Case Report and Review

Cellular and molecular mechanisms of the enhanced survival benefits of the β$_I$-adrenoceptor biased agonist, carvedilol, in diabetic cardiomyopathy with heart failure: a case report and literature review

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Abstract

The incidence of diabetic cardiomyopathy, the leading cause of heart failure amongst diabetic patients, is on the increase in the same proportion with the ageing of the population. Reactive oxygen species (ROS) and mitochondrial dysfunction are front runners in the mechanisms of the pathobiology of diabetic cardiomyopathy. Carvedilol reverses mitochondria to nucleus stress signalling and the retrograde response to offer survival advantages over other beta adrenoceptor antagonists due to its peculiar mechanisms of action, especially its anti-oxidant effect which is tenfold above that of vitamin E. The nitric oxide and hydrogen sulphide dependent vasodilator carvedilol is a biased agonist at β$_I$-adrenoceptors involving β$_I$-arrestin-mediated downstream transactivation of the epidermal growth factor receptor (EGFR) and extra-cellular signal-regulated kinase (ERK) which signals to increase Akt-mediated cardioprotection, anti-apoptosis, mitochondrial biogenesis and insulin sensitivity. Upregulation of Transforming growth factor beta (TGF-β) activity and increased central sympathetic outflow by central neurons may be a sequel of increased superoxide generation from free fatty acids (FFA) and shear stress mediated uncoupling of endothelial nitric oxide synthase (eNOS), hyperglycaemic stress, ET-I activation and AT I$_A$-R upregulation. The anti-oxidant carvedilol reduces cardiac catecholamine toxicity by inhibition of ROS-mediated upregulation of central Rho$_A$ and ROCK II kinase to decrease central sympathetic activation and baroreceptor imbalance while attenuating eNOS mRNA destabilisation. It thus successfully redresses the sympatho-cholinergic imbalance, chronotropic incompetence and enhanced arrhythmogenesis in heart failure. Carvedilol also blocks transforming growth factor-beta (TGF-β)-mediated calcineurin phosphatase activity and thus decreases extracellular matrix (ECM) accumulation and cardiac hypertrophy. This case report is of an elderly Nigerian male patient with diabetes induced dilated cardiomyopathy who responded well to active management with adjunctive carvedilol after the apparent non-response to adjunctive metoprolol. After 3 months on carvedilol treatment, ejection fraction rose from 39±2% to 45± 4% and there was also improvement in well-being as reflected in the Geriatric Depression Scale which fell from 14.20 ± 5 to 8.50 ± 4. Carvedilol may thus be the ideal beta-blocker for patients with diabetes mellitus with cardiomyopathy and deserves regular deployment.

Keywords: Diabetic cardiomyopathy, congestive heart failure, carvedilol, survival benefits, mechanisms.

INTRODUCTION

The prevalence of congestive heart failure (CHF) is increasing *pari passu* with the ageing of the population and it is the most rapidly growing cardiovascular disease worldwide (Silke, 2006) with mortality rates comparable with those for malignant disease. In tandem, there is also an absolute increase in the incidence of diabetes and its complications amongst adults aged 65 and older (Halter et al., 2014). Patients with CHF have an 8 year survival rate of 25% and suffer 1 million hospitalisations and 260,000 deaths annually from this condition in the U.S. (Wilkins and Molkentin, 2004). There is increased incidence of CHF in diabetic patients (Boudina and Abel, 2007; Refsgaard et al., 2002) even after correcting for confounding variables such as hypertension, obesity, hypercholesterolaemia and coronary artery disease and both diabetes and failing hearts may induce the same pattern of foetal gene expression (Hayat et al., 2004; Razeghi et al., 2001; Rosa et al., 2013). Clinical diabetic cardiomyopathy with CHF (Seferovic and Paulus, 2015) may induce a metabolic shift from mitochondrial respiration to glycolysis with attendant deficient ATP production (Wei et al., 2009).In diabetes, diastolic dysfunction (with preserved ejection fraction) occurs early and is made more apparent in the presence of hypertension (Boudina and Abel, 2007). Echocardiographic changes consistent with systolic dysfunction (reduced ejection fraction) and left ventricular hypertrophy which portend an increased risk for heart failure particularly in the presence of co-existing hypertension have also been described in diabetic populations,. Investigators have pointed out that abnormalities of diastolic rather than systolic performance (Pacher, 1990) may be the more important determinant of the clinical status and exercise intolerance of patients with chronic heart failure.

