What is optimal medical therapy?

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Abstract: While the enthusiasms triggered by revascularization procedures in chronic ischemic syndromes are fading, medical therapy is regaining a central role in the management of this condition. The latest guidelines from both sides of the Atlantic recommend medical therapy as the initial management and stress the need for either "maximal" or "optimal" or, more recently, "guideline-dictated" medical therapy, which should include one or two antianginal agents. The limitations of these recommendations in this era of growing awareness of the multifactorial nature of myocardial ischemic syndromes are briefly summarized. ■ *Heart Metab*. 2019;78:17-19

Treatment of any medical condition is aimed at prolonging patients' survival and at improving quality of life. The efficacy of any medical (or surgical) therapy should be established with regard to its effects on these two parameters. These elementary concepts are not so obvious when it comes to treatment of chronic myocardial ischemic syndromes. The first point is that, as of today, no treatment has been conclusively shown to improve mortality and/or morbidity in chronic ischemic syndromes.[1] So we cannot look at survival as a ranking parameter among possible treatments, nor can we promise patients that they will live longer with any treatment. In practice, to identify the "best possible," if not the "optimal," therapy, we can rely only on quality of life, survival being of little, if any, help.

Acceptance of quality of life as the primary target of treatment has several relevant implications. Quality of life is not always easy to assess, even applying established scoring systems, like the Seattle Angina Questionnaire, because angina perception may be influenced by factors not directly related to ischemia severity and/or duration, including social, economic, psychological, and environmental conditions.[2] There-

fore, it does not directly express treatment efficacy. Moreover, the precipitating mechanisms of ischemia may change in time or overlap, modifying the response to treatment.[3]

Recently, "chronic myocardial ischemia" is being perceived more and more as a lifelong condition, that will require lifelong treatment. This new perception calls for greater attention to the side effects and clinical tolerability of drugs. It is quite obvious that, if the primary goal of treatment is to help patients to live a better life, agents that, in the long run, may worsen the quality of life (because of depression, fatigue, constipation, erectile dysfunction, etc) should be avoided. So, in the definition of "optimal medical therapy," not only efficacy but also tolerability and lack of serious side effects become relevant.

Current guidelines have given conflicting recommendations, shifting from "optimal" to "guidelines-dictated" medical therapy.[3] When the word "optimal" was used, the implication was that therapy should include "one to two antianginal" medications in order to be "optimal." It is difficult to accept this statement, purely based on the number of prescribed drugs, with no consideration of the efficacy in ameliorating patients' symptoms.

Apparently, the more recent trend to recommend "guidelines-dictated" medical therapy should be easier to follow, were it not for the major limitations of this approach.

Most current guidelines propose a ranked list of antianginal medications, identifying first-line agents and second-line agents. To further complicate medical decisions, guidelines admit that there are circumstances where the second-line agents can become first-line.[3]

This approach has been recently challenged, based on the following observations:

1. In these therapeutic recommendations there is no effort to match the mechanism of action of the antianginal agent with the precipitating mechanism of myocardial ischemia. This is even more surprising in guidelines that acknowledge the multifactorial nature of chronic ischemic syndromes, which can be associated with fixed or dynamic stenosis, with focal or diffuse coronary vasospasm, with microvascular dysfunction, and possibly with other, not yet well understood mechanisms.[3,4]

2. These recommendations do not consider the clinical profile of the patients who, more and more often, present comorbidities that can contraindicate some of the "first-line" agents: hypertension, diabetes, peripheral vascular disease, depression.[5]

3. These recommendations do not appear to be evidence-based. In a recent analysis of published trials over the last 50 years, no superiority emerged for any of the agents listed as first-line versus those listed as second-line.[6,7]

It must be admitted, however, that most studies have major methodological limitations, because patients were enrolled independently of the pathogenetic mechanism of angina and this may explain why no superiority has ever emerged. In a more focused approach is it easy to predict that, eg, Ca-channel blockers would prove more effective and better tolerated than β-blockers if tested in a cohort of patients with vasospastic angina.[8] And most published trials focus exclusively on short-term efficacy, with limited if any data on long-term clinical tolerability. Probably, none of the two "first-line" agents would compare with trimetazidine in microvascular angina, in angina in patients without significant coronary obstructions, etc.[9] In addition, none would match trimetazidine in clinical tolerability in any patient subset. However, head-to-head comparisons have not been performed, and probably never will.

In addition, the ESC Guidelines distinguish between antianginal agents and "disease-modifying agents."[3] The second group includes aspirin, ACE inhibitors, and statins. Given the space limits of this manuscript, we will not discuss this second group, where the only novelty are recent data challenging the protective role of aspirin, and we will focus on the concepts that can help in prescribing the "best possible antianginal therapy."

How do we define the "best possible" treatment strategy for a patient with chronic myocardial ischemia? Once a clinical diagnosis of angina pectoris (as distinct from chest pain) has been established, a number of sequential steps should be considered.[10]

Based on a careful history-taking, clues as to the precipitating mechanism should be sought. When angina is easily predictable, being consistently associated with physical exercise, at a relatively constant workload, the presence of a severe stenosis as the main culprit for the symptoms is highly probable. Conversely, angina occurring in an unpredictable fashion and in the absence of any identifiable precipitating cause suggests functional factors.[11,12] Microvascular angina can be induced by exercise, but the threshold is highly variable and it is not associated with regional contractile dysfunction at echostress.[13-15]

In summary, right after the diagnosis of angina pectoris an effort is required to identify the most likely precipitating mechanism as a condition to wisely choose the best antianginal agent. Next, a detailed assessment of the cardiovascular system must be conducted to identify factors that can be useful in the choice of the best drug, such as heart rate, LV function, arterial pressure, etc. Lastly, attention must be paid to comorbidities.[16] With the progressive aging of angina patients, most of them suffer from systemic comorbidities, the most frequent being hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and peripheral arterial disease. putting together these three levels of information, a tailored choice for the antianginal medication can be made. Treatment should be started as soon as possible, ie, as soon as this information has been made available, and prolonged over time. Repeated checks for efficacy, patient compliance, absence of side effects, and possible changes in the pathogenesis of the ischemic syndrome, must be planned.

Following these steps, the efficacy and tolerability of life-long medical therapy can be substantially improved *(Table I)*. Admittedly, this is just an effort to be consistent with the new understanding of myocardial ischemic syndromes, and it is not based on scientific evidence, because there is very little evidence available, and it appears unlikely that we will have new trials in this area in the foreseeable future. But, this effort is inevitable, giving that alternative approaches, including PCI, still have to prove their superiority over medical therapy, and given that in the largest fraction of angina patients an invasive approach cannot be considered, either because no coronary obstructive lesion is found at angiography or because, if found, it is not amenable to revascularization.[17]

1. Identification of the precipitating mechanism(s) of angina
2. Profiling the patient's cardiovascular system
3. Diagnosing systemic comorbidities
4. Assessing patient's tolerance and side effects
5. Programmed checks for efficacy, side effects, angina mechanism

Table I *Steps from the diagnosis of angina pectoris to the best possible medical therapy.*

Conclusion

The growing awareness that myocardial ischemia can be precipitated by multiple mechanisms, and that these mechanisms may overlap in the same patient and may change in time, mandates a tailored approach to drug choice in chronic myocardial ischemic syndromes. An effort should be made in each patient to identify the mechanism responsible, to assess the global cardiovascular status, and to consider the comorbidities in order to identify the most appropriate drug combination. ∎

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