

A Novel High-Visibility Radiopaque Tantalum Marker for Biliary Self-Expandable Metal Stents

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Background/Aims: Radiopaque metal markers are required to improve X-ray absorption by self-expandable metal stents (SEMSs) to enable precise stent placement. A new tantalum radiopaque marker was recently developed using an ultrasonic spray technique. The aim of the present study was to evaluate the safety and visibility of tantalum markers. **Methods:** A total of three beagle dogs were used for a gastrointestinal tract absorption test. Five tantalum markers were placed in the stomach of each dog endoscopically. Excreted tantalum markers were collected, and their weights were compared to the original weights. In radiopacity tests, marker radiopacities on X-ray images were quantified using ImageJ software and compared with those of commercially available metal markers. Finally, the radiographic images of six patients who underwent biliary SEMS placement using tantalum marker Nitinol SEMSs (n=3) or gold marker Nitinol SEMSs (n=3) were compared with respect to marker brightness on fluoroscopic images. **Results:** Absorption testing showed that the marker structures and weights were unaffected. Radiopacity tests showed that the mean brightness and total brightness scores were greater for tantalum markers (226.22 and 757, respectively) than for gold (A, 209 and 355, respectively; B, 204.96 and 394, respectively; C, 194.34 and 281, respectively) or platinum markers (D, 203.6 and 98, respectively). On fluoroscopic images, tantalum markers had higher brightness and total brightness scores (41.47 and 497.67, respectively) in human bile ducts than gold markers (28.37 and 227, respectively). **Conclusions:** Tantalum markers were found to be more visible than other commercially available markers in X-ray images and to be resistant to gastrointestinal absorption. (**Gut Liver 2019;13:366-372**)

Key Words: Marker; Self expandable metallic stent; Tantalum

INTRODUCTION

Endoscopic biliary stenting is a well-established method and considered the gold standard for the palliative treatment of inoperable malignant biliary obstructions.¹ Plastic stents have been widely used for biliary drainage, but stent failure due to clogging caused by protein in bile juice, bacterial growth, or biliary secretions is common after a short period of time because the stents are relatively small in diameter (7 to 11.5 Fr); thus, stent replacement is required every 3 to 4 months to maintain biliary drainage.² To overcome this disadvantage, self-expandable metal stents (SEMSs) expandable to 24 to 36 Fr that remain patent for a longer time were developed. SEMSs are usually positioned under fluoroscopic guidance such that one end is 1 to 2 cm beyond the proximal end of a biliary obstacle and the other end protrudes 1 cm into the duodenum.³ This positioning is important because if a stent is positioned with a long intraduodenal portion, it can cause peritoneal or retroperitoneal perforations and bleeding ulcers. Therefore, providing adequate radiological stent visibility is important for achieving biliary drainage without stent-related adverse events. In addition, accurate stent placement is facilitated by real-time visualization at the time of stent delivery. All commercially available biliary SEMSs are made of Nitinol or stainless-steel alloys, and these alloys may provide radiological visibility along the entire stent length. However, as the contours of SEMSs made from these metal alloys are inadequately depicted on fluoroscopic images, radiopaque markers are used.⁴ Most of the radiopaque materials used to produce markers for biliary stents are composed of high-density materials, such as gold or platinum, which are expensive (the cost of gold wire in 2017 was 42 US dollars per

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gram). In addition, stents with radiopaque markers are made by coiling gold or platinum wire around the stents by hand. These metals have another disadvantage because their electrochemical potentials differ markedly from those of Nitinol or stainless steel, and this difference can cause severe galvanic corrosion of the stent alloys. To prevent this corrosion, stent alloys must have a protective coating to provide an insulating layer between the stent alloy and noble metals. Therefore, there is a need for better radiopaque markers that address these limitations of noble metal markers.

Tantalum is a high-density, highly corrosion-resistant metal that has been widely used for half a century in implantable medical devices designed for bone and soft tissues.⁵ Tantalum is a radiopaque metal that is mainly used in vascular stents, and numerous studies have reported that it improves stent radiopacity.⁶⁻⁸ Létourneau-Guillon *et al.*⁷ evaluated the imaging characteristics of Nitinol stents with a distal tantalum marker and found that tantalum improved the stent visibility on X-ray images. In another study, tantalum and Nitinol wires with the same diameter (0.6 mm) were compared on X-ray images, and tantalum wires were found to be more radiopaque.⁸ Regarding the biocompatibility of tantalum, no problems have been reported. Many tantalum-containing medical devices have been approved

by the U.S Food and Drug Administration and are widely used in clinical practice.⁹ Furthermore, tantalum is relatively inexpensive compared to noble metals and causes negligible galvanic corrosion because the electrochemical potentials of tantalum and Nitinol are similar.

