Progress in interventional cardiology: challenges for the future

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Summary
Cardiovascular disease is the leading cause of death in the western and developing countries. Percutaneous transluminal coronary interventions have become the most prevalent treatment option for coronary artery disease; however, due to serious complications, such as stent thrombosis and in-stent restenosis (ISR), the efficacy and safety of the procedure remain important issues to address. Strategies to overcome these aspects are under extensive investigation. In this review, we summarise relevant milestones during the time to overcome these limitations of coronary stents, such as the development of polymer-free drug-eluting stents (DES) to avoid pro-inflammatory response due to the polymer coating or the development of stents with cell-directing drugs to, simultaneously, improve re-endothelialisation and inhibit ISR amongst other techniques most recently developed, which have not fully entered the clinical stage. Also the novel concept of fully biodegradable DES featured by the lack of a permanent foreign body promises to be a beneficial and applicable tool to restore a natural vessel with maintained vasomotion and to enable optional subsequent surgical revascularisation.

Keywords
Coronary interventions, stent implantation, neo-intima formation, stent thrombosis, in-stent restenosis

Introduction
Cardiovascular disease is the number one cause of death in the world and exceeds the number of deaths due to other diseases such as cancer and AIDS altogether. Conform to the World Health Organisation, 30% of all global death is attributed to cardiovascular disease, and despite the considerable progress in the therapeutic strategies, the number will continue to increase in the next decades.

For this review, the PubMed Database was searched for accessible literature to include, searching for “coronary interventions, bare metal stents, drug-eluting stents, new generation stents, biodegradable stents, coronary bifurcation stenosis” published through June 2014. Furthermore, guidelines from the European Society of Cardiology (ESC), the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) were integrated.

Besides drugs, which represent the principal strategy in primary and secondary prevention, percutaneous transluminal coronary intervention has rapidly become the main therapeutic strategy for cardiovascular diseases and worldwide numbers of coronary interventions exceed coronary bypass operations. Since Stephen Hales placed the first catheter in the ventricle of a living horse in 1711 (1), it took more than 200 years until the procedure was applied to humans. In his pioneering self-experiment, Werner Forssmann underwent the first human cardiac catheterisation in 1929 (2). The first coronary intervention in a living human being was a balloon dilation, performed in 1977 by Andreas Grünzig in Zürich (3). This revolutionary method has been adopted by cardiologists rapidly and was further developed, so 10 years later, the first coronary bare metal stent (BMS) implantation was performed in Toulouse by Jacques Puel (4). The stent implantation has successfully overcome the negative remodelling and partial re-narrowing of the vessels, reducing the rate of restenosis to approximately 15–30% compared to 30–60% after balloon dilatation. Moreover, the thrombotic occlusion or dissections after balloon dilation could be effectively treated. Thus, in May 2000, the National Institute for Health and Care Excellence (NICE) in the United Kingdom declared coronary stent implantation as standard procedure for patients suffering from a myocardial infarction (2003 NICE technology appraisal guidance 71 for coronary stents, 2008 NICE technology appraisal guidance 152 for drug-eluting stents).
Complications of coronary interventions

Besides the benefit, the new vascular interventions proved to be followed by some serious complications, such as stent thrombosis and in-stent restenosis (ISR).

Stent thrombosis

With a very high fatality rate (more than 40%), stent thrombosis proves to be the sword of Damocles of interventional cardiology. Even if the patient survives the primary stent thrombosis, the prognosis still remains unfavourable (5, 6). The endothelial denudation exposes the vascular subendothelial layer to prothrombogenic circulating mediators, thus favoring stent thrombosis (7).

