INTRODUCTION

Since the introduction of multidetector computed tomography (CT), CT angiography has emerged as a new tool in the diagnosis and monitoring of coronary heart disease. Additionally, noninvasive assessment of coronary stents is an attractive potential application of multidetector CT technology ***(Schoepf et al., 2004).***

But stent imaging is a challenge at CT, mainly because of high-attenuation stent-related artifacts. The blooming effect caused by a combination of partial volume averaging and behardening results in higher CT attenuation values in the stent lumen and enlarges the apparent size of the stent struts, leading to an artificial appearance of narrowing of the lumen ***(Nieman et al., 2003).*** In recent years, coronary artery disease has been increasingly treated by coronary stent placement. Although stent implantation has been shown to greatly reduce restenosis after balloon angioplasty ***(Schoenhagen et al., 2004)*** in-stent restenosis can occur in 20-35% of patients for bare metal stents ***(Morice et al., 2006)*** and 5-10% for drug-eluting stents, as demonstrated by intravascular ultrasound.

Invasive coronary angiography remains the gold standard technique for detection of in-stent restenosis. However, coronary angiography has limitations due to its invasiveness and association with potential risks of morbidity and mortality.

Given the high number of patients who receive coronary stents yearly, a non-invasive imaging technique for detection of in-stent restenosis will be clinically important and beneficial.

Multi-detector row computed tomography (MDCT) is increasingly used for non-invasive imaging of coronary artery disease and has been reported to have a high diagnostic accuracy in the detection of coronary artery stenosis, especially when the latest fast 64-detector row scanners are used ***(Fine et al., 2006).***

However, imaging of coronary stents by MDCT is more difficult than native coronary artery. This is due to the presence of the metal within the stents that can cause artifacts interfering with the interpretation of lumen patency.

Although several reports have shown that MDCT may be used to evaluate stent patency, more precise evaluation of the lumen within stent is markedly affected by the blooming artifacts that can cause an appearance of artificial enlargement of the metallic stent struts ***(Kruger et al., 2003).***

Results of both in vitro and vivo studies have shown that reliable direct assessment of the stent lumen with 4-detector row CT is not possible ***(Maintz et al., 2003).***

With increasing number of detector rows, promising results of MDCT in coronary artery disease have been reported with improved spatial and temporal resolution. However, it is unclear

whether this also applies to the assessment of coronary stent implantation.

Thus, the aim of this study was to perform a meta-analysis, based on the currently available published results, of the diagnostic accuracy of 16-or more detector rows MDCT angiography for the detection of coronary in-stent restenosis compared to invasive catheter angiography.

AIM OF THE WORK

To evaluate the role of MSCT in assessing instent restenosis (utilizing distal contrast enhanced vessel attenuation) compared to conventional coronary angiography

Chapter (1)
INSTENT RESTENOSIS

Percutaneous coronary intervention (PCI) has seen a tremendous increase and tends to be the most frequently used method for myocardial revascularization ***(Mack et al., 2004).***

An impressive array of stent improvements, newer drug regimens and technological advances have emerged and broadened the therapeutic spectrum for interventional cardiologists worldwide. The recurrence of luminal narrowing due to recoil, arterial vessel re-modeling and intimal hyperplasia induced by artery injury and disease progression, has compromised the results of balloon angioplasty. The use of stents during PCI achieved both a significant decrease in the incidence of acute complications and an improvement in patients' outcomes ***(Serruys et al., 1994).***

The initial idea was for the implanted stent to serve as a scaffold that would maintain the artery's patency permanently. In reality, in-stent restenosis (ISR) compromises the long-term results ***(Kasaoka et al., 1998, Akiyama et al., 1998)***.

The introduction of drug-eluting stents (DES) aimed to reduce restenosis, the major drawback of bare-metal stent (BMS) implantation.

Undoubtedly, a drastic improvement was observed but much to physicians' disappointment, restenosis remains the Achilles' heel of PCI, even in the DES era.

