Published in final edited form as:

BMJ Qual Saf. 2014 November ; 23(11): 957–964. doi:10.1136/bmjqs-2014-003114.

Learning from mistakes in clinical practice guidelines: the case of perioperative beta-blockade

Mark D. Neuman, M.D., M.Sc.^{1,2}, Charles L. Bosk, Ph.D.^{1,2,3}, and Lee A. Fleisher, M.D.^{1,2}

¹ Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania

² The Leonard Davis Institute of Health Economics, University of Pennsylvania

³ Department of Sociology, University of Pennsylvania

Abstract

For more than two decades, the role of beta-blockers in preventing cardiac complications after major surgery has been the subject of contentious scientific and policy debate. Based on two small but highly publicized randomized trials published in 1996 and 1999, prominent U.S. organizations embraced preoperative beta-blocker initiation as a “best practice” and an opportunity for widespread safety improvement. Yet only a few years later, expert recommendations regarding preoperative beta-blockers were revised and downgraded when subsequent research failed confirm promising early findings and called attention to potential harms associated with beta-blocker overuse. In this paper, we trace the history of preoperative beta-blocker recommendations as a case study in lessons to be learned from reversals of guideline recommendations based initially on evidence drawn from randomized, controlled trials. Ultimately, we find that the policy significance that stakeholders ascribed to early beta-blocker studies combined with the prestige that experts assigned to the randomized controlled trial as a form of evidence to short-circuit discourse on the risks of preoperative beta-blocker initiation and led it to be elevated prematurely as a best practice. As such, the story of preoperative beta-blockers illustrates threats to objectivity in guidelines that can emerge from policy imperatives that lend primacy to the rapid translation of research into practice and from perspectives that unduly emphasize the strengths of randomized trials.

Corresponding author address: Mark D. Neuman, M.D., M.Sc., Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, 423 Guardian Drive, 1119A Blockley Hall, Philadelphia, PA 19104, Office: (215) 746-7468, Fax: (215) 349-5078, neumanm@mail.med.upenn.edu.

Contributorship statement: All authors contributed to the planning, conduct, and reporting of the work described in the article. MDN, CLB, and LAF jointly developed the idea for the article. MDN performed literature searches and obtained feedback from key informants. MDN, CLB, and LAF analyzed and interpreted the data. MDN wrote the first draft of the article; CLB and LAF provided extensive critical revisions on article drafts. MDN is the guarantor and he accepts full responsibility for the finished article. MDN had access to all study data, and controlled the decision to publish.

Additional contributions: Michael Cirullo provided research assistance. We received valuable feedback on a previous version of this manuscript from Mary Dixon-Woods, Renee Fox, Sandy Schwartz, Robert Aronowitz, Kim Eagle, Allan Detsky, and Amir Qaseem.

Competing interests: The authors have no competing financial interests to disclose. LAF has been a volunteer member and chair of ACC/AHA guideline committees from 1996 to the present; no compensation was provided for his work on these guidelines.

INTRODUCTION

For more than two decades, the role of beta-blockers in preventing cardiac complications after surgery has been among the most hotly contested and controversial topics in medical practice. Based on two small randomized trials published in the late 1990's,^{1,2} leading physicians and experts in patient safety embraced preoperative beta-blocker initiation as a therapeutic victory for high-risk surgical patients: an apparently simple and effective treatment that promised, for the first time, to prevent life-threatening postoperative cardiac events.

Yet nearly as soon as preoperative beta-blocker initiation had come to be seen as a “best practice,” its status was cast into doubt. New randomized trials published between 2005 and 2008 failed to confirm promising early findings and highlighted the potential for harm with beta-blocker overuse.³⁻⁶ Recommendations that had previously urged widespread preoperative beta-blocker initiation among high-risk patients⁷⁸ were softened or reversed.⁹¹⁰ Debates over whether or not beta-blockers were safe for surgical patients displaced discussions on how to promote their use on a large scale.

On one level, what may be most remarkable about the rise and fall of preoperative beta-blocker guidelines is how unremarkable it seems. Preoperative beta-blockade is only one of several recent examples in which expert endorsements of promising therapies changed markedly when new evidence highlighted potential harms that had been overlooked by these endorsements. Yet the beta-blocker story differs in important ways from canonical examples of reversals in recommendations for medical practice. Prominent retellings of how expert recommendations changed regarding hormone replacement therapy (HRT) for women after menopause, for example, have emphasized the pitfalls of relying on non-randomized studies rather than randomized controlled trials in defining therapies' benefits and harms.¹¹¹² In contrast, preoperative beta-blocker initiation was elevated rapidly to the status of a best practice specifically *because* randomized trials had suggested that it could be effective. As we shall see, the beta-blocker story shows how the prestige that medical researchers and clinicians afford to randomized controlled trials can obscure important uncertainties surrounding new treatments, particularly when placed in political contexts that prioritize the rapid translation of research into practice. As such, it provides an important counterpoint to dominant narratives of evidence reversal in medicine, and helps to explain other recent examples where guidelines went wrong not because they overlooked the need for randomized trials, but because of experts' very faith in such trials.

