General introduction, aims and outline

CORONARY ARTERY DISEASE

Although cardiovascular death rates has decreased over the past decades, ischemic heart disease remains the number-one cause of death worldwide (Figure 1).[1-3] Moreover, the increasing overall life-expectancy of men and women across the globe will lead to an increasing prevalence of coronary artery disease. This eventually could lead to a growing number of patients with complex coronary artery disease and advanced cardiovascular risk-profiles requiring revascularisation by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). A more complex patient with coronary artery disease requires a well-defined and structured approach to determine the optimal revascularisation strategy. In order to provide evidence-based patient-tailored treatment suggestion, adequate preoperative risk assessment and multidisciplinary discussions in the form of a structured heart team meetings are warranted.[4,5]

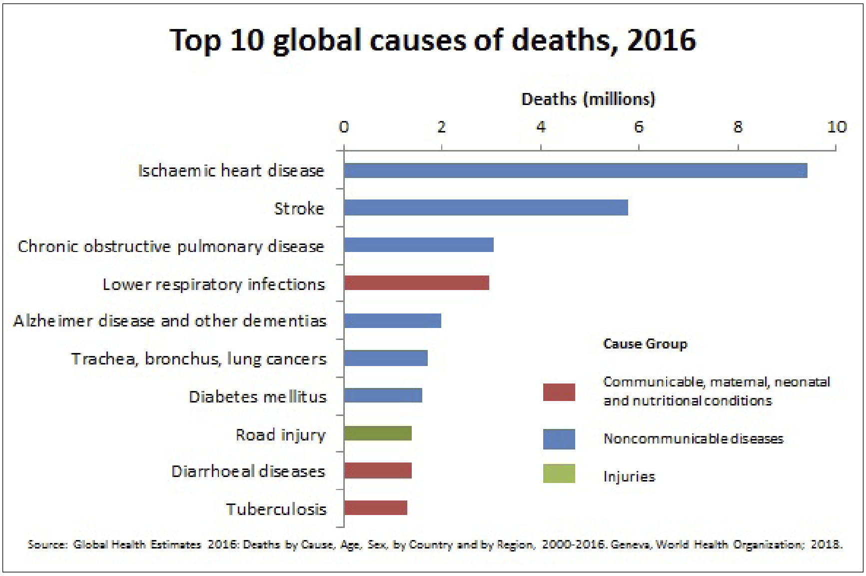

Figure 1. The World Health Organization Top-10 causes of death in 2016.[1]

The coronary heart team approach is designed to provide an evidence-based, multidisciplinary, patient-tailored treatment recommendation for a patient requiring myocardial revascularisation.[6] Treatment strategies consist of i) medical treatment, ii) percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The heart team consists of a cardiac surgeon, an interventional cardiologist, a clinical/non-interventional cardiologists and if necessary additional specialists.

Heart team meetings played a crucial role in well-respected randomized controlled trials (RCTs), such as the SYNTAX trial and the EXCEL trial.[7,8] Patients enrolled in these trials were discussed by a heart team that evaluated whether equivalent revascularisation could be achieved with either CABG or PCI. When clinical equipoise between the revascularisation strategies was determined, patients were randomized to either CABG or PCI. This method of randomization was crucial to adequately compare the treatment strategies head-to-head in PCI versus CABG trials. It furthermore encouraged open and structured discussions between cardiac surgeons and cardiologists to optimize coronary artery disease treatment strategy which ultimately leads to improved clinical outcomes.

The performance of such heart team meetings in 1000 consecutive patients with coronary artery disease discussed in the Thoraxcentre of the Erasmus University Medical Centre Rotterdam were assessed and clinical outcomes after treatment were determined.[9] Of 960 unique cases, almost one-third had complex left main or triple vessel coronary artery disease. Almost all patients (90%) were treated within 6 weeks after first referral, as advised by European Guidelines for myocardial revascularisation.[10] Furthermore, the majority of heart team decisions followed guideline-directed recommendations for treatment of patients with LM with 2- or 3VD (CABG: 71%)) and isolated LM or with 1VD (PCI: 81%). The recommendation for patients with 3VD was evenly divided between CABG and PCI (both 46%). Only 6% of patients with 1VD and 12% of patients with 2VD received medical therapy. This resulted in 5-year mortality rates of 26.9% for patients with LM and 2VD or 3VD, 17.1% for patients with 3VD without LMCAD and only 3.4% for patients with isolated LMCAD or 1VD. To conclude, the heart team approach at the Rotterdam Thoraxcentre was in agreement with contemporary myocardial revascularisation guidelines.

