Point of View

Therapeutics in Clinical Cardiovascular Practice. Experiences and Evidence

Flávio Danni Fuchs

Hospital de Clínicas de Porto Alegre - Faculdade de Medicina da Universidade Federal do Rio Grande do Sul - Porto Alegre, RS - Brazil

The quality of evidence in Cardiology has been intensified in the last years. By exceeding classic pharmachological and biological foundation, evidence-based methods of classic medicine, particularly randomized clinical assay, were applied to clinical scenario, allowing for discriminating among efficient, inert and injurious therapies. Classic studies, such as the one that demonstrated the inefficiency of mammary artery ligature surgery in the treatment of refractory chest angina, were predominantly carried out in cardiovascular diseases. The assimilation of methods of evidence-based medicine by corporations with corresponding investment in research and promotion, has expanded therapeutic and diagnostic possibilities quite much. However, it has been experienced a time of distortions in the relationship among corporations, academy and professionals, resulting from a strong corporate bias, which influences priorities of research, disclosure and prescription. Public cost limitations require cardiologists to strongly qualify in knowing the paradigms of evidence-based medicine, to explore the accuracy of cardiovascular therapy with a socially tolerable cost.

Evidence-based medicine: origin and development

Evidence-based medicine has been ratified as new medical paradigm. It consists of the conscious, explicit and judicious use of the best evidences available in medical literature to make decisions on patient care[1].

That definition is universal and does not deeply disagree with ethical principles of medical profession. The physician has always performed medicine by basing on the best evidence available. What has really changed in the last decades was the quality of the evidence. Scientific evidences produced in the first half of last century, predominantly by physiology and pathology, has provided medicine with a strong biological basis, by eliminating magic and fantasy. In clinical scenario, however, diagnostic and therapeutic processes were not comparatively assessed, by understanding that observation and systematized description were sufficient to distinguish between what was false and what was true. It was understood that medical intervention in men consisted in a single experiment, which was similar to the one performed in hard sciences. However, there are many reasons that may explain the evolution to the cure, being the intrinsic effect of treatment the only one. Practically every disease naturally evolves to the cure or undergoes a period of control. Such condition, associated to the art of some therapists, to placebo effect and the regression to the mean, determines the success of many therapies[2]. The use of therapies clear intrinsic effect with is the condition that separates physicians from non-scientific therapists, charlatans and others.

The detection of intrinsic effect of treatments was at first done by pharmacogical experiments. In those, the intervention control was required, so it would be possible to document that the effect observed in the experiment resulted from the intrinsic activity from the medicine and not from the experimental vehicle or ritual. Results from pharmachological studies in the first half in the last century were assembled in the classic text by Goodman and Gilman, whose first edition goes back to 1941. The 20th century scientific therapy was then recognized as based on medications that showed efficient in experimental models.

Pharmachological evidence validated the use, in Cardiology, of medications that have been useful so far, such as digitalis and nitrates. On the other hand, it was unable to demonstrate the clinical usefulness of many other medications. An example of that is dipyridamole, a drug with vasodilator activity, but without antianginous effect. Its coronary artery dilator effect was shown deleterious (coronary stealing syndrome), which is an effect that has been currently explored for ischemia induction.

It was clear that something else than the pharmachological effect would have to be evidenced to justify the use of drugs and other therapies, which means, the demonstration of the clinical effect on the specific objective of the treatment, be it symptomatic or preventive[3]. Such effect was qualified as **efficacy** in the context of evidence-based medicine. The new division of knowledge that dedicated to study the efficacy of medications and their safety, in men, was Clinical Pharmacology[2].

Clinical Pharmacology, concerning the assessment of treatment usefulness, becomes mixed up with evidence-based medicine. Phases I (safety and kinetic observations in normal men) and II (the same, but in sick men) are the first ones. In phase III lies the greatest merit of Clinical Pharmacology, for bringing the controlled experimental method to the clinical scene, which is similar to pharmacological experiment. Unlike the research with isolated organs or tissues, or with experiment animals, the research in men required that the constitution of comparison groups were carried out in an absolutely casual manner (randomization). So, a different clinical course among comparison groups can be attributed to the treatment allocated to one of them.

