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Monitoring In Vivo Absorption of a Drug-Eluting Bioabsorbable Stent With Intravascular Ultrasound-Derived Parameters

A Feasibility Study

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Objectives The aim of this study was to investigate the feasibility of using quantitative differential echogenicity to monitor the in vivo absorption process of a drug-eluting poly-l-lactic-acid (PLLA) bioabsorbable stent (BVS, Abbott Vascular, Santa Clara, California).

Background A new bioabsorbable, balloon-expanded coronary stent was recently evaluated in a first-in-man study. Little is known about the absorption process in vivo in diseased human coronary arteries.

Methods In the ABSORB (Clinical Evaluation of the BVS everolimus eluting stent system) study, 30 patients underwent treatment with the BVS coronary stent system and were examined with intracoronary ultrasound (ICUS) after implantation, at 6 months and at 2-year follow-up. Quantitative ICUS was used to measure dimensional changes, and automated ICUS-based tissue composition software (differential echogenicity) was used to quantify plaque compositional changes over time in the treated regions.

Results The BVS struts appeared as bright hyperechogenic structures and showed a continuous decrease of their echogenicity over time, most likely due to the polymer degradation process. In 12 patients in whom pre-implantation ICUS was available, at 2 years the percentage-hyperechogenic tissue was close to pre-implantation values, indicating that the absorption process was either completed or the remaining material was no longer differentially echogenic from surrounding tissues.

Conclusions Quantitative differential echogenicity is a useful plaque compositional measurement tool. Furthermore, it seems to be valuable for monitoring the absorption process of bioabsorbable coronary stents made of semi-crystalline polymers. (J Am Coll Cardiol Intv 2010;3:449–56) © 2010 by the American College of Cardiology Foundation

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Coronary stenting has resolved mechanical problems related to balloon dilation of diseased coronary arteries, such as acute recoil and late negative lumen remodeling (1,2), and drug-eluting stents (DES) have largely overcome the problem of restenosis due to excessive neointimal proliferation (3). However, delayed endothelialization of the stent surface after DES deployment might predispose some patients to late stent thrombosis (4–6). Recently, bioabsorbable devices have been introduced as an alternative therapy to permanently implanted metallic DES designs and are currently in clinical testing to evaluate whether they overcome the aforementioned problems. They preserve the mechanical benefits of lumen scaffolding after balloon dilation while allowing late lumen enlargement and secondary intervention or surgery at the stented site after absorption, if necessary (7–10).

Monitoring the absorption process of biodegradable devices in vivo is difficult, because information can only be derived indirectly. There are only a few reports describing this absorption process (11), and most of them are ex vivo and/or animal experiments (7,11,12). It would be of great interest to monitor the rate and degree of absorption over time and relate it to other parameters such as restoration of vasomotor function, coronary vessel dimensions, and alterations of plaque composition (4).

Abbreviations and Acronyms

DES = drug-eluting stent(s)
EEM = external elastic membrane
ICUS = intracoronary ultrasound
NIH = neointimal hyperplasia
PLLA = poly-l-lactic acid

In the ABSORB (Clinical Evaluation of the BVS everolimus eluting stent system) study (7) intracoronary ultrasound (ICUS) was used to measure dimensional parameters (including lumen, stent, and vessel areas) as well as to quantify plaque composition (10). The objective of the current study was to investigate the feasibility of applying ICUS-derived plaque compositional measurements (e.g., differential echogenicity) (13) as a surrogate to quantify the likely extent of absorption of the new poly (L-actide) (PLLA) BVS stent (Abbott Vascular, Santa Clara, California) (7) at different points in time.

Methods

Study population. The study design of the multicenter ABSORB trial has been described previously (7,10). In brief, 30 patients at 4 different sites were enrolled with de novo lesions in a native coronary artery, which could be covered by a single BVS stent. Exclusion criteria were evolving myocardial infarction, left main disease, ostial or bifurcation lesions, total occlusions, moderate to heavy calcified lesions, thrombotic lesions, or a left ventricular ejection fraction <30%. All patients signed an informed consent document, and the local ethical committees approved the study.

Study procedure. The target lesions were electively treated applying standard interventional procedures with mandatory pre-dilation and device implantation with inflation not exceeding the balloon-rated burst pressure of 16 atm. If necessary, post-dilation was allowed with a balloon shorter than the implant length. Bailout to cover possible edge dissections was permitted with standard metallic stents.

