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International RCT-based guidelines for use of preoperative stress testing and perioperative beta-blockers and statins in non-cardiac surgery

Alexandra N. Nowbar *, Graham D. Cole, Matthew J. Shun-Shin, Judith A. Finegold, Darrel P. Francis

International Centre for Circulatory Health, Imperial College London, UK

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ABSTRACT

Background: Cardiologists frequently advise on perioperative care for non-cardiac surgery and require guidance based on randomised controlled trials that are not discredited by misconduct or misreporting. Regional political bodies currently do not provide this. We therefore examined the credible randomised controlled trial (RCT) evidence on key cardiac perioperative questions which currently have 14 recommendations.

Methods: Three aspects of perioperative measures were considered: perioperative statins, preoperative stress-testing and perioperative beta-blockade. One author searched PubMed for RCTs considering these topics. All authors independently assessed the RCTs and then collaboratively composed guidelines.

Results: Perioperative *statin* therapy has been examined by three RCTs, DECREASE III and IV, which are discredited and a third containing serious inconsistencies undermining its validity.

Preoperative *stress testing* has been examined by two RCTs: one discredited trial, DECREASE II, and a second which found no benefit.

Perioperative *beta-blockade* has been examined by eleven RCTs, two of which are discredited. The nine remaining trials together suggest that perioperative beta-blockade increases mortality.

Conclusions: When the non-credible RCTs are omitted, the evidence base on these three subjects is much smaller than previously believed: 14 recommendations can be replaced by 3.

Current guideline arrangements collectively paralyse the numerous signatories from making urgent amendments after initial publication, even when important new information comes to light. Clinicians simply have to wait for the routine five-year expiry.

We present a concise scientifically based guideline and commit to updating it responsibly.

1. Introduction

The ESC recognises that its guidelines have "potential legal significance to the extent that they represent the state-of-the-art." [1] The ESC guideline [2] on perioperative management in non-cardiac surgery has inadvertently participated in a rare experiment of nature lasting many years, which tested whether readers can trust guideline recommendations to truly represent the current state of the art.

In 2011, the general public learned [3] that the DECREASE family of studies were "fabricated," [4] "fictional" [4] and "scientifically negligent." [4] These publications had been the bedrock of a section of the ESC guidelines recommending peri-operative beta-blockade [2,4,5].

The ESC announcement [6] in response to the invalidation of the DECREASE research was that the guidelines remained correct and arose from the consensus judgement of large numbers of experts convened for this purpose. In 2013, it announced [7] that it had decided to replace the guidelines in late 2014. It is unclear how this differed from the routine 5-year expiry date of the original 2009 guideline.

The current system, relying on very large groups of experts meeting every 5 years, may not be appropriate for matters of patient safety where action might be expected to be quicker and clearer.

Two years after the science was invalidated, readers would not know from downloading the guideline at the journal that the class I recommendation for perioperative beta-blockade appears harmful to survival [5]. Readers searching instead at the ESC website [8,9] currently see a red-topped box entitled "Current versions available to download" (Fig. 1). Clicking on "full text" gives the original guideline. There is no indication that the beta-blocker recommendation is now considered dangerous. Only curious readers who click on a note entitled "Regarding the situation of …" a named doctor, would see any suggestion that all may not be well.

This has been an extreme case of misguidance: it became public knowledge in 2011 that the guideline was exactly opposite to the mortality results of the credible trials. Yet the system seems to have prevented four dozen of the world's leading experts from alerting clinicians for several years. We may never know how many more recommendations are known by guideline signatories to be harmful since public revelations like this [3,4] are the exception and not the rule when incorrect reports enter the literature. [10–15].

When the guideline maintenance system produced a scientifically incorrect [6] response to realisation that recommendations appear to be

* Corresponding author at: International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, 59-61 North Wharf Road, London W2 1LA, UK. Tel.: +44 207 594 1093, fax: +44 208 082 5109.
E-mail address: Alexandra.nowbar09@imperial.ac.uk (A.N. Nowbar).

