



The SWEDEPAD study: a model to follow, or is not all that glitters gold?

Estudio SWEDEPAD: ¿un ejemplo a seguir o no es oro todo lo que reluce?

A few months ago, the SWEDEPAD study was published in the prestigious journal *The Lancet*. The results were so significant that they were published in two separate articles, "SWEDEPAD 1" and "SWEDEPAD 2" (1-3). This is a study on the efficacy of paclitaxel-eluting devices versus standard devices for the treatment of patients with chronic lower limb ischemia. The conclusions of these studies have been so decisive that even an editorial in the *European Journal of Vascular and Endovascular Surgery* has drawn attention to the use of paclitaxel-eluting devices.

In 2025, we believed that the fears surrounding paclitaxel—originated by Katsanos's meta-analysis—had been overcome thanks to multiple analyses by drug regulatory agencies (both American and European), systematic reviews, and subsequent meta-analyses on the subject. However, Pandora's box has been opened once again. Nevertheless, in the following paragraphs, I would like to encourage the scientific reader to reflect on the design, methodology, and results trumpeted far and wide by the authors of SWEDEPAD and *The Lancet*.

As we begin an avid reading of the study, our attention is drawn to the appendix, which appears as supplementary material. It discusses the study design, which achieves such exemplary standards and scientific quality that it should be studied in medical schools as a model for how to design a multicenter, blinded, randomized, controlled registry. The data are obtained from the Swedish National Quality Registry for Vascular Surgery (Swedvasc), which is the world's longest-running national registry (founded in 1987) and which, since 1994, has encompassed all centers performing vascular procedures in Sweden.

The primary objective of SWEDEPAD 1 was the rate of ipsilateral major amputation at one year of follow-up among patients with critical lower limb ischemia treated endovascularly with paclitaxel-eluting or non-paclitaxel-eluting devices. From 2014 to 2023, 2,400 patients were randomized, of whom 2,355 were included in the intention-to-treat analysis (1,180 in the paclitaxel group and 1,175 in the non-paclitaxel group). All patients are classified as Rutherford categories 4, 5, and 6, except for one patient who is category 2 and three in category 3 (the reasons for their inclusion in the study are unknown). After a median follow-up of 2.67 years, the authors conclude that paclitaxel-eluting devices do not reduce the rate of ipsilateral major amputations after 5 years of follow-up.

Secondary endpoints include the reoperation rate, which was lower in the paclitaxel group at one year of follow-up ($p = 0.042$), a difference that disappeared after five years of

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follow-up. No differences in mortality were found between the treatment groups. These findings may seem questionable given that only 18.9% of patients reached the five-year follow-up mark.

In this study, the use of primary stents was 13.2%, which ultimately rose to 31.8% (30.4% in the paclitaxel group and 33.2% in the non-paclitaxel group). The decision regarding primary stenting or bailout stenting was left to the operator's discretion, as was the choice between a bare-metal stent and a drug-eluting stent. The only information provided on this matter appears in the appendix, which reports a total of 358 drug-eluting stents used (13.2% Zilver PTX and 2.5% Eluvia out of all paclitaxel-eluting devices) among the total of 736 patients in whom one or more stents were implanted (a figure that is also unknown). The lack of detail regarding stent treatment, which affects nearly one-third of the treated patients, means we do not know what the actual treatment was in either of the treated groups, which may constitute the first major bias in this study.

The SWEDEPAD 1 study may also be subject to another type of bias: class bias. By this we mean that as many as 14 different types of paclitaxel-releasing devices were used (including, in three cases, patients treated with everolimus-releasing devices and another patient treated with a zotarolimus-releasing device; the reasons for including these patients in the study are also unknown). Despite all this, 44.9% of the paclitaxel-releasing devices were the Lutonix (BD) balloon. Based on the extensive experience documented in the literature regarding the use of paclitaxel-releasing devices, we know that not all are the same; each has its own dose, excipients, and characteristics.

