GUIDELINES: UNITY AND BALANCE

Around a year ago, I contributed an editorial entitled "Clinical guidelines in Brazilian health system"[1] commenting on the article "Utilization of clinical guidelines by health plan operators in the Brazilian health system",[2] which was published in this journal and provided an analysis of the implementation of clinical guidelines, especially related to cardiology, in the Brazilian Health System. The authors of the above mentioned article concluded that, in spite of the fact that the use of guidelines in the decision making process was rare, the cardiovascular guidelines were the most frequently used.

Also regarding cardiology, the assessment of the guidelines of the American College of Cardiology and American Heart Association was recently published in the JAMA,[3] and the conclusions of such assessment highlighted that the recommendations of these guidelines were largely based on lower levels of evidence or expert opinion. This article also suggests that medical researchers should conduct clinical trials with the purpose of providing those areas of cardiology lacking evidence with information and that physicians should be cautious when considering recommendations that are not based on solid evidence. Finally, the authors of the article added that the guideline writing process should consider the impact of weak evidence on the clinical practice.

Despite being based on a systematic review of the literature, some methodological aspects of the guideline writing process allow the expression of interests in an unbalanced manner, which triggers conflicts. Some of these aspects are: establishment of rates and recommendations lacking support from evidence, failure in recognizing the limits of the scientific information available, failure in identifying the population benefited, disregard of the several different points of view, such as that of the health system, and ambiguous expression of clinical doubt, evidence, and recommendation.

In an oversimplified and tendentious manner, the literature, the media and many opinion makers have attempted to establish a direct critical relation between the results of research, the several interests involved and the health system based solely on the content and method employed in the design of guidelines. However, aspects and elements having the same or a stronger impact on the results of the health care provided to patients by the health system are completely disregarded by such analysis:

Aspects related to the relation between scientific evidence and clinical practice: A countless amount of clinical scenarios have characteristics that hinder their analysis by means of ideally strong study designs; however, on the other hand, several new technologies could be easily tested using adequate study designs although they are imposed by means of uncritical and populist marketing. Furthermore, the local assessments of effectiveness are not even mentioned as the main source of support for the validation of solid evidence in the clinical practice;

Aspects related to the clinical practice: Decisions made by physicians vary a lot and they depend on certain aspects such as work conditions, skills acquired, continuous professional updating, personal expectations, level of experience, and reflexive ability. Knowing the original concepts of evidence-based medicine is essential to make physicians immune against marketing and the owners of knowledge;

Aspects related to the priorities and points of view of the health system managers: International health care programs are flooded with thousands of new options in terms of diagnosis and treatment; however, they do not have the necessary structural conditions and time to develop strategies and establish priorities with regard to the incorporation of these new technologies. With the exclusive focus on the amount of financial resources, the natural trend is reducing criticism to the point that there is no more criticism, resulting in immobilization of decisions, leaving the minorities unprotected, reducing equity, stimulating the need of court decisions, with lack of investments in phase IV research, and looking for answers in a literature that is not related to any health care process;

Aspects related to the point of view of the patients targeted by the recommendations: Knowing how the flow of the decision process will affect the real patient and fulfilling all the different local needs is only possible by listening to and directly or indirectly considering (by means of medical experience) the points of view and conditions of the population involved, including those patients in special situations. Education and relationship processes involving the population may also increase adherence to ethical and evidence-based decisions and reduce the delusion caused by unethical sensationalism based on external interests.

The critical assessment of guidelines whose writing process is not related to these aspects does not contribute to the quality of the health care provided to the patient. On the contrary, criticism focusing exclusively on the method provides arguments to those who do not wish to have an instrument that shows the weaknesses of the scientific evidence used to support many of the current medical practices, or who, due to lack of knowledge, feel that their practice is being restricted.

The design of evidence-based clinical guidelines should be part of a process of health care quality, focused on the implementation, guaranteeing the minimal conditions that will enable appropriate understanding and use of their content and recommendations. This is only feasible with the engagement of all those involved, respecting ethical procedures and focusing on the patient while joining different interests to perform the following actions:

Design of guidelines that take into consideration clinical judgment, knowledge about the best evidence and fulfillment of patients' needs;

Medical education initiatives, providing instruments that facilitate the decision making process, as well as the understanding of the quality of evidence, and the patients' benefits and risks;

Initiatives that promote the education of the population, providing believable information that facilitates adherence to the proposals of decision and to the relationship between patients, physicians, and the health system;

Involvement of the health system managers in the guideline writing process, incorporating the focus on applicability and also on the controlled use of the recommendations, enabling the detection of limitations and benefits;

Alignment of the actions that regulate the health system with the content of the guidelines, valuing efficacy and, mainly, effectiveness, as an instrument to make decisions regarding the recognition of new procedures and treatments.

