INTRODUCTION
Heart failure is the fastest growing cardiovascular disease in North America in individuals older than 75. Success in the past one to two decades in the management of heart failure came after better understanding of the pathophysiology and the role of neurohumoral activation as a result of myocardial damage. The use of angiotensin-converting enzyme inhibitors (ACEIs), beta adrenergic receptor blockers, angiotensin receptor blockers (ARBs) and aldosterone antagonists showed significant reduction in morbidity and mortality. In the past decade, the major advances in this field have been related to the use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT). However, despite these advances, the morbidity and mortality from heart failure continue to be very high.

The review provides an overview of new advances in the management of heart failure with a focus on studies and data published in the past 2 years.

RESYNCHRONIZATION-DEFIBRILLATION FOR AMBULATORY HEART FAILURE TRIAL
The aim of the Resynchronization-defibrillation for Ambulatory heart Failure Trial (RAFT) multicenter...
study was to evaluate whether adding CRT to an ICD could improve outcomes in patients with New York Heart Association (NYHA) class III heart failure compared with an ICD alone. Initially, patients with NYHA class II or III heart failure, left-ventricular ejection fraction of 30% or less, and an intrinsic QRS duration equal to or more than 120 ms or a paced QRS duration of 200 ms or more were randomized to receive an ICD alone or an ICD and CRT. After new data suggested a mortality benefit of CRT in patients with NYHA class III, the protocol of the RAFT study was revised to include patients in NYHA class II only. Of 1789 patients enrolled, 904 patients received an ICD alone and 894 received an ICD and CRT. At enrollment, 80% of the patients were NYHA class II and 20% were class III. The primary study outcome was defined as death from any cause or hospitalization for heart failure. At a mean follow-up of 40 months, the primary outcome occurred significantly more often in the ICD group (40.3%) than in the CRT–ICD group (33.2%) (Table 1). Compared with the ICD group, there was a relative reduction of 25% in mortality in the ICD–CRT group, a 24% relative reduction in cardiovascular deaths and a 32% relative reduction in heart failure hospitalizations. Subgroup analysis showed similar results in class II and III heart failure both in death and hospitalization for heart failure and in death alone (Fig. 1).

In conclusion, the addition of CRT to an ICD in patients with NYHA class II–III heart failure, a wide QRS and left-ventricular dysfunction reduced death and heart failure hospitalizations. The results of this trial confirm and extend the indications for CRT in patients with heart failure and will likely change clinical practice guidelines in the near future.

ROLE OF EPLERENONE IN PATIENTS WITH LESS SYMPTOMATIC HEART FAILURE (EMPHASIS-HF TRIAL)

The benefit of the blockade of the aldosterone receptor on morbidity and mortality in patients with severe heart failure is well established. The Randomized Aldactone Evaluation Study (RALES) showed that spironolactone, in addition to standard therapy, substantially reduced the morbidity and mortality among patients with severe heart failure, NYHA class III or IV. Further research, this time with the selective aldosterone antagonist eplerenone, in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) showed that the drug, when added to optimal medical therapy, significantly reduced cardiovascular hospitalization and mortality in patients with acute myocardial infarction complicated by heart failure and left-ventricular dysfunction. Finally, Zannad et al.
established the role of eplerenone in patients with less symptomatic heart failure in the EMPHASIS-HF trial (a comparison of outcomes in patients in NYHA class II heart failure when treated with eplerenone or placebo in addition to standard heart failure medicines). The authors randomized 2737 patients with NYHA class II heart failure and left-ventricular ejection fraction equal to or less than 35% to receive eplerenone up to 50mg daily or placebo on top of evidence-based therapy. The primary end point was cardiovascular death or hospitalization for heart failure. A median follow-up period of 21 months was reached when the study was stopped prematurely according to prespecified rules. Cardiovascular death or heart failure hospitalization occurred statistically less often at 18.3% in the active treatment arm compared with 25.9% in the placebo arm (Fig. 2). There was a 37% reduction in the composite of death from cardiovascular causes or hospitalization for heart failure, a 24% reduction in cardiovascular death, and a 42% reduction in hospitalization for heart failure. The number needed to treat to postpone one death per year was 51 and to prevent one primary outcome from occurring was 19. Eplerenone was well tolerated and side effects were comparable with the placebo arm. The incidence of hyperkalemia was greater in the eplerenone arm; however, rates of serious hyperkalemia requiring study drug withdrawal were not different between the two groups. Similarly to other studies of aldosterone antagonists, this study highlights the importance of serial monitoring of serum potassium and creatinine (Table 2).

