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

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Chapter 1

Introduction and outline
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Percutaneous coronary intervention of chronic total coronary occlusions

Half a century ago Andreas Gruentzig, the founding father of interventional cardiology, performed the first successful percutaneous coronary balloon angioplasty in human in 1977.(1) Ever since, percutaneous coronary intervention (PCI) revolutionized treatment of obstructive coronary artery disease. Within a decade, operator experience, evolving PCI materials -and techniques, increased the procedural rate of success to > 90% for all non-occlusive coronary lesions. In contrast, chronic totally occluded coronary lesions (CTO) remained the last frontier with historical lower rate of procedural success (60%) and higher incidence of restenosis.(2-4) Currently, CTO lesions are observed in approximately 18.4% of all patients who undergo non-emergent coronary angiography, excluding patients with previous coronary artery bypass grafting (CABG). Most of these patients > 50% are treated medically, 25% receive CABG and 30% undergo any PCI, of which only 10% of CTOs are attempted with a success rate of 70%.(5) CTO-PCI reduces angina and the need for CABG and it improves quality of health. Nevertheless, cardiologists are often reluctant to invest in a time and resource consuming procedure.(6) In the absence of well-designed randomized trials, there is on-going debate on the therapeutic benefit of CTO-PCI compared to medical treatment for CTO. After the introduction of drug-eluting stents CTO-PCI made a major leap forward. Together with development of sophisticated CTO materials and novel recanalization techniques like retrograde approach and dissection re-entry, the procedural success rate improved to 86-92%.(7-10)

History of balloon angioplasty and coronary stents for chronic total occlusions

First reports on balloon angioplasty for CTO described low and decreasing success rates of 82%, 62% and 25% depending on the duration of the occlusion, one week, one to three months or greater than three months, respectively.(11) Recurrence was related to a higher degree of residual narrowing after PCI and to the duration of the occlusion.(2) Newly designed steerable guide wires and laser techniques improved the rate of success to 72% when in experienced hands. Despite, balloon angioplasty significantly reduced the need for coronary artery bypass grafting (CABG).(12) The rate of recurrence (21% reocclusion and 47% restenosis) remained high due to competitive collateral flow and suboptimal local result. Nevertheless, balloon angioplasty was safer in CTO than non-occlusive lesions. In the presence of well-developed collaterals the myocardial territory behind the CTO vessel was protected from periprocedural myocardial infarction caused
by balloon-induced coronary dissections. Therefore, CTOs were often reviewed as the experimental laboratory for developments in PCI techniques to further reduce the need for CABG. (Figure 1).

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**Figure 1.**

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In the late eighties, first generation bare-metal stents (BMS; Palmaz-Schatz stent) were implanted to further diminish the rate of restenosis by preventing acute recoil after balloon angioplasty in CTO. An early study showed restenosis reduction of 27.9% versus 56.6% with bare-metal stents compared to conventional balloon angioplasty in CTO-PCI at six months follow-up. (3) In the following years, several randomized clinical trials (GIS-SOC, TOSCA, STOP, SPACTO, SICCO, MAJIC) compared bare-metal stents to conventional balloon angioplasty including our first “PRImary Stenting of Occlude Native coronary arteries” (PRISON) study (Table 1). Overall, stenting reduced the 6-month rate of angiographic restenosis and reocclusions from 61% to 39% and 18% to 9%, respectively. The rate of target lesion revascularization was reduced from 29% to 16%.

The next major step forward was the introduction of drug-eluting stents (DES). Anti-proliferative chemotherapeutics were mounted on bare-metal stents to prevent early neo-intima formation and thereby repeated revascularizations. The PRISON II study was the first randomized trial comparing sirolimus-eluting stents with bare-metal stents in the treatment of totally occluded native coronary arteries. Angiographic late luminal loss was reduced with more than 1 mm, together with reductions of in-stent and in-segment...
restenosis from 39% to 7% and from 46% to 12% respectively. Since restenosis was the major limitation of CTO-PCI, these findings were important for further innovation, development and expansion of the field. Next, the interventional community became more cautious after observing late and very late stent thrombosis with first generation sirolimus -and paclitaxel drug-eluting stents.(23) These adverse events were more frequently seen after treating long lesions and CTO.(24-26) Several new second- and third-generation DES platforms, with thinner struts, different rapamycin analogues, and permanent or biodegradable polymers, were introduced to further improve angiographic and clinical outcome.(27-30) In this thesis, we focus on the efficacy and safety of the next second- and third-generation DES platforms to treat CTO, the most complex lesion type in coronary artery disease.

