How can we know if treatment for heart failure is effective?

Como saber se o tratamento da insuficiência cardíaca é eficaz?

Juliano Novaes Cardoso[1,2], Carlos Henrique Del Carlo[1,2], Milena Curiati[2], Cristina Martins dos Reis[2], Euler Brancalhão[2], Marcelo Lima[1,2], Nilson Aranha[2], Ana Lúcia Zarzana[2], Antonio Carlos Pereira Barretto[1,2]

Received from the Cardiology Service of Hospital Santa Marcelina, São Paulo, São Paulo (SP), Brazil.

ABSTRACT

Heart failure is a disease that progresses with high morbidity and mortality, but the correct treatment using neurohormonal inhibitors could alter its natural history. Although more and more patients have been treated, drugs are sometimes prescribed at doses lower than those known to be effective. In heart failure, a marker of treatment efficacy is lacking, since symptomatic improvement does not indicate that the patient will remain stable in the long term. The aim of this study was to evaluate the need for a marker of improvement during treatment. Reverse remodeling, present in clinical trials of drugs that reduced the mortality of patients with heart failure, is a marker of good response to treatment and can be used as a marker of treatment efficacy. Lack of reverse remodeling is indicative of greater severity of the case or of insufficient treatment. The same is true of the analysis of hemodynamic response when there is a reduction in intracardiac pressures, documenting that the treatment is effective. The persistence of heart rate above 70 bpm is another important marker of poor prognosis, and indicative of the need for treatment optimization. Reverse remodeling, improved ejection fraction, hemodynamic improvement, and reduction in heart rate are markers of treatment efficacy and are followed by significant reduction in mortality, and may be used to guide treatment.

Keywords: Heart failure/mortality, heart rate, brain natriuretic peptide/blood; Peptide Fragments/blood; angiotensin converting enzyme inhibitors/therapeutic use; Diuretics/therapeutic use; Prognosis

RESUMO

A insuficiência cardíaca é uma doença que evolui com alta morbimortalidade, mas o tratamento correto, que emprega bloqueadores neuro-hormonais, pode modificar sua história natural. Embora cada vez mais os pacientes recebam tratamento, muitas vezes os fármacos são prescritos em doses menores do que as reconhecidas como eficazes. Na insuficiência cardíaca, falta um marcador de eficácia do tratamento, pois a melhora sintomática não indica que o paciente permanecerá estável em longo prazo. O objetivo deste estudo foi avaliar a necessidade de emprego marcador de melhora durante o tratamento. A reversão da dilatação cardíaca, presente nos ensaios clínicos dos fármacos que reduziram a mortalidade dos portadores de insuficiência cardíaca, é um marcador de boa resposta ao tratamento e pode ser empregada como marcador de eficácia do tratamento. A ausência de reversão é indicativa de maior gravidade do caso ou de tratamento insuficiente. O mesmo é verdadeiro em relação à análise da resposta hemodinâmica, quando ocorre redução das pressões intracardíacas, documentando que o tratamento está sendo eficaz. A persistência de frequência cardíaca acima de 70 bpm é outro marcador importante de pior prognóstico e indicativo de necessidade de melhora no tratamento. A reversão da dilatação cardíaca, a melhora da fração de ejeção, a melhora hemodinâmica e a redução da frequência cardíaca são marcadores de eficácia do tratamento e são acompanhadas de redução significativa da mortalidade, podendo ser empregadas para orientar o tratamento.

Descritores: Insuficiência cardíaca/mortalidade; Frequência cardíaca; Peptídeo natriurético encefálico/sangue; Fragmentos de peptídeos/sangue; Inibidores da enzima conversora da angiotensina/uso terapêutico; Diuréticos/uso terapêutico; Prognóstico

INTRODUCTION

Heart failure (HF) is a prevalent disease with high morbidity and mortality, which, in advanced forms, has malignant characteristics[1]. The treatment, using angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, spironolactone, eplerenone, hydralazine and nitrate provides improvement of symptoms and reduction in mortality of patients with HF[1-6]. It is also important to remember that these drugs should be used in doses optimized to improve outcome in HF patients, as it was demonstrated in large studies[1-7].

