

Malfunctions and Adverse Events Associated With Off-Label Use of Biliary Stents in the Peripheral Vasculature

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Biliary stents are approved by the U.S. Food and Drug Administration only to treat biliary strictures resulting from cancer. However, these devices are often used “off-label” to treat peripheral vascular disease. This study was designed to determine the number and type of malfunctions and adverse events associated with off-label use of biliary stents in the peripheral vasculature. Confirmed biliary stent malfunctions and adverse events were identified by reviewing biliary stent-related adverse events reported to the U.S. Food and Drug Administration between January 2003 and December 2006. The annual number and type of biliary stent malfunctions and adverse events and the annual number of off-label biliary stent implants were determined. More than one million biliary stents were implanted off-label in the peripheral vasculature during the study period. Most biliary stent malfunctions (81.2% of 1036 malfunctions) and adverse events (87.9% of 561 adverse events) occurred during off-label stent use in the peripheral vasculature. From 2003 to 2006, the annual number of malfunctions increased 80% and adverse events more than doubled, although malfunction and adverse event rates did not significantly increase. Stent malfunctions were most often the result of premature dislodgement or deployment. Retained product, additional percutaneous interventions, or surgery were the most frequently observed adverse events associated with off-label stent use. Thirteen deaths were reported during off-label use. Off-label use of biliary stents in the peripheral vasculature occurs frequently and is increasing in rate. Most adverse events and device malfunctions associated with biliary stent use occur during off-label use. Endovascular treatment of peripheral arterial disease is an important therapy that has benefited many patients. Efforts should be directed at improving the evaluation of peripheral vascular device performance to better identify the patient subsets that will most benefit from this promising therapy.

Keywords: peripheral arterial disease, stent, public health, regulatory affairs, percutaneous intervention

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INTRODUCTION

Biliary stents are expandable devices indicated for the palliative treatment of biliary strictures resulting from malignant neoplasm.¹ Some physicians choose to use these stents in a manner different from their U.S. Food and Drug Administration (FDA)-approved indication.^{2,3} Indeed, as much as 90% of biliary stent use occurs in an “off-label” fashion with treatment of peripheral vascular disease a common off-label use.²⁻⁴

Peripheral arterial disease affects millions of patients and is a significant cause of morbidity and mortality.^{5,6}

Limb ischemic symptoms can occur in a substantial proportion of patients and often results in the need for invasive therapies when noninvasive strategies such as medical therapy and exercise training are inadequate.⁵⁻⁷ Invasive management options for the treatment of peripheral arterial disease include surgical or endovascular interventions with the latter becoming increasingly common.⁷

The FDA is responsible for the safety and effectiveness of medical devices marketed in the United States. Although the FDA has approved several stents for use in the peripheral vasculature, more than 100 stents are approved for nonvascular indications.⁸ Because the amount and type of data required by the FDA for nonvascular indications is substantially less than that required for vascular indications, this route of device approval has created a "back door" through which stents may be marketed.² As a result, many stents currently used to treat peripheral vascular disease are used with minimal data supporting their clinical effectiveness and safety.

This study was designed to assess the number and rate of reported device malfunctions and clinical adverse events associated with the off-label use of biliary stents in the peripheral vasculature.

METHODS

Device-related malfunctions and adverse events

All adverse events reported to the FDA between January 2003 and December 2006 affecting biliary stents (FDA product code FGE designated "biliary catheter and accessories") were included in the study.⁹ Reports not involving metal biliary stents were excluded from further analysis. Manufacturers are required to report to the FDA any medical device-related event or malfunction that caused or could have caused serious injury or death to a patient. These reports are entered into the publicly searchable Manufacturer and User Facility Device Experience (MAUDE) database.¹⁰

Each MAUDE report involving a biliary stent was reviewed in detail and classified according to device performance (1) device malfunction; (2) no device malfunction or indeterminate [insufficient data to classify event] and clinical outcome (1) adverse event; (2) no adverse event or indeterminate [insufficient data to classify event].