Besides assessing the efficacy of treatments, Clinical Pharmacology estimates adverse effects of medications. Common

Mailing address: Flávio Danni Fuchs - Rua Ramiro Barcelos, 2350 - 90035-603 - Porto Alegre, RS - Brazil - E-mail: ffuchs@hcpa.ufrgs.br

adverse effects are identified in randomized clinical trials, especially in those controlled by placebo. Many patients complain about adverse effects even when they use placebo (nocebo effect), being those that exceed the nocebo effect the real adverse effects of drugs. Rare adverse effects are only identified in populational use of the medication, during pharmacovigilance phase (phase IV). The identification of anti-inflammatory COX-2 selective inhibitor risk for cardiovascular system is an important example[4].

Epidemiology also contributed to the formation of evidence-based medicine. Its methods of systemized observation of reality, cohort, cross-sectional, alecological and case and control studies were grouped with randomized clinical assays in Clinical Epidemiology[5]. The series of cases and the quasi-experiments, typical of clinical medicine, were also aggregated to its research methods, directed towards risk assessment, diagnosis, treatment and prognostic. However, the greatest clinical evidence-oriented medical innovation lies in the treatment.

Classic studies of evidence-based medicine

The first randomized clinical assay, the pillar of evidence-based medicine concerning treatment effects, was only published in 1948[6]. In such study, patients with tuberculosis treated with streptomycin, showed a 50% mortality reduction in 6 months (22% versus 44%). That one and other eleven studies were appointed as classics among randomized clinical assays[7]. The observation of those pioneer studies shows the great medical revolution they provided, consisting of the basis of evidence-based medicine. In total, 7 among the 12 classics were carried out with cardiovascular diseases.

The first study included in was probably the first one to demonstrate the powerful placebo effect of surgeries[8]. It consisted of the ligature of mammary artery as a therapeutic measure in patients with refractory angina. As incredible as it may seem today, there were many hypotheses to explain how the ligation of an artery that nourished a striated muscle led to angina relief Cobb et al. randomized 17 patients with severe angina for mammary artery ligature or *sham* surgery, completely identical to intervention, except for the non-ligature. The assessment was carried out by researchers who did not know the procedure performed, as well as the patients. In each group, 5 patients reported improvement, and in one that improvement was pronounced, having returned to normal activity. His/Her artery had not been ligated.

The superb effect of heparin on pulmonary na embolia, with NNT of only 2 patients to prevent from a severe event[9], the impressive superiority of penicillin G benzatin over oral penicillin and sulfa in the prevention of rheumatic fever[10], the efficacy of diuretic-based therapy to prevent from events in severe hypertensive patients[11], the inefficacy of bypass surgery between the temporal artery and the middle cerebral artery in acute stroke[12], and the efficacy of low aspirin dose in acute myocardial infarction and its synergy with streptokinase[13] are other examples. The most recent cardiological classic is CAST[14], possibly the study that most strongly influenced the modern cardiological practice. CAST demonstrated that antiarrhythmics able to abolish ventricular arrhythmias in high risk patients, recovered from myocardial infarction, increased mortality rate in more than 300%. The idea that substitute outcome, correction of arrhythmias, was not able to predict the efficacy in preventing from hard endpoint (mortality), was clearly demonstrated in this study. For hard endpoints, the denomination of primordial endpoint was proposed, which corresponds, in practical terms, to the condition perceived as relevant by the patient himself/herself[15].

Many other studies parallel or after the assigned classics contributed to the consolidation of evidence-based medicine in Cardiology, by confirming or denying theoretical expectations. The latter ones have a greater impact, as they reinforce the idea that only by assessing the usefulness of treatments in men, and with primordial outcomes, absolute safety, benefit it is possible to estimate the inertia or risk of therapies. The failure of hormone reposition therapy in the prevention of cardiovascular diseases (associated to the alarming increase of incidence of breast cancer) is an important example, as it has contradicted the whole expectation of experimental and clinical studies with surrogate outcomes[16].

