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Investigation of Reported Adverse Events for Bioresorbable Coronary Artery Stents

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Abstract **-** With an estimated number of 610,000 annual deaths in the United States alone, Coronary Artery Disease (CAD) is among the leading causes of death worldwide. Severe cases of CAD are traditionally treated through coronary artery bypass grafting, a surgical procedure highly invasive in nature. Stenting has subsequently gained popularity as a minimally invasive alternative to treat milder cases of CAD. However, bare-metal stents often cause complications such as restenosis and jailing of arterioles, and drug-eluting stents aimed at mitigating restenosis did not solve the arteriolar jailing. Thus in 2016, the FDA approved the Abbott Absorb Bioresorbable Vascular Scaffold (BVS) System, a bioresorbable drug-eluting stent designed to provide temporary arterial support and dissolve, thereby avoiding permanent metal implants. Despite theoretical advantages of this design, clinical adoption has been limited. This study investigates the reasons behind the limited use of bioresorbable drug-eluting stents by analyzing reported adverse event data (injuries, malfunctions, deaths) from the Manufacturer and User Facility Device Experience (MAUDE) database. The data showed a proportionally larger number of injuries associated with bioresorbable stents in comparison to bare-metal stents, a statistic driven primarily by major cardiac events. The ABSORB III pivotal clinical study found higher adverse event rates associated with the BVS system when compared to bare-metal stents; these findings resulted in the 2017 FDA implementation of a Class I recall for the Absorb BVS stent. The COVID-19 pandemic may have also contributed to the observed spike in reported adverse events in 2020 as a product of increased healthcare challenges and overall worse patient health. The results of this study highlight a need for improved treatment options or stent designs to enhance CAD patient outcomes.

Keywords**:** Angina, Coronary artery disease, Intimal dissection, Myocardial infarction, Stenosis, Thrombosis

1. Introduction

Coronary Artery Disease (CAD) is one of the leading killers of men and women both in the United States and worldwide.1 CAD is the cause for an annual approximate of 610,000 deaths in the United States only, which is about 1 in 4 deaths.2 Coronary artery bypass grafting is a surgery performed to treat narrowed or blocked coronary arteries in severe cases. Due to the highly invasive nature of bypass surgery, a minimally invasive alternative method known as stenting has become increasingly popular to treat milder cases of CAD. Stents are inserted into an artery in the wrist or groin, with a catheter and balloon attached (Fig. 1). The balloon inflates to widen the artery, expanding the stent to fit the artery wall. Stents were initially made with bare metal; however, the permanence of the metal was seen to cause complications with restenosis and re-blocking of the artery, as well as jailing arterioles, which compromises the coronary artery's ability to reach inner regions of the heart. Drug eluting stents—stents coated with a drug-loaded polymer—aim to forestall restenosis, but do not solve the jailing of arterioles. Thus, the Abbott Absorb Bioresorbable Vascular Scaffold (BVS) System (Fig. 2), a bioresorbable drug-eluting stent, was approved by the FDA in 2016, and is designed to resolve this issue—the stent is inserted, elutes a drug and expands the artery, and subsequently the stent is absorbed by the body (Fig. 3). The stent provides a temporary mechanical support for the artery such that the artery can be restored to its original form. The stent is absorbed once the artery no longer requires support, so that the artery is not permanently held by a metal stent. Despite the theoretical advantages of bioresorbable drug-eluting stents, clinical adoption of these stents has been limited, suggesting that physicians are hesitant to move toward using absorbable stents. This study aims to investigate the reasons for the limited use of bioresorbable stents, by dissecting data for reported injuries, malfunctions, and deaths related to the stents, in order to inspire the design of more efficient stents to treat CAD. Unlike previous studies about this topic, this paper analyzes trends in

reported event data to show the relationship between usage of the BVS stent and other events, including the COVID-19 pandemic.