However, in HF treatment monitoring, there is not an objective marker of efficacy because symptomatic improvement does not indicate that the patient will remain stable in the long term. The aim of this study was to evaluate the need for the use of improvement markers during treatment.

1. Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil.
2. Hospital de Santa Marcelina, São Paulo, SP, Brazil.

Date of submission: Aug 21, 2012 - Accepted: 08/06/2013
Conflicting interests: none.

Correspondence address:
Juliano Novaes Cardoso
Rua Joaquin Ferreira 147/161 A2 – Água Branca
CEP: 05033-080 – São Paulo, SP, Brasil
E-mail: jnovaescardoso@yahoo.com.br

We reviewed articles in Portuguese and English, available in PubMed and SciELO databases. We selected the most clinically relevant articles. The keywords defined were: heart failure, heart rate and mortality.

Neurohormonal blockade

Studies show that the use of drugs that block the neurohormonal system (ACEI, ARB, beta-blockers, spironolactone and eplerenone) provides a reduction in mortality in HF[4-6]. In one study[1], there was a 50% reduction in mortality in the first year of follow-up in a population admitted between 2005 and 2006 compared to a population admitted in the year 2000. This occurred due to the more frequent use of drugs blocking the neurohormonal system. In HF treatment, the guidelines should be followed, but usually there is no objective data to indicate whether the prescribed treatment is correct and effective[2,3].

Through clinical evaluation, the reduction in symptoms is a strong indication that the patient is improving and that the treatment is thus being effective. Patients in functional class II live longer and better than those in functional class III or IV. Thus, symptomatic improvement is a good indicator of treatment efficacy, but in many situations, this information may not accurately assess the prognosis of the disease[7]. Furthermore, symptoms can be relieved with the prescription of diuretics, which are recognized as drugs that do not have a great influence on the change of prognosis, since they seem not to reduce mortality related to HF[8].

B-type natriuretic peptide

B-type natriuretic peptide (BNP or pro-BNP) dosage was tested during patient follow-up and assessed as a test that can help showing whether treatment is being effective[9-11]. In the study STAR-BNP, the treatment guided by BNP levels was more effective in reducing events than the treatment only guided by clinical parameters[9]. Patients who had treatment guided by BNP levels received higher doses of diuretics, ACE inhibitors and beta-blockers and were less readmitted than those based only on purely clinical data[9]. However, the results of randomized trials comparing the effectiveness of knowledge or not of the levels of BNP/proBNP to guide the need for HF treatment optimization were not homogeneous and some did not document the benefit observed in the study STAR-BNP[9-11]. When serial dosage is used, a reduction in levels with the treatment is indicative of better progress, and persistence of high levels may indicate greater severity of illness or need for revision of the treatment regimen[12]. When used with discretion, it is especially useful in cases of doubt, but its routine use is not a consensus to guide the optimization of treatment.

Hemodynamic evaluation

Repeated hemodynamic measurements have proven to be a useful technique in guiding treatment[13-15]. In decompensated HF, the use of hemodynamic echocardiography helps identifying whether the patient is compensated or not, information that allows treatment orientation, to intensify or not the prescription of drugs[13]. The prescription of higher doses of vasodilators, or the addition of hydralazine and nitrate, led to better compensation of these patients and better outcome after discharge[13]. CHAMPION study showed that the use of an implanted device to assess the pulmonary capillary wedge pressure has allowed demonstrating that it was high in many cases. This procedure allowed us to identify patients who could have their treatment intensified with increased doses of vasodilators, especially hydralazine and nitrate. There was a reduction in high pressure and in the incidence of death and hospitalization due to worsening of HF[15]. Data from these studies have documented the importance of obtaining objective numbers to indicate whether a therapy regimen was effective or not. Some of these patients identified as having high pulmonary capillary wedge pressure have not showed clinical symptoms; however, the optimization of treatment based on hemodynamic data resulted in better progress. Interestingly, the best result in these studies was always associated with increased doses and more intense treatment, suggesting that in most advanced HF, hemodynamic and neurohormonal changes are more intense and require intensified treatment, regardless of the clinical situation[13-15]. This technique should be increasingly employed since it has been proven effective; however, the costs may reduce its applicability[15].