Recently, a round radiopaque tantalum marker was developed and applied in biliary SEMs. Because the marker has a larger surface area than conventional metal markers, it is expected to provide improved visibility on radiographic images. The aim of the present study was to evaluate the safety of this novel tantalum marker and compare its X-ray opacity with that of gold and platinum markers.

MATERIALS AND METHODS

1. Radiopaque marker and stents

A tantalum marker is shown in Fig. 1A. The marker consisted of a tantalum layer sandwiched between two silicone membranes, which were made by compounding silicone (MED-6640; NuSil, Carpinteria, CA, USA) and xylene (Samchun Chemicals, Seoul, Korea) at a volume ratio of 2 to 5. Initially, this silicone/xylene mix was sprayed directly onto the surface of as-supplied Nitinol stents using an ultrasonic spray-coating machine (Medi-



Fig. 1. A novel tantalum marker, the ultrasonic coating machine used, and a Nitinol alloy SEMs with novel tantalum markers. (A) Schematic image of a novel tantalum marker and photograph of a marker on a stent. (B) Ultrasonic spray coating machine (Medi-Coat 2jx, Sono-Tek). (C) Nitinol alloy stent with a novel tantalum marker (NEXENT biliary stent, Next Biomedical).

Coat 2jx; Sono-Tek Corp., Milton, NY, USA) (Fig. 1B) to produce a thin surface coating. Tantalum metal powder was then sprayed using the ultrasonic spray-coating machine to form a spot of tantalum on the silicone membrane. Finally, the tantalum spot was covered in the same manner with silicone. The diameter of the tantalum marker was 2 mm, and its thickness (including the two silicone layers) was 200 μm . For experiments, 12 tantalum markers were produced on each stent (NEXENT biliary stent, Incheon, Korea), that is, four spots were produced on the center and distal and proximal ends of each stent (Fig. 1C).

2. Absorption of markers in the gastrointestinal tract

Three male beagle dogs with a median body weight of 13.6 kg were used. Dogs were provided with water *ad libitum* but fasted overnight before the endoscopic procedure. An intramuscular injection of atropine sulfate (0.04 mg/kg), xylazine (2 mg/kg), and tiletamine-zolazepam (5 mg/kg) was administered for pre-anesthetic sedation. Animals were intubated, and general anesthesia was achieved using 0.5% to 2% isoflurane in 70% nitrous oxide/30% oxygen administered through an endotracheal tube. With the dog on its side on a fluoroscopy table, a conventional endoscope (GIF-Q260J; Olympus Co., Tokyo, Japan) equipped with rat-tooth forceps in its working channel was used to insert a tantalum marker through the mouth, into the stomach, and onto the stomach mucosa. A total of five markers were inserted into each dog. Subsequently, abdominal X-rays were taken at 0, 2, 4, 6, 8, 24 and 33 hours, when all markers had been excreted. During this period, the animals were allowed free access to food and water. The excreted markers were collected and weighed,

and the weights were compared with those of the original markers to determine weight loss in the gastrointestinal tract. The experimental protocol was approved by the Institutional Animal Care and Use Committee of Inha University Hospital, and the study was conducted in accordance with the guidelines issued by the United States National Institute of Health (NOTUS IACUC 17-KE-232).

3. Marker radiopacity

X-ray microscopy images of the tantalum markers were compared with those of gold (A, Niti-S, Taewoong Medical; B, Hanaro, M.I. Tech; C, EGIS, S&G Biotech) and platinum (D, Zilver, Cook Medical) markers. Five stents were placed directly on a fluoroscopy table at a focus-film distance of 10 cm, and radiographic images were obtained over 0.5 s using an X-ray unit (PET-325) at 62 kVp and 200 mA. The radiopacity of each marker was measured using ImageJ software (National Institutes of Health, Bethesda, MD, USA; <https://imagej.nih.gov/ij/>). To quantify the radiopacities, the mean gray values (MGVs) of markers were measured using a pixel grayness histogram in a computer graphics program (Adobe Photoshop CC; Adobe Systems, Inc., San Jose, CA, USA).¹⁰ In the X-ray images, markers were divided into 20 \times 20 pixel regions, and the MGVs were measured. Images were enlarged to define the area of each marker accurately. The MGVs of the markers were quantified using a 0 (black) to 255 (white) scale. The MGVs of all markers were measured, and the mean MGVs of the specimens were calculated.

