Review

CT Coronary Angiography for the follow-up of coronary stent

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Abstract. The treatment of coronary artery stenosis has progressively shifted over the past decades, from surgical (CABG) to percutaneous (PCI and stenting). The recent introduction of drug-eluting stents further reduced the occurrence of in-stent re-stenosis (ISR). However, a non-negligible number of patients need imaging/functional tests when symptoms recur. Multi-Slice CT Coronary Angiography (CT-CA) is a clinical reality for the evaluation of coronary artery stenosis, but still under evaluation in the follow-up of coronary stents. Several factors may impair proper depiction of in-stent lumen even with the most recent CT equipments. In highly selected populations CT-CA may play a clinical role even though the performance requirements both from the technical standpoint (i.e. CT scanner) and from the training (i.e. operators' experience) are still very demanding. In the meantime CT technology should improve towards higher contrast, spatial and temporal resolution in order to achieve the results that may be proper for clinical implementation. (www.actabiomedica.it)

Key words: Multi-Slice CT; Coronary Angiography; In-Stent Re-Stenosis; Clinical Applications; Non-Invasive Imaging

Introduction

In the past 10 years the introduction of Drug-Eluting Stents (DES) for the treatment of significantly obstructive (>50% lumen reduction) coronary artery disease (CAD) has significantly improved the outcome of percutaneous treatments (1). In particular, the reduction in the occurrence of In-Stent Re-Stenosis (ISR) has further widened the indications for Percutaneous Coronary Interventions (PCI) reaching up to becoming the reference standard in both stable (elective PCI) and acute/unstable settings (primary PCI) (1). However, still a variable sub-set of patients develop ISR (6-20% depending on comorbidities, cardiovascular risk factors, compliance to pharmacological treatment, etc). This patients will present with recurrent chest pain, and evaluation with invasive coronary angiography (CAG) is still required. Different tests are available for the assessment of recurrent angina in patients who underwent PCI. For instance, stress ECG, stress Echo-Cardiography, Stress Myocardial Perfusion Imaging (Stress MPI). An alternative test could be Multi-Slice Computed Tomography Coronary Angiography (CT-CA). This technique has rapidly evolved in the past few year and has become a clinical standard for the exclusion of CAD in patients with intermediate pre-test probability due to its very negative predictive value. When applied to coronary stents it has shown several limitations and the literature is still poor in this field.

In this paper we will review the current performance and the potential of CT-CA for the evaluation of patients with coronary artery stents.

Technical features of CT-CA

A non-invasive alternative approach for ISR detection may be offered through current generation Multi-Slice CT (MSCT) scanners; 4- and 16-slice MSCT scanners have been of limited value in the assessment and follow-up of patients with coronary stents. This is mainly due to the heavy artifacts determined by the metallic struts of the stent. Objects with very high attenuation values, such as stents, produce the so called "*blooming*" effect. It consists of an enlarged appearance of the stent (up to 10 times the actual size of the metallic strut) and may obscure at least 30% of the in-stent coronary lumen in the best scenario (2, 3). In addition, patients who underwent PCI, may carry coronary vessels calcifications to different extent, with a progressive reduction in image quality (2). The amount of intra-coronary attenuation, due to the contrast material protocol adopted for the angiographic CT scan, may also become an issue. In fact, a low intra-coronary attenuation (<300HU) increases the difficulty in the assessment of in-stent patency. Residual motion artifacts due to high/irregular heart rates may also deteriorate image quality.

For all these technical reasons making the diagnosis of ISR with CT-CA can be quite difficult.

New technical developments are bringing to the market CT scanners with increased performance. For many years technology in this field developed following the law of "more slices = better images". Things are changing. Some manufacturers are developing in this direction (Siemens Medical with 128 slices, Philips Medical with 256 slices and Toshiba Medical with 320 slices). Others are developing into higher spatial resolution (i.e. new detector hardware) technology (GE medical). Others are developing into higher temporal resolution (Siemens Medical with Dual Source technology). Others are developing also into concomitant Dual Energy platforms (GE Medical and Siemens Medical). It is not clear at the moment weather one development will prevail on the others. We know for sure that current benchmark (i.e. 64-slice CT-CA) is already performing very well in experienced hands.