Ventricular remodeling

HF is usually a progressive disease and patients have ventricular remodeling, with increasing cardiac dilatation, and increasing reduction in ejection fraction[16-18]. Treatment with ACE inhibitors, ARBs, beta-blockers and spironolactone modifies such course, reversing cardiac dilatation and improving ejection fraction[2,3]. This reversal of cardiac dilatation is another way to evaluate whether the treatment of HF is being effective. An effective treatment should reverse cardiac remodeling. It is noteworthy that all effective drugs, and procedures such as cardiac resynchronization, provide reverse remodeling. This reversal has been demonstrated in studies with ACE inhibitors, ARBs, beta-blockers and spironolactone[18-22]. Non-reversal signals that drug doses prescribed are insufficient or that the severity of the disease is so great that the patient does not respond as desired to the proposed regimen.

Although the analysis of reverse remodeling has not been systematically used as a guide to check treatment effectiveness, several studies have shown that patients who have had reverse remodeling progressed in a better way compared to patients who did not show this reverse remodeling[16,18,21,22]. In the study by Cioffi et al., patients who had reverse remodeling presented a mortality of about 10% in the first year of follow-up, compared to 30% in those with no reverse remodeling[21].

Reverse remodeling is especially observed with the treatment with beta-blockers[18,21-23]. The FAST-Carvedilol study revealed that reverse remodeling occurred in the first three months of treatment in the group receiving the higher dose of carvedilol (mean dose 16.10mg twice daily *versus* 6.99mg twice daily) (Figure 1)[23].

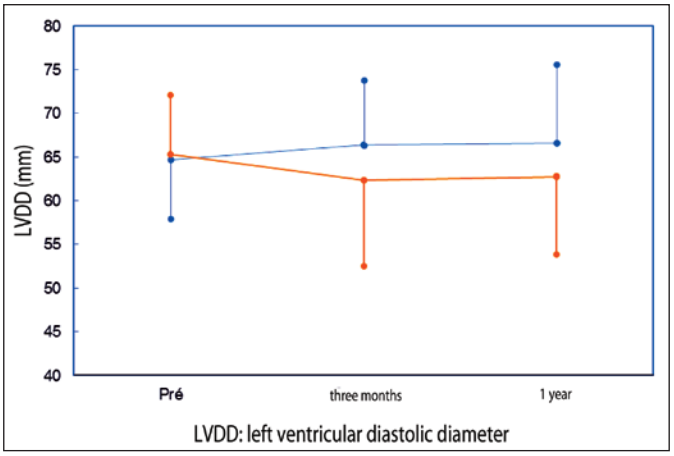
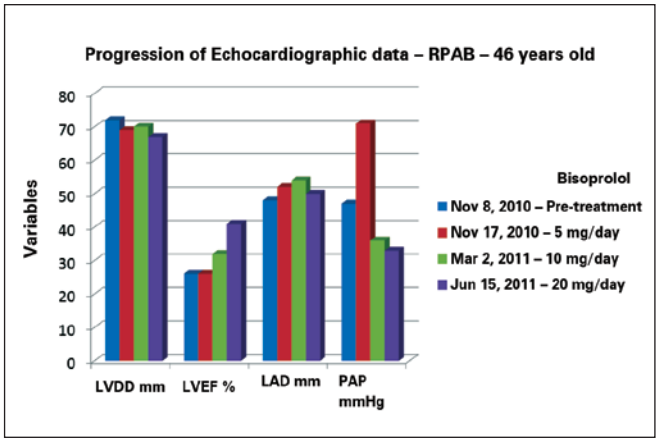
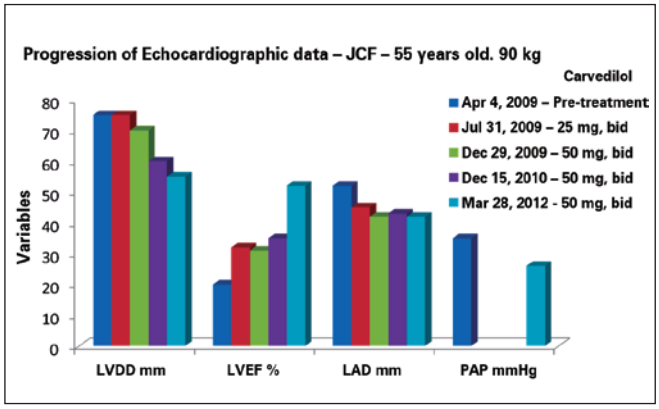


Figure 1. Reverse remodeling observed[23].



LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; PAP: pulmonar artery pressure.

Figure 2. Progression of reverse remodeling observed in a 46-year-old patient from March 2, 2011, when a dose of bisoprolol was increased to 20 mg/day.



LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; PAP: pulmonar artery pressure.

Figure 3. Progression of reverse remodeling observed in a 55-year-old patient from July 31, 2009, when a dose of carvedilol was increased to 50mg, bid.

Thus, after instituting HF treatment, doses should be optimized, as recommended by guidelines, always seeking to prescribe the drugs in doses that have been used in clinical trials. During its progress, a new echocardiographic study should be ordered, to check if treatment provided reverse remodeling. If so, treatment may be considered effective and there is no need to revise therapy doses or regimens[18,21-23]. If the reverse remodeling is not documented, it is a sign that the treatment is not effective and that it should be optimized, either with increased dose of the drugs or the prescription of new drugs, or the indication of some another procedure.

This procedure can be used as a guide to treatment, and in patients who showed no reverse remodeling, drugs doses, especially of beta-blockers, can be increased. This procedure has allowed ventricular reverse remodeling, which, with the usual dose, had not occurred. Figures 2 and 3 show two cases where the reverse remodeling occurred when the dose of beta-blocker was increased to 20mg/day, indicating that even with doses usually indicated by guidelines, some patients do not have the appropriate response, and higher doses become necessary. Importantly, in most cases, the prescription of drugs in the doses indicated by the guidelines will provide a good response in patients[24]. In the absence of response, increasing the dose may promote the expected response.

Heart rate

Increased heart rate (HR) is another marker that treatment may be insufficient. The decompensated HF usually occurs with increased HR, due to the activation of compensatory mechanisms, in particular by increased adrenergic activity[25]. In recent years, a growing number of studies have shown that the HR above 70 bpm per minute identifies patients at greatest risk of events[26-31]. The risk is proportionate to patient's HR[28,29]. On the other hand, reduction of this HR reduces these risks[26,27,31]. Thus, the identification of HR above 70 bpm in a patient with HF, with optimized treatment, identifies patients who should have their treatment incremented. Meta-analysis of studies with beta-blockers showed that part of the benefit of reverse remodeling is associated with decreased HR provided by treatment[30]. It is not only beta-blockers that provide HR reduction. Ivabradine is an if channel blocker and has proven effective in the reduction of HR in patients in sinus rhythm[26,27]. In the presence of FC above 70 bpm, the dose of beta-blocker can be increased, digoxin can be used or ivabradine can be prescribed. The SHIFT study showed that prescribing ivabradine reduces HR, and the incidence of events in these patients[27,31]. The HR reduction with ivabradine also reverses cardiac dilation[32]. In follow-up treatment, the HR that the patient presents with treatment should be considered. It is an easily obtained variable and literature data have shown that a not so increased HR is already a marker of poor prognosis[28,29,31].

Thus, in the presence of HR above 70 bpm, treatment should be reviewed and reduced.

CONCLUSION

In a disease such as HF, which has malignant characteristics and can greatly reduce quality of life and increase mortality, the well-oriented treatment is crucial to reverse these aspects. Treatment based solely on data from clinical improvement alone has not proven to be optimal. Measurements of hemodynamic variables, reverse remodeling, and HR make this evaluation more objective and may signal that the patient's treatment needs to be incremented.