CONSTRUCTION OF AN EVIDENCE-BASED PRACTICE: THE EMERGENCE OF PERIOPERATIVE BETA-BLOCKADE

Preoperative beta-blocker research grew out of longstanding efforts to characterize cardiac postoperative events as a distinct clinical syndrome. Set in motion by Lee Goldman's 1977 bedside risk scoring system,¹³¹⁴ the study of cardiac risk in non-cardiac surgery was already a defined area of academic inquiry by the mid-1990's. Yet despite ample research on risk stratification, practitioners lacked effective treatments known to reduce cardiac risk. When the American College of Cardiology and the American Heart Association's (ACC/AHA)

first guidelines on preoperative care appeared in 1996, for example, they included detailed recommendations concerning risk assessment, but offered minimal guidance regarding treatment.¹⁵

This changed in December 1996 when Dennis Mangano, an anesthesiologist at the University of California, San Francisco, published results from a trial that randomized 200 patients either to preoperative treatment with atenolol, a generic beta-blocker, or to placebo. The results, which appeared in the *New England Journal of Medicine*, were almost too good to be true: compared to placebo, atenolol was associated with large, sustained decreases in postoperative mortality.¹ Among patients who survived to hospital discharge, for example, 90% of those randomized to receive atenolol were alive at two years, versus 79% of those randomized to receive placebo ($P=0.019$).¹

Notably, Mangano's study employed a randomized, placebo-controlled trial design; by the mid-1990's, the randomized, placebo-controlled trial had been securely established in medical thought as the "gold standard" of medical evidence. This phenomenon, which grew in part out of the US Food and Drug Administration's 1970 decision to require such trials for the approval of new medications, was promoted by subsequent efforts over the following decades by practitioners within the new fields of biostatistics,¹⁶ clinical epidemiology, and evidence-based medicine¹⁷ to encourage the use of randomized trial designs in research and the application of their findings to clinical practice.

Mangano's study had an immediate impact. In August 1997, the American College of Physicians (ACP) published its own guideline on preoperative care, which included a dramatic "stop-the-presses" addendum calling attention to an "important publication that we believe should alter current practice."¹⁸ In it, the authors highlighted the both the long duration of effect ascribed to atenolol in Mangano's report as well as the study's randomized, placebo-controlled design; ultimately, they recommended the immediate adoption of Mangano's findings on a large scale, urging "the perioperative use of atenolol in patients with coronary artery disease or risk factors for coronary artery disease (as per the criteria of Mangano and colleagues.)"¹⁹

In the lay press, atenolol was hailed as an "Rx for deaths after surgery."²⁰ An editorial in the leading anesthesiology journal characterized beta-blockers as "incredibly useful, incredibly underused" and as carrying "remarkable...short and-long term benefits."²¹ Others characterized preoperative beta-blockade as being nearly risk-free, as its known downsides, which included hypotension and bradycardia, were "not only uncommon, but...also readily responsive to therapy."²²

Yet Mangano's work also had its critics. In a detailed, point-by-point critique of Mangano's paper, Jacqueline Leung, another UCSF anesthesiologist and a former collaborator of Mangano's, wrote in 1999 that "the recent popularized use of perioperative beta blockade is based on misinformation."²³ Patients in Mangano's study who took beta-blockers at home but were randomized to placebo had had their home beta-blockers discontinued before randomization, potentially creating "withdrawal" effects that might have led to relatively worse outcomes in this group.^{24,25} Further, Mangano's findings regarding 2-year survival

were based on an analysis of patients who had survived to hospital discharge. Yet these survival differences no longer met criteria for statistical significance when analyzed in a proper “intent-to-treat” approach that included all subjects.²⁶

Such concerns were somewhat allayed in 1999, when Don Poldermans and colleagues at Erasmus Medical Center in Rotterdam published results from a second randomized, placebo-controlled trial of preoperative beta-blockade. Poldermans’s study—also published in the *New England Journal*—enrolled 112 vascular surgery patients at high risk of postoperative cardiac events, and its results echoed the dramatic findings of Mangano’s earlier study. Compared with placebo, beta-blockers were associated with a ten-fold reduction in the risk of any postoperative cardiac event at 30 days from 34% to 3.4% ($P<0.001$).²