After implantation, an ICUS examination was performed. In a minority of the cases at 1 center (n = 12), pre-implantation ICUS was also available. After the initial procedure, follow-up ICUS examinations were performed at 6 months and at 2 years. The ICUS catheters were 20-MHz phased array catheters (Volcano Therapeutics, Santa Clara, California) pulled back automatically at a constant speed of 0.5 mm/s; the acquired images were digitally stored for later quantification.

BVS stent design. The BVS device is made of semi-crystalline polymer (PLLA), which is supposed to be fully reabsorbed in the human body between 2 and 3 years (7,10). The backbone of the device is coated with a more rapidly bioabsorbable poly (D, L-actide) layer containing the antiproliferative drug everolimus (Novartis, New York, New York). During the absorption process the molecular weight of polymer chains is progressively reduced as ester bonds between lactide repeat units are hydrolyzed. Eventually, the resulting lactic acid and its small molecular weight oligomers migrate out of the polymer matrix and are rapidly metabolized in surrounding tissues and blood to the pyruvate or Krebs energy cycles. When this process is imaged by ICUS, individual cross-sectional images show a diminishing gray-level intensity of the struts over time (Fig. 1).

Quantitative ICUS. Before quantification, all ICUS examinations were retrospectively image-based gated by the validated Intelligate method (14). This method automatically selects, from a continuous, nonelectrocardiogram-gated ICUS examination, the near end-diastolic frames and builds a new gated study. The advantages of gating are a smooth appearance of the coronary vessel in longitudinal reconstructed views instead of the typical saw-tooth shape appearance of nongated ICUS (15). This provides an improved quantitative accuracy as well as enhanced matching of baseline and follow-up studies (16,17). The ICUS studies were analyzed side-by-side on a single computer screen. The stented areas were identified by the first and the last cross-sectional ICUS frame in which stent struts could be identified and/or where the proximal or distal metallic markers could be identified (Fig. 2). To match the 2-year follow-up (and the pre-implantation ICUS studies) in which the stent struts were not always apparent, other identifiable landmarks such as side-branches and calcium spots were also used.

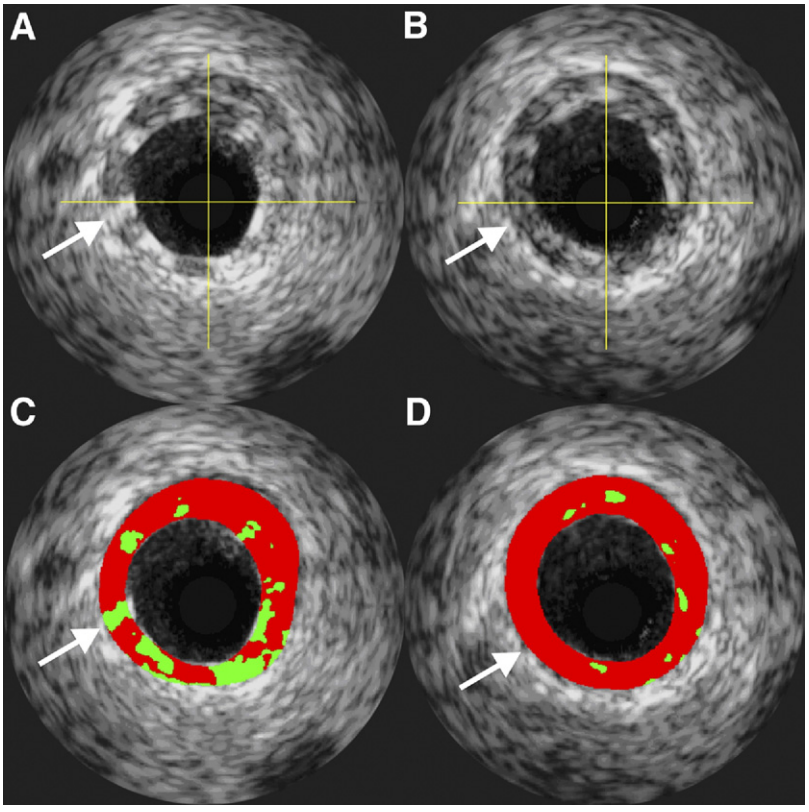

Figure 1. ICUS and Echogenicity Appearance of the BVS Device

(A) Intracoronary ultrasound (ICUS) image immediately after BVS device implantation. The blooming parallel dashes in the image **(arrow)** are the individual struts. **(B)** Approximately the same location acquired at 6-month follow-up. The diminished appearance of the struts can be clearly appreciated. **(C and D)** The same ICUS images as in **A** and **B**, respectively, with hypoechogenic **(red)** and hyperechogenic **(green)** areas by the quantitative echogenicity software presented as a color overlay. The diminished appearance of the hyperechogenic components is apparent in **D**.

