CT imaging of bioresorbable stents – A primer for radiologists

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Target audience

• Cardiothoracic imaging radiologists
• Cardiologists
• General radiologists with interest in cardiac imaging
• Physicians-in-training
• Radiology technologists
• Medical students
Outline

• History and Types of coronary stents
  – Bare-metal stents (BMS)
  – Drug-eluting stents (DES)
  – Bioresorbable stents (BRS)
    • Advantages of BRS
    • Composition and lifespan of BRS

• BRS visualization by angiography, IVUS, OCT and CT

• Clinical outcomes of BRS implantation

• Review of CT studies with BRS

• Teaching points/ Conclusion
History and types of coronary stents
History of coronary stenting

1977 – First percutaneous transluminal coronary angioplasty (PTCA) (fig. 1) was performed on an awake patient by Dr Andreas Gruentzig. Dr Gruentzig also developed the first balloon inflation device.

Studies showed less residual stenosis and higher rates of patency within weeks after reperfusion with PTCA in comparison to thrombolysis.

PTCA technique was nonetheless far from ideal. Up to 30-50% of patients had occurrence of restenosis, occlusions and early recoil in the first year post reperfusion.

Figure 1. A) Angioplasty catheters. B) Radial artery intervention-Seldinger technique. C) Balloon catheter visualization by angiography. (arrow).
Bare-metal stents- first stents

1986 – First stent, a bare-metal stent (BMS), implantation in a human coronary artery took place.

1994 – Food and Drug Administration USA (FDA) approved the use of coronary stents in clinical setting.

A large randomized controlled trial, named CADILLAC trial (2,082 patients), demonstrated a lower occurrence of death, revascularization, reinfarction, or stroke in patients who were treated with BMS (fig. 2) in comparison to only PTCA.

Figure 2. Permeable cobalt-chromium bare-metal stent (4.0x20 mm) implanted into the right coronary artery (yellow arrow).
Drug-eluting stents

2002-2004 – Homologation of drug-eluting stent by FDA (USA)\(^1\)

Although treating patients with BMS was better than with PTCA, in 10-40% of patients *in-stent restenosis* was observed by 6 months of post-implantation due to intimal hyperplasia\(^3\).

New stents have thus emerged that had *antiproliferative* struts coating and were called drug-eluting stents (DES). In comparison to BMS, they offered *smaller* rates of death, of stent thrombosis, of target-vessel and target-lesion revascularization\(^3\).

*In-stent restenosis* was however noticed in DES (fig. 3).

*Figure 3.* In-stent restenosis of a drug-eluting stent of about 50% (arrows) located in the right coronary artery of a 47-year-old woman. A) a curved multiplanar reconstruction and B) orthogonal view of the restenosis.
BRS stents- a novelty

July 2016 – FDA approves first bioresorbable vascular scaffold stent (BRS)\(^4\).

BRS provide temporary mechanical support to the dilated vessel as well as a drug delivery system for a definite time period after percutaneous coronary intervention (PCI), after which the bioresorbable scaffold resorbs.

Absorb and DESolve are two types of stents that are most frequently implanted nowadays (fig. 4).

Advantages of BRS

BRS offer potential advantages:

- Avoidance of permanent caging of the stented arterial segment as a result of stent bioresorption

- Preservation of physiologic \textit{vasomotion} of stented segment

- Allow late \textit{luminal gain} and late expansive arterial \textit{remodeling}

- Once bioresorption is completed, permanent dual \textit{anti-platelet therapy} can be stopped\textsuperscript{5}

- Allow \textit{bypass} grafts on stented segments
The Absorb and DESolve BRS, the most frequent bioresorbable stents in use, have a poly-L-lactic acid (PLLA) scaffold, with a poly-D,L-lactic acid (PDLLA) coating. They are associated with an antimigratory agent, such as everolimus or novolimus\(^6\), which reduce proliferation of smooth muscle cells\(^7\).

Absorb BRS releases similar amounts of everolimus as the Xience drug-eluting stent- a new generation DES\(^8\).

BRS resorbs in the bloodstream on an average time of 2 years, in contrast to bare-metal or drug-eluting stents which will remain throughout the patient's life.
Bioresorbable stents:
imaging techniques
Most clinical trials with BRS were performed using invasive techniques such as conventional coronary angiography (CCA) (fig. 5-6), intravascular ultrasound (IVUS) (fig. 8) or optical coherence tomography (OCT) (fig. 9).

During CCA stent implantation, it is important to adjust the final stent dimensions to the lumen diameter, as the stent underexpansion was found to play a role in early stent thrombosis and in-stent restenosis of BMS, DES and BRS stents in the mid- and long-term.

