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CRITICAL ANALYSIS OF STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: HEART FAILURE

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: INSUFICIÊNCIA CARDÍACA

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ABSTRACT

In this article we critically analyze articles that have been important in modifying our clinical practice. In heart failure, a disease with characteristics of malignancy, it is always important to adopt conducts that improve this natural history. The first article is a European Registry, the BIOSTAT-CHF, that documents two important points in clinical practice. The first is that, despite scientific evidence, physicians continue to not prescribe drugs proven to be effective, as they should, and the second point is that, when they do prescribe them, they prescribe low doses that do not improve the patients' evolution. The second and third papers analyzed state that it is possible to improve the evolution of individuals with HF by reducing the heart rate when elevated, despite the prescribed treatment, and that a more complete neuro-hormonal block reduces mortality. In a disease with this potential severity, prescribing ivabradine and sacubitril/valsartan substantially improves the quality of life and reduces decompensation and mortality in people with HF. The fourth paper reports that discontinuation of treatment when reversion of cardiac remodelling occurs could lead to the worsening of the clinical situation in around 50% of patients and that its reintroduction promotes improvement again, but not for all worsening patients. These papers showed us ways to treat heart failure more effectively.

Keywords: Heart Failure; Heart Rate; Remodelling.

RESUMO

Neste artigo analisamos criticamente artigos que foram importantes para modificar nossa prática clínica. Na insuficiência cardíaca, doença com características de malignidade, é sempre importante adotarmos condutas que melhorem essa história natural. O primeiro artigo é um Registro europeu, o BIOSTAT-CHF, que documentou dois pontos importantes da prática clínica. O primeiro é que, apesar das evidências científicas, os médicos continuam não prescrevendo os medicamentos de comprovada eficácia como deveriam e o segundo é que quando os prescrevem indicam doses baixas e que essas doses baixas não melhoram a evolução dos pacientes. O segundo e terceiro artigos analisados documentaram que é possível melhorar a evolução dos indivíduos com IC, reduzindo a frequência cardíaca quando elevada, apesar do tratamento prescrito e que um bloqueio neuro-hormonal mais completo reduz a mortalidade. Prescrever, numa doença com essa potencial gravidade, a ivabradina e o sacubitril/valsartana melhora substancialmente a qualidade de vida e reduz a descompensação e a mortalidade nas pessoas com IC. O quarto artigo documentou que a suspensão do tratamento quando ocorre reversão do remodelamento cardíaco leva a agravamento do quadro clínico em cerca de metade dos pacientes e sua reintrodução promove melhora novamente, mas não de todos que pioraram. Os artigos indicam caminhos para um tratamento mais eficaz da IC.

Descritores: *Insuficiência Cardíaca; Frequência Cardíaca; Remodelação.*

In Cardiology, most approaches are based on Evidence--Based Medicine, especially for Heart Failure (HF). Treatment with neurohumoral blockers has revolutionized the treatment of HF, greatly improving its evolution, prognosis and quality of life for patients with this syndrome.[1] The management is well established and well known and had not been changed for years.[1]

Since beta-blocker studies in HF in the late 1900's and early 2000's, we had no new major drug studies that had an impact on their evolution, and at least two studies have recently appeared.[2,3]

Despite the documentation of the effectiveness of classic medicines and being well known, it is observed that the

prescription of these medicines is not performed as it should. Medications of proven efficacy: converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), spironolactone, and beta-blockers are prescribed at lower doses than those that have been shown to be effective.[1] Despite increasing doses over the years, there is still a significant percentage of prescriptions with low doses.

BIOSTAT-CHF Registry, a prospective study in which physicians were encouraged to prescribe neurohormonal blockers in order to reach full doses of these drugs, proved two important points that we observe in clinical practice.[4] Most physicians, even encouraged, did not prescribe drugs at doses considered optimal, with only about 60% prescribing ACE inhibitors or ARBs at 50% or more of the target dose and 40% prescribing beta-blockers at or above 50% of the target dose.[4] In this study conducted in Europe, it was curious to note that doctors from the Nordic countries achieved a significantly higher percentage of prescriptions at the recommended doses, a fact not observed in the same proportion in Latin countries. Doctors from the Nordic countries show us that it is possible to prescribe them at the correct doses.[4]

The other point that the study showed was that patients receiving drugs at doses below 50% of the target dose had worse outcomes, higher mortality and higher hospitalization rates. (Figure 1)[4]