The comparison between the ICUS studies acquired at the different time points is not based on a match between individual cross-sections but rather on a comparison of the complete stented segments, making the method less dependent on alignment between individual frames.

The lumen–intima interface and the outer vessel border, identified at the external elastic membrane (EEM) crossing, were measured at an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) with validated semi-automated quantitative ICUS analysis software (CURAD vessel analysis, Wijk bij Duurstede, the Netherlands) (18). The contours of these analyses were used to determine the areas and volumes in plaque compositional analysis.

Differential echogenicity analysis. In-house–developed and previously validated (13), fully automated quantitative echogenicity analysis software was applied to quantify the plaque composition and to evaluate its possible use to quantify the absorption process of the BVS stents. The applied algorithms of this software have been previously published (13). In brief, the mean gray-value of the adventitia is used to classify tissue components as either hypoechogenic (e.g., gray-values lower than the mean adventitia level) or as hyperechogenic (e.g., gray-values at higher levels than that of the adventitia). The adventitia is defined as a layer extending from 0.2 to 0.5 mm outside of the EEM, the contour, which is detected during the quantitative analysis process. To avoid artifacts, tissue within acoustic shadowed areas is excluded, and very high gray level pixels such as metallic stents are identified as upper tissue. After the tissue identification process, the fraction of hypoechogenic versus hyperechogenic tissue volume is calculated (together they are set at 100%) for the entire investigated segment.

Echogenicity was measured before intervention (when available), after implantation, at 6 months, and at 2-year follow-up. To investigate the relative absorption at 6 months, for patients in whom pre-implantation ICUS was available, the change in echogenicity of the stented region was calculated with the following formula:

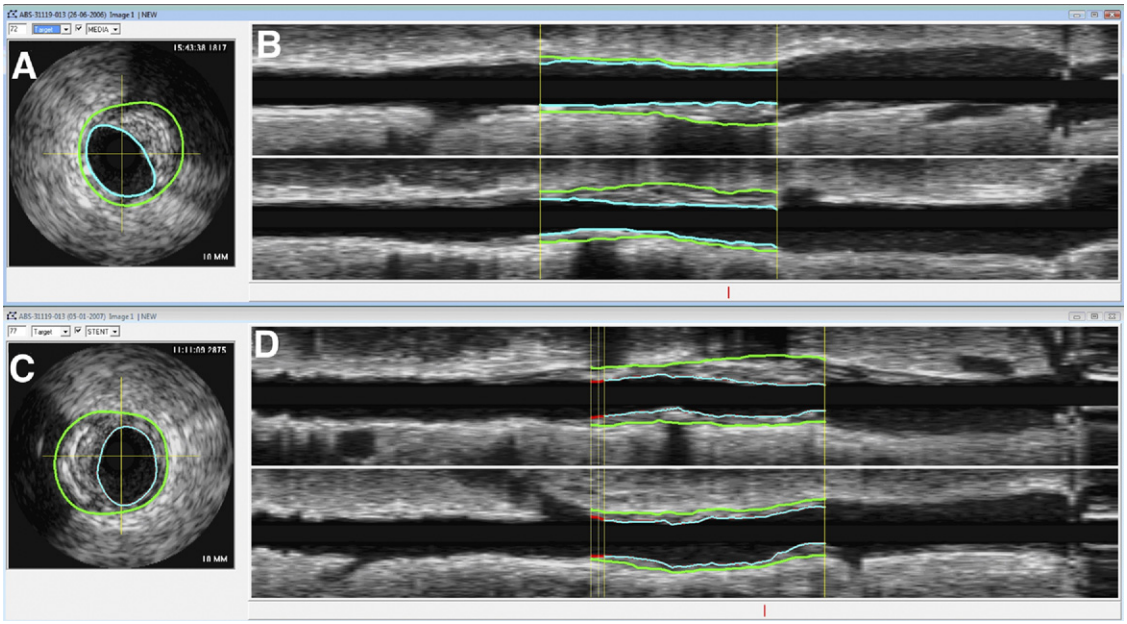

Figure 2. Side-by-Side QCU Analyses of Post-Implantation and 6-Month Follow-Up

An example of the side-by-side quantitative coronary ultrasound (QCU) analyses of the BVS-treated regions. An **(A)** individual cross-section and **(B)** reconstructed longitudinal view of a post-implantation examination. **(C and D)** Equivalent images in the same patient, at 6-month follow-up. The **left-hand side** of **B** and **D** is the distal part of the coronary artery, and the **right-hand side** is the proximal vessel. The **blue lines** indicate the stent contour, the **green lines** indicate the outer vessel border, and the **red lines** indicate the lumen border. At baseline the echogenicity measurements are calculated between the stent and the outer vessel border, between the **blue and green lines (A)**, and at 6 months the areas are between: 1) lumen and outer vessel (between **red and green lines**, neointima included, **C**); and 2) stent and outer vessel (between **blue and green lines**, neointima excluded, **C**).

$$\%\text{DifferentialEchogenicity} = \frac{(\%\text{Hyper6M} - \%\text{HyperPre}) - (\%\text{HyperPost} - \%\text{HyperPre})}{(\%\text{HyperPost} - \%\text{HyperPre})} \cdot 100\%$$

where HyperPre = the amount of %Hyperechogenicity before BVS implantation, post = after implantation, and 6M = %Hyperechogenicity at 6-month follow-up.

The same formula was also applied to calculate the relative change at 2-year follow-up by replacing the parameter of %Hyper6M with %Hyper2YR.

The presence of neointima tissue at follow-up potentially affects the differential echogenicity calculations. To study this effect at the 6-month follow-up, the composition of the stented volume was determined for: 1) the region between the lumen- and EEM-contour (neointima tissue included), and 2) between the BVS stent and the EEM contour (neointima tissue excluded).

In vivo quantitative echogenicity validation. Although quantitative echogenicity has been validated ex vivo as a coronary plaque compositional tool, in vivo validation remains a challenge, because there is no true "gold standard." Therefore, most methods are validated ex vivo with histopathology as a reference (13,19).

The ABSORB trial provided an excellent opportunity for in vivo validation of a plaque compositional measurement tool such as echogenicity by providing the possibility to image a coronary plaque and analyze its composition, reassess this composition after introduction of a hyperechogenic structure (the BVS stent), and then further assess changes over time as the stent absorbs and disappears.

Furthermore, the reproducibility or the robustness of the echogenicity method has been validated in vivo within this study. The effects of balloon dilation (change of dimensions and location of the plaque) and implantation of the hyperechogenic stent onto the mean gray-value of the adventitia (e.g., the calibration parameter) was studied in patients in whom pre- and post-implantation ICUS was available. The mean adventitia gray-level values as determined from these pre- and post-implantation ICUS images, within a time window of approximately 20 to 30 min, were compared and presumed to remain unchanged.

Statistical analysis. Continuous variables are expressed as mean ± SD and compared by means of a paired *t* test. Overall ICUS parameters (stent lengths, volumes, and echogenicity) across all time points were compared with repeated measure analysis of variance. Two post-hoc tests (between post-implantation and 6-month follow-up and between 6-month and 2-year follow-up) were performed with Bonferroni corrections (p value for significance <0.025) for p values <0.05 on analysis of variance.

Table 1. Quantitative Pre- and Post-BVS Stent Implantation Results

	Pre (n = 12)	Post (n = 12)	p Value
Stent length (mm)	12.6 ± 1.7	13.4 ± 2.9	0.1
Plaque volume (mm^3)	114 ± 41	111 ± 35	0.6
Calcification volume (mm^3)	0.3 ± 0.3	0.2 ± 0.3	0.6
Upper volume (mm^3)	0.1 ± 0.2	0.9 ± 1	0.02
Hyper volume (mm^3)	5.9 ± 5.9	17.2 ± 8.1	<0.001
Hyperechogenicity (%)	5.6 ± 4.8	17.8 ± 10.6	<0.001

This table shows the quantitative pre- and post-BVS stent implantation results for the 12 patients in which pre-implantation intracoronary ultrasound was available. The p values are calculated by a paired 2-tailed student *t* test.

