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

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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

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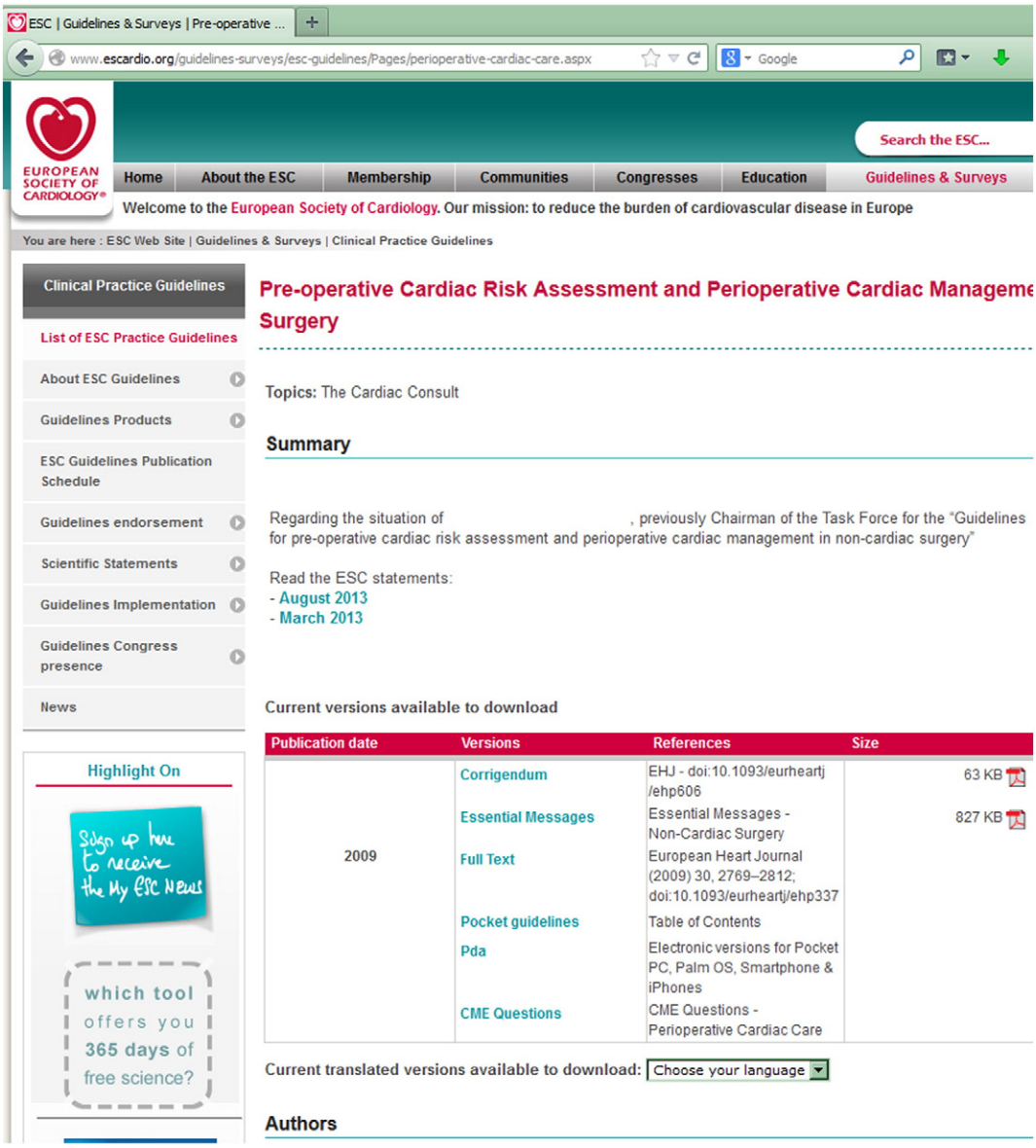

Fig. 1. ESC perioperative cardiac management guideline at the ESC website [8] as it appeared at 27 October 2013 [9]. (For privacy reasons, any individual names have been blanked out.) The corrigendum listed was for a typographical error and not for the matter of patient safety.

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

from two groups of authors (or one group, if the presence of a single author in common is considered a link).

Two of the three trials have clear publically discussed reasons to not be used as the basis for recommending therapy. The end point events in DECREASE IV [21] did not match the actual hospital records or clinical discharge reports and appear to have been fictitious. The institutional internal enquiry found that the adjudication committee of three (cardiologist, anaesthesiologist and surgeon) was fictional. One person had made the adjudications alone and had left no reason for why patients had been judged to have had events. No supporting documentation such as ECGs or blood test results could be found, except for the hospital records which contradicted the data used for publication [4,5].

DECREASE III was published in the *New England Journal of Medicine* in September 2009. Less than 2 years later, when the university investigation panel asked for its source documentation, apparently nothing could be found to verify the existence of the trial as published. The committee concluded that there was "no reason to inform the journal" and that "further fact-finding with regard to this project is not indicated."

The third study was a double-blind randomised trial of 100 patients undergoing vascular surgery, with a 45-day course of atorvastatin or placebo. It sought reduced perioperative events in the atorvastatin arm, which indeed was what was found: 8% versus 26% ($p = 0.031$) at 6 months [22].

This study has serious failings, which make it an unsound basis for recommending therapy. First, its sample size calculation is stated to have been based on a 22% event rate at 6 months in a previous paper [23]. In reality, the source article states that the rate was 12% at 6 months. Such a transcription error would cause a study to be approximately 4-fold undersized.

Second, the authors indicate that they designed their study to detect a relative risk reduction of 95%. This study design is not credible as no therapy has ever been so effective in preventing myocardial infarction. If the true effect size was, for example, half of this, this overestimate would have contributed a further ~4-fold undersizing of the study.

Third, the survival data published cannot be correct. The paper reports that of the 50 patients in each arm, none were lost to follow-up. Therefore, every patient surviving to each displayed time point should be exactly 2%. With this in mind, in the Kaplan–Meier graphs, almost all the numerical values in the survival follow-up figure contradict the graphical values shown.

Finally, for 50-patient groups with no loss to follow-up, event-free survival rates must again be multiples of 2%. They are quoted as 91.4% and 73.5%, values that are not possible.

3.2. Stress testing

Ninety-eight studies were screened, and of these, 2 met the inclusion criteria: DECREASE II [24] and Falcone et al [25]. These 2 randomised controlled trials examined preoperative stress testing for vascular surgery.

The enquiry [3] into DECREASE II found no evidence that patients had given the informed consent described for randomisation. There were "several serious errors and breaches of protocol." The description of how the outcomes had been evaluated was fictional. The enquiry gave the following reason for its decision to allow the paper to stand in the literature as valid science [3]:

> "The social and clinical relevance of the potential withdrawal of this publication is now small, particularly because the Dobutamine Stress Echo (DSE) has now virtually disappeared from clinical practice as a predictor of peri-operative complications"

On this basis, the last opportunity to insist upon a retraction was allowed to lapse [3]:

> "the Committee considers that further fact-finding with regard to this project is not indicated"

The second RCT of stress testing was a pilot study of 99 subjects. Patients were randomised to stress testing ($n = 46$) according to the ACC/AHA guidelines before vascular surgery or to no stress testing ($n = 53$) [25]. There was no difference in the primary end point (unstable angina, myocardial infarction, congestive heart failure or death before hospital discharge) between groups at 12 months. Ischaemia was detected in seven patients in the stress testing group. Two patients in the stress testing group reached the primary end point, one with detected ischaemia and one without, and four patients in the no stress testing group reached the primary end point.

3.3. Beta-blockers

A recent meta-analysis from our group identified eleven randomised controlled trials examining the use of perioperative beta-blockade [5]. Nine of the trials were found to be secure as DECREASE I and DECREASE IV have been discredited [4,5]. The results suggest a 27% increase in mortality with perioperative beta-blockade.

4. Discussion

There is insufficient evidence to recommend a specifically perioperative regime of statins or preoperative stress testing in non-cardiac surgery. Perioperative beta-blockade, in the protocols used in the credible randomised controlled trials, shows no sign of decreasing mortality and indeed shows evidence meeting standard criteria for statistical significance for elevating mortality.

4.1. Perioperative course of statins

There are no credible randomised controlled trials of a specifically perioperative course of statins for non-cardiac surgery. Of the three trials published in the field, two have been publicly discredited and one from a largely independent group contains unexplained anomalies so severe that it is not credible.

Planning a well-designed trial would face challenges. One such challenge is timing of initiation of therapy. This may have to be shortly before surgery for logistical reasons. Previous credible trials (of beta-blockers) in such patients have exclusively initiated therapy within 24 hours prior to surgery. Two studies did report having recruited significantly earlier than this permitting them to have initiated therapy at an average of 37 days [26] and 34 days [21] before surgery, respectively, and had an elaborate uptitration process. Unfortunately these trials were DECREASE I and DECREASE IV from which the source documentation (including all evidence that any uptitration occurred) appears to have been mislaid. We may never learn how this feat was achieved.

Identifying a stratum of patients to randomise would be another challenge. Those already taking statins should be excluded, as should those who have good reason to be on statins but have not yet started therapy. The Heart Protection Study [27] showed that patients with peripheral arterial disease have a 22% reduction in major vascular events from statins, and this appeared to be identical for patients with LDL below or above 3.0 mmol/l. On this basis, perhaps all patients with vascular disease, and particularly those with vascular disease severe enough to warrant surgery, should be offered a statin long term.

Statins appear to be effective in reducing risk regardless of whether that risk arises from lipid levels or from other factors such as age, high blood pressure, smoking or family history [28] or diabetes [29]. As generic statins are now cheap and easily available, one possibility might be to offer statins to all patients with vascular disease severe enough to require an operation, and many others whose risk status merits it.

There seem to be no grounds for cessation of statin therapy at any arbitrary time point after surgery since the risk remains lifelong and grows with age.

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4.2. Stress testing to detect ischaemia

There does not appear to be randomised controlled trial evidence indicating that it is worthwhile routinely subjecting patients without angina to preoperative stress testing by exercise ECG or dobutamine stress echo. In patients with angina, there is existing randomised controlled trial guidance for their management [30].

If patients newly report angina, not previously brought to medical attention, at perioperative assessment, management is challenging. There is a trade-off between, on the one hand, the harm of delay and expense of full invasive investigation and intervention and, on the other hand, the potential harm from allowing the surgery to continue without completion of angina investigation and treatment. There are no randomised controlled trials to provide systematic guidance. Since the trials so far conducted have not shown definitive results, there may be reluctance to organise, fund and implement an adequately powered trial on this question. As clinicians, we may need to continue our present convention of making decisions without a fixed guideline basis.

A further problem is that there appears to be no RCT evidence that usefully guides clinicians after a positive stress test result. A negative preoperative stress test has high negative predictive value [31] so might be claimed to provide useful reassurance for patients and clinicians. However, providing reassurance to asymptomatic patients is not automatically a wise use of healthcare resources.

Meanwhile, the low positive predictive value [31] means many false positives. When false positives prompt further invasive tests and interventions, there is a potential to cause harm, either from the cardiac intervention or from the resulting delay in the originally planned surgery, and there will be extra costs which cause indirect harm (unless resources are unlimited).

4.3. Beta-blockers

A meta-analysis of the credible RCT data, excluding the discredited DECREASE family and reanalysing on an intention-to-treat basis a trial that had excluded in-hospital deaths, has been recently published by our group [5]. It found that perioperative beta-blockade reduced myocardial infarction but increased mortality.

There is a substantial minority of opinion in the clinical community that perioperative courses of beta-blockade are worthwhile as shown by reader comments [32]. This may stem from their undoubted efficacy in reducing myocardial infarction [5,33]. and uncertainty over dosing regimes [34]. Nevertheless there is no sign of reduction in all-cause mortality. In the perioperative period, there are many causes of death. While reduction in myocardial infarction rate is desirable, some of the other causes of death may be enhanced by beta-blockers, such that the net effect on mortality is adverse.

4.4. Guideline recommendations

We present the guidelines developed through this process in a concise document at the end of this report.

4.5. Differences between our guideline and the ESC guideline

The guideline developed here is intended as a replacement for the ESC guideline on perioperative cardiac care which is a bulky document that continues to encourage physicians to carry out interventions that may increase mortality [2,5]. The guideline developed here differs from the ESC guideline in several ways described in Table 1.

4.6. Study limitations

Our working group is not composed of delegates formally representing the interests of various subspecialty groups of cardiology but instead individuals who take personal responsibility for the accuracy of our analyses and for updating them should they be found to be erroneous or based on falsified or fraudulent data.

We have not considered every possible intervention for perioperative care. We have focussed on those for which there is interest from our cardiological colleagues to have reliable advice conveyed from RCTs. For example, we have not covered the management of haemodynamically unstable ventricular tachycardia as we believe our colleagues already know that this should be treated with defibrillation.

Our guideline development process does not attempt to draw conclusions from observational studies. It uses randomised controlled trials, which are the correct source of information for deciding on the comparative effectiveness of management plans [35] because observational studies used as a basis for therapeutic decisions have proved very misleading in the past [17,18].

We do not claim that our guideline development has authority to direct behaviour of clinicians in any country. We only aim that it delivers factually correct advice based on the highest available level of evidence.