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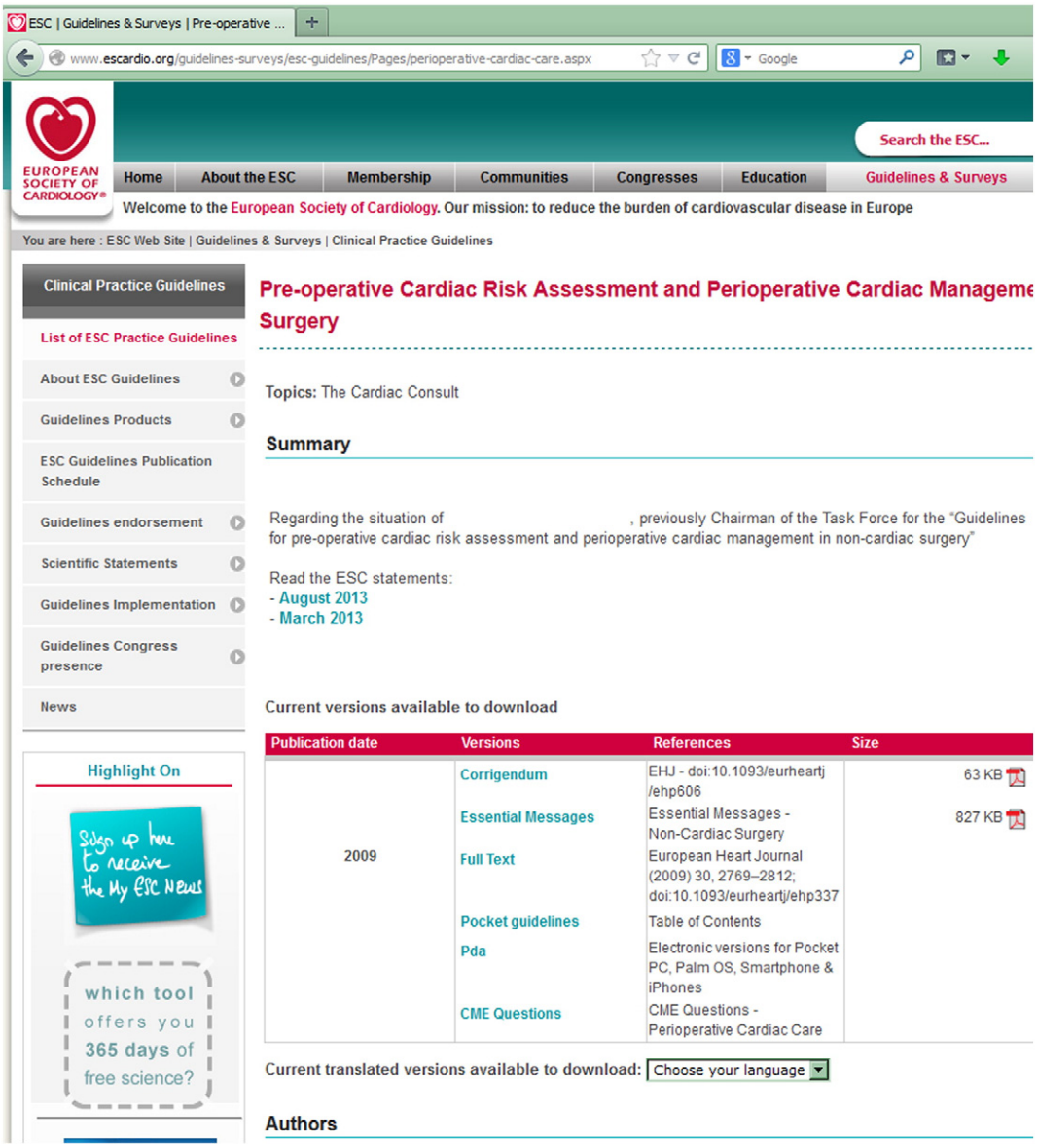

Fig. 1. ESC perioperative cardiac management guideline at the ESC website [8] as it appeared at 27 October 2013 [9]. (For privacy reasons, any individual names have been blanked out.) The corrigendum listed was for a typographical error and not for the matter of patient safety.

favouring an increase in mortality, the reliability of the other recommendations in that guideline document also became doubtful. Some of the recommendations, such as that haemodynamically unstable ventricular arrhythmias should be treated with defibrillation, may not need reiteration in a specifically perioperative guideline. Cardiologists are likely to turn to perioperative guidelines for only 3 common key questions.

In this document, we analyse the credible RCT data pertaining to these questions:

Should a perioperative course of beta-blockers be recommended?

Should a perioperative course of statins be recommended?

Should preoperative stress testing, such as stress echocardiography, be recommended?

2. Methods

Our analysis of the scientific basis of these three questions focussed on randomised controlled trials (RCTs). Observational studies have been misleading many times in the past, especially for physiologically plausible concepts. Routine pharmacological suppression of ventricular ectopics after myocardial infarction turned out to be harmful when trialled properly [16]. Observational studies of the prognostic association of mechanical dyssynchrony in heart failure suggested powerful ability to identify those who would benefit [17], but this approach was discovered to increase mortality when tested by RCT [18]. Intra-aortic balloon-pump therapy in myocardial infarction, firmly recommended on the strength of multiple observational studies, has repeatedly delivered disappointing neutrality when trialled properly [19].

One author conducted PubMed searches (Online Appendix 1) for randomised controlled trials examining each of two topics: perioperative statins and preoperative stress testing.

Eligible studies were randomised controlled trials in non-cardiac surgery with an end point of cardiac events or mortality. The clinical question of perioperative beta-blockade has been considered and the relevant trials analysed in a recent meta-analysis [5].

All authors were required to sign a statement indicating they had read the RCTs and any associated misconduct reports as a condition for authorship. The authors independently assessed the evidence and met to synthesise a joint position.

3. Results

3.1. Perioperative course of statins

Two hundred and forty-three studies were screened, and of these, 3 met the inclusion criteria: DECREASE III [20], DECREASE IV [21] and Durazzo et al [22]. These three randomised controlled trials examining the use of a perioperative course of statins for vascular surgery were