Combination therapy in heart failure

Health & Medicine

The ability of the heart to pump blood Is impaired and It can no longer meet the bodys metabolic requirements Table 1 . New York Heart Association Classiflcation of HeartFailure. Remme W], Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. European Heart Journal. [Online] 2001; 22(17): 1527-1 560. during the rest or exercisel. By treating HF we try to relieve patients symptoms, Improve their quality of life, prevent hospitalization and most importantly prolong their life. The treatment Includes Improved diet (reduced salt intake), physical activity and pharmacological treatment.

There are numerous angiotensin-receptor blockers (ARBs), vasodilators, angiotensin-converting enzyme (ACE) inhibitors Ramipril) and beta-blockers (Carvedilol). We will have a look at the last two classes. They have been PATHOPHYSIOLOGY The previous hemodynamic model was not adequate and was therefore replaced by neurohormonal model, which involves Reninangiotensin-aldosterone-system sympathetic nervous system 1 , (RAAS) 3 is summarized in Figure 1. The activation of RAAS leads to vasoconstriction, oedema and myocardial fibrosis, which are induced by Angiotensin Ill . roven to be very efficient in HF by numerous clinical studies2-4. SYMPTOMS AND SIGNS HF involves many symptoms such as dyspnoea fatigue, and ankle oedema. l The signs of HF are achycardia (> 100 beats per minute), tachyarrhythmia, tachypnoea, distended Jugular murmur and S3 and S4 heart sounds. The Figure 1 . pathophysiology of heart failure and different levels of therapeutic intervention. Taken from: Perrenoud J]. Heart failure (Part 1). European Geriatric Medicine. [Online] 2011; 2(3): 159-171. ccurrence of these symptoms and signs depends on

One of the earliest neurohormonal changes in HF is the severity of heart failure and whether it is caused sympathetic activation and it has a primary role in vein, peripheral oedema, hepatomegaly, heart by systolic dysfunction or diastolic dysfunction . isease progression. Left ventricular remodeling, cell death and changes in gene expression are believed to be the main mechanisms that induce ejection fraction8-11. Because it is very potent, small myocardial doses of the tablet should be taken at the start of damage nervous stimulation 10. treatment (3. 125mg) twice daily.

The dose is Heart failure can be categorized in predominantly gradually increased up to maximum of 50mg twice systolic dysfunction where the emptying of the left daily8. ventricle is not optimal and predominantly diastolic dysfunction where the filling of the left ventricle is Molecular targets ot optimall -6. As mentioned above, its major molecular targets are membrane receptors (? l, ? 2 and 01). It acts on ion TREATMENT channels (Ca2+ and K+) as well. Carvedilol inhibits As mentioned above, the disease can be treated cardiac voltage-dependent potassium IKr channels using several different drug classes4.

Multidrug with high potency, voltage-dependent calcium therapy is widely used in patients with heart failure. channels as well as Ca2+-permeable transient receptor potential (TRP)familychannels in Failure Zealand cardiomyocytes and in vascular smooth muscle Carvedilol Trial) have been conducted to test the ells. Furthermore, a study conducted by (Kikuta et benefits of different combinations of drugs. It was al. , 2006) suggests that the drug blocks ATP- proven that these therapies significantly reduce the sensitive (KATP) and G-protein-activated (KG) risk of mortality and improve

the symptoms. otassium However, hyperinsulinemia and hypoglycemia. It is believed implementing multi drug therapy. ACE inhibitors that the KG channel is opened by G protein in can cause hypotension, cough, and worsen the renal response to stimulation of G-protein-coupled function. Cough can cause patient noncompliance, uscarinic acetylcholine receptors in atria and sino- which in turn may result in the need of different drug therapy. Beta-blockers can cause bradycardia, channel would result in anti-cholinergic effects in hypotension, fatigue and fluid retention.

Also, in the heartl 2. Study patients there with Australian-New are risksdiabetes, associated beta-blockers channels. This results in could Pharmacodynamics Carvedilol is a racemic mixture of R and S Carvedilol enantiomers. Both enantiomers show al receptor Carvedilol is a non-selective beta-blocker (? l and inhibition. However, only S enantiomer inhibits ? ? 2) has drenoreceptors. It competitively blocks both ? l and vasodilatation and antioxidant effects. Previously it ? 2 receptors. The drug reduces high blood pressure be mainly due to the al and ? blockage.

The inhibition contraindicated in HF as it has negative ionotropic of al receptor lowers total peripheral vascular effect. However, studies have shown that carvedilol resistance. Hence, it reduces afterload and balances in combination with ACE inhibitors improves the negative ionotropic effect the ? inhibition. As a function of the heart, especially left ventricular result, the stroke volume and cardiac output are al-blocker. elieved that Furthermore, carvedilol it should maintained or even increased. The systemic arterial The effects of carvedilol are summarized in figure pressure is lowered without reducing the renal 3. lood flow13-14. The antioxidant effects carvedilol and

some of its metabolites are due to the presence of carbazole moiety (shown in Figure 2). In myocardial cell membrane carvedilol inhibits lipid peroxidation. Moreover, endothelial, vascular and neuronal smooth muscle cells from reactive oxygen species. Metabolite SB209995 is much more potent antioxidant than carvedilol itself. Animal studies have shown (Feuerstein et l. , 1998) heart failure imbalances the production of reactive oxygen species and the oxidant defense mechanism. The consequence is an excess of free radicals.

This may result in cytotoxic effects as well as cardiovascular remodelingl 3. Figure 3. Molecular targets, pharmacodynamics and clinical implications of carvedilol. Cheng J, Kamiya K, Kodama l. Carvedilol: Molecular and Cellular Basis for its Multifaceted Therapeutic Potential. cardiovascular Drug Revvtevs. coniine] 2006; 19(2): 152-71. Therapeutic efficacy Many different controlled clinical studies were made in order to determine the efficacy of carvedilol. The most known are COPERNICUS, CAPRICORN and USCHFS. They have all shown significant reduction in morbidity and mortality in comparison placebol 5-16.

COMET investigating the difference between carvedilol and metoprolol efficacy. The study showed that the allcause mortality was lower with carvedilol (34%) Figure 2. Chemical structure of carvedilol (with postulated active sites) and its active metabolites. * denotes the point of assymetry. Taken from: Cheng J, Kamiya K, Kodama l. Carvedilol: Molecular and Cellular Basis for its Multifaceted Therapeutic Potential. cardiovascular Drug Rewtevs. coniine] 2006; 19(2): 152-71. Carvedilol aids lipid metabolism as it prevents the oxidation of low-density lipoproteins (LDL).

It is known that LDL has destructive effects endothelial cells. Carvedilol also inhibits the Renin-angiotensin system (RAS). Hence, the production of Angiotensin II is lowered. Furthermore, studies on cardiac rat myocytes showed that carvedilol enhances the production of nitrite. It is therefore believed that it can increase the NO synthesis through some adrenoreceptor independent mechanism. However, the role of excessive amounts of NO in the diseased heart remains unclear 13-14. than with metoprolol (40%) as shown in figure 417. Figure 4.

All-cause Mortality between Carvedilol and Metoprolol. Poole-Wilson PA, Swedberg K, Cleland JGF et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomized controlled tnal.