Percutaneous complete revascularization strategies using sirolimus-eluting biodegradable polymer-coated stents in patients presenting with acute coronary syndrome and multivessel disease: Rationale and design of the BIOVASC trial

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on Behalf of the BioVasc Trial Investigators

Background Complete revascularization in patients with an acute coronary syndrome and multivessel disease is superior compared to culprit-only treatment. However, it is unknown whether direct complete or staged complete revascularization should be pursued.

Methods The BIOVASC study is an investigator-initiated, prospective, multicenter, randomized, 2-arm, international, open-label, noninferiority trial. We will randomize 1,525 patients 1:1 to immediate complete revascularization (experimental arm) or culprit-only plus staged complete revascularization (control arm). Patients will be enrolled in approximately 30 sites in Belgium, Italy, the Netherlands, and Spain. The primary end point is a composite of all-cause mortality, nonfatal myocardial infarction, any unplanned ischemia-driven revascularization (excluding staged procedures in the control arm at the predetermined time), and cerebrovascular events (MACCE) at 1 year post index procedure.

Conclusions The BIOVASC study aims to further refine the treatment algorithm for acute coronary syndrome patients with multivessel disease in terms of optimal timing for complete revascularization (Clinicaltrials.gov NCT03621501). (Am Heart J 2020;227:111-117.)

Invasive coronary angiography followed by percutaneous coronary intervention (PCI) is the treatment of choice in patients presenting with ST-segment elevation myocardial infarction (STEMI)[1] and non–ST-segment elevation acute coronary syndrome (NSTE-ACS).[2] Up to 60% of these patients have multivessel disease (MVD).[3-5] Patients with STEMI have less ST-segment resolution upon recanalization and a worse prognosis when they have MVD compared with single-vessel disease.[6,7] Initial retrospective data in STEMI patients with MVD suggested a lower mortality for culprit-vessel PCI only versus multivessel PCI.[8] However, since then, several randomized controlled trials (RCTs) have shown that complete revascularization is superior to culprit-only revascularization in terms of major adverse cardiac events (MACE).[9-12] This was mainly driven by softer end points, namely, revascularization or angina, but not hard end points like myocardial infarction or death. The recently published COMPLETE trial demonstrated for the first time also a benefit in a primary combined end point of cardiac death

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or repeat myocardial infarction in patients undergoing staged complete revascularization (SCR) as compared to a culprit-only strategy in STEMI patients.[13] The aforementioned studies on this topic, however, did not primarily focus on the timing of complete revascularization, namely, immediate versus staged. The potential benefit of immediate complete revascularization (ICR) during the index procedure remains therefore unclear. The 2017 European Society of Cardiology (ESC) STEMI-ACS guidelines granted a class II, level of evidence A, indication for routine complete revascularization in patients with STEMI and MVD[1] but did not specify when to treat nonculprit vessels. Although the 2015 ESC NSTE-ACS guidelines did not specifically advise a culprit-only or multivessel PCI strategy,[2] the 2018 guidelines on myocardial revascularization stated that complete revascularization of significant lesions should be attempted in patients with NSTE-ACS and MVD.[14] Furthermore, they suggested 1-stage complete revascularization because this strategy improved the primary composite end point of clinical events at 1-year follow-up in the SMILE study.[15]

Upon this background, we designed the "Percutaneous Complete Revascularization Strategies Using Sirolimus-Eluting Biodegradable Polymer-Coated Stents in Patients Presenting With Acute Coronary Syndrome and Multivessel Disease" (BIOVASC) Trial (Clinicaltrials.gov NCT03621501). BIOVASC aims to further refine the treatment algorithm for ACS patients (STEMI and NSTE-ACS) with MVD in terms of optimal timing for complete revascularization. Patients will be randomized 1:1 to either (1) ICR during the index procedure or (2) culprit-only PCI plus SCR within 6 weeks after the index procedure.

Methods

Study design

The BIOVASC study is an investigator-initiated, prospective, multicenter, randomized, 2-arm, international, open-label, noninferiority trial. Patients will be 1:1 randomized to ICR (experimental arm) or culprit-only plus SCR (control arm). Patients will be enrolled in approximately 30 sites in Belgium, Italy, the Netherlands, and Spain. The respective local Ethical Committees approved the protocol. The study will be conducted according to the Declaration of Helsinki, ISO 14155, and 21CFR Part 11. International Conference on Harmonisation-Good Clinical Practice will be used as guidance.