Before stent implantation, CCA allows to measure the estimated healthy lumen diameter at the stenosis site by interpolating from the lumen diameter of proximal and distal reference segments.
Figure 6: A) Conventional Coronary Angiography (CCA). Severe stenosis of mid left anterior descending artery (arrow), prior to stenting. B) Angiography after bioresorbable stent (3.0 mm x 18 mm) implantation, with an excellent angiographic result (arrows). The small platinum indicators at the stent extremities are not visible, neither the bioresorbable scaffold.
CT lumen analysis with BRS

CT gives measurement of irregularly shaped short-axis area of the coronary artery lumen in mm, in addition to different diameter values of this cross-section (mean, minimal or maximal diameters)\(^{10}\).

In contrast, only diameter measurement is possible with CCA.

**Eccentric lumen stenoses** may be difficult to measure with the longitudinal view of CCA, as seen with the following example, in Figure 7 in orthogonal view B:

\[
\text{% Stenosis (max lumen diameter)} = \frac{(3.02-2.22)}{3.02} = 27\%
\]

\[
\text{% Stenosis (min lumen diameter)} = \frac{(2.60-1.26)}{2.60} = 52\%
\]

**Figure 7.** 61-year-old woman with 60 % bioresorbable stent restenosis of mid-left anterior descending artery (arrow head). Platinum markers are shown with arrows. Red line indicates the site of the greatest stenosis, and its parameters are shown in the orthogonal view B. In the orthogonal view A, the reference segment parameters could be seen.
BRS imaging with IVUS

Intravascular ultrasound (IVUS) is another invasive technique of coronary imaging used in many stent studies.

Grey-scaled IVUS with its axial resolution of 200 μm allows to slightly differentiate plaque components, while virtual histology (VH)-IVUS can detect necrotic core, fibrous or fibrofatty plaque and dense calcium with the exception of thin fibrous cap\(^1\).\(^1\)

BRS struts are only moderately visible by IVUS (fig. 8). Post-implantation follow-up analysis usually measures vessel, scaffold and plaque areas, mean lumen volume, as well as plaque and calcification volumes and remodeling index\(^12\),\(^13\).

Figure 8. Intravascular ultrasound (IVUS) post-implantation of BRS in a patient with severe stenosis of mid left anterior descending artery. (Same patient as in figure 6.) Adequate strut apposition is shown (arrows). Stent struts are usually moderately visible in IVUS, as seen here.
BRS imaging with OCT

Optical coherence tomography (OCT) is yet another invasive coronary imaging technique, used in BRS stent studies.

Its resolution of 10-15 μm provides good specificity and sensitivity in determination of plaque type and allows to measure the thickness of a fibrous cap. Differentiation of the lipid pool from calcium is however limited.

Moreover, shallow penetration of OCT of 1 to 3 mm makes the assessment of the entire plaque volume challenging\textsuperscript{11} (fig. 9).

\textbf{Figure 9.} Bioresorbable scaffold struts visualization with OCT, after BRS implantation in a patient with severe stenosis of mid left anterior descending artery. (Same patient as in figure 6 and 8.) Struts typically appear as black boxes with OCT (arrows).
BRS imaging with CT scan: comparison with metallic stent imaging

Most stents have a metallic scaffold which causes CT blooming artifacts (fig. 10), potentially leading to severe impairment to the diagnosis of intrastent restenosis.

Different image-processing matrices are being used to reduce blooming, such as edge-enhancing kernels\(^\text{14}\) (fig. 10); despite improved stent strut definition with these dedicated reconstruction algorithms, significant artificial thickening of the metallic stent walls persists.

Figure 10. Reduced stent blooming artifacts and improved strut definition with sharp (XCD) in comparison to smooth (XCB) kernel. 69-year-old female, first obtuse marginal artery stent. 256-slice CT acquisition with prospective ECG-gating, and image reconstruction with a medium-soft (XCB, left) and edge-enhancing (XCD, right) reconstruction kernels, multiplanar reformat.
The BRS platform is made of degradable polymers, with metal-free struts that do not cause blooming artifacts.

BRS struts are totally invisible with coronary CT angiography, even after immediate implantation. However, BRS can be identified through the small platinum indicators at their extremities (fig. 11).

**Figure 11. Bioresorbable stent, mid-circumflex artery.** 58-year-old man, conventional angiography showed 80% mid-circumflex stenosis and followed with implementation of a bioresorbable stent (BRS, Abbott Absorb 3.5 x 28 mm). Under the BRS clinical register (Dr Samer Mansour et al.), a 256-row CT scan with prospective synchronization to ECG was performed one month following angioplasty.

Only proximal and distal metallic markers are visible on scan (white arrows). One could also note positive remodelling (arrow head) and two calcification loci proximal to the lesion (yellow arrows). Good permeability of the stent is observed. No significant artifacts are visualized.
Figure 12. CT angiography correlation with conventional angiography.