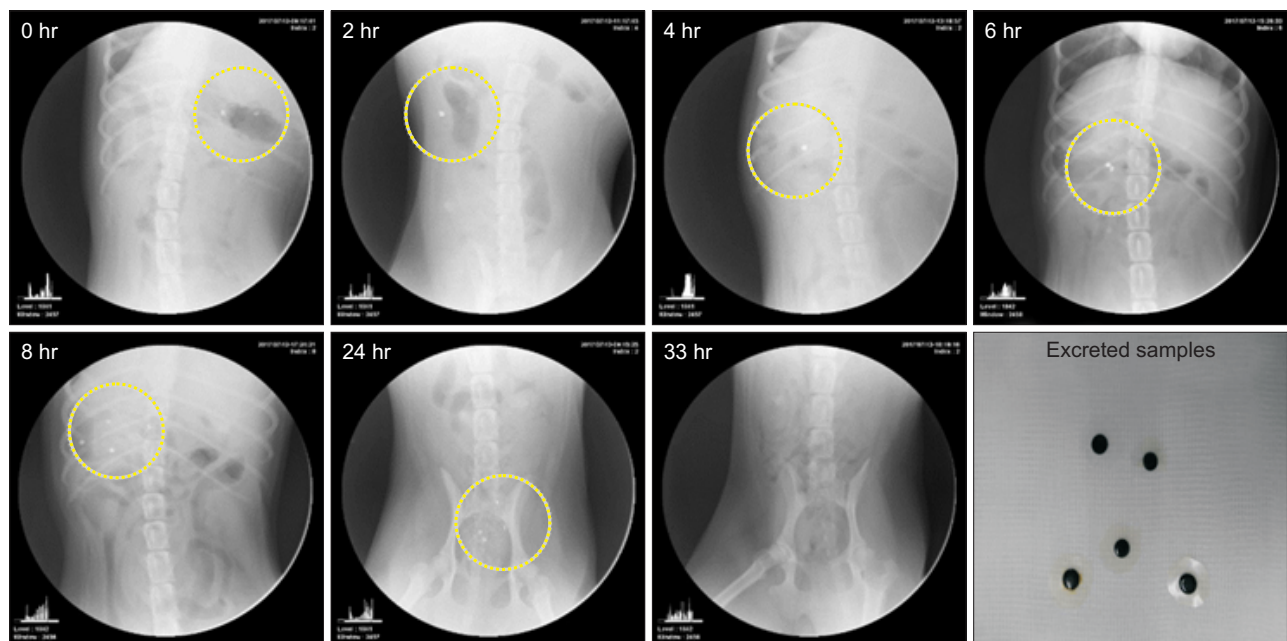


Fig. 2. Radiographic images of tantalum markers in a beagle. All markers were well-visualized in radiographs and passed within 33 hours. Dotted line circles indicate markers in X-ray images.

4. Definitions

The brightness score was defined as the mean MGTV at the center of a marker. The total brightness score was defined as the sum of all brightness scores of a marker.

5. Clinical radiopacity testing

The radiographic images of six patients with an unresectable malignant extrahepatic biliary stricture were used for clinical radiopacity testing. All patients underwent endoscopic biliary drainage by endoscopic retrograde cholangiopancreatography, which was conducted by an experienced pancreaticobiliary endoscopist. A Nitinol stent with tantalum markers (NEXENT biliary stent; Next Biomedical, Incheon, Korea) was placed in three patients, and a conventional Nitinol stent with a gold marker (n=3, Niti-S biliary uncovered stent; Taewoong Medical, Kimpo, Korea) was inserted in the other three patients. The stent diameter (10 mm) and length (60 mm) were the same in each case. After successful placement of the stent across a stricture, radiographic images were obtained by fluoroscopy. Using these radiographic images, the brightness scores of markers were calculated as described above.