I consider this article important because it is a real-life registry and it has been documented that it is possible to modify the evolution of HF patients, but in order to achieve this improvement it is necessary to prescribe drugs at doses that have been proven effective.[1,4] The Registry documented, in the real world, that using low doses did not improve patient outcomes and that prescribing higher doses (50% or more of full dose) significantly reduced mortality.[4] We need to keep this in mind and always try to prescribe medications at doses that have been shown to be effective.[1,4]

The reason for prescribing lower doses is usually due to the severity of the patients, many with low blood pressure, the lack of experience most doctors have in treating patients with HF, and especially because of the clinician's fear of side effects with increased doses. In Europe they added that Latino patients are smaller (lighter) than Nordic patients and this could influence tolerability to the prescribed dose, leading to lower dose prescriptions by Latino doctors, as noted in BIOSTAT-CHF Registry.[4]

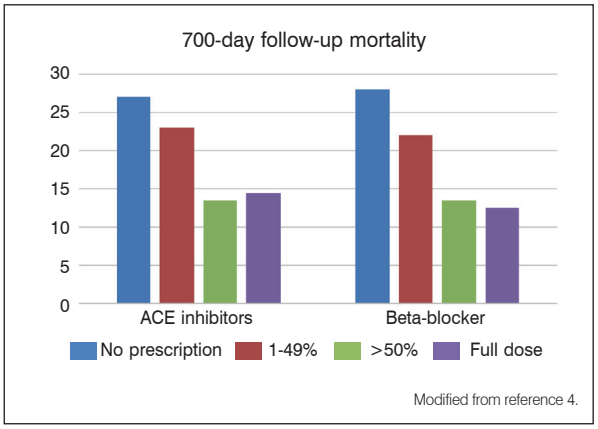

Figure 1. 700-day follow-up mortality according to prescribed dose of ACE inhibitors and beta-blocker.

Although treatment with neurohormonal blockers has substantially reduced mortality and improved patients' quality of life, compared with other diseases, HF remains severe disease and new treatments are needed and may further improve outcomes.

SHIFT STUDY

In 2010, we had the publication of SHIFT study, with an interesting and well-based proposal that reducing the heart rate of patients with sinus rhythm would improve patient outcomes.[2] The concept that reducing frequency would be important in HF was already known. based on observations from studies with beta-blockers.[1,5]

In analyzing the results of the beta-blocker studies, a relationship between the reduction in heart rate and mortality was documented. For each reduction of 5 beats per minute there was an 18% reduction in the mortality rate.[5]

Record analysis and several HF treatment studies have documented that heart rate above 70 beats per minute in patients is associated with increased mortality. Thus, today the high heart rate (above 70 bpm) should be recognized as a prognostic marker and should be treated and we should try to reduce it.[1,2,6]

In patients undergoing HF treatment, persistence of heart rate above 70 bpm often indicates that the beta-blocker dose is low and that the patient is not beta-blocked, either because he/she cannot tolerate the dose increase or because we have not increased the dose out of fear. In either situation, the frequency above 70 bpm is indicative of increased risk of hospitalization and death and should be addressed in our treatment.[2] It is important to note that even patients well treated with full doses of beta-blockers have a heart rate above 70 bpm. In two studies performed with patients receiving full doses of beta-blockers, we observed that over 35% of patients had heart rates above 70 bpm.[7,8]

Considering heart rate above 70 bpm as an indication of treatment, if the patient is in sinus rhythm with the treatment that we think is possible, we should prescribe ivabradine to reduce this high heart rate. The SHIFT study documented that these ivabradine-treated patients had an 18% reduction in the risk of death and hospitalization.[2] In a malignant disease such as HF, this reduction helps to change such a negative natural history.

In clinical practice, we should combat our inertia in the office and whenever we find a patient with a heart rate above 70 bpm we should intervene, trying to reduce it. Studies have shown that frequencies close to 60 bpm are those with the best outcome.[6] It is worth remembering that ivabradine is very well tolerated with minimal incidence of collateral events and that helping to control heart rate helps us reduce HF's morbidity/mortality.[2]

Frequency above 70 bpm is a limit to indicate the need for review of treatment, but the risk of death is greater the higher the frequency, so be aware of this easily obtainable propaedeutic data and upon finding the high frequency, take the attitude of optimizing the medications that were taking, if pertinent prescribe ivabradine, because

by reducing the high heart rate we will be improving the prognosis for the patient, reducing hospitalizations and mortality due to HF.[2]