Study population

All patients between 18 and 85 years old who present with STE-ACS or NSTE-ACS (including unstable angina and non–ST-segment elevation myocardial infarction [NSTEMI]) and accepted for PCI will be screened.

Inclusion and exclusion criteria

General inclusion and exclusion criteria are depicted in Table I. Of note, only patients with MVD and a clear culprit lesion are eligible for enrolment, and culprit lesion identification in NSTE-ACS patients will be based on previously reported criteria.[2] Significant coronary artery disease is defined as at least 70% stenosis in a vessel $\geq$2.5 mm by visual estimation or positive coronary physiology testing. Invasive coronary imaging assessment is per operator's discretion. Exclusion criteria comprise prior coronary artery bypass surgery, cardiogenic shock defined as previously described,[16] and presence of a chronic total occlusion.

Informed consent

All patients must give informed consent prior to enrolment in the study. In the event that the patient is unable to provide written informed consent because of acute setting, an initial verbal consent from the patient could be obtained. If a patient is providing verbal consent, an impartial witness must be present during the entire informed consent discussion. Where a patient has initially verbally consented, written consent should be sought from the patient as soon as the patient is capable of signing the consent form.

Randomization

Patients are deemed enrolled into the trial after randomization and treatment assignment using a Web-based randomization module. After informed consent has been obtained and after the diagnostic angiogram has confirmed multivessel disease with a clear culprit but prior to PCI, patients will be randomized using random block size randomization, with lower boundary of 4 and upper boundary of 8. Furthermore, patients are stratified according to hospital.

Treatment

Figure 1 depicts the flowchart of the study. In the immediate complete arm, upon treatment of the culprit lesion, PCI is attempted in all other lesions that are deemed significant during the index procedure. In the control arm, only the culprit lesion will be treated during the index procedure, and other lesions that are deemed significant will be addressed at a later stage either during the index hospitalization or through an elective readmission within 6 weeks of the index procedure. Timing for the staged intervention needs to be documented at the end of the index procedure. Additional invasive coronary imaging is at the operator's discretion.

To avoid bias related to the use of different stent platforms, coronary stenting will be performed with the Orsiro platform (Biotronik AG, Bűlach, Switzerland). The ORSIRO DES has ultrathin cobalt chromium struts of 60-80 μm (depending on stent size) with a bioabsorbable polymer coating releasing sirolimus..[17,18]

Antithrombotic regimen after the index procedure is per treating physician's discretion but should conform to the most recent ESC guidelines for STE-ACS and NSTE-ACS.[1,2] In particular, dual antiplatelet therapy is

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 y and ≤85 y • Presentation with ACS (UA, NSTEMI, or STEMI) • The patient is an acceptable candidate for treatment with a drug-eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, manufacturer's Instructions for Use, and the Declaration of Helsinki. • Patient indication, lesion length, and vessel diameter of the target lesion(s) are according to the "Instructions for Use" that comes with every Biotronik Orsiro (sirolimus-eluting stent) system. • The patient is willing and able to cooperate with study procedures and the required follow-up visits. • The subject or legal representative has been informed of the nature of the study and agrees to its provisions and has provided an EC-approved written informed consent, including data privacy authorization.	• Age <18 y and >85 y • Single coronary artery disease • If it is unclear which lesion is the culprit lesion • Patients in cardiogenic shock • Patients who cannot give informed consent or have a life expectancy of less than 1 y • Absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to any of the study medications, including both aspirin and P2Y12 inhibitors • Enrolment in another study with another investigational device or drug trial that has not reached the primary end point. The patient may only be enrolled once in the BIOVASC study • PCI in the previous 30 d • Presence of a chronic total occlusion • Previous CABG • Women of childbearing potential who do not have a negative pregnancy test result within 7 d before the procedure and women who are breastfeeding • Planned surgery within 6 m after PCI unless dual antiplatelet therapy is maintained throughout the perisurgical period

UA, unstable angina; *CABG*, coronary artery bypass surgery.

recommended for 12 months after the index procedure in patients without indication for anticoagulation. Ischemic and bleeding risk should be considered in particular in case of patients with atrial fibrillation and need of anticoagulation therapy as per current guidelines.[19]

Given the trial design, both physicians and patients cannot be blinded to treatment allocation.