Poldermans’s study had its own limitations. It examined a small, highly selected patient sample²⁷²⁸ and was terminated early due to apparent evidence of benefit, increasing the potential for a misleading finding.²⁹³⁰ Even so, an accompanying editorial cited Poldermans’s “extraordinary” results and proclaimed that “the era in which physicians can only guess at how to reduce a patient’s risk of perioperative cardiac complications seems to be ending.”³¹ To others, the results of the 1996 and 1999 trials accorded “in gratifyingly intuitive fashion”³² with physiologic principles, establishing that “for the first time, in addition to accurately identifying patients who are at increased risk for cardiovascular events, we can intervene to lower that risk.”³³

Such enthusiasm translated into recommendations for clinical practice. In 2001, the U.S. Agency for Healthcare Research and Quality (AHRQ) released “Making Health Care Safer,” its first major review of evidence on “practices relevant to improving patient safety.” The AHRQ report, prepared by investigators at UCSF and Stanford University, reviewed 79 practices and rated 11 “most highly in terms of strength of the evidence.” Of these 11—each of which was characterized as a “clear opportunity for safety improvement”—preoperative beta-blocker initiation for high-risk patients was the second most highly rated, and was described as a “major advance in perioperative medicine” whose “wider use...should be promoted and studied.”⁷³⁴

A year later, the revised ACC/AHA guidelines on perioperative care also incorporated new recommendations in favor of wider preoperative beta-blocker use. A new Class I recommendation (“procedure/treatment *should* be performed/administered”) endorsed preoperative beta-blocker initiation for high-risk patients who met similar criteria to those used in Poldermans’s trial; a less definitive Class IIa recommendation (“*it is reasonable* to perform procedure/administer treatment”) stated that beta-blockers also had potential to benefit a broader group of moderate-to-high risk patients similar to those enrolled in Mangano’s 1996 study.³⁵

These recommendations informed larger efforts to promote preoperative beta-blocker use. In 2003, the Leapfrog Group, a U.S. coalition of public and private health care purchasers, classified preoperative beta-blockade for high-risk patients as a hospital quality standard.³⁶³⁷ Hospitals and clinical departments undertook strategies to promote local

adherence to beta-blocker guidelines.^{38,39} In clinical practice, use of preoperative beta-blockade increased rapidly between 1999 and 2005,⁴⁰ reflecting one observer's sentiment that "the paradigm is shifting from predicting which patient is at high risk...to minimizing the likelihood of such an event with specific perioperative pharmacologic therapy."⁴¹

SECOND THOUGHTS

Despite the elevation of preoperative beta-blocker initiation as a "best practice" by expert groups, some investigators continued to question the validity of the evidence. In a meta-analysis published in July 2005, P.J. Devereaux, of McMaster University in Hamilton, Ontario, found "the evidence that perioperative beta-blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions to be drawn."⁴² That same month, Peter Lindenauer, an internist at Baystate Medical Center in Springfield, Massachusetts, published a retrospective cohort study in the *New England Journal of Medicine* that examined outcomes with and without perioperative beta-blocker therapy among more than 700,000 non-cardiac surgical patients. Among high-risk patients, Lindenauer found preoperative beta-blockade to be associated with a reduced risk of in-hospital death; yet among the lowest-risk patients, preoperative beta-blockade was found to be associated with substantially *greater* postoperative mortality.⁴³

Along with Devereaux's and Lindenauer's reports, three new randomized trials between April 2005 and November 2006 cast further doubt on Mangano's and Poldermans's initial findings. Together, the Perioperative Beta Blockade (POBBLE) trial, the Metoprolol After Vascular Surgery (MaVS) trial, and the Diabetic Postoperative Morbidity and Mortality (DiPOM) trial enrolled more than four times the number of patients studied by Mangano and Poldermans combined; none of them observed any difference in postoperative outcomes with preoperative beta-blockade versus placebo.⁴⁻⁶

In May 2008, Devereaux's own randomized trial of 8,351 patients—named the PeriOperative Ischemic Evaluation (POISE)—showed lower rates of postoperative myocardial infarction, but higher rates of stroke and death, among high-risk surgical patients who were randomized to preoperative metoprolol versus placebo.³ POISE was criticized for its use of large, fixed doses of preoperative beta-blockers, which critics considered to be riskier than titrated dosing approaches based on physiologic endpoints.⁴⁴⁻⁴⁶ Yet POISE, along with POBBLE, MaVS, and DiPOM, nonetheless provoked further uncertainty about the value of preoperative beta-blockers for surgical patients.