Mechanism and factors contributing to stent restenosis

BMS implantation bears a restenosis rate of around 25% ***(Serruys et al., 1994, Fischman et al., 1994)***. A great number of randomized trials comparing DES with BMS have shown that the former significantly reduce the incidence, not only of angiographic, but also of clinical restenosis to a uniquely low, one-digit range (<10%) ***(Moses et al., 2003, Stone et al., 2004).***

However, its prevalence will be greater in view of the fact that, in the real world, DES are being increasingly used in complex lesions such as those in the left main artery, bifurcations, small vessels, vein grafts, chronic total occlusions, acute coronary syndromes and diabetic patients.

In these patient populations, "off-label" use has led to an ISR rate exceeding 10% ***(Stone et al., 2005, Tanabe et al., 2004).***

Another unsettling issue is that DES restenosis does not always present benignly, with myocardial infarction being the initial clinical manifestation in up to 10% of patients ***(Abizaid et al., 1998)***.

A number of predisposing factors have been associated with restenosis and can be divided into *lesion-related, procedure-related and patient-related.*

Vessel and lesion characteristics that could predict a high probability for ISR are vessel size, tortuosity, calcification, total occlusion and lesions located in the left anterior coronary artery (LAD).

Technical failures of the implantation, such as small post-procedural minimum lumen diameter, higher residual percent diameter stenosis, underexpansion, overexpansion, stent fracture, non-uniform distribution of stent struts and malapposition

Patient related factors have been linked with this phenomenon, such as the presence of diabetes mellitus ***(Kip et al., 1996)***. Genetic factors, such as the PIA polymorphism of glycoprotein IIIa ***(Kastrati et al., 1999),*** the insertion/deletion polymorphism and the plasma activity of angiotensin I-converting enzyme ***(Ribichini et al., 1998)*** have been reported to be important patient-related risk factors of ISR.

Current evidence suggests that inadequate and predominantly focal delivery of the antiproliferative agent (mainly sirolimus or paclitaxel) into the vessel wall, localized hypersensitivity, polymer disruption and drug resistance are likely to be involved in DES restenosis ***(Nebeker et al., Ahn et al., 2007).***

Classification of ISR

An earlier classification of lesions into either diffuse (lesion length >10 mm) or focal (<10 mm) has proved inadequate to predict the rate of target vessel revascularization (TVR). Nowadays, the angiographic pattern of restenosis based on Mehran's classification for ISR seems to have important prognostic value and may be used for further clinical assessment ***(Mehran et al., 1999)***.

- ***Mehran classification (Figure)***

Class I: Focal ISR group. Lesions are #10 mm in length and are positioned at the unscaffolded segment (ie, articulation or gap), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR).

Class II: "Diffuse intrastent" ISR. Lesions are.10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s)

Class III: "Diffuse proliferative" ISR. Lesions are.10 mm in length and extend beyond the margin(s) of the stent(s).

Class IV: ISR with "total occlusion." Lesions have a TIMI flow grade of 0.

Recurrent ISR was more frequent with increasing grades of classification, as with diabetes.

Target lesion revascularization (TLR) increased according to ISR class, ranging from 19% to 83% for classes I to IV, respectively ($p<0.001$).

Corbett et al. characterized 150 and 149 restenotic lesions in sirolimus-eluting (SES) and paclitaxel-eluting stent (PES) groups, respectively, and concluded that focal restenosis remains the most common pattern with SES. In contrast, just under half of restenosis in PES have the more severe non-focal pattern. Recently, ***Rathore et al.*** studying 838 patients with ISR, reported 47% and 19.3% rates of focal ISR for SES and BMS treated patients, respectively. The majority of ISR is focal, but a considerable part presents as non-focal. It is the latter type of ISR that is associated with a higher need for revascularization. Therefore the type of ISR plays an undoubtedly prominent role in the clinical outcome.

