الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

# Post-Market Evaluation for the Safety and Effectiveness of *Paclitaxel Coated Balloon and Paclitaxel Eluting Stent Devices*

**Study Category:**

☑ Post-Market Evaluation Study

☐ Risk Assessment Study

## BACKGROUND

The safety of Paclitaxel eluting stent and Paclitaxel coated balloon has been evaluated extensively by international regulatory offices and specialized societies, due to the long term risks of the mortality following the application of them. FDA released a safety communication on the 17th of January 2019 about the potential for increased long-term mortality after use of paclitaxel-coated balloons and paclitaxel-eluting stents (collectively "paclitaxel-coated products") to treat peripheral arterial disease (PAD) in the femoropopliteal artery.

Nevertheless, and considering the fact that there is an expanded market for Paclitaxel eluting stent and Paclitaxel coated balloon in Saudi Arabia, SFDA takes the initiative to evaluate the safety of Paclitaxel eluting stent and Paclitaxel coated balloon in light of the recent accumulation of clinical data.

## CLINICAL BURDEN

### 1 Paclitaxel coated balloons and paclitaxel eluting stents needs

Peripheral artery disease (also called peripheral arterial disease) is a common circulatory problem in which narrowed arteries reduce blood flow to the limbs. Developing Peripheral artery disease means that there is no enough blood flow to the extremities usually the legs which result in leg pain when walking (claudication). Peripheral artery disease (PAD) is also likely to be a sign of a more widespread accumulation of fatty deposits in your arteries (atherosclerosis). This condition may be reducing blood flow to your heart and brain, as well as your legs [1]. One of the main symptoms of peripheral artery disease is the have leg pain when walking (claudication). Claudication symptoms include muscle pain or cramping in the legs or arms that's triggered by activity, such as walking, but disappears after a few minutes of rest. The location of the pain depends on the location of the clogged or narrowed artery. If peripheral artery disease progresses, pain may even occur when at rest or when the patients lying down (ischemic rest pain). Hence, the symptoms of PAD ranging from leg pain when walking (claudication) to tissue loss may result from Lower extremity PAD in the femoropopliteal segment which may in the end lead to amputation (critical limb ischemia)

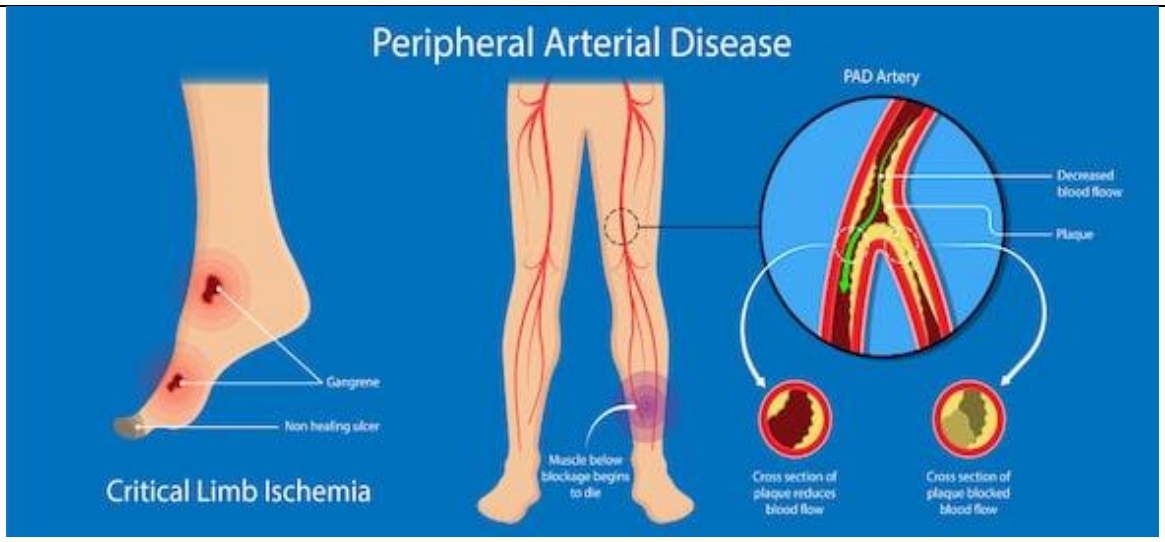



Figure1: Illustration of the peripheral arterial disease [2]