Changes in clinical practice guidelines reflected this uncertainty. In 2006, even before POISE had been completed, the ACC/AHA downgraded their earlier Class IIa recommendation regarding preoperative beta-blockade for large groups of moderate-to-high risk patients.⁴⁷ In 2009, the ACC/AHA downgraded their recommendation regarding beta blocker initiation in the highest-risk patients from Class I to Class IIa and added a new Class III recommendation ("procedure/treatment *should NOT* be performed/administered") to warn *against* the initiation of high-dose preoperative beta-blockade for beta-blocker naïve patients.¹⁰

AHRQ also made changes to their recommendations regarding preoperative beta-blockade. In 2001, preoperative beta-blockade had been the second most “highly-rated” of 79 patient-safety practices reviewed by the AHRQ team; yet in the second edition of “Making Health Care Safer,” released in 2013, it did not appear among AHRQ’s 22 “strongly encouraged” or “encouraged” patient safety practices.⁹ Instead, citing research that had appeared since 2001 to show “that perioperative beta blockers have mixed benefits and harms,” the 2013 AHRQ report stated that “preoperative beta blockers...should not be considered a patient safety practice for all patients.”⁹

AFTERMATH

Beyond the conflicting results of the beta-blocker trials themselves, discourse on perioperative care became still more complicated in 2011 when Don Poldermans was dismissed from his position at Erasmus University for violations of academic integrity, including the possible fabrication of research data.⁴⁸ While none of Poldermans’s documented infractions pertained to his 1999 study, his dismissal compounded existing confusion surrounding the proper interpretation of his research and led to calls for further re-evaluation of guidelines.^{49, 50, 51}

Yet the controversy surrounding Poldermans’s breaches of academic integrity is best viewed as a worrisome footnote to a larger story. By 2011, the status of preoperative beta-blockers as an evidence-based practice had already come full circle. Over approximately 15 years, preoperative beta-blockade had been elevated to the status of a “paradigm-shifting” best practice and a symbol of safe medical care only to fall out of favor again as accumulating evidence called attention to previously overlooked potential harms (see Figure 1).

To a degree, experts’ willingness to endorse Mangano’s and Poldermans’s trials was linked to their knowledge of concurrent efforts to promote the broader utilization of beta-blockers for other conditions in which they had been shown to offer health benefits, such as the care of patients after myocardial infarction.^{52, 53} To their advocates, the similarities in the effects ascribed to beta-blockers in early preoperative trials and in historical studies of beta-blockers after acute myocardial infarction made the “too good to be true” findings of the 1996 and 1999 trials seem paradoxically “intuitive.” It became easy, in the words of one researcher, to give beta-blockers “a free pass” in terms of their likely risks for surgical patients.⁵⁴ Insofar as they took the safety of beta-blockers in surgical populations for granted based on their experiences with beta-blockers in other contexts, expert endorsements of early beta-blocker trials underestimated the true risks of initiating beta-blocker therapy prior to surgery.

In this sense, the story of perioperative beta-blocker recommendations stands in contrast to other episodes in the history of medicine in which experts have argued over the primacy of physiologic plausibility versus randomized controlled trial evidence as the proper basis for medical decision-making. Early debates about the efficacy of coronary artery bypass grafting (CABG), for example, centered on cardiologists’ and cardiac surgeons’ differing beliefs regarding the adequacy of changes in physiology, as measured by angiography, versus statistical evaluation of health outcomes, as proof of CABG’s efficacy.^{55, 56} In

contrast, proponents of Mangano's and Poldermans's trials emphasized the apparent *concordance* between the direction of effects demonstrated in these trials and prevailing beliefs regarding the salutary effects of beta-blockade on cardiovascular physiology. This apparent concordance made the posited benefits of beta-blockers for perioperative treatment seem self-evident, and contributed to guideline authors' seeing the extraordinary magnitude of Mangano's and Poldermans's findings as evidence in itself of their trials' veracity rather than as a cause for further questioning.

The course of perioperative beta-blocker recommendations over time also illustrates the extent to which interpretations of trial evidence were influenced not only by questions of scientific rigor, but also by the larger political and professional importance that observers assigned to these findings. Beyond suggesting a novel treatment for a clinical problem, Mangano's and Poldermans's findings also lent new legitimacy both to perioperative medicine as a clinical domain and to the nascent patient safety movement itself. Prior to Mangano's 1996 paper, experts in perioperative medicine could make statements about a given patient's risk, but lacked the ability to do anything to change that risk; yet once it appeared, they gained a powerful new ability to intervene that lent importance to their role in clinical care and a new significance to their longstanding practices of risk stratification. In a similar vein, by re-framing post-operative cardiac events as "patient safety problems," AHRQ researchers could also claim Mangano's and Poldermans's trials as victories insofar as they provided patient safety advocates an opportunity to align their own nascent movement with the conventions of evidence-based medicine.