Results

Study patients. Pre-implantation ICUS was performed in 12 of the 30 patients enrolled in the ABSORB study (Table 1). Immediate post-implantation ICUS acquisition was successful in 27 patients, 26 ICUS examinations were acquired at 6 months, and 21 ICUS examinations were obtained at 2-year follow-up. In 7 patients, complete serial ICUS data were available.

Quantitative echogenicity validation in vivo. In the 12 patients with pre- and post-implantation ICUS, the mean adventitia gray-levels (the calibration parameter) showed similar values for the treated segments before (152 ± 16) versus after (152 ± 16) implantation (p = 0.92).

Before versus after BVS implantation. The struts appear as hyperechogenic spots within the plaque but, unlike calcific spots, cause no acoustic shadowing (Fig. 1).

The %hyperechogenicity of the plaque was significantly increased (Table 1, Fig. 3), after stent implantation. There were no significant differences found in measured stent length and levels of calcified tissue (Table 1).

6-month and 2-year follow-up. The average %hyperechogenicity of the plaques showed a continuous decrease over the follow-up period, with the most pronounced changes within the first 6 months (Table 2, Fig. 3).

Calcification did not increase significantly during the first 6 months but showed a small but significant increase between 6 months and 2 years (Table 2).

Analysis of the 7 patients with ICUS at all time points (true serial comparison) showed that the %hyperechogenicity at 2 years within the treated segments was close to the pre-implantation values (%hyperechogenicity pre-implantation = 4.9%, after stenting = 19.6%, 6 months = 8.5%, 2 years = 5.9%) (Fig. 4). The relative decrease in %hyperechogenicity in the 12 patients with pre-implantation ICUS was at 6 months (67 ± 27%; applying formula 1) and at 2 years (91 ± 25%; applying the adapted formula 1; n = 7), indicating that the absorption process was likely to be complete.

The influence of the neointimal hyperplasia (NIH) at 6 months on the %hyperechogenicity results showed that, with NIH included, %hyperechogenicity was 9.4 ± 6.3%, compared with 9.8 ± 6.6% if NIH was excluded (p = 0.01, n = 25) (Fig. 4). Although the difference was significant, the absolute influence is limited (Fig. 4).

Discussion

This study shows that the acoustic properties of coronary plaques in BVS-treated segments are heavily influenced by the polymer stent implantation and that the effect can be quantified with quantitative echogenicity. The treated re-

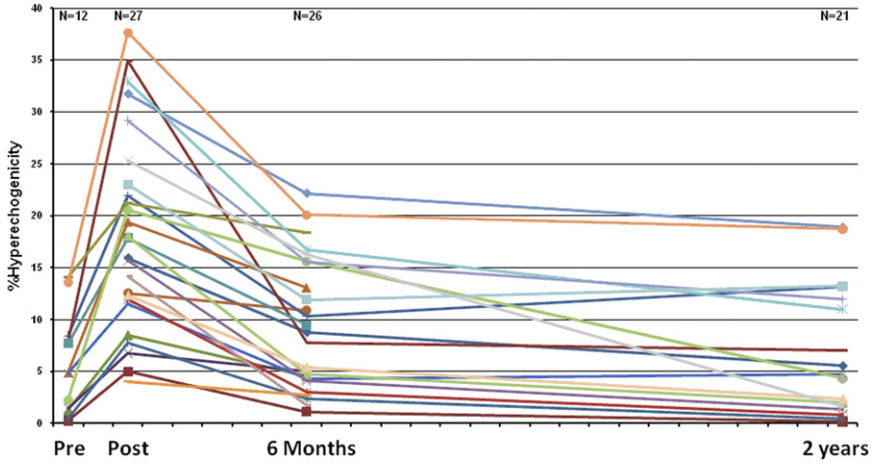

Figure 3. Changes Over Time of Patients Who Received a BVS

The hyperechogenicity values and changes at each time point in each patient. The impact of implantation of the BVS device on the hyperechogenicity values is large. In most patients, the absorption of the scaffold is the greatest in the first 6 months.