There is not one single action able to cause the impact expected by all those involved: to reduce conflicts, to rationalize costs, to increase benefits, to decrease risk, and mainly to guarantee equity.

Wanderley Marques Bernardo

Professor de Graduação, Pós-Graduação e Coordenador dos Núcleos de Medicina Baseada em Evidência nas Faculdades de Medicina da Universidade de São Paulo e UNILUS. Coordenador Técnico do Programa Diretrizes AMB/CFM, São Paulo, SP.

António Vaz Carneiro

MD, PhD, FACP - Centro de Estudos de Medicina Baseada na Evidência, Faculdade de Medicina de Lisboa, Portugal.

Edmund Chada Baracat

Professor Titular de Ginecologia da Faculdade de Medicina da Universidade de São Paulo – USP e Diretor Científico da Associação Médica Brasileira, São Paulo, SP.

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Smoking cessation – challenges to be faced

Current estimates indicate that smoking is responsible for approximately 5.4 million of deaths/year all over the world,[1] and it is one of the highest risk factor for death, being second only to hypertension.[1,2] Smokers live an average of 10 years shorter than non-smokers and have a worse quality of life.[3] In spite of the information available about the harmful effects of smoking, 1.3 billion people still smoke worldwide.[1] In Brazil, around 23% of the population older than 18 years old smokes.[4] The main reasons for such a high prevalence rate of smokers are as follows: tobacco-related diseases are chronic, the tobacco industry is allowed to produce marketing campaigns, tobacco is inexpensive, and quitting smoking is difficult, since most smokers are nicotine-dependent and social, economic, and cultural aspects are associated with that difficulty.

The prevalence of smokers is much higher among individuals with psychiatric diseases (above 50%). These individuals are usually heavy smokers and are at higher risk for relapses after quitting smoking, which should not prevent them from receiving attention from programs aimed at helping smokers to stop smoking.

In the current issue of the journal, Azevedo et al.[5] present the results of a treatment offered to smokers at a psychiatric outpatient clinic; 47% of the subjects had symptoms of anxiety and depression and 28% had a history of drug abuse and alcoholism. In this study, despite only part of the group could be medicated, the combined use of group therapy and medication in 171 patients achieved a success rate of 62% after 25 weeks of follow-up, which is much higher than the previous studies published in the literature.[6] The authors suggest that this success rate is related to the large number of motivational sessions attended by the group of patients. However, these data need to be confirmed, since a meta-analysis including 46 studies revealed a success rate between 18% and 24% for a similar number of sessions.[6] In addition to the limitations mentioned in the article, the facts that it was not a controlled study and that the confirmation of smoking cessation was checked only by telephone restrict the interpretation of the results. The most important aspect of this study is related to the emphasis on the need of offering treatment to patients with psychiatric disorder, except for situations in which there are severe symptoms and smoking cessation may exacerbate the disease. In such cases, patients should be more closely controlled before beginning the treatment.

Also in the current issue of the journal, Souza et al.[7] present a study using the Brazilian version of the Modified Reasons for Smoking Scale, comprising 21 structured questions grouped in several different combinations that characterize seven motivational domains associated with smoking. This is the first Brazilian study to be published using this scale, which has been recently validated for the Portuguese language by the same authors.[8]

The authors based the importance of the study[7] on the fact that the reasons leading individuals to smoke are not restricted to nicotine dependence, since there are also behavioral and psychosocial components which have not been well understood yet and whose dimension could be better measured by this scale, thus serving as an additional supportive component for the programs of smoking cessation. The study revealed that the scale presented adequate factorial structure and psychometric properties, showing the lowest scores in the following domains: dependence, tension reduction/relaxation, and hand-mouth activity, which were significantly associated with lower scores on the Fagerström nicotine dependence test.

In spite of the evidence that smoking nicotine-free cigarettes does not cause dependence, reinforcing the role played by nicotine in the addiction,[9] there are not doubts regarding the obscure aspects related to the pharmacology of nicotine and the presence of other factors involved in smoking persistence.[9,10]

Panday et al., in a study conducted in South Africa,[11] revealed that 11.6% of the smokers aged 14-16 years, who smoked an average of 6-10 cigarettes/week, had high dependence and 56% of them reported more than two symptoms of abstinence. The reasons why individuals with high dependence or presenting with abstinence symptoms are able to smoke less than 10 cigarettes a week are not clear yet. Furthermore, there are studies evidencing failure in the use of medication, such as nicotine replacement and bupropion, to aid young people to quit smoking.[6]

On the other hand, Volpp et al.[12] presented new data in a recently published study involving 878 smoking employees of a large company, with approximately 50% of them receiving counseling and financial incentives to quit smoking and the other half receiving only information. Those smokers who received financial incentives achieved a success rate after 12 months of 14.7% compared to 5% in the group that received only information (odds ratio 3.28-fold higher). The success rate was confirmed using urinary cotinine measurement. The reasons for that result have not been well explained, but this finding can serve as a stimulus for this type of treatment, since it is less expensive and smokers do not need to use medication, which makes them less vulnerable to adverse effects.

The reasons for smoking scale used by Souza et al.,[7] as stated by the authors, has been rarely used outside the United States, and few studies on its use have been published even in the United States. The actual clinical usefulness of its administration in programs and actions aimed at smoking cessation still need to be demonstrated. The validation for the Portuguese language[8] and the consistent data regarding its use, as demonstrated in the study by Souza et al.,[7] open this opportunity to Brazilian researchers.

The difficulties faced by smokers to quit smoking make it very important to improve the methods to help them, which is the objective of the studies published in the current issue.

Ubiratan de Paula Santos
Coordenador do Ambulatório de Cessação de Tabagismo da Disciplina de Pneumologia do InCor- Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - HCFMUSP, São Paulo, SP

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Use of C-reactive protein to prevent atherosclerosis: between Jupiter and Mars

There is no doubt about the fact that lowering cholesterol levels using statins decreases the mortality and morbidity rates caused by cardiovascular diseases in individuals who do not present with a previous manifestation of atherosclerosis.[1,2] However, the real benefit and cost-effectiveness ratio of these treatments will depend on the absolute risk of cardiovascular outcomes. The current guidelines recommend that the calculation of the cardiovascular risk in 10 years should be based on age, total cholesterol levels, HDL-cholesterol, blood pressure, and smoking to guide the beginning and intensity of the treatment with statins in primary prevention patients.[3] Nevertheless, there is evidence that many patients who could have a clinical event in the future are not treated because they are considered to be at low cardiovascular risk.[4] It is the so-called "detection gap," which affects mainly younger individuals and women. Several tools have been used to improve the stratification of patients' cardiovascular risk, from research on subclinical atherosclerosis with imaging studies[5] to the use of laboratory biomarkers such as high sensitivity C-reactive protein (CRP),[6] among others.