Definitions

A biliary stent was considered to have malfunctioned only if: 1) manufacturer analysis confirmed the malfunction or 2) the device was not returned to

the manufacturer for analysis but the malfunction was witnessed and confirmed by a trained healthcare provider on the scene. Only malfunctions that occurred during clinical use were counted. Malfunctions that occurred before insertion of the device into a patient were not included. Unsubstantiated claims of device malfunction or reports containing insufficient information to adjudicate the event were not counted as device malfunction.

Clinical adverse events were defined as clinical events that resulted in permanent disability, inappropriate or unintended retention of hardware, or required intervention.

Rates of reported malfunction and clinical adverse events

The annual number of off-label biliary stent implants in the peripheral vasculature was determined from financial market research reports, manufacturer U.S. Securities and Exchange Commission annual reports, and annual biliary stent and percutaneous peripheral vascular market growth rates.¹¹⁻¹⁶ Annual reported biliary stent malfunction rates and biliary stent clinical adverse event rates associated with off-label use of the device in the peripheral vasculature were then calculated by dividing the annual number of reported malfunctions and adverse events by the annual number of off-label biliary stent implants.

Statistical methods

Statistical comparisons were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). A two-sided *P* value of 0.05 or less was interpreted as being statistically significant. Student *t* and χ^2 tests were used to compare continuous and discrete outcomes, respectively. Mantel-Haenszel χ^2 tests were used to assess for trends during the study period. Although the number of biliary stents implanted in the peripheral vasculature was determined, sensitivity analysis was performed to account for potential inaccuracies in manufacturer reporting of sales and financial analyst reporting of biliary stent and peripheral vascular device sales and market growth.

RESULTS

Number of off-label biliary stent implants

The annual number of peripheral vascular biliary stent implants increased 21.4% from 227,145 in 2003 to 275,795 in 2006 (*P* for trend = 0.08). In total, from 2003 to 2006, approximately one million biliary stents were implanted off-label in the peripheral vasculature.

Number and location of device malfunctions

From 2003 to 2006, 1036 confirmed biliary stent malfunctions were reported. Malfunctions were greater than eight times more likely to occur during use of the biliary stent in the peripheral vasculature than in the biliary or gastrointestinal tract (210.3 ± 50.2 versus 25.3 ± 4.1 device malfunctions per year, $P = 0.005$) (Table 1). In total, 841 (81.2%) malfunctions occurred during use of a biliary stent in the peripheral vasculature. Most often, these malfunctions occurred during treatment of peripheral arterial disease [680 (80.9%)] with malfunctions during treatment of peripheral venous disease or graft disease (saphenous vein grafts and dialysis fistulas) occurring less frequently (Table 1). Malfunctions during treatment of infrarenal [409 malfunctions (60.1%)] and renal [193 malfunctions (28.4%)] arterial disease accounted for 88.5% of all peripheral arterial biliary stent-related malfunctions. Malfunctions occurring in the biliary or gastrointestinal tract accounted for fewer than 10% of all observed malfunctions during the study period (Table 1).

Number and location of clinical adverse events

Between 2003 and 2006, 561 confirmed clinical adverse events associated with biliary stent use were reported to the FDA. Like malfunctions, adverse events occurred much more often during biliary stent use in peripheral vessels than in a biliary or gastrointestinal location (123.3 ± 46.4 versus 12.3 ± 10.9 clinical adverse events per year, $P = 0.01$) (Table 1). In total, 493 (87.9%)

adverse events occurred during biliary stent use in the periphery, most often during treatment of peripheral arterial disease. Adverse events occurred most often during treatment of infrarenal [259 events (46.2%)] or renal [82 events (14.6%)] arterial disease. Adverse events during device use in the biliary or gastrointestinal tract accounted for fewer than 9% of all observed adverse events (Table 1).

