Drug Trends in Cardiology

New ESC heart failure guidelines with South African expert comment

The new ESC heart failure guidelines, an update of the 2008 version, was released at the ESC Heart Failure Congress in Belgrade this weekend. This is the first time the guidelines have been presented at the Heart Failure Congress as opposed to at the annual European Society of Cardiology (ESC) Congress.

Major updates are in the provision of new algorithms for the diagnosis of patients with suspected heart failure, treatment for systolic heart failure patients with reduced ejection fraction (HF-REF), and the management of acute heart failure.[1,2] The diagnostic algorithm recognises the increasing importance of cardiac MRI and includes mid-regional proBNP as a 'rule-out' blood test in patients with acute heart failure.

The pharmacological therapy section of the guideline has been updated to specifically relate the treatment to clinical outcome effects and provides the level of evidence supporting a use of the particular agent (Table 1). The cornerstone use of ACE inhibitors has been acknowledged with a class I, level A recommendation as has the use of the ARBs (also class I, level A). 'ARBs, as they become generically available, can also be regarded as a cornerstone therapy, particularly as drug adherence is such an important issue', Dr Erik Klug (cardiologist, Johannesburg) noted at the recent Physicians Congress held in Cape Town.

In these 2012 guidelines, there is a new indication for the mineralocorticoid/aldosterone receptor antagonists (MRA), eplerenone in patients with systolic heart failure (HF-REF) and mild symptoms. This broadens the indication for a MRA to essentially all HF-REF remaining symptomatic, despite adequate treatment with a beta-blocker and ACE inhibitor or ARB. A further innovation is the recommendation that ivabradine be added to an ACE inhibitor, beta-blocker (at maximum tolerated doses) and MRA to HF-REF patients in sinus rhythm with a persistently high heart beat above 70 beats/min (Table 2).

The new guidelines devote substantial space to co-morbidities, given their importance in relation to symptoms and progress, and therapeutic decision making. In this way, the guidelines recognise that heart failure and left ventricular systolic dysfunction (LVSD) may alter therapies for co-morbidities and that co-morbidities may also influence the use of heart failure therapies.

Co-morbidities such as chronic obstructive pulmonary disease (COPD), diabetes, hypertension, kidney dysfunction and cardiorenal syndrome are discussed and guidelines presented. Recent evidence has also pointed to the value of physicians managing patients with chronic heart failure and co-morbidities.[3]

Comment from Dr Martin Mpe

Cardiologist in private practice, Pretoria and a member of the CVJA editorial board

The update of the 2008 guidelines is intended to advance the treatment of heart failure in the light of the new scientific evidence from recent clinical trials. The purpose is to improve the clinical outcomes from contemporary interventions with improvement in both morbidity and mortality. This comes at a price since stringent application of the recommendations has cost implications on the already financially strained healthcare systems all over the world.

Local adaptations of these guidelines are mandatory and should be sensitive to local circumstances. For the majority of patients, the logical approach is to ensure access to the 'maximum' recommended pharmacological intervention as the minimum standard of care.

Special investigations in the setting of heart failure have been re-emphasised, which leads to further increase in cost. The escalation of therapy depends on special investigations over and above the symptom response.

The main changes, as presented by the chairperson of the Task Force for the review committee of the 2012 ESC heart failure guidelines committee, John JV McMurray, are the following:

An expanded indication for mineralocorticoid (aldosterone) receptor antagonists (MRAs)

The use of MRAs following the use of ACEI/ARB and beta-blockers in symptomatic patients implies a revisit on the wider use of eplerenone. Spironolactone has an unpleasant side effect of gynaecomastia in a significant number of users, which may be more in combination with the use of digoxin. I would imagine that

TABLE 1. PHARMACOLOGICAL TREATMENTS INDICATED IN POTENTIALLY ALL PATIENTS WITH SYMPTOMATIC (NYHA FUNCTIONAL CLASS II–IV) SYSTOLIC HEART FAILURE

Recommendations	Class[a]	Level[b]
An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤ 40% to reduce the risk of heart failure hospitalisation and the risk of premature death.	I	A
A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤ 40% to reduce the risk of heart failure hospitalisation and the risk of premature death.	I	A
An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤ 35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of heart failure hospitalisation and the risk of premature death.	I	A

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation; [b]Level of evidence.

