Fallacies of Evidence-Based Medicine in Cardiovascular Medicine

Evidence-based medicine (EBM) has gained a dominant role as the backbone of modern medical activities since its definition about 20 years ago. It serves the purpose to unify and optimize patient management and minimize scientific bias and fraud. The article looks, in the realm of cardiovascular medicine, at the banes of overly rigorous application of EBM with insufficient counterbalancing of other decision criteria. It exemplifies based on fictitious and real trials where EBM does not make sense, can be misleading, or has been inappropriately applied. Closure of the patent foramen ovale and percutaneous coronary intervention are focused upon as 2 major examples. Without abrogating the merits of EBM, concern has to be raised about the risk of increasingly putting EBM first. Neglecting experience and common sense in patient-management as a consequence is not in the interest of mankind.

Evidence-based medicine (EBM) has emerged as a technical term in the 90s.[1,2] It has since matured to an integral part of medical decision making and acting. Initially it was defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[3] It did also integrate individual clinical expertise and patient desire. This part appears to have gotten lost to a great deal on the way. Applying EBM today almost exclusively means applying the Oxford classification (http://www.cebm.net/index.aspx?o=5653) (Table 1[4,5]).

The Stance of the Medical Industry Regarding Evidence-Based Medicine

There is a strong interest of the medical industry to produce evidence in large cohorts with nonselective inclusion criteria, all against the recommendations of EBM publications.[6] Such evidence promises a large future client population. Many persons will be treated without benefit but that is what it is all about. Here are a fictitious and rather farfetched and a down-to-earth example:

A producer of reading glasses randomizes the world population into 2 halves. One half is fitted with reading glasses, the other 1 with plain glasses. An identical reading test in both cohorts proves a significant advantage of the reading glasses. The study is published with the conclusion that in a well-controlled double-blind (excuse the expression) trial of all-comers, there was a significant advantage for reading glasses over plain glasses. Hence, all persons should only read with reading glasses (class of recommendation I, level of evidence B, Table 1). Persons over 40 years made the difference. For the younger ones, this recommendation is nonsense. Even in older persons, there is a subgroup with mild myopia who do not significantly benefit from reading glasses.

A randomized trial to test an antihypertensive drug includes patients with a systolic blood pressure of ≥130 mm Hg. Provided a large enough cohort, the drug may well prove a significant benefit in terms of clinical end points. The patients with a systolic blood pressure >150 mm Hg made the difference. The study should have been limited to them but the inclusion of the patients with blood pressures 130 to 150 mm Hg massively augments the future client population.[7]

Rigor of Publication in Evidence-Based Medicine

Biased presentation making the new things look better and the old things look worse than they really are,[8] as well as fraud, manipulations, and dredging of data, are common in medical publications and need to be prevented. This mandates a certain publication rigor but carries the risk that particularly the leading medical journals tend to get caught up in their own rules and regulations. For apprehension that they be proved wrong about their publication, they wait sometimes too long to condone good things, depriving patients of these for years.

For every trial, a research protocol has to be published or deposited with authorities before beginning the study. Changes after that are fraught with tremendous efforts, comparable to the initial launch. Unexpected results that were not named as end points in the initial protocol cannot be published. Neither can results of subgroups that were not predefined, events that happened after the protocolled study duration, or surprise findings that were not anticipated. The intention-to-treat (ITT) principle is the holy grail. Patients can only contribute to the group they were randomized to, even in case they received no treatment or the treatment of another group, for whatever reason.

