Medical Treatment of Heart Failure with Reduced Ejection Fraction – Prognostic Indication

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Abstract

An up-to-date review on guideline directed medical therapies that aim to improve prognosis in HFrEF patients. Research on medical interventions that may improve prognosis in patients with chronic heart failure has had great success in the past decades. Therefore, there are well- established classes of drugs – ACEi, beta- blockers, MRAs – that should be used as first line treatment in all patients with heart failure. In the past few years newer therapeutic approaches have been shown to improve prognosis in patients with heart failure but, since the evidence generated by these newer classes of drugs is less than that of the first three classes of drugs these therapies should be implemented only after an initial treatment with the first line drugs has been implemented. This article reviews the advances that have achieved in the treatment of heart failure in terms of a prognostic benefit.

Keywords: Heart Failure; Guidelines; Therapy; Prognosis

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Introduction

Research on medical interventions that may improve prognosis in patients with chronic heart failure has had great successes in the past decades. Therefore, there are well-established classes of drugs – ACEi, beta-blockers, MRAs – that should be used as first line treatment in all patients with heart failure.[1] In the past few years newer therapeutic approaches have been shown to improve prognosis in patients with heart failure but, since the evidence generated by these newer classes of drugs is less than that of the first three classes of drugs these therapies should be implemented only after an initial treatment with the first line drugs has been implemented.

The main goals of medical therapy in heart failure are to prevent hospital admissions and to improve survival.[1] Because of detrimental effects on long term outcomes seen with some previously studied drugs despite showing promising effects on surrogate end points it has been required, by the main regulatory agencies (EMA and FDA), that all drugs before being approved for the treatment of heart failure were required to show a benefit on mortality and morbidity.[1]

Numbers Needed to Treat (NNT) have been used in the past to indicate the effectiveness of a given treatment. However, since treatments approved for the treatment of heart failure have been tested in different time periods and using different background therapies NNT will not be used in this article in order to avoid unfair comparisons between treatments that have not been tested head to head.

Neurohumoral antagonist drugs acting on the Renin Angiotensin Aldosterone System [ACE inhibitors MRAs and a dual vasopeptidase inhibitor] and on the Sympathetic Nervous Control of the cardiovascular system [beta-adrenergic blockers] have been shown to improve survival in patients with systolic HF and should be considered at different stages in the treatment of every patient. Drugs acting on the sequaele of neurohormonal activation such as the heart rate reducing agent ivabradine have also been shown to improve mortality and should also be considered when appropriate. These medications should be considered in all patients with chronic heart failure in conjunction with a diuretic when there is the need to relieve the symptoms and signs of congestion.[2–16] (Figure 1). Angiotensin II type I receptor blockers are often considered equivalent to ACEi but since they did not show any effect on overall mortality in patients with HFrEF, their use should be limited only to those patients intolerant of an ACE-inhibitor.[17–18]

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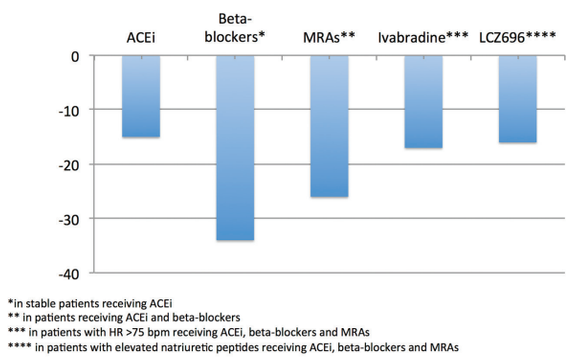

Figure 1. Drugs that reduce mortality in heart failure with reduced ejection fraction

