Drug eluting stents: Current status and new developments

İlaç kaplı stentler: Mevcut durum ve yeni gelişmeler

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ABSTRACT

Despite the favorable impact of drug eluting stents on stent restenosis, their long-term reliability is considered worrisome by some because of stent thrombosis. Often attributed to adverse reactions to the stent platform, both the drugs and polymer characteristics have been further advanced with current technologies. The present review discussed current drug eluting stents and new developments.
(Anadolu Kardiyol Derg 2012; 12: 676-83)
Key words: Drug eluting stent, bare metal stent, stent restenosis, development

ÖZET

İlaç kaplı stentlerin stent restenozundaki olumlu sonuçlarının yanında stent trombozu nedeniyle uzun dönem güvenirliği endişe oluşturmaktadır. Stent platformunun olumsuz etkileri ile ilişkilendirilse de, ilaçlar ve polimer özellikleri yeni teknolojiler ile daha da geliştirilmiştir. Bu derlemede mevcut ilaç kaplı stentler ve yeni gelişmeleri tartıştık. *(Anadolu Kardiyol Derg 2012; 12: 676-83)*
Anahtar kelimeler: İlaç kaplı stent, çıplak metal stent, stent restenozu, gelişme

Introduction

Coronary artery stents have provided a breakthrough in the percutaneous treatment of coronary artery disease. Bare metal stents (BMS), first used in 1986 by Sigwart et al. (1) became widely used in 1994 with the publication of the Benestent studies, comparing stents to balloon angioplasty (2). In-stent restenosis and stent thrombosis were identified as the two main problems in the long-term outcomes. The rate of restenosis was quite high after balloon angioplasty due to vascular recoil and constrictive remodeling (40-60%). The rate of restenosis following BMS implantation has been reported between 20% and 40% based on clinical features (3, 4). Stent thrombosis was also high, despite extensive "multidrug" anticoagulant therapy, during the first three weeks. Advances in antiplatelet therapy, mainly the use of ticlopidine and aspirin without the plethora of anticoagulant therapy, nearly eliminated the rate of stent thrombosis following BMS and reduced the rate of bleeding complications; however, the rate of stent restenosis remained high.

Today, restenosis is explained by three mechanisms: early elastic recoil, late vessel remodeling and neointima formation. Maximal neointimal thickening in BMS usually occurs within 6 months following stent implantation. Neointimal development is the result of a cascade of molecular and cellular events initiated by platelet activation, leukocyte infiltration, proliferation of smooth muscle cells and production of extracellular matrix materials (5). Smooth muscle cell proliferation, the target of drug eluting stents (DES), has been effectively reduced with their use. However, healing after DES placement is concomitantly delayed and this has inadvertently introduced new problems.

The widespread use of DES began with the publication of the RAVEL trial that showed extremely low restenosis rates (6). Compared to BMS, the first generation DES (sirolimus and paclitaxel eluting stents) effectively reduced the rate of stent restenosis; but brought along problems of safety terms of an increase in the

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Accepted Date/Kabul Tarihi: 06.08.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 18.09.2012

doi:10.5152/akd.2012.220

rate of late stent thrombosis and presence of chronic endothelial dysfunction. It should be noted however that the rate of DES stent thrombosis was lower than the initial rates of stent thrombosis in the early days of BMS.

Safety of drug eluting stents: Stent thrombosis

The hypothesis that late stent thrombosis occurs due to late re-endothelialization in the coronary artery after DES mostly depends on angioscopy and autopsy studies (7). This has been the subject of many preclinical and clinical studies and is still questionable as there is still a large unexplained variability in the regression models explaining late stent thrombosis by autopsy studies (8). A significant increase was reported in the rate of stent thrombosis during the 1st and 4th years after sirolimus and paclitaxel eluting stent implantation (0.6% and 0.7%, respectively) as compared to BMS (0.2%) (9). However; Stettler et al. (10) compared sirolimus and BMS on the 1st and 4th years (0.3% DES and 0.2% BMS) and reported no evidence for an increase in the rate of late stent thrombosis. Nevertheless, a significant increase has been reported in the rate of late stent thrombosis in other clinical studies that compared paclitaxel eluting stent with sirolimus eluting stent (cumulative incidence on the 4th year is 3.6% and 2.7%, respectively, p=0.02) (11,12). On the other hand, preclinical and clinical studies have demonstrated that this significant increase in the rate of stent thrombosis is associated not only with late endothelialization (13). Various clinical angioscopy studies have propounded the presence of late endothelialization after DES (14). Control angioscopies performed in animals after DES implantation have demonstrated that stent surface was not endothelialized; however, histological examination showed completely endothelialized stent surface (13). Based on the histological results, angioscopy imaging might be considered to be unable to show endothelialization properly.