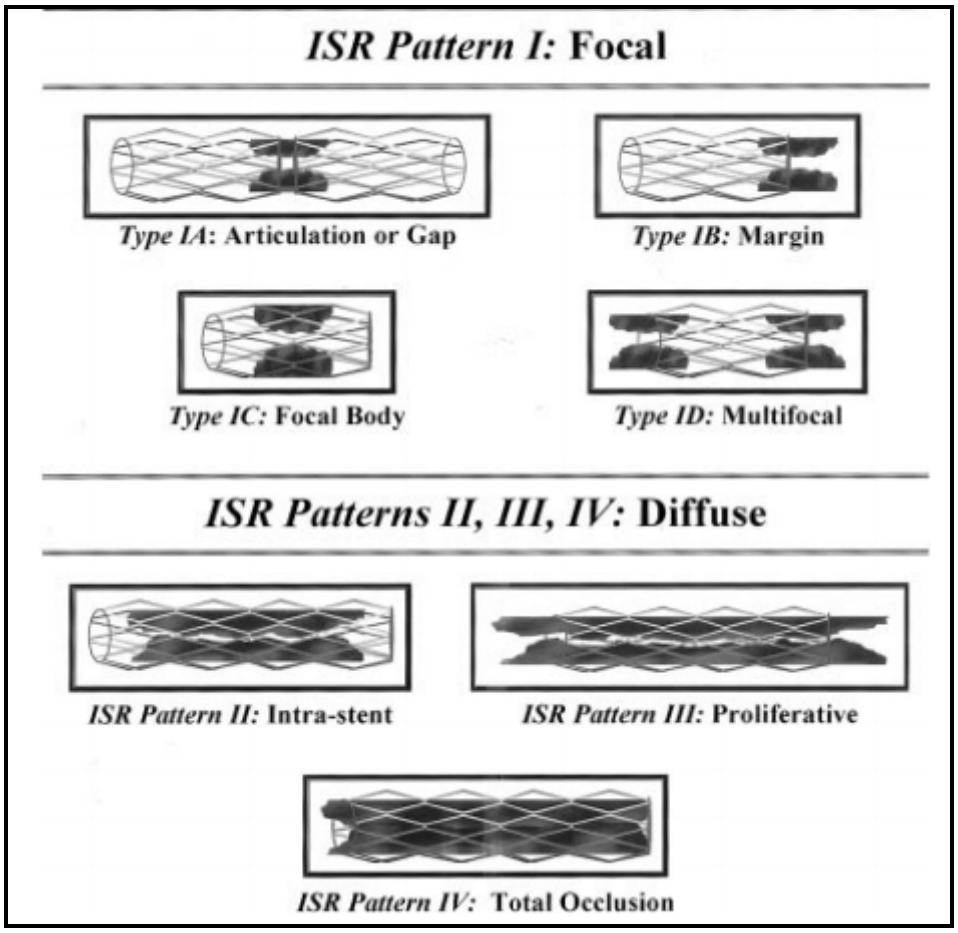

Fig. (1): Schematic image of 4 patterns of introduced classification of ISR in relation to previous dichotomous description of focal vs diffuse ISR. Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent.

IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, MN) consisting of a

rotating 30- or 40-MHz transducer within a 3.2F imaging sheath. Quantitative volumetric IVUS analysis was performed ***(Park et al., 2003, Mintz et al., 2000).*** Using computerized plannimetry stent and reference segments were assessed every 1 mm. In-stent measurements were also obtained every 1 mm and included external elastic membrane (EEM), stent, lumen (intrastent lumen bounded by the borders of the stent and IH), peristent plaque+media (PM=EEM minus stent), and intimal hyperplasia (IH=stent minus intrastent lumen) areas and volumes.

Percent IH (%IH) was defined as IH area divided by stent area. All volumes were calculated using the Simpson rule and then normalized for analysis length (normalized volume). Stent underexpansion was defined as minimal stent area (MSA) 5mm^2 ***(Sonoda, 2004)***. Significant IH was defined as %IH area 50%. Significant luminal narrowing was defined as IVUS-measured lumen area 4mm^2 ***(Abizaid et al., 1998, Nishioka et al., 1999).***

In the present study, identification of ISR was based on IVUS-measured significant luminal narrowing; and ISR lesions were classified as follows.

1. Focal ISR was defined as lumen area 4mm^2 and 10 mm in length confined to the body of stent (focal body type), or extending to the margins of stent (lumen area at the proximal or distal edge 4.0 mm^2, focal marginal type).

2. Multifocal ISR was defined as either multiple focal ISR lesions confined to the body of the stent (multifocal body type)without involvement of the stent margins or multiple focal ISR lesions that included marginal involvement (multifocal marginal type).
3. Diffuse ISR was defined as lumen area 4mm^2 and 10 mm in length confined to the body of stent (diffuse body type) or extending to the margins of the stent (diffuse marginal type). The mechanism of ISR was assessed at the minimum lumen site.

