



# Minimally invasive surgical coronary artery revascularization—current status and future perspectives in an era of interventional advances

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**Abstract:** We are currently witnessing rapid advances in coronary artery disease (CAD) diagnostic- and treatment technology, which include exciting developments in the utilisation of artificial intelligence, stem cell and genetic therapy and pharmacological innovation that complement contemporary percutaneous coronary interventions (PCI) and patient preference for less invasive interventions. Progressive expansion of international CAD treatment guidelines with subsequent changes in referral patterns that favour less invasive interventions, increased patient expectations, industry driven marketing and an increasingly aging population with significant procedural risks, continue to re-define the role of conventional coronary artery bypass grafting (CABG) by sternotomy access in the treatment of CAD. However, the undisputed benefits of CABG over PCI in various clinical scenarios were recently re-confirmed and subsequently resulted in renewed interest in the development and application of less invasive surgical revascularization procedures. Reports by experienced minimally invasive surgical coronary artery revascularization (MISCAR) centres suggest short- and long-term outcomes that are comparable with conventional CABG and created an exciting platform for further MISCAR innovation while contributing to the global initiation of exciting upcoming MISCAR programs. This manuscript outlines the feasibility, current status and preliminary data of recent advances in contemporary CAD diagnostic- and therapeutic technology, provides an overview of the contemporary CAD revascularization decision-making evidence and describe the future perspectives of MISCAR in an era of rapid advances in less invasive CAD prevention-, diagnostic- and therapeutic technology. We trust that this overview will contribute to future research and changes in clinical practice.

**Keywords:** Minimally invasive cardiac surgery; coronary artery revascularization; percutaneous coronary interventions (PCI)

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## Introduction

### Background

We are currently witnessing rapid evolution in coronary artery disease (CAD) prevention-, diagnostic- and therapeutic technology, which include the application of artificial

intelligence- (1-7), nano- (8-19), stem cell- and gene therapy technology (20-37), robotic intervention platforms (38-42), transcatheter coronary intervention technology (43-57), virtual and augmented reality (AR) (58-62) and less invasive surgical revascularization techniques (63-80). The current role of coronary artery bypass grafting (CABG) by conventional

sternotomy access as a preferred therapeutic option in the treatment of CAD is continuously being redefined by a progressive paradigm shift towards less invasive interventions (81,82), patient preferences (83), industry driven marketing and an aging population with higher procedural risks (84,85). The recent reconfirmation of the prognostic- and freedom from major adverse cardiac events (MACE) and other outcome advantages of conventional CABG over modern percutaneous coronary interventions (PCI) in various clinical scenarios (86-106) resulted in renewed interest in surgical revascularization and minimally invasive surgical coronary artery revascularization (MISCAR) techniques (107,108). Experienced MISCAR centres report equivalent outcomes compared to conventional CABG by sternotomy access for single- and multi-vessel CAD and expanded the application of MISCAR in combination with PCI to be a fundamental component of hybrid revascularization (109-112).

### *Rationale and knowledge gap*

The progressive application of MISCAR approaches into routine surgical practice provides exciting less invasive surgical CAD revascularization alternatives within the context of rapid non-surgical diagnostic- and therapeutic technology advances. The potential impact of these new strategies on patient outcomes, patient expectations and on CAD referral patterns are uncertain and it is imperative that current and future cardiac surgeons and interventionists remain aware of technological advances that are influencing and defining future CAD prevention, diagnosis, and treatment.

### *Objective*

This review outlines the recent technological advances in CAD diagnostic and treatment technology, provides an overview of current CAD revascularization decision-making evidence and describes the potential future role of MISCAR in an exciting era of rapid evolution in less invasive CAD prevention, diagnosis and treatment.