It has been reported that re-endothelialization rates in swine coronary arteries on the 28th day were similar after DES and BMS (15). In a study that compared re-endothelialization rates in rabbit iliac arteries on the 14th and 28th days after four different DES (everolimus, zotarolimus, paclitaxel, sirolimus) and BMS implantations, re-endothelialization rates were the highest with everolimus and BMS on the 14th day and were similar with all stents on the 28th day (16). While delayed endothelialization cannot be disregarded as a player in late stent thrombosis, it is not the only player. We have hypothesized that rather than endothelial absence, endothelial dysfunction plays a major role. A dysfunction that can be the result of direct drug effects, but also from inflammation as induced by the stent coating, or even from the pre-existing plaque.

Endothelial dysfunction

Acetylcholine leads to vasodilatation by causing nitric oxide (NO) release from the endothelium of a normal coronary artery. However, it causes vasoconstriction in the event of inadequate endothelial NO release or presence of leaky endothelium allowing direct access of acetylcholine to smooth muscle cells, where it can directly induce a contractile response. This method is used to investigate coronary endothelial dysfunction. Compared to BMS, more intense abnormal vasoconstrictor response to acetylcholine has been observed in the patients that underwent sirolimus and paclitaxel DES implantation (17, 18). Animal studies have revealed decreased eNOS secretion in the group that underwent paclitaxel DES implantation as compared to BMS group and it was considered that such a decrease would lower the anticoagulant character of the endothelium (19). In light of this information, we can say that stent thrombosis is a multifactorial event including endothelial dysfunction as the result from plaque character, polymer coating, drug release kinetic, and resultant inflammation (13).

Stent platform

Stents are prepared to be flexible and easily expandable, and have pores for the lateral branches. Stent design influences short- and long-term outcomes. Stainless steel was used as the stent platform in the first generation DES (sirolimus and paclitaxel eluting stents), whereas cobalt chromium was used in the second generation DES (everolimus and zotarolimus eluting stents). Cobalt chromium alloy strengthens the stent and allows for strut thickness while maintaining radiopacity. It has lower risk for allergy since it contains less nickel as compared to stainless-steel (20). Table 1 summarizes stent platform and polymer characteristics of DES.

Stent coat

Metallic scaffold of DES is surrounded by polymer matrix containing drug. Polymer binds the drug to the stent and regulates the drug to spread throughout the vessel. An ideal DES polymer should be non-thrombotic, non-inflammatory, and non-toxic and should facilitate vascular healing by accelerating re-endothelialization.

Polymers that are used for stent coating can be mainly classified as follows; (a) biostable (non-biodegradable) synthetic polymers [polyethylene-co-vinyl acetate, poly-n-butyl methacrylate, poly(styrene-b-isobutylene-b-styrene), polyurethane, silicone] (b) biodegradable polymers (polyglycolic or polylactic acid) (c) biological polymers (phosphorylcholine, hyaluronic acid, fibrin) and combinations thereof (5, 20). It should be clearly understood however, that in addition to the bulk of the drug containing polymers, the stents are often also treated by primer layers that may equally affect the vasculature. Especially if a biostable primer layer is used in combination with degradable coating such as parylene C.

Drugs

Drugs with anti-inflammatory, anti-thrombogenic, anti-proliferative and immunosuppressive characters are the candidates to be used in DES, which aims to prevent stent restenosis. Drugs with above-mentioned characteristics may inhibit one or more pathways, associated with restenosis (21).