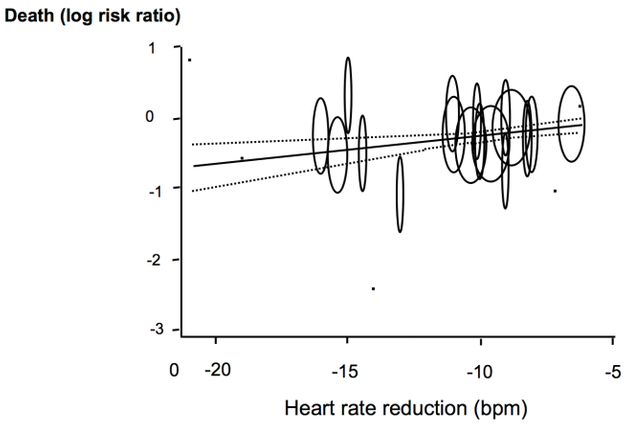

Figure 2. Relation between the magnitude of heart rate reduction and outcomes in heart failure (McAliser FA et al. Ann Intern Med. 2009: 150: 784–94)

Angiotensin-converting enzyme inhibitors [ACEi]

There is overwhelming evidence to support the use of ACEi in patients with heart failure. ACEi have been shown to reduce mortality and morbidity in patients with all different forms of heart failure and reduced ejection fraction (post-infarction, post-acute, chronic, left ventricular dysfunction).[2–4] Therefore, ACEi must always be considered in all patients with heart failure, NYHA class I-IV and an LVEF < 40%.[1]

Given their mortality benefit ACEi must represent the initial therapeutic choice, alone or in association with a diuretic, and their dose should be up-titrated to the evidence-based dose or, in any case to the maximum tolerated dose in order to achieve an adequate inhibition of RAAS.[3]

ACEi may increase K+ levels and therefore caution should be posed when they are administered to patients with elevated K+ levels while they are contra-indicated in patients with moderate hyperkalaemia (K+ > 6.0 mmol/L). Drugs or substances that increase K+ plasma levels such as K+ supplements and K+-sparing diuretics, e.g. amiloride and triamterene, may potentiate the effect of ACEi on K+ and their use must be restricted when an increase in K+ is observed. Dose adjustment may be needed in patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) and in those with arterial hypotension (systolic blood pressure < 90 mmHg).

Beta-Blockers

The pivotal trials with beta-blockers in heart failure were conducted in symptomatic patients despite treatment with an ACE inhibitor and, in most cases, a diuretic.[5–11] Although these treatments are regarded as complementary and most often a beta-blocker and an ACE inhibitor are started together after diagnosis of HFrEF there is no trial evidence to support this practice. Studies aiming at implementing beta-blockers before adequate up-titration of an ACEi have shown an increase in hospitalisations for heart failure.[10] Unlike ACEi, Beta-blockers should be initiated in clinically stable NYHA Class II-IV patients with LVEF <40%. Implementation of beta-blockers in patients not receiving adequate ACEi has been shown to increase hospitalisation rates. Therefore, it is not recommended to start a beta-blocker before having started an ACEi. However, there is agreement in the guidelines that beta-blockers and ACEIs can be started together in stable patients.[1]

The striking effect of beta-blockers in reducing the risk of sudden cardiac death and overall mortality observed in the past should be nowadays be reconsidered given the use of ICDs. It is most probable that the overall effect of beta-blockers on mortality will be maintained but the size of the effect will be probably lower than that predicted by the early studies in patients not having an ICD implanted.

It must be noted that most beta-blocker trials included patients with heart failure who were younger (mean age 61–64) than those seen in clinical practice (mean age >70). Furthermore, large international surveys have shown that only a minority of patients with heart failure receive beta-blockers at a dose that is recommended as target. This under-dosing may reflect a lack of tolerability in patients who are typically relatively old and have co-morbidities. However, the CIBIS-ELD study showed that only 20% of patients randomised to carvedilol or bisoprolol may tolerate full dose beta-blockade.[19]

Several meta-analyses have shown that the prognostic effect of beta-blockers is not related to the dose but to the degree of heart rate reduction supporting the prognostic importance of heart rate in heart failure (see Figure 2).

Recently, an individual patient meta-analysis of the large randomised placebo controlled studies has shown that beta-blockers have a neutral effect on mortality and morbidity in patients with HFrEF and atrial fibrillation.[20] Therefore, beta-blockers should only be considered for rate control in patients with HFrEF who are in AF. Their benefit is likely to be greater in those with high (>110 bpm) heart rate. Because of their anti-ischaemic effect beta-blockers should be always considered in patients with an ischaemic origin of HF.