## **Advances in diagnostic- and transcatheter CAD treatment technology**

### *Artificial intelligence (AI)*

Various commercially available AI algorithms that detect electrocardiographic changes suggestive of CAD are already in use as wearable- or smartphone-based

application platforms that potentially speed the process of acute cardiac event diagnosis, pre-hospital care, definitive interventions and post-procedural continuity of care (1,2). Baxt and colleagues (3) recently reported the accuracy of an AI algorithm consisting of 40 variables to predict the probability of ischemia with a sensitivity and specificity of 88.1% and 86.2% respectively in 2,204 patients with acute coronary syndrome (ACS). Wu *et al.* (4) reported the sensitivity, specificity, positive- and negative predictive value of AI predicting ACS in 269 patients presenting with chest pain using 42 variables as 90.9%, 93.3%, 76.9% and 97.7% respectively. AI algorithms are also progressively applied in quantifying coronary artery calcification by non-invasive cardiac imaging with reported shortened processing times when compared to operator interpretation (5) and improved correlation in identifying high CAD plaque morphology (6). Apart from AI applications in electrocardiogram (7), external validation of AI are under investigation as increased funding for AI research coincides with rapid development of clinical databases, smartphone and wearable device technology platforms.

### *Nanotechnology*

Nanoscale molecular engineered derivatives of bulk molecules provide increased surface area to volume, modifiable properties, shapes, sizes and compositions as hollow or solid structural platforms (8). Nanotechnology combined with biosensors are currently under investigation to expedite the early detection of CAD biomarkers by high-affinity target molecule binding that amplify the biomarker presence. Almas and colleagues (9) reported on the low cost, simplicity, and ability to identify all relevant ACS biomarkers within the first 4 hours of an event, which may potentially provide favourable prognostic implication by improving quality of ACS detection and meeting healthcare needs in non-specialist healthcare facilities. Nanosized hydroxyapatite- and carbon nanoparticulated coatings provide platforms for improved control of coronary artery stent drug release that enhances endothelialization, reduce restenosis and neo-intimal formation and decreases platelet adhesion (10-16). Electrospun nanosized fibrous scaffolds as synthetic grafts as alternatives to autologous conduits for CABG are also under investigation (17), as is the use of nanotechnology in gene eluting stents (18-21). Despite all the exciting advances, extensive nanotechnology feasibility and outcome studies are required to justify its progression from translational medicine to routine clinical practice.

### *Vascular growth factors and stem cell therapy*

The current application and clinical outcomes of vascular growth factor and stem cell technology in the treatment of CAD were reported in non-randomized and randomized trials (22-32) and confirmed its potential role in establishing controlled angiogenesis to ischemic myocardial regions and in myocardial cell regeneration. Stamm and colleagues (33) described improved left ventricular ejection fraction following injection of mononuclear stem cells within 3 months of the ACS event. Yousef and colleagues (34) reported improved exercise capacity, reduced mortality and image defined scar tissue at 5-year follow-up. Bolli *et al.* (35), Chugh *et al.* (36) and Makkar *et al.* (37) independently suggested that the application of cardiac derived stem cells may improve left ventricle ejection fraction, viable left ventricle mass, improve quality of life, reduce scar mass and improve regional contractility. Stem cell and vascular growth factor technology may become exciting future contributors to CAD treatment once the exact mechanisms of action, the ideal stem cell source, the optimal route of administration and long term safety are better defined.

### *Advances in transcatheter coronary artery interventions technology*

PCI is recognised as one of the ten most significant medical breakthroughs of our century (43), with current 3<sup>rd</sup> generation polymer-based biodegradable drug eluting stents (DES) consisting of cylindrical hollow struts that improved deliverability, flexibility, radial force, radio-opacity, and structural integrity. The incorporation of nano-particle coatings into the connecting elements improve consistent release of antiproliferative- or immunosuppressive drugs compared to previous generations (44-50). Latest 4<sup>th</sup> generation bioresorbable DES, which are fabricated from magnesium-, iron- and zinc alloys (51,52), are designed to progressively degrade with the intention of decreasing vessel size mismatch, chronic inflammation and subsequent late stage thrombosis and restenosis observed with previous generation metallic stent platforms (53). These stents will preserve the options of future surgical or PCI re-vascularization and decrease the risk of late stent thrombosis (54). However, challenging deliverability, increased platelet deposition, increased scaffold fracture risk and rheological disturbances, are amongst 4<sup>th</sup> generation DES short-term concerns (49). DES are currently manufactured by laser cutting, electrode discharge