One of the prevalent condition that affect the aging population is the peripheral arterial disease (PAD). The prevalence of PAD is range from 3% to 10%. in people aged < 70 years and from 15% to 20% in people aged >70 years as estimated by several epidemiologic studies [3]. PAD contributes significantly to the morbidity and mortality of adults. In addition to that, PAD consider a significant economic burden The high rates of initial and repeat revascularization procedures is the main reason of the high hospitalization costs for patients with PAD . [83]

There are many endovascular therapies for PAD include percutaneous transluminal angioplasty (PTA), stenting, bypass surgery and atherectomy. These therapies are often associated with a high incidence of restenosis (i.e., re-narrowing of the treated vessel segment) due to a neointimal proliferation - *migration of vascular smooth muscle cells primarily in the innermost layer of an artery or vein*- in response to vessel injury. Over the past decade, drug-coated devices, including drug-coated balloons (DCB) and drug-eluting stents (DES), have been approved to treat *de novo* and restenotic lesions in the superficial femoral arteries (SFA) and proximal popliteal arteries (PPA) in PAD patients. One of these drug-coated devices is Paclitaxel eluting stent and Paclitaxel coated balloons

## 2 Paclitaxel coated balloons and paclitaxel eluting stents specification

### 2.1 Paclitaxel

The paclitaxel was developed at the beginning as an anti-cancer anti-proliferative agent. It is essentially insoluble in water, so for intravenous administration to cancer patients, it is dissolved in an oil base to form the drug Taxol. Then it has been introduced to be use for coronary stenting. Because paclitaxel is not soluble in water, it is not suitable alone for systemic therapy, but is more applicable for contact-based, local delivery, as in drug-eluting stents. One obvious example is its use as a local anti-proliferative to reduce restenosis. The main difference between paclitaxel as used in cancer treatment versus stenting is the dose. Paclitaxel-eluting stents administer tiny doses in comparison to Taxol in cancer treatment. Microtubules are responsible about cell division so paclitaxel works by stabilizing microtubules by rendering them nonfunctional. The drug has unique multifunctional effects that inhibit the restenotic process. It promotes the polymerization of stable nonfunctioning mictrotubules and thus inhibits all microtubule-dependent activities. As a result, it can inhibit multiple cellular components of the restenotic process. In addition, paclitaxel is highly lipophilic, which contributes to more efficient drug transfer off the stent and into the tissue. Lastly, paclitaxel has a dose-dependent inhibitory effect on smooth muscle cell proliferation. Because smooth muscle cells are more sensitive to paclitaxel than endothelial cells, it reduces restenosis without compromising the healing of the arterial wall [5].

The design of DCB and DES allow for an initial drug dose followed by a sustained cytostatic drug level to inhibit smooth muscle cell proliferation and neointimal growth, leading to reduced restenosis rates. The kinetics of drug release rely on several factors, including drug dose density, degree of coating crystallinity, the type of the carrier excipient, and total drug load. While increased drug crystallinity generally helps achieve higher tissue uptake and prolonged retention, an increased amorphous content usually facilitates a durable coating of the drug on the balloon during tracking of the device to the target lesion, Currently-marketed devices initially source similar crystalline paclitaxel, but the processing of individual devices likely results in differing ratios of amorphous and crystalline content. [6]

Paclitaxel eluting stent and Paclitaxel coated balloons may be combined with an excipient. The excipient enables uniform distribution of the drug on the device and facilitates drug transfer

upon balloon inflation or stent implantation during contact with the endoluminal surface. The choice of an excipient impacts various device properties, including systemic drug loss during transit to the lesion site, tissue retention, drug release during inflation/implantation and local drug transfer. Microparticle formation from these coatings is often observed, which may embolize to the downstream systemic circulation. The amount of particulate formation varies depending on device design and processing [7].