A caricature example that has been alluded to before[9] would be a small study examining if a skydive out of an airplane is safer with or without a parachute. The parachute is the new technique and the study is designed as a superiority trial. The follow-up period is limited to 3 minutes and the primary end point is mortality. The plane then flies so high that none of the trialists touches ground by 3 minutes. Moreover, some probands change groups by mistake. Publication rigor results in a conclusion paragraph in the study publication that reads: "The study was negative in mortality reduction and it is therefore not recommended to wear a parachute when skydiving." Moreover, it will be mentioned that there were side effects only in the parachute carriers (a scratch on the cheek or a sprained thumb occurring while

See page 693 for disclosure information.

https://doi.org/10.1016/j.amjcard.2018.11.004

Table 1
Simplified classes for therapeutic recommendations and levels of evidence, modified from the European Society of Cardiology[4,5]

Class of recommendation
I. Evidence or general consent that a therapy or a procedure are beneficial, useful, and effective. → Therapy or procedure are recommended and indicated.
II. Conflicting evidence or divergence of opinion about the usefulness or efficacy of a therapy or a procedure.
IIa. Evidence and opinion are positively weighted concerning usefulness and efficacy of a therapy or a procedure. → Therapy or procedure should be considered.
IIb. Usefulness and efficacy of a therapy or a procedure are not well established by evidence or general opinion. → Therapy or procedure may be considered.
III. Evidence or general opinion that a therapy or procedure are neither useful or efficient and may be harmless in some cases. → Therapy or procedure are not recommended.
Level of evidence
A: Supportive data of multiple randomized clinical trials or meta-analyses.
B: Supportive data of one or several large nonrandomized trials.
C: Consent of experts or small trials or retrospective trials or registries.

donning the parachute). Even if the follow-up period had been designed long enough for everybody to touch ground, the mortality benefit might not have been statistically significant because of the contamination of the ITT analysis by some mixed-up trialists.

The closure of the patent foramen ovale (PFO) is a real example along these lines. For years, neurologists recommended not to close the PFO after an initial cerebral embolism suspected to be related to the PFO. The first 3 randomized trials[10–12] had all missed their superiority end points according to the ITT analyses, mostly due to an insufficiently long predefined follow-up period and to inclusion of predominantly low-risk patients but also due to crossover patients.[12] High-risk patients intuitively (and in hindsight fortunately for them) received PFO closure outside the studies, above all in countries where this was legal and funded. All trials showed a numerical benefit but failed statistical significance. In the PC trial (randomized clinical trial comparing the efficacy of percutaneous closure of PFO with medical treatment in patients with cryptogenic embolism),[11] there were 7 recurrent cerebral events in the medical group and 1 in the PFO closure group according to the current definition of a recurrent event. In RESPECT (randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment),[12] which was stopped according to protocol after 25 recurrent cerebral events, 16 events were attributed to the control group and 9 to the PFO closure group, resulting in a p value of 0.08. Four of the events in the PFO group happened in patients without a closure device. So, by ITT analysis, the study missed the significance in the primary end point. By per-protocol analysis, the p value was 0.007 if the 4 patients in the PFO closure group with a recurrent event but no device are ignored (16 vs 5 patients) or even lower if they are counted for the control patients (20 vs 5, as-treated analysis). The blame of calling these superiority trials negative is on the publication rigor of the journal. The blame of not seeing that PFO closure was at least equivalent to long-term blood thinners and should be offered to patients as a valuable therapy method is on the neurologists and conservative cardiologists. It takes little imagination to anticipate that a longer follow-up will make the difference significant on the basis that the curves continuously spread over a short follow-up time. A brief outpatient procedure (referred to as mechanical vaccination)[13] with minimal risk, assumed cost of 20,000 US$[14] and effective cost of less than 10,000 US$ is a bargain compared with lifelong oral anticoagulation with its geometrically accruing bleeds. Antiplatelets were not competitive.[12] Publication rigor calls such extrapolations of results hypothesis generating. A longer follow-up of randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment indeed reached significance.[15] Interestingly, the now attained p value of 0.046 convinced everybody that the PFO should be closed whereas the earlier p value of 0.08[12] had convinced the majority that it should not be closed. It is better not to guess how many patients had experienced preventable recurrent strokes until finally the p value had passed the threshold and corrected the general attitude. Two additional trials[16,17] dealing with more dangerous PFOs also reached the primary end point of superiority with a significant p value, ultimately ushering in a nod to PFO closure that should have happened a decade earlier.