machining, waterjet cutting, photochemical etching and braiding and knitting techniques, but advanced in AR, 3D printing, and deep learning are already applied to provide lesion specific data that will facilitate patient-specific device design (49,50). This technology will enable the manufacturing of customized stents according to patient-, target vessel- and lesion characteristics (49,53), which will attempt to address the challenges of the unfavourable inflammatory- and subsequent fibrosis-, immunogenicity-, degradation- and cytotoxic processes. Innovative biocompatible smart DES (56) can measure blood flow using wireless miniaturized ultrasonic transducers that transmit and receive information and may potentially prevent restenosis while simultaneously monitoring post-implantation outcomes in real time. The recently reported ISAR-TEST4 trial (57) compared the 10-year clinical outcomes of three generations of limus-eluting stents with different polymer coatings in 2,603 CAD patients, who were randomized to treatment with biodegradable polymer-based sirolimus-eluting Yucon Choice PC<sup>TM</sup> (n=1,299, Translumina, New Delhi, India), permanent polymer-based everolimus eluting Xience<sup>TM</sup> (n=652, Abbott, Illinois, USA) and 1<sup>st</sup> generation permanent polymer based sirolimus eluting Cypher<sup>TM</sup> (n=652, Cordis Corporation, California, USA) stents respectively. The 10-year incidence for MACE were 47.7%, 46.0% and 54.9% for Yukon Choice PC<sup>TM</sup>, Xience<sup>TM</sup> and Cypher<sup>TM</sup> respectively (P=0.003), with mortality reported to be 31.8%, 30.3% and 37.2% respectively (P=0.02). Stent thrombosis occurred in 1.1% of Yukon Choice PC<sup>TM</sup>, 0.8% of Xience<sup>TM</sup> and 2.4%<sup>TM</sup> of Cypher patients (P=0.03). The authors concluded that biodegradable polymer based and 2<sup>nd</sup> generation permanent polymer-based provided comparable clinical outcomes at 10 years, which were significantly superior to 1<sup>st</sup> generation DES.

### *AR technology in catheterization laboratories*

The much-anticipated application of virtual reality and AR technology in modern catheterisation laboratories facilitate live procedural ultrasound, imaging datasets, 3-D anatomy, angiograms and holograms (*Figure 1*) in a virtual mid-air environment through wearable visors (58-61). In conjunction with robotic catheter navigation systems, these systems allow controlled catheter manipulation and micro-movements without constant operator exposure to the routine radiation field. The Corindus-CorPath system obtained FDA approval and was recently acquired by



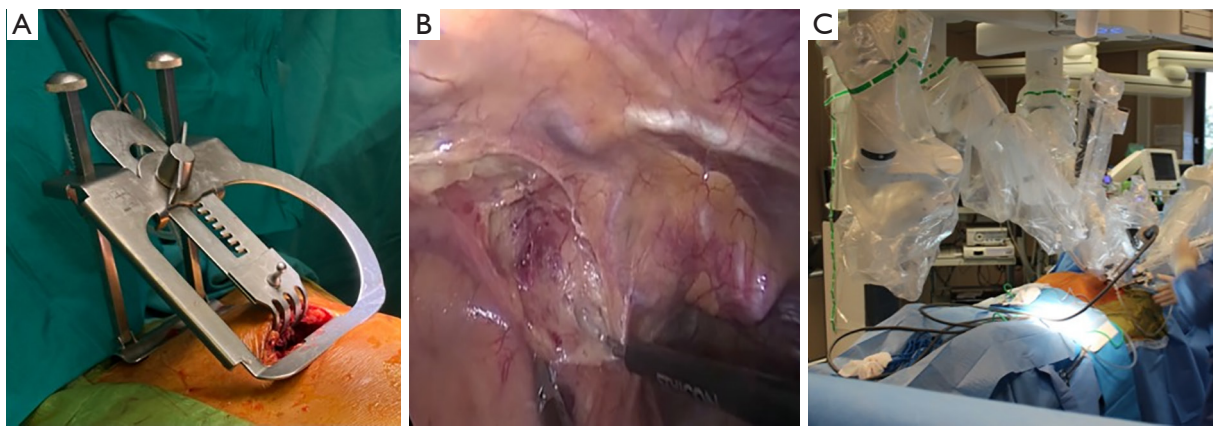
**Figure 1** Virtual reality technology facilitates live procedural anatomy, angiograms, and holograms in a virtual mid-air environment through wearable visors. The Philips Azurion image-guided therapy platform (Phillips, Amsterdam, Netherlands), combined with Microsoft HoloLens 2 mixed reality computing platform (Microsoft, Washington, USA) are under development as a concept for the operating room of the future. The use of this image was approved by the manufacturer (Philips, Amsterdam, the Netherlands) and was not previously published in this format.