### 2.2 Drug coated balloon vs Drug eluting stent

Drug-eluting balloons is deliver the drug on site with a precise control of the drug dosage. Therefore, there is not systemic exposure to the drug because the concentration is effective and sufficient. It has an advantage when compare with the stent which is possibility of a homogeneous drug transfer where as in the stent, the drug is only delivered at the contact site of the stent struts with the vessel wall. The stent struts cover approximately 15% stented vessel wall area, which result in low tissue concentrations of the ant proliferative agent in these areas

| Drug-Eluting Stent | Drug-Eluting Balloons |
|---|---|
| Slow release | Immediate release |
| Persistent drug exposure | Short-lasting exposure |
| Approximately 100–200 µg per dose | Approximately 300–600 µg per dose |
| Polymer | No polymers |
| Stent mandatory | Premounted stent optional |
| | Matrix optional |

Table 1: characteristic of drug-eluting stent versus drug eluting balloon [8]

| RISKS AND COMPLICATIONS |
| --- |
| Paclitaxel eluting stent and Paclitaxel coated balloons are reported to be associated with the increase of long term mortality rate complications that impact patient's safety. Literatures were reviewed to evaluate the pre-clinical safety for Paclitaxel eluting stent and Paclitaxel coated balloons which has been approved by FDA. It was shown that there was no evidence of potential device-related safety concerns. In addition, the literatures were reviewed for RCTs and meta-analysis to evaluate the safety of Paclitaxel eluting stent and Paclitaxel coated balloons. It demonstrates that there is good safety profile for these devices, however, some of the longer-term follow-up RCTs have shown hints of increased late patient mortality with the use of Paclitaxel eluting stent and Paclitaxel coated balloons in the absence of obvious causal links [4]<br><br>Recently, there is a debate about the safety of Paclitaxel eluting stent and Paclitaxel coated balloon in term of long term mortality among international regulatory organizations. **MHRA** have formed an independent Expert Advisory Group (EAG) to review the available information on paclitaxel eluting stent and paclitaxel coated balloon after the concern that has been raised by Katsanos et al. The EAG group is made up of leading UK clinicians from specialist societies, including interventional radiology, vascular surgery and scientists with toxicology, medicines and statistical expertise. Their publication's findings show that there is a possible increase in the mortality rate from 2 to 5 years in PAD patients treated with paclitaxel coated balloons and paclitaxel eluting stents compare with PAD patients treated with non-coated balloons or bare metal stents. The causal relationship for this observation has not been identified yet. This may reflect limitations in the way the data were analyzed. The devices have valid CE certificates and still remain on the UK market.<br><br>**USFDA** have issued 2 field safety notices in the database regarding Paclitaxel eluting stent and Paclitaxel coated balloon and all of them have been given recall class III. There are a number of paclitaxel-coated balloons or paclitaxel-eluting stents approved or under study for peripheral vascular use in the FDA is currently evaluating available long-term follow-up data to determine if there are any long-term risks associated with paclitaxel-coated products. This will include an evaluation of long-term follow-up data from studies that supported approval of paclitaxel- |

coated balloons or paclitaxel-eluting stents in the U.S. and other available data sets. This review will focus on causes of death, the paclitaxel dose delivered, and patient characteristics that may impact clinical outcomes. Additional statistical analyses will be performed to clarify the presence and magnitude of any long-term risks.

## EVALUATION OUTCOMES

The safety and effectiveness of Paclitaxel Coated Balloon and Paclitaxel Eluting Stent Devices for the treatment of **(PAD)** were evaluated considering two main sections: the clinical paper review and the clinical experience review. While the first aims to review the published papers in the topic, the second will explore the opinions of other regulatory offices, international specialized societies, and most importantly the opinions of the local experts, represented. These two elements will be then used to draw an overall evaluation regarding the risk of increasing the long-term mortality rate of paclitaxel eluting stent and paclitaxel coated balloons, which will be demonstrated form of current-evidence-based recommendations about the device safety.

**Part 1: Clinical paper review**

**I) <u>An overview of the search criteria</u>**

Table 2 specify the search criteria, it specify the inclusion criteria and the quality measures for the review. As a result, 91 articles were acquired, and screened first for duplication, and then through scanning the abstract as guided by the clarified inclusion criteria.

Lastly, 9 specific articles were obtained and read in full. Figure 2 shows a schematic representation of the search findings on evaluating the safety of Paclitaxel eluting stent and Paclitaxel coated balloons.