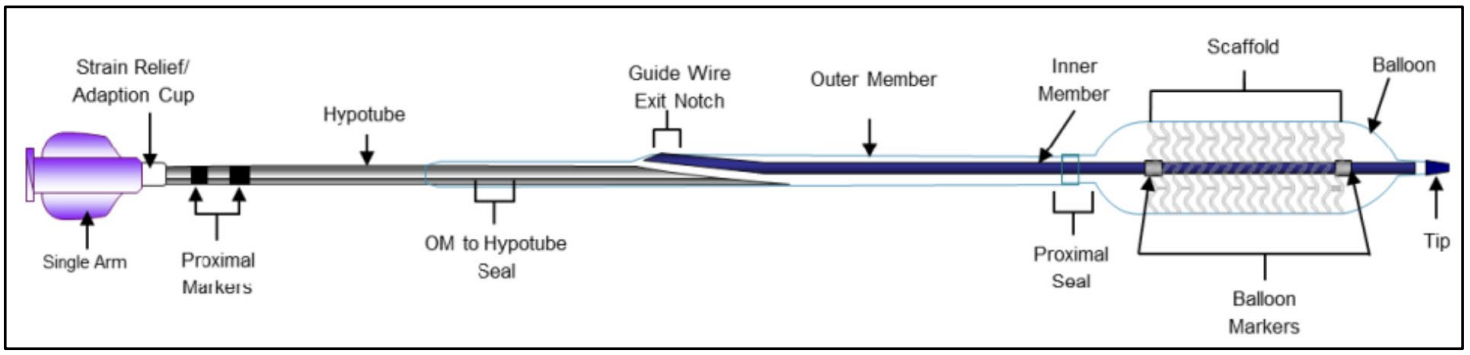

Fig. 1. Delivery system with balloon dilatation catheter for coronary stents.3

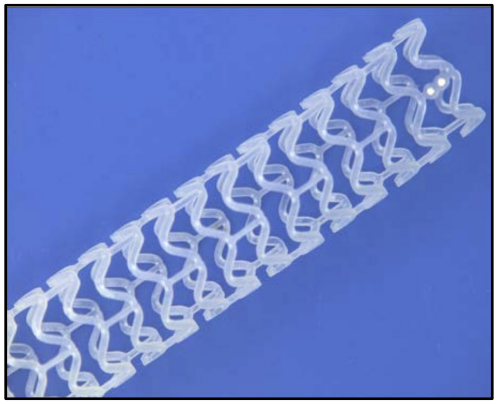

Fig. 2. Digital Photograph of the 3.5 mm Medium BVS in Expanded Form.3

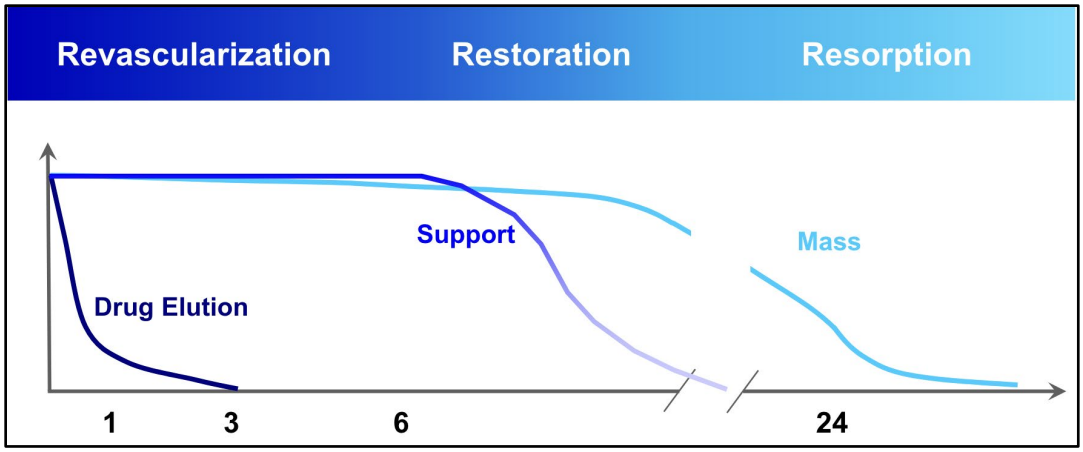

Fig. 3. BVS System mechanism of action. Elutes antiproliferative drug during first three months post-insertion to prevent restenosis, provides temporary support to target artery during first two years post-insertion, and becomes absorbed once arterial support is no longer needed.3

2. Materials and Methods

This study utilized the Manufacturer and User Facility Device Experience (MAUDE) database, a database of reported adverse events, including injuries, malfunctions, and deaths in the United States for all Food and Drug Administration (FDA) approved medical devices within the United States.4 Reports are made by mandatory reporters, including device

manufacturers, importers, and facilities that use those devices, as well as voluntary reporters, including healthcare professionals, patients, and product consumers.

Reported adverse event data were collected for both Bioresorbable Vascular Scaffolds (BVS) and bare-metal coronary stents as a basis for comparison. The MAUDE database was searched for adverse events (injuries, malfunctions, and deaths) associated with the following product codes:

1. MAF—Coronary Stent; "This device is a metal scaffold placed via a delivery catheter into the coronary artery or saphenous vein graft to maintain the lumen."[5]
2. PNY—Absorbable Coronary Drug-Eluting Stent; "An absorbable scaffold with a drug coating placed via a delivery catheter into the coronary artery or saphenous vein graft to maintain the lumen. The drug coating is intended to inhibit restenosis."[6]

3. Results

There is an overall decreasing trend in reported adverse events over time for bare-metal stents (Fig. 4). Additionally, a crossover between the amount of reported malfunctions and injuries occurs between 2015 and 2016; prior to 2016, more malfunctions connected to bare-metal stents were reported than for injuries. Starting from 2016 onward, more injuries were reported than malfunctions per year.

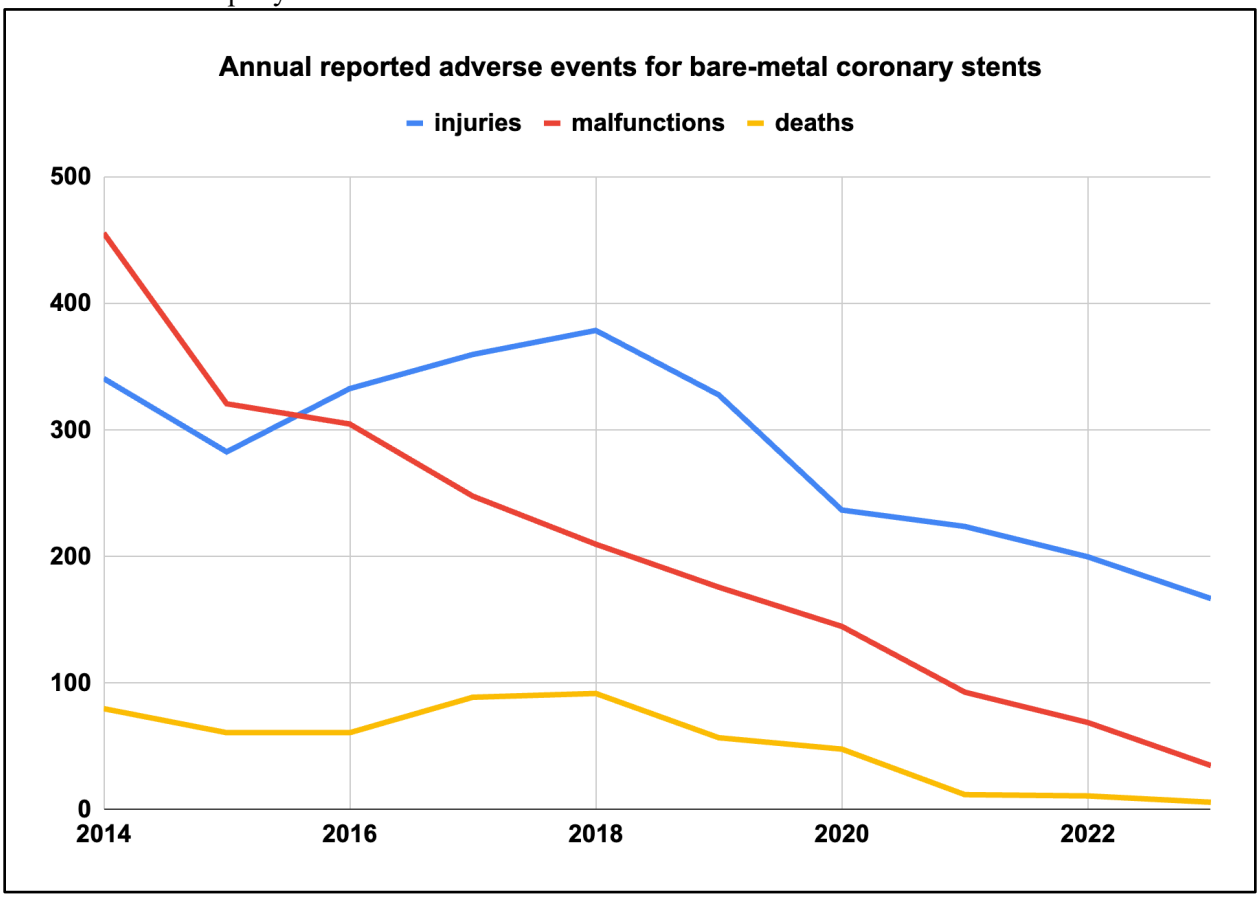

Fig. 4. Reported adverse events by year for bare-metal coronary stents in the MAUDE database.