And the PFO story goes on. Three randomized trials studying PFO closure as a therapy for high-grade migraine also invariably showed a numerical benefit but missed the significance in their primary superiority end points, arbitrarily defined years earlier.[18–20] Again, the studies published as negative according to the publication rigor are in fact positive. The respective nonsignificant primary end points of the PRIMA (percutaneous closure of PFO in migraine with aura)[19] and PREMIUM (prospective, randomized investigation to evaluate incidence of headache reduction in subjects with migraine and PFO using the Amplatzer PFO Occluder to medical management)[20] trials met statistical significance in the sister trial where they figured as secondary end points. Swop the primary end points and voilà, 2 positive randomized trials.[21] Again, neurologists scotomize and conclude that the superiority trials failed and PFO closure should not be done, neglecting that PFO closure at least is not worse than medical treatment. Not offering PFO closure as alternative treatment, precludes migraine patients from the collateral benefit of being protected against paradoxical systemic embolism for the rest of their lives. Publication rigor did not permit to mention that and but a few caught it spontaneously.

Common Sense and Evidence-Based Medicine

It is imperative to keep common sense switched on and to read not only the final conclusion when digesting apparently correctly produced randomized evidence.

The recently published ORBITA trial (objective randomized blinded investigation with optimal medical therapy of angioplasty in stable angina)[22] appears to prove that there is no difference if a significant coronary stenosis, as per fractional flow reserve (FFR), causing stable angina pectoris (AP) be stented or simply treated medically. The British study randomized roughly 200 such patients to implantation

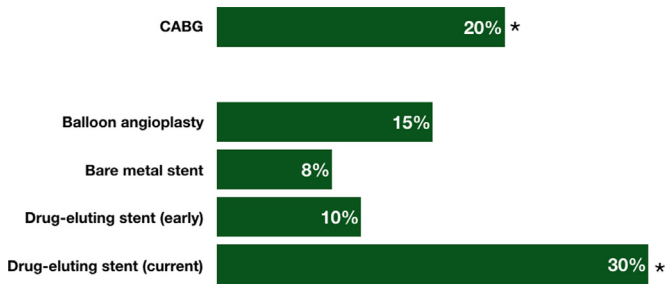

Figure 1. (Modified from[26]). Relative mortality reduction by various techniques for coronary revascularization compared with medical therapy alone. Coronary artery bypass grafting (CABG) is usually reserved for sicker patients with a high medical mortality and significantly reduces mortality. Initial balloon angioplasty showed a trend for improving life expectancy. This trend was almost completely lost with the initial bare metal stents and only partially regained by the initial drug-eluting stents. Current drug-eluting stents, however, improve mortality significantly like CABG.
*Significant in randomized trials.