**SYSTOLIC HEART FAILURE TREATMENT WITH INHIBITOR IVABRADINE TRIAL**

Beta adrenergic receptor blockers improve left-ventricular function and prognosis in patients with chronic heart failure. Their mechanism of action is multifactorial, only part of which is due to reduced heart rate. However, they have other cardiac and noncardiac side effects that can limit their use and dosage. Heart rate is a risk factor for mortality in cardiovascular outcomes; a subgroup analysis of a

![Graphs showing outcomes of eplerenone versus placebo](image)

**FIGURE 2.** Kaplan–Meier rates of primary and other outcomes comparing eplerenone versus placebo. CI, confidence interval.
Table 2. Side effects of eplerenone compared with placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Eplerenone (N=1360)</th>
<th>Placebo (N=1369)</th>
<th>P value</th>
<th>Eplerenone (N=1360)</th>
<th>Placebo (N=1369)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>979 (72.0)</td>
<td>1007 (73.6)</td>
<td>0.37</td>
<td>188 (13.8)</td>
<td>222 (16.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>109 (8.0)</td>
<td>50 (3.7)</td>
<td>&lt;0.001</td>
<td>15 (1.1)</td>
<td>12 (0.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16 (1.2)</td>
<td>30 (2.2)</td>
<td>0.05</td>
<td>0</td>
<td>3 (0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Renal failure</td>
<td>38 (2.8)</td>
<td>41 (3.0)</td>
<td>0.82</td>
<td>4 (0.3)</td>
<td>6 (0.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypotension</td>
<td>46 (3.4)</td>
<td>37 (2.7)</td>
<td>0.32</td>
<td>0</td>
<td>3 (0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Gynecomastia or other breast disorders</td>
<td>10 (0.7)</td>
<td>14 (1.0)</td>
<td>0.54</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The data are given as number of patients (%).

randomized controlled trial [heart rate as a prognostic risk factor in patients with coronary artery disease and left ventricular systolic dysfunction (BEAUTIFUL)] showed a 34% increased risk of cardiovascular death in patients with coronary artery disease, left-ventricular dysfunction and heart rate of 70 or higher compared with a heart rate below 70. In the Cardiac Insufficiency Bisoprolol study of bisoprolol in chronic heart failure, 1 year mortality was progressively lower in the placebo group according to baseline heart rate, as heart rate dropped from above 84 to 73–84 to below 73, with an additional incremental drop in mortality in each group when the heart rate was lowered further with bisoprolol. Ivabradine belongs to a new class of drugs that inhibit the If current in the sinoatrial node, reducing heart rate, but do not affect myocardial contractility and conduction. In the Systolic Heart failure treatment with If inhibitor ivabradine Trial (SHIFT), patients with moderate to severe heart failure on optimal medical therapy were randomized to either ivabradine or placebo with a median follow-up of 22.9 months; 3268 patients received ivabradine, whereas 3290 were in the placebo group. Most of the patients were NYHA class II or III at the time of randomization. The primary end point was cardiovascular death or heart failure hospitalization. The use of standard betablockers was high at baseline, at 90% in the placebo group and at 89% in the study group. Study patients were started on ivabradine 5mg twice daily and the goal was to increase this to 7.5mg twice daily at 1 month. Elderly patients were started at 2.5 mg. The mean baseline heart rate was 80 and dropped to 64 at 1 month and 67 after 32 months in the ivabradine group, compared with 75 at both 1 and 32 months in the placebo group. Among patients treated with ivabradine, there was 18% relative risk reduction in cardiovascular death or hospital admission with worsening heart failure (P<0.0001, absolute risk reduction 4.2%). The beneficial effect was mainly due to an improvement in heart failure admission and death from heart failure (relative risk reduction 26%). Whether or not this drug is useful in all heart failure patients with systolic dysfunction needs to be determined. These results apply only to patients with heart failure who have heart rate 70 or more and are on optimal heart failure therapy. Limitations of the study include exclusion of patients with atrial fibrillation or flutter and the inclusion of only a few elderly patients. It remains possible that the clinical effect of ivabradine could be diminished if further titration of the beta-blocker is possible. However, this drug may represent an ideal opportunity when that scenario is not feasible. Recent data suggest significant improvement in quality of life in the ivabradine group which correlates very nicely and positively with the extent of heart rate reduction.