REFERENCES

1. Barretto AC, Del Carlo CH, Cardoso JN, Morgado PC, Munhoz RT, Eid MO, et al. Hospital readmissions and death from Heart Failure- rates still alarming. Arq Bras Cardiol. 2008;91(5):335-41.
2. Bocchi EA, Braga FG, Ferreira SM, Rohde LE, Oliveira WA, Almeida DR, Moreira Mda C, Bestetti RB, Bordignon S, Azevedo C, Tinoco EM, Rocha RM, Issa VS, Ferraz A, Cruz Fd, Guimarães GV, Montera Vdos S, Albuquerque DC, Bacal F, Souza GE, Rossi Neto JM, Clausell NO, Martins SM, Siciliano A, Souza Neto JD, Moreira LF, Teixeira RA, Moura LZ, Beck-da-Silva L, Rassi S, Azeka E, Horowitz E, Ramires F, Simões MV, Castro RB, Salemi VM, Villacorta Junior H, Vila JH, Simões R, Albanesi F, Montera MW; Sociedade Brasileira de Cardiologia. [III Brazilian Guidelines on Chronic Heart Failure]. Arq Bras Cardiol. 2009;93(1 Suppl 1): 3-70. Portuguese.
3. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues DA, et al. Atualização das Diretrizes Brasileiras de Insuficiência Cardíaca Crônica 2012. Arq Bras Cardiol [Internet]. 2012[citado 2013 Jan 21];98(Suppl 1):1-33. Disponível em: http://publicacoes.cardiol.br/consenso/2012/Diretriz%20IC%20Crônica.pdf
4. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66547 patients hospitalized between 1986 and 1995. Circulation. 2000;102(10):1126-31. Comment in: Circulation. 2000;102(10):1076-8.
5. Lee DS, Mamdani MM, Austin PC, Gong Y, Liu PP, Rouleau JL, et al. Trends in heart outcomes and pharmacotherapy: 1992 to 2000. Am J Med. 2004;116(9):581-9.
6. Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmissions rate and mortality rates in patients with heart failure. Arch Intern Med. 2004;164(21):2315-20. Comment in: Arch Intern Med. 2005 ;165(11):1311; author reply 1311-2.
7. Muntwyler J, Abetel G, Gruner C, Follath F. One-uear mortality among unselected outpatients with heart failure. Eur Heart J. 2002;23(23):1861-6. Comment in: Eur Heart J. 2002;23(23): 1804-6.
8. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9): 797-805. Comment in: N Engl J Med. 2011;364(21):2066-7; author reply 2069; N Engl J Med. 2011;364(21):2066; author reply 2069; Praxis (Bern 1994). 2011; 100(11):671-2; N Engl J Med. 2011;364(21):2067; author reply 2069;. N Engl J Med. 2011; 364(9):877-8; Hosp Pract (1995). 2013;41(1):129-31; Ann Intern Med. 2011;155(2):JC1-5; Kardiol Pol. 2011;69(8): 869-70; Am J Kidney Dis. 2011;58(3):340-2; Curr Cardiol Rep. 2012;14(3):251-3; N Engl J Med. 2011;364(21):2067;author reply 2069.
9. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure. The STARS-BNP Multicenter Study. J Am Coll Cardiol. 2007;49(16):1733-9. Comment in: J Am Coll Cardiol. 2007;50(21):2097-8; author reply 2098-9.
10. Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, et al. Management of chronic heart failure guided by individual N-Terminal Pro-B-Type natriuretic peptide targets: results of the PRIMA (Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol. 2010;56(25):2090-100. Comment in: J Am Coll Cardiol. 2010;56(25):2101-4; J Am Coll Cardiol. 2011;58(1):90; author reply 90-1.
11. Felker GM, Hasselblad V, Hernadez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J. 2009;158(3):422-30.
12. Michtalik HJ, Yeh HC, Campbell CY, Haq N, Park H, Clarke W, et al. Acute changes in N-terminal pro-B-Type natriuretic peptide during hospitalization and risk of readmission and mortality in patients with heart failure. Am J Cardiol. 2011;107(8):1191-5.
13. Rohde LE, Palombini DV, Polanczyk CA, Goldraich LA, Clausell N. A hemodynamically oriented echocardiography-based strategy in the treatment of congestive heart failure. J Card Fail. 2007; 13(8):618-25. Comment in: J Card Fail. 2007;13(8):626-8.
14. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM Jr, Magalski A, Zile MR, Smith AL, Smart FW, O´Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW; COMPASS-HF Study Group. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure. The COMPASS-HF study. J Am Coll Cardiol. 2008;51(11):1073-9. Comment in: J Am Coll Cardiol. 2008;51(11):1080-2.
15. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377(9766):658-66. Comment in: Lancet. 2011; 377(9766):616-8; Lancet. 2011;377(9784):2176-7; author reply 2177; Lancet. 2011;377(9784):2176; author reply 2177.
16. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):VI17-23.
17. Wong M, Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure (Val-HeFT) echocardiographic data. J Am Coll Cardiol. 2004; 43(11):2022-7.
18. Cioffi G, Stefenelli C, Tarantini L, Opasich C. Chronic left ventricular failure in the community: prevalence, prognosis and predictors of the complete clinical recovery with return of cardiac size and function to normal in patients undergoing optimal therapy. J Card Fail. 2004;10(3):250-7.

19. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation. 1992;86(2):431-8.
20. Chan AK, Sanderson JE, Wang T, Lam W, Yip G, Wang M, et al. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. J Am Coll Cardiol. 2007;50(7):591-6. Comment in: J Am Coll Cardiol. 2007;50(7):597-9.
21. Cioffi G, Tarantini L, De Feo S, Pulignano G, Del Sindaco D, Stefenelli C, et al. Pharmacological left ventricular reverse remodeling in elderly patients receiving optimal therapy for chronic heat failure. Eur J Heart Fail. 2005;7(6):1040-8.
22. Hoshikawa E, Matsumura Y, Kubo T, Okawa M, Yamasaki N, Kitaoka H, et al. Effect of left ventricular reverse remodeling on long-term prognosis after therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and betablockers in patients with idiopathic dilated cardiomyopathy. Am J Cardiol. 2011;107(7):1065-70.
23. Melo D, Pereira-Barretto AC, Ramires JA. The impact f rapid use of beta-blockers on ventricular remodeling and mortality in end-stage heart failure [Abstract]. J Am Coll Cardiol. 2011; 57(Suppl A):17.
24. Pereira-Barretto AC. Reversibilidade da disfunção ventricular. Experiência clínica de consultório médico. Arq Bras Cardiol. 2001;77(6):541-4.
25. Braunwald E. The Denolin lecture. Congestive heart failure: a half century perspective. Eur Heart J. 2001;22(10):825-36.
26. Fox K, Ford I, Steg PG, Tendera M, Ferrari F; BEAUTIFUL investigators. Ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction (BEAUTIFUL): a randomized, double-blind, placebo-controlled trial. Lancet. 2008;372(9641):807-16. Comment in: Cardiovasc J Afr. 2008; 19(6):323-24, discussion 324; Curr Hypertens Rep. 2009; 11(1):45-7; Lancet. 2008;372(9656):2113; author reply 2113-4; Lancet. 2008;372(9641):779-80; Curr Hypertens Rep. 2009; 11(1):45-7; Curr Hypertens Rep. 2009;11(1):45-7.
27. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubosto-Brama A, Lerebours G, Tavazzi L; SHIFT investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. Lancet. 2010;376(9744):875-85. Erratum in: Lancet. 2010;376(9757):1988. Comment in: Lancet. 2010;376(9744):847-9; Lancet. 2010;376(9758):2069; author reply 2069-70; Curr Heart Fail Rep. 2011;8(1):1-3; Lancet. 2010; 376(9758):2069; author reply 2069-70; Kardiol Pol. 2010; 68(11):1299-302.
28. Castagno D, Skali H, Takeuchi M, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pfeffer MA, McMurray JJ, Solomon SD; CHARM Investigators. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. J Am Coll Cardiol. 2012;59(20):1785-95. Comment in: J Am Coll Cardiol. 2012;59(20):1796-8.
29. Cullington D, Goode KM, Clark AL, Cleland JG. Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target? Eur J Heart Fail. 2012;14(7):737-47.
30. Swedberg K, Komajda M, Böhm M, Borer J, Robertson M, Tavazzi L, Ford I; SHIFT Investigators. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: finding from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. J Am Coll Cardiol. 2012;59(22):1938-45. Comment in: J Am Coll Cardiol. 2012;59(22):1946-7.
31. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol. 2008; 101(6):865-9. Comment in: Am J Cardiol. 2008;102(4):506-7.
32. Tardif JC, O'Meara E, Komajda M, Böhm M, Borer JS, Ford I, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiographic substudy. Eur Heart J. 2011;32(20):2507-15. Comment in: Eur Heart J. 2011;32(20):2481-2; Nat Rev Cardiol. 2011;8(11):609.