CONCLUSION: PREOPERATIVE BETA-BLOCKER RECOMMENDATIONS IN CONTEXT

The story of preoperative beta-blockers differs in important ways from other well-documented historical examples of reversals in practice recommendations. From the 1970's through the late 1990's, for example, Hormone Replacement Therapy (HRT) was widely recommended to treat symptoms of menopause and prevent heart disease in older women based largely on evidence from non-randomized, observational studies. Yet after randomized, placebo-controlled trials in 1998 and 2002 showed that estrogen replacement actually *increased* the risk of heart disease, stroke, and cancer, earlier recommendations in favor of widespread estrogen use came to appear to have been misguided. As such, the rise and fall of HRT has typically been used to illustrate the perils of basing recommendations for clinical practice on non-randomized studies versus randomized controlled trials. As Jerry Avorn has noted:

The only real hero to emerge from [the] complicated story [of HRT] is the randomized controlled trial. On the guilty side is its country cousin the observational study, which the estrogen debacle indicated as a codefendant or at least as an unintentional coconspirator.¹¹

In contrast, early recommendations in favor of preoperative beta-blockers occurred specifically *because* randomized controlled trials suggested potential benefits. Unlike the story of HRT recommendations, the rise and fall beta-blocker recommendations took place

not because of a failure to recognize the limitations of non-randomized versus randomized studies; instead, it happened largely because of the prestige that expert observers were willing to assign to the randomized controlled trial as a form of evidence. To borrow Avorn's terminology, early beta-blocker advocates "heroized" Mangano's and Poldermans's initial studies specifically because of their randomized designs; as a result, these same experts were willing to trust the study results in spite of important limitations, including their relatively small sample sizes, their single-center designs, and, in the case of Poldermans's trial, the early termination of the trial for perceived benefit.

In this way, the rise and fall of preoperative beta-blocker recommendations offers a useful starting point for understanding other instances that occurred over these same years where promising, trial-tested therapies—such as tight glucose control in the intensive care unit^{57,58,59} and activated protein C for sepsis⁶⁰⁻⁶²—initially gained experts' endorsements as "best practices" only to fall out of favor a few years later. As with preoperative beta-blockers, each of these therapies provided new hope for the treatment of highly morbid conditions; in each case, experts latched onto the findings of one or two randomized trials and rapidly incorporated them into guideline recommendations. And in each case, initial expert recommendations for these therapies were revised and downgraded only a few years later when early endorsements were shown to have overlooked important potential harms.

We can only speculate as to why, in these instances, findings of early randomized trials were taken up so rapidly, particularly in light of historical observations of substantial delays in the translation of research findings into expert recommendations for care.⁶³ Pre-operative beta-blocker initiation, tight glucose control in the ICU, and activated protein C for sepsis may have risen rapidly to "best practice" status potentially because of the lack of other efficacious therapies to treat the clinical conditions they addressed. Further, their rapid incorporation into guidelines may have been facilitated by their appearance alongside advances in information technology in the 1990's and 2000's that changed how new research findings were communicated, or by the increasing relevance of practice guideline recommendations to health policy over time.⁶⁴

Like other recent observations of changes over time in research surrounding other evidence-based treatments,^{65,66,67} the story of preoperative beta-blockers echoes current concerns regarding widespread problems in replicating medical research findings, and the pitfalls of using arbitrary statistical thresholds to make determinations about the effects of medical treatments.⁶⁸ Moreover, it aligns with recent trends towards questioning views of biomedical evidence that place randomized trials at the top of a hierarchy of strength,⁶⁹⁻⁷¹ and efforts to develop approaches towards guideline creation that move away from automatic categorizations of evidentiary strength based on the designs of research studies.⁷²

On a more fundamental level, though, the story of beta-blocker recommendations shows how a sense of political urgency to discover and implement effective practices can lead to negative consequences when it is allowed to obscure uncertainties implicit even in evidence drawn from randomized controlled trials. Practice guidelines make possible the elision of distinctions between treatments that are supported by the "best available evidence" and

treatments that will actually work as intended in practice. In so doing, they serve the purpose of providing clinicians and health policy makers with recommendations for action; yet they also potentially complicate more gradual efforts to understand what unanticipated risks might accompany the dissemination of new treatments.