Dominant stent underexpansion was defined as stent area 5mm^2 and IH 50% at the minimum lumen site. Dominant intimal hyperplasia was defined as stent area 5mm^2 and IH 50% at the minimum lumen site. Mixed underexpansion and intimal hyperplasia was defined as stent area 5mm^2 and IH 50%.

Chapter (2)

DEVELOPMENT OF CT CORONARY ANGIOGRAPHY IN ASSESSMENT OF INSTENT RESTENOSIS

Coronary CT angiography evolved as a valuable tool in the diagnostic workup of patients after coronary revascularization therapy.

As CT imaging of coronary stents depends on patient and stent characteristics, patient selection is crucial for success. Ideal candidates have stents with a diameter of 3mm and more. Nevertheless, even with most recent CT scanners, about 8% of stents are not accessible mostly due to blooming or motion artifacts.

While the diagnosis of ISR is currently based on the visual assessment of the stent lumen, functional information on the hemodynamic significance of in-stent stenosis became available with the most recent generation of dual source CT scanners.

Rationale for CT Imaging of Coronary Stents

As complex noninvasive diagnostic tests such as myocardial single photon emission computed tomography (SPECT) yield only moderate results for detecting ISR ***(Dori et al., 2003, Park, in press)***, direct stent imaging appears to be

worthwhile. Coronary catheter angiograms are costly and associated with a 0.1% mortality ***(Chandrasekar et al., 2001)***, whereas coronary magnetic resonance (MR) angiography after coronary stenting is still in an experimental stage ***(Spuentrup et al., 2005)***. Thus, coronary computed tomography (CT) angiography evolved as the only non-invasive diagnostic test allowing for direct visualization of coronary stents and, therefore, non-invasive detection of ISR, stent thrombosis and stent fractures.

CT Imaging of Coronary Stents: The Past

The first report on localizing a coronary stent with unenhanced electron beam CT (EBCT) was published in 1995 ***(Yamoka et al., 1995)***. Few groups generated a small amount of data on the use of EBCT for assessing coronary stent patency. Due to the limited spatial resolution of EBCT, direct visualization of the stent lumen was not possible and an indirect approach was applied to assess stent patency.

For this purpose, contrast enhancement was determined distally to the stent and compared with the contrast enhancement pattern proximal to the stented segment, in the thoracic aorta or the left ventricle. Stent patency was assumed if the contrast enhancement distally to the stent matched the proximal coronary, aortic or left ventricular contrast enhancement pattern ***(Schmermund et al., 1996, Knollmann et al., 2004)***. Applying this technique, one has to be aware that

contrast enhancement distal to any obstructed stent is influenced by retrograde filling via collateral vessels. Using this approach, a sensitivity of about 48–100% for detecting ISR or stent occlusion with a high negative predictive value of 80.5–100% was achieved (Table 1) ***(Pump et al., 2000)***.

Table (1): Summary of studies on EBCT imaging for assessing coronary stent patency.

Author/year	Patients (*n*)	Stents (*n*)	Nonevaluable (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Schmermund et al. 1996 [15]	22	na	9	100	100	100	100
Pump et al. 1998 [17]	177	285	7.2	82.3	97.6	77.8	98.2
Pump et al. 2000 [18]	202	321	4	78	98	82	97
Knollmann et al. 2004 [16]	117	152*	9.3	48	90.1	67.7	80.5
Zhou et al. 2005 [19]	25	35	8	85	92.9	75	96.5
Total/mean	543	793	7.5	78.7	95.7	80.5	94.4

na: not available; PPV: positive predictive value; NPV: negative predictive value; *stented segments.

For several reasons, including the inability to quantitatively assess the degree of ISR and its limited availability, EBCT imaging of coronary stents did not gain clinical acceptance and was soon pushed aside by multislice CT (MSCT).

Table 1: Summary of studies on EBCT imaging for assessing coronary stent patency. With the simultaneous introduction of 4-slice CT scanners by all major vendors in 1998 and introduction of gating techniques for cardiac MSCT in 2000 ***(Ohnesorge et al., 2000)***, 4-slice CT became the first intensely used non-invasive imaging modality for assessing coronary artery stents. With its limited temporal and spatial resolution, direct visualization of the stent lumen was almost