Beta-blockers are contra-indicated in patients with symptomatic bradycardia and in those with second- or third-degree AV block unless they have been implanted with a permanent pacemaker. Beta-blockers are also contraindicated in patients with significant peripheral arterial disease and in those with critical limb ischaemia and in those with asthma or with a history of asthma. Although the new ESC/HFA guidelines suggest that if cardio-selective beta-blockers are indicated, asthma is not necessarily

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an absolute contraindication, the benefit/risk of these drugs in this class of patients is negative. Chronic Obstructive Pulmonary Disease is not a contra-indication for the use of beta-blockers in patients with heart failure.

Beta-blockers should be used with caution in patients with recent (< 4 weeks) exacerbation of heart failure (e.g. current or recent hospital admission with worsening HF), and in those with severe heart failure (NYHA class IV). In patients with signs of congestion – i.e. hypotension systolic < 90 mmHg, ascites, raised JVP, peripheral oedema – congestion should be relieved and 'euvolaemia' should be achieved before starting a beta-blocker.

In beta-blocker naïve patients it is always advisable to start with a low dose and to double the dose slowly at not less than 2-week intervals monitoring heart rate, blood pressure, and clinical status. When starting beta-blockers or during the up-titration phase it is important to detect potential clinical deterioration. Therefore, patients should be encouraged to weigh themselves daily in the morning after waking and to report any persistent weight increase of > 1.5–2.0 kg/day. In elderly and fragile patients as in patients with more advanced stages of heart failure a slower up-titration may be needed. Beta-blockers may induce fatigue through several mechanisms. If fatigue occurs the dose of beta-blocker should be halved.

Mineralocorticoid/aldosterone receptor antagonists [MRAs]

MRAs are drugs that block the receptors that bind aldosterone. First and second generation MRAs also bind, with different degree of affinity corticosteroid and sex steroid receptors. Newer MRAs have high affinity to block aldosterone receptors. Spironolactone and Eplerenone have been shown to reduce mortality and events in patients with HFrEF treated with an ACEi and a beta-blocker.[12–13] Potassium canrenoate is an active metabolite of spironolactone approved in some European Countries for the treatment of patients with HFrEF and it is the metabolite responsible for most of the pharmacodynamic effect of spironolactone.

MRAs are recommended in all symptomatic (NYHA II-IV) patients with HFrEF (LVEF ≤ 35%) already receiving an ACEi and a beta-blocker in order to reduce mortality and HF hospitalization. [1,12–13] MRAs are well tolerated and the occurrence of hyperkalaemia has been low in the randomised studies conducted with spironolactone and eplerenone. It is advisable, however, to start MRAs after having checked renal function and electrolytes (particularly K+), starting with a low dose (see above) and and up-titrating to target dose over 4-8 weeks after having checked K+ levels. Thereafter, K+ levels should be checked at 12 weeks; 6, 9, and 12 months and 4-monthly thereafter. A closer monitoring may be needed in patients with borderline high K+ levels. MRAs should be used with caution in patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2) and in those with elevated serum potassium levels (> 5.0 mmol/L). The dose of MRAs should be halved if K+ rises above 5.5 mmol/L or eGFR <30 mL/min/1.73 m^2. MRAs should be stopped and adequate measures should be undertaken if K+ rises to >6.0 mmol/L or eGFR <20 mL/min/1.73 m^2.

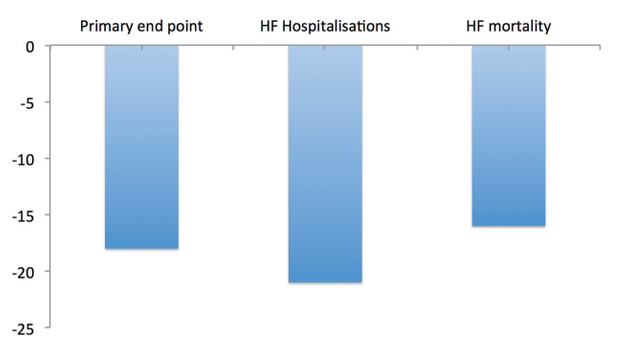

Figure 3. Effect of ivabradine on mortality and morbidity in patients with HFrEF (Svedberg K et al. Lancet. 2010 Sep 11: 376(9744): 875–885)

Ivabradine

Ivabradine is a drug that slows heart rate through inhibition of the If channel in the sinus node. The net effect of ivabradine is a prolongation of diastole with a prolongation of diastolic filling period. Unlike beta-blockers this effect is obtained with a preservation of ventricular relaxation and with lower left ventricular end diastolic pressures. Because of its specific effect on the sinus node ivabradine should only be used in patients in sinus rhythm.