The advantages of more slices (between 128 and 320slices) are inherent to the very short scan time (1-2s) and to potential for myocardial perfusion. The "price" might be related to constraints in temporal resolution and an increased radiation dose. The advantages of high resolution technology are inherent to better image quality with the same radiation dose or to the same image quality with a lower radiation dose. The advantages of higher temporal resolution are inherent to a reduced use of beta-blockers administration or to better image quality while keeping the heart rate below 65bpm. The advantages of a dual energy platform are inherent to totally unexplored spectral imaging capabilities.

In clinical setting the actual usefulness of 64-slice CT-CT for the evaluation of ISR remains under investigation. The most important features of a test useful in the clinical setting is its reliability of not missing the cases having the disease (sensitivity) in this case ISR, and achieving this with reasonably few falsely overdetected cases (specificity). Additionally, when the searched events have a low occurrence rate, as it is now the case for simple lesions treated with DES, a correct exclusion of ISR (high negative predictive value – NPV) allows to focus on the small number of patients with a positive test result, in whom invasive angiography would be performed to confirm and treat the ISR, or definitively exclude it.

Diagnostic Accuracy of MSCT-CA for ISR detection

In Table 1 we report the most recent studies (3-8) that analyzed the accuracy of CT-CA for the detection of ISR, as compared to CAG, using the current standard technology which is 64-slice. These are mainly single centre cohort studies (41-182 patients) with highly selected patients (e.g., exclusion of all patient with previous allergic reaction to iodinated contrast agent, impaired renal function, contraindication to beta-blockers, atrial fibrillation, obesity, and those who had an acute coronary syndrome at the time of scheduled angiography). Usually, the stents were visually classified for the presence or absence of binary ISR (lumen reduction ≥50%). Moreover, 56% of the analysed stents were large stent (>3 mm). These studies, including 817 stents, showed that at experienced sites and with careful data acquisition and evaluation, sensitivities ranging from 84% to 100% and specifities ranging from 81% to 98% can be archieved for the detection of ISR. However, the rate of evaluable coronary stented segments ranged from 58% to 100% (707 stent, mean value 90.7%). These studies excluded not assessable segments with poor quality images from analysis, which inflated accuracy estimates. The median positive predictive value for the detection of ISR was low (72%) and with a range from 47% to 92% unacceptable for the clinical applications of CT-CA. Remarkably, a very high NPV (97% to 100%) was uniformly found (Table 1; Figure 1, 2). Although these results may partly be secondary to the relatively low prevalence of coronary ISR in these studies, they indicate that in such patient groups, modern MSCT scanners with adequate image acquisition protocols may be used to reliably rule out the presence of significant coronary ISR, particularly among patients with implanted thin-strut DES (8). Clearly, CT-CA has limitations and should not be expected to widely replace invasive diagnostic cardiac catheterization in the foreseeable future. Spatial resolution limits the ability of CT-CA to provide exact, quantitative measures of ISR severity. Furthermore, as a purely anatomical imaging modality, the evaluation of ISR through CT-CA will remain incomplete, since the method does not yield additional hemodynamic information about the functional significance of ISR that certainly may influence clinical decision-making in this setting. In addition to limitations caused by calcium and rapid coronary motion, patients with atrial fibrillation or other arrhythmias as well as patients with contraindications to iodinated contrast agent or patients with impaired renal function cannot be studied. Even more important, patient radiation exposure tends to be understated or “forgotten” in the clinical studies and in the clinical practice. This exposure represents a serious downside to this imaging modality, with the 10 to 20 mSv exposure dose of the scan corresponding to an estimated 1 new (fatal or nonfatal) cancer for every 1000 to 500 scans (9).