Table 2. Quantitative Post-BVS Stent Implantation: 6-Month and 2-Year Follow-Up Results

	Post (n = 17)	6-Month (n = 17)	2-Year (n = 17)	p Value		
				ANOVA*	Post 6 Months	Post 2 Years
Stent length (mm)	12.8 ± 2.3	13.2 ± 3.1	13.2 ± 3.8	0.55	0.06	0.55
Plaque volume (mm^3)	88 ± 37	107 ± 39	93 ± 38	0.54	<0.001	0.41
Calcification volume (mm^3)	0.2 ± 0.3	0.3 ± 0.3	0.5 ± 0.6	0.04	0.51	0.04
Upper volume (mm^3)	1.1 ± 1.1	0.16 ± 0.3	0.04 ± 0.1	0.001	<0.001	<0.001
Hyper volume (mm^3)	15.6 ± 7	9.7 ± 7	6.2 ± 5.4	<0.001	<0.001	<0.001
Hyperechogenicity (%)	20.9 ± 9.9	10 ± 6.7	6.9 ± 6.3	<0.001	<0.001	<0.001

This table presents the quantitative post-BVS stent implantation and the 6-month and 2-year follow-up results for 17 patients in which intracoronary ultrasound was available at these time points.
*Repeated-measures analysis of variance (ANOVA) was performed for 17 patients. The post hoc analyses were performed with Bonferroni corrections (significant level of p value is 0.025).

gion showed an increase in hyperechogenic tissue components immediately after implantation, which diminished over time during the absorption process. Although ultrasound might overestimate the absolute amount of hyperechogenic tissue, due to the "blooming" effect of the polymeric material on ultrasound, this increased sensitivity to detect the polymer could be clinically useful. Quantitative differential echogenicity might be used as a surrogate to monitor the absorption process in vivo, assuming that a decrease in echogenicity parallels stent absorption. The differential echogenicity measurements in this study show that the %hyperechogenic tissue components in the treated regions are, by 2-year follow-up, almost back to the levels measured before implantation, suggesting that the implant has either fully reabsorbed or is echogenically undifferentiable. This finding is consistent with animal studies in which histopathology 2 to 3 years after implantation found that the locations of the stent struts were now filled by proteoglycans with occasional micro-calcification (10). In addition to monitoring the absorption of the BVS implants, this study provided an excellent in vivo validation of ICUS-derived plaque compositional measurement tools and showed that quantitative echogenicity is a robust method.

The use of bioabsorbable materials for coronary stents was proposed 1 decade ago (20), with the BVS bioabsorbable drug-eluting device design showing encouraging results in the first-in-man ABSORB trial (7). Multiple imaging methods were used, including angiography, ICUS, optical coherence tomography, and noninvasive multislice computed tomography) (21). Currently only ICUS is capable of quantifying the absorption process. Other imaging modalities might provide complementary information on the "healing" process. For example optical coherence tomography shows the formation of neointima with much greater

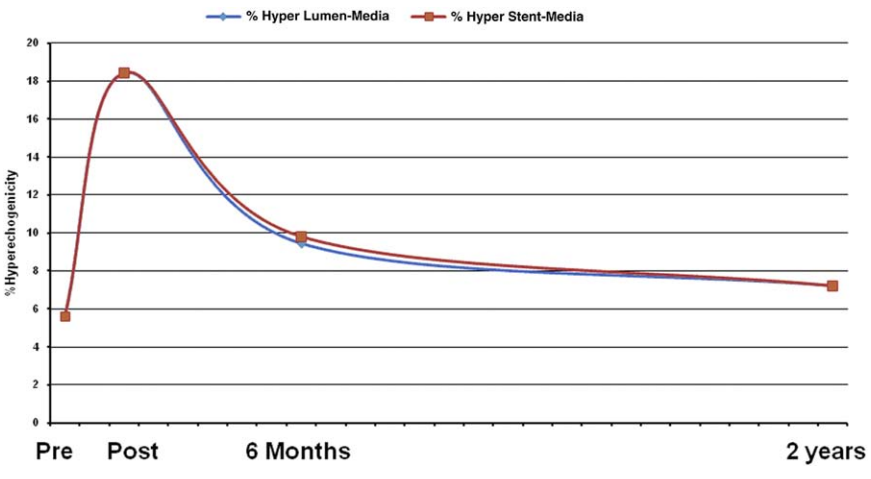

Figure 4. Mean Acoustic Tissue Property Changes of the Plaque in BVS-Treated Segments

