Percutaneous coronary intervention with evolving stent technology for treating totally occluded native coronary arteries

Teeuwen, K.

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Chapter 11

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Discussion and future perspectives

For long time, CTOs have been judged as experimental laboratory for development of percutaneous coronary interventions in complex coronary artery disease. In the early days, balloon delivery systems, guide-wire and stents technology benefitted importantly from these challenging lesions. In this thesis we evaluate the next generation drug-eluting stents in successful recanalized CTOs. In the first part (Chapter 2 to 8), we investigate several drug-eluting stents over the course of three randomized trials (PRISON II to IV). The major findings were the following. We observed low rate of late luminal loss with most second –and third generation drug-eluting stents. Late luminal loss, as surrogate endpoint for restenosis, was lowest with first-generation sirolimus-eluting stents and second-generation Resolute-zotarolimus –and everolimus-eluting stents. Third-generation hybrid sirolimus-eluting stents showed little higher late luminal loss and the rate was highest with second-generation Endeavor zotarolimus-eluting stents. The rates of target lesion revascularization were in accordance with the observed rate of late luminal loss. Furthermore, we observed an improved safety profile with the lowest rate of definite stent thrombosis with second-generation everolimus-eluting stents and hybrid sirolimus-eluting stents (0.6% and 0.6%). The rates were comparable between first generation sirolimus-eluting stents and second-generation Resolute zotarolimus-eluting stents (1.0-2.0%, 1%) and highest with Endeavor zotarolimus-eluting stents (4%) at 12-months. Additionally, over the course of these trials, patient and CTO lesion complexity level increased and results should be interpreted accordingly. On the other hand, the trials were not powered for clinical endpoints and these results remain exploratory. Finally, we have to await long-term follow-up of second– and third-generation drug-eluting stents to assess the incidence of very late stent thrombosis.

Three major stent innovations contributed to these results. Most importantly, cobalt-chromium alloys replaced early generation stainless steel. Thereby, strut thickness was reduced from 140 µm (SES) to 91 µm (both ZES), 81µm (EES) or even 80 µm, stent sizes ≥ 3.0 mm diameter and 60µm, < 3.0 mm diameter with hybrid SES.

Furthermore, open cells were created in the stent alloy by reducing the numbers of connectors between hoops (from 6 to 3 crowns), while maintaining radial and longitudinal strength. Moreover, these novel alloys were more flexible, allowed easier stent placement in tortuous and calcified coronaries, and prevented stent fractures, due to metallic fatigue, in coronary segments exposed to heavy motion during the cardiac cycle.
Secondly, antiproliferative drugs were introduced. Sirolimus or rapamycin is a macrocyclic lactone produced by Streptomyces hygroscopicus. Rapamycin is an immunosuppressive agent used to treat autoimmune disease and skin disease or prevent rejection of organ transplant. Zotarolimus and everolimus are both rapamycin analogues. Rapamycin on bare-metal stents significantly reduced neointima formation and thereby restenosis. However, rapamycin or analogues do not adhere appropriately to metallic surface. Therefore, polymers are indispensable for adequate drug delivery to the vessel wall. Polymers require several characteristics to optimize drug-elution: biocompatibility, drug-release, adherence to the stent and maintaining integrity in coronary environment. First generation SES were embedded with mixtures of durable polymers, resulting in optimal early neointima inhibition by slow release of drugs to 80% at 30 days. However, clinical warnings arose after observing higher rates of very late stent thrombosis, even more pronounced after CTO PCI. Histopathological examinations showed late hypersensitivity reactions to permanent polymers, resulting in development of more biocompatible polymers. Endeavor and Resolute ZES both used more biocompatible polymer based on phosphorycholine coating. However, the drug release with Endeavor was markedly increased to 98% in only 14 days, leading insufficient neointima suppression and thereby restenosis. Therefore, “Biolinx” mixture of polymers was developed for the Resolute ZES with slow drug release leading to improved angiographic and clinical results. The everolimus-eluting stents were mounted with biocompatible permanent fluoropolymer, which were shown to be less inflammatory and to reduce platelet aggregation. Finally, new biodegradable polymers were developed mostly based on poly-L-lactic acid (PLLA). In the hybrid SES ultra-thin struts were combined with PLLA polymer. Until now, these biodegradable polymers were not superior to biocompatible permanent polymers in the era of thin and ultra-thin strut stents, and we have to await if fully degradable polymers lead to fewer adverse events in long-term follow-up.