SURGICAL MYOCARDIAL REVASCULARISATION

On February the 25th, 1964, Vasilii I. Kolesov was the first surgeon that performed bypass surgery with the use of an internal thoracic artery (ITA) to the left anterior descending (LAD) coronary artery in a patient, performing a sutured anastomosis.[11] Michael DeBakey performed a venous aorta-coronary bypass later that year. Both techniques are still being used in contemporary CABG procedures.[12] It was René A. Favaloro that further developed CABG by consecutively operating patients with coronary artery disease that required revascularisation, and reporting on the surgical and clinical outcomes.[13] In this specific publication he described the clinical experience of 150 patients receiving CABG with the use of bilateral internal thoracic arteries (BITA) at the Cleveland Clinic in Ohio, USA. As of today, the potential benefits of performing BITA revascularisation in selected patients is still being debated. In a high-definition core skills video tutorial, the surgical technique of performing CABG with a BITA Y-graft (e.g. LITA-Y-RITA ; LIMA-Y-RIMA) at the department of Cardiothoracic Surgery in the Erasmus Medical Centre, Rotterdam, is elucidated.[14]

Although surgical revascularisation was a relative experimental treatment when it was first introduced in the 1960s, for many patients it was their last resort to treat angina when medical therapy appeared insufficient. Perioperative mortality and morbidity rates were high during the early days of CABG. Therefore, meticulous selection of eligible patients to undergo surgical revascularisation appeared to be crucial (e.g. patients without recent myocardial infraction (MI), without severe left ventricular dysfunction or the need for other concomitant procedures).[15,16] To objectively compare CABG to other treatment modalities, structured and randomized studies were warranted. First CABG was only compared to medical treatment, however after the introduction of PCI, studies comparing revascularisation treatments head-to-head (PCI versus CABG) were designed. Over the past decades, CABG grew out to being one of the most often performed major surgical procedures, nonetheless the number of CABG procedures vary among countries.[17,18]

To further diminish adverse event rates, surgical and technical improvements deemed necessary. Cardiopulmonary bypass (CPB) systems improved and the systemic inflammatory response related to CPB was thereby reduced.[19] New surgical techniques such as off-pump coronary artery bypass (OPCAB) surgery, anaortic clampless CABG, minimally invasive direct coronary artery bypass (MIDCAB) surgery and eventually Hybrid coronary revascularisation (e.g. LITA to LAD with CABG followed by PCI of remaining coronary lesions) gained ground over the past years.[20] Currently, according to the 2018 European myocardial revascularisation guidelines, CABG is the gold standard for patients with complex and multivessel coronary artery disease requiring myocardial revascularisation.[10]

PERCUTANEOUS MYOCARDIAL REVASCULARISATION

Over the past decades percutaneous coronary intervention (PCI) has made a substantial impact on the way physicians treat patients with coronary artery disease requiring myocardial revascularisation. What once was the solitary playground of CABG, PCI is now a suitable alternative for selected patients with coronary artery disease requiring revascularisation.

A historical milestone took place when Andreas Grüntzig performed the first coronary balloon-angioplasty procedure in an awake patient with coronary artery disease on September the 16th, 1977 at the University of Zürich.[21] Although a major breakthrough, balloon angioplasty appeared not always to be an angina-relieving or life-saving procedure due to the risk of immediate restenosis of the coronary lumen. Julio Palmaz noted the shortcomings of balloon angioplasty and focused on developing a metal coronary stent. A decade later, the first successful in-human PCI procedure, by stenting a single-vessel lesion, was performed by Julio Palmaz and Richard Schatz in São Paola, Brazil in December 1987.[22]

