Coronary computed tomography angiography in planning of percutaneous coronary interventions in bifurcation lesions – study design and rationale

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Abstract

Percutaneous treatment of coronary bifurcations is a complex issue due to numerous possible techniques and high risk of complications. Because of increasing interest in non-invasive imaging in interventional cardiology and growing quality of obtained images, we designed a prospective, randomized, single-blinded trial to evaluate the role of coronary computed tomography angiography (CCTA) in the planning of percutaneous coronary interventions (PCI) of bifurcation lesions. Eighty eligible patients scheduled for PCI of bifurcations in stable coronary artery disease will undergo additional CCTA examination and will be randomized 1 : 1 to either planning of PCI using angiography and CCTA or to PCI planning with use of angiography alone. Primary endpoints will include PCI strategy (one or two stents), technique, size of implanted stents and direct angiographic effect of the procedure. Immediate PCI effect measured with intravascular ultrasound (IVUS) and the effect on fractional flow reserve (FFR) in the side branch (in a subgroup of patients), as well as plaque morphology assessed in CCTA, patient radiation exposure and amount of contrast will be compared in secondary analysis. The study is intended to clarify the influence of CCTA analysis on the technique and direct effect of PCI of bifurcations and to provide evidence on the relevance of performing a CCTA scan prior to PCI of bifurcation lesions.

Key words: computed tomography, bifurcations, planning, coronary interventions.

Introduction

Percutaneous coronary interventions in bifurcation lesions are the most challenging procedures due to their complexity and higher risk of adverse effects, including in-stent restenosis and stent thrombosis [1]. On the other hand, a bifurcation is involved in about 20% of all PCI, which means that the issue of its optimization remains fundamental [2]. Several possible techniques are used, including provisional side-branch stenting, spot stenting, T-stenting, culottes, V-stenting, crush stenting, etc. Moreover, there is a growing number of dedicated bifurcation devices. Since provisional stenting technique with one stent is commonly advised as a first-line approach [3], in some cases it may lead to side branch (SB) compromise and the need for second stent implantation, which is considered non-inferior in terms of adverse effects [4]. To date, no universal protocol of performing PCI in bifurcations is available. Procedure planning is routinely based on visual estimation of angiography, sometimes facilitated by quantitative coronary analysis (QCA) software.

Coronary computed tomography angiography (CCTA) is a diagnostic modality of growing recognition in coronary artery imaging, characterized by high sensitivity and specificity in the diagnosis of lesion severity. The advantages of CCTA in comparison with angiography (CA) include the possibility of assessing the vessel wall (instead of the lumen only), detection of vessel remodeling, analysis of calcification pattern and visualization of distal segments of chronically occluded vessels. Estimation of lumen compromise in non-calcified lesions may be more reliable in CCTA than in CA, which was suggested in studies using intravascular ultrasound (IVUS) [5]. Coronary computed tomography angiography also provides better insight into the morphology of overlapping and crossing vessels in comparison with angiography. Sensitivity and specificity of CCTA in detection of significant bifurcation lesions were assessed in comparison with CA as 96% and 99% respectively [6]. The CCTA classifies bifurcations into Medina subtypes as precisely as angiography and has even better performance in assessment of the angle between the main branch (MB) and SB [7].

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Studies carried out to date suggest that analysis of CCTA in the process of planning of bifurcation PCI may reveal additional information helpful in PCI planning and influencing the result of the procedure as assessed by IVUS. It has been suggested that analysis of CCTA before stenting of "simple" lesions influences the strategy leading to better lesion coverage and stent deployment [8-10].

There are no reliable data on the assessment of the role of CCTA in planning of bifurcation stenting. The majority of these procedures are planned on the basis of coronary angiography, sometimes, especially in cases involving the left main stem, accompanied with IVUS [11]. Coronary computed tomography angiography, which is less expensive and less invasive in comparison to IVUS, to some extent may be regarded as a surrogate of IVUS.