The results of our PRISON studies were in line with other published data of the used stents in de novo lesion or all-comer populations, except for the PRISON IV trial. In the latter study, non-inferiority was not met for hybrid SES compared to EES with higher in-segment late lumen loss and rate of binary restenosis with hybrid SES. In contrast, the BIOSCIENCE study investigated hybrid SES versus EES in all-comers and showed comparable rate of target vessel revascularization. Interestingly, sub-analysis in the PRISON IV trial showed that the increment of binary restenosis with hybrid SES primarily occurred in patients with CTO treatment in small vessels. Additionally, optical coherence tomography (OCT) showed improved neointima coverage and increased percentage of malapposition and evaginations with hybrid SES. Unfortunately, we could not evaluate
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Stent integrity in the absence of baseline post stenting OCT. The most presumable cause of this difference remains speculative, since both stents have three major differences in the smaller stent groups, biodegradable versus durable polymer, ultra-thin (60 µm) versus thin-struts (81 µm) and different rapamycin analogues.

In the future, several new innovations will replace our already outstanding arsenal of current drug-eluting stent devices. The next generation should at least satisfy the following requirements; ultra-thin struts, outstanding mechanical integrity, easy deliverability and optimal elution of anti-proliferative drugs.

The first generation stainless steel sirolimus-eluting stent offered outstanding radial force. However, thick struts enhanced the risk of stent thrombosis and the almost cage like design with six connector hoops made the stent device inflexible and hard to deliver in tortuous, calcified and small vessels. The last generation of ultra-thin strut cobalt-chromium stents are flexible and reduce stent thrombosis. However, they are at the lower boundary of achieving enough mechanical strength to prevent early or late recoil and subsequent restenosis.

In the last decade, the most innovative development in coronary stent devices led to the first biodegradable non-metallic biovascular scaffold (Absorb, Abbott Vascular, Santa Clara, CA, USA) made of poly-L-lactic acid with strut thickness of 153 µm and mounted with everolimus. After promising first results, the company pulled the device of the market after observing increased rates of target vessel myocardial infarction in the randomized Absorb II, Absorb III and AIDA trial.(2-4) Angiography demonstrated a decreased acute gain when compared to metallic stent devices. The scaffold device showed good results in patients with CTO in first reported small registries.(5) However, in-scaffold late lumen loss was two- to three-fold higher in CTO patients compared to conventional metallic drug-eluting stents. In-scaffold late lumen loss is a strong predictor for future revascularization.(6) Newly bio-engineered non-metallic stent or scaffold devices should at least have comparable radial force with lower strut thickness to compete with metallic stents, especially for treatment of CTO.