The concept of diabetic cardiomyopathy

The concept of diabetic cardiomyopathy (DCM) as first introduced (Rubler et al., 1972) describes diabetes associated changes in the structure and function of the myocardium that is not directly attributable to other confounding factors such as coronary heart disease and hypertension (Chaval et al., 2013; Boudina and Abel, 2010). DCM is directly related to hyperglycaemia (Rubler et al., 1972). Diabetes promotes heart failure with two-thirds of patients with type 2 diabetes mellitus (DM) dying of heart failure. Though insulin therapy may be cardioprotective under a normoglycaemic state (Carvalho et al., 2011), hyperglycaemia, hyperinsulinaemia and intensive insulin therapy have prothrombotic effects (Lemkes et al., 2010), increase ceramide synthesis in skeletal muscle (Hansen et al., 2014) and increase the risk of cardiovascular dysfunction and the death rate by

twofold in patients with type 2 DM (Nichols et al., 2001; Kleinman et al., 1988). Chronic insulin stimulation degrades insulin receptor substrate I δ 2 (IRS I and IRS 2) proteins and causes insulin resistance *in vitro.*In tandem, excessive insulin signalling to Akt is detrimental for cardioprotection (Fullmer et al., 2013). Cardiac deletion of IRSI and IRS2 prevents protein kinase B (Akt) – FOXO I phosphorylation, which serves as an indicator of insulin sensitivity, and causes cardiac dilatation and heart failure in mice (Qi et al., 2013; Fullmer et al., 2013; Zdychova and Komers, 2005). Cardiac inactivation of Akt after the loss of IRSI and IRS2 may serve as a central mechanism for the induction of heart failure (HF).

Mechanisms of clinical diabetic cardiomyopathy

The mechanisms contributing to clinical DCM (Figure 1) include increased oxidative stress and cell death and may be represented in the following sequence: i) Hyperglycaemia and increase free fatty acid metabolism lead to overproduction of superoxide (ROS) by the mitochondrial electron transport chain which causes strand breaks in DNA. ii) Nuclear DNA strand breaks leads to poly (ADP-ribose) polymerase (PARP) activation which inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH) by inducing the ADP-ribosylation of GAPDH. Activation of PARP is prevented by UCP-I; and GAPDH also plays a role in DNA repair. iii) The result of GAPDH inhibition and the increased expression of pyruvate dehydrogenase kinase 4 (PDK4) which attenuates pyruvate dehydrogenase (PDH) activity (Boudina and Abel, 2010; Hayat et al., 2004)is the increased flux of glycolytic intermediates through four metabolic pathways as follows, a) the aldose reductase or polyol pathway, b) the formation of advanced glycation end-products (AGEs) via the Maillard's reaction (Del Nogal-Avila et al., 2013), c) the formation of diacylglycerol, resulting in protein kinase C (PKC) activation, d) the increased flux via the hexosamine biosynthesis pathway (HBP) and generation of uridine N-acetyl-glucosamine (UDP-GlNac), a substrate used for protein glycosylation. Increased Free fatty acid metabolism increases HBP flux by inhibition of glucose metabolism. O-linked glycosylation of proteins leads to altered transcription activity, for example, of the specificity protein I(SPI) group of transcription factors which regulates nucleus- and mitochondrial-encoded cytochrome C oxidase subunit genes, calcium homeