Mini Review

The reversal of cardiology practices: interventions that were tried in vain

Vinay Prasad[1], Adam Cifu[2]

[1]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [2]Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, IL, USA

Corresponding to: Vinay Prasad, MD. Medical Oncology Service, National Cancer Institute, National Institutes of Health, 10 Center Dr. 10/12N226, Bethesda, MD 20892, USA. Email: vinayak.prasad@nih.gov.

Abstract: Medical reversal happens when new trials—better powered, designed or controlled than predecessors--contradict current standard of care. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial and CAST study are notable examples of investigations that overturned current practice by demonstrating that these interventions offered no survival benefits. In this mini-review, we summarize our experience reviewing a decade of original articles in *the New England Journal of Medicine* with an eye towards investigations that reversed cardiology practice. From the management of arrhythmias to lipids to percutaneous coronary intervention (PCI) and finally, hemodynamics, reversals in the cardiology literature cover a broad set of practices. These reversals are instructive in that many of the therapies overturned were widely adopted and based on either sound physiologic reasoning or observational trials.

Keywords: Medical reversal; evidence based medicine; bias; contradiction; PCI; stenting; statins; primary prevention

Submitted Sep 23, 2013. Accepted for publication Oct 20, 2013.
doi: 10.3978/j.issn.2223-3652.2013.10.05
Scan to your mobile device or view this article at: http://www.thecdt.org/article/view/2854/3787

Introduction

Current medical practice rests on an uneven evidence-base. Some therapies are supported by large, well-done multicenter randomized controlled trials (RCTs) powered for hard endpoints (mortality, morbidity); others are biologically plausible interventions bolstered by single center retrospective data; and a final subset of therapies were theorized, once considered plausible, passed down through generations, and have become ingrained and unquestioned; heirlooms of eminence based medicine. For this reason, much of what doctors do, encouraged by performance metrics and professional guidelines, may simply be in error (1). These interventions have real costs and real harms, but do not offer real benefits. What percent of current medical practice is wrong? Empirical studies evaluating hundreds of widespread practices that were tested in more powerful, better controlled, or better designed trials provide a sober verdict. Nearly half of medical practices (46%) may be in error (2-4). They are, what we call, *medical reversals*. Medical reversals occur when current practice is found to be no better than placebo (or its omission) in well done clinical trials. Emblematic cases, such as hormone replacement therapy in post-menopausal women (5), and the routine stenting of stable angina (6), suggest that reversals cast a long shadow. These practices did not fall out of favor because they were improved upon; instead, they never worked. They were in error during the years they were in favor. They were also in error during the years after they were proven flawed before proponents abandoned them (7). Finally, they can be seen as grievous professional errors, undermining trust in the medical system and surviving as misunderstood fodder for a growing anti-science movement.

The field of cardiology has been a leader in evidence-based medicine, and, though this commitment has greatly improved patient care, it has also revealed notable examples of reversal. These cases are instructive, and reflecting upon them provides a unique perspective, improving one's

critical appraisal of all medical practices. Although, many practices in cardiology are justified by robust randomized controlled trials (RCTs), the majority of cardiovascular practices remain untested. Only a fraction (11%) of American College of Cardiology (ACC) and American Heart Association guidelines (AHA) are based upon level A evidence (48% on level C) (8); leaving many on-going practices vulnerable to future reversal. In this mini review, we will survey key reversals over the last decade in the field of cardiology, and some of their broad lessons. Courageous investigators who are willing to challenge long-standing dogma have the power to push cardiology to still greater heights.

Reversals in cardiology

Previously, we reviewed all 2,044 original articles that appeared in the *New England Journal of Medicine* over the decade 2001-2010 (3). In that time, 363 articles tested standard of care, with 146 (46%) articles contradicting it (6). Here, we draw upon that dataset, as well as provide select examples from subsequent years [2010-2013] to demonstrate the breadth of reversed practices in cardiology. We will cover five broad categories: rhythm management, lipid management, percutaneous coronary intervention (PCI) and stenting, hemodynamics, and other reversals.

Rhythm management

Although randomized controlled trials have been utilized since the 1940s, the ability of the RCT to truly upend current medical practice was not realized until the early 1990s with the publication of the Cardiac Antiarrhythmic Suppression Trials (CAST) (9). CAST tested whether prevailing management—the use of Class 1c antiarrhythmic agents (flecainide, encainide, and later moricizine) improved outcomes for patients who recently suffered a myocardial infarction (MI). Cardiac dysrhythmia was (and remains) one of the most common causes of early death post-MI. Prior research had implicated the frequency of premature ventricular contractions (PVCs) to these arrhythmic deaths, and anti-arrhythmic agents consistently suppressed PVCs. Thus, the idea that these drugs would improve outcomes was widely held. In fact, cardiologists were so confident these agents improved outcomes that recruitment to CAST was slow, as many felt it was unethical to allow patients a chance of receiving placebo (10). CAST however reached the exact opposite conclusion, showing increased rates of death from the use of these drugs, contradicting nearly a decade of widespread practice, and showing that even the best mechanistic reasoning could be wrong. The results of CAST imply that premature ventricular contractions are either (I) not causally related to death or (II) the off target effects of treating PVCs with these drugs outweigh the benefits. Some estimate that 50,000 Americans died because of this erroneous practice during the years it was in favor (11).

Over the last decade, several equally seminal trials further contradicted prevailing rhythm management. In the 1990s, it was widespread practice to convert patients with atrial fibrillation to sinus rhythm based on the assumption that sinus rhythm was physiologically beneficial and normal. However, no study had examined the role of rhythm control on the hardest endpoints (stroke, myocardial infarction, and mortality). In 2002, the AFFIRM study (12), and a paired RCT (13), showed that a primary rhythm control method was not superior to a primary rate control method for patients with atrial fibrillation (anti-coagulation was used based on provider discretion). In AFFIRM, over 4,000 patients were randomized and followed for a mean of 3.5 years. There was no difference in strokes or myocardial infarction between the groups. Overall mortality, the primary endpoint, was statistically similar, though more deaths occurred among patients assigned to rhythm control.

By 2008, at least 6 trials had undermined the primacy of a rhythm control strategy in atrial fibrillation; however, rhythm controlled remained preferred among patients with atrial fibrillation and systolic heart failure—a population long believed to benefit from coordinated atrial activity (14). The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial randomized 1,376 patients with symptomatic heart failure, an ejection fraction (EF) of less than 35%, and atrial fibrillation to these two strategies and followed them for a mean of just over three years (14). AF-CHF found no differences in death from cardiovascular causes, any cause, stroke or worsening heart failure—further challenging prevailing notions.

In the early 2000's guidelines issued by the AHA/ACC and the European Society of Cardiology that recommended strict rate control (resting heart rate <80 beats per minute and exercise heart rate <110 beats per minute) for patients with atrial fibrillation. This recommendation was based upon expert opinion that this would prevent heart failure and stroke and improve quality of life. In 2010 these guidelines were tested against a more lenient standard (resting heart rate <110 beats per minute. A large randomized trial, called RACE-II, randomized over 600 patients, and followed them

for 3 years (15). A lenient rate control strategy was found to be non-inferior to a strict rate control for the outcomes of a primary cardiovascular composite outcome, death from all causes, symptom control (dyspnea, fatigue and palpitations), and hospitalizations. A lenient rate control strategy was much easier to achieve and maintain among patients with permanent atrial fibrillation. Together, atrial fibrillation studies in the last 10 years have shown that more care is not better care.

Lipid management

The statin class of medications, inhibitors of HMG-CoA reductase, were studied extensively in the first decade of this century. While undoubtedly statins confer enormous benefit for some patients (e.g., those who are post MI), several landmark trials have suggested that their use should be more limited than current practice.

Two studies tested whether persons with heart failure (even when precipitated by coronary artery disease and MI) benefit from statins. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) group randomized patients over the age of 60, with NY Heart II-IV, ischemic heart failure, with diminished EF to 10 mg of rosuvastatin or placebo (16). Although the intervention group experienced a fall in low-density lipoprotein (LDL) and c-reactive protein (CRP), there was no difference in deaths, cardiovascular deaths, and coronary events (16). The (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza-Heart Failure) GISSI-HF trial randomized over 4,600 patients over the age of 18 with heart failure from any cause to rosuvastatin 10 mg or placebo (17). At a median follow up of 3.9 years, there were no differences in death from any cause, or hospitalizations for cardiovascular reasons, despite marked LDL reductions. Gastrointestinal side effects were more common among statin users.

Statins have also failed to confirm benefits in other high-risk populations long thought to benefit. Although the use of statins was widespread among patients on hemodialysis (who have particularly high rates of cardiovascular events), two trials contradicted this practice. The AURORA study (18) randomized over 2,700 patients who were undergoing hemodialysis to 10 mg of rosuvastatin or placebo, and followed them for a median of 3.8 years. Although the average LDL cholesterol was 43% lower among statin users at three months, the trial found no benefit on the following outcomes: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and death from any cause. These findings were bolstered by the 4D trial, which randomized 1,255 patients with type II diabetes who were on hemodialysis to 20 mg of atorvastatin daily or placebo (19). Although LDL levels were markedly reduced among statins users at four weeks, at a median follow up of over four years, there was no difference in death from all causes, cerebrovascular events, and the primary composite endpoint of: cardiovascular death, nonfatal myocardial infarction, and stroke.

A third study is often referenced to call these findings into dispute; however, it fails to provide a higher level of evidence. The SHARP trial randomized over 9,000 patients with chronic kidney disease (over 3,000 were on dialysis and over 6,000 were not) to a combination of simvastatin-ezetimibe (20 mg, 10 mg, respectively) or placebo and followed them for a median of 4.9 years. Although the trial is reported as positive, an analysis of the specific endpoints leaves some doubt. There was a 2% absolute risk reduction in a composite of non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or arterial revascularization (from 13.4% to 11.3%). There was no difference in non-fatal myocardial infarctions or coronary mortality. However, regarding the most important endpoint, mortality, there was the suggestion that while the combination of drugs reduced death from vascular causes, the drugs increased death for non-vascular reasons, such that death from all causes was no different between the groups. Additionally, the authors did not provide a detailed list of outcomes separately for those on hemodialysis or those not on it; thus it is unclear that SHARP contradicts AURORA or 4D.

Considering 4D, AURORA, CORONA, and GISSI-HF together—a central lesson emerges: many patients whom physicians felt were *most likely* to benefit from statin therapy, failed to show clear benefits. Ridker and Wilson, also noting this finding, conclude, "in 2013, trial data demonstrate the difficulty of recommending statins to all high-risk patients without regard for underlying clinical conditions".

When it comes to non-statin medications, several classes of medications have been contradicted. The addition of fenofibrate to statin therapy—a widespread practice for patients who failed to meet lipid targets—was found to offer no benefit in the ACCORD study. In ACCORD, a total of 5,518 patients with type 2 diabetes who were on simvastatin were randomized to fenofibrate or placebo (20). At a mean follow-up was 4.7 years, there was absolutely no difference in fatal cardiovascular events, nonfatal myocardial

infarction, nonfatal stroke, or death from all causes.

Extended release Niacin was an 800 million dollar a year industry when the results of the AIM-HIGH study were published (21). Although the drug was widely used to raise HDL among patients who achieved target LDL with a statin medication, the AIM HIGH study failed to validate this practice. In AIM HIGH (22), over 3,400 patients with established cardiovascular disease who achieved LDL goals were randomized to extended-release Niacin or matching placebo. The trial was halted at a mean follow up of three years for futility, as there was no difference between the groups in the outcomes of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or hospitalization for a high-risk acute coronary syndrome. There were non-significantly more deaths from any cause and stroke as first event of the primary outcome among users of niacin.

What are the take homes lessons of the last decade when it comes to lipid management? First, the trials discussed above argue that lipid targets cannot be considered reliable surrogate endpoints. The medical literature is rich with examples of studies that used surrogate endpoints leading us to adopt ultimately harmful drugs (23). Future studies of statins should be powered to examine important clinical endpoints, and whether novel biomarkers will be able to overcome these deficits remains to be seen (24).

Second, when it comes to using drugs for primary prevention, we contend that overall mortality should be the realistic bar against which these medications are judged (25). The cost of lipid medications in the US is in the tens of billions of dollars annually (25), and there remains uncertainty as to whether any alteration of lipid levels can improve overall survival among patients who have not yet experienced a cardiovascular event. The best meta-analysis to date meticulously excludes all secondary prevention patients using individual patient level data from 11 statin clinical trials (26). Despite follow up of 244,000 person-years, no significant improvement in overall mortality was noted. These findings should give us great pause in prescribing statins for primary prevention.

Percutaneous intervention and stenting

Coronary artery stents are lifesaving when used to prevent re-occlusion after primary percutaneous coronary intervention during ST elevation MI, and high-risk non-ST elevation MI. However, the use of percutaneous intervention and stenting in nearly all other situations has been fiercely disputed. Over the last decade several trials contradicted common and widespread practices. This evidence suggests that billions of dollars were probably wasted on deploying stents in patients without evidence-based indication. Unfortunately, recent data suggests these trials have done little to slow the use of inappropriate stenting (27).

Three trials capture the majority of reversed stenting indications. The COURAGE trial (6) randomized over 2,000 patients with known, stable coronary artery disease, and objective evidence of ischemia to the best medical therapy with or without routine stenting. Although the intervention group had 1,444 lesions treated with stents, at a follow up of 4.6 years, there were no differences in a composite of death, myocardial infarction, and stroke. The Occluded Artery Trial (OAT) randomized over 2,000 patients with stable symptoms who had a chronic total occlusion of an infarct related artery more than three days and less than 28 days after an MI to a strategy of best medical therapy with or without routine PCI (28). At four years of follow up, PCI did not reduce the composite endpoint of death, re-infarction, or heart failure. And, the ASTRAL trial (29) randomized over 800 patients with atherosclerotic renovascular disease to optimal medical therapy with our without PCI to the renal artery. At five years follow up there was no significant difference in systolic blood pressure; and a greater reduction in diastolic blood pressure in the control group. There were no differences in renal events, major cardiovascular events, and death. Finally two deaths were related to the intervention, leading authors to strongly question the net benefit of the procedure.

Proponents of stenting favor different trials, such as the FAME 2 trial and PRAMI. Again, as we noted with statin therapy, neither of these studies offers a higher level of evidence. In FAME 2, over 800 patients were randomized to PCI and stenting, guided by the use of fractional flow reserve (FFR), or optimal medical management (30). The trial was halted before the median follow up reached one year because of efficacy. FAME 2 found no difference in MI, cardiovascular death, death from any cause, or stroke. The trial did find a difference in urgent and non-urgent revascularization favoring the intervention group. Urgent revascularization was defined as a hospitalization leading to PCI within the first two years. There were more cases of stent thrombosis in the intervention group. Although FAME 2 is presented as positive, in many ways the outcome is similar to the COURAGE study. No difference in any meaningful endpoint, and the results could be explained by bias. The authors of FAME 2 acknowledge this limitation,

writing, "although randomization was concealed, it is possible that the awareness of the presence of a stenosis influenced decisions regarding revascularization". Additionally, calling the outcome urgent revascularization may be misleading, as some cases may not have been truly "urgent" (acute coronary syndrome).