There is no preset plan for a 5-year revision as it is not known whether this is the time at which useful new trial data will be available. We intend to update the guideline when there is additional relevant data, or if any of the trial data on which the guideline depends becomes invalidated.

Where there is no adequate RCT basis, we have not issued an opinion-based recommendation. This is because the opinion of one group of people is not a respectful basis on which to impose an

Table 1
Contrasting features of ESC versus international guidelines.

	ESC [2]	International
Should I offer an intervention?	Currently 4 levels of advice requiring 74 words in total and a table to explain them	Only one level of advice
How do we know the intervention is beneficial?	Currently 3 levels of advice requiring 36 words in total and a table to explain them	Recommendations based on RCTs
Assessment of source study quality?	RCTs with evidence of unsound reporting, or known by the authors to be reported incorrectly, are included	RCTs with evidence of unsound reporting will be excluded with reasons given
Vintage?	5-year cycle even when discovered to be invalid or harmful. In one third of cases no replacement appears even after 5-year expiry.	Authors commit to reviewing and re-publishing when evidence changes significantly ("re-sign or resign")
Ability for readers to discuss and disagree	Document does not describe mechanism for readers to correct errors.	Corrections actively welcomed via journal correspondence or pubpeer.org
Action on invalidation of a trial on which recommendation is based (e.g. "fabrication"[6] or "scientific negligence"[6])	No policy	Policy to retract guideline recommendation
Patient-protective activity when source discredited	Guideline signatories are hindered from acting independently to alert clinicians in the interest of patient safety.	All authors must take individual responsibility to rescind their support for the guideline if they later learn it is incorrect. Not permitted to wait for consensus.

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obligation on our colleagues. Colleagues' opinions may differ from ours, and since there is no reliable scientific underpinning, there is no reason to consider our opinions more valid.

5. Conclusions

Development of guidelines for the three main questions which concern cardiologists in the routine perioperative care of patients undergoing non-cardiac surgery requires careful analysis of the published randomised controlled trials. The guideline recommendations developed by this process are shown at the end of this report. The credible evidence base for actions to be taken is much thinner than readers might expect for a mature discipline.

There seems to be no functioning system for immediate cancellation of guideline recommendations when their underlying research is discredited. Without such a safety mechanism, guidelines remain in force recommending therapies even once information comes to light indicating that they are causing excess deaths.

6. Supplementary Data on Methods

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.12.309.