Siemens Healthineers (Berlin, Germany), who reported the first neuro-cooling for a cerebral aneurysm in November 2019 using integrated robotic and AR technology. Robotcath (Robocath, Rouen, France) introduced their R-One™ integrated technology in Europe after obtaining European CE mark approval in 2019 and reported their 100% technical procedural success and without MACE in the R-EVOLUTION trial, which was a prospective, multi-centre, single arm pre-clinical study in 62 patients with 64 coronary lesions undergoing elective PCI (62). The integration of AR and robotic technology also facilitate virtual fractional flow reserve (FFR) assessments through computational fluid dynamic algorithms that create virtual mid-air 3-D coronary imaging with FFR measurements for all the vessel segments and allow operators to determine a post-PCI FFR if a vessel was re-expanded to native lumen size by virtually stenting.

### **Advances in coronary artery revascularization evidence**

Contemporary international registries (113,114) confirm

that coronary revascularization by PCI and surgery remain the most commonly performed cardiac procedures. CABG accounts for more than 50% of all cardiac surgical procedures in our current era. The undisputed excellent outcomes of conventional CABG utilizing internal thoracic artery (ITA) to the left anterior descending artery (LAD) and total arterial revascularization of other target vessels within various clinical scenarios and contemporary PCI technology have recently been reconfirmed (86-106). Van den Eynde and colleagues (86) recently performed a Bayesian network meta-analysis of 119 studies to compare early and late outcomes of contemporary coronary interventions in the setting of multi-vessel disease (MVD). They analysed 700,458 patients who underwent PCI (n=213,536), on-pump-CABG (P-CABG, n=438,443), off-pump-CABG (OPCABG, n=44,980) and hybrid coronary revascularization (HCR, n=3,199) with a median follow-up of 2.8 years (interquartile range, 1–5 years). Left mainstem pathology was present in a mean of 7.9% (range, 2.3–23.5%), 19.3% (range, 14.1–25.8%) and 0.1% (range, 0–55.3%) of P-CABG, OPCABG and PCI patients respectively. The EUROSCORE risk profiles were significantly higher ( $P<0.05$ ) in the surgical groups (range, 3.2–7.4%) compared to those in PCI (range, 1.8–3.1%) and HCR (range, 1.5–1.9%). They observed that the mean number of vessels treated were 3.2 (2.9–3.4), 2.8 (2.5–3.1) and 2.9 (2.8–3.0) for P-CABG, OPCABG and PCI interventions respectively, without any difference in early TVR, MACE or major adverse cardiac and cerebrovascular events (MACCE). However, analysis of long-term outcomes identified an increased PCI risk for MACE and MACCE (range, 59% to 79%) compared with the surgical interventions, with PCI presenting increased TVR risk of 203%, 156% and 127% compared to OPCABG, OPCABG and HCR respectively. The authors concluded that surgical revascularization remain superior to PCI after 12 months in patients with MVD for mortality, myocardial infarction, TVR, MACE, MACCE and supported the 2018 combined ESC/EACTS guidelines that advocated surgical revascularization as the preferred strategy in MVD with or without diabetes mellitus. Their findings also concur with meta-analyses of 6 randomised controlled trials (n=6,055) by Sipahi and colleagues (97), who demonstrated a 27% reduction in mortality, 42% reduction in myocardial infarction and 71% reduction in TVR with surgical revascularization compared to PCI. A recent collaborative individual patient pooled analysis of 11 randomized controlled trials involving 11,518 patients by



**Figure 2** Harvesting of the ITA under direct vision (A) or by utilizing endoscopic (B) or robotic technology (C). ITA, internal thoracic artery.