The use of adequate secondary preventive treatment appeared to be of utmost importance to prevent restenosis and ensure stent patency.[23] To further optimize stent durability and decrease neo-intimal hyperplasia, drug eluting stents (DES) were developed.[24] As scientific and technological developments continued, first generation DES were followed up by second generation DES.[25,26] Currently, the field of stent developments keeps moving forward as third generation DES and bioresorbable stents are being used in contemporaneous PCI procedures.[23,27,28] According to the 2018 European myocardial revascularisation guidelines, PCI is a suitable treatment in selected patients with non-complex 1-or 2-vessel coronary artery disease.[10]

REVASCULARISATION STRATEGIES HEAD-TO-HEAD

Over the past decades, the boundaries of revascularisation strategies for patients with coronary artery disease have shifted, especially in patients with left main coronary artery disease and three-vessel disease. Where CABG once was the golden standard for myocardial revascularisation in left main disease, now PCI appears to become a suitable alternative in selected patients with non-complex coronary artery disease.[8,29] In patients with complex multivessel coronary artery disease (e.g. those patients with three-vessel disease and/or complex coronary anatomy) CABG remains the treatment of choice. The basis for these insights came from the international, multicenter randomized studies, such as the SYNTAX, FREEDOM, NOBLE and EXCEL trials, among others.[7,8,30,31] These trials empowered continuous advancements in the treatment of patients with coronary artery disease (Figure 2) and contributed to treatment-recommendations in the European and North-American myocardial revascularisation guidelines.[7,8,30,31] Besides distinguishing potential treatment benefits of either medical therapy, PCI or CABG in patients with coronary artery disease, these trials furthermore aimed to identify specific risk-predictors, such as diabetes and renal insufficiency, that may influence short-and long-term treatment outcomes. The evidence presented by PCI versus CABG trials was accompanied with low rates of mortality and morbidity, indicating the constant developments of stent technology and improvements in surgical technique.

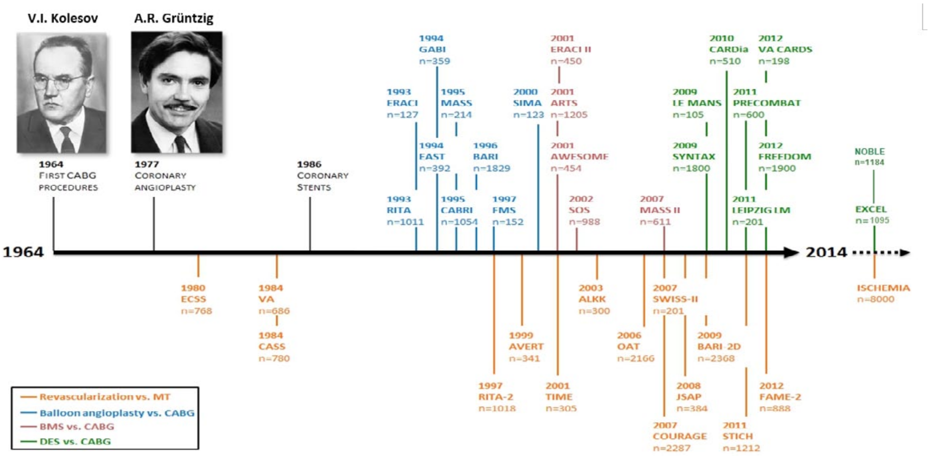

Figure 2. Scientific contributions in determining the optimal treatment strategy (medical therapy, percutaneous or surgical myocardial revascularisation) for patients with coronary artery disease.

To ensure continuous scientific and clinical advancements within the field of myocardial revascularisation, it is also beneficial to analyse revascularisation outcomes in patients that are treated within your own local institution, instead of only focussing on outcomes reported by large randomized and registry studies. Therefore, the life-long outcomes of patients that underwent PCI with balloon angioplasty or CABG in the Thoraxcentre at the Erasmus University Medical Centre in Rotterdam, were analyzed.[32] Included patients underwent primary revascularisation 40 years ago. At that time, these revascularisation treatments aimed to achieve complete revascularisation of significantly obstructed coronary segments of the major coronary arteries. During follow-up, the mean life-expectancy in 1041 patients treated with CABG was 18 years and 17 years in 856 patients treated with PCI. Important predictors of long-term survival were coronary artery disease complexity, hypertension, diabetes mellitus, nicotine abuse and left ventricular dysfunction. Overall, CABG and PCI demonstrated to be excellent treatment strategies for patients with coronary artery disease treated in the Thoraxcentre of the Erasmus University Medical Centre over 40 years ago.