In reality, FAME 2 is quite similar to COURAGE. In FAME 2, 9.9 stents were placed to prevent one future instance of revascularization. Looking only at urgent revascularization, 17 stents were required to prevent one event. In COURAGE 11.7 stents were required to prevent one future revascularization (PCI or CABG). The general point here is that it is not obvious that this is a worthwhile trade off—placing a dozen stents early to prevent placing one later—is cost effective by no standard, and with longer follow up, the number of stents needed to prevent a revascularization will only grow. Clarity to the debate on physiologically guided stenting will come from the forthcoming International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number, NCT01471522), which uses myocardial perfusion imaging (a functional FFR equivalent) to guided PCI to best medical therapy and examines hard outcomes. The trial is ongoing.

The PRAMI study looks at using PCI for secondary prevention. In PRAMI, 465 patients presenting with ST elevation MI who were receiving therapy to the infarct related artery were randomized to routine preventive PCI to all non-infarct related vessels or usual care (31). The trial was again halted early based on a positive composite endpoint. A total of 410 stents were placed in 234 patients randomized to intervention, and the intervention group experienced fewer non-fatal MIs, and refractory angina episodes. There was no mortality difference. This is clearly a very different patient population than in the trails above. These are not patients with stable coronary disease (the COURAGE population who comprise the majority of PCI in America). This difference likely explains the benefit here that does not exist in the prior trials. That said, calculating the number of stents needed to avert a bad outcome is a useful exercise. In PRAMI, these are the numbers: 30.9 stents to prevent one nonfatal MI, 22.3 stents to prevent one refractory angina, and 12.9 stents to prevent one nonfatal MI or refractory angina. The number of stents required to avert a nonfatal MI or case of angina in PRAMI is large and the economic viability of this strategy is unclear. Furthermore, the impact of this intervention on survival is unknown.

What are the take home lessons of PCI over the last ten years? When it comes to treating patients with stable coronary artery disease, the message is clear. Routine PCI does not change rates of myocardial infarction, cardiac death or all cause death. It does decrease future revascularizations—a benefit that diminishes over time—and does so at a tremendous price, with nearly 10-20 stents required to prevent one future case of revascularization. The results of PRAMI, while interesting, only apply to a select subgroup, and FFR will soon be put to a more rigorous test. While it was intuitively logical that PCI would improve survival in stable CAD, this has been contradicted in the literature.

A final comment on PCI in stable patients is that repeatedly it is asserted that stenting may not improve survival, but does decrease angina pain. This is bolstered by another publication from the COURAGE investigators (32), showing diminished pain scores among the intervention group at 6 to 24 months (benefits vanish by three years). However, these claims are biased, as the COURAGE study was not sham controlled; thus the benefits of stenting on subjective outcomes (particularly angina) may simply reflect a placebo response. Angina pain is well known to be susceptible to a robust placebo response (33) from invasive procedures, as was first shown in 1953 by Cobb *et al.*, in a sham controlled randomized trial of internal mammary artery ligation (34). To make any reliable claims that some intervention decreases angina pain, a study must be sham controlled. It is worth noting that, as conducted, COURAGE remains very good at drawing conclusions about hard, objective outcomes, such as survival; but, as is often the case, a more rigorous control arm is required to draw equally sound conclusions about subjective outcomes.

Hemodynamics

International guidelines recommend intra-aortic balloon counterpulsation pumps (IABP) as a class 1 recommendation in the treatment of cardiogenic shock. Published in 2012, the IABP-SHOCK II trial (35) randomized 600 patients with cardiogenic shock to the use of IABP. At a follow up of 30 days, there was no difference in deaths (despite the fact that 40% of events had occurred), nor were there differences in process-of-care measures, such as the length of stay in the intensive care unit, serum lactate levels, hemodynamic stabilization, the dose and duration of pressors, and renal function. Given the results of IABP-SHOCK II and a recent meta-analysis, editorialists noted that. "the data do not support the routine use of IABP in patients with acute

myocardial infarction complicated by cardiogenic shock, and the level I guideline recommendation is now strongly challenged (36)."