Fig. 5 shows a spike in injuries and deaths associated with absorbable drug-eluting stents in the year 2017, and a spike in all adverse events associated with absorbable drug-eluting stents in the year 2020. A general downward trend in adverse events is evident, with the exception of the data from 2020.

Comparing Fig. 4 and Fig. 5, the fraction of reported adverse events that are injuries is greater for absorbable stents than for bare-metal stents. Relative to the number of stents of each type being implanted, the proportion of all implanted absorbable stents that are associated with injuries is much greater than that for bare-metal stents, despite the actual number

of injuries reported for the two stents being comparable. Injuries also account for a greater proportion of reported adverse events for absorbable stents than for bare-metal stents. In 2016, the first year of FDA approval for the absorbable drug-eluting stents, 86.7% of total reported adverse events for the absorbable stents (BVS) were injuries, in contrast to 47.6% for bare-metal coronary stents.

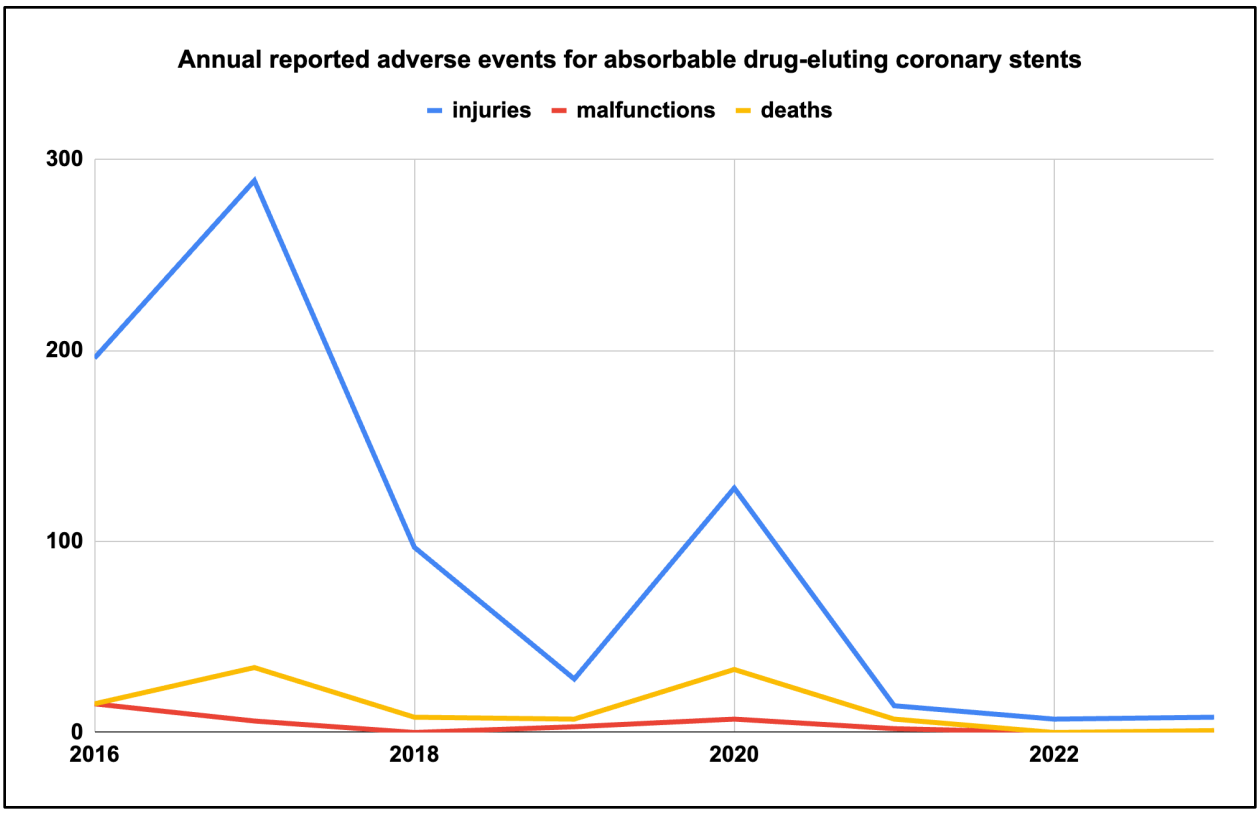

Fig. 5. Reported adverse events by year for absorbable drug-eluting coronary stents in the MAUDE database.

Fig. 6 shows spikes in reported major cardiac injuries (angina, thrombosis, intimal dissection, myocardial infarction, stenosis) associated with absorbable drug-eluting coronary stents in the years 2017 and 2020. The increase in overall reported injuries associated with these coronary stents in 2020 (seen in Fig. 5) was completely driven by an increase in serious coronary events. Definitions of the cardiac injuries are given below:

1. Angina: cardiac chest pain, usually when there is inadequate blood flow in the coronary arteries, such that the heart is not receiving enough oxygen
2. Thrombosis: clotting of artery blocks blood flow
3. Intimal Dissection: tear in the inner layer of the coronary artery; medical emergency
4. Myocardial Infarction: complete blockage blood flow through the coronary artery, resulting in a heart attack
5. Stenosis: narrowing of an artery