Ivabradine reduced the combined endpoint of mortality and hospitalization for HF in patients symptomatic HFrEF with LVEF ≤ 35% in the SHIFT study (see Figure 3).[14–15] The benefits have been shown in patients often receiving treatment with a beta-blocker, an ACEI (or ARB), and an MRA. The SHIFT study has shown that the mortality benefit of ivabradine is related to its heart rate reducing effect and that is greatest in patients achieving a heart rate <60 bpm.[21] The combined analysis of the SHIFT study in patients with HFrEF and of the Beautiful study in patients with ischaemic left ventricular dysfunction have shown that treatment with ivabradine was associated with significant relative risk reductions in cardiovascular outcomes including 13% relative risk reduction for the composite of cardiovascular mortality and 19% for HF hospitalization alone. The analysis also showed significant relative risk reductions for the composite of cardiovascular mortality, HF hospitalizations, or myocardial infarction (MI); cardiovascular mortality and non-fatal MI; and MI hospitalization. [22] These findings support the importance of treatment with ivabradine for improvement of clinical outcomes in patients with LV dysfunction whether or not presenting with heart failure.

The international guidelines have acknowledged the prognostic benefits of ivabradine and indicate the drug for the treatment of patients treated with an ACEi, a beta-blocker and a MRA with left ventricular dysfunction and those with Class (II-IV) HFrEF (LVEF <35%) with heart rate > 70 bpm to reduce heart failure hospitalisations and cardiovascular mortality.[1]

In patients with HFrEF with a LVEF ≤ 35% who are unable to tolerate or have contra-indications for a beta-blocker, ivabradine should be considered to reduce the risk of heart failure hospitalizations and cardiovascular death.

The European Medicines Agency has requested an analysis of the SHIFT trial with ivabradine in order to identify the heart rate threshold above which ivabradine confers a survival benefit and it was found that the mortality benefit of ivabradine is apparent

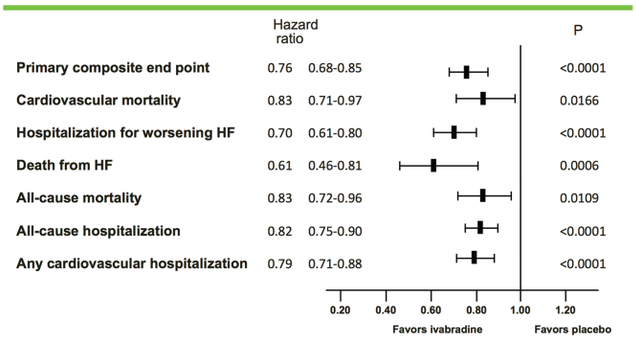

Figure 4. Effect of ivabradine on outcomes in patients with HFrEF and HR ≥75 bpm (Böhm M et al. Clin Res Cardiol. 2012)

for heart rates ≥ 75 bpm, with a 17% reduction in overall mortality and a 39% reduction in death from heart failure (see Figure 4). Ivabradine is very safe to use and has few drug to drug interactions, however, caution should be exercised in patients developing resting heart rate < 50 bpm during treatment and in those with liver dysfunction. Ivabradine should not be used in patients receiving verapamil, or diltiazem. However, these two drugs are contraindicated in HFrEF anyway.

Studies in patients receiving beta-blockers have shown that the association of ivabradine and a beta-blocker is more effective than increasing the dose of the beta-blocker in achieving target heart rate, improving exercise capacity and functional performance. Therefore, ivabradine/beta-blockade is to be preferred to a full implementation of beta-blocker alone.

Treatment with ivabradine should be started at 5 mg twice daily and the dose should be stepped up after 2–4 weeks, if target heart rate has not been reached, to the target dose of 7.5 mg twice daily.