of a drug-eluting stent or medical treatment alone after a run-in phase for adjustment of antianginal drugs. In both arms, patients were blinded by earphones (again excuse the pun) and by prolonging the diagnostic catheterization procedure to their treatment strategy, stenting or nothing. This study protocol would not have passed ethical committee approval in many countries. After a follow-up of 6 weeks, there was only a nonsignificant improvement in terms of exercise tolerance or spontaneous symptoms in the patients in whom the lesion had been stented. This result is not compatible with common sense. Stenting a significant single coronary lesion in a patient with typical AP reliably removes symptoms and improves exercise tolerance immediately after the procedure; and this for good except for patients with restenosis (<5% with current drug-eluting stents) or disease progression (unlikely in just 6 weeks). How can the study results be reconciled with reality? Some placebo improvement may have occurred in patients assuming they received a stent whereas they did not. Moreover, some psychosomatic symptom continuation may have occurred in patients assuming they did not receive a stent whereas they did. Treatment optimization before randomization may additionally have blunted symptoms altogether.[23] The only irrefutable and worrisome information gainable from this study is that FFR measurement, usually declared as innocuous, caused a coronary dissection necessitating implantation of a stent in 6% of patients randomized to receive no stent. This does not take into account the damage done by FFR assessment to patients randomized to stenting. It is all but certain that the cohort not receiving a stent made a bad deal. Their procedure in the study was not shorter because of the sham design. In real life, it would have been shorter by about 5 minutes, the time required to implant a stent. The stent would carry a total acute and long-term risk of about 2% to cause any problem. The untreated stenosis carries even with optimized drugs a risk of at least 0.5% per year of a plaque rupture with acute myocardial infarction (MI) or even death. Add to this a probability of >50% to require a stent in subsequent years. Moreover, the stent allows reduction of antianginal therapy such as β blockers with well-known side effects reducing quality of life. One has to dig into the supplementary appendix to find data on serious adverse events within the 6-week study period: 0 serious adverse events in the percutaneous coronary intervention (PCI) group and 8 in the placebo group (whereof 1 acute coronary syndrome, 1 pulmonary edema, and 1 hospitalization for chest pain). You do not need to be a clairvoyant to predict that with longer follow-up a trial like ORBITA will turn positive in favor of PCI regarding the likes of AP, MI, or death. The 6-week follow-up period of ORBITA, basically corresponds to the 3-minute follow-up in the parachute example above. Of note, the study investigators refrain from concluding that patients with stable AP and a significant lesion should not be stented[22] and, in fact, stented 85% of patients in the control arm at the end of the 6-week follow-up. The editorialists obviously missed that fact and called ORBITA the last nail in the coffin of PCI for stable AP.[24] EBM does not allow, let alone impose, to publish what happened after the predefined study period. From experience, we know that such studies have little effect on the way indications for PCI be handled around the world. The COURAGE (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial[25] had conceded some improvement in symptoms to PCI but no mortality reduction and therefore advised against it. If prolongation of life was a sine-qua-non of medical interventions, most of them would no longer be supported and entire disciplines would dwindle or even disappear, such as dermatology, ophthalmology, orthopedic surgery, and dentistry. Treatment of coronary artery disease somewhat justifies the call for improvement of life expectancy. Modern stenting can meet that (Figure 1).[26] Plain old balloon angioplasty came close to significant mortality reduction. The first bare-metal stents increased mortality compared with plain old balloon angioplasty because of the problem of delayed stent thromboses producing out of the hospital MI. The first generations of drug-eluting stents were slightly improved in that respect. Their reputation of having a higher risk of stent thrombosis than bare-metal stents, reigned for the better of a decade after 2006 but was a myth grown on misinterpreted EBM.[8] Current drug-eluting stents with their very small risk of stent thrombosis for the first time in PCI history achieve significantly improved longevity. They can compete with coronary artery bypass grafting also in that respect.

Conclusions

Young physicians tend to obey EBM religiously. They do seek advice with older colleagues if they or their next of kin are the patient. Every patient deserves to be treated like that. The patient must be fully informed about evidence,

but also about personal and general experience and opinion. The conclusion sentence in the abstract of the most recent publication will not do. The patients' interest goes beyond short-term follow-up as they are the ones experiencing the long-term follow-up. The synthesis of correctly and fully interpreted EBM, personal experience, experience of trusted peers, and the wish of an adequately informed patient is the winner. It does not make sense to request evidence for all medical activities. Some things are obvious. Some preventions or therapies take decades to prove their value like a vaccine against Alzheimer that needs to be applied in childhood. Mid-term innocuousness and likely effectiveness should be all that is required for them. How sad to find out after 50 years that countless destinies could have been better, had one seen the writing on the wall and not gone by the book. Why not return to the habit of the time before the term EBM was coined and use evidence at its best as a decision-making instrument that is equivalent (one third each) to experience and good clinical judgment, that is, common sense, smartness, and foresight. Currently, EBM is responsible for possibly 90% of medical management decisions and that is hardly what we would want for ourselves as patients. At least for a while, continuously updated EBM algorithms available at the consultation desk or bedside will unfortunately be the mainstay of practicing medicine to the end of minimizing the risk for being sued. If things turn bad because EBM misled, there are no frowns. One day, EBM will be perfectioned to also encompass common sense paired with experience and intelligence according to the principles of epistemology. Be patient.

Disclosures

The investigators have received speaker and proctor fees of Abbott.

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