A) 256-slice ECG-gated CT angiography. Bioretordable stent (2.5 x 18 mm) on left anterior descending artery, 14 months after implantation. Mixed intrastent plaque with severe lumen stenosis (arrowhead). Platinum markers (arrows).

B) Conventional coronary angiography. Severe intra-stent stenosis was confirmed (arrowhead). Platinum markers are not visible.
As the spatial resolution increases, the image noise does so too. The iterative reconstruction algorithms, implemented in many CT scanners, allow to reduce the radiation dose and to reduce the noise, by taking many iterations of an image\textsuperscript{15}.

Such algorithm would allow clearer images of BRS intrastent lumen and allow to decrease the blooming artifacts of its markers.

A technique of radiation reduction called prospective axial ECG-gating or ECG-triggering, consists of turning the beam off during systole. It can reduce radiation by 80\% in comparison with continuous helical acquisition\textsuperscript{16}.

With optimal radiation reduction strategies, CT should be an option of choice for noninvasive follow-up of patients with BRS.
BRS CT imaging: assessment parameters

Assessment parameters of intrastent lumen and arterial walls:

- **Lumen diameters**
  - Minimal, average and maximal
- **External (vessel) diameter**
  - Minimal, average and maximal
- **Lumen and external (vessel) areas**
- **Lesion length**
- **Remodeling index**
  - External lesion area (or diameter) / External reference area (or diameter)
  - Remodeling is a physiological response of the artery to lumen stenosis; however been associated with high risk plaque

- **Plaque composition analysis from -1000HU to +3000HU**
  - Where composition of < 30 HU (hypoattenuation) suggests fatty unstable plaque
  - Composition of >220 HU indicates calcifications in the plaque

Low attenuation, remodelling index >1.05, coarse calcifications and microcalcifications are predictors of plaque instability.
BRS imaging with CT: lumen assessment

BRS usually allow adequate assessment of in-stent lumen.

\[
\% \text{ stenosis (area)}^{17} = \left( \frac{\text{reference area} - \text{minimal area}}{\text{reference area}} \right) * 100\%
\]

\[
\% \text{ stenosis (minimal diameter)} = \text{idem as with areas.}
\]

In figure 13, calculation of \% stenosis with areas gives 61\% stenosis, while calculation with minimal diameters gives 52\% of stenosis.

**Qualitatively** this stenosis was diagnosed to be at 60\% with CT scan images.

**Figure 13.** 61-year-old woman with 60 \% bioresorbable stent restenosis of mid-left anterior descending artery (arrow head). Platinum markers are shown with arrows. Red line indicates the site of the greatest stenosis, and its parameters are shown in the orthogonal view B. In the orthogonal view A, the reference segment parameters could be seen.
BRS imaging with CT: remodeling index

Remodeling index = External lesion area (or diameter) / External reference area (or diameter)

Positive remodeling is when index > 1.05

In this example:

Remodeling index (max diameters) = 7.50/3.04 = 2.5

Remodeling index (areas) = 34.2/6.49 = 5.3

Here, the difference between remodeling index (max diameters) and remodeling index (areas) is 2X
BRS imaging with CT: plaque volume assessment

In addition, BRS allow, for the first time, in-stent plaque imaging with CT without the need of metal artifact reduction strategies.
BRS clinical outcomes
BRS: clinical trials

**ABSORB II randomized control trial (RCT) \(^{18}\):**

- Comparison of everolimus-eluting BRS with an everolimus drug-eluting stent (DES) in 501 patients, using intravascular ultrasound (IVUS)

- Clinical outcomes at one-year follow-up were similar between BRS and DES.

**ABSORB III (RCT) \(^{19}\):**

- Comparison of everolimus-eluting BRS with a everolimus-DES in 2008 patients

- Showed noninferiority of BRS for target lesion failure at one-year follow-up.
### Table 1. BRS clinical outcomes: comparison with DES\textsuperscript{20,21,19}

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>Stents implanted</th>
<th>No of patients</th>
<th>Follow-up</th>
<th>Clinical outcomes(\dagger)</th>
<th>Stent thrombosis(\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wöhrle et al.</td>
<td>EES</td>
<td>53</td>
<td>1 year</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>CIBELES study</td>
<td>SES vs EES</td>
<td>207</td>
<td>1 year</td>
<td>15.9% vs 11.1%</td>
<td>3% / 0%</td>
</tr>
<tr>
<td>Absorb cohort A</td>
<td>Absorb BRS</td>
<td>30</td>
<td>5 years</td>
<td>3.3% at 18 mo - 5 years</td>
<td>0%</td>
</tr>
<tr>
<td>Absorb cohort B</td>
<td>Absorb BRS</td>
<td>101</td>
<td>2 years</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Absorb II</td>
<td>Absorb BRS/ Xience DES</td>
<td>335/166</td>
<td>1 year</td>
<td>5% / 3%</td>
<td>0.9% / 0%</td>
</tr>
<tr>
<td>Absorb EXTEND</td>
<td>Absorb BRS</td>
<td>512</td>
<td>ongoing</td>
<td>4.3%§</td>
<td>0.8%</td>
</tr>
<tr>
<td>Absorb III</td>
<td>Absorb BRS/ Xience DES</td>
<td>1322/686</td>
<td>ongoing, upto 5 years</td>
<td>3% / 2.5%</td>
<td>1.5% / 0.7%</td>
</tr>
</tbody>
</table>