Number and types of device malfunctions

Malfunctions occurring during biliary stent use in the peripheral vasculature were most often the result of malfunctions of the stent [742 malfunctions (74.9%)], delivery system [163 malfunctions (16.5%)], or balloon [85 malfunctions (8.6%)] (Table 2). Stent malfunctions were most often attributable to premature dislodgement of the stent from the delivery system, premature or inappropriate deployment of the stent, or physical damage to the stent occurring during implantation. Delivery system malfunctions most often resulted in the inability to advance or remove the delivery system or in dislodged or retained pieces (other than the stent itself). Various other malfunctions occurred less frequently (Table 2).

Number and types of adverse events

The most frequently observed adverse events occurring as a result of biliary stent use in the peripheral vasculature were inappropriately retained product, unanticipated additional percutaneous intervention, or the

Table 1. Number and anatomic location of device malfunctions and clinical adverse events.

Stent location	Device malfunctions		Clinical adverse events	
	No.	Percent	No.	Percent
Peripheral vascular	841	81.2	493	87.9
Arterial	680	65.6	403	71.8
Infrarenal	409	39.5	259	46.2
Renal	193	18.6	82	14.6
Suprarenal	51	4.9	34	6.1
Mesenteric	6	0.6	2	0.4
Carotids/vertebral	21	2.0	26	4.6
Venous	28	2.7	18	3.2
Graft	15	1.4	13	2.3
Unknown vascular	118	11.4	59	10.5
Biliary/gastrointestinal	101	9.7	49	8.7
Other*	6	0.6	9	1.6
Unknown	88	8.5	10	1.8
Total	1036	100	561	100

*Coronary artery, pulmonary artery, and so on.

Table 2. Number and types of device malfunctions for biliary stents used in peripheral vasculature.

Type of device malfunction	Device malfunctions	
	No.	Percent
Stent	742	74.9
Dislodgement	287	29.0
Deployment	220	22.2
Physical damage	169	17.1
Migration	66	6.7
Balloon	85	8.6
Failure to inflate/deflate	51	5.2
Burst	34	3.4
Catheter/delivery system	163	16.5
Unable to advance/remove	59	6.0
Dislodged/retained piece	54	5.5
Physical damage	38	3.8
Guidewire	8	0.8
Other	4	0.4
Total	990	100.0

need for surgery (such as surgery to retrieve a retained product or to repair a ruptured vessel); in total, these adverse events accounted for two thirds of all peripheral vascular adverse events associated with biliary stent use (Table 3). Not surprisingly, vascular injury, including vessel perforation, dissection, or thrombosis, also occurred in a substantial number of patients. Stroke or transient ischemic attack (17 patients) and ischemic limb or organ (16 patients) occurred occasionally. Death occurred in 13 patients as a result of off-label biliary stent use in the periphery.

Examples of actual reported device malfunctions and clinical adverse events are displayed in Table 4.

Annual malfunction and adverse event rates

The annual number of reported malfunctions during off-label biliary stent use in the peripheral vasculature increased 80.3% during the study period from 137 malfunctions in 2003 to 247 in 2006 (P for trend = 0.12). The annual rate of confirmed malfunction for biliary stents used to treat peripheral vascular disease increased 50% from 0.06% in 2003 to 0.09% in 2004, but was then stable throughout the study period (P for trend = 0.19) (Fig. 1).

The annual number of reported adverse events during off-label biliary stent use in the peripheral vasculature increased 152% from 61 in 2003 to 154 in 2006 (P for trend = 0.12). The annual rate of reported adverse event during peripheral use of biliary stents more than doubled from 2003 to 2005 before declining slightly in 2006 (P for trend = 0.14) (Fig. 1).

Table 3. Number and type of clinical adverse events for biliary stents used in the peripheral vasculature.