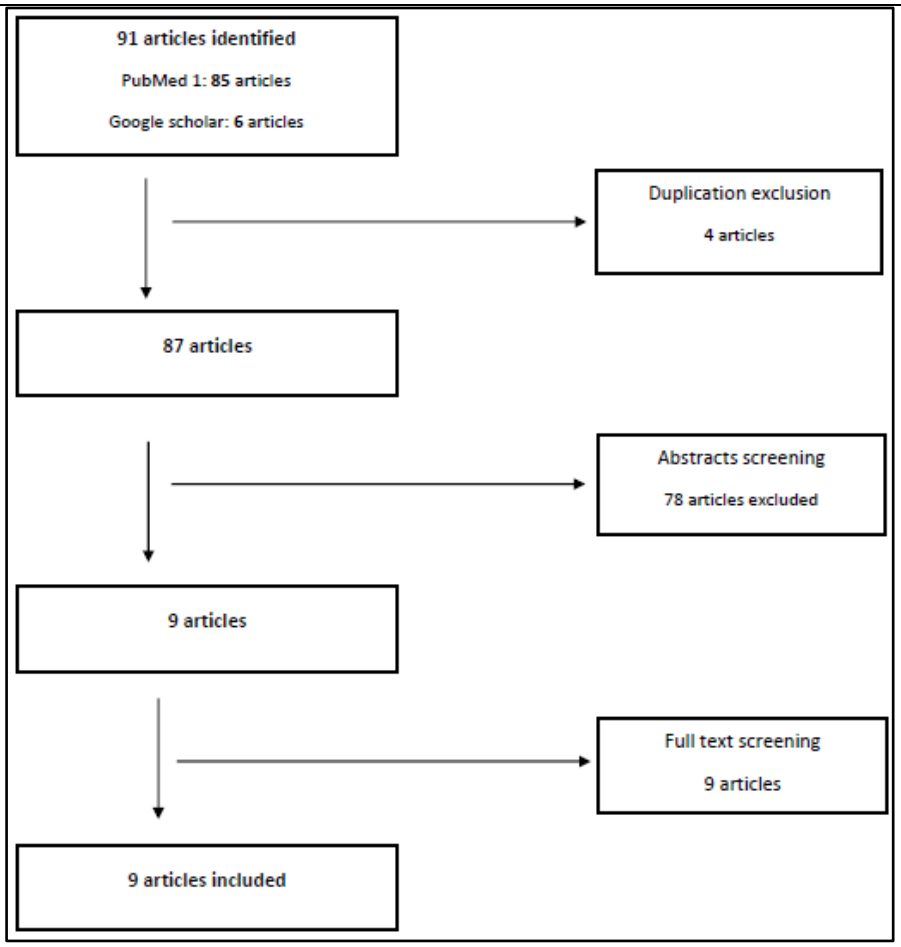



Figure 2: Schematic representation of the search findings.

## II) Summary of the paper review findings

- A number of 9 studies were included after applying the inclusion criteria and the quality measures, which include 6 RCTs and 3 meta-analyses that compare the mortality rate of the applying the standard PTA and paclitaxel coated devices.
- Figure 3 shows a comparison of the mortality rate of standard PTA and paclitaxel coated devices at a follow up period of 2 years and 5 years. The major observation suggests a significant correlation between morality rate and time. Paclitaxel coated devices is seen to have higher mortality rate than standard PTA which were seen to be 1.7% at a follow up of 2 years and at a follow up of 5 years the difference was seen to be increased significantly at a difference in the mortality rate of 5.9%.