Head (102) concluded that the 5-year all-cause mortality associated with PCI was 11.2%; compared to 9.2% with surgical revascularization. Although these reports suggest that surgery is superior to PCI in MVD, the authors demonstrated that PCI and surgery were comparable in lower SYNTAX scores, which is also appropriately reflected in current revascularization guidelines (81,82). The extended 10-year follow-up of the PRECOMBAT trial (103) concurred with the results of other trials (80,81) and reconfirmed higher repeat TVR with PCI (16.1 *vs.* 8.0%,  $P < 0.05$ ) compared to CABG for left mainstem disease. The composite of death, MI, stroke or ischaemia-driven re-intervention were 29.8% after PCI and 24.7% after CABG (HR 1.25, 95% CI: 0.93–1.69). A secondary analysis of the SYNTAX database with an external validation cohort was performed to validate an updated SYNTAX score II, which compares the relative merits of PCI and CABG over a 10-year period (106). The 2020 SYNTAX score II considers eight prognostic factors and two effect modifiers (three-vessel disease *vs.* left mainstem disease only and anatomical SYNTAX score) to predict both the 5-year risk of MACE (defined as all-cause death, non-fatal stroke or non-fatal MI) and the 10-year mortality risk in patients receiving either PCI or CABG. The implementation of this score in clinical practice will play a key supportive role to compare treatment options based on individual risk estimates.

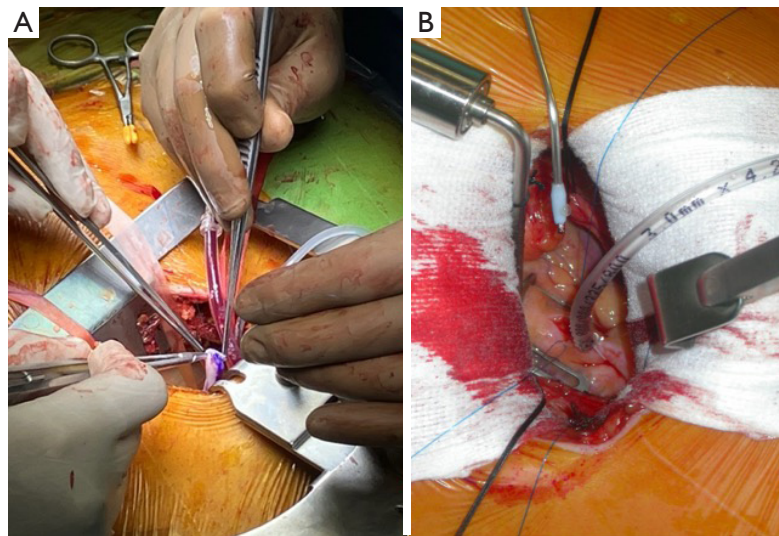
### **New developments in minimally invasive surgical coronary artery revascularization**

The current paradigm shift towards less invasive coronary interventions are paralleled by innovative MISCAR procedural and technological advances that comply

with traditional CABG principles, graft patency, clinical outcomes and patient satisfaction (63–80). Various institutions and collaborative reports now describe innovative variations in robotic- and non-robotic MISCAR techniques, with reports that outline risk reduction strategies for safe implementation of MISCAR programs also emerging (115–121). Harvesting of the left ITA under direct vision (*Figure 2A*) or bilateral ITA using endoscopic (*Figure 2B*) or robotic technology (*Figure 2C*) followed by the construction of ITA to LAD and other target vessel anastomosis under direct vision through a mini-thoracotomy (*Figure 3*) or total endoscopically, with or without the use of cardiopulmonary bypass, are regarded as fundamental components to contemporary MISCAR strategies.