Clinical Impact

While the overwhelming need for a non-invasive, cost-effective test that can safely rule out significant ISR is unquestioned, the appropriate patient popula-

Table 1. Diagnostic Accuracy of CT-CA for detection of In-Stent Re-Stenosis

	Gaspar[§] (3)	Rixe (4)	Van Mieghem (5)	Ehara (6)	Cademartiri (7)	Carrabba (8)	All
Patients (n)	65	64	70	81	182	41	503
Stents (n)	111	102	162	163 (125^)	192	87	817 (779^)
Evaluable stents (n; %)	111 (100)	59 (58)	162 (100)	110/125^ (89)	178 (93)	87 (100)	707/779^ (90.7)
Stent diameter (±SD; mm)	3.3±0.5	3.28±0.4	3*	n.e.	3.1±0.4	2.96±0.43	3.16
Stent diameter (range; mm)	n.e.	2.75 - 5	3 - 3.5*	<3-4.5	2.5 - 4.5	2.25 - 4	2.25-5
Stent diameter >3 mm (n; %)	n.e.	32 (31)	162 (100)	146 (89)	66 (34)	49 (56)	455 (56)
Sensitivity (%)	88.9	86	100	91	95	84	90.8
Specificity (%)	80.6	98	91	93	93	97	92.1
Accuracy (%)	82	NE	93	93	NE	96	91
PPV (%)	47.1	86	67	77	63.3	92	72
NPV (%)	97.4	98	100	98	99.3	97	98.1

[§]Gaspar et al used 40-slice MDCT which has a similar spatial resolution to the 64-slice scanner

*Abbreviations: ^ = lesion; SD = standard deviation; * = median; PPV = positive predictive value; NPV = negative predictive value*