Follow-up

Patients will be followed up to 5 years after the index procedure. This will include a clinic visit at 30 days and 12 months and telephone contact at 2 and 5 years to obtain clinical information comprising vital status, cardiovascular drug use, repeat hospitalization, revascularization procedures, myocardial infarction, and cerebrovascular events.

End points

The primary end point is a composite of all-cause mortality, nonfatal myocardial infarction, any unplanned ischemia-driven revascularization (excluding staged procedures in the control arm at the predetermined time), and cerebrovascular events (MACCE) at 1 year post index procedure. The secondary end points include MACCE at 30 days and at 2 and 5 years, individual components of the composite primary end point at 30 days and at 1, 2, and 5 years, (3) probable/definite stent thrombosis, target vessel revascularization any clinically relevant bleeding (not related to coronary artery bypass grafting; Bleeding Academic Research Consortium (BARC 3 and 5)) at 30 days and 1 year, safety and efficacy of ICR in patient subgroups with specific demographics, clinical indications, and/or vessel or lesion characteristic, net adverse clinical events at 30 days and 1 year (composite of major bleeding BARC 3 and 5 and all-cause mortality, MI, and stroke), need for renal replacement therapy at 30 days, and quality of life at 30 days and 1 year using the Seattle Angina Questionnaire and the EQ5D5L.

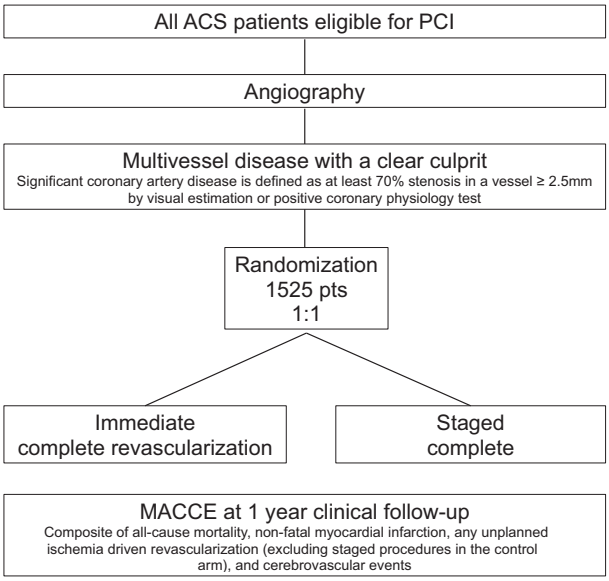
Statistical considerations

Sample size calculation. We assumed that a complete revascularization with a residual syntax score ranging between 5 and 10 will be associated with an 11% incidence of the primary end point in patients randomized to SCR and 10.5% in patients randomized to ICR.[20] The enrolment of 1,486 patients (743 patients per arm) would provide a power of 80% at a 2-sided α level of .05 to demonstrate noninferiority of ICR as compared to SCR, with an absolute noninferiority margin of 4.0%. With respect to a 2.5% attrition rate, we thus plan to enroll a total of 1,525 ACS patients.

Significance testing

We will apply a hierarchical testing strategy. We will first test noninferiority of ICR as compared to SCR. Subsequently, if criteria for noninferiority are met, we will test superiority for ICR as compared to SCR. Noninferiority is met if the upper boundary of the 2-sided 95% CI of the difference in the incidence of MACCE between SCR and ICR is less than 4.0% in favor of SCR. All statistical tests are

Figure 1



Study flowchart.

2-sided and will use a significance level of $\alpha = .05$. CIs will be presented with 95% degree of confidence.