After analyzing the surprising conclusions reported by the authors in the SWEDEPAD 1 study, the findings of SWEDEPAD 2 may lead us to question the credibility of Swedish medical practice. The primary objective was to assess quality of life, measured using a 6-item questionnaire called "VascuQol-6" after one year of follow-up of patients treated for intermittent claudication via endovascular procedures. A total of 1,155 patients were randomized, with 577 treated with paclitaxel-eluting devices and 578 treated with devices without paclitaxel. Despite its exemplary methodological design, what is particularly striking is that 39.7% of patients were in Rutherford clinical categories 1 and 2. As all readers know, all guidelines published by the various scientific societies of vascular surgery, angiology, interventional radiology, cardiology, or any other specialty dealing with claudicating patients recommend interventional treatment (either endovascular or open surgical) starting at Rutherford category 3. Therefore, we should ask ourselves: is it ethical to treat these types of patients? Despite this, should it be publicized in one of the world's most important scientific journals, such as *The Lancet*? Why are these criticisms not also included in the editorial of the journal serving as the official publication of the European Society for Vascular Surgery?

If we continue to analyze the SWEDEPAD 2 study, we find that the rate of primary or bailout stenting reached 42.8% of patients. This percentage is double that of most studies involving patients treated with paclitaxel-eluting balloon angioplasty (for example, the IN.PACT study reported a stenting rate of 21.2% in patients with more complex lesions). The primary drug-eluting stent was the Zilver PTX (18.1%), followed by the Eluvia (3.9%). We also do not know their indications. As in SWEDEPAD 1, SWEDEPAD 2 suffers from a class bias stemming from differences in the paclitaxel-eluting balloons included in the study (primarily Lutonix [38.9%] and IN.PACT Admiral [20.9%]).

In terms of results, no differences were found between the two groups regarding quality of life after one year of follow-up, nor in the rates of reoperations, ipsilateral major amputations, or mortality. The median follow-up for the series was 7.1 years, a fact that is curious, to say the least, when compared to the median follow-up of SWEDEPAD 1, which was 2.67 years. If both publications stem from the same study, SWEDEPAD, how can there be such a disparity in follow-up among patient populations? If the study began in November 2014, were claudicating patients included first and critically ischemic patients last? A careful reading of the appendices does not clarify this.

Another secondary outcome is the reoperation rate. In the article's discussion, they refer to reintervention as an "outcome" variable, comparing it to the "quality of life" variable. However, they offer no reflection on the indications for reintervention in a population of claudicating patients, nearly 40% of whom had mild or moderate claudication, or why 30% of these patients underwent reintervention during follow-up.

After all that, here comes the most significant and widely publicized finding of this study (for which it was not designed, but which has received widespread media coverage): the group of patients treated with paclitaxel-releasing devices had higher mortality after 5 years of follow-up, a difference that disappeared by the seventh year. This finding, which may seem curious, cannot constitute the central focus of the study's results, especially considering that 25% of the data were censored after 5 years of follow-up. We can think of multiple sources of bias that could lead to this specific finding, and we hope they will be analyzed in future articles.

Finally, I encourage the reader to examine the discussion section of the article. In it, the finding regarding the difference in mortality at 5 years of follow-up (a secondary objective of the study) accounts for 124 of the 279 lines of discussion. In other words, 44% of the discussion in an article published in *The Lancet* is based on the finding of a secondary variable that was observed only at 5 years of follow-up—neither before nor after—when 25% of the cases had been censored. Furthermore, it prompted the publication of an editorial in the *European Journal of Vascular and Endovascular Surgery* urging caution regarding paclitaxel.

After all these reflections, we may conclude that not everything labeled as science is as it seems, and not everything published in leading journals of scientific progress today can be taken as gospel. We are unaware of the editorial, business, promotional, or self-serving motives behind this potential scientific sensationalism, but we encourage all readers to develop critical scientific reading skills in order to adopt an objective, impartial, honest, and rigorous scientific approach.

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