TELEMONITORING IN PATIENTS WITH HEART FAILURE

Anker et al. discussed the role of telemedicine in remote management of patients with heart failure. While some prospective clinical trials have not shown a benefit, other meta-analyses show that telemedicine can reduce morbidity and mortality. However, telemedicine methods vary from computer-based models to programs managed by healthcare providers. For example, Chaudhry et al. randomized 1653 patients with a recent hospital admission with heart failure to undergo either telemonitoring or usual care on top of optimal medical therapy. Both groups received the same educational materials developed by the Heart Failure Society of America. The primary end point

Heart for Life
was the death or admission from any cause within 6 months after enrollment; 826 patients were assigned to telemonitoring, whereas 827 patients were assigned usual care. At the end of the study, there were no significant differences between the two groups in the primary end point, which occurred in 51.5% in the usual care group and 52.3% in the telemonitoring group. It is noteworthy that, of patients who were assigned to undergo telemonitoring, 14% never used the system, and by the end of study only 55% of patients were still using the system at least three times per week. Inglis et al. carried out a systemic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients. Telemonitoring reduced all-cause mortality by 34% [relative risk (RR) 0.66, P<0.001] and there was a similar but nonsignificant trend noted for telephone support (P=0.08). Heart failure hospitalizations were significantly lower with telephone support, by 23% (P=0.0001), and by 21% (P=0.008) with telemonitoring versus usual care. This meta-analysis supported the benefit of different forms of telemedicine in the management of patients with heart failure, although only telemonitoring appeared to reduce mortality. Even without telemedicine, it is important to remember the critical role of healthcare providers in educating patients about warning signs and symptoms of deterioration in their heart failure condition and how to treat it before it requires hospitalization.

INTERPRETATION OF THESE NEW STUDIES

How should the clinician interpret and incorporate these studies into patient management? Firstly, there is overlap in the patient populations in the above studies; for example, most patients in the RAFT study were on baseline beta-blocker therapy and many took spironolactone. There are strong clinical trial data to recommend a primary prevention ICD in otherwise healthy patients with left ventricular ejection fraction less than 30%, whether they have NYHA class II or III symptoms. There is now good evidence to add CRT not only for class III but now for class II patients; however, only those patients with left bundle branch block and a wide QRS benefit from the addition of CRT. Similarly, there are now data to add the aldosterone blocker, eplerenone, to patients with class II symptoms. Cumulative studies show that the use of beta-blockers and ACEIs in heart failure is a class effect; and it is suggestive but not known yet whether there will be similar benefit from spironolactone as with eplerenone. Spironolactone is currently cheaper than eplerenone, but it causes gynecomastia in some men. In practice, differentiation between class II and III patients is difficult and subjective. Patients in the eplerenone study qualified based on a previous hospitalization with heart failure so, at one point, they had class III–IV symptoms. The SHIFT study showed that the addition of ivabradine on top of baseline beta-blocker therapy resulted in further heart rate slowing and improvement in outcomes. In patients with heart rate of 70 or more, it is speculative but possible that there might have been a similar benefit from an increase in their beta blocker dose even without ivabradine. Whether patients should have all three treatments added, namely CRT, eplerenone and ivabradine, is unknown, and their incremental clinical and cost benefit has not been established. The cost of adding CRT to ICD is modest, and in the short term drugs will be cheaper than a device. In reality, many patients may only meet the inclusion criteria for one or two of the new therapies. Telemedicine holds promise in monitoring patients with chronic heart failure to reduce hospitalization and reduce mortality; however, there are different methodologies, and institutions have to decide which intervention works in their setting, and then monitorits success.