CRP is an acute-phase plasma protein mainly produced by hepatocytes. It is a member of the pentraxin family.[6] There is much evidence of its role in the atherogenesis, such as: increased expression of VCAM, ICAM-1, E-selectin, MCP-1, increased smooth muscle cell migration, in vivo endothelial dysfunction, among others.[6] Several clinical trials have demonstrated its role as a marker of cardiovascular risk. The following are the most important ones: Physicians Health Study (PHS), Women's Health Study (WHS), Honolulu Heart Study, Nurses Health Study, MONICA (Monitoring Trends and Determinants in Cardiovascular Disease), and Cardiovascular Health Study.[7] Based on such evidence, CRP was included in the 4th Brazilian Guideline of Atherosclerosis Prevention as a risk aggravator, that is, high CRP levels could cause an increase in the cardiovascular risk and change the treatment goals.[3] Ridker et al. suggested the inclusion of CRP in a clinical score (Reynolds Risk Score) in order to improve the stratification of cardiovascular risk.[8] However, recent studies using new statistical methods to test the presence or absence of the additional utility of biomarkers compared the traditional risk factors have not confirmed the usefulness of CRP as a risk marker.[9,10] Currently, it is well known that the definition of the traditional measures of association, such as odds ratios or hazard ratios, are not enough to assess the real predictive value of a biomarker with regard to the complete set of risk factors for atherosclerosis.[11] Lloyd-Jones et al.[9] analyzed the value added by the CRP to the traditional risk factors in large clinical trials using c-statistics and areas under receiver-operating characteristic curves (AUCs) for models with traditional risk factors before and after adding CRP: WHS 0.81 vs. 0.81; Rotterdam Study 0.746 vs. 0.748; MONICA 0.735 vs. 0.750; Reykjavik Cohort 0.645 vs. 0.65; Framingham Offspring Study 0.74 vs. 0.74; Framingham Heart Study 0.80 vs. 0.80; Cardiovascular Health Study 0.73 vs. 0.72. These authors concluded that the determination of CRP does not change the AUC, that is, it does not improve risk discrimination compared to the traditional risk factors and, therefore, there is not consistent evidence to recommend its use in the routine clinical practice.[9] More recently, a Sweden cohort study, involving 5,067 participants without cardiovascular disease, assessed the role of six biomarkers, among which was CRP, in the prediction of cardiovascular risk.[10] During a median follow-up of 12.8 years, there were 418 cardiovascular and 230 coronary events. CRP did not increase the discriminant power of the traditional risk factors when it was analyzed alone for cardiovascular events (increase in c-statistics of 0.003; $p = 0.14$) and it showed a slight increase when analyzed in combination with N-BNP (brain natriuretic peptide, increase in c-statistics of 0.007; $p = 0.04$).[10] The study also concluded that the biomarkers could be able to produce a slight increase in the reclassification of intermediate-risk individuals; however, this would be the case mainly when reclassifying to a lower risk level,[10] which would not change the clinical practice, since the treatment of the present risk factors would not be interrupted. The studies by Lloyd-Jones et al. and Melanger et al.[9,10] raised questions about the biomarkers and initiated a great debate within the context of preventive cardiology over the use (or not) of CRP to assess cardiovascular risk.

Several studies have demonstrated that statins, in addition to lowering LDL-cholesterol (LDL-C), can also reduce CRP levels, which would be a sign of an anti-inflammatory effect of this class of drugs. The natural question that results from that is: what is the clinical consequence of that? The PROVE-IT TIMI-22 study assessed the effects of an intensive regimen (atorvastatin 80 mg/day) vs. a moderate regimen (pravastatin 40 mg/day) to lower the cholesterol levels of acute coronary syndrome patients. In addition to demonstrating the benefit of the intensive regimen in terms of a more significant reduction of cardiovascular events (RR = -16%, number needed to treat = 25), the study also showed that the patients who achieved the dual goal of LDL-C < 70 mg/dL and CRP < 2 mg/L comprised the subgroup that had the highest decrease in the number of events, even when compared to the individuals who achieved only one of the goals.[12] The A to Z study demonstrated a similar finding in patients with acute coronary syndrome using intensive and conservative simvastatin strategies.[13] The REVERSAL study, which measured the progression of atherosclerosis using intravascular ultrasonography in intensive and moderate treatments of cholesterol reduction, demonstrated that the individuals who remained below the median for LDL-C and CRP had a slower rate of progression of atherosclerosis.[14] Thus, new hypotheses regarding the dual goal attainment started to be proposed: reduction of cholesterol and reduction of the inflammatory process. The JUPITER study (Justification for the Use of Statins in Primary Prevention: an International Trial Evaluating Rosuvastatin) was designed with the purpose of testing the hypothesis that patients with normal LDL-C (< 130 mg/dL) and elevated CRP (> 2 mg/L) might benefit from statin treatment (rosuvastatin 20 mg/day).[15]

The JUPITER study included primary prevention patients, 50-year-old or older men, 60-year-old or older women, all of them with LDL-C lower than 130 mg/dL (median 108 mg/dL) and CRP higher than 2 mg/L (median 4.25 mg/L).[15] The primary end point

included myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death for cardiovascular causes. The study included 17,802 patients, who were randomly assigned to rosuvastatin 20 mg/day or placebo. The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin lowered LDL-C levels by 50% and CRP by 37%. The rates of primary end point were 0.77 and 1.35 per 100 person/year of follow-up, respectively for rosuvastatin and placebo (the hazard ration for rosuvastatin was 0.56; 96%CI 0.46-0.69, $p < 0.00001$). There was also a decrease in the rate of death from any cause in favor of rosuvastatin (hazard ratio 0.80; 95%CI 0.67-0.97; $p = 0.02$).[15]