ARNI – angiotensin receptor neprilysin inhibitor

ARNI is a new therapeutic class of drugs that block the angiotensin II type 1 receptor and inhibit the neutral endopeptidase system. This latter system degrades natriuretic peptides and bradykinin together with other peptides. The first in class is LCZ696 that is a molecule that combines the moieties of Valsartan and Sucubutril in one single drug substance. LCZ696 simultaneously blocks the angiotensin II type 1 receptors and increases circulating levels of A-type natriuretic peptide (ANP) and B type natriuretic peptide (BNP). The increased NP levels enhance diuresis, natriuresis, and myocardial relaxation and inhibit renin and aldosterone secretion. LCZ696 is the first molecule of this class and has been developed by co-crystallization of valsartan and sacubitril in one single agent.

The PARADIGM-HF study compared the long-term effects of LCZ696 with those of Enalapril on mortality and morbidity in patients with ambulatory, symptomatic HFrEF with LVEF ≤ 35% (only a small minority of patients with LVEF <40% were included in the early phases of the study), elevated plasma NP levels (BNP ≥ 150 pg/mL or NT-proBNP ≥ 600 pg/mL or a BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL if they had been hospitalized for HF within the previous 12 months), an estimated GFR (eGFR) ≥ 30 mL/min/1.73 m^2 of body surface area, who were able to tolerate enalapril 10 mg b.i.d.[16]

In these patients LCZ696 reduced the composite end point of death from cardiovascular causes or hospitalization for heart failure by 20%, death by 16% and need for hospitalisation by 21% (see Figure 5). For these reasons LCZ696 is recommended by the ESC/HFA guidelines for the treatment of out of hospital patients with HFrEF who remain symptomatic despite the treatment with an ACEi a beta-blocker and an MRA that also have elevated natriuretic peptides and are able to tolerate 10 mg bid of enalapril.

The recommended starting dose of LCZ696 is 100 mg (49 mg/51 mg) twice daily, the dose should be doubled at 2–4 weeks to the target dose of 200 mg (97 mg/103 mg) twice daily if tolerated. If patients experience low systolic blood pressure ≤95 mmHg, symptomatic hypotension, hyperkalaemia, or renal dysfunction, adjustment of concomitant medicinal products, or down–titration or discontinuation of LCZ696 is recommended. Treatment with LCZ696 should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg.

LCZ696 may induce symptomatic hypotension, especially in the elderly and for this reason caution in its uptitration should be exercised in patients with low blood pressure levels. The PARADIGM-HF study reduced the likelihood of angioedema with LCZ696 by recruiting only those patients who tolerated ACEi therapy and, given the absence of safety data in ACEi naïve patients the drug should not be used in ACEi naïve patients and ACEIs should be withheld for at least 36 hours before initiating LCZ696.

ARBs – Angiotensin II type I receptor blockers and double RAAS blockade

The role of ARBs in the treatment of patients with HFrEF has changed in the past few years and now, in line with the scientific evidence ARBs are only recommended as an alternative in those few patients who are intolerant to an ACE inhibitor.[1] The CHARM programme showed that Candesartan was able to reduce cardiovascular mortality, but not overall mortality, in patients with HF.[17] On the other hand the Val-HEFT study showed that Valsartan had only a marginal effect on heart failure hospitalisations (but not on the overall days in hospital) in patients with HFrEF.[18] A meta-analysis including 33 randomised controlled trials with 68 405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks showed that while dual blockade (ACEi+ARB) of the RAAS was not associated with a clinical benefit in reducing all cause mortality (relative risk [RR] = 0.97; 95% CI 0.89–1.06) and

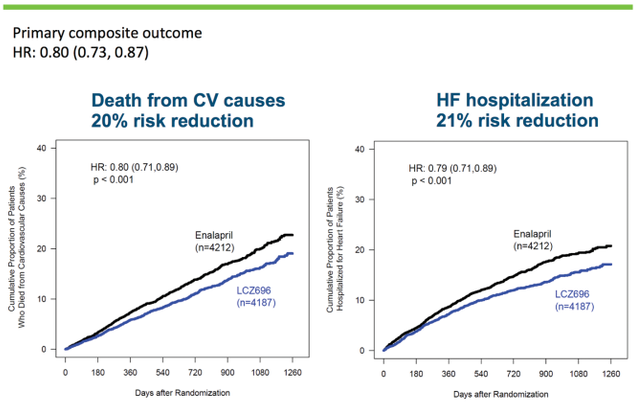

Figure 5 Effect of LCZ696 on the components of the primary end point in the PARADIGM-HF study