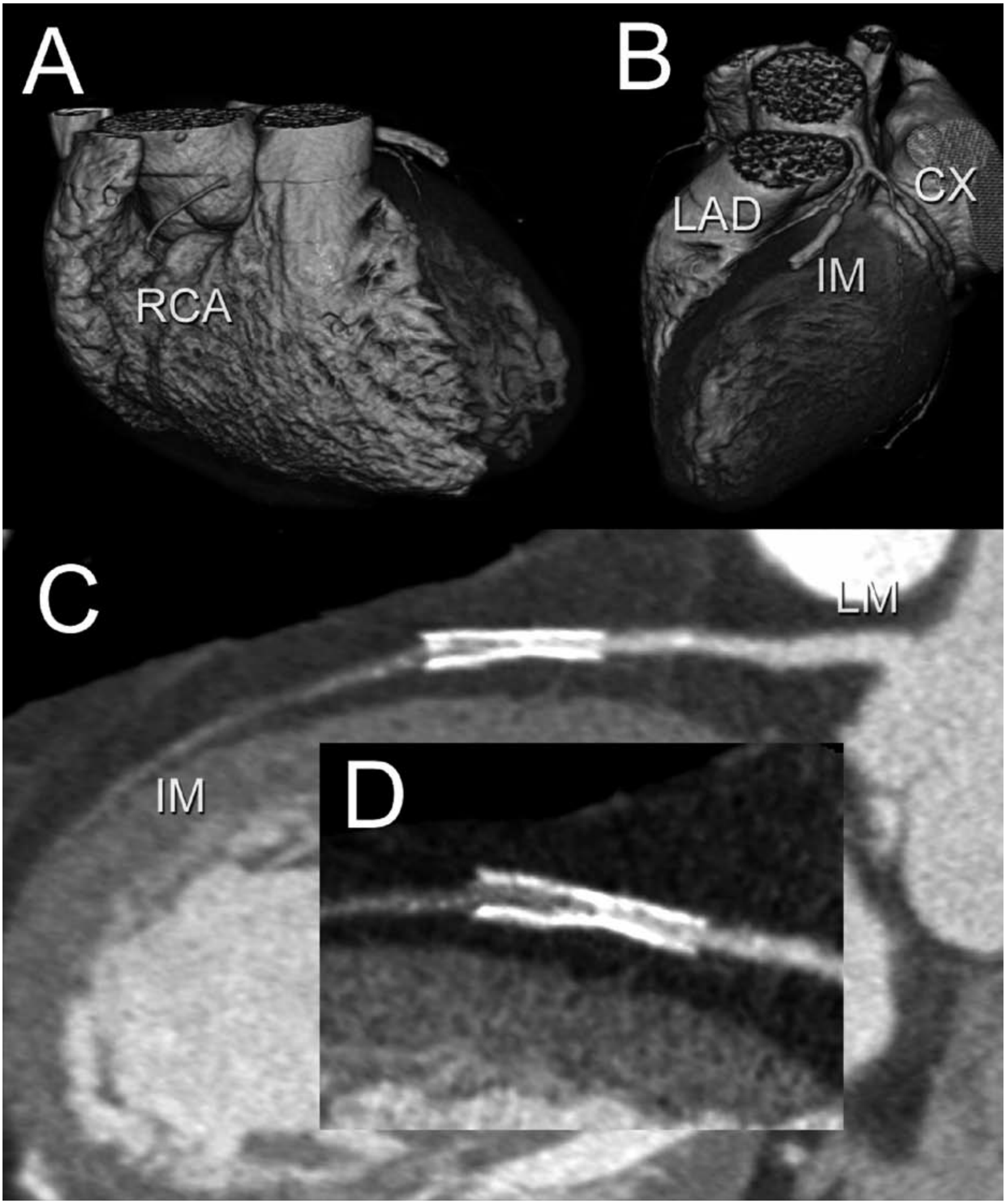

Figure 1. Example of CT-CA in patients with recurrent angina after PCI on the IM. In a patient with left dominance (A) the CT-CA shows a stent in the IM branch (B). The multiplanar reformats along the vessel length (C-D) using standard (C) and high kernel filtering (D), show a hypodense layer in the distal segment of the stent with a resulting stenosis >50% (ISR). The stent appears to be also irregularly expanded.
Abbreviations: CT-CA = CT Coronary Angiography; PCI = Percutaneous Coronary Interventions; LAD = Left Anterior Descending; RCA = Right Coronary Artery; CX = Left Circumflex Artery; IM = intermediate Branch; ISR = In-Stent Re-stenosis