RESULTS

1. Absorption test

Five tantalum markers were placed in the stomach of each of three dogs. Abdominal radiographs were obtained 33 hours after marker placement. The markers were clearly depicted on the X-ray images, and markers in the gastrointestinal tract were observed on serial X-ray images (Fig. 2). All markers were excreted within 33 hours. All collected markers were undamaged and showed no changes in weight (retrieved vs original weight: subject A, 1,495 mg vs 1,492 mg; subject B, 1,182 mg vs 1,167 mg; and subject C, 1,652 mg vs 1,627 mg) (Table 1).

Table 1. Tantalum Marker Weights Obtained during the Absorption Test

Subject	Weights of markers (mg)	
	Initial dose (5ea)	Excretion dose (5ea)
A	1,492	1,495
B	1,167	1,182
C	1,627	1,652
Mean±SD	1,429±236	1,443±239

Table 2. The Radiopacities of Different Markers on X-ray Examination

	Marker (material)				
	Novel marker (tantalum)	A (gold)	B (gold)	C (gold)	D (platinum)
Brightness score	226.22	209.02	204.96	194.34	203.60
Total brightness score	757	55	394	281	98

2. Radiopacity test

Fig. 3 shows an X-ray image of a Nitinol stent with metal markers. The metal markers are more clearly depicted than the Nitinol, and the brightness scores of the tantalum markers were higher than those of the other markers (A, Niti-S, Taewoong Medical; B, Hanaro, M.I. Tech; C, EGIS, S&G Biotech; D, Zilver, Cook Medical). The mean brightness scores of the tantalum and noble metal markers A, B, C, and D were 226.22, 209.02, 204.96, 194.34, and 203.60, respectively. In addition, the areas of the tantalum markers on the radiographs were much greater than those of the other markers. The total brightness scores of the tantalum and noble metal markers A, B, C, and D were 757, 355, 394, 281, and 98, respectively (Table 2).

3. Clinical radiopacity test

All tantalum and gold markers were detected in the fluoroscopic images (Fig. 4). The mean and total brightness scores of the tantalum markers were greater than those of the gold markers (41.47 vs 28.37 and 497.67 vs 227, respectively) (Table 3). No metal stent-related adverse events occurred in any patient.

DISCUSSION

In the present study, the novel tantalum marker was found to be highly visible in radiographic images with greater radiopac-

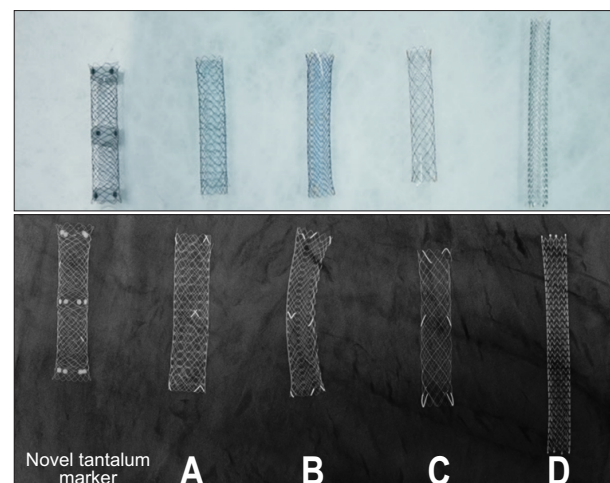


Fig. 3. Radiographic images of Nitinol alloy stents with different metal markers. All metal markers were visualized in radiographs (A, Niti-S, Taewoong Medical; B, Hanaro, M.I.T. Tech; C, EGIS, S&G Biotech; D, Zilver, Cook Medical).