Another interesting novel dedicated stent for long lesions and CTO involves a long ultra-thin strut tapered sirolimus-eluting stent (Biomine Morph; Meril, Bonn, Germany). This sirolimus-eluting stent with biodegradable polymers, offers stent lengths up to 60 mm with a tapered design. Strut thickness is 65 µm with a tapered difference of 0.5 mm diameter between proximal and distal stent edge. To improve mechanical strength, there is closed-cell design at the proximal -and distal stent-edge and open-cells in the middle, to enhance stent flexibility and facilitate stent delivery. The tapered design reduces the risk of distal edge dissections. Together with the available long sizes, the number of ad-
ditional overlapping stents can be reduced, which diminishes the risk of restenosis. A small registry showed that implantation of the device was feasible and safe in CTO with comparable clinical outcome to other conventional drug-eluting stents.(7) Further efficacy improvements can be related to new drugs mounted on devices. As demonstrated in our late PRISON II study the process of intima hyperplasia or neoatherosclerosis continues over time after 90 days eluting of rapamycin agent. Recently, another ultra-thin strut cobalt-chronium stent (MiStent; Micell Technologies, Durham, NC, USA) was introduced with bioresorbable polymer containing a microcrystalline form of sirolimus, which extends the sirolimus-elution in the vessel wall up to nine months.(8) Early angiographic and optical coherence tomography showed favourable results with very low late lumen loss. In a large randomized trial, the MiStent was non-inferior to thin-strut everolimus-eluting stent with permanent polymer (Xience; Abbott Vascular, Santa Clara, CA, USA) with regard to the composite device oriented endpoint.(9) Interestingly, the cumulative rate of ischemia driven target lesion revascularizations seem to diverge after 120 days in favour of the MiStent. These findings might be explained by early-resorbed polymers and extended release of sirolimus and merit long-term follow-up. Future stent devices could also elute other types of local drugs. For instance, anti-inflammatory drugs next to anti-proliferative agents to reduce neoatherosclerosis formation after implantation. Most recently, the first trial with anti-inflammatory drug (canakinumab) demonstrated significant reduction in cardiovascular events and these promising results could enhance further developments for local anti-inflammatory drug-elution in future devices.(10)

The second part (Chapter 9 to 10) describes physiological changes of the distal coronary segment, micro-vascular resistance and absolute coronary recovery after treatment of the CTO vessel. In daily practice, operators are often confronted with the decision to stent or defer stenting of additional distal disease after treating the CTO segment. In our pooled analysis from the PRISON III and IV trial, we showed that binary stenosis in the distal segment at baseline can be safely deferred from stenting. At follow-up, the majority of the distal segments demonstrated significant lumen gain after restoration of antegrade flow, even more pronounced in patients with binary restenosis at baseline. The rate of target vessel revascularization was comparable between patients with and without residual binary restenosis in the distal segment at baseline. On the contrary, the rate of revascularization was almost doubled in patients treated with additional stents in the distal segment at baseline. Therefore, our results support a “watchful waiting” strategy in the event of additional disease distal to the target CTO lesion with a low threshold for follow-up angiography in the following weeks. In the final case report, we
showed new data of absolute flow and microvascular resistance recovery of large re-opened right coronary artery CTO and the providing donor artery measured by novel “continuous thermodilution” method. After only one week, microvascular resistance dropped significantly in the right coronary artery leading to 86% increase in absolute coronary flow. In the providing left anterior descending artery resistance increased slightly and absolute coronary flow decreased mildly due to regression of collateral blood flow. Obviously, these results need to be confirmed in larger sample size study. However, almost doubling of coronary flow in the CTO vessel at follow-up corresponded well with earlier findings of late lumen gain. Moreover, as demonstrated by our PRISON IV OCT sub-study, the “late lumen gain phenomenon” leads to increased malapposition and uncovered struts compared to non-occlusive lesions.

Therefore, an expandable stent device, able to adapt to the late lumen gain phenomenon, could potentially be advantageous in CTO, to achieve better stent strut apposition and coverage. Currently only one self-expandable coronary stent device (sirolimus-eluting STENTYS stent system; STENTYS S.A, Paris, France) is available on the market. This nitinol stent expands after implantation and is mostly used for specific indications like lesions in large coronaries, lesions with more than 1 mm difference in proximal -and distal reference vessel diameter, and in patients with ST-elevation myocardial infarctions with a large thrombus burden. The strut thickness is 100 to 133 µm for medium -and large diameter size stents. Although, the concept sounds promising the rate of target vessel failure and stent thrombosis was higher compared to conventional drug-eluting stents in real world observation.(11) Currently, there is no data available on the use of this device in CTO. However, in practice these stents are more difficult to deliver. Therefore they are probably less suited for treating CTO.