### ***MISCAR healthcare economics compared to conventional CABG and PCI***

The extensive initial capital investment in acquiring hybrid MISCAR operating facilities, robotic- and endoscopic technology (122,123), special retractors and other equipment potentially limit its application, especially in developing countries. Leyvi and colleagues (123) reported no increase in hospitalization or 30-day morbidity-mortality costs between robotic MISCAR and conventional CABG by sternotomy access at their institution. However, same admission hybrid PCI revascularization significantly increased index hospitalization costs ( $P = 0.02$ ). Cohen and colleagues (124) observed that the mean initial procedural- and total hospitalisation costs for MVD or left mainstem CABG by sternotomy access were \$3,415 less and \$10,036 more per patient respectively compared to PCI. However, over the



**Figure 3** Construction of a multi-vessel anastomosis under direct vision through a mini-thoracotomy (A) and off-pump single vessel anastomosis without rib-spreading (B).

subsequent 5 years, higher PCI re-admission rates, TVR and medication cost resulted in significantly higher PCI follow-up costs compared to surgery. With the continuous expansion of complex PCI indications and referral patterns that favour PCI, Jacobson and colleagues (125) utilised linear modelling to estimate the costs of 1,071 elective-, urgent- and emergency PCI complications. The authors observed that the mean unadjusted total costs were  $\$27,865 \pm \$39,424$  and concluded that PCI complication costs present a significant economic burden. Investigations that compare MISCAR economics with the total peri-interventional and long-term costs of protected PCI-procedures using expensive assist device support with its associated complications, chronic total occlusion PCI procedures and technology and the utilisation of costly AR technology as part of routine PCI practice, will provide valuable insight into complex PCI and MISCAR healthcare economics. Non-robotic MISCAR approaches as described by Babliak *et al.* (80,126) and Çaynak *et al.* (127) that utilise re-usable retractor systems gained favour in developing countries despite the lack of favourable cost evidence and are rapidly evolving into the preferred MISCAR approaches in countries with economic restraints.

#### ***The application of MISCAR in multi-vessel disease***

Various innovative MISCAR programs recently reported the extended application of MISCAR to achieve complete

surgical coronary revascularization within the context of MVD. Babliak and colleagues (80,126) described their technique of total coronary revascularization through a left mini-thoracotomy and reported their outcomes in 229 consecutive patients with MVD, of which 20.5% underwent total arterial revascularization. Their multi-vessel grafting technique through a 6–8 cm skin incision and 4<sup>th</sup> intercostal space anterior mini-thoracotomy includes the use of ITA and /or radial arteries, cardiopulmonary bypass, manoeuvres to optimize the operative field, antegrade cardioplegia delivery and aortic cross-clamping. Previous publications from this group reported mean of  $3.1 \pm 0.7$  anastomosis without peri-operative mortalities, myocardial infarctions or sternotomy conversions. Left ITA, right ITA, radial artery and saphenous vein conduits were utilised in 93.5%, 2.4%, 14.7% and 87.0% of patients respectively. Their total procedural-, cardiopulmonary bypass- and cross-clamp times were  $258.8 \pm 43.9$ ,  $135.8 \pm 26.6$ ,  $71.2 \pm 19.4$  minutes respectively, with a mean hospitalization of  $6.3 \pm 1.3$  days. Çaynak and colleagues (127) reported their series of 184 consecutive patients with MVD using a similar MISCAR approach. The left ITA was used in all procedures with a mean of  $3.3 \pm 0.5$  distal anastomosis performed with a mean hospitalization of  $5.1 \pm 1.2$  days. Both authors concluded that MISCAR is safe, feasible and is now considered the routine approach for MVD in their respective institutions without any exclusion criteria. Balkhy *et al.* (72,73,75,77), Bonatti *et al.* (41,65,69,79), Halkos *et al.* (67) and other pioneers

of robotic MISCAR reported their extensive experience in total arterial revascularization, but the cost constraints limit its generalised application at present.