The final effect of PCI can be quantitatively measured with angiographic parameters, including minimal (in-stent) lumen diameter, reference lumen diameter and lumen diameter at the ostium of SB. More reliable assessment of the direct effect of stenting can be done using IVUS, by measuring in-stent lumen areas, reference lumen areas, residual plaque burden and possible acute complications such as stent malapposition, which may need optimization to ensure a good long-term outcome. Another method of assessment of stenosis severity is fractional flow reserve (FFR) [12], giving information on the physiological effect of the vessel narrowing. Fractional flow reserve measurement after stent deployment provides data on the residual functional vessel compromise [13].

Since there are no data on the role of CCTA in planning of bifurcation stenting and its impact on the direct effect of PCI, we designed a prospective randomized single-center pilot study to evaluate whether the assessment of CCTA together with angiography at the stage of planning PCI of bifurcations affects the technique and the direct effect of stenting.

Study design

Single-center, single-blinded, prospective, randomized clinical trial.

Hypotheses

1. Additional assessment of CCTA prior to PCI of coronary bifurcation lesion will influence the PCI technique and choice of stent parameters.
2. Additional assessment of CCTA prior to PCI of coronary bifurcation lesion will lead to better immediate effect of stenting, as assessed with quantitative angiographic parameters, IVUS and FFR in comparison to CA-planned PCI.

Study population

Inclusion and exclusion criteria are shown in Table 1. Figure 1 describes the study flowchart. The study is approved by the local ethics committee and will be performed in accordance with the Helsinki II Declaration. All the participants will sign informed consent.

Study endpoints

1. Primary endpoints:
   a) PCI strategy (single-vessel vs. two-vessel stenting);
   b) PCI technique (provisional stenting, culottes, crush, spot, etc.);
   c) Size and type of implanted stents;
   d) Direct angiographic PCI effect described as minimal lumen diameter in MB and SB;
   e) Difference in TIMI Frame Count (TFC) between pre- and post-PCI angiograms in MB and SB. Details on the TFC calculation are described further.
2. Secondary endpoints:
   a) Immediate PCI effect measured by IVUS (e.g. MLA, stent expansion, reference plaque burden, etc.);
   b) Functional effect of PCI on the blood flow in SB measured by FFR;
   c) Correlation between plaque morphology in CCTA and modification of PCI technique;
   d) Amount of contrast used and patient radiation exposure;
   e) PCI strategy, technique and stent parameters analyzed as eventually performed;
   f) Frequency of preliminary strategy change during PCI procedure.

Study procedures

Analysis of coronary angiography

Quantitative analysis of the diagnostic coronary angiography used for PCI qualification will be performed in all included patients. QCA software will be used to assess the target bifurcation lesion. The following parameters will be determined in every patient:

- Bifurcation classification according to Medina;
- Angle between MB and SB;
- Lesion length in MB and SB;
- Plaque morphology and localization in relation to SB;
- Lumen diameters in selected sites of bifurcation (Figure 2);
- TIMI flow in MB and SB;
- TFC in MB and SB.

Methods of assessment of TIMI and TFC have been described elsewhere [14, 15]. The method of TFC assessment will be modified to meet the requirements of bifurcation lesions. TIMI Frame Count for the main branch and side branch will comprise the number of frames required for the contrast to pass from the ostium of the artery to the selected distal landmark. For both branches the proximal landmark will be the first frame in which dye fully enters the artery with the analyzed bifurcation (LM, LAD, Cx or RCA). For MB and SB the most distal, yet clearly identifiable branch distal to the bifurcation will be selected as a distal landmark.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Planned PCI of bifurcation in unprotected coronary artery
2. Diameter of side branch > 2 mm
Exclusion criteria
1. Persistent atrial fibrillation or other arrhythmia
2. Allergy to contrast medium
3. GFR < 50 ml/min
4. Two or more diagnostic procedures with high radiation exposure (> 4 mSv)
5. PCI of in-stent-restenosis
6. PCI of CTO

Coronary computed tomography angiography

Coronary computed tomography angiography will be performed in all patients, at least 48 h after diagnostic angiography and at least 48 h before planned PCI, on a SOMATOM Definition Flash 128-row scanner (Siemens, Forchheim, Germany). Prior to the scan every patient will receive 0.8 mg of nitroglycerin s.l. Patients with heart rate > 65/min without contraindications to β-adrenolytics will receive a bolus of 2.5 mg metoprolol *i.v.* (maximum dose 10 mg). An ECG-gated retrospective acquisition protocol will be applied. The following data will be quantitatively assessed with dedicated software (Circulation, Siemens):

- Bifurcation classification according to Medina;
- Angle between MB and SB;
- Lesion length in MB and SB (length of a segment that should be stented in the opinion of the observer);
- Plaque morphology (e.g. lipid rich, ruptured) and localization in relation to SB;
- Lumen diameters and areas in selected sites of bifurcation (Figure 2). The lumen areas will be measured automatically and manually adjusted if necessary;
- Location of calcifications at the bifurcation site;
- Plaque burden and remodeling index will be calculated for each segment of bifurcation.

Plaque location and morphology, lumen areas and lesion length will be assessed in standard multiplanar reconstructions or curved multiplanar reconstructions, while the angle between MB and SB will be determined in volume rendering reconstruction.

Planning of percutaneous coronary intervention

In patients randomized to PCI planning with CCTA and CA, the operator will carefully review CCTA images of the lesion together with a physician experienced in CCTA analysis. The preliminary treatment strategy will include the PCI technique, number and size of stents (to assure optimal lesion coverage), number of leaders, predilation, postdilation and final kissing dilatation. The stent diameter will be planned according to the proximal and distal reference diameters. The suggested stent length will correspond to the distance between the proximal and distal sites with maximum lumen and minimum amount of plaque. Pre- and postdilation with high pressures will be advised especially in heavily calcified lesions.

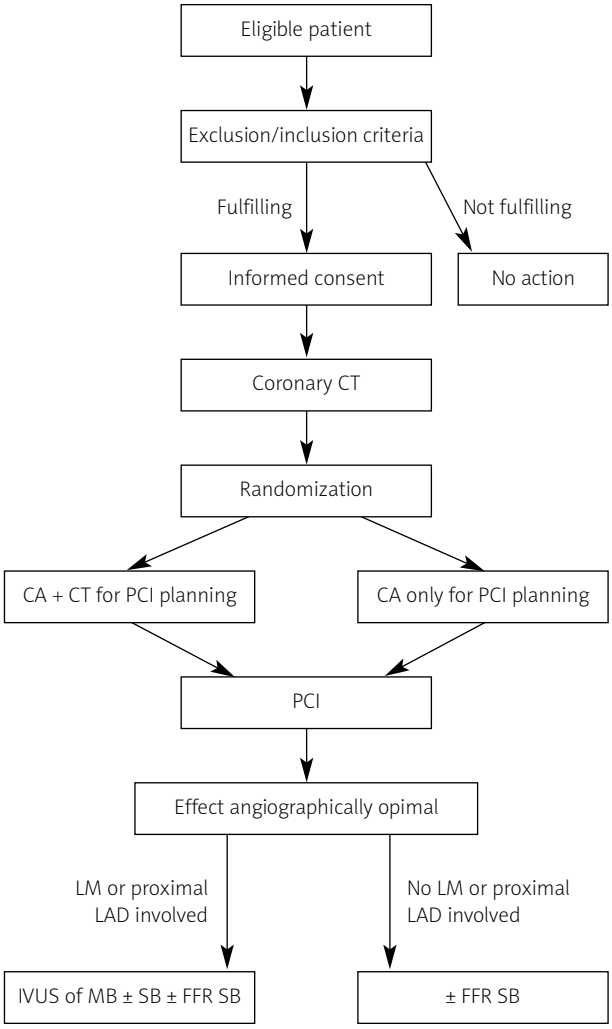

Fig. 1. Trial flowchart

In patients randomized to PCI planning with CA, the operator will be blinded to the CCTA findings. The choice of treatment strategy, stent number and size and additional procedures will depend on the angiographic images. The operator will aim at optimal coverage of the lesion in MB and (for two-stent-techniques) in SB.