The IABP's use has been further challenged by at least 2 studies that have examined its role among patients with 3-vessel disease during non-emergent, high risk PCI. Although this was a widespread practice bolstered by guidelines and retrospective studies, both groups found no difference in a composite of death, acute myocardial infarction, cerebrovascular event, or additional revascularization prior to hospital discharge (37,38).

Other reversals

A final practice meant to improve survival is the use of continuous positive airway pressure (CPAP) for patients with obstructive sleep apnea (OSA) and congestive heart failure (CHF). For these patients, positive end expiratory pressure is thought to diminish preload, shift the Starling curve, and improve cardiac output. And, indeed, the Canadian Positive Airway Pressure trial (39) found that, among 258 patients with OSA and CHF (who were awaiting heart transplant) that use of CPAP could improve cardiac EF, decrease circulating norepinephrine, and decrease nocturnal episodes of apnea. Unfortunately, these surrogates did not translate into either improved transplantation free survival, hospitalization or quality of life. Although the editorialist was quick and correct to note that these results should not be extrapolated to all patients with OSA who require CPAP, he also notes that generally for patients with OSA: there are no large-scale, randomized trials of cardiovascular events or survival with the treatment (CPAP). Although therapy should always be tailored to the individual patient, the intriguing data from Bradley, Yaggi, and their colleagues provide a timely reminder of the importance of evidence-based recommendations in any widespread therapeutic strategy, particularly when treatment options carry a substantial economic burden (40).

Conclusions

Medicine is an uncertain science. Our decision-making is based on statistical and inductive inference. We can never be absolutely confident in any practice, no matter how many studies confirm its efficacy, and even randomized controlled trials may be subsequently contradicted. However, the current rate of contradiction in medicine is far greater than the uncertainty of statistics, and randomized controlled trials, when large and well done, remain the strongest truth claim (41). Our work on medical reversal shows that when practices, supported only by inferior evidence, are retested in powerful randomized trials, nearly half of them fail. If all practices were deployed only after a single unbiased RCT held to traditional, nominal levels of significance ($P<0.05$), then reversals would happen 5% of the time; rather than the 46% that we have found.

The reason that many more practices are contradicted than the uncertainty of statistics is because many practices are accepted based on expert opinion, pathophysiologic rationale, and retrospective studies. The IABP was a device that enjoyed a level 1 indication for cardiogenic shock (level 1 meaning only that practitioners generally agree), although it had never been tested in a randomized trial. IABP-SHOCK II's results contradicted clinical practice, millions of dollars of care. The COURAGE study contradicted 85% of all stents in America and upwards of ten billion dollars of annual expenditures (6,27).

Nothing in medicine is sacrosanct, and practices that garnered favor based on little to no evidence should be retested in thoughtful studies. When a practice claims to improve a subjective endpoint, sham controls should be used when possible (42), and primary endpoints should be pre-specified and remain unchanged from the protocol stage to the published manuscripts (43). When a practice concerns matters of life and death, overall survival is the realistic bar against which it should be judged. There is no shortage of practices based on a paucity of evidence. An analysis of all Cochrane reviews in 2011 found that 45% of practices examined still rest on an incomplete evidence base (44). As such, we challenge investigators to question conventional wisdom, and launch studies that will differentiate the treatments that help patients from those that are done in vain. If nearly half of all practices are flawed, then such investigations all but guarantee a dazzling and meaningful career.

Acknowledgements

The views and opinions of Dr. Prasad do not necessarily reflect those of the National Cancer Institute or National Institutes of Health.