Seen in this light, the up-and-down story of preoperative beta-blockers appears not as lone aberration in judgment on the part of a few experts, but as case study that offers practical lessons in how to make guidelines more “trustworthy” going forward. In particular, it stresses the importance of avoiding over-reliance on one or two prominent studies as the basis for definitions of best practices; the pitfalls of hierarchical systems that automatically assign randomized trials to a higher category of evidentiary “strength” than other types of studies; and the potential value of built-in systems for “pre-mortem” analyses to assess the potential harms that might accrue if recommendations—particularly those with major implications for practice—are later found to have been misguided.

Ultimately, guidelines’ stated goal of improving health through better care may be best served not by dogmatic adherence to expert advice, but by active discourse that places individual recommendations within their larger scientific, social, political, and historical context. The story of preoperative beta-blocker guidelines illustrates the extent to which making guidelines more trustworthy requires that we understand in greater detail the processes by which individual recommendations form and evolve over time. Moreover, it requires that experts, clinicians, and policy makers alike be prepared to quickly modify our understanding of best practices as new evidence becomes available.

ACKNOWLEDGMENTS

Funding/Support: This study was supported by a grant to MDN from the National Institute on Aging, Bethesda, MD (grant 1K08AG043548).

Role of the Sponsors: Sponsors had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

References

1. 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. [PubMed: 8929262]
2. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, 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(24):1789–94. [PubMed: 10588963]
3. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, 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. [PubMed: 18479744]
4. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg*. 2005; 41(4):602–9. [PubMed: 15874923]
5. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery:

- randomised placebo controlled, blinded multicentre trial. *BMJ*. 2006; 332(7556):1482. [PubMed: 16793810]
6. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J*. 2006; 152(5):983–90. [PubMed: 17070177]
 7. Shojania, KG.; Duncan, BW.; McDonald, KM.; Wachter, RM. U.S. Agency for Healthcare Quality and Research; Rockville, MD: 2001. Making Health Care Safer: A Critical Analysis of Patient Safety Practices (Evidence Report/Technology Assessment, No. 43); p. 1-8.
 8. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery-- Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg*. 2002; 94(5):1052–64. [PubMed: 11973163]
 9. Shekelle, PG.; Wachter, RM.; Pronovost, PJ.; Schoelles, K.; McDonald, KM.; Dy, SM., et al. U.S. Agency for Healthcare Research and Quality; Rockville, MD: 2013. Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices. (Evidence Report No. 211.); p. 169-71.
 10. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol*. 2009; 54(22):e13–e118. [PubMed: 19926002]
 11. Avorn, J. Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs. Vintage; New York: 2005.
 12. Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. *N Engl J Med*. 2011; 364(5):476–80. [PubMed: 21288100]
 13. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977; 297(16):845–50. [PubMed: 904659]
 14. Neuman MD, Bosk CL. What we talk about when we talk about risk: refining surgery's hazards in medical thought. *Milbank Q*. 2012; 90(1):135–59. [PubMed: 22428695]
 15. Eagle KA, Brundage BH, Chaitman BR, Ewy GA, Fleisher LA, Hertzner NR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 1996; 27(4): 910–48. [PubMed: 8613622]
 16. Marks, H. Cambridge University Press; Cambridge: 1997. The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990.
 17. Daly, J. University of California Press; Berkeley, CA: 2005. Evidence Based Medicine and the Search for a Science of Clinical Care.
 18. Palda VA, Detsky AS. Perioperative assessment and management of risk from coronary artery disease. *Ann Intern Med*. 1997; 127(4):313–28. [PubMed: 9265434]
 19. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. *Ann Intern Med*. 1997; 127(4):309–12. [PubMed: 9265433]
 20. Podolsky D, Beddingfield KT. Rx for Deaths after Surgery. *U.S. News and World Report*. 1996:75.
 21. Warltier DC. Beta-adrenergic-blocking drugs: incredibly useful, incredibly underutilized. *Anesthesiology*. 1998; 88(1):2–5. [PubMed: 9447848]
 22. Sutton T, Rock P. Pro: beta-blockers should be used in all patients undergoing vascular surgery. *J Cardiothorac Vasc Anesth*. 1999; 13(4):490–5. [PubMed: 10468269]
 23. Leung JM. Diabetes and not lack of treatment with atenolol predicts decreased survival after noncardiac surgery. *Anesthesiology*. 1999; 90(4):1226–7. [PubMed: 10201703]
 24. Petros JA. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med*. 1997; 336(20):1452. author reply 53-4. [PubMed: 9148146]