Table 1. Stent platform and polymer character of drug eluting stents

Stent name	Stent platform	Polymer	Drug	Strut Thickness (μm)
First generation stent				
Taxus Express	Stainless-steel	Poly (styrene-b-isobutylene-b-styrene)	Paclitaxel	132
Cypher	Stainless-steel	Polyethylene-co-vinyl acetate and poly (n-butyl methacrylate)	Sirolimus	140
Second generation stent				
Endeavor ZES	Cobalt-chromium	Phosphorylcholine	Zotarolimus	91
Endeavor Resolute	Cobalt-chromium	Biolinx polymer, blend of 3 polymers: hydrophobic C10, hydrophilic C19 and polyvinyl pyrrolidone	Zotarolimus	91
Xience V	Cobalt-chromium	Poly vinylidene fluoride and hexafluoropropylene copolymer	Everolimus	81
Promus	Platinum-chromium		Everolimus	81
Third generation stent with biodegradable polymers				
Supralimus	Stainless-steel	Poly-L-lactide, polyvinyl pyrrolidone, polylactide-co-capro-lactone, and polylactide-co-glycolide	Sirolimus	80
BioMatrix	Stainless-steel	Abluminal polylactic acid	Biolimus A9	112
AXXESS	Nitinol	Abluminal polylactic acid	Biolimus A9	180
Nobori	Stainless-steel	Abluminal polylactic acid	Biolimus A9	125
JACTAX HD	Stainless-steel	Abluminal polylactic acid	Paclitaxel	97

Limus family

Limus family can be summarized in two groups; the mammalian target of rapamycin (mTOR) inhibitors [rapamycin (=sirolimus), everolimus, zotarolimus and biolimus A9] and calcineurin inhibitors (tacrolimus and pimecrolimus) (22, 23). The mTor inhibitors are cytostatic drugs and show their effects by stopping the cell cycle at G1 phase. Sirolimus acts by binding to FK506 binding protein-12 and inhibits restenosis cascade by blocking inflammation, neointimal hyperplasia, collagen synthesis and migration of smooth muscle cells (24). Zotarolimus and everolimus as well inhibit smooth muscle cell and T cell proliferation by binding to FK506 binding protein-12 (24). Novolimus and myolimus are new mTOR inhibitors, which have been also clinically tested (25, 26).

Tacrolimus is an immunosuppressive agent that inhibits calcineurin by binding to FK506 binding protein-12 and as well as inhibits T-lymphocyte signal conduction and pro-inflammatory cytokine synthesis. Despite its significant anti-inflammatory effect, inhibitor effect of tacrolimus on human smooth muscle cell is almost 100 times less than that of sirolimus (20). While successfully reducing intimal thickness in preclinical studies, clinical benefit has not been proven. Thus, tacrolimus drug eluting Janus stent has not been successful in reducing restenosis in clinical trials (27) and neither was the Mahoroba trial (28). The optimal drug release rate in diseased vessels may well be different from relatively healthy vessels in preclinical models.

Paclitaxel

Paclitaxel is a lipophilic molecule with anti-neoplastic and anti-mitotic characters. It binds to β-tubulins and stops the cell cycle at G2/M phase by stabilizing microtubules, and preventing their depolymerization, thus freezing cells in mitosis. Contrary to Limus family drugs, paclitaxel shows cytotoxic effect. Besides, it inhibits proliferation and migration of smooth muscle cells, which are effective on stent restenosis (20, 29).

Dexamethasone

Evidence on the importance of inflammation in neointimal hyperplasia and restenosis has been growing. Dexamethasone and corticosteroids in general, have a potent anti-inflammatory effect and inhibit the proliferation of fibroblasts, smooth muscle cells and macrophages. Preclinical studies have found dexamethasone eluting stents to be safe and beneficial in terms of stent-induced inflammation. Their favorable effects on restenosis have been reported in limited number of clinical studies. There are ongoing randomized-controlled studies investigating these results (30).

Actinomycin D

Actinomycin D is a kind of antibiotic, which is used in malignant neoplasms due to its anti-proliferative character. It affects the s-phase of the cell cycle and is a potent inhibitor of cell proliferation. The efficacy of actinomycin eluting stent was investigated in ACTION study; however, the study was terminat-

ed prematurely due to the increase rate of stent restenosis (31). This increase was attributed to local drug toxicity.