Disclosure: The authors declare no conflict of interest.

References

1. Prasad V, Cifu A, Ioannidis JP. Reversals of established

medical practices: evidence to abandon ship. JAMA 2012;307:37-8.
2. Prasad V, Gall V, Cifu A. The frequency of medical reversal. Arch Intern Med 2011;171:1675-6.
3. Prasad V, Vandross A, Toomey C, et al. A decade of reversal: an analysis of 146 contradicted medical practices. Mayo Clin Proc 2013;88:790-8.
4. Prasad V, Cifu A. Medical reversal: why we must raise the bar before adopting new technologies. Yale J Biol Med 2011;84:471-8.
5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
6. 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;356:1503-16.
7. Tatsioni A, Bonitsis NG, Ioannidis JP. Persistence of contradicted claims in the literature. JAMA 2007;298:2517-26.
8. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA 2009;301:831-41.
9. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781-8.
10. Moyé LA, Tita AT. Defending the rationale for the two-tailed test in clinical research. Circulation 2002;105:3062-5.
11. Moore TJ. Deadly medicine: why tens of thousands of heart patients died in America's worst drug disaster. New York: Simon & Schuster. 1995.
12. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
13. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
14. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.
15. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73.
16. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.
17. Gissi-HF Investigators, Tavazzi L, Maggioni AP, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.
18. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
19. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48.
20. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74.
21. Giugliano RP. Niacin at 56 years of age--time for an early retirement? N Engl J Med 2011;365:2318-20.
22. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255-67.
23. Svensson S, Menkes DB, Lexchin J. Surrogate outcomes in clinical trials: a cautionary tale. JAMA Intern Med 2013;173:611-2.
24. Prasad V, Bonow RO. The cardiovascular biomarker conundrum: challenges and solutions. JAMA 2011;306:2151-2.
25. Prasad V, Vandross A. Cardiovascular primary prevention: how high should we set the bar? Arch Intern Med 2012;172:656-9; discussion 659.
26. Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010;170:1024-31.
27. Winstein KJ. A simple Health-Care fix fizzles out. The Wall Street journal. 2010. Available online: http://online.wsj.com/news/articles/SB10001424052748703652104574652401818092212
28. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006;355:2395-407.
29. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med 2009;361:1953-62.
30. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991-1001.
31. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J

Med 2013;369:1115-23.
32. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of Life in patients with stable coronary disease. N Engl J Med 2008;359:677-87.
33. Benson H, McCallie DP Jr. Angina pectoris and the placebo effect. N Engl J Med 1979;300:1424-9.
34. Cobb LA, Thomas GI, Dillard DH, et al. An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med 1959;260:1115-8.
35. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
36. O'Connor CM, Rogers JG. Evidence for overturning the guidelines in cardiogenic shock. N Engl J Med 2012;367:1349-50.
37. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. JAMA 2010;304:867-74.
38. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. Circulation 2012;126:1717-27.
39. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025-33.
40. Somers VK. Sleep--a new cardiovascular frontier. N Engl J Med 2005;353:2070-3.
41. Ioannidis JP. Why most published research findings are false. PLoS Med 2005;2:e124.
42. Prasad V, Cifu A. A medical burden of proof: Towards a new ethic. BioSocieties 2012;7:72–87.
43. Chan AW, Hróbjartsson A, Haahr MT, et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004;291:2457-65.
44. Villas Boas PJ, Spagnuolo RS, Kamegasawa A, et al. Systematic reviews showed insufficient evidence for clinical practice in 2004: what about in 2011? The next appeal for the evidence-based medicine age. J Eval Clin Pract 2013;19:633-7.

Cite this article as: Prasad V, Cifu A. The reversal of cardiology practices: interventions that were tried in vain. Cardiovasc Diagn Ther 2013;3(4):228-235. doi: 10.3978/j.issn.2223-3652.2013.10.05