Data distribution and model checking. For the analysis of dichotomous data, χ^2 tests (with continuity correction) will be used, presented with the 95% CI for the difference in proportions (normal approximation, large sample theory). If expected cell frequencies are small (less than 5), then Fisher exact tests will be used instead. For the analysis of continuous data that were measured at 1 point in time, 1-way analysis of variance (ANOVA) and unpaired Student *t* tests will be used. For the analysis of continuous data that were repeatedly measured over time, 2-way ANOVA and paired Student *t* tests will be used. If the assumptions underlying ANOVA (normal distributions of residuals, homogeneity of variances) or Student *t* tests (normal population distribution, particularly relevant for small samples) are not satisfied, then nonparametric tests will be applied instead. The incidence of end point events over time will be studied by the method of Kaplan-Meier. It is assumed that the censoring is not linked to factors which are associated with the (event-free) survival time variable and that the individuals censored at any time are representative of those individuals at risk of an end point event at that time (ie, the censoring process is assumed to be uninformative). If the number of censored cases seems high, then this assumption will be explored. The log-rank test will be used to study differences in the incidence of end point events over time in relation to allocated treatment. For the analysis of the relation between allocated treatment and the incidence of study end points, Cox proportional hazards (PH) regression model will be applied. The PH assumption will be assessed by visual judgment of the log-minus-log (event-free) survival plots.

Statistical analyses

Statistical analyses will be performed by an independent statistician unaware of the treatment arm assignments until the analyses have been completed and according to the statistical plan.

All efficacy analyses will be performed for the intention-to-treat (ITT), per-protocol, and as-treated populations. The ITT population is considered the main analysis population.

For the primary efficacy analyses, the following parameters/statistics will be determined for each of the comparator groups:

- Total number of primary efficacy end point events; total sum of the follow-up (years) since randomization until the incidence of the primary efficacy end point
- The incidence rate of the primary end point, which is defined as the number of primary efficacy end point events divided by the total sum of the follow-up
- The cumulative event-free survival for the primary efficacy end point as well as the cumulative incidence.

The relation between randomly allocated treatment and the incidence of the primary efficacy end point will be described by:

- The difference in cumulative event-free survival as well as the difference in cumulative incidence

- A crude, unadjusted hazard ratio. Cox PH regression analysis will be conducted with randomly allocated treatment as independent predictor variable and the incidence of the primary efficacy end point as dependent outcome variable.
- Adjusted hazard ratios. Two multivariable Cox PH regression analyses will be applied. In the first model, the effect of randomly allocated treatment will be adjusted for age and gender only. In the second model, the effect of randomly allocated treatment will be adjusted for age, gender, body mass index, diabetes, heart failure, renal insufficiency, type of ACS, 2- or 3-vessel disease, and number of stents, whereas a generalized estimating equation will be used for the estimation of model parameters, taking into consideration that observations in subjects who are recruited in the same hospital might not be entirely independent.

Prespecified main subgroup analysis for the primary end point will comprise age (<70 vs ≥70 years), gender, ACS (STE-ACS vs NSTE-ACS), diabetes (insulin dependent versus non–insulin dependent versus no diabetes), culprit artery (left anterior descending artery vs circumflex artery vs right coronary artery). Additional exploratory subgroup analysis will include evaluation of number of stents (2 stents, or 3 or more stents), stent length, presence or absence of chronic kidney disease, body mass index (<18.5, 18.5-24.9, 25-30, and >30 kg/m^2), syntax score analysis, treatment during office hours versus out of office hours, and 2- versus 3-vessel disease.

Monitoring

Site monitoring. Each site will be visited for monitoring 2 times, starting as soon as possible after the first patient has been enrolled. These site monitoring visits will be conducted to monitor compliance with the Clinical Investigation Plan and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. A prespecified 25% of included patients will be monitored. The monitor will perform source data verification by reviewing original patient documentation.

End point adjudication process. An independent Clinical Events Committee (CEC) of medical experts will review all specific serious adverse event data to adjudicate primary and secondary end points. The members of the CEC will not be participating in the trial as principal or co-investigators. The committee membership will include expertise in (interventional) cardiology, cardiac surgery, electrophysiology, and neurology. All patient identifiable data will be anonymized for the CEC members.

Data Safety Monitoring Board. The Data Safety Monitoring Board (DSMB) is composed of an odd number of members (physicians from the fields of cardiology and interventional cardiology and 1 biostatistician), who are not directly involved in the conduct of the trial. The DSMB will review the study on a periodic basis. Based on the safety data, the DSMB may recommend modifying or stopping the trial. Final decisions regarding trial modifications will be taken within the Steering Committee.

Funding

This is an investigator-initiated study. The Erasmus University Medical Center in Rotterdam is the sponsor of the trial. Biotronik AG granted an unrestricted research grant to the sponsor.

Biotronik AG has not been involved in the trial design and will have no role in the collection, analysis, and interpretation of data or in the manuscript preparation.

The study investigators have sole access to the raw study data and are responsible for all study-related analyses, conclusions, and manuscript drafts.

Discussion

The BIOVASC study will evaluate whether ICR is noninferior to SCR in patients with an ACS and MVD. Staged complete revascularization is defined as treatment of nonculprit lesions within 6 weeks after treatment of the culprit lesion during index procedure. We expect no relevant differences due to timing in the SCR arm, which was confirmed by the COMPLETE timing substudy where treatment of nonculprit lesions during index hospitalization or after discharge but within 45 days had similar beneficial effects on both co-primary end points.[21]

So far, timing for complete revascularization has been underrepresented in the literature yet seems clinically relevant. Immediate complete revascularization during an index procedure precludes the need for repeated arterial catheterization with its inherent risk of vascular and bleeding complications and additional cost. It may prevent early ischemic events from remaining potentially unstable significant coronary lesions. Furthermore, ICR may relieve potential anxiety in a patient who is cognizant of lingering significant coronary artery disease that needs planned treatment at a later stage. Conversely, ad hoc complete revascularization may come with more procedural contrast and radiation exposure. Vasomotor dysregulation, hyperadrenergic state, and impaired microcirculation may result in overestimation of coronary lesion severity and consequent overtreatment of hemodynamically nonsignificant disease. In addition, the prothrombotic milieu during ACS may theoretically increase the risk for coronary and stent thrombosis and procedure-related MI.

Three small RCTs not powered for clinical outcomes reported no differences between immediate or SCR in patients with STEMI and MVD.[22-24] Ochala et al did show a significant increase in left ventricular function on echocardiogram at 30 days in immediate complete versus

staged complete. However, at 6 months, this effect had faded.[23] One randomized trial in patients with NSTEMI suggested favorable clinical outcome with an immediate complete strategy, mainly driven by fewer target vessel revascularizations.[15] Several retrospective studies investigated timing of complete revascularization in STEMI patients,[25-27] showing an increased mortality in the ICR group. A pairwise and network analysis including 4 prospective and 14 retrospective STEMI studies reported higher mortality with immediate multivessel PCI versus culprit-only or staged complete PCI.[28] Two other meta-analyses by Tarantini et al and Li et al confirmed this clinical penalty for immediate complete PCI versus culprit-only or staged complete in STEMI.[29,30] Conversely, other meta-analyses demonstrated lower rates of recurrent MI with immediate versus staged complete PCI.[31,32] Another meta-analysis including only 4 randomized trials with STEMI or NSTEMI patients suggested more repeat revascularizations and a trend toward more MACE with staged versus immediate complete PCI.[33] Taken together, there are limited data with conflicting outcomes about timing of complete revascularization in patients with ACS and MVD. Larger randomized controlled trials are therefore warranted.

BIOVASC aims to provide further insights into the clinical implications of ICR across the entire ACS spectrum, to evaluate different effects in STEMI versus NSTEMI, and also to explore the impact of revascularization timing on early and late quality of life. The iMODERN (NCT03298659) and MULTISTARS AMI (NCT03135275) are both also investigating timing of complete revascularization. However, in both studies, only patients with STEMI and MVD are included. The iMODERN will randomize 1,146 patient in 1:1 way to immediate iFR-guided complete revascularization or a staged magnetic resonance imaging perfusion-guided complete revascularization within 6 weeks after STEMI. Primary end point is a composite of all-cause death, recurrent MI, and hospitalization for heart failure at 1 year. The MULTISTARS AMI intends to randomize 700 patients with STEMI to immediate or SCR. Primary end point is a composite of all-cause death, nonfatal myocardial infarction, unplanned ischemia-driven revascularization, hospitalization for heart failure, and stroke at 1 year.

In conclusion, there is now compelling evidence in favor of complete multivessel revascularization rather than culprit vessel only in patients with STEMI and MVD. BIOVASC aims to further refine this paradigm and focuses on the timing to achieve complete revascularization not only in the STEMI population but across the entire ACS spectrum.

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