The introduction and development of dual anti-platelet therapy using a combination of acetylsalicylic acid and adenosine diphosphatepolyphosphate receptor blockers could effectively reduce stent thrombosis rates. Acetylsalicylic acid (aspirin) has been considered the preventive agent of choice in the early days of coronary intervention. However, dual antiplatelet therapy using aspirin and another agent was proven to significantly increase the success in reducing the risk of future cardiovascular events (8). The thienopyridine ticlopidine was found in the mid-1990s to significantly decrease the number of deaths, target-lesion revascularisations, and myocardial infarctions during the first 30 days following stent implantation (9). However, the administration of ticlopidine was followed by severe complications, such as neutropenia (10) or thrombotic thrombocytopenic purpura (11, 12). Later, the use of clopidogrel increased and its efficacy was proven in a great number of clinical settings (CLARITY-TIMI, COMMIT trial, CURE trial, CREDO trial, CHARISMA trial) (13). Lopidogrel, a prodrug, is converted into its active derivative in the liver. It then irreversibly binds to the platelet P2Y12 receptor and inhibits adenosine diphosphate-induced platelet aggregation (14). It is metabolised by esterases into inactive metabolites, and depending on the polymorphisms in the cytochrome P450 system, the actual availability of active metabolites varies significantly.

Therefore, despite the proven beneficial effect, there are patients with clopidogrel resistance or malignant diseases, which do not respond to the antithrombotic treatment and develop stent thrombosis. More recently, two drugs were approved by the Food and Drug Administration as antiplatelet treatment for patients with acute coronary syndromes planned to undergo percutaneous coronary intervention. Prasugrel, just as clopidogrel, is an adenosine-diphosphate inhibitor. Moreover, prasugrel activation by the cytochrome P450 is not influenced by common genetic polymorphisms (8). Therefore, it has been shown to inhibit platelet activation in a more rapid, consistent and effective manner than clopidogrel (15, 16). The other newer antiplatelet drug, ticagrelor, is a reversible, direct-acting inhibitor of the adenosine diphosphate inhibitor and, as well as prasugrel, inhibits adenosine diphosphate–induced platelet aggregation more rapidly than do standard or higher doses of clopidogrel (17). Both newer drugs are used in combination with acetylsalicylic acid; these combination therapies have been shown to excel the acetylsalicylic acid-clopidogrel combination treatment in a number of clinical settings, decreasing the use of glycoprotein Ilb/IIIa inhibitors such as tirofiban or abciximab. These combinations are now recommended in the guideline in myocardial revascularisation from 2014 by the European Society of Cardiology (ESC), the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) (18).

A special attention was directed to patients that, due to other diseases such as atrial fibrillation or previous heart valve replacement, need permanent anti-coagulation therapy with antagonist for vitamin K (warfarin). These patients under triple therapy with combined dual anti-platelet drugs as well as warfarin after stent implantation are characterised by an elevated rate of bleeding complications (19, 20). Due to the fact that these patients usually suffer from many other coexisting diseases, the mechanisms, risks and benefits of this approach are still not well defined, and current guidelines have included recommendations based on expert opinion (19).

New oral anticoagulants (NOACs), such as thrombin antagonists dabigatran, rivaroxaban or apixaban are an alternative for vitamin K antagonists to prevent stroke in patients with non-valvular atrial fibrillation (21, 22). However, despite their improved efficacy/safety ratio (predictable efficacy without need for monitoring, fewer interactions with food and other drugs and shorter plasma half-life over warfarin), all these drugs have one disadvantage: there is no long-term data (23, 24). Therefore, before prescribing a NOAC to a patient with atrial fibrillation and coronary artery disease, a risk–benefit analysis should be made concerning anticoagulation in general and the choice of the specific anticoagulant.

The recent guidelines of the European Society of Cardiology recommend an initial triple therapy for one month (in case of stable coronary artery disease) or six months (in case of acute coronary syndrome) followed by a combination of anticoagulation with single antiplatelet therapy (aspirin or clopidogrel) to complete 12 months after stent implantation for patients with firm indication for oral anticoagulation and low bleeding risk. For high bleeding risk patients receiving a stent for the treatment of both stable coronary artery disease as well as acute coronary syndrome, triple therapy is recommended for one month followed by a combination of anticoagulation with aspirin or clopidogrel for up to 12 months. For selected patients at especially increased bleeding risk, anticoagulation and aspirin or clopidogrel may be considered as an alternative approach for the complete treatment period after stent implantation. As data on the use of NOACs as well as prasugrel and ticagrelor in patients requiring triple therapy is sparse and because there are no well-established therapies to reverse the anticoagulant effects of NOACs, European and American guidelines do not recommend the use of these agents for triple therapy, especially if patients are at increased bleeding risk (18, 25).