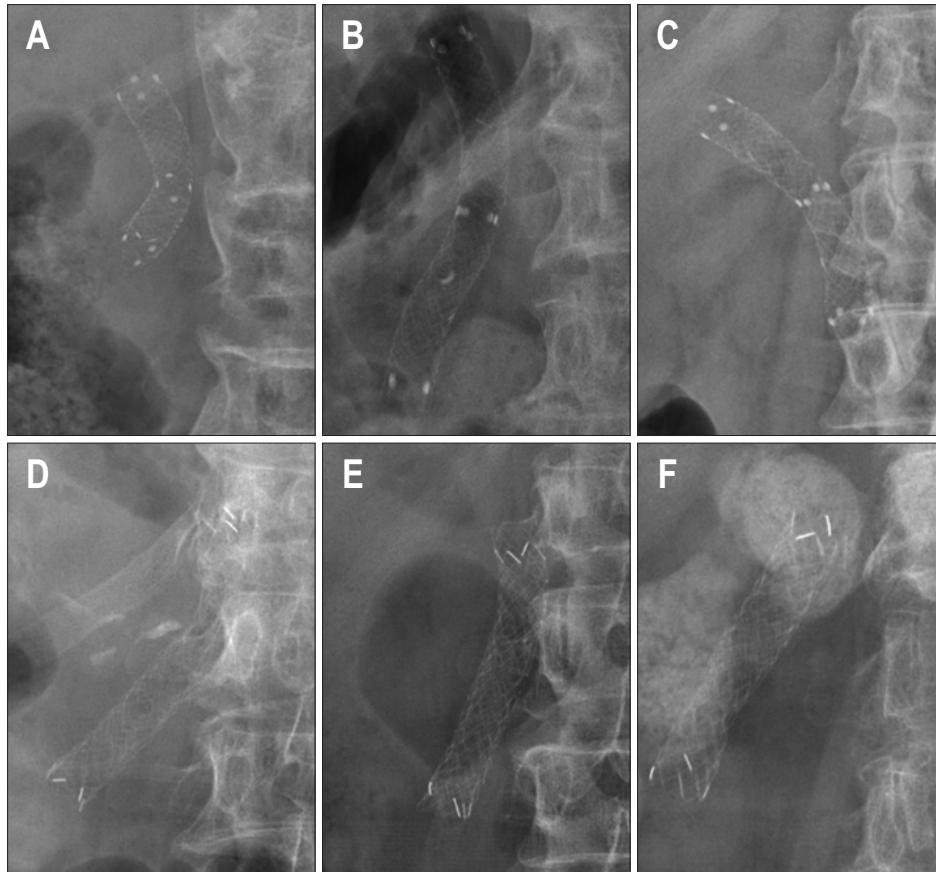


Fig. 4. Fluoroscopic images of tantalum and gold markers. Tantalum markers (A–C) were more clearly visible in fluoroscopic images than gold markers (D–F).

Table 3. Radiopacities of the Tantalum Marker and Conventional Gold Marker on Fluoroscopic Examination

	Novel tantalum marker	Gold marker
Brightness score	41.47	28.37
Total brightness score	497.67	227

ity than noble metal markers. Furthermore, the tantalum markers showed minimal absorption in the gastrointestinal tract.

Tantalum is a hard, dense, blue-gray, lustrous transition metal that is highly corrosion resistant, inert and inherently radiopaque because of its high atomic number.¹¹ Because of these properties, tantalum has been used as a radiopaque marker for over 50 years.^{12,13} Numerous studies have been conducted to determine whether tantalum implants cause tissue reactions,^{13–15} but to date, no reports of inflammatory responses in soft tissue or bone or of metal erosion have been published. The biocompatibility of tantalum is attributed to the formation of an inert oxide film with a negligible ability to induce adverse biological responses. As expected, the novel tantalum marker was found to be highly resistant to absorption in the gastrointestinal tract.

Tantalum markers have several advantages. Most importantly, they are more visible on radiographs than commercially available markers. Few metals have the ability to obstruct the passage of X-rays, and only gold, platinum, and tantalum pro-

vide sufficient X-ray attenuation to be considered radiopaque. The radiopacities of these three metals are similar because the metals have similar atomic numbers (tantalum 73, gold 79, and platinum 78). In the present study, the brightness scores of these metal markers were also similar, but tantalum had a significantly higher total brightness score because the tantalum markers had larger surface areas. Tantalum is available in the form of nanoparticles, which enables it to be applied to stents by spraying; in this way, larger areas than those achieved by coiling, riveting or micro-welding can be coated with tantalum. Consequently, the tantalum markers on the Nitinol stents examined had a diameter of 2 mm, which is larger than the diameter of the noble metal markers on conventional stents. The correlation between marker size and X-ray visibility was investigated by Nagy,¹⁶ who compared the X-ray visibilities of $6.2 \times 10^{-6} \text{ mm}^3$ and $2.4 \times 10^{-5} \text{ mm}^3$ tantalum powder markers and found that the X-ray visibility of the tantalum markers was increased by 0.07% when the area of the tantalum markers was increased by 0.0073 mm^3 .