25. Lustik SJ, Chhibber AK, Eichelberger JP. Effects of atenolol on postoperative myocardial ischemia. *Anesthesiology*. 1998; 89(3):794–5. [PubMed: 9743424]
26. Howell SJ, Sear JW, Foex P. Peri-operative beta-blockade: a useful treatment that should be greeted with cautious enthusiasm. *Br J Anaesth*. 2001; 86(2):161–4. [PubMed: 11573652]
27. Auerbach AD, Goldman L. beta-Blockers and reduction of cardiac events in noncardiac surgery: clinical applications. *JAMA*. 2002; 287(11):1445–7. [PubMed: 11903032]
28. Auerbach AD, Goldman L. beta-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA*. 2002; 287(11):1435–44. [PubMed: 11903031]
29. Feldman T, Fusman B, McKinsey JF. Beta-blockade for patients undergoing vascular surgery. *N Engl J Med*. 2000; 342(14):1051–2. author reply 52-3. [PubMed: 10755896]
30. Fleisher LA, Eagle KA. Clinical practice. Lowering cardiac risk in noncardiac surgery. *N Engl J Med*. 2001; 345(23):1677–82.
31. Lee TH. Reducing cardiac risk in noncardiac surgery. *N Engl J Med*. 1999; 341(24):1838–40. [PubMed: 10588971]
32. Selzman CH, Miller SA, Zimmerman MA, Harken AH. The case for beta-adrenergic blockade as prophylaxis against perioperative cardiovascular morbidity and mortality. *Arch Surg*. 2001; 136(3):286–90. [PubMed: 11231847]
33. Cina RA, Froehlich JB, Hamdan AD. Perioperative beta-blockade to reduce cardiac morbidity in noncardiac surgery. *Int Anesthesiol Clin*. 2001; 39(4):93–104. [PubMed: 11581539]
34. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. *JAMA*. 2002; 288(4):501–7. [PubMed: 12132984]
35. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 2002; 39(3):542–53. [PubMed: 11823097]
36. Birkmeyer JD, Dimick JB. Potential benefits of the new Leapfrog standards: effect of process and outcomes measures. *Surgery*. 2004; 135(6):569–75. [PubMed: 15179361]
37. Brooke BS, Dominici F, Makary MA, Pronovost PJ. Use of beta-blockers during aortic aneurysm repair: bridging the gap between evidence and effective practice. *Health Aff (Millwood)*. 2009; 28(4):1199–209. [PubMed: 19597222]
38. Lindenauer PK, Fitzgerald J, Hoople N, Benjamin EM. The potential preventability of postoperative myocardial infarction: underuse of perioperative beta-adrenergic blockade. *Arch Intern Med*. 2004; 164(7):762–6. [PubMed: 15078646]
39. Schmidt M, Lindenauer PK, Fitzgerald JL, Benjamin EM. Forecasting the impact of a clinical practice guideline for perioperative beta-blockers to reduce cardiovascular morbidity and mortality. *Arch Intern Med*. 2002; 162(1):63–9. [PubMed: 11784221]
40. Wijeyundera DN, Mamdani M, Laupacis A, Fleisher LA, Beattie WS, Johnson SR, et al. Clinical evidence, practice guidelines, and beta-blocker utilization before major noncardiac surgery. *Circ Cardiovasc Qual Outcomes*. 2012; 5(4):558–65. [PubMed: 22740011]
41. Grayburn PA, Hillis LD. Cardiac events in patients undergoing noncardiac surgery: shifting the paradigm from noninvasive risk stratification to therapy. *Ann Intern Med*. 2003; 138(6):506–11. [PubMed: 12639086]
42. Devereaux PJ, Beattie WS, Choi PT, Badner NH, Guyatt GH, Villar JC, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2005; 331(7512):313–21. [PubMed: 15996966]
43. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med*. 2005; 353(4):349–61. [PubMed: 16049209]
44. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? *Lancet*. 2008; 371(9627):1813–4. [PubMed: 18479743]