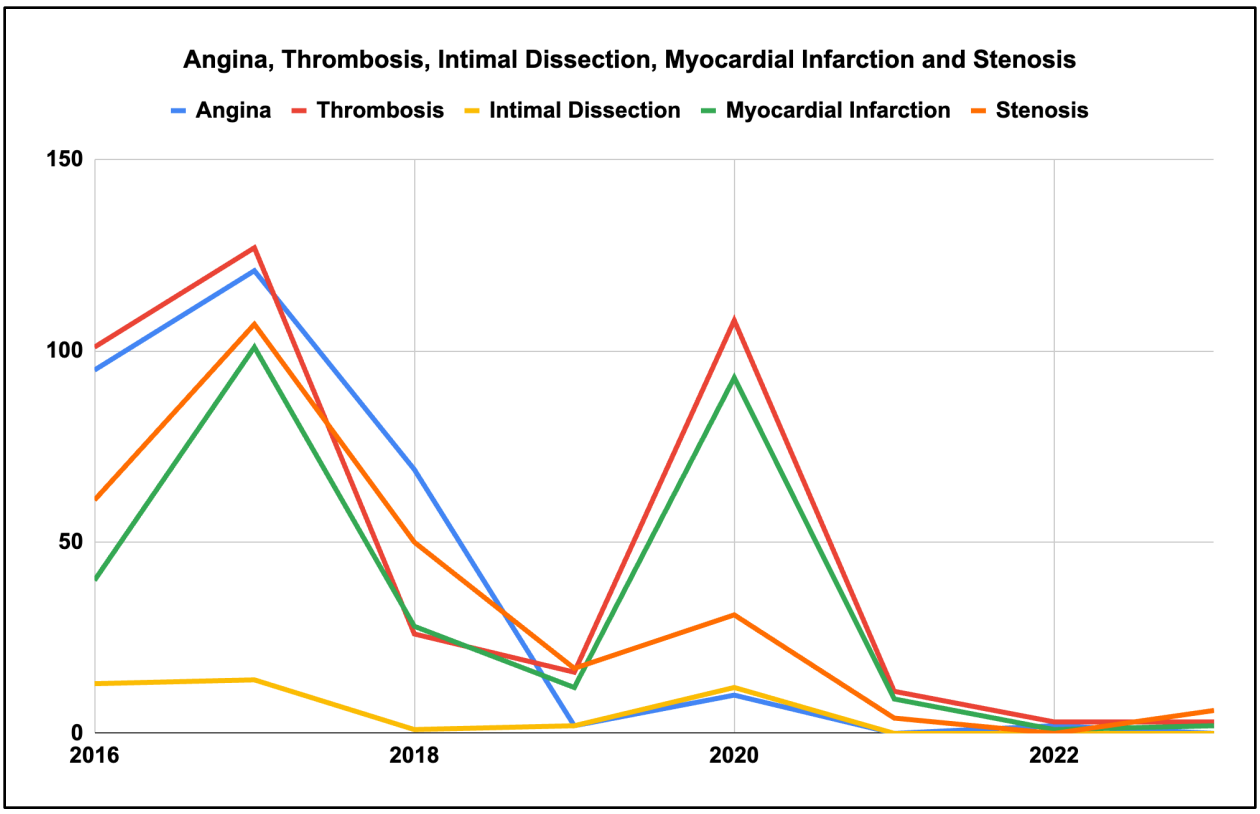

Fig. 6. Reported major coronary events by year for absorbable drug-eluting coronary stents in the MAUDE database.

4. Discussion

There are various limitations of the method described in this study, specifically the parameters of the data found in the MAUDE database. In most cases, the device problem associated with a reported adverse event was unidentified. There is an opportunity for more detailed reporting that would benefit the understanding of this study. Another drawback of utilizing the MAUDE database is the mandated and voluntary reporter system; there may be duplicate or unreported adverse events, and the possibility of inaccurate or incomplete reports that would affect the data collected. Additionally, a causation relationship between the device and the reported adverse event cannot be established. There may be conditions under which the reported event was not a direct result of the device, but instead a result of other risks to the patient. Regardless of these drawbacks, the MAUDE database still provides important data for patient and physician outcomes and experiences for the two devices being discussed.

Bare-metal stents exhibited a crossover in the numbers of reported injuries vs. reported malfunctions in 2016 (Fig. 4). This crossover suggests that bare-metal stent companies were able to reduce malfunctions more than injuries within the first few years of product usage. Injuries accounted for a much larger percentage of adverse events for absorbable stents than for bare-metal stents (86.7% vs 47.6% in 2016). Usage of absorbable stents may have been limited before 2017 because injuries were a much larger fraction of the total adverse events for the BVS absorbable stent system in comparison to the bare-metal stents.

Furthermore, the types of injuries reported for the BVS absorbable stent are completely driven by major coronary events (Fig. 6). This finding is consistent with clinical trials conducted on the BVS device in the ABSORB III trial, and the FDA's findings on these absorbable stents.