The second advantage of tantalum markers is that the manufacturing process is straightforward. Markers were prepared using an ultrasonic coating technique, which provides a new means of achieving smooth uniform coatings on stents. This technique uses high-frequency ultrasound and not only allows precise control over the coating thickness but also en-

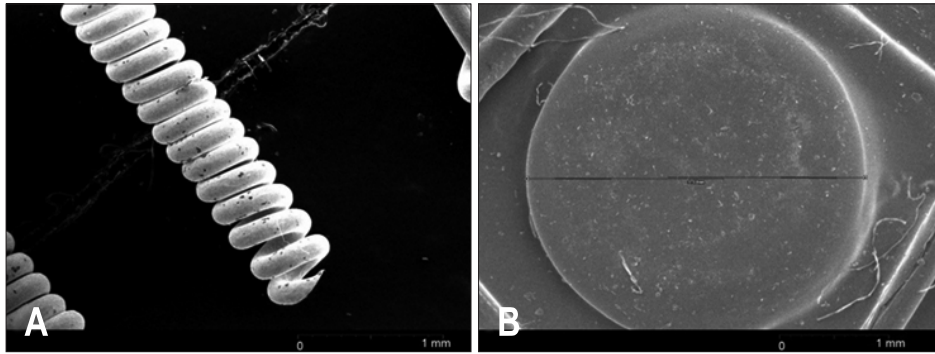


Fig. 5. Scanning electron microscope images of a conventional ring-type gold marker (A) and a tantalum marker (B) (x50).

ables nanometer- to micrometer-sized droplets to be sprayed.¹⁷ Commercially, ultrasonic coating is mainly used for coating coronary stents, but to the best of our knowledge, no attempts have been made to apply this technique in manufacturing biliary SEMSs. The majority of radiopaque markers used in commercially available biliary SEMSs are ring-type markers that are produced by manually coiling gold or platinum wire at the center, proximal, and distal ends of stents. Therefore, the process is highly labor intensive, and product variability is an issue. In addition, ring-type markers have sharp ends, which introduce the risk of tissue injury (Fig. 5A) and can impair stent function by breaching surface membranes on fully covered SEMSs. On the other hand, the process of manufacturing novel tantalum markers is fully automatic, and as described above, markers can be made by simply spraying tantalum powder onto a silicone-based membrane, which markedly simplifies the production process and reduces production costs. In addition, the smooth surface of tantalum-marked Nitinol stents reduces the risk of stent-induced injury (Fig. 5B). Finally, tantalum is considerably less expensive than noble metals. Usually, approximately 24 cm of gold wire is required to manufacture a single gold marker for a biliary SEMS, and this amount of gold wire cost approximately 3 US dollars in 2017, whereas the cost of tantalum powder per stent was ~0.54 US dollars. One US company fabricates 27,000 metal stents per annum and spends ~80,000 US dollars on gold for marker stents. If this gold could be replaced by tantalum, the estimated cost savings would be ~65,000 US dollars per year. Furthermore, the cost would be appreciably reduced by lower production costs.

The main limitation of the present pilot study is that it was performed using a limited number of subjects. However, the study demonstrates that the novel tantalum marker resists absorption in the gastrointestinal tract and that these markers are more visible by fluoroscopy than noble metal markers. The second limitation is that the marker retention time (33 hours) was insufficient to proper absorption resistance. In addition, because the present study was conducted using a small animal model, we could not place tantalum-marked stents in bile ducts. Thus, a large animal study is required to determine assess long-term absorption resistance in bile ducts. Third, no long-term follow-

up study was performed. Patients with biliary tract cancer who undergo palliative biliary SEMS placement have a mean survival time of greater than 4 months; thus, a longer-term study is required to properly determine the safety and efficacy of tantalum markers in humans.

In conclusion, the developed tantalum marker was found to be highly resistant to gastrointestinal absorption and more visible on radiographs than commercial noble metal markers. This improved visibility will be useful clinically because it will undoubtedly facilitate accurate stent placement by improving real-time visualization at the time of delivery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Author contributions: J.S.P. made substantial contributions to the study concept and design, acquisition of data, analysis and interpretation of data and contributed to drafting the manuscript and revising it critically for important intellectual content. K.H.Y. made substantial contributions to the study concept and design, acquisition of data, analysis and interpretation of data. S.J. agreed to be accountable for all aspects of the work and to resolve issues related to the accuracy or integrity of the study. D.H.L. was involved in drafting the manuscript and revising it critically for important intellectual content. D.G.K. agreed to be accountable for all aspects of the study and to resolve issues related to its accuracy or integrity.

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