45. Riedel B, Shaw A, Le Manach Y, Aronson S. Beta-blocker therapy in non-cardiac surgery. *Lancet*. 2008; 372(9644):1146–7. [PubMed: 18926268]
46. Keane M. Beta-blocker therapy in non-cardiac surgery. *Lancet*. 2008; 372(9644):1145. author reply 46. [PubMed: 18926267]
47. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. *J Am Coll Cardiol*. 2006; 47(11):2343–55. [PubMed: 16750714]
48. Erasmus Medical Center. Erasmus MC dismisses professor. Rotterdam; Nov 17. 2011 2011
49. Chopra V, Eagle KA. Perioperative mischief: the price of academic misconduct. *Am J Med*. 2012; 125(10):953–5. [PubMed: 22884175]
50. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in non-cardiac surgery. *Heart*. 2013
51. Luscher TF, Gersh B, Landmesser U, Ruschitzka F. Is the panic about beta-blockers in perioperative care justified? *Eur Heart J*. 2014
52. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA*. 1997; 277(2):115–21. [PubMed: 8990335]
53. Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA*. 1998; 280(7):623–9. [PubMed: 9718054]
54. Auerbach AD. Personal Communication. 2013
55. Jones DS. Visions of a cure. Visualization, clinical trials, and controversies in cardiac therapeutics, 1968-1998. Isis. 2000; 91(3):504–41. [PubMed: 11143786]
56. Jones, DS. Broken Hearts: The Tangled History of Cardiac Care. Johns Hopkins University Press; Baltimore, MD: 2012.
57. Inzucchi SE, Siegel MD. Glucose control in the ICU--how tight is too tight? *N Engl J Med*. 2009; 360(13):1346–9. [PubMed: 19318385]
58. LaPar DJ, Isbell JM, Kern JA, Ailawadi G, Kron IL. Surgical Care Improvement Project measure for postoperative glucose control should not be used as a measure of quality after cardiac surgery. *J Thorac Cardiovasc Surg*. 2014; 147(3):1041–8. [PubMed: 24418668]
59. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001; 345(19):1359–67. [PubMed: 11794168]
60. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001; 344(10):699–709. [PubMed: 11236773]
61. Eichacker PQ, Natanson C, Danner RL. Surviving sepsis--practice guidelines, marketing campaigns, and Eli Lilly. *N Engl J Med*. 2006; 355(16):1640–2. [PubMed: 17050887]
62. Thachil J, Toh CH, Levi M, Watson HG. The withdrawal of Activated Protein C from the use in patients with severe sepsis and DIC [Amendment to the BCSH guideline on disseminated intravascular coagulation]. *Br J Haematol*. 2012; 157(4):493–4. [PubMed: 22225506]
63. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *JAMA*. 1992; 268(2):240–8.
64. Gray, BH.; Gusmano, MK.; Collins, SR. Health Aff. Millwood; 2003. AHCPR and the changing politics of health services research. *Suppl Web Exclusives:W3-283-307*

65. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med.* 2007; 147(4):224–33. [PubMed: 17638714]
66. Prasad V, Cifu A, Ioannidis JP. Reversals of established medical practices: evidence to abandon ship. *JAMA.* 2012; 307(1):37–8. [PubMed: 22215160]
67. Neuman MD, Goldstein JN, Cirullo MA, Schwartz JS. Durability of class I American College of Cardiology/American Heart Association clinical practice guideline recommendations. *JAMA.* 2014; 311(20):2092–100. [PubMed: 24867012]
68. Ioannidis JP. Why most published research findings are false. *PLoS Med.* 2005; 2(8):e124. [PubMed: 16060722]
69. Tonelli MR. Integrating evidence into clinical practice: an alternative to evidence-based approaches. *J Eval Clin Pract.* 2006; 12(3):248–56. [PubMed: 16722902]
70. Neuman MD, Bosk CL. Medicine and the radiant city. *Lancet.* 2013; 381(9873):1176–7. [PubMed: 23573526]
71. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med.* 2014; 29(7):1060–4. [PubMed: 24452418]
72. Tonelli MR, Curtis JR, Guntupalli KK, Rubenfeld GD, Arroliga AC, Brochard L, et al. An official multi-society statement: the role of clinical research results in the practice of critical care medicine. *Am J Respir Crit Care Med.* 2012; 185(10):1117–24. [PubMed: 22589312]

Figure 1. Timeline of recommendations made by three U.S. organizations regarding preoperative beta-blocker initiation, 1997-2013

Items highlighted in green indicate statements broadening the indications for preoperative beta-blocker initiation; items in yellow indicate statements restricting these indications. The broken line charts the cumulative number of patients randomized to preoperative beta-blockers versus placebo across six key trials (lead author in parentheses): (A) Multicenter Study of Perioperative Ischemia (McSPI) atenolol study (Mangano)¹; (B) Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE-I; Poldermans)²; (C) Perioperative Beta Blockade (POBBLE; Brady)⁴; (D) Diabetic Postoperative Morbidity and Mortality (DiPOM; Juul)⁵; (E) Metoprolol After Vascular Surgery (MaVS; Yang)⁶; (F) PeriOperative Ischemic Evaluation (POISE; Devereaux)³. As shown, statements in favor of expanding beta-blocker use from 1997 through 2002 occurred at a time when a relatively small number of patients had been studied randomized trials; as further evidence appeared between 2005 and 2008, guideline statements were revised to recommend more restricted use of preoperative beta-blockers. Abbreviations: ACP: American College of Physicians; AHRQ: U.S. Agency for Healthcare Research and Quality; ACC/AHA: American College of Cardiology/American Heart Association.