The average changes in echogenicity of the BVS-stented regions (n = 7) of patients in whom pre-implantation imaging was available. The **red line** represents the measurements with neointima tissue included, and the **blue line** represents the measurements with neointima tissue excluded. At 2-year follow-up, the %hyperechogenicity is almost back at the level measured before implantation, suggesting that the absorption process is almost completed. The polymeric stent struts appear much larger in the ultrasound images than their real dimensions.

resolution than ICUS, but optical coherence tomography alone cannot quantify the absorption process. Radiographic techniques are not useful, because the PLLA material is radiolucent.

The determination of the degradation rate of bioabsorbable scaffolds is an important issue, because their mechanical properties diminish as the degradation progresses. In in vitro studies, these properties are examined by evaluating mass loss, crystallinity, and tensile stress (22). These parameters are impossible to measure in vivo in humans.

The use of ultrasound to monitor the degradation process of biopolymers has been proposed previously and was tested in an in vitro setup (12). Wu et al. (12) showed that the degradation behavior of biodegradable polymers can be closely monitored by ultrasonic techniques. Wu et al. measured differences in wave speeds, in contrast to the current study, where changes in acoustic parameters were quantified by changes in echogenicity. Despite the different methods, both studies found that the ultrasonic properties of the biopolymers change significantly during the degradation process until finally, at the time of total degradation, there were no acoustic signals identifying the presence of polymeric materials.

This study also shows that differential echogenicity is a robust technique and can detect both large plaque compositional changes, such as between pre- and post-implantation, and also smaller changes, such as those occurring between the 6-month and 2-year follow-up. Another ICUS-derived plaque compositional measurement tool (IVUS-VH, Volcano Therapeutics) was also used in the ABSORB study. This method uses the raw radiofrequency signals of the ICUS catheter to identify plaque composition (19). Serruys et al. (10) reported that IVUS-VH measurements showed a significant increase of the detected amount of calcium and necrotic tissue components between pre- and post-BVS implantation in 12 patients with pre- and post-implantation ICUS data. At 6-month follow-up IVUS-VH showed a significant decrease in these 2 tissue components, which seemed to be related to absorption of the stent. However, and in contrast to our findings where the %hyperechogenic tissue showed a continuous gradual decrease over time, IVUS-VH showed an increase of calcium and necrotic tissue between 6 months and 2 years, although statistically nonsignificant. The differences between the 2 methods might have been caused by IVUS-VH software misclassification. Specifically, the PLLA material might be classified falsely as calcium, because the methods algorithm does not accommodate specific ultrasound scattering characteristics for PLLA material. By contrast, the stent appears bright hyperechogenic on ICUS images and is being replaced after 3 years by proteoglycans, which appear hypoechogenic on ICUS. It is likely that differential echogenicity is more sensitive to detect changes in the PLLA material over time in the human coronary artery.

Study limitations. The study population, in particular those with ICUS images at all time points, is small, as is usual in first-in-man studies.

The presented method is limited by the physical properties of ICUS such as spatial resolution, which is related to the design and operating frequency of the ultrasound transducer(s). Dramatic changes in the plaque morphology in the stented regions during the follow-up period could possibly affect ICUS-derived methods. However, previous research evaluating the sirolimus-eluting stent did not show compositional changes significantly affecting echogenicity measurements during the first 2 years (4). The method also relies on the accuracy of the analysis, because it uses the lumen and the EEM contour to identify the plaque and adventitia locations within the images.

The curve of the average %hyperechogenicity, as shown in Figure 3, is extrapolated from limited time points. Additional information will be forthcoming in a follow-up study evaluating an improved version of the BVS device; one-half of the population will undergo a follow-up at 6 months, and the other one-half will undergo a follow-up at 12 months, and both groups will also have a follow-up at 2 years. The differential echogenicity methodology requires further ex vivo and in an in vitro validation against histopathology (ex vivo) to changes in crystallinity and mass loss (in vivo).

Conclusions

Quantitative differential echogenicity seems to be a robust plaque compositional measurement tool. Furthermore, it showed encouraging results when applied as a monitoring tool for the absorption process of bioabsorbable coronary stents made of semi-crystalline polymers.

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