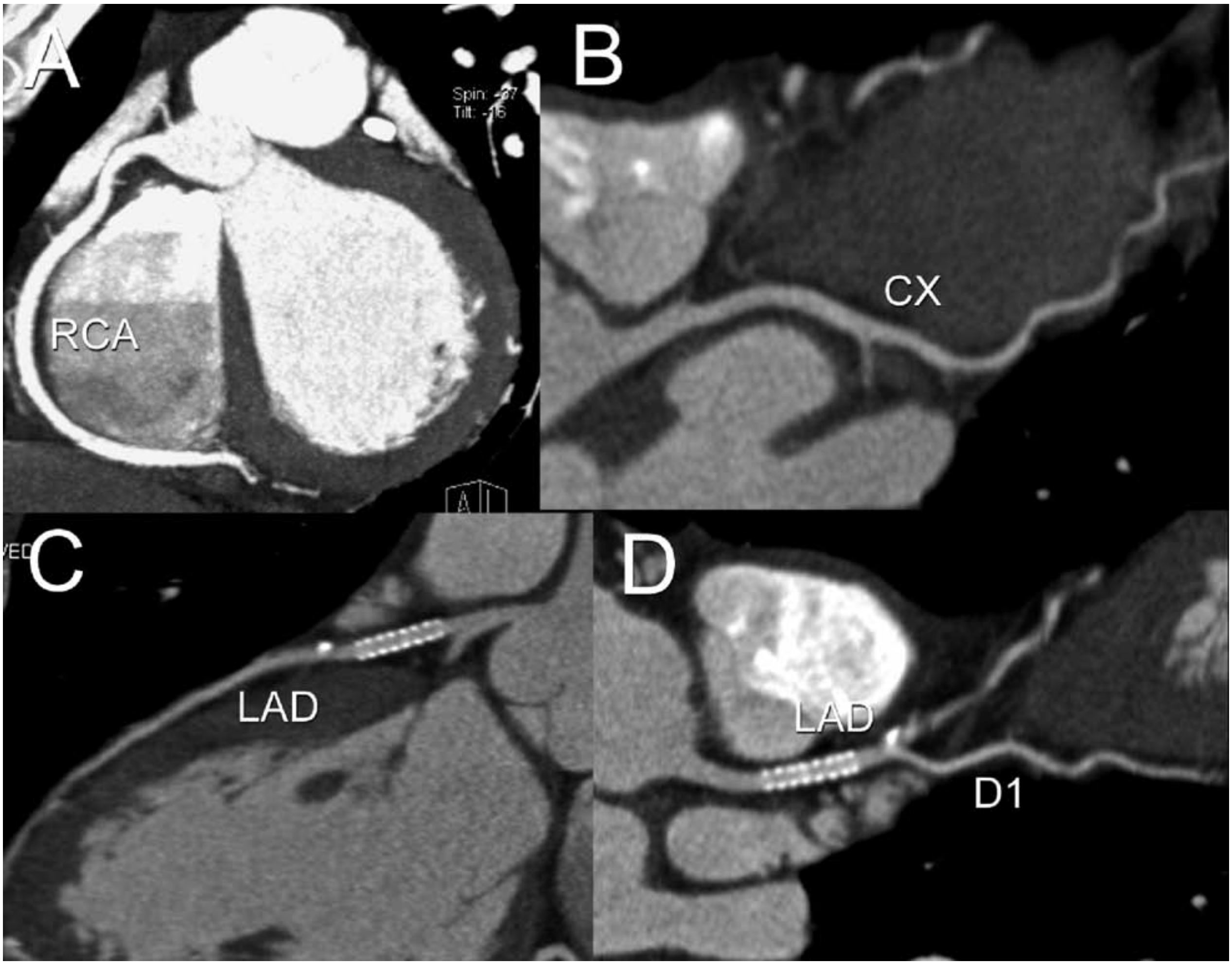

Figure 2. Example of CT-CA in patients with atypical chest pain after PCI on the LAD. In a patient with right dominance (A) and normal RCA and CX (A-B), the CTCA shows a stent in the LAD (C-D). The multiplanar reformats along the vessel length (C-D), show a clear and regular in-stent lumen.
Abbreviations: CT-CA = CT Coronary Angiography; PCI = Percutaneous Coronary Interventions; LAD = Left Anterior Descending; RCA = Right Coronary Artery; CX = Left Circumflex Artery; IM = intermediate Branch; D1 = first diagonal branch.

tion that most likely may benefit from CT-CA remains to be demonstrated (Figure 3). Asymptomatic patients should not undergo CT-CA routinely after revascularization. Asymptomatic patients should be only clinically followed-up. At present "Screening applications" of CT-CA in asymptomatic stented patients are not backed by clinical data. Nevertheless, among the high-risk population with implanted left main coronary artery stents a recent study (5) showed that the CT-CA may be effective to exclude ISR and potentially may obviate the need for routine follow-up invasive angiography, which is recommended at 2 and 6 months (10), or at least CT-CA may represent an intermediate step (2 months) of follow-up. Symptomatic patients whose clinical presentation suggests a very high likelihood of having a ISR (e.g., with absolutely typical chest pain and an unambiguously positive stress test) will most likely have no benefit from so-called "non-invasive angiography" of any kind, because CT-CA is only a purely diagnostic tool and, as opposed to invasive coronary angiography, there is no option for immediate intervention. However, the high

