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Editorial

Which came first: The chicken or the egg? Reflecting on the role of polymer and drug in coronary drug-eluting stents

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Being born in a duck yard does not matter, if only you are hatched from a swan's egg

[Hans Christian Andersen]

Those of us who have entered interventional practice in 2004 (GBZ, ER) are always amazed by the momentous changes in percutaneous coronary interventions, whereas senior colleagues and surgeons (GF, AG) bear also testimony of how invasive cardiology was changed by innovative physicians and companies. Indeed, several important developments have occurred in the last two decades, spanning from intracoronary imaging to atherectomy [1]. But in our opinion, the greatest successes were the introduction of drug-eluting stents (DES) and refinements in antiplatelet therapy, going from the widespread adoption of dual antiplatelet therapy (DAPT) based on aspirin and clopidogrel (Sanofi, Paris, France), to the concept of front-loading, and the introduction of more potent P2Y12 inhibitors such as prasugrel (Eli Lilly, Indianapolis, IN, USA) and ticagrelor (AstraZeneca, London, UK) [2]. While medical therapy remains the cornerstone of high-quality cardiovascular prevention and care, the thorough systematic review and meta-analysis by Picard and colleagues published in this issue of the *Internation Journal of Cardiology* urges our to reappraise in detail the important features of DES, which determined their past, current, and, likely, future success (Table 1) [3].

Current generation DES are typically balloon-expandable devices, consisting of a metallic platform, a polymer, and a drug with anti-restenotic effects [1,2,4]. Early embodiments were characterized by stainless steel platforms, permanent polymers, and very potent drugs (either in terms of active agent, or as dose): Cypher (Cordis, Miami Lakes, FL, USA) and Taxus (Boston Scientific, Natick, MA, USA). These devices had succeeded in animal studies at preventing neointimal hyperplasia, and provided sobering results at short and mid-term follow-up in clinical studies including well selected patients. Notably, DAPT was recommended for 2 to 3 months only, in this early era of DES [5]. Subsequent studies and longer follow-up of pilot and pivotal trials suggested however that these first-generation DES were fraught with a substantial risk of persistent inflammation and suppression of endothelialization, possibly leading to late restenosis and stent thrombosis.

The subsequent round of developments lead to second-generation DES, mainly Xience (Abbott Vascular, Santa Clara, CA, USA), Promus (Boston Scientific), Endeavor (Medtronic, Minnapolis, MN, USA), and Resolute (Medtronic). These devices were characterized by metallic alloy platforms (e.g. cobalt chromium), safer drugs, and more biocompatible permanent polymers. Their successful results (especially for permanent polymer everolimus-eluting stents [PP-EES] such as Promus and Xience, and permanent polymer zotarolimus-eluting stents [PP-ZES] such as Resolute) lead de facto to the disappearance of first-generation DES. Thanks to continuously favorable data on these devices, new products which aimed to refine them without contradicting altogether their basic design features, were progressively introduced into practice.

The strategies proposed were either the adoption of a bioresorbable polymer, such as in bioresorbable polymer everolimus-eluting stents (BP-EES) such as Synergy (Boston Scientific) or in bioresorbable polymer biolimus-eluting stents (BP-BES) such as Biomatrix (Biosensors, Singapore), or the elimination of polymer altogether, such as polymer-free biolimus-eluting stents (PF-BES) such as Biofreedom (Biosensors).

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Table 1
Key features of selected coronary drug-eluting stents, focusing on drug and polymer.

Device	Company	Type	Polymer	Drug	Stent
Alex	Balton	BP	Poly-lactide-*co*-glycolide	Sirolimus	Cobalt chromium alloy
Biofreedom	Biosensors	PF	None	Biolimus A9	Cobalt chromium alloy
Biomatrix	Biosensors	BP	Poly-lactic acid	Biolimus A9	Stainless steel
Cypher	Cordis	PP	Poly-ethylene-*co*-vinyl acetate	Sirolimus	Stainless steel
Endeavor	Medtronic	PP	Phosphorylcholine	Zotarolimus	Cobalt chromium alloy
Nobori	Terumo	BP	Polylactic acid	Biolimus A9	Stainless steel
Orsiro	Biotronik	BP	Polylactic acid	Sirolimus	Cobalt chromium alloy
Promus Element	Boston Scientific	PP	Fluoropolymer	Everolimus	Cobalt chromium alloy
Resolute	Medtronic	PP	BioLinx (C19 polymer, polyvinyl pyrrolidinone, C10 polymer)	Zotarolimus	Cobalt chromium alloy
Synergy	Boston Scientific	BP	Poly-lactic-*co*-glycolic acid	Everolimus	Platinum chromium alloy
Taxus	Boston Scientific	PP	Styrene Isoprene Butadiene	Paclitaxel	Stainless steel
Xience	Abbott Vascular	PP	Fluoropolymer	Everolimus	Cobalt chromium alloy

BP = bioresorbable polymer; PF = polymer free; PP = permanent polymer.

Indeed, since the infamous DES scare of 2006, permanent polymers had often been viewed skeptically, and, at best, as a necessary evil [6]. Thus, the basic pathophysiologic and engineering underpinning was that any DES which could provide adequate anti-restenotic effects at short and mid-term, while loosing all its polymer and drug components after 6 to 12 months, could be safer than any permanent polymer DES. This concept was epitomized by the quest for totally bioresorbable devices, such as Absorb (Abbott Vascular). Yet, science and medical practice often surprise or disappoint us, unless we view setbacks as teaching moments to improve our management strategies. Indeed, in as much as Absorb proved inferior to current generation DES, DES with bioresorbable polymer or without any polymer have not clearly surpassed to date in terms of safety and efficacy their permanent polymer counterparts [7].

Indeed, Picard et al. pooled 4 randomized trials (4631 patients), 3 (2286) comparing BP-EES vs PP-EES, and 1 (2345) comparing BP-EES vs PP-ZES, with follow-up ranging between 1 and 5 years, and aiming to appraise as outcomes of interest death, cardiac death, myocardial infarction, target lesion/vessel revascularization, stent thrombosis, and the composites of major adverse cardiac events and target lesion failure [3]. Despite their careful work, no significant difference was found between BP-EES and the other devices, either at overall or subgroup analyses focusing on control device. Notably, point effect estimates tended to favor BP-EES for target vessel revascularization/failure and stent thrombosis, whereas better results seemed to be achieved by PP-EES for death, myocardial infarction, and major adverse cardiac events. Yet, these results are most likely due to play of chance and overinterpretation is clearly discouraged.

As with any meta-analysis, limitations apply, and include the lack of individual patient data, the risk of low power for inferential estimates as well as inconsistency appraisal and small study effect testing. In addition, lumping together different stents just because of the presence of permanent polymer risks increasing heterogeneity, and simultaneously raises issues of selective inclusion of trials [8]. Indeed, despite the methodological complexity of network meta-analyses, the last word on the comparative safety and effectiveness of new-generation DES with bioresorbable polymers or without any polymer at all will probably come from such evidence synthesis tool, capable of accounting for different devices and, possibly, also different DAPT regimens [9].

In conclusion, BP-EES have similar efficacy and safety in comparison to current generation DES with permanent polymer. Leaving device choice to individual decision making, other factors, such as deliverability, cost and ancillary DAPT duration, should probably play a greater role for interventional cardiologists.

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Conflicts of interest

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

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