Evidence-based medicine: limitations and inapropriate use

The current cardiological practice is soundly founded by the results from evidence-based medicine. Some more renitent colleagues still despise it conceptually, despite incorporating its results in clinical practice. They are right in an aspect, which means that there is no dogmatic view on its supremacy. In same way, they agree with those who acknowledge the unequivocal revolution of evidence-based medicine, but point out limitations in its widespread application. The following limitations are among them.

Extension of concepts of evidence-based medicine - The number of papers using evidence-based medicine concepts is countless. As Clinical Epidemiology and Clinical Pharmacology have been incorporated to Medicine teaching only few years ago, and not in all schools, colleagues have difficulties in acknowledging methods and language of evidence-based medicine. Design of studies, randomization criteria, assignment of surrogate, intermediate and primordial outcomes, frequency and association measurements (means, medians, percentiles, standard deviations, confidence intervals, relative risk, odds ratio), effect measurements (relative risk reduction, absolute reduction, NNT), systematic errors, random errors, among others, constitute parameters in which sufficiency for reading is required, regardless of the ample literature on cardiovascular therapeutics. Nevertheless, for many, a result with $P<0.05$ is scientific and reliable (even more reliable with P values lower than that), by ignoring that outcome qualification, effect magnitude and experimental group adequacy, among other attributes of the study are of greater importance.

Corporate bias - Initial studies of evidence-based medicine were predominantly carried out and funded by academy and public institutions. Regulatory agencies began to require that medication registration was based on quality pharmacological-clinical studies. As a result from that requirement and for their own interest, there was a progressive and massive investment from big pharmaceutical corporations in sponsoring and carrying out randomized clinical trials, by adding to the traditional investment in pre-clinical pharmacology.

As a rule, that investment resulted in quality and progress. Not only in medications, but also in other therapeutic and diagnostic devices, research sponsored or carried out by the sector led to a great expansion of resources for quality cardiological assistance, in the patient's benefit. However, it has been verified in the last years that disclosure practices of those studies and even the relationship

between corporations and academy have been often away from apropriate standards. It has been observed that industries influence all stages of development and incorporation of new technologies, from pre-clinical research to guideline formulation. So, leading medical journals publish whatever is produced, and what is produced is mostly financed by the sector. Negative result studies are part of losses forecast by the corporations, with many of them being presented. Others, however, are not published. Ongoing clinical assays, in which negative results are anticipated, such as Convince study, are summarily interrupted[17], with serious breaking of the pact between patients and researchers[18]. Less evident negative results, however, tend to be made up and shown in a positive way.

The assessment of efficacy of anti-hypertensive medications, especially regarding first option choice, has been particularly susceptible to tendencies resulting from pharmaceutical sector promotion. Among many examples, there is INSIGHT study[19] reanalysis in patients with diabetes mellitus[20]. The apparent superiority of nifedipine over diuretics in the prevention of total mortality shown in reanalysis was due to the inexplicable multiplication of fatal outcomes, in more than twice higher than those described in the original study[21].

Not only in hypertension are examples of distortion in planning and understanding of randomized clinical assays found. Clopidogrel has been aggressively conquering commercial ground, by having been compared to ticoplidine, the group prototype, only in minor studies.

Examples as those commented illustrate the critical moment of opinion making in Cardiology, which is also critical in other areas of therapeutics and diagnosis. Outside Cardiology the conflicts are even more intense, provided the little tradition of research applied to many medical specialties. But they surely are transitory situations, as even with a temporary difficulty in discerning between what is false and what is true, there will be a continuous approach with the truth. For example, the usefulness of diuretics, preferential medications in hypertension handling[22], has been progressively acknowledged at least regarding the association among antihypertensives.

Studies on cost-effectiveness and assessment of technology in healthcare - The sound recognition of evidence in terms of intervention efficacy is not the end of the story yet. It is necessary to estimating the magnitude of the benefit (size of effect), measured by absolute risk reduction. With that, the number of patients that need to be treated (NNT) is calculated to prevent from an event. Such information is included in cost-effectiveness calculation, which will show the amount necessary resources to be beneficial to a patient. The joint analysis of all information related to efficacy, effectiveness and cost-effectiveness are under the responsibility of healthcare technology assessment, an area under fast development.