New Developments

New developments in stent platforms

Element™ Stent

The Element Stent Platform (Boston Scientific) is made up of platinum-chromium alloy. It is a denser alloy as compared to cobalt-chromium and stainless steel. It has a strut thickness of 81 μm and exhibits high radial durability and radiopacity. The Element platform has been used in two stents: everolimus eluting stent (PROMUS Element; Boston Scientific) and paclitaxel eluting stent (TAXUS Element; Boston Scientific). In a randomized, multicenter PLATINUM study comprising 1.532 patients, the PROMUS Element was compared with the cobalt-chromium PROMUS everolimus eluting stent (Boston Scientific) and no significant difference was found in terms of target vessel revascularization, stent thrombosis, and cardiac event (32). Moreover, the paclitaxel eluting TAXUS Element and compared to the TAXUS Express stent in TAXUS PERSEUS Workhouse study where no significant difference was found in terms of one-year outcomes (33).

Bifurcation stents

Bifurcation stents have been designed to overcome the difficulties encountered during bifurcation procedures. The rate of restenosis was found between 28% and 54%, notably because the first generation bifurcation stents (Multi-Link Frontier™, SLK-View™, Petal™, Sideguard™, Twin-Rail™, Nile Croco™, Tryton™, Sidekick™) were not drug eluting (34). Paclitaxel and biolimus eluting stents are available among new generation bifurcation stents.

TAXUS Petal (Boston Scientific) stent is more potent and shows more radiopacity than stainless steel because of its platinum-chromium platform. It uses the same polymer with TAXUS Express. The stent has a hole for side-branch opening. The rate of target vessel revascularization was found to be 11.7% in the first study on human; the rotational alignment affected the success of the procedure since it had to be performed during the procedure (35).

Axxess (Devax Inc.) stent has been designed to be self-expanding with nickel-titanium platform and in cone-shaped to be suitable for bifurcation anatomy. This design facilitates reaching the distal branches. The Biolimus A9 eluting side branch stent has a polymer coating with a drug eluting and biodegradable character. Nine-month outcomes of DIVERGE study revealed a low cardiac event rate of 7.7% and a target vessel revascularization rate of 4.3% (36).

Nile Pax™ (Minvasys) is a polymer free paclitaxel eluting stent with cobalt-chromium platform. It has been designed for bifurcation lesions with a hole in the middle. The early-period results of BIPAX study revealed high success rates; however, the long-term results have not been published yet (37).

STENTYS (Stensys S.A.S.) is a self-expanding stent with nitinol platform and has interconnections, which can be disconnected by balloon angioplasty, to provide easy access to side-branches. OPEN I study reported that it was used with high success rates in coronary bifurcation lesions and that the rate of the 6th month cardiac event and late lumen loss was quite low (38).

New developments in stent polymers

Durable polymers

Endeavor Resolute

The Endeavor Resolute (Medtronic) is the next generation of zotarolimus eluting stent. It consists of driver cobalt chromium stent platform and 3 different polymers: hydro-phobic C10 polymer to control drug release; biocompatible and hydrophilic C19 polymer; and polyvinylpyrrolidone. This polymer provides 85% of drug release in 60 days and the remaining in 180 days (36). In the RESOLUTE All-comers trial, in which 2.300 patients were randomized into 1:1 Endeavor Resolute or Xience V (Abbott, everolimus DES) implantation groups and were compared in terms of primary end points (target vessel revascularization rate and cardiac death) after 12-month follow-up period, Endeavor Resolute stent was found to be noninferior to Xience V stent (39).

Biodegradable polymers

Paclitaxel eluting stents

Infinnium stent (Sahajanand) is composed of stainless steel platform and heparinized biodegradable polymer consisting of poly-l-lactide, poly-dl-lactide-co-glycolide, poly-l-lactide-co-caprolactone and polyvinylpyrrolidone. PAINT (Percutaneous Intervention with Biodegradable-Polymer Based Paclitaxel Eluting, Sirolimus-Eluting, or Bare Stents for the Treatment of De Novo Coronary Lesions) study compared the Infinnium stent and biodegradable polymer and sirolimus eluting Supralimus stent with BMS. It was observed that both DES significantly decreased the neointimal hyperplasia, as well as the number of interventions at the end of one year, as compared to the BMS; however, sirolimus DES more efficiently decreased the angiographic neointima as compared to the Infinnium stent. Nevertheless, it failed to demonstrate an association between this efficacy and better clinical outcomes. No significant differences were identified between the groups in terms of mortality, stent thrombosis and infarction (40).