TABLE 2. OTHER TREATMENTS WITH LESS CERTAIN BENEFITS IN PATIENTS WITH SYMPTOMATIC (NYHA CLASS II–IV) SYSTOLIC HEART FAILURE

Recommendations	Class[a]	Level[b]
ARB		
Recommended to reduce the risk of heart failure hospitalisation and the risk of premature death in patients with an EF ≤ 40% and unable to tolerate an ACE inhibitor because of cough (patients should also receive a beta-blocker and an MRA).	I	A
Recommended to reduce the risk of heart failure hospitalisation in patients with an EF ≤ 40% and persisting symptoms (NYHA class II–IV), who are unable to tolerate an MRA, despite treatment with an ACE inhibitor and a beta-blocker.[c]	I	A
Ivabradine		
Should be considered to reduce the risk of heart failure hospitalisation in patients in sinus rhythm with an EF ≤ 35%, a heart rate remaining ≥ 70 beats/min, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).[d]	IIa	B
May be considered to reduce the risk of heart failure hospitalisation in patients in sinus rhythm with an EF ≤ 35% and a heart rate ≥ 70 beats/min who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).[d]	IIb	C
Digoxin		
May be considered to reduce the risk of heart failure hospitalisation in patients in sinus rhythm with an EF ≤ 45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate ≥ 70 beats/min). Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).	IIb	B
May be considered to reduce the risk of heart failure hospitalisation in patients with an EF ≤ 45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).	IIb	B
H-ISDN		
May be considered as an alternative to an ACE inhibitor or ARB, if neither is tolerated, to reduce the risk of heart failure hospitalisation and risk of premature death in patients with an EF ≤ 45% and dilated LV (or EF ≤ 35%). Patients should also receive a beta-blocker and an MRA.	IIb	B
May be considered to reduce the risk of heart failure hospitalisation and risk of premature death in patients in patients with an EF ≤ 45% and dilated LV (or EF ≤ 35%) and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).	IIb	B
PUFAs		
An n-3 PUFA[e] preparation may be considered to reduce the risk of death and the risk of cardiovascular hospitalisation in patients treated with an ACE inhibitor (or ARB), beta-blocker and an MRA (or ARB).	IIb	B

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CHARM-Added = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Added; EF = ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.
[a]Class of recommendation; [b]Level of evidence; [C]In the CHARM-Added trial, candesartan also reduced cardiovascular mortality;
[d]European Medecines Agency has approved ivabradine for use in patients with a heart rate ≥ 70 beats/min;
[e]Preparation studied in cited trial; the GISSI-HF trial had no EF limit.

there will be a significant increase in the use of eplerenone with the perceived benefit of a better side-effect profile.

A new indication for the sinus node inhibitor ivabradine

This agent will enjoy much wider use in a substantial number of patients, given the qualifying criteria for use. I would hope that the pricing will improve with increase in the number of prescriptions.

An expanded indication for cardiac resynchronisation therapy (CRT)

With the proper selection of patients, there is still a significant proportion of patients who qualify for CRT. The cost implication is a given, but in the long run, this is cost saving in comparison to the cost of repeated hospitalisations and indirect cost of death.

New information on the role of coronary revascularisation in systolic heart failure

The changing epidemics in coronary artery disease risk factors, especially in the developing world, will mean an increase in invasive interventions in the heart failure population as well. Infrastructural and human resource development are also imperative for the standard of care to be adequate in the not-so-distant future.

Recognition of the growing use of ventricular assist devices (VADs)

This is idealistic and will still not be a widely available treatment avenue. This is of course of major importance where the indication for appropriate use is met. The cost implication as well as availability remain deterrents for most nations.

The emergence of transcatheter valve interventions

This is a further reflection of the evolution in the practice of medicine and cardiology in particular. I find these exciting but the economic realities dampen one's enthusiasm. There may be a balance in the future as these interventions become more widely used and readily available.

1. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J*. Doi 10.1093/eurheartj/ehs104..
2. ESC Press Conference, Belgrade, 20 May 2012.
3. Boom NK, Lee DS, Tu JV. Comparison of processes of care and clinical outcomes for patients newly hospitalised for heart failure attended by different physician specialists. *Am Heart J* 2012; **163**: 252–259.