A prospective analysis of the JUPITER study also revealed that there was a higher decrease in the vascular events in patients who achieved LDL-C < 70 mg/dL and CRP < 2 mg/L compared to individuals who achieved one or none of these goals.[16] The results of the PROVE-IT and JUPITER studies triggered another great debate: should CRP levels be monitored to assess the effectiveness of the treatment in the same way as the cholesterol levels? Should a dual goal, LDL-C and CRP, be set to improve prevention? In addition to being used for risk assessment, should CRP also be used to monitor the treatment? This issue has been the reason for strong debates in cardiology. Even though we strongly believe in the inflammatory theory of atherosclerosis, in our opinion, having a dual-goal treatment incorporated into the guidelines is a very distant reality. Since statins, in addition to lowering CRP levels, also reduce cholesterol, (and as a matter of fact, these drugs were created and approved with that purpose), it is difficult, even using complex statistical methods, to separate the isolated effects of reduced cholesterol and CRP levels on the clinical outcomes.[16] Therefore, it is not possible to demonstrate the isolated benefit of improving the inflammation caused by these drugs. To solve this problem, there is need of further studies assessing drugs that reduce only the inflammatory process without affecting the lipids, and we are very far from achieving that.

According to our point of view, the immediate consequence of the JUPITER study will be to change the goals of LDL-C levels for patients at moderate risk (risk > 10% in 10 years) for at least < 100 mg/dL or < 70 mg/dL. However, even though it is a multicentric trial of great impact, the JUPITER study also raises some questions that remain unanswered. The lack of inclusion of patients with CRP < 2 mg/L challenges the fact that CRP itself really indicates a group of individuals that would benefit from the use of statins. If the authors of the JUPITER study really wish to test CRP as a tool to indicate the use of statins, they should include a group with CRP < 2.0 mg/L, randomized or not for statins. We should keep in mind that a reduction of 53 mg/dL in the LDL-C, such as the one found in the JUPITER study, could reduce cardiovascular risk, regardless of the baseline values of LDL-C, in more than 25% according to the meta-analysis of the Cholesterol Treatment Trialists' (CTT).[1] Half of the patients involved in the JUPITER study (n = 8,895) were not at low risk and, therefore, had a Framingham score higher than 10%, that is, they represent a population in which the benefit of using statin would be expected even with median LDL-C of 108 mg/dL.[15] The duration of follow-up of the JUPITER study was short (median = 1.9 years), which makes it impossible to draw conclusions regarding a longer use of statins in this population. However, there is an important aspect that diminishes the relevance of this limitation, the longer the cholesterol levels are reduced using statins the stronger the impact of the benefits reached.[1]

Another issue is related to the impact of the JUPITER study in terms of public health. Should all patients who meet the inclusion criteria of the JUPITER study be treated with statin? What is the cost-benefit ratio? How many individuals in Brazil would fit this profile? We cannot answer that, but an estimate from the USA calculated that 6.5 million of U.S. individuals would be potential candidates for treatment with statin after the JUPITER study.[17] We should consider that risk factors such as obesity and smoking also increase CRP and these patients should always be stimulated to change their lifestyle. We still believe that the treatment of patients should be conducted according to the current guidelines, mainly based on the cardiovascular risk, keeping in mind that the higher the risk the higher the benefit of the treatment with statins. Individuals at higher risk should obviously be treated with a more intensive regimen regarding LDL-C, and the JUPITER study corroborates the data from previous studies.[1,2] Finally, according to our point of view, the use of CRP in the clinical practice will certainly depend on better designed clinical trials; however, to date, its use seems to depend on the caprices of the Gods of Olympus: it depends on the good will of Jupiter, the father of all gods and, due to all the debate going on, it depends on his son Mars, the god of war.

Marcio H. Miname1
Raul D. Santos2*

Médico, Pós-Graduando da Disciplina de Cardiologia da Faculdade de Medicina da Universidade de São Paulo - FMUSP, São Paulo, SP

Professor Livre Docente da Faculdade de Medicina da Universidade de São Paulo – FMUSP; Diretor da Unidade Clínica de Lípides Instituto do Coração –InCor - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo, SP

***Correspondence:**
Unidade Clínica de Lípides InCor-HCFMUSP
Av. Dr. Eneas C Aguiar, nº 44 – 2º andar - Sala 4 -Bloco 2
São Paulo – SP, Brazil
Cep: 05403-900
E-mail: raul.santos@incor.usp.br

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