### *The role of MISCAR in hybrid coronary revascularization*

MISCAR provides an excellent platform for HCR (109-112), where the well-established survival benefits of ITA to LAD (71,87,88) are combined with contemporary PCI technology that outperform venous conduits for multi-vessel revascularization of non-LAD lesions. Hybrid coronary revascularization is usually performed within 3 to 5 days following MISCAR, but is also applicable to previous PCI to non-LAD lesions. Experienced centres offer MISCAR using bilateral ITA for total arterial revascularization of the left coronary system combined with PCI of remaining right coronary artery lesions. The MISCAR conduit patency and quality can be assessed during the subsequent PCI procedure and may potentially offer the additional reported benefits of decreased blood transfusion requirements, shorter hospitalization and rapid regain of preoperative functional status. Hage and colleagues (109) performed a propensity matched comparative analysis between 216 and 147 patients who underwent multi-vessel OPCABG and HCR respectively and noticed no difference in peri-operative stroke, myocardial infarction, re-exploration for bleeding, blood transfusion requirements, in-hospital mortality or length of intensive care admission between the groups. Peri-operative re-intervention rate was lower with OPCABG (0% *vs.* 3.4%;  $P=0.03$ ), while HCR was associated with decreased prolonged ventilation rates (0.7% *vs.* 4.0%,  $P=0.02$ ) and length of hospitalization ( $4.5\pm 2.1$  *vs.*  $8.1\pm 5.8$  days,  $P<0.001$ ). HCR was also associated with improved long-term survival (96% *vs.* 85%,  $P=0.054$ ) and freedom from angina (90% *vs.* 73%,  $P<0.001$ ) with similar freedom from reintervention between HCR and OPCABG (92% *vs.* 91%,  $P=0.80$ ) after a mean follow-up of 81 months (range, 48–113 months) and 96 months (range, 53–115 months) for OPCABG and HCR respectively. The authors concluded that HCR provides faster peri-operative recovery rates and comparable short- and long-term outcomes to OPCABG. A propensity matched analysis by Giambruno (110) of 682 and 147 patients who underwent multi-vessel P-CABG and HCR respectively, reported similar conclusions. Reynolds and colleagues (111) concluded from an HCR and conventional CABG comparative meta-analysis that included 25 studies that the potential benefits of HCR are paralleled by significantly

increased in-hospital costs compared to CABG. Ganyukov and colleagues (112) randomized 155 consecutive multi-vessel CAD patients to CABG, HCR or multi-vessel PCI and concluded that residual angina and MACCE were similar at 12-month follow-up, with multi-vessel PCI providing shortest hospitalization and return to work duration. The authors did not identify any midterm indication of HCR value compared to CABG or PCI in isolation and encouraged longer follow-up. Whether HCR will impact patient preference, referral patterns and health resource utilization will be determined further investigations.

### *Extended application of MISCAR in refractory coronary ischemia*

MISCAR may also facilitate the creation of trans-myocardial channel revascularization by laser technology in patients with complex patterns of diffuse CAD with no options of non-surgical or surgical revascularization (128-132). Multiple randomized controlled trials, augmented by recently available long-term results, have validated the safety, effectiveness, and substantially improved health outcomes through the application of this technology used in isolation (129) or as an adjunctive therapy (130,131) to achieve more complete revascularization in selected patients with severe residual angina resulting from diffuse disease progression. Bridges and colleagues (132) formulated recommendations for the appropriate therapeutic application of TMR following the format of the American Heart Association and American College of Cardiology guidelines and identified class I indications for TMR as sole therapy and IIA for as an adjunct to CABG with various levels of evidence. They concluded that TMR may be an acceptable form of therapy for selected patients with refractory angina or when complete revascularization cannot be achieved surgically and has subsequently been endorsed by the Society of Thoracic Surgeons in the USA.

### *Robotic- vs. non-robotic MISCAR outcome reporting*

Comparative outcomes between MISCAR and CABG by sternotomy access are well described (133-135) and current research is now directed at comparing the outcomes of the various MISCAR approaches (136-138). Non-robotic MISCAR approaches utilise special retractor systems or endoscopic camera technology for ITA harvesting under direct vision or under endoscopic guidance respectively.