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References

[1] Schwartz PJ, Breithardt G, Howard AJ, Julian DG, Rehnqvist Ahlberg N. Task force report: the legal implications of medical guidelines—a task force of the European Society of Cardiology. Eur Heart J 1999;20:1152–7.
[2] Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery, European Society of Cardiology (ESC), Poldermans D, Bax JJ, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Eur Heart J 2009;30:2769–812.
[3] Erasmus Medical Centre. Investigation into possible violation of scientific integrity. http://www.erasmusmc.nl/5663/135857/3664573/3397899/report_summary_investigation_integrity; 2011 . [accessed 3 Nov 2013].
[4] Erasmus Medical Centre. Report on the 2012 follow-up investigation of possible breaches of academic integrity. http://cardiobrief.files.wordpress.com/2012/10/integrity-report-2012-10-english-translation.pdf; 2012 . [accessed 3 Nov 2013].
[5] Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery. Heart 2013. http://dx.doi.org/10.1136/heartjnl-2013-304262.
[6] European Society of Cardiology. Dismissal of Professor Don Poldermans from the Erasmus Medical Center (NL). http://www.escardio.org/about/press/press-releases/pr-11/Pages/Dismissal-Don-Poldermans.aspx . [accessed 3 Nov 2013].
[7] European Society of Cardiology. ESC Statement. http://www.escardio.org/about/press/press-releases/pr-13/Pages/esc-statement-poldermans-guidelines-non-cardiac-surgery.aspx . [accessed on 3 Nov 2013].
[8] European Society of Cardiology. Pre-operative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery. http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/perioperative-cardiac-care.aspx . [accessed on 3 Nov 2013].
[9] Web Archive. European Society of Cardiology. Pre-operative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery. http://web.archive.org/web/20131027143648/http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/perioperative-cardiac-care.aspx . [accessed on 3 Nov 2013].
[10] Francis DP, Mielewczik M, Zargaran D, Cole GD. Autologous bone marrow-derived stem cell therapy in heart disease: discrepancies and contradictions. Int J Cardiol 2013;168(4):3381–403. http://dx.doi.org/10.1016/j.ijcard.2013.04.152.
[11] Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. Lancet 2010;376(9756):1916–22. http://dx.doi.org/10.1016/S0140-6736(10)61272-X.
[12] Berry C, van 't Veer M, Witt N, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol 2013;61(13):1421–7. http://dx.doi.org/10.1016/j.jacc.2012.09.065.
[13] Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg 2005;130(6):1631–8.
[14] Howard JP, Nowbar AN, Francis DP. Size of blood pressure reduction from renal denervation: insights from meta-analysis of antihypertensive drug trials of 4121 patients with focus on trial design: the CONVERGE report. Heart 2013;99(21):1579–87. http://dx.doi.org/10.1136/heartjnl-2013-304238.
[15] Simonetti G, Spinelli A, Gandini R, et al. Endovascular radiofrequency renal denervation in treating refractory arterial hypertension: a preliminary experience. Radiol Med 2012;117:426–44.
[16] Investigators CAST. Preliminary Report: effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–12.
[17] Nijjer SS, Pabari PA, Stegemann B, et al. The limit of plausibility for predictors of response: application to biventricular pacing. JACC Cardiovasc Imaging 2012;5(10):1046–65. http://dx.doi.org/10.1016/j.jcmg.2012.07.010.
[18] Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369(15):1395–405. http://dx.doi.org/10.1056/NEJMoa1306687.
[19] Sjauw KD, Engström AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? Eur Heart J 2009;30(4):459–68. http://dx.doi.org/10.1093/eurheartj/ehn602.
[20] Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med 2009;361(10):980–9. http://dx.doi.org/10.1056/NEJMoa0808207.
[21] Dunkelgrun M, Boersma E, Schouten O, et al. Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). Ann Surg 2009;249(6):921–6. http://dx.doi.org/10.1097/SLA.0b013e3181a77d00.
[22] Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39(5):967–75.
[23] Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335(23):1713–20.
[24] Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006;48(5):964–9.
[25] Falcone RA, Nass C, Jermyn R, et al. The value of preoperative pharmacologic stress testing before vascular surgery using ACC/AHA guidelines: a prospective, randomized trial. J Cardiothorac Vasc Anesth 2003;17(6):694–8.
[26] Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789–94.
[27] Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg 2007;45(4):645–54.
[28] Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled tria. Lancet 2003;361(9364):1149–58.
[29] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364(9435):685–96.
[30] Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356(15):1503–16.
[31] Das MK, Pellikka PA, Mahoney DW, et al. Assessment of cardiac risk before nonvascular surgery: dobutamine stress echocardiography in 530 patients. J Am Coll Cardiol 2000;35(6):1647–53.
[32] O'Riordan M. Perioperative beta-blocker controversy begins again with new meta-analysis 2013. http://www.medscape.com/viewarticle/808775 [accessed 3 Nov 2013].
[33] Study Group POISE, Devereaux PJ, Yang H, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839–47. http://dx.doi.org/10.1016/S0140-6736(08)60601-7.
[34] Replies to Meta-analysis of secure randomised controlled trials on Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery. http://heart.bmj.com/content/early/2013/07/30/heartjnl-2013-304262.abstract/reply#heartjnl el 17807 [accessed on 18 January 2014].
[35] Sen S, Davies JE, Malik IS, et al. Why does primary angioplasty not work in registries? Quantifying the susceptibility of real-world comparative effectiveness data to allocation bias. Circ Cardiovasc Qual Outcomes 2012;5(6):759–66. http://dx.doi.org/10.1161/CIRCOUTCOMES.112.966853.

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

Error correction policy

Readers who consider the recommendations in this guideline to be incorrect are invited to express this via the journal correspondence column or via pubpeer.

Recommendations

Statins

Guideline 1. There are no credible randomized controlled trials. There are no grounds for specifically-perioperative statin use.

Stress testing

Guideline 2. There is only one credible randomised controlled trial. It does not show any endpoint benefit of testing asymptomatic patients preoperatively. Furthermore, there are no trial data to advise on how to manage a perioperative patient, should the stress test be positive.

Beta-blockers

Guideline 3. Beta-blockade should not be routinely initiated for perioperative protection because trial data indicate an increases in mortality. This is based on the 9 credible randomized trials.

Contributor policy

Readers are invited to contribute to the next iteration of this guideline as authors if they are willing to commit the time required for diligent reading and analysis of the source science, to collaborate equally on the development of the final publication and to fulfil an ongoing responsibility to correct or retract it if necessary. There is no necessity to hold political office.

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