CONCLUSION

In this review, we focused on three major clinical trials with positive results that will influence care and reviewed the evolving role of telemedicine in remote management of patients with heart failure.

Drug Treatment of Hyperuricemia to Prevent Cardiovascular Outcomes: Are We There Yet?

Introduction

Hyperuricemia is a serum biochemical abnormality defined as elevation of urate concentrations above the saturation level in human serum at 37°C, corresponding to a concentration of 6.8 mg/dL. The best understood consequence of hyperuricemia is the development of gout, which is the clinical manifestation of deposition of monosodium urate crystals, leading to flares of intense articular pain and swelling and, in the long-term, to the development of urate deposits in tissues (tophi). The preclinical stage of gout is called ‘asymptomatic hyperuricemia’, but a growing body of evidence from the musculoskeletal literature is questioning this concept because subclinical joint damage can occur during the so-called asymptomatic phase.

The second question about the concept of asymptomatic hyperuricemia originates from increasing evidence that an independent association, and possibly a causative link, exists between hyperuricemia and the development of cardiovascular disease.

Laboratory and Animal Studies

An animal model led to renal vascular disease characterized by cortical vasoconstriction, afferent arteriolar swelling, and glomerular hypertension. Reductions in serum urate, through administration of the nonreversible xanthine oxidase inhibitor febuxostat, partially attenuated these abnormalities. Hemodynamic abnormalities found in hyperuricemic rats have been reversed by administration of a superoxide scavenger, supporting a link between elevated urate levels and damage induced by reactive-oxygen species (oxidative stress). How urate, known as an extracellular molecule, gains entry into vascular endothelial cells to exert its postulated cardiovascular effects is still unknown, but the mechanism could be similar to that described in afferent renal arterioles through URAT-1, an integral membrane protein that serves as a urate transporter.

Serum Urate and Hypertension

Multiple population-based human studies have established an association between increased levels of serum urate and subsequent development of hypertension. Meta-analyses have further confirmed a positive association between hyperuricemia and hypertension. The main limitation and criticism of these epidemiologic studies is the degree to which they control for potential confounders, since even in carefully designed analyses, residual confounding due to kidney dysfunction, exercise levels, socioeconomic factors, and elements of metabolic syndrome is difficult to dismiss.

Interventional studies are scarce, but results are compelling in favor of an association. In a small randomized, controlled, crossover trial, 30 treatment-naïve adolescents (aged 11–17 years) with stage 1 hypertension and hyperuricemia (serum urate ≥6mg/dL) were randomized to receive oral allopurinol 200 mg daily or placebo. After the allopurinol treatment periods, systolic and diastolic BP were both significantly lower than after the placebo periods. In addition, mean plasma renin activity was significantly decreased. These results were supported by findings from another small study, in which oral allopurinol 300 mg daily was administered for 12 weeks to 48 adult patients with hyperuricemia. After the follow-up period, both systolic and diastolic BP had small but significant reductions when compared with pre-treatment levels and with a group of normouricemic controls. Studies at different stages of development are trying to determine if urate-lowering therapy can be advocated in hypertension.