Multifactorial predictors for the development of stent thrombosis depending on the lesion constitution, implantation procedure, implanted stent, patient characteristics or the anti-platelet therapy are considered. Decreased left ventricular function, diabetes mellitus, renal failure, acute or recurrent myocardial infarctions and also patient non-compliance regarding the recommended drug
Simsek et al. Coronary interventions

Treatment increase the risk of stent thrombosis. Additionally, lesions with high calcium content in small coronary arteries, venous bypasses or complex lesions such as coronary bifurcations, ostial or recurrent plaques evoke severe damages after stent implantation, multiplying the pro-thrombotic risk by the elicited vascular subendothelial factors (26, 27). The nature of the stent itself impacts the rate of stent thrombosis, such as the design or the loaded polymer and coating (28, 29) as well as the hypersensitivity of the patient to the used drugs (30, 31). Moreover, inadequate stent expansion, the non-optimal reconstructed coronary perfusion after implantation, the implantation of an additional stent within the first stent thrombosis, residual (edge) dissection or stent fracture are considered to significantly increase the risk of stent thrombosis (32, 33). Thus, despite the substantial progress in the field, stent thrombosis continues to impose a pestering limitation to both bare metal stent (BMS) and drug-eluting stent (DES) implantation (6, 34).

In-stent restenosis

The neointima formation during ISR has similarities to restenosis after coronary angioplasty, representing a dysregulated reparative vascular response after endothelial denudation and overstretching of the vessel wall. The vascular injury after balloon dilation and stent implantation induces inflammatory pathophysiological processes and determines the proliferation and migration of vascular smooth muscle cells (SMC) of the arterial wall into the exposed subendothelial layer. These events continue until the completion of re-endothelialisation. Therefore, many strategies were developed to locally inhibit the inflammatory and proliferative processes, such as coating the balloons and stents with different cytostatic drugs.

Stent development

Bare metal stents (BMS)

The first generation of BMS were made of stainless steel and have been reported to reduce coronary ISR rates to 22–32% at six months compared with balloon angioplasty alone (40–48%)(35). Consecutively, the incidence of post-interventional thrombosis increased dramatically; this could be antagonised effectively by the introduction of dual anti-platelet therapy. The second generation of BMS with refined stent geometry and modified metal alloys significantly improved mechanical stent properties, such as flexibility and surface profile, thereby facilitating stent delivery in tortuous or highly calcified lesions. Also, second generation BMS feature reduced stent strut dimensions. These stent improvements helped to reduce also ISR rates; however, complex, instable lesions (36), characterised by thin fibrous cap, concomitant with accumulation of large cholesterol crystals and marked infiltration with inflammatory cells (37–39), are still characterised by an elevated incidence of ISR (40, 41). These lesions are triggered by the bidirectional effect of metabolic conditions on inflammatory response, such as in risk patients with diabetes mellitus (37) or renal failure (42).

Drug-eluting stents (DES)

Drug-coated stents were developed to reduce ISR rates. The metal skeleton of the stent is coated with a multi-layered polymer film, which assures the drug delivery locally at the implantation site. The first generation DES were the so-called Cypher-Stent and the Taxus-Stent, which both consist of a multi-layered polymer carrier substrate, releasing Sirolimus or Paclitaxel, respectively, with cytostatic, anti-proliferative and anti-inflammatory effects on proliferating cells of the vessel wall (43–45).

Figure 1: Schematic therapeutical intervention in a patient with an acute coronary syndrome. While drugs are indispensable for the treatment of coronary disease, percutaneous coronary intervention is the primary treatment option for acute coronary syndrome. However, coronary treatment may be followed by complications, such as restenosis and/or thrombosis (Table 1).
The newer generation DES are made of platinum or cobalt-chromium alloys (46), conferring increased radial strength and thinner stent struts, which reduces the peri-interventional vascular trauma and endothelial injury, thereby decreasing ISR rates and accelerating re-endothelialisation. These stents are provided with a fluoropolymer coating, in order to increase biocompatibility, and contain sirolimus derivatives such as everolimus or zotarolimus (47).

More recently, alternative degradable coatings were developed to avoid a permanent polymer-mediated inflammatory stimulus on the vessel wall (48, 49). However, the long-term reliability of degradable polymer coatings in accelerating re-endothelialisation and optimising vascular healing still needs to be proven.

Nowadays, for patients with acute coronary syndrome, coronary intervention is the treatment of choice (Figure 1). After implantation, the current therapeutic strategies follow some specific targets. As long as the stent struts are exposed to the blood flow, the risk of thrombosis is increased. Therefore, an efficient anti-platelet aggregation therapy needs to be applied, in order to prevent in-stent thrombosis. Almost all drugs currently used for DES have a pronounced anti-proliferative activity on smooth muscle cells, thus reducing restenosis rate. However, they do not provide a specific inhibition, therefore the proliferation of endothelial cells is also reduced, thereby increasing the risk of thrombus formation. For these DES, a prolonged administration of anti-aggregation drugs is mandatory (Figure 2). The inhibition of inflammatory signals decreases the recruitment of immune cells into the vessel wall and thus reduces the risk of restenosis. Current therapeutic strategies are summarised in Table 1.

However, some important predictors, identified by many clinical studies as being associated with higher restenosis rates, must be taken into account when the intervention is decided (Table 2) because, once ISR takes place, another catheter intervention is imminent. When ISR occurs in a BMS, usually a DES is implanted in an onion-skin manner inside the initial BMS. However, treatment of ISR after DES implantation is very difficult. Despite the reduced efficacy in de novo coronary stenosis treatment (50), the advent of drug-eluting balloons helped to treat DES ISR (51), since a short contact of the highly lipophilic drug-eluting balloons to the vessel wall demonstrated efficacy in DES ISR treatment.

Biodegradable stents
The occurrence of ISR and stent thrombosis is associated with the direct contact of exposed cells beneath the endothelial layer and non-endothelialised stent struts to the blood. The development of fully biodegradable stents is a concept which differs in principle from the permanent stent implantation in the vessel. The stabilisation of the vessel wall during the healing process needs to be guaranteed; after dissolution of the stent, an intact vessel without foreign body and with full ability to vasodilation is expected to be restored. These stents are thought to provide an advanced drug re-
lease platform with continuous delivery of loaded drugs during dissolution. Also, coronary artery visualisation by non-invasive coronary imaging methods such as magnetic resonance tomography or computed tomography is improved with bioabsorbable stents (52–55). At six months after intervention, arterial remodelling has reached a stable phase where the need both for scaffolding to prevent arterial recoil as well as for the release of an anti-proliferative drug is discontinued. Therefore, fully bioabsorbable polymer stents represent an intriguing alternative to permanent DES.

The Igaki-Tamai stent was the first fully bioabsorbable stent to be implanted in humans; the coronary deployment of this stent that was made from poly-lactic acid was very challenging (56). A magnesium-based degradable stent was absorbed too quickly in clinical trials (52). Today, the most promising material for biodegradable stents still is chemically modified poly-lactic acid (57); although the first clinical trial with the so-called bioresorbable vascular scaffold (BVS) stent had to be aborted because of an elevated late lumen loss that has been attributed to some inflammatory reactions and the mechanical properties of the stent (58), after an adaptation of the stent geometry, the second BVS generation yielded improved clinical results in a recent pilot trial (54, 59) and, having been CE (Conformité Européene) approved in Europe in 2011, has nowadays gained considerable clinical relevance. However, the experience for the use of BVS in bifurcation lesions as well as across major side branches or calcified vessels is still limited (60, 61).

In addition to poly-lactic acid, several copolymers have been investigated for bioabsorbable stents; poly-ε-caprolactone and poly-glycolic acid (62) yielded promising early or preclinical results, but polyhydroxybutyrates and blends thereof (63) caused considerable inflammatory reactions. Innovative early clinical concepts are represented by the poly-tyrosine derived polycarbonate polymer-based REVA-stent and by the BTI stent, consisting of poly-anhydride that includes two molecules of salicylic acid and one molecule of adipic acid and releases salicylate during degradation (64). Also, a certain number of additional candidate stent materials is under investigation but did not undergo the translation from bench to (pre-) clinical trials.