Type of clinical adverse event	Clinical adverse events	
	No.	Percent
Retained product	110	22.3
Additional percutaneous intervention	110	22.3
Surgery	105	21.3
Vascular injury*	91	18.5
Stroke/transient ischemic attack	17	3.4
Threatened limb/organ	16	3.2
Death	13	2.6
Bleeding	11	2.2
Other†	20	4.1
Total	493	100

*Vessel perforation, dissection, thrombosis, pseudoaneurysm, and so on.

†Includes allergy, cardiac, infection, chronic pain, and so on.

Sensitivity analysis

Sensitivity analysis was conducted to account for potential inaccuracies in manufacturer reporting of biliary stent sales and in financial analyst reporting of biliary stent sales, peripheral vascular device sales, and market growth. The observed increasing trends in the number of off-label biliary stent malfunctions and adverse events were unaffected by even 25% increases or decreases in annual biliary stent sales, peripheral device sales, or annual market growth.

DISCUSSION

Biliary stents are expandable devices indicated for the palliative treatment of biliary strictures resulting from malignant neoplasm.¹ This study demonstrates that off-label use of biliary stents occurs frequently, is increasing in number, and has occurred in more than one million patients since 2003. In addition, hundreds of biliary stent-related malfunctions and adverse events were reported to the FDA between 2003 and 2006 with nearly 90% of the observed incidents transpiring during off-label stent use in the peripheral vasculature.

Peripheral arterial disease affects millions of patients. Clinical management can be challenging, particularly when substantial symptoms persist despite more conservative, noninvasive treatment strategies such as exercise training.⁵ Some patients exhibit lifestyle-limiting disability as a result of claudication or limb ischemia and may require more aggressive treatment modalities, including endovascular or surgical revascularization.⁵

The clinical outcomes of endovascular interventions for peripheral arterial disease vary depending on the arterial segment targeted. The most common site of lower extremity atherosclerosis is the superficial femoral artery.⁶ Primary stent placement in this location has not been shown to be reliably superior to balloon angioplasty alone,^{6,17} although some studies suggest a benefit.¹⁸ In contrast, stenting of iliac vessels appears to result in higher initial success rates and a reduction in long-term failures when compared with balloon dilation alone.⁷ Use of drug-eluting stents for the treatment of peripheral arterial disease has not been shown to be superior to bare-metal stents.⁶ Although some trials of stenting versus balloon angioplasty for peripheral arterial disease have been performed, they have been limited by their small size, lack of noninterventional medical control groups, and relatively short duration of follow up.^{6,7,17} Stenting compared with surgical revascularization is even less well studied.⁵⁻⁷

The American College of Cardiology–American Heart Association 2005 practice guidelines for the management of patients with peripheral arterial

Table 4. Examples of biliary stent malfunction and adverse event descriptions.

Event description	Device malfunction?*	Adverse event?*
While attempting to stent the renal artery, the balloon ruptured and the stent partially deployed. During percutaneous attempts to remove the stent, it migrated to the femoral artery. The patient required surgery to remove the stent.	Yes	Yes
A stent was implanted in the iliac artery. During postdilation of the stent, a vessel perforation occurred. The patient required surgery when further complications occurred that led to the patient's death.	No	Yes
During a renal artery stent procedure, the balloon burst on inflation. The device was removed without complication.	Yes	No

*See text for details.

disease conclude that stenting is effective as primary therapy (Class I indication) for common iliac and external iliac stenoses and occlusions and as salvage therapy (after failed balloon dilation) for iliac, femoral, popliteal, and tibial arteries.⁵ This stands in contrast to the paucity of FDA-approved stents for peripheral vascular indications and may contribute to the substantial amount of off-label biliary stent use. These recommendations also underscore the variability and complexity of peripheral arterial disease and highlight the fact that not all peripheral vessels are the same. A variety of factors influence procedural and device clinical success, including lesion severity and location, lesion in-flow and distal runoff, local vessel forces such as torsion, compression, flexion, extension, and contraction, and the lesion and limb's physiological response to intervention.⁷ As such, evidence that a stent is safe and clinically effective in one vascular location does not guarantee safety and effectiveness in another location. Similarly, because of important differences in stent design, manufacturing, and drug coating, approval of one stent does not guarantee the clinical success and safety of another stent in the same vascular territory.