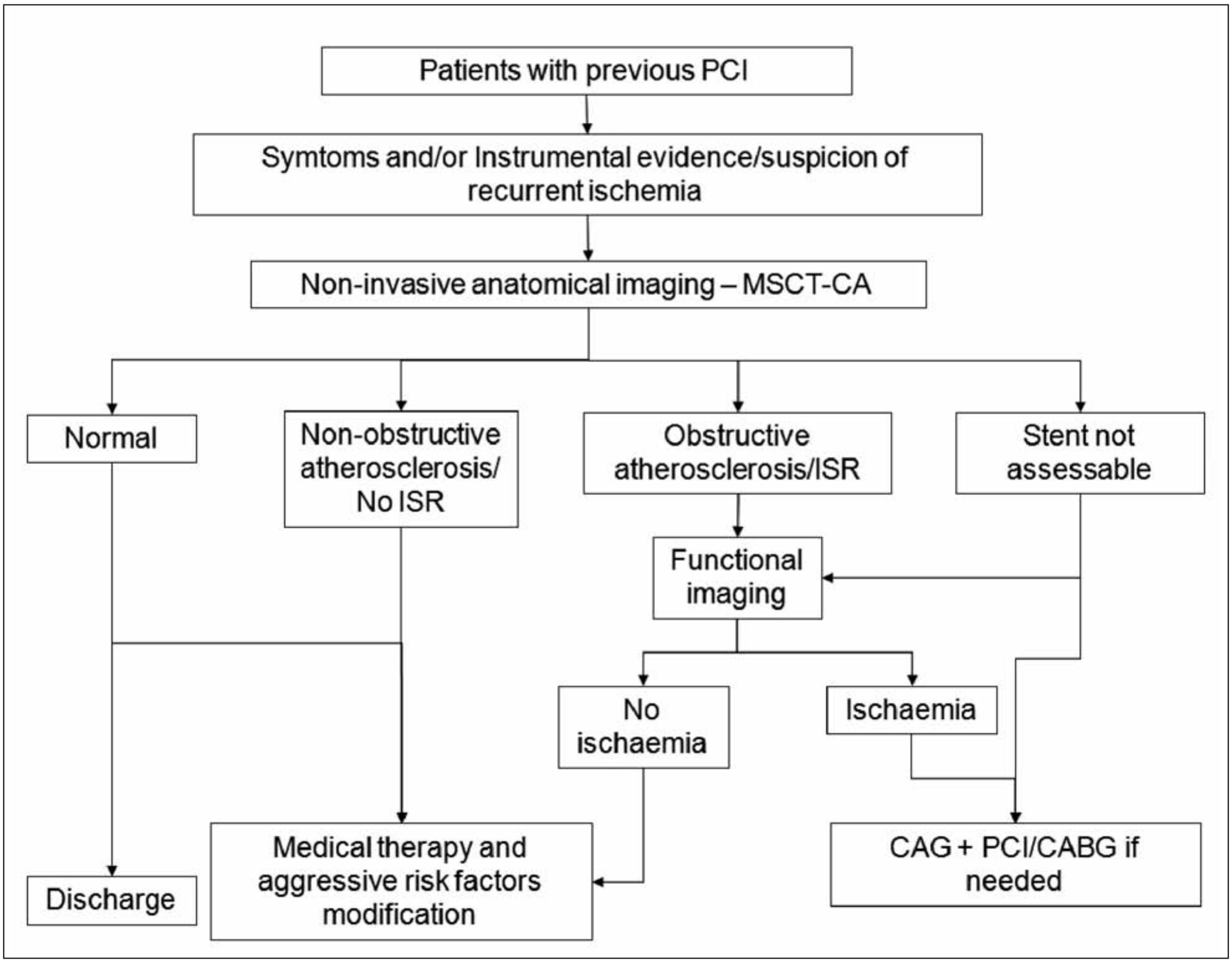

Figure 3. The figure shows a potential algorithm for the implementation of CT-CA in the clinical practice in the follow-up of patients with previous PCI. After eventual risk stratification with clinical assessment and instrumental tests (e.g. stress ECG, etc), the patient with suspected ISR undergoes non-invasive anatomical imaging with CT-CA. If CT-CA is of otpimal quality and reveals no CAD/ISR the patient is safely discharged or undergoes/continues the medical therapy. When CT-CA demonstrates the presence of atherosclerosis without significant stenosis/ISR (<50% lumen reduction) the patient can also be managed with medical therapy. On the contrary, when CT-CA reveals the presence of obstructive CAD/ISR (≥50% lumen reduction), the patient should be sent for functional assessment (e.g. stress Imaging). The next decision is based on the demonstration of inducible ischemia. In case of not assessable stent, the patient, depending on clinical settings, should undergo first functional Imaging or directly to CAG. *Abbreviations: CT-CA = CT Coronary Angiography; PCI = Percutaneous Coronary Interventions; CAG = Conventional Coronary Angiography; CABG = Coronary Artery Bypass Graft; CAD = Coronary Artery Disease; ISR = In-Stent Re-stenosi*