In this thesis we show that evolution in stent technology overall delivered safer and effective devices. CTO challenge every aspect of new stent devices. Together with an unmet clinical need for this expanding treatment, evolution will undoubtedly lead to future innovations, and more dedicated CTO stent devices, to further improve treatment of coronary artery disease.
Summary and conclusions

The main goal of this thesis is to assess the angiographic efficacy and clinical safety of the next generation drug-eluting stents in PCI for chronic total coronary occlusions.

In Chapter 2, we evaluate the five years angiographic follow-up of MACE-free patients of the PRISON II trial. This trial was the first randomized study demonstrating superior angiographic outcome of first generation sirolimus-eluting stents compared to conventional bare-metal stents after successful recanalization of totally occluded native coronary arteries. Primary results demonstrated major reduction in angiographic late lumen loss (> 1 mm), binary restenosis 41% to 11% and target vessel revascularization 22% to 8%. The main findings of this study at five years showed increased additional late lumen loss between nine months and five years in the group of sirolimus-eluting stents compared to bare-metal stents. Our results demonstrated, that the process of intima proliferation and/or neoatherosclerosis is continuously and is not completely halted after sirolimus-eluting stent implantation.

In Chapter 3, the PRISON III trial compared the next or second-generation zotarolimus-eluting stents (Endeavor and Resolute ZES) to SES in totally occluded chronic total occluded native coronary arteries (TCO/CTO). Halfway through the study, Endeavor ZES ceased to be commercially available and was replaced by Resolute ZES. The steering committee decided to split the trial in two phases. A pre-planned interim analysis showed that primary superiority endpoint, in-segment late lumen loss, of SES compared to Endeavor ZES was met. In the second phase superiority between SES and Resolute ZES was unlikely to be met. Therefore, in an exploratory context, non-inferiority was established between both stents in a post-hoc analysis. Clinical events were comparable between device comparisons in both phases.

In Chapter 4, we evaluate three years clinical outcome of the PRISON III trial. At three-years clinical events between SES and Endeavor ZES or SES and Resolute ZES were comparable. The higher rate of late lumen loss with Endeavor ZES did not translate into higher incidence of revascularizations, myocardial infarctions, stent thrombosis or death. Of note, this trial was not powered for clinical event evaluation and therefore the occurrence of clinical events in this trial should be interpreted in an exploratory context.

The next or third generation ultra-thin strut sirolimus-eluting stent (hybrid SES) with biodegradable polymer was compared to the most reputable stent, thin-strut everolimus-eluting stent (EES) with durable polymer, in recanalized CTOs in the prospective, randomized, multi-centre, single-blinded PRISON IV trial. In Chapter 5, we describe the rational and design of this study.
In Chapter 6, we present the final results of the PRISON IV study. At nine months follow-up the primary non-inferior endpoint of in-segment late lumen loss was not met for hybrid SES compared to EES with an increased rate of in-stent and in-segment binary restenosis. Clinical outcome was comparable with low rate of stent thrombosis. In Chapter 7, we describe results of a predefined subgroup of 60 patients who underwent optical coherence tomography at nine months follow-up. In correspondence to the angiographic results, hybrid SES showed improved stent strut coverage and lower rate of uncovered struts compared to EES. On the contrary, the rate of malapposition and evaginations was higher with hybrid SES. In Chapter 8, we perform sub-analysis to assess the impact of small and larger stent diameters of hybrid SES and EES on restenosis, since hybrid SES consists of different strut thickness for both groups (80 µm, stent sizes ≥ 3.0 mm diameter and 60µm, < 3.0 mm diameter). Interestingly, the underperformance of hybrid SES was only prevalent in small vessels. However, it remains speculative, if dissimilarity in mechanical integrity between small -and larger stents, or permanent against biodegradable polymer, caused observed differences in late luminal loss and binary restenosis. In Chapter 9, we describe results from a substudy of pooled angiographic and clinical data from the PRISON III and IV trial. In this study, we investigated clinical implications of distal vessel stenosis after CTO-PCI. In this analysis we showed that patients with additional restenosis in the distal segment could be safely deferred from immediate stenting. The majority of distal segments showed significant mean lumen gain. The rate of target vessel revascularization was comparable between patients with and without binary restenosis in the distal segment after CTO treatment at baseline. On the contrary, patients treated with additional stents for distal disease showed more than two fold increase in target vessel revascularization at follow-up compared to a “watchful waiting” strategy.