Percutaneous coronary intervention

The final strategy will be left to the discretion of the operator. After attainment of an angiographically optimal result, additional examination will be performed in subgroups of patients:

1) IVUS in patients with LM or proximal LAD involved;
2) FFR in a subgroup of 30 consecutive patients, if technically feasible. The decision of feasibility of performing

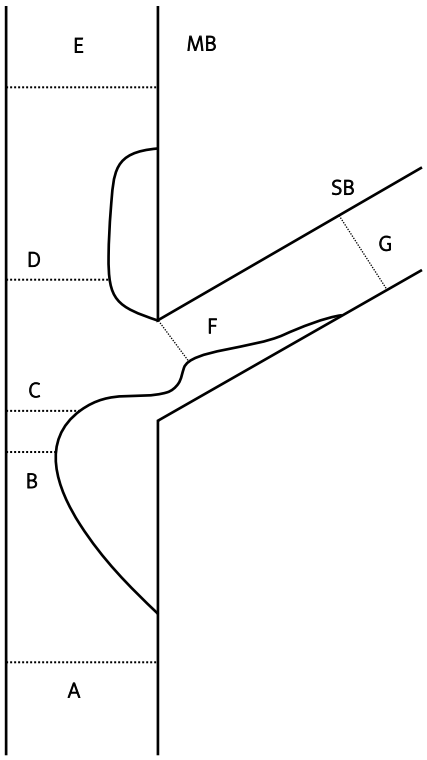

Fig. 2. Diagram of measurements of bifurcation lesions determined in QCA, CCTA and IVUS

A – proximal reference in MB; B – maximum stenosis proximally in MB; C – side branch ostium; D – maximum stenosis distally in MB; E – distal reference in MB; F – maximum stenosis in SB; G – reference in SB. Reference segments are described as the most normal looking segments within 10 mm from the lesion site, before any major side branch

FFR will be made for each patient prior to randomization on the basis of available clinical and imaging data.

Intravascular ultrasound images will be acquired retrograde in MB and, if technically feasible, in SB using a Volcano (San Diego, California) or Boston Scientific (Natick, Massachusetts) 40 MHz catheter advanced 10 mm distally to the lesion. The operator will have the possibility of optimizing the PCI in case of suboptimal lesion coverage or stent malapposition. The IVUS loops will be left to the off-line analysis including:

- Minimal lumen diameters and areas in the proximal and distal parts of the stent in MB and SB (Figure 2), as well as of the reference sites,
- Minimal lumen areas and diameters of the external elastic membrane of the vessel in the indicated sites of the bifurcation,
- Plaque burden and remodeling index will be calculated for each segment of the bifurcation.

In the selected patients FFR will be measured with a coronary guidewire (Pressure Wire® Aeris, St Jude Medical) during adenosine-induced hyperemia. 140 µg/kg/min adenosine will be administered *i.v.* for 2 min, while the wire will be positioned in the side branch for the P_d/P_a measurement. If well tolerated by the patient, the measurement will be taken in the main branch as well.

Study group and statistical analysis

Since it is a pilot study, we expect 40 patients in each group to be included in the analysis. A subgroup of 30 consecutive patients (15 in each group) will undergo the FFR measurement.

Continuous data with normal distribution will be presented as means ± SD and non-normally distributed data as median with IQR. For assessment of differences between continuous variables, the independent samples *t*-test, paired *t*-test, Wilcoxon test and Mann-Whitney test will be applied. Categorical variables will be compared with the χ^2 test.

The main null hypothesis is that there is no difference between the two study arms in terms of number of stents used, selected technique, size and type of implanted stents (measured by intention-to-treat) as well as the minimal lumen diameter in SB and MB assessed directly after attaining an angiographically satisfactory result.

The patients' recruitment started in July 2012 and is expected to be accomplished within 2 years (June 2014).

Conclusions

This prospective, randomized, single-blinded pilot clinical study with procedural and angiographic as well as IVUS and FFR endpoints is aimed at determining the usefulness of coronary computed tomography in planning of PCI of bifurcation lesions. If the study hypotheses are confirmed, there will be evidence supporting routine analysis of coronary computed tomography scans prior to PCI of bifurcations, and, in selected cases, performing additional coronary computed tomography to facilitate optimal planning of the procedure.

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