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cardiovascular mortality (RR = 0.96; 0.88–1.05) compared with monotherapy, it was only associated with a reduction in heart failure hospitalisations (RR = 0.82, 0.74–0.92) and with an increased risk of hyperkalaemia (RR = 1.55; 1.32–1.82), hypotension (RR = 1.66; 1.38–1.98) and renal failure (RR = 1.41; 1.09–1.84) thereby suggesting that dual blockade of the renin-angiotensin system is associated with an excessive risk of adverse events not balanced by an effect on mortality or on hospitalisations.[23] The EMA suggested that the benefits of double RAAS blockade outweigh risk only in a selected group of patients with HFrEF in whom other treatments are unsuitable. The ESC/HFA guidelines on heart failure suggest that ARBs are only indicated for the treatment of patients with HFrEF who cannot tolerate an ACEI because of serious side effects and that the combination of ACEI/ARBs should be limited only to symptomatic patients with HFrEF who are unable to tolerate an MRA. In this case the double blockade of the RAAS must be used under strict supervision.

Metabolic agents

Trimetazidine is a metabolic modulator that blocks free fatty acid oxidation and improves glucose oxidation thereby improving the metabolic efficiency of the heart. Trimetazidine has been tested in several small studies in patients with HFrEF. Three meta-analyses of the available data suggest that Trimetazidine may improve prognosis in patients with HFrEF.[24–26] Trimetazidine is therefore indicated where appropriate in patients with HFrEF. A specific benefit of trimetazidine is observed in patients with an ischaemic origin of left ventricular dysfunction as well as in the elderly and in diabetic patients.[27–30]

Diuretics

Diuretics reduce signs and symptoms of congestion in patients with HFrEF. Although their effects on mortality and morbidity have not been formally tested in a randomised controlled study, a meta-analysis has shown that in patients with chronic HFrEF loop and thiazide diuretics reduce the risk of death and worsening HF compared to placebo.[31]

Different diuretics have different effects with loop diuretics having a shorter but stronger diuresis than thiazides and the combination may be used to treat resistant oedema. Since the main aim of diuretic therapy is to reduce congestion and maintain euvolaemia the dose should be adjusted over time. Although in selected cases patients and can be trained to self-adjust their diuretic dose, the adjustment should be in the majority of cases supervised by a healthcare professional. More recently new subcutaneous delivery systems of diuretics have been developed for easier titration of diuretic dose in patients with the more advanced stages of the disease.

Therefore, the treatment of patients with HFrEF should be implemented gradually through steps that take into account the prognostic benefits of the different classes of drugs. Diuretics should always be used for the control of fluid balance and their dose should be appropriately adjusted according to patient conditions in order to maintain euvolaemia. The initial step of the treatment of patients with HFrEF should include ACEi and beta-blockers taking into account that beta-blockers can be started together with ACEi but not before ACEi had been started. Beta-blockers should be used only in NYHA class II-III patients and they should not be used in haemodynamically unstable patients, should be used with caution in patients with recent (< 4 weeks) exacerbation of heart failure or in those with signs of congestion or hypotension. In the few patients that have intolerance to ACEi an ARB may be considered.

These drugs should be titrated to the maximum tolerated dose. If symptoms persist an MRA must be considered carefully monitoring electrolytes. If the patient is still symptomatic ivabradine and LCZ696 should be considered. These two drugs are not alternative but may be complementary as ivabradine can be safely started in all patients in sinus rhythm where it is indicated and in all those many patients with low blood pressure values that may need to down-titrate beta-blockers dose in order to be able to receive LCZ696.

Declarations of Interest

The author declares he has no conflicts of interest.

Acknowledgements

The author states that he they abide by the requirements for ethical publishing in biomedical journals.[32]

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