The FDA bases its premarket device evaluation on the complexity of the device and the device's intended use as indicated by the device manufacturer.¹⁹ As such, the amount and type of data required by the FDA for a stent intended for use in the palliative treatment of patients with cancer is substantially less than that required for a stent intended for chronic long-term implantation for a vascular indication. Specifically, biliary stent approval typically does not require clinical trial data.² This contrasts with coronary drug-eluting

stents whose approval required randomized, blinded studies involving more than 1000 patients and vascular stents, which require clinical trials involving hundreds of patients.^{2,20} Because of the more stringent vascular premarket approval process, some manufacturers may seek a biliary indication for a stent while anticipating that substantial off-label use is likely to occur. Indeed, some vascular companies include biliary stents on their vascular web sites, advertise them at cardiovascular scientific conferences, and market them in Europe for vascular indications.²

The FDA's MAUDE database, used for this analysis, is subject to underreporting of device failures.¹⁹ The rates of reported device malfunction and adverse events in this investigation, therefore, are likely to underestimate the true malfunction and adverse event rates and are not intended to represent actual adverse event rates for off-label use of biliary stents. Instead, these rates indicate that the *reported* rate of adverse events has been stable and that the observed increase in the number of events has been the result of an increase in off-label procedures and not an apparent decrease in device reliability.

Actual clinical trials or active clinical device implant registries are better measures of adverse event and malfunction rates but are not available for off-label biliary stent use. Studies of peripheral arterial interventions have demonstrated acute adverse event rates in as many as 9% of patients, including uncontrolled vascular dissection, vascular perforation, device malfunction, and death.^{18,21,22} In short, although this investigation demonstrates a substantial number of device malfunctions and adverse events associated

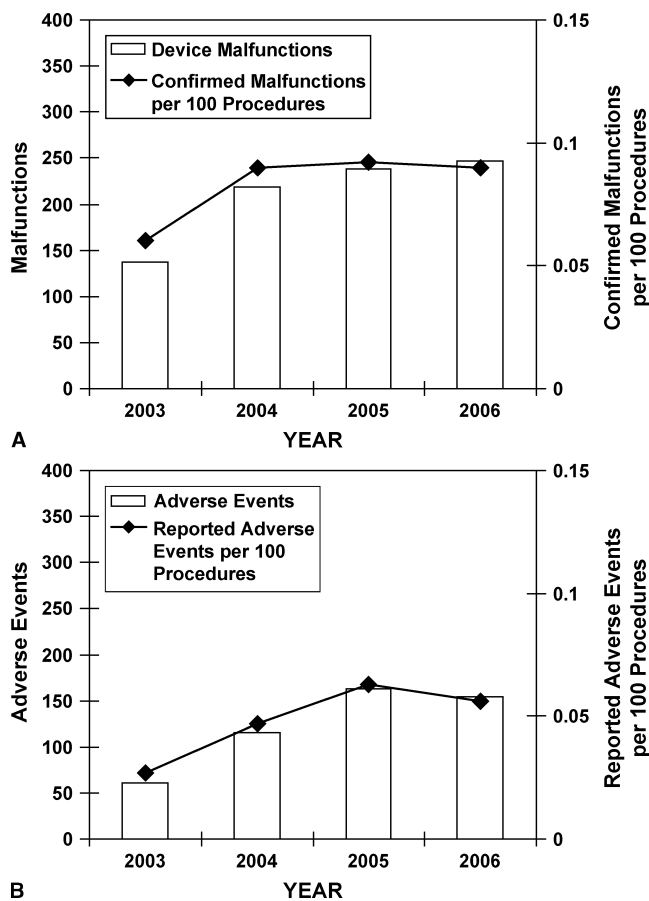


FIGURE 1. (A) The annual number (left vertical axis, bars) and rate (right vertical axis, line) of reported biliary stent malfunctions during use in the peripheral vasculature are shown. The annual number of malfunctions increased 80% during the study period. See text for details. (B) The annual number (left vertical axis, bars) and rate (right vertical axis, line) of reported adverse events during use of biliary stents in the peripheral vasculature are shown. The annual number of adverse events more than doubled during the study period. See text for details.