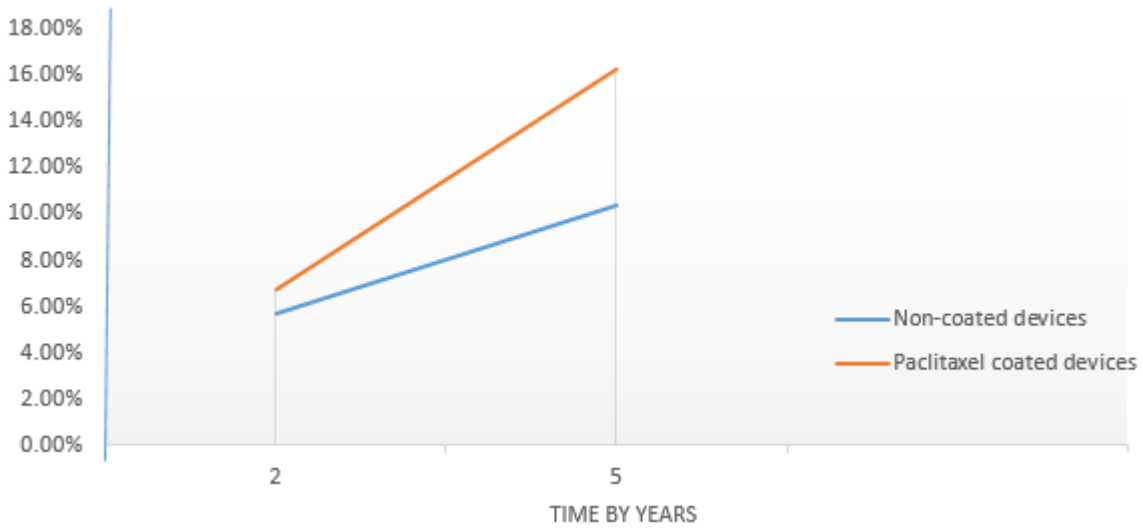



Figure 3: A comparison of the mortality rate of non-coated devices and paclitaxel coated devices.

**Part 2: The opinion of global specialized societies and associations in Paclitaxel coated balloons and paclitaxel eluting stents**

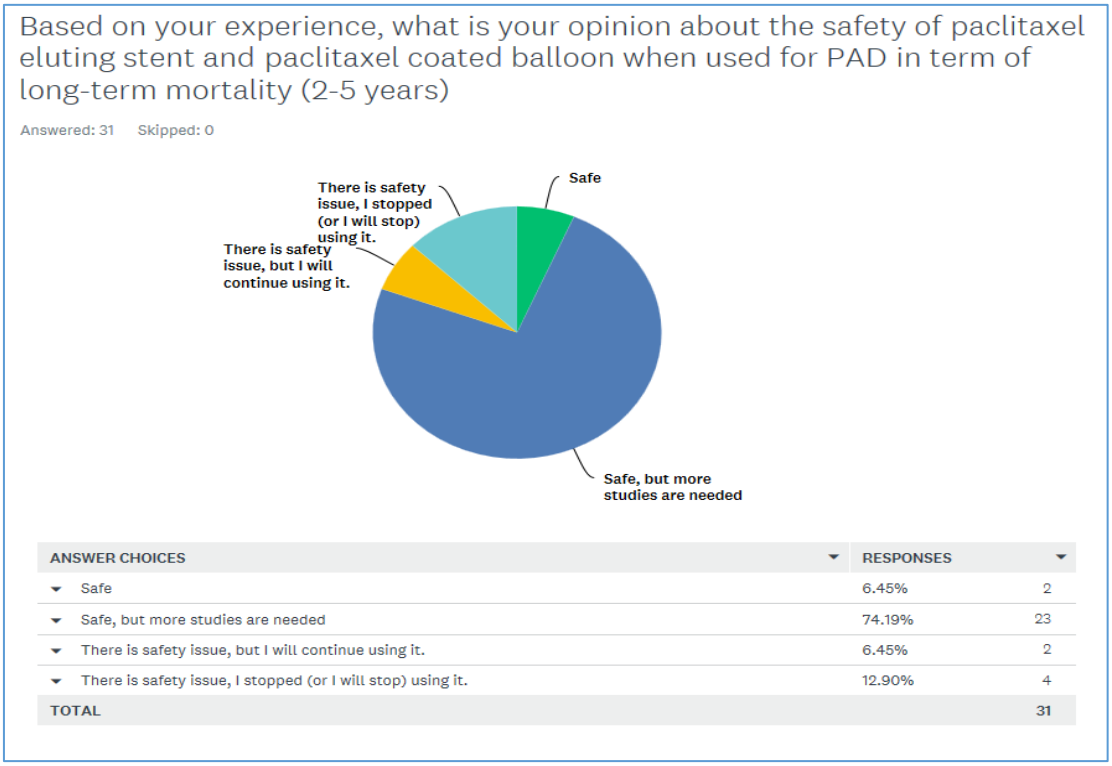
**American heart Association** has conducted a systematic review and meta-analysis of RCTs to investigate the safety issue of paclitaxel coated balloons and paclitaxel eluting stents in the femoral and/or popliteal arteries. The primary safety measure was all-cause patient death. A random effects model was used for the risk ratios and risk differences. 28 RCTs with 4663 patients were analyzed. All-cause patient death was similar between paclitaxel-coated devices and control arms at 1 year (28 RCTs with 4432 cases). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control. All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel Meta-regression showed a significant relationship between the absolute risk of death and the exposure to paclitaxel (dose-time product) (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