NPV may make the clinical application of CT-CA useful in patients who are considered for invasive coronary angiography, because they are symptomatics but do not have a high pretest likelihood of ISR or have inconclusive stress test. If CT-CA clearly demonstrates patency of coronary stents and absence of significant progression of disease in non-stented segment, invasive angiography is not necessary. The actual clinical utility of CT-CA may be the ability to rule out ISR in the stented patients; this certainly may be feasible given the high NPV, which should be even higher in the patients with expected low rate of ISR, as such as in a DES patient. Interestingly, Rubinshtein et al (11) recently have described the potential benefit of CT-CA in patients referred to the emergency department (ED), including revascularized patients, for the assessment of an acute chest pain syndrome. This study demonstrated applicability of the technique to selected patients with intermediate risk in whom the incremental value of non-invasive imaging had a significant impact on patient management. Despite these encouraging data, if CT-CA has the potential to change the clinical practice with respect to ED triage remains to demonstrate, and further studies to examine the logistics and risk-benefit are needed.

Conclusions

The *"proof-of-concept"* pilot studies established the potential role of CT-CA in evaluating ISR in patients deemed as ideal candidates for CT-CA scan. But, the magnitude of benefit achieved by CT-CA among "real world" stented patients remains to be demonstrated (12). Meanwhile, the lack of additional hemodynamic information about ISR detected by CT-CA remains the main limitation, and the use of standard stress tests continue to have a major impact on clinical decision making in stented patients with recurrent chest pain.

References

1. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; 350: 221-31.
2. Schuijf JD, Bax JJ, Jukema JW, et al. Feasibility of assessment of coronary stent patency using 16-slice computed tomography. *Am J Cardiol* 2004; 94: 427-30.
3. Gaspar T, Halon DA, Lewis BS, et al. Diagnosis of coronary in-stent restenosis with multidetector row spiral computed tomography. *J Am Coll Cardiol* 2005; 46: 1573-9.
4. Rixe J, Achenbach S, Ropers D, et al. Assessment of coronary artery stent restenosis by 64-slice multi-detector computed tomography. *Eur Heart J* 2006; 27: 2567-72.
5. Van Mieghem CA, Cademartiri F, Mollet NR, et al. Multislice spiral computed tomography for the evaluation of stent patency after left main coronary artery stenting: a comparison with conventional coronary angiography and intravascular ultrasound. *Circulation* 2006; 114: 645-53.
6. Ehara M, Kawai M, Surmely JF, et al. Diagnostic accuracy of coronary in-stent restenosis using 64-slice computed tomography. *J Am Coll Cardiol* 2007; 49: 951-59.
7. Cademartiri F, Schuijf JD, Pugliese F, et al. Usefulness of 64-slice multislice computed tomography coronary angiography to assess in-stent restenosis. *J Am Coll Cardiol* 2007; 49: 2204-10.
8. Carrabba N, Bamoshmoosh M, Carusi LM, et al. Usefulness of 64-slice multi-detector computed tomography for detecting drug-eluting in-stent restenosis. *Am J Cardiol* 2007, in press.
9. Health Risks From Exposure to Low levels of Ionizing Radiation: Biological effects of Ioniziang Radiation Seventh Committee, Phase 2 (2006). Available at: http://books.nap.edu/openbook.php?isbn=030909156X. Accessed August 18,2007.
10. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice. *Circulation* 2006; 113: e166-e286.
11. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation* 2007; 115: 1762-68.
12. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006; 114: 1761-91.

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