JACTAX Liberté stent (Boston Scientific) has stainless steel platform and is coated with biodegradable polylactide polymer and paclitaxel. The polymer is 18 times thinner than that of TAXUS Liberté stent. Paclitaxel release continues for 90 days and polymer is completely absorbed in 6 to 9 months. In OCTDESI (Optical Coherence Tomography Drug Eluting Stent Investigation), 60 patients were randomized into JACTAX-low-dose and high-dose-paclitaxel, and TAXUS Liberté stent groups and no significant difference was found between JACTAX stent and TAXUS Liberté stent in terms of stent coverage (41). The 6-month rate of uncovered struts per patient was reported as 5.3±14.7% for TAXUS Liberté, 7.0±12.2% for JACTAX HD, and 4.6±7.3% for JACTAX LD (p=0.81).

Sirolimus eluting stents

Excel stent (JW Medical Systems) has stainless steel platform and is coated with biodegradable polylactic acid polymer and elutes sirolimus. The polymer is completely absorbed in 6 to 9 months. CREATE (Multi-Center Registry Trial of EXCEL Biodegradable Polymer Drug-Eluting Stent) trial investigated the efficacy of Excel stent in 2.077 patients and found the rate of major cardiac event as 3.1% in 18 months. The most promising outcome of this study was the rate of stent thrombosis, which has been reported to be 0.87% despite the fact that 80.5% of the patients discontinued clopidogrel after the 6th month (42).

Supralimus stent (Sahajanand Medical Technologies) has stainless steel platform and is coated with biodegradable polymer mix of polylactide, polyvinylpyrrolidone, polylactide-co-caprolactone, polylactide-co-glycolide polymer and sirolimus. Half of the sirolimus is released in 9 days and the remaining is released in 48 days. Polymer is completely degraded within 7 months. The efficacy and safety of Supralimus stent was demonstrated in PAINT and eSERIES studies. Since the PAINT study has been mentioned above, we will talk about eSERIES study in brief. This study included approximately 1100 patients with acute coronary syndrome and found the rate of target vessel revascularization as 2.7% and the rate of stent thrombosis as 0.6% on the 12th month (43).

NEVO stent (Cordis) has cobalt-chromium platform and is coated with bioabsorbable polylactide-co-glycolide polymer and sirolimus. The stent platform incorporates polymer and hundreds of small reservoirs filled with drug. Endothelial-polymer contact has been reduced by 75% with this method. Polymer absorption occurs in a short time of 90 days. NEVO Res-Elution I, a multicenter randomized noninferiority study, compared NEVO stent and TAXUS Liberté stent in 394 patients. Six-month follow-up period demonstrated that NEVO stent is superior to TAXUS Liberté stent. Stent thrombosis was not observed in the NEVO stent group (44).

Nonpolymeric stent

Nonpolymeric stents aim to protect endothelium against the adverse effects of polymer, to accelerate endothelial healing and to use dual antiplatelet for shorter period.

YUKON stent (Translumina) has polymer-free stainless steel platform. There are micropores over its surface acting as reservoir for sirolimus. In the ISAR-TEST study, YUKON stent was compared with permanent polymer paclitaxel-eluting stent TAXUS and 5-year outcomes have been reported recently. No difference was found between the groups in terms of clinical outcomes (45).

VESTAsyn stent (VESTAsyn) is another stent with polymer-free, sirolimus eluting stainless steel platform. It has nano-thin microporous hydroxyapatite surface coating and allows for the release of a lower dose of drug (46). Sirolimus is released within 3 months, whereas hydroxyapatite coating is completely absorbed in 9 to 12 months. Randomized VESTASYNC II study (n=120) compared VESTAsyn stent with BMS and found in-stent late lumen loss to be significantly lower in VESTAsyn group (p=0.03) (47).

Amazonia Pax stent (Minvasys) is the only stent with polymer-free, paclitaxel eluting cobalt-chromium platform. Total thickness of the stent is 78 µm and the drug is completely released in 45 days. Four-month follow-up outcomes of PAX A study demonstrated no significant difference between TAXUS stent and Amazonia Pax stent in terms of in-stent late lumen loss (48).

BioFreedom stent (Biosensors) has polymer-free, Biolimus A9 eluting stainless steel platform. The first human study compared BioFreedom stent including standard dose and TAXUS Liberté stent and found no difference in terms of in-stent late lumen loss in 12 months (49).