PARADIGM-HF STUDY

In 2014, a new study resulted in a change in our management of HF.[3] PARADIGM-HF study compared the outcome of patients treated with enalapril, a proven HF treatment, with sacubitril valsartan, a new drug with a dual mechanism of action.[3] In addition to blocking the renin angiotensin system, as do ACE inhibitors and ARBs, neprilysin and angiotensin receptor (INRA) inhibitors block the breakdown of B-type natriuretic peptide (BNP) increasing vasodilation by increasing vasodilators such as natriuretic peptides.[3]

PARADIGM-HF study showed that this new drug was more effective than traditional enalapril, reducing mortality and HF hospitalizations by 20% in the primary endpoint, but also reducing all-cause mortality by 20% and hospitalizations by 21% In view of this result, in the presence of HF patients, we should prescribe this new drug, which is more effective than the usual treatment with ACE inhibitors and ARBs.[3]

It is important to remember that when exchanging the ACE inhibitor for sacubitril valsartan we should suspend the ACE inhibitor for 36 hours and then administer the new drug. If the patient is taking an ARB, the change may be immediate at the next dose.[3]

In a disease with characteristics of malignancy such as HF we should always prescribe the drugs that promote the best results.[1,3]

Similar to what we approach for ACE inhibitors, ARBs and beta blockers, sacubitril valsartan should be prescribed in order to reach the target dose. Lower doses do not promote the same results as higher doses. Thus the 24/26 mg twice daily dose may be prescribed to start treatment, but every 15 days we should increase the dose to 49/51 mg twice daily and then 97/103 mg twice daily. Higher doses promote more impactful results.

Experience has shown that the drug is well tolerated and promotes lower potassium elevation and lower urea and creatinine elevation than ACE inhibitors or ARBs.

One question that has arisen is whether in virgin HF patients we can start treatment with this drug, since PARADIGM--HF study switched from ACE inhibitor to the new drug. Given the more significant results with the new drug I see no need to start treatment with a less effective drug and then change if the result is not desired.

Since the launching of sacubitril valsartan we should continue to prescribe triple therapy with a beta-blocker, spironolactone and now sacubitril valsartan so that our patients have a chance to have a better outcome.[1,3]

TRED-HF STUDY

The last study we selected was TRED-HF published in 2019 which addresses the possibility of drug withdrawal after reversal of cardiac remodeling.[9] The question of whether or not to discontinue medication after an improvement in ejection fraction or reduction in cardiac dilation is recurrent and until this publication had not been scientifically researched.[9]

In this study, we randomly assessed the outcome of patients who had their treatment discontinued after elevation of the ejection fraction to values greater than 50% or that the final diastolic volume had normalized and had lower NT-proBNP levels at 250 ng/L. Fifty-one patients were included, divided into two groups, one in which treatment was continued and one in which it was discontinued. After six months of follow-up, 11 (44%) patients in the group who had the drugs discontinued achieved the primary objective of presenting loss of ventricular function characterized by reduction of ejection fraction by more than 10% or reaching values below 50% or dilation of the LV of 10% LV or reappearance of LV dilation.[9] After six months the groups were reversed and similar results were observed again with about 40% of patients showing worsening of ventricular function when treatment was discontinued.[9] With the reintroduction of treatment 85% went back to presenting ejection fraction greater than 50%.[9]

This result shows that about 40% of patients with dilated cardiomyopathy who had remodeling reversal (improvement in cardiac function) with treatment on discontinuation of therapy regained dilation and worsening ventricular function.[9] Reintroduction improves ventricular function, but not in all patients.

Taken together this study highlights that the risk of the patient worsening with discontinuation of treatment is greatly increased.

This study only included patients with dilated cardiomyopathy and we do not know if these results apply to HF of other etiologies. The sample is small and does not allow analysis of subgroups that could indicate which patients would have worse outcome with treatment discontinuation.

When addressing HF, a severe, evolutionary disease with characteristics of malignancy, the evidence indicates that treatment improves its prognosis. The best result is observed with the adoption of the best existing therapeutic scheme, using all existing "weapons" to fight this serious disease. In early or poorly symptomatic forms correct treatment prevents progression and in advanced forms reduces its severity. In patients who improve with treatment their suspension may be deleterious and it should be emphasized that treatment with low doses of drugs was not proven to be effective and should be avoided, and the doses of proven efficacy used in the studies should always be used. documented effectiveness.[1]

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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