While current developments in the field of biodegradable stents are very encouraging, many issues still need to be investigated in the future. The polymers, stent designs and geometries need to be optimised regarding the radiopacity, radial strength and flexibility. Besides the technical properties, the coating or charging with cell-specific drugs is an important issue that requires extensive investigation before translation into the clinical practice. Clinical studies need to address and confirm superior safety and efficacy of biodegradable stents.

### Bifurcation stenosis

Clinical practice has shown that the patients with severe stenosis at the bifurcation of coronary arteries suffer from an elevated risk to develop stent failure such as stent thrombosis and ISR (65). The

| Table 1: Current therapeutic strategies for treatment of acute coronary syndrome. |
|---------------------------------|-------------------------------|-----------------|---------------------------|-------------------------------|
| **Type of intervention**       | **Complications**             | **Anticoagulation therapy** | **Treatment period** | **Revascularisation therapy** |
| Conservative Therapy           | Bleeding                      | ASS              | permanent                | Repeated Lysis               |
| Balloon angioplasty            | Dissection/Recoil             | ASS + Clopidogrel/prasugrel/ticagrelor | 30 days | Repetition possible |
| DEB                             | Dissection/Recoil/IST         | ASS + Clopidogrel/prasugrel/ticagrelor | 6–12 months | Repetition possible |
| BMS (metal backbone)           | IST/ISR                       | ASS + Clopidogrel/prasugrel/ticagrelor | 30 days | DES |
| DES I (metal backbone + permanent polymer releasing drugs [Sirolimus, Paclitaxel]) | IST/ISR | ASS + Clopidogrel/prasugrel/ticagrelor | 6–12 months | DEB/ DES/ Bypass |
| DES II (platinum/cobalt-chromium backbone + permanent/ bio-degradable polymer releasing drugs [Everbilimus, Zotarilimus, Biolimus]) | IST/ISR | ASS + Clopidogrel/prasugrel/ticagrelor | 3–12 months | DEB/ DES/ Bypass |
| BVS                             | IST/ISR                       | ASS + Clopidogrel/prasugrel/ticagrelor | 3–12 months | Repetition possible/DES |
| Bypass                          | Perioperative risks +/-ASS    | permanent        | BMS, DES                 |

DEB: Drug-eluting balloon; BMS: bare metal stent; DES I: first-generation drug-eluting stents; DES II: second-generation drug-eluting stent; BVS: biodegradable vascular scaffold; IST: In Stent Thrombosis; ISR: In Stent Restenosis; ASS: acetylsalicylic acid.
Frontiers in Cardiovascular Research

Simsekyilmaz et al. Coronary interventions

The treatment of bifurcation lesions is exceedingly challenging, and the efficacy of dedicated bifurcation stents has not been proven yet (66–68). Bifurcation stents offer limited deliverability or ease of implantation and exhibit high intraprocedural complication rates. Many techniques, such as kissing balloon angioplasty, T-stenting, crush technique, culotte, simultaneous kissing stents, V-stenting, and Y-stenting have been proposed; however, well-designed randomised trials evaluating specific stenting techniques are necessary to determine the best practice for bifurcation lesions (67, 68).

The most common and preferred clinical procedure is POT (proximal optimisation technique), consisting in the deployment of a standard stent in the main branch and an intervention in the side branch only if necessary using another standard stent, maybe followed by kissing balloon inflation. Kissing balloon inflation was the first specific bifurcation technique being developed and proposed to optimise stent apposition, improving side branch access while correcting stent deformation or distortion. However, when two standard stents are used, while expanding the second stent, the first stent is pushed onto the artery wall; this results in three layers of metal adjacent to the vessel wall. These multi-layered stent struts promote turbulent flow conditions, augment ISR and stent thrombosis predisposition and might occlude the vessel by themselves or produce deleterious artery dissection. More complex approaches may further increase the risk of stent fracture, stent thrombosis, repeated target lesion revascularisation and even myocardial infarction. Novel drug-eluting bifurcation stents are currently not routinely used, and larger randomised studies comparing DES are not available.