**Pathophysiology of chronic total coronary occlusions**

Chronic total coronary occlusions represent the final atherosclerotic stage of coronary artery disease. They are associated with long-term mortality.(31) Most often, CTO develop gradually with unrecognized or mild atypical symptoms. In the first phase, inflammation together with accumulation of lipid particles leads to atherosclerotic plaque growth and positive vessel remodelling. In the next phase, extending plaque burden compromises the lumen resulting in diminished antegrade coronary flow. In the course of several weeks to months, coronary auto-regulation recruits ipsi- and contralateral collaterals to protect the myocardial territory behind the CTO from ischemia. In the following phase, thrombotic occlusion occurs at the lesion site due to competitive antegrade and collateral retrograde flow.(32) Histopathology exams revealed several differences between shorter -and longer duration CTO lesions. Younger aged occlusions showed more fibrous collagen and lipid rich plaque with organized thrombus in the lumen area. In contrast, older aged CTOs demonstrated more hard fibrous tissue with dens calcium formations (Figure 2). Neovascular channel formation or bridging collateral formation occurs in the adventitia in younger CTO compared to more luminal in older CTO.(33,34) Furthermore, exposed to aortic pressure, proximal caps are often hard, calcified and ambiguous, as opposed to more tapered distal caps with loose fibrous tissue. The latter finding can be favorable for retrograde wire crossing. Finally, older occlusions showed advanced negative remodeling in the distal vessel.(35)
### Table 1. Randomized Trials Comparing Bare-metal Stent versus Conventional Balloon Angioplasty in Chronic Total Coronary Occlusions

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stent type</th>
<th>n of patients</th>
<th>months</th>
<th>% balloon</th>
<th>% stent</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>GISSOC 1998</td>
<td>Palmer-Schatz</td>
<td>110</td>
<td>9</td>
<td>88%</td>
<td>68%</td>
<td>32%</td>
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<tr>
<td>TOSCA 1999</td>
<td>Palmer-Schatz</td>
<td>410</td>
<td>6</td>
<td>96%</td>
<td>70%</td>
<td>55%</td>
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<td>SICCO 1999</td>
<td>Palmer-Schatz</td>
<td>119</td>
<td>6</td>
<td>96%</td>
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<td>SPACTO 1999</td>
<td>Wiktor stent</td>
<td>85</td>
<td>6</td>
<td>79%</td>
<td>64%</td>
<td>32%</td>
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<tr>
<td>STOP 2000</td>
<td>AVE microstent</td>
<td>96</td>
<td>6</td>
<td>72%</td>
<td>71%</td>
<td>42%</td>
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<tr>
<td>PRISON 2004</td>
<td>NIR</td>
<td>200</td>
<td>6</td>
<td>90%</td>
<td>33%</td>
<td>22%</td>
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<tr>
<td>MAJIC 2004</td>
<td>Wiktor stent</td>
<td>221</td>
<td>6</td>
<td>88%</td>
<td>55%</td>
<td>57%</td>
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<tr>
<th>Trial</th>
<th>Stent type</th>
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<th>stent</th>
<th>p-value</th>
<th>balloon</th>
<th>stent</th>
<th>p-value</th>
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</thead>
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<td>GISSOC 1998</td>
<td>Palmer-Schatz</td>
<td>34%</td>
<td>8%</td>
<td>0.003</td>
<td>22%</td>
<td>5%</td>
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<td>Palmer-Schatz</td>
<td>20%</td>
<td>11%</td>
<td>0.024</td>
<td>15%</td>
<td>8%</td>
<td>0.03</td>
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<tr>
<td>SICCO 1999</td>
<td>Palmer-Schatz</td>
<td>24%</td>
<td>8%</td>
<td>&lt;0.001</td>
<td>42%</td>
<td>22%</td>
<td>0.025</td>
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<td>SPACTO 1999</td>
<td>Wiktor stent</td>
<td>24%</td>
<td>2%</td>
<td>&lt;0.001</td>
<td>40%</td>
<td>25%</td>
<td>ns</td>
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<tr>
<td>STOP 2000</td>
<td>AVE microstent</td>
<td>16%</td>
<td>8%</td>
<td>ns</td>
<td>42%</td>
<td>25%</td>
<td>ns</td>
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<td>PRISON 2004</td>
<td>NIR</td>
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<td>8%</td>
<td>ns</td>
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<td>0.80</td>
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<tr>
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<td>9%</td>
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<td>49.5</td>
<td>30.6</td>
<td>&lt;0.005</td>
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*≥ 50% diameter stenosis

**Definition of Total Coronary Occlusions and Chronic Total coronary Occlusions**

Since the rate of procedural success for CTO-PCI is highly dependent on the duration of coronary occlusions, clinical and angiographic outcome should be interpreted accordingly. Over the last decades, earlier definitions with shorter-duration cut-offs were used, including in our subsequent PRISON trials.

In this thesis, we followed the evolution of definitions over time. In the PRISON II and III trial, total coronary occlusion (TCO) was defined as, the absence of antegrade contrast distal to the occlusion (TIMI [Thrombolysis In Myocardial Infarction] flow grade 0) or only minimal antegrade flow of contrast distal to the occlusion (TIMI flow grade I). The duration of the occlusions should be at least two weeks, estimated by clinical, sequential angiographic information or both. In the PRISON IV trial, the TCO definition was changed to an estimated duration of at least four weeks. In all PRISON studies, chronic total occlusion (CTO) was defined as, coronary occlusion with TIMI flow 0 and an estimated duration greater than three months standing. (36,37)
In Chapter 2-5, we generally use the classification of TCO to describe the study population, since the prevalence of true CTO was little less than 50% in the PRISON II and III trial. Nevertheless, additional subanalyses were performed on patients with CTO. In Chapter 6-10, describing data of the PRISON IV trial, we use the classification of CTO to describe the study population, with a prevalence of more than 90% CTO.

Figure 2.
Representative images of long-duration chronic total occlusion and short-duration chronic total occlusion without coronary artery bypass graft. (A and C) Low-power images of long-duration and short-duration chronic total occlusion without coronary artery bypass graft. (B and D) High-power images of boxed areas in (A) and (C), respectively. The matrix is predominantly made up of collagen type I in (B). In (D), the matrix predominantly consists of proteoglycan and fibrin. CTO, chronic total occlusion.
Coronary physiological effects of percutaneous revascularization of chronic total occlusions

Darcy's law is the basic of coronary hemodynamic, where a pressure difference equals coronary flow times coronary resistance. Interplay between coronary flow and collateral flow in the presence of a CTO remains a complex research topic already finding interest in physicians in the era of balloon angioplasty. Often misinterpreted, the myocardial territory behind the CTO is a persistent ischemic zone, even in the presence of well-developed collaterals. However, reopening can alleviate ischemia comparable to PCI of non-occlusive lesions. Dependent on the duration of the occlusion, histopathology examination showed advance negative remodelling in the vessel distal to the CTO. Yet, after immediate reopening, the distal vessel and supplying myocardium remains in temporary hibernated state with transient impairment of vasomotor function and abnormal response to endothelial dependent stimuli. At several weeks or months follow-up vasomotor function normalizes with significant luminal growth of the distal vessel. Consequently, operators are challenged to choose the appropriate stent length and diameter directly after recanalization, in a still spastic vessel, and decide whether or not to treat more distal disease. Currently, there is ample evidence about this issue, except that increased stent length is associated with restenosis. Previous studies investigated physiological changes of reopened CTO vessels by indirect measures like angiographic lumen changes or fractional flow reserve. However, little is known about the exact recovery of absolute coronary flow and microvascular resistance over time in recanalized CTO vessels and the providing donor coronary artery. Recently, a novel method was developed to accurately measure absolute coronary flow by continuous thermodilution. In comparison to previous methods continuous thermodilution is easy to perform, highly accurate and operator-independent. Future research in coronary physiology can hopefully provide us more insights and knowledge about recovery of absolute coronary flow and CTO vessel dimensions, to further improve and optimize our stent treatment.
References


CTOs are the most challenging lesions for PCI. They are highly prevalent during coronary angiography and still most often treated medically or by coronary artery bypass grafting (CABG). Successful percutaneous recanalization and treatment of these long troublesome fibrocalcified lesions require knowledge, operator skills, wide set of ancillary materials and coronary stents for vessel patency. Despite, historically hampered by reocclusions, the introduction of drug-eluting stents led to impressive reduction in restenosis, making CTO-PCI a true competitor of coronary artery bypass grafting.

In this thesis, we evaluate the efficacy and safety of coronary stents in the complex subset of CTOs. In the first part we focus on the evolution of stent technology from bare-metal stents to third generation ultra-thin strut drugs-eluting stents with biodegradable polymer in CTOs. In Chapter 2, we evaluate the five-year angiographic follow-up of MACE-free patient from the PRISON II trial randomizing BMS to 1st generation sirolimus-eluting DES. In Chapter 3 and 4, the next generation DES (zotarolimus-eluting Endeavor and Resolute stents; ZES) were investigated in patients with TCO in the PRISON III trial. Angiographic follow-up was performed at nine months and clinical follow-up at 12 months and three years. The next PRISON IV trial was designed to compare the second- and third-generation DES in chronic total coronary occlusions. In Chapter 5, we present the rational and design of this trial. In this study, the next generation sirolimus-eluting stents with ultra-thin struts (SES) and biodegradable polymer were compared to second-generation everolimus-eluting stents with thin-struts and durable polymer (EES). Primary angiographic and clinical results are shown in Chapter 6. Additionally, optical coherence tomography (OCT) is performed in a predefined subgroup to assess malapposition and stent strut coverage, described in Chapter 7. In the last Chapter 8, we analyse the impact of smaller and larger stent sizes of SES and EES on surrogate angiographic and OCT endpoints.

In the second part of this thesis, we focus on the interplay between coronary physiology and effects of CTO recanalization after stenting. In Chapter 9, we evaluate the clinical implications of distal vessel stenosis after CTO-PCI in an angiographic sub-analysis of pooled data from the PRISON III and IV trial. In the final Chapter 10, we present a case, evaluating a novel accurate method to measure coronary blood flow and myocardial resistance recovery after CTO-PCI.

Outline of this thesis

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