Drug-eluting stents (DES) are: EES- everolimus eluting-stents and SES- sirolimus eluting-stents; \(\dagger\) Clinical outcomes (or MACE) are reported as published, such as a composite of target lesion revascularization, target vessel myocardial infarction and cardiac death; \(\ddagger\) Definite or probable thrombosis; mo- months; § rate of ischemia-driven target-lesion revascularization.
Key CT studies with BRS
Key BRS CT studies

In vitro or clinical studies involving CT imaging of BRS are still scarce.

They confirmed an excellent in-stent lumen visibility allowed by BRS, and also demonstrated good patency outcomes.

An *in vitro* study by Gassenmaier et al.\textsuperscript{22} done on 27 common stents (one poly-L-lactide BRS) implanted into plastic tubes showed:

- that when using dual-source CT the in-stent lumen visibility is up to 80% in metal stents and 100% in BRS.

- that BRS causes no blooming artefacts and aside from the platinum markers are not visible on CT angiography, allowing complete lumen visibility.
**Table 2. Parameters measured in BRS CT studies**

<table>
<thead>
<tr>
<th>Minimal luminal diameter (mm)</th>
<th>Minimal luminal area (mm²)</th>
<th>Mean luminal area (mm²)</th>
<th>Average lumen volume (mm³)</th>
<th>Diameter stenosis (%)</th>
<th>Area stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>n/a</td>
<td>3.6 ± 0.9</td>
<td>5.2 ± 1.3</td>
<td>n/a</td>
<td>19 ± 9</td>
</tr>
<tr>
<td>B</td>
<td>n/a</td>
<td>3.5 ± 1.0</td>
<td>5.1 ± 1.4</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>C</td>
<td>n/a</td>
<td>3.25 ± 2.20 to 3.25 ± 4.33</td>
<td>n/a</td>
<td>72.12 at 18 mo 73.85 at 60 mo</td>
<td>n/a</td>
</tr>
<tr>
<td>D</td>
<td>2.9 ± 0.5</td>
<td>5.1 ± 2.3</td>
<td>6.7 ± 2.5</td>
<td>n/a</td>
<td>15.9 ± 10</td>
</tr>
</tbody>
</table>

A) An 18-month study by Serruys et al. (Lancet 2009) with 25 patients. B) A study by Nieman et al. in J Am Coll Cardiol 2013 (ABSORB trial cohort)- a quantitative CT analysis was performed in 61 patients within 18 months post BRS implantation. C) A study by Onuma et al. (JACC Cardiovasc Interv 2013) conducted with ABSORB A cohort. CT angiography was performed at 18 months (25 patients) and at 5 years (18 patients). D) A 12-month CT study was done by Verheye et al. (JACC Cardiovasc Interv 2014) with 12 patients with DESolve stent. All studies (A-D) showed good BRS patency.

n/a- not available; SD- standard deviation; values are reported as mean ± SD or as median ± interquartile range where applicable; mo- months
Teaching points

• Most stents have a metallic scaffold which causes CT blooming artifacts, potentially leading to severe impairment to the diagnosis of intrastent restenosis.

• The bioresorbable stent (BRS) platform is made of resorbable polymers, with metal-free struts that do not cause blooming artifacts.

• BRS struts are invisible with coronary CT angiography, even after immediate implantation. However, BRS can be identified by the small platinum indicators at their extremities.

• BRS usually allow adequate assessment of in-stent lumen and, for the first time, in-stent plaque imaging with CT, without the need of metal artifact reduction strategies.
Conclusion

- BRS are a promising alternative to bare-metal and drug-eluting metallic stents, with good clinical results and increased CT assessability of in-stent lumen.

- Practicing radiologists should be aware of this new stent technology.

- The specific structure of BRS makes them recognizable on cardiac CT.

- Although bioresorbable stents are subjects to traditional cardiac CT artifacts, their assessment does not require specific metal artifact reduction strategies.
References

15. Deseive S et al. JACC Cardiovasc Imaging 2015; 8:888-96
Thank you

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« (...) For brevity’s sake I shall use the expression ‘rays’; and to distinguish them from others of this name I shall call them ‘X-rays’¹. »

Wilhelm Röntgen

¹http://quotesgram.com/x-ray-quotes/ (visited on 13 Dec 2016)