Direct vision MISCAR often require larger skin incisions to facilitate both ITA harvesting and multi-vessel anastomosis through as single working port, which may result in costal-cartilage dislocation, fractures, limited ITA visualization and potential shorted ITA lengths (136) compared to the full-length ITA visualization achieved with multi-port endoscopic and robotic MISCAR approaches. Gofus and colleagues (137) performed a retrospective propensity matches comparison of 735 patients who underwent MISCAR by direct vision (n=603) and by robotic assistance (n=132) and identified no difference in peri-operative complications or all-cause mortality (mean follow-up 5.6 years). However, they observed that post-operative blood loss (300 *vs.* 450 mL, P=0.002), artificial ventilation time (6 *vs.* 7 hours, P=0.018) and hospitalization (6 *vs.* 7 days, P=0.001) favoured robotic MISCAR and concluded that robotic technology provided attractive advantages over non-robotic MISCAR approaches.

### **Future perspectives in minimally invasive surgical coronary revascularization**

Various expert centres currently perform MISCAR without exclusion criteria as a routine for all isolated surgical coronary revascularization and encouraged upcoming programs to partner with experienced institutions to overcome the well described learning curves while ensuring uncompromising quality control and maintaining excellent clinical governance (115-120). However, various studies question the validity of MISCAR as a new “gold-standard” revascularization alternative to conventional OPCAB by sternotomy access (133-135). Rogers and colleagues (134) randomized 93 patients to OPCAB and 91 patients to MISCAR at 2 institutions and observed that MISCAR was associated with longer mean operative times (4.1 *vs.* 3.3 hours), fewer 3-vessel revascularization (2% *vs.* 17%), shorter mean intubation time of 65 minutes (P=0.017), higher analgesia requirement, poorer lung function at discharge and a 10% higher average cost compared to OPCAB by sternotomy access. Florisson and colleagues (135) emphasised the potential increased risk of incomplete revascularization (29% *vs.* 0%) and re-admission within 3 months (20.0% *vs.* 2.0%) observed with MISCAR compared to OPCAB and concluded that MISCAR is associated with increased morbidity compared to OPCAB without mid-term mortality difference. Progressive robotic- and non-robotic MISCAR skills development, cadaveric and simulation training, team visits to established

MISCAR providers, familiarity with risk reduction strategies and careful patient selection, are regarded as important components of initiating a safe and sustainable MISCAR program. Pettinari and colleagues (107) reported a rapid increase in robotic MISCAR programs in Europe and recommended active participation in robotic MISCAR registries (138). There is no doubt that the application of MISCAR will continue to develop as a preferred revascularization alternative or as an adjunct to PCI. The learning curves associated with MISCAR (115-120), complex PCI (139,140) and the reported correlation between high procedure volume and favourable clinical outcomes that safely maintain these programs (141,142) are well described. As both surgical and transcatheter coronary artery interventions are progressively becoming less invasive and increasingly complex within the context of an aging and higher risk patient profile, suggestion by experienced cardiovascular interventionists to redesign training of future coronary operators as a sub-speciality or “hybrid coronary surgeon-interventionists” in the extensive knowledge and technical surgical/interventional skills required, may potentially be justified (143). The future of coronary artery revascularization is exciting and will most likely be shaped by a collaborative MISCAR-PCI partnership.

### **Strengths and limitations**

This manuscript provides a comprehensive and in-depth overview of contemporary advances in the treatment of CAD with special emphasis on the rapid expansion and future application of MISCAR approaches. No meta-analyses checklist systems were utilised and the risk of bias for each included reference were not subjected to PRISMA 2020 analysis.

### **Conclusions**

We are currently witnessing rapid advances in CAD treatment technology and techniques that will incorporate MISCAR, PCI, nano, stem cell and pharmacotherapeutics in combination or as isolated interventions as new evidence emerge. The renewed interest in the re-established benefits of CABG over PCI and the introduction of MISCAR into routine clinical practice, suggest a continuous favourable evolution and future for surgical revascularization. Significant multidisciplinary collaborative efforts will continue to develop multi-faceted and novel CAD treatment strategies at reduced costs and with sustained



continued efforts, the future for MISCAR as a fundamental component in CAD therapeutics is promising.

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