Bioabsorbable stents

The rationale for a fully degradable stent is that upon complete resorption of the platform, the vessel could return to its normal function without being caged by metal. The risk of late stent thrombosis would be non-existent upon strut resorption. A shorter duration of dual antiplatelet therapy and allowing further surgical revascularization in the stent implantation area are considered among the advantages of bioabsorbable stents (36). Polymer of bioabsorbable stents are often composed of polylactides such as polylactic acid, or polycarbonate. They are completely metabolized in approximately 12 to 18 months. In addition, degradable metallic stents are under development.

IGAKI-TAMAI stent (Kyoto Medical Planning Co Ltd.) polymer is composed of polylactic acid. The stent is completely absorbed in 18 to 24 months. It is both thermal self-expanding and balloon expandable stent. It reaches to original size in 0.2 second at 70°C, whereas this time is 20 to 30 minutes at 37°C. The first human study revealed neither stent thrombosis nor major cardiac event at the end of 6-month follow-up. The rate of angiographic restenosis was found to be 10.5% since it is not drug-coated. Preclinical studies found that the version of the stent with a coating of paclitaxel effectively reduced the rate of stent restenosis (34, 36).

Bioresorbable Vascular Scaffold (BVS) (Abbott Vascular) is composed of poly-l-lactic acid and poly-D, L-lactide and contains everolimus. It requires for more than 2 years for complete absorption. ABSORB (A Bioresorbable Everolimus-Eluting Coronary Stent System for Patients with Single De-Novo Coronary Artery Lesion), a multicenter prospective and the first human study, observed no stent thrombosis after 3-month follow-up period. The rate of major cardiac event was found 3.3% during 6-month follow-up period; however, no major cardiac event was observed between 6th month and 3rd year (50, 51).

REVA stent (REVA Medical) is composed of bioabsorbable tyrosine polycarbonate polymer and metabolized into amino acids, ethanol and carbon dioxide in approximately 36 months. RESORB study found that the degree of neointimal hyperplasia was similar to that of BMS. In ReZolve stent (REVA Medical), a second generation DES, sirolimus is released in 30 days, where-

as stent degradation is completed in 12 months. Since neointimal suppression was found inadequate in the first human studies, studies with high dose sirolimus have been planned (36).

Antibodies and cell capturing stent

Genous Bio-engineered R-stent (OrbusNeich) is a BMS with stainless steel platform and an immobile anti CD34 antibody on the surface. Preclinical studies have demonstrated that it accelerates endothelialization and does not influence neointimal thickness (52). However, CD34 antibodies are not specific to endothelial progenitor cells; thus, there is concern that they might increase neointimal proliferation by influencing other hematopoietic stem cells (such as smooth muscle progenitor cell). The TRIAS study (n=193) compared two-year follow-up outcomes of Genous stent and TAXUS stent and no significant difference was found in terms of target vessel revascularization, cardiac death and myocardial infarction (53). Moreover, the new generation Combo stent (OrbusNeich), in which endothelial progenitor capture and DES technology were used together, has been tested in clinical studies. Endothelial progenitor capture technology, low-dose sirolimus and biodegradable polymer were used in Combo stent. REMEDEE (Randomized Evaluation of an Abluminal sirolimus coated Bio-Engineered Stent) study, an ongoing study, have randomized the patients to compare the outcomes of TAXUS Liberté stent and Combo stent (36).

Conclusion

The rate of stent restenosis has begun to decrease after the use of DES. New studies and technologies have focused on enhancing the long-term efficacy and safety of DES, and creating DES with a more temporary character by making them completely degradable. This development is often called the fourth revolution in PCI. As was mentioned above, there are various stents having different stent platform as well as drug and polymer characteristics. Better knowledge of the advantages and disadvantages of each of these devices could eventually lead to a situation where the choice of stent is based on lesion characteristics, risk factors for the patient, risk for bleeding, and compliance to long-term dual antiplatelet therapy. In light of ongoing studies and technologies, advances in DES are promising for invasive cardiologists in terms of treatment of coronary artery disease.

Conflict of interest: None declared

Authorship contributions. Concept-G.E.; Resource - G.E., H.V.B.; Data collection&/or Processing - G.E., H.V.B.; Literature search - G.E.; Writing - G.E., H.V.B.; Critical review - H.V.B.; Other - H.V.B.

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