In the final Chapter 10, we describe a case report on the recovery of absolute coronary flow and resistance after successful CTO-PCI, using a novel method “continuous thermodilution” to accurately assess measure coronary flow. After only one week, micro-vascular resistance dropped significantly with an almost doubled absolute coronary flow in the treated CTO vessel. In the contra-lateral providing coronary artery microvascular resistance increased mild leading to slight decrease in flow. These findings obviously need to be reproduced in larger sample size studies.
Samenvatting en conclusies

In dit proefschrift wordt de veiligheid en effectiviteit van volgende generatie medicatie afgevende coronaire stents (drug-eluting stents; DES) voor de behandeling van chronisch totaal afgesloten coronair vaten (CTO) beschreven.

In hoofdstuk 2, evalueren wij de angiografische uitkomsten van patiënten in de PRISON II studie, welke na vijf jaar vrij zijn van majeure negatieve cardiovasculaire gebeurtenissen (o.a. cardiale dood, myocardinfarct, stent trombose en hernieuwde revascularisatie). De PRISON II studie is de eerste trial die superieure angiografische uitkomsten toont bij het gebruik van eerste sirolimus-eluting stents van de eerste generatie in vergelijking met conventionele metalen stents in patiënten met CTO. De primaire uitkomst toont een belangrijke reductie van angiografische late lumen vernauwing (> 1mm), binaire restenose van 41% naar 11% en revascularisaties in het behandelde coronairvat van 22% naar 8%. De belangrijkste bevindingen van deze late angiografische substudie tonen een toename van additionele late lumen vernauwing tussen negen maanden en vijf jaar in de groep met sirolimus-eluting stents in vergelijking met de conventionele metalen stents. Onze resultaten tonen dat het proces van intima-proliferatie en/of nieuwe atherosclerose vorming continue is en niet volledig wordt gestopt na het plaatsen van een sirolimus-eluting stent.

In Hoofdstuk 3, beschrijven wij de resultaten van de PRISON III studie, waarbij de zotarolimus-eluting stent van de tweede generatie (Endeavor en Resolute) wordt vergeleken met de sirolimus-eluting stent van de eerste generatie voor de behandeling van CTO. Halverwege de studie is de Endeavor stent niet meer leverbaar, hij wordt vervangen door de Resolute stent. Na deze wijziging besluit de stuurgroep van de studie om de trial in twee fasen te splitsen. Op een vooraf geplande tussentijdse beoordeling is de primaire uitkomst, segmentale late lumen hervernauwing, superieur in het voordeel van de sirolimus-eluting stent ten opzichte van de Endeavor zotarolimus-eluting stent. De tweede fase toont geen superioriteit van de sirolimus- of Resolute zotarolimus-eluting stent. Een beschrijvende post-hoc analyse toont wel non-inferioriteit aan tussen beide stents. Klinische gebeurtenissen (o.a. cardiale dood, myocardinfarct, stent trombose en revascularisatie) zijn vergelijkbaar tussen beide stents in beide studie fasen.