The current thesis depicts analyses of clinical outcomes after myocardial revascularisation in subgroups of patients randomized to PCI versus CABG in the SYNTAX and EXCEL trials.

AIMS

This thesis provides an overview of the results of contemporaneous revascularisation strategies in patients with three-vessel (3VD) and/or left main coronary artery disease (LMCAD). We sought to distinguish treatment benefits and risk predictors for short-term (<1 year), mid-term (1 – 3 year) and long-term (≥10 year) follow-up in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Furthermore, we assessed the impact of using intraoperative quality assessment tools during CABG that could further improve surgical and patient-related outcomes.

OUTLINE

The short-term outcomes after CABG versus PCI in patients with LMCAD are described in **Chapter 2**, in which the predictive performance of the Society of Thoracic Surgeons (STS) mortality, stroke and length of hospital stay (LOS) risk score models in patients with left main coronary artery disease (LMCAD) undergoing PCI or CABG in in the multicentre randomized EXCEL trial, is reported. This study aimed to elucidate perioperative risk stratification in patients with LMCAD undergoing contemporary revascularisation.

The mid-term outcomes (1 – 3 year) after myocardial revascularisation in patients with LMCAD randomized to PCI versus CABG in the EXCEL trial are examined in **chapter 3** and **chapter 4**. The impact of patient and surgical characteristics, such as left ventricular ejection fraction (LVEF) and the use of bilateral internal thoracic arteries (BITA) during CABG, are assessed in relation to post-operative clinical outcomes. Moreover, **chapter 5** depicts a critical appraisal of the plethora of published meta-analyses on PCI versus CABG in patients with LMCAD and discusses major short-comings of this publication trend.

Long-term outcomes, treatment benefits and risk-predictors after percutaneous versus surgical myocardial revascularisation were assessed in **chapter 6** to **10**. These chapters focus on survival outcomes up to 10-years follow-up and beyond in the investigator-driven SYNTAX Extended Survival (SYNTAXES) study. In **chapter 6**, 10-year all-cause death in patients the randomized to PCI versus CABG in the original SYNTAX cohort (n=1800; PCI=903 vs CABG=897) was analysed . Survival estimates at 10 years were determined in pre-specified subgroups of patients with *de novo* 3VD, LMCAD, diabetes, those without diabetes and according to coronary artery disease complexity defined by the SYNTAX score (low, intermediate and high SYNTAX scores). Additionally, long-term survival was assessed in those patients that were deemed unsuitable for randomization based on their clinical and angiographical characteristics and were therefore included in a PCI nested-registry (CABG-ineligible patients) and a CABG nested-registry (PCI-ineligible patients) (**chapter 7**). In **chapter 8** the impact of performing CABG with the use of multiple arterial grafts versus the use of a single arterial graft (MAG versus SAG) on 12.6-year all-cause death was assessed in patients that underwent CABG in the SYNTAX trial. **Chapter 9** evaluated the effect of PCI and CABG with incomplete versus complete revascularisation and the impact of any residual SYNTAX score on all-cause death outcomes at 10-year follow-up. Finally, the predictive performance of the SYNTAX score on long-term adverse events and vital status after PCI versus CABG is reported in **chapter 10**.

The final two chapters focus on appraising techniques that could further improve outcomes after surgical myocardial revascularisation. The impact of using intraoperative quality assessments by transit-time flow measurements (TTFM) was assessed with a systematic review and meta-analysis in **chapter 11**. Moreover, the multicenter, prospective REQUEST study set out to evaluate the impact of using TTFM in combination with high frequency ultrasound (HFUS) in 1016 patients undergoing CABG. This study (**chapter 12**) aimed to determine the number and type of surgical procedure changes that were made based on intraoperative guidance information using the combination of TTFM and HFUS.

A summary of the current thesis is reported in **chapter 13**, which is followed by the general discussion and conclusion in **chapter 14**. The post-script is described in **chapter 15** to **18**.

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