Complementary strategies

However, the molecular events involved in ISR and stent thrombosis are orchestrated by complex interactions between circulating and resident cells and repair mechanisms (69). After arterial injury and disruption of the endothelial layer, exposed SMCs are activated, proliferate and secrete inflammatory mediators, such as chemokines and cytokines (70). Thus, they initiate a cascade of events to repair and regenerate the vascular wall. However, these processes are often overdue, resulting in an oversized intima formation and narrowed lumen. Some of the molecular factors and possible therapeutic strategies have been identified in the last years. For example, CXCL12, expressed also by SMCs, stimulates the arrest of lymphocytes and recruits smooth muscle progenitor cells and endothelial progenitor cells to the site of injury (71). Endothelial cells are early activated, proliferate under CXCL1 stimulation (7) or are recruited from the circulated cells as progenitors over CXCR2 receptor, starting to reconstitute the endothelial layer (72, 73). Many strategies for stimulating angiogenesis and sustaining the endothelial cell function proved to be efficient in reducing plaque formation and ISR (74, 75).

Based on this knowledge, stents were generated loaded with anti-CD34 antibodies (76), specific DNA aptamers (77) or integrin signaling peptides (74) to trigger re-endothelialisation by capturing endothelial progenitor cells from the blood flow and reduce ISR efficiently.

Further, CCL2 is also released by the exposed SMC and can be retained and immobilised on adherent platelets, initiating the CCR2-dependent monocyte arrest in the context of hypercholesterolaemia (78). Monocyte recruitment during the repair processes has been demonstrated to play an important role in neointima formation after injury. By targeting the involved chemokines and chemokine receptors, such as CCL2/CCR2 (79), CCL5 (80) or CX3CL1 (81), monocyte recruitment could be reduced and consecutively, neointima formation could be prevented.

Studying the molecular events, many other alternative therapies might be revealed and could be used to reduce ISR in experimental and clinical settings (82–84).

### Table 2: Rate of angiographic restenosis six months after PCI. Complicated lesions include In-Stent Restenosis, bifurcation/long stenosis, stenosis in small vessels and in high risk-group patients (diabetes, renal failure, bleeding history).

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>Rate of restenosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coronary</td>
<td>Complicated lesions</td>
</tr>
<tr>
<td>Balloon Dilatation</td>
<td>37–48%</td>
<td>47–58%</td>
</tr>
<tr>
<td>DEB</td>
<td>27–32%</td>
<td>17–24%</td>
</tr>
<tr>
<td>BMS</td>
<td>22–32%</td>
<td>30–40%</td>
</tr>
<tr>
<td>DES I</td>
<td>9–14%</td>
<td>15–35%</td>
</tr>
<tr>
<td>DES II</td>
<td>6–12%</td>
<td>11–22%</td>
</tr>
<tr>
<td>BVS</td>
<td>6–14%</td>
<td>-</td>
</tr>
</tbody>
</table>

DEB: Drug-eluting balloon; BMS: bare metal stent; DES I: first-generation drug-eluting stents; DES II: second-generation drug-eluting stent; BVS: biodegradable vascular scaffold.

Conclusions

In the last 10 years, an impressive progress in terms of implantability, efficacy and safety of coronary stents has been made, driven by the implementation of drug coatings and mechanical optimisations, and in particular the reduction of the thickness of stent struts while maintaining its radial strength. However, in cohorts with intermediate and high risk, such as in the context of complex...
bifurcation disease or in patients with diabetes mellitus, the clinical results remain unsatisfactory. Therefore, improvements in non-invasive imaging, shortening the duration of dual antiplatelet therapy, or enabling a secondary surgical revascularisation, as it would be given by biodegradable stents are of great importance and have priority for the research community involved in clinical practice. Promising strategies are currently studied and developed. They have become available recently or will be available in the near future. Using polymer-free drug-eluting, biodegradable stents, such as DES with a reduced pro-inflammatory effect, could enable the process of restoring a natural vessel, whereas the establishment of cell-specific drug combinations could simultaneously promote the re-endothelialisation as well as the inhibition of ISR.

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Conflicts of interest
None declared.

References

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Frontiers in Cardiovascular Research

Simsekylilmaz et al. Coronary interventions