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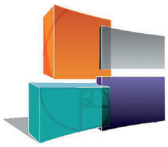

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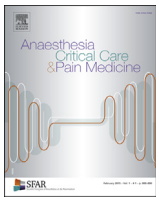

Editorial

Should we still prescribe Levosimendan for low cardiac output after cardiac surgery? Perhaps in the good patients!

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The first clinical study on Levosimendan referenced in PubMed was published in the early nineties. Ever since that, dozens of randomised controlled trials (RCT) and meta-analyses evaluating the benefit of this drug in the context of cardiac surgery were published but, because of conflicting results, clear guidelines are still lacking.

Zhu et al. hypothesised that conflicting results could be explained by patient heterogeneity. In the current issue of Anaesthesia Critical Care and Pain Medicine, they report the results of a systematic review and meta-analysis focusing on a specific subgroup of patients, i.e., those with low cardiac output syndrome following cardiac surgery and with a preoperative left ventricular ejection fraction (LVEF) of less than 40% [1]. In this much more homogeneous population of patients, the authors failed to show any significant benefit of levosimendan on 30-day mortality, postoperative acute kidney injury or myocardial infarction. Again, this result is conflicting with some previously published meta-analyses reporting a benefit of levosimendan administration in patient with low LVEF [2,3].

How is it possible to interpret such a vast though conflicting amount of scientific evidence: is it bad clinical research? Good research on a useless medication? Or, maybe should we refrain from throwing the baby out with the bathwater? Indeed, a major reason for conflicting RCT results and, at the same time for negative meta-analyses, is patient heterogeneity. Even though, Zhu et al. tried to address this issue by focusing on patients with low preoperative LVEF, heterogeneity across studies and even more so across patients may be related to a variety of characteristics, some of them not necessarily observed or even known. Any clinician has once witnessed in a given patient a specular effect of a drug proven to be unbeneficial in previous RCTs. Although this may largely be explained by an evaluation bias, each patient is unique, and the patients we are taking care of on a daily basis are often very different from the average population included in RCTs. Thus, before concluding that a drug is useless (or useful), one should be very cautious in understanding the population of patients included and excluded from RCTs and meta-analyses. Even in the presence of well-designed RCTs and meta-analyses, external validity is often a serious concern [4]. This is sometimes very apparent in studies where the number of subjects screened for inclusion is far larger than the number finally included in the analysis, because of very stringent inclusion criteria. Thus, looking at the first part of the flowchart, i.e., anything happening before randomisation and even before inclusion is of paramount importance to better understand the population the results can apply to. Rothweel [4] even proposed a checklist for clinicians, and recommendations for greater consideration of external validity in the design and reporting of RCTs. In the case of levosimendan, the drug may still be useful in patients excluded from the 5 studies included in the analysis by Zhu et al. [1], e.g., patients with a low glomerular filtration rate.

Meta-analyses add an additional layer of complexity to this problem. First, meta-analyses are known to be susceptible to the risk of publication bias, i.e., the risk of bias in pooled estimation of treatment effect related the fact that negative studies, even of good methodological quality, are less likely to be published. Moreover, the studies included in a meta-analysis may be very unbalanced in terms of sample size. For instance, in Zhu et al. [1], the studies by Mehta et al. [5] and Cholley et al. [6] represent almost 80% of the total sample. In this case, the pooled estimation of treatment effect may be largely driven by one or few studies representing the large majority of the global sample size. Again, in this context, the results of the meta-analyses will essentially apply to the population of patients included in the largest studies.

Results of RCTs and meta-analyses are even more difficult to interpret in case of high heterogeneity in treatment effect across patients or clusters of patients. The question of treatment heterogeneity is rarely addressed in RCTs. In the world of evidence-based medicine in general, the so-called evidence essentially relies on populational average treatment effect. However, the response to treatment at the individual level may largely differ for the average effect observed at the population level. With the exception of subgroup analyses, treatment heterogeneity is almost never explored in RCTs and in meta-analyses. One of the reasons is that inter-patient variability is very difficult to accurately quantify. Indeed, from a statistical standpoint, it is difficult to distinguish the portion of treatment effect variability related to a true heterogeneity between patients, from the portion related to the intrinsic variance of the statistical estimator. Machine learning approaches will probably be very

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useful in the future to better characterise underlying clusters of patients and maybe help the clinician to identify the outliers who will respond to a treatment while the average population is unresponsive.

Hence, rather than discouraging the use of the drug, or worse stopping its commercialization, inconsistent results leading to inconclusive meta-analyses should prompt the scientific community to further investigate specific subgroups that may benefit from this therapeutic option. In order to leverage the already existing evidence and thus to avoid new RCTs naive from previous results, it is particularly useful to combine them into individual patient data meta-analyses. This allows not only boosting the statistical power by increasing the sample size, but more importantly digging deeper into patients' characteristics and identifying clusters of patients in whom treatment effect may justify additional investigations.

Thus why concluding when not sure? After all, the patient I will take care of tomorrow may benefit from Levosimendan.

Disclosure of interest

The authors declare that they have no competing interest.

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