Serum Urate, Coronary Artery Disease, and Stroke

Reported associations between serum urate concentrations and macrovascular clinical end-points have been inconsistent. A meta-analysis of prospective studies of the association between hyperuricemia and coronary heart disease (CHD) showed a modest increase in incidence and no significant association with CHD mortality. A recent large study in a Taiwanese population confirmed a lack of association between hyperuricemia and CHD mortality, although a small, but significant, 10% increased hazard per each mg/dL of serum urate increase was associated with coronary artery disease (CAD) mortality. Smaller clinical studies had previously suggested an association between CAD incidence and hyperuricemia. Eighty patients younger than 35 years of age, and who were clinically diagnosed with acute myocardial infarction, were divided between patients with CAD by angiography (n = 36) and patients...
with normal angiography (n = 44). After adjusting for demographic characteristics and cardiac risk factors at baseline, mean serum levels of urate (7.0 mg/dL in patients with CAD vs 4.9 mg/dL in patients without CAD) were significantly different between the two groups (p = 0.003).

An association between serum urate and stroke or surrogate markers for cerebrovascular disease has also become evident in recent years. A meta-analysis of prospective epidemiologic studies reported a modest increase in stroke incidence and mortality in patients with hyperuricemia. Using T2 white-matter, hyperintense signals in magnetic resonance imaging as a marker of brain ischemia, significantly greater frequencies of T2 white-matter defects were associated with higher levels of serum urate in 46 individuals (with serum urate concentrations of >5.75 mg/dL [men] or >4.8 mg/dL [women]) compared with 131 controls.

**Serum Urate and Heart Failure**

Elevated levels of serum urate have been described in association with incident heart failure, and also in association with increased mortality in patients with established heart failure. A report using 29 years of follow-up data from the Framingham Offspring study stated that subjects with serum urate levels >6.3 mg/dL (almost all men) had a 6-fold higher incidence of heart failure than subjects with serum urate <3.4 mg/dL (almost all women). Despite large epidemiologic studies describing an association between serum urate levels and heart failure mortality, interventional studies using xanthine oxidase drugs have led to conflicting results in patients with left ventricular dysfunction. It is also unclear if any potential benefit from xanthine oxidase therapy is due to urate-lowering effects or to a nonspecific antioxidant effect of these drugs.

**Serum Urate and Total Cardiovascular Mortality**

In 1999, the Framingham Heart Study Group published results of its ancillary analysis on the association of serum urate with cardiovascular disease and cardiovascular death. No significant association was found in men or women after adjustment for cardiovascular risk factors and diuretic use, raising the question of whether previously reported associations were confounded by other factors. Subsequently, most studies found results in favor of an association: the most important study was a longitudinal followup analysis from individuals recruited in the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Survey. This study described a significant independent association between higher concentrations of serum urate and cardiovascular mortality in both men and women. In general, the association was stronger for women than men. Finally, a large population study in Taiwanese individuals with low cardiovascular risk (n = 90,393) showed an increase in total cardiovascular mortality for both men (HR 1.23; 95% CI 1.03, 1.43) and women (HR 1.69; 95% CI 1.33, 2.16) with hyperuricemia.

**Serum Urate and Metabolic Syndrome**

Multiple studies have also shown it to be closely associated with hyperuricemia.

**Should We Recommend Urate-Lowering Therapies for Individuals with Asymptomatic Hyperuricemia and High Cardiovascular Risk?**