**Part 3: Saudi user experience**

Saudi experts have been consulted about the risk of increasing the mortality rate for patients who treated with paclitaxel eluting stent and paclitaxel coated balloon, in an evaluation check that contains the following questions:

- **Q1:** Based on your experience, what is your opinion about the safety of paclitaxel eluting stent and paclitaxel coated balloon when used for PAD in term of long-term mortality (2-5 years)? They have been given four choices to answer this question as safe, safe, but more studies are needed, there is safety issue, but I will continue using it, and there is safety issue, I stopped (or I will stop) using it.
- **Q2**: Do you have any comments you want to add about the raised issue of safety of paclitaxel Coated Balloon and paclitaxel Eluting Stent Devices when used for PAD. in term of long term mortality (2-5 years)?

**The results:** Thirty-one experts have been consulted and their answer for the first question is illustrated in figure 4, where the majority (74%) think that the device is safe, but more studies are needed to evaluated the device safety at the long-term.




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Safe | 6.45% | 2 |
| Safe, but more studies are needed | 74.19% | 23 |
| There is safety issue, but I will continue using it. | 6.45% | 2 |
| There is safety issue, I stopped (or I will stop) using it. | 12.90% | 4 |
| TOTAL | | 31 |

Figure 4: Saudi expertise opinion about the safety of paclitaxel eluting stent and paclitaxel-coated balloon.

However, and with respect to the second question, the majority of the responders believe that the paclitaxel eluting stent and paclitaxel-coated balloon when used for PAD are safe and effective and the benefit of using them outweigh the risk. Nevertheless, some of the experts have different opinion regarding the reliability of the original study that highlight the case-safety signal.

**Overall Conclusion**

The objective of this post-market evaluation is to evaluate the safety of paclitaxel coated balloon and paclitaxel eluting stent in term of long term mortality comparing with non-coated devices. The literature review shows that there was a good evidence that using paclitaxel-coated devices in the femoropopliteal artery was related to significantly long term increased risk of death comparing with non-coated devices. International regulatory organizations mentioned that there is a possible increase in the mortality rate from 2 to 5 years in PAD patients treated with paclitaxel coated balloons and paclitaxel eluting stents compare with PAD patients treated with non-coated devices. The global societies and associations have conducted systematic review and meta-analysis of RCTs to investigate the safety issue of paclitaxel coated balloons and paclitaxel eluting stents in the femoral and/or popliteal arteries. They come up with that, there was a relationship between the risk of long-term mortality and the exposure to paclitaxel. Saudi user experience has been taken about the safety issue of paclitaxel-coated devices and they believe that, the devices are safe however, more studies are needed. To conclude that, more studies are needed to evaluate the safety of paclitaxel eluting stent and paclitaxel coated balloon in term of long-term mortality comparing with non-coated devices.

**SFDA ACTIONS**

Considering the results of the post-market evaluation of the safety and effectiveness of Paclitaxel Coated Balloon and Paclitaxel Eluting Stent Devices for the treatment of (PAD), the following actions were taken by SFDA:

- Request a post-market follow up studies from the manufacturers confirming the safety of the devices.

- Publish a safety communication letter including the following information:

"SFDA would like to draw your attention to the meta-analysis studies that show an increase in late mortality rate (2-5 years) after the application of paclitaxel coated balloon and paclitaxel eluting stent to treat patients with peripheral arterial disease (PAD). However, there are limitations in these meta-analyses, the benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality)".

**Recommendations for Healthcare Providers**

- Continue monitoring patients who have been treated with paclitaxel –coated balloon and paclitaxel eluting stents per the current standards of the care for longer than 2 years.
- Report any incident / adverse event or suspected adverse events experienced with the use of paclitaxel-coated balloons and paclitaxel-eluting stents through National center for medical devices reporting (NCMDR) https://ncmdr.sfda.gov.sa, or the Saudi Vigilance System https://ade.sfda.gov.sa/, to help the SFDA identify and better understand the risk associated with the devices.

**ACKNOWLEDGMENT**

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For further information or inquiries related to this study, you may contact us at: cia.md@sfda.gov.sa

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