No modern society has conditions to extend efficacious therapies to all its citizens. Limits established by the customer are indisputable (every one is free to decide how much he/she is going to invest in an attempt of health recovering or maintenance). However, few times the judgment and costing are under the responsibility of the patient or his/her family. Third parties – the government or insurance companies – are then urged to pay the bill. Costing from the government interests all citizens. So, technical, economical and emotional aspects that are associated to decisions are taken to political level. A particularly critical moment has been experienced in this context in Cardiology, concerning several efficient therapies, but of high cost and with high NNTs. There will not surely easy for "SUS" to extended to all cases with indication the use of automatic defibrillators[23] and cardiac resynchronization therapies[24] in heart failure patients. Cardiologists are, in individualized medical care of patients and in advisement to public organs, deeply involved in decision making process, which at last must be under the responsibility of society as a whole.

Conclusion

This look to the development and methods of evidence-based medicine, with few examples, tried to illustrate its progressive importance in the indication of medical interventions. It is impossible to ignore it, and should be handling old and new cardiologists habilitate in this new paradigm, in order to get more efficient cardiovascular therapeutics at an acceptable cost.

References

1. Evidence-based medicine working group. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992; 208: 2420-5.
2. Fuchs FD. Farmacologia Clínica, contribuição para a terapêutica racional. In: Fuchs FD, Wannmacher L, Ferreira MBC (eds). Farmacologia Clínica: Fundamentos da Terapêutica Racional. 3ª.ed. Rio de Janeiro: Guanabara Koogan, 2004: 3-7.
3. Fuchs FD. O médico e a questão dos medicamentos: uma análise crítica sobre os fundamentos da prescrição de fármacos. Ciência e Cultura 1988; 40: 652-55.
4. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286: 954-9.
5. Duncan BB, Schmidt MI. Epidemiologia clínica e a medicina embasada em evidências. In: Duncan B, Schmidt MI, Giugliani ERJ (eds.). Medicina Ambulatorial: Condutas Clínicas em Atenção Primária, 2ª.ed. Porto Alegre: Artes Médicas, 1996.
6. Marshall G, Blacklock JW, Cameron C et al. Streptomycin treatment of pulmonary tuberculosis. Br Med J 1948; 2: 769-82.
7. Fuchs FD, Klag MJ, Whelton PK. The classics: a tribute to the fiftieth anniversary of the randomized clinical trial. J Clin Epidemiol 2000; 53: 335-42.
8. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med 1959; 260: 1115-18.
9. Barrit DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960; 1: 1309-12.
10. Albam B, Epstein JA, Feinstein AR et al. Rheumatic fever in children and adolescents: a long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. Ann Intern Med 1964; 60(suppl 5): 1-129.
11. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. JAMA 1967; 202: 1028-34.
12. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass surgery to reduce risk of ischemic stroke. N Engl J Med 1985; 313: 1191-200.
13. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2: 349-60.
14. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators: Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406-12.
15. Fuchs SC, Fuchs FD. Métodos de investigação farmacológico-clínica. In: Fuchs FD, Wannmacher L, Ferreira MBC (eds). Farmacologia Clínica: Fundamentos da Terapêutica Racional. 3ª.ed. Rio de Janeiro: Guanabara Koogan, 2004: 8-23.
16. Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002; 288: 321-33.
17. Black HR, Elliott WJ, Grandits G et al. CONVINCE Research Group. Principal Results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial. JAMA 2003; 289: 2073-82.
18. Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. JAMA 2003; 289: 2128-31.
19. Brown MJ, Palmer CR, Castaigne A et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study (INSIGHT). Lancet 2000; 356: 366-72.
20. Mancia G, Brown M, Castaigne A et al. Outcomes with nifedipine GITS or co-ami-

zolide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003; 41: 431-6.
21. Fuchs FD. May we die twice? Hypertension 2003; 42: e8.
22. Fuchs FD. Diuretics: drugs of choice for the initial management of patients with hypertension. Expert Rev Cardiovasc Ther 2003; 1: 35-41.
23. Bardy GH, Lee KL, Mark DB et al. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225-37.
24. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005 Mar 7; 352: [Epub