Hoofdstuk 4, beschrijft de klinische gebeurtenissen van patiënten uit de PRISON III studie na drie jaar. De grotere neiging tot restenose met de Endeavor stent vertaalt zich niet in een hogere incidentie van cardiale dood, revascularisaties, myocardinfarct of stent trombose. Het aantal patiënten in deze studie is statistisch niet groot genoeg om enige definitieve conclusies te trekken en derhalve zijn de resultaten beschrijvend.
In de PRISON IV studie wordt de sirolimus-eluting stent van de derde generatie, met ultra dunne struts en bio-oplosbare polymeren (hybrid SES) vergeleken tegenover de everolimus-eluting stent van de tweede generatie, met dunne struts en permanente polymeren (EES) in patiënten met een CTO. De rationale en het ontwerp van de studie wordt beschreven in Hoofdstuk 5.

In Hoofdstuk 6, presenteren wij de resultaten van de PRISON IV studie. Het primaire eindpunt, non-inferioriteit in segmentale late lumen restenose, wordt niet gehaald met een verhoogde incidentie van in-stent en in-segmentale late lumen restenose met de hybrid SES in vergelijking met de EES. De klinische uitkomsten zijn vergelijkbaar met een lage incidentie van stent trombose. In Hoofdstuk 7, beschrijven wij de resultaten van een subgroep van 60 patiënten, waarbij op 9 maanden een optical coherence tomography wordt uitgevoerd. In overeenstemming met de angiografische resultaten, toont de hybrid SES een verbeterde nieuwe intima bedekking van de stent struts in vergelijking met EES. In tegenstelling is de incidentie van struts die los liggen van de vaatwand en micro-holte vorming hoger met Hybrid SES. In Hoofdstuk 8, onderzoeken we de relatie van smalle en grotere stent-diameters van hybrid SES en EES op het optreden van restenose. De EES heeft dezelfde strut-dikte (80 µm) voor alle stent-diameters, echter de hybrid SES heeft verschillende strut diktes (80 µm, stent diameter ≥ 3.0 mm en 60µm, stent diameter < 3.0 mm) voor grotere -en kleinere stent diameters. De resultaten tonen alleen een verhoogde incidentie van restenose met hybrid SES bij de kleinere stent diameters. Het blijft echter speculeren of deze verschillen in late lumen en binaire restenose berusten op een verschil in mechanische integriteit van de stents of verschil in gebruik van oplosbare tegenover permanente polymeren.

In Hoofdstuk 9, beschrijven we een analyse uit de samengestelde angiografische en klinische data van de PRISON III en IV studies. In deze studie onderzoeken we de gevolgen van een vernauwing in het distale coronair vat na CTO interventie. De resultaten van deze analyse tonen dat een aanwezige distale binaire vernauwing niet direct behandelt hoeft te worden met een stent plaatsing. Verder treedt er bij de meerderheid van de patiënten een significante lumen verwijding plaats bij controle angiografie. De incidentie van revascularisaties in het behandelde vat is vergelijkbaar tussen patiënten met en zonder een vernauwing in het distale coronair vat. In tegenstelling hebben patiënten die wel zijn behandeld met extra stents voor een distale vernauwing een meer dan twee keer verhoogde incidentie van revascularisaties in vergelijking met een conservatief beleid.

In het laatste Hoofdstuk 10, beschrijven we een casus over het herstel van absolute coronair doorstroming en weerstand na revascularisatie van een CTO. De absolute coronair doorstroming en micro vasculaire weerstand worden gemeten met een nieuwe, zeer
accurate methode genaamd “continue thermodilutie”. Slechts een week na CTO interventie is er een significante daling van de weerstand en bijna een verdubbeling van de coronaire doorstroming in het behandelde vat. In de contralaterale donor coronair arterie stijgt de microvasculaire weerstand matig met een geringe afname van coronaire doorstroming. Deze bevindingen moeten bevestigd worden in een grotere studie populatie.
Chapter 11

References


