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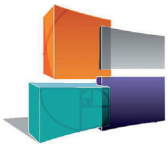

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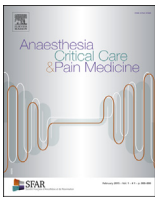

Editorial

CON: Levosimendan should be used in clinical practice for patients with significantly impaired left ventricular function undergoing cardiac surgery

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Like many people in the UK, I am struggling to get to grips with the concept and process of the much-heralded exit from the European Union. A second referendum is one of the options proposed and the proponents of Brexit furiously suggest that those who want to remain will wish to repeat the voting process until they obtain the required result. So it also seems with clinical evidence at times, and none more so than with the curious case of Levosimendan. What are we clinicians to make of this conflicting evidence?

It is known that up to 20% of patients undergoing cardiac surgery may suffer acute cardiovascular dysfunction [1]. Impaired pre-operative cardiac function is the most significant risk for post-operative dysfunction and this may progress to a low cardiac output syndrome, a state which, if untreated, induces organ dysfunction and an increased risk of death [2]. Overall, we cannot consider inotropic support following cardiac surgery beneficial for the patient and in fact is likely to constitute a hazard due to the undesirable effects of all of the members of this class of drugs [3]. In this issue of the journal, Dr Zhu and colleagues publish a systematic review and meta-analysis of the use of this calcium sensitising inotropic drug in patients with significantly reduced cardiac function who are undergoing cardiac surgery [4]. The pharmacological profile of Levosimendan as a calcium sensitiser is appealing, although it is known to exhibit a significant vasodilatory effect. Early smaller single centre studies seemed to demonstrate an impressive effect on haemodynamics and mortality [5,6,7]. This was confirmed by meta-analyses of these smaller studies and a particular benefit was highlighted for those patients with reduced left ventricular function [8,9]. The stage was set to confirm these benefits with 3 large randomised controlled trials which would support the routine use of Levosimendan in patients with significantly impaired cardiac function undergoing heart surgery.

Two of these trials were published simultaneously by the New England Journal of Medicine in March 2017. The CHEETAH trial was a multicentre, randomized, double-blind placebo controlled trial, it was a pragmatic study targeting significant perioperative cardiac dysfunction in the first 24 hours after any type of cardiac surgery involving cardiopulmonary bypass. Despite enrolling 506 patients, the trial was stopped for futility as there was no difference in 30 day mortality, nor any of the secondary outcomes [10]. The LEVO-CTS study was a similarly high quality multicentre, randomised, placebo controlled phase 3 trial, although differing in that the study drug was administered immediately prior to surgery in patients with a left ventricular ejection fraction 35% or less who were undergoing cardiac surgery with cardiopulmonary bypass [11]. Despite randomising 885 patients, there was no difference in mortality or secondary endpoints. The investigators were able to conclude that Levosimendan was safe to use in this group of patients, but they were unable to conclude that it was at all effective. As is customary a meta-analysis quickly followed, which included the two aforementioned trials in evaluating the effect of Levosimendan versus placebo on mortality [12]. Sanfilippo and colleagues did not find a mortality difference when including all 6 studies, however by eliminating the CHEETAH study (which was the study containing the lowest risk of bias) and including only the low left ventricular ejection fraction (EF) studies, they were able to demonstrate a small effect in favour of lower mortality with Levosimendan. In the same meta-analysis, the authors showed a small advantage of Levosimendan over placebo in preventing the need for renal replacement therapy in the same group of patients.

In September 2017, the third large Levosimendan trial arrived. Professor Cholley and colleagues completed the LICORN trial, which was published in the Journal of the American Medical Association (JAMA). Like the previous two trials, this was a randomized double-blind placebo controlled trial conducted in 13 French cardiac surgical centres. Patients undergoing first time coronary artery bypass (CABG) or combined valve CABG with an ejection fraction of 40% or less were randomised to either Levosimendan or placebo. Unlike the other two trials, the primary outcome was not mortality, but a composite of indicators of low cardiac output syndrome including catecholamine or mechanical support or need for renal replacement. Among 333 patients who were randomised and completed the trial, there was no difference in the primary outcome between the Levosimendan group and the

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placebo group. The investigators concluded that they could not support the use of Levosimendan for the described indication.

We now take up the story with this latest meta-analysis presented in this issue of the journal. Unlike the previous meta-analysis, the current one includes the LICORN study and it also includes the smaller Erb study from 2014 [13,14]. In common with the Sanfilippo analysis it includes the studies by Mehta, Levin and Shah - which randomised patients with LV ejection fraction less than 30% undergoing off-pump coronary revascularisation only [5,11,12,15]. This current work also excludes the studies by Landoni and Sharma – which investigated haemodynamics and length of stay in patients with a low LVEF undergoing combined coronary and mitral repair procedures. These two studies were included in the Sanfilippo article [10,16]. All of the included studies had significant left ventricular impairment and the study drug was commenced prior to surgical incision. The inclusion of the LICORN study in particular in this new meta-analysis would seem to provide the result and subsequent conclusion that Levosimendan is not effective in this population of patients. The authors discuss a number of limitations of their study, which may influence this – particularly that a high proportion of the placebo group did in fact receive other inotropes.

So where does this leave us all, busy clinicians who want to improve the survival chances of our patients with poor LV function who are scheduled for surgery? There is now a robust and recent body of evidence that suggests we should not give them Levosimendan in the pre-incision period. There is also good quality evidence that we should not give them this inotrope even if they become haemodynamically unstable following surgery. It has also recently been demonstrated ineffective in an undifferentiated septic population [17]. Our pharmacists are pointing out to us that this is a very expensive drug compared with its comparators with no evidence to support its use, although there is little evidence to support the use of any inotropic drug, yet they may be more cost effective. Do we demand larger studies? A suggested inclusion number is 3000 patients, yet the CHEETAH study was stopped at around 500 for reasons of futility. A number of eminent figures have analysed and discussed this recent research at a meeting convened by the manufacturer, but should we be concerned about implicit bias in these considerations [18]?

What may we conclude from two years of intense focus on this inotrope? Certainly, we can agree that it is safe based on the evidence, but I find it difficult to agree with the argument that it is effective. I certainly would not use it as a first line agent. I may not use it as a second line agent, but I would certainly want to have Levosimendan available for use in my sickest patients. Now we know Levosimendan is a safe choice, possibly we can anticipate more trials comparing with treatments other than placebo.

Disclosure of interest

The author declares that he has no competing interest.

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