The FDA instituted a Class I recall of the absorbable drug-eluting stent Absorb Bioresorbable Vascular Scaffold (BVS) System in June of 2017. A Class I recall is the most serious recall that can be issued by the FDA, and is defined as "a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death."[7] The manufacturer's reason for the recall was stated to be "due to studies showing elevated rates of major adverse events, specifically, myocardial infarction and scaffold thrombosis when compared to patients treated with

the Xience metallic drug eluting stent."[8] Because the BVS system was the first and only absorbable coronary stent approved by the FDA, this recall removed all available absorbable coronary stents from the market.

The FDA decision to recall the Absorb BVS stent was based on the results of the ABSORB III clinical trial. The ABSORB III trial was a 5 year pivotal clinical study done on a total of 2,008 BVS patients. A pivotal clinical study is unique in its aim to show the safety and efficacy of a new medical device, drug, or clinical procedure. The BVS absorbable drug-eluting stent was initially approved based on one-year data of the study, which showed the two stents had comparable rates of adverse events. However, as a condition of approval, the FDA required Abbott Vascular to continue the ABSORB III study and follow the patients involved for five years.

At the two-year mark of the ABSORB III trial, however, an increased rate of major adverse cardiac events was seen in patients treated with BVS in comparison to patients treated with XIENCE, 11% and 7.9% respectively (p=0.03). A 1.9% rate of blood clotting (thrombosis) in BVS patients versus 0.8% in XIENCE patients was also seen at the two-year mark.9

FDA issued a letter to healthcare providers in May of 2017 to provide the trial results and recall the Absorb BVS stent, as well as provide recommendations to personnel and patients. Customers were instructed to immediately halt the usage of the devices. Patients experiencing new cardiac symptoms were advised to seek clinical care, and file voluntary reports of any adverse events related to the BVS system. Health care personnel were still required to follow the FDA reporting requirements. The full list of recommendations for healthcare providers issued by the FDA is given below:

1. "Follow the instructions for target heart vessel selection (e.g., avoiding BVS use in small heart vessels) and optimal device implantation that are included in the BVS physician labeling."
2. "Advise patients experiencing any new cardiac symptoms such as irregular heartbeats, chest pain, or shortness of breath to seek clinical care. For more information about risks associated with the BVS, refer to the BVS physician labeling."
3. "Advise BVS patients to follow the recommendations for DAPT prescribed by their health care providers."
4. "Report any adverse events related to the BVS that come to your attention. If you suspect a problem with the BVS, we encourage you to file a voluntary report through MedWatch, the FDA Safety Information and Adverse Event Reporting Program. Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements should follow the reporting procedures established by their facilities."[9]

At the three-year mark of the trial, an 8.6% rate of target vessel myocardial infarction (TVMI) was observed for BVS patients, in comparison to a 5.9% rate in patients who had been treated with Abbott Vascular's metallic XIENCE stent (p = 0.03). Additionally, a 2.3% rate of developing blood clots (thrombosis) was seen with the BVS stent, versus a 0.7% rate with the XIENCE stent (p=0.01).[10]

The observed spike in adverse events for absorbable stents in the MAUDE database in 2017 coincides with the Class I recall of these devices. The year 2017 would have been the two-year mark for many BVS patients, and increased rates of serious cardiac events connected to the stent may have become evident by this point. The increased awareness of adverse cardiac events connected to the BVS system following the letter to healthcare providers may have further increased numbers of reported events. The number of reported injuries dropped significantly in 2018, which may be a reflection of the decreased use of absorbable stents following the recall.

The observed spike in adverse events for absorbable stents in the MAUDE database in 2020 coincides with the COVID-19 pandemic. The COVID-19 pandemic presented unique and unprecedented challenges to the healthcare system, as providers struggled to balance the need to monitor chronic disease patients with the need to limit the spread of infectious disease. Among these challenges are limitations on healthcare personnel and facilities, as well as limitations in hospital beds and other healthcare resources, all of which were focused towards the care of COVID-19 patients.

The 2020 spike in adverse events for absorbable stents may be attributed to a variety of reasons. Due to the increased stresses on healthcare personnel during the COVID-19 pandemic, there may have been greater chances of medical errors occuring that would have contributed to the 2020 spike in adverse events for the BVS system. It is also possible that patients who had previously had the BVS stent implanted were experiencing more adverse events as a result of the patients themselves being affected by COVID-19. The coronavirus that causes COVID-19 is known to cause cardiac inflammation, and thus may have increased patients' risk for major cardiac events. With compromised health conditions, the reported adverse events may have been attributed to a patient's absorbable coronary stent, even if the adverse event had not stemmed from the stent. Additionally, during the COVID-19 pandemic, patients were advised to remain home away from healthcare facilities with the exception of emergencies, which therefore limited opportunities for in-person healthcare. As a result, early signs for a

major coronary event may have been missed while patients did not attend in-person appointments as regularly during the pandemic. Furthermore, the quarantine procedures put in place during the COVID-19 pandemic may have raised patient stress levels; consequently, patients with coronary stents may have experienced more serious cardiac events. Further research will be necessary to discern the full impact of the COVID-19 pandemic on cardiovascular disease management.

5. Conclusion

The limited clinical adoption of absorbable drug-eluting stents is due to clinical trial results that showed increased rates of major adverse coronary events for absorbable stents as compared to metallic stents, especially at the two-year mark following stent placement. Records of reported adverse events for BVS stents in the MAUDE database are consistent with this conclusion. After the FDA Class I recall of these stents, the Abbott Vascular BVS system is no longer commercially available. Reports of adverse events after the 2017 recall are therefore from procedures that had been performed before the recall.

Despite the BVS absorbable stent no longer being available for patient use, the concept of absorbable stents have found a new application. The FDA issued a Premarket Approval (PMA) of the Esprit BTK Everolimus Eluting Resorbable Scaffold System in April of 2024 for below the knee peripheral arteries.[11] Infrapopliteal disease can be treated by stenting, and these stents are also manufactured by Abbott Vascular. Despite the failure of the absorbable drug-eluting stents to achieve success for treating coronary artery disease, they have been pivoted to a new market for BTK peripheral artery disease. However, further research will be needed to confirm the safety and efficacy of the BTK bioresorbable scaffold. If successful, it may provide insight for better designs for coronary stents in the future with possibilities including adjusting the rate of bioresorption to increase efficacy, or it may confirm that permanent stents are necessary for optimal treatment of CAD.

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