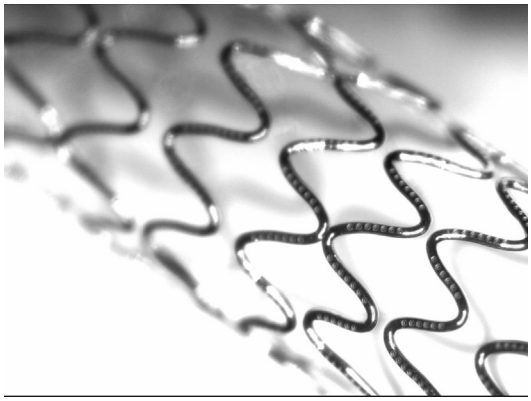

Figure 4. Drug-filled stent. Note sinusoidal strut design with laser-drilled elution ports on exterior aspects of the stent providing access to the drug-filled core. Reproduced with permission from Medtronic.

efficacy profiles. However, in a recent single-centre study of 193 patients comparing it with the Taxus Liberté, it was associated with a nonsignificant higher rate of ISR at 1 year.[95] The study, designed to enrol 1300 patients, was stopped early considering this suggestion of higher target vessel failure rates.

The failure of the Genous stent might in part reflect an incomplete understanding of EPC biology and/or misplaced emphasis on 'capturing' EPCs. As alluded to previously, EPC dysfunction, in addition to reduced EPC numbers, is associated with the development of ISR.[20,90] Enhancement of EPC function at sites of vascular insults therefore represents a natural alternative strategy. Indeed, we have reported encouraging results in animal models using this alternative approach, including improved re-endothelialization and reduced neointimal formation after stent deployment.[34,87] Notwithstanding, the negative results in clinical trials might not mark the end of stents designed to exploit intrinsic mechanisms of re-endothelialization considering the unique benefits of this approach—most notably, its potential implications on the need for platelet inhibition. Conceivably, earlier re-endothelialization would reduce the risk of ST thereby allowing for earlier discontinuation of dual antiplatelet therapy. The GATEWAY Registry specifically investigating early dual antiplatelet therapy discontinuation with Genous stents might suggest a niche role for such a stent in patients at high bleeding risk.

Polymers

Considering the deleterious effects polymers are known to have on vascular healing, novel techniques aimed at eliminating the polymer are being explored. To this effect, "bioresorbable" polymers aim to provide the early benefits of a traditional DES and avoid adverse long-term concerns related to polymer-induced delayed healing. To date numerous bioresorbable systems with varying drug/stent/polymer profiles are approved for use; however, the literature supporting these devices is still limited to short-term outcomes.[96] Similarly, polymer-free stents remove all hazards associated with the polymer, but require new approaches to anneal drugs to the stent strut surface including saturating the metallic surface, direct chemical bonding, or attaching the compound via nonpolymeric biodegradable substances. This technology, although theoretically promising, is still early in its development with only short-term outcomes reporting acceptable safety and efficacy at this point.[97] Finally, drug-filled stents employ a BMS surface with a hollow drug-filled core, using peripheral holes to allow for drug elution. Progression in laser drilling technology allow anywhere from 500 to 5000 holes to be placed on an 18-mm stent without compromising radial strength, providing polymer-free titratable elution similar to a coated stent while potentially enabling further control over elution dynamics (Fig. 4). Although certainly exciting, such designs are still at an early stage of development and will require direct comparisons with traditional DESs to ascertain the efficacy of this novel technology.

Bioresorbable stents

Bioresorbable materials are also being used to construct the actual stents, with the intent of providing mechanical support initially when elastic recoil and constrictive remodelling are of concern but then absorbing thereafter. Hence, they offer the theoretical advantage of reducing long-term risks associated with existing metallic struts including stent fracture, impaired vessel homeostasis, and neoatherosclerosis, while allowing for computed tomography evaluation of stented coronaries and providing graft targets for surgical revascularization if needed.[98,99] Early animal studies using a polyglycolic acid stent showed inferior performance with stent failure leading to luminal loss as early as 2-4 weeks, highlighting the need for polymers with improved degradation profiles.[100] Novel technologies led to the development of a lactic acid-based polymer (PLLA) with early clinical studies using this PLLA stent (sometimes referred to as a scaffold) suggesting an acceptable safety and efficacy profile in a small observational study with limited follow-up.[101] Numerous other resorbable stenting systems are under development though identifying the ideal balance between drug elution and degradation dynamics remains a challenge. Encouragingly, the **A Bioab**sorbable Everolimus-Eluting Coronary Stent System (ABSORB) trial demonstrated safety and efficacy of the everolimus-eluting PLLA stent at 2 years,[102] with a sustained low MACE rate and no cases of ST noted out to 4 years.[103] As well, the second-generation Absorb bioresorbable vascular scaffold revision 1.1 features enhanced radial strength with sustained outcomes up to 2 years follow-up.[104] These promising studies have laid the groundwork for the ongoing ABSORB II trial, the first randomized trial comparing the Absorb bioresorbable vascular scaffold revision 1.1 with the Xience Prime.[105] Overall, although the theoretical gains of bioresorbable stents are certainly enticing, we await the results of ongoing randomized trials to better characterize any potential advantages over existing stenting systems and ensure equivalent safety profiles.

Conclusions

The advent of DESs has undoubtedly improved outcomes in patients undergoing PCI. Although first-generation DESs advanced our treatment of obstructive coronary disease, ISR and ST presented important limitations. Second-generation stents have refined the struts, polymers, and drugs eluted, thereby improving early and late outcomes (Supplemental Fig. S1). Nonetheless, as our understanding of the pathophysiology behind these processes continues to evolve, so too will our therapeutic approaches.

Moving forward, significant advancements in the fields of molecular biology and genetics coupled with ever-improving technology and nanomaterials will enable staggering innovations in endoluminal prostheses—perhaps even ushering an era of "personalized PCI." In this way, patients could be profiled at the bedside based on specific genetic or proteomic parameters that might be suggestive of a specific risk of restenosis or thrombosis that would then dictate the type of stent that should be inserted. Although more work is required, the progress to date is encouraging and continues to occur at a pace that is truly remarkable.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.09.012.