with off-label biliary stent use, it also highlights the need for additional clinical data to evaluate the clinical safety and effectiveness of this therapy. Active post-market surveillance systems or device registries similar to the National Cardiovascular Data Registry currently used by the American College of Cardiology to track percutaneous coronary interventions, carotid stenting, and implantable defibrillator use would be useful for assessing the acute adverse event rates associated with percutaneous peripheral arterial interventions.

The frequent off-label use of biliary stents for peripheral vascular indications implies an unmet clinical need in the management of these patients. With the aging of the U.S. population, the number of patients

with vascular disease can be expected to grow.⁶ It is incumbent on physicians, national cardiovascular societies, industry, and regulators to expedite the acquisition of the necessary clinical data and to promote rationale, evidence-based use of peripheral interventions and to reconcile the apparent contradiction in national stenting guidelines for peripheral arterial disease and the current regulatory status of stents used for this purpose. Although the FDA does not regulate the practice of medicine, the off-label use of a product by more than one million patients is a public health issue that must be addressed. Frequent off-label use of a device does not serve the physician, the manufacturer, the FDA, or the patient. Off-label use is difficult to track and as such, guidelines for operator proficiency, for appropriate device use, for acceptable complication rates, and for reimbursement are all negatively impacted.²³ Although physicians may use any legally marketed device to treat any condition within a legitimate patient-physician relationship, a physician's failure to follow the written instructions for use for a medical device and the failure to disclose the off-label use to a patient can expose physicians to significant liability.^{19,23}

Limitations

Some reported device "failures" in the FDA's MAUDE database are cryptic and contain insufficient information to determine whether a true device malfunction or adverse event occurred. By counting only confirmed device malfunctions and severe adverse events, this study demonstrates that numerous biliary stent-related malfunctions and adverse events occur in an off-label setting and that this is a significant public health issue. However, devices that are used for purposes unintended by the manufacturer, devices that are pushed beyond their design limits by the operator, and devices that are otherwise used inappropriately may "malfunction," although whether this malfunction is device- or operator-dependent may be difficult to determine. Only with well-conducted clinical trials can the cause of and solution to these frequent events be scientifically addressed.

Several additional important questions remain unanswered. Although numerous biliary stent-related malfunctions and clinical adverse events have occurred, it is not possible to assess the relative risk and benefit for patients undergoing biliary stent implantation for peripheral vascular disease with currently available data. Indeed, patients may benefit greatly from this therapy and experience a substantial reduction in symptoms and limb ischemia. Although hundreds of device malfunctions and adverse events were reported, only with well-conducted clinical trials can the clinical effectiveness of the devices be determined. Finally, although this study included dozens of stents from

13 manufacturers, no specific device comparisons were possible.

CONCLUSIONS

This study demonstrates that: 1) off-label use of biliary stents in the peripheral vasculature occurred in more than one million patients between 2003 and 2006; 2) the annual number of off-label procedures is increasing; 3) adverse events and device malfunctions associated with off-label biliary stent use affect hundreds of patients annually; and 4) the vast majority of reported biliary stent-related malfunctions and adverse events occur during off-label use. The endovascular treatment of peripheral arterial disease is an important therapy that has benefited many patients. With the aging of the U.S. population, the number of patients who will require peripheral revascularization will continue to increase. Efforts should be directed at improving the evaluation of peripheral vascular device performance to better identify the patient, peripheral vessel, and lesion characteristics that will most benefit from this promising therapy.

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