Significant progress has been made in confirming an association, possibly causal, between hyperuricemia and cardiovascular outcomes. A true causal relationship between hyperuricemia and cardiovascular diseases seems plausible. However, caution is necessary, as previous epidemiologic associations have been proven wrong by well-controlled prospective studies. Conversely, urate-lowering therapies are not devoid of adverse effects, which are sometimes severe or life-threatening. Uricase analogs (rasburicase, pegloticase) are potent and expensive parenteral therapies with a high potential for adverse reactions. In light of available evidence, together with safety considerations for currently available therapies, pharmacologic urate-lowering therapies cannot be advocated for the treatment of hyperuricemic patients without gout solely on the basis of a cardiovascular indication. Certainly, nonpharmacologic interventions aimed at lowering or preventing a further rise in serum urate can be safely recommended in individuals with hyperuricemia. Weight loss in overweight individuals may be beneficial. In addition, reduced intake of meat, seafood, beer, and liquor can be recommended. Before considering urate lowering as a valid approach for the treatment of cardiovascular conditions. Despite their known adverse effects, xanthine oxidase inhibitors appear to be the most promising agents for prevention and treatment of cardiovascular outcomes associated with hyperuricemia. Allopurinol has been tested in small, open-label studies and in various other clinical trials aimed at improving cardiovascular outcomes. A final consideration regarding the choice of therapy is economic.

St Jude Is Latest to Launch Blood Pressure Device

St Jude Medical Inc said it won European approval to begin selling a device that lowers blood pressure by creating tiny scars along the renal nerves. The St Jude device, called the EnligHTN Renal Denervation System, is intended for patients whose high blood pressure is resistant to drug therapy, or about one quarter of those who have hypertension. The ablation procedure, known as renal denervation, involves threading a catheter through the renal arteries from the femoral artery. The catheter delivers radiofrequency energy to create tiny lesions along the renal sympathetic nerves that help regulate blood pressure. The lesions disrupt the nerve supply to decrease systolic blood pressure.

Reuters Health Information 2012

ACE Inhibitors Tied to Increased Angioedema Risk

Pooled data suggest that renin-angiotensin system (RAS) inhibitors - in particular, angiotensin converting enzyme (ACE) inhibitors - may increase the risk of angioedema. In rare cases, patients died from their angioedema. African Americans were roughly twice as vulnerable to developing angioedema as whites. ACE inhibitors are among the most efficacious and safest drugs available to the practicing physician and are extensively used all over the globe. However despite this widespread use, angioedema remains a potential adverse event of this drug class. In head-to-head comparisons in seven trials, the risk of angioedema was 2.2 times higher with ACE inhibitors than with ARBs. With both such agents the incidence of angioedema was higher in heart failure trials compared to hypertension or coronary artery disease trials without heart failure. Of the patients on ACE inhibitors, 384 developed angioedema during a mean duration of 129 weeks giving a weighted incidence of 0.30%. For ARBs, 52 developed angioedema during a mean duration of 120 weeks (0.11%). Of those given a DRI, seven developed angioedema during a mean duration of 24 weeks (0.13%). The incidence with placebo was 0.07%. Overall, the incidence of angioedema with ARBs and DRI was not significantly different from placebo and less than half that with ACE inhibitors. In two of trials, there was a death associated with ACE inhibitor related angioedema.

Am J Cardiol 2012.

One Troponin Test to Identify Low-Risk Patients Fast

A simple strategy of measuring just contemporary central-laboratory troponin I within two hours of presentation as the sole biomarker in conjunction with ECG and the TIMI risk score can identify a large group of chest-pain patients who are at low risk of cardiac events and are suitable for safe early discharge from the ER. There haven't been many papers on combining clinical risk stratification with a troponin test. There is a lot of interest in the high-sensitivity troponin test for identifying a low-risk population, but this is not available in many places yet. While we are waiting for this test to come through, we have come up with an approach than can be used here and now. He noted that at present guidelines recommend two troponin tests for chest-pain patients in the ER, six to 12 hours apart. So patients are normally admitted overnight. Our approach allows 20% of patients to leave fairly quickly.

Am Coll Cardiol 2012; DOI:10.1016/j.jacc.2012.02.035.

Dear Doctor,

We are happy to present the 25th issue of “Insight Heart”. It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on “Heart failure and Hyperurecemia”. We will appreciate your thoughtful comments.

Thanks and regards.

For further information: Product Management Department, SQUARE Centre, 48, Mohakhali C/A, Dhaka-1212
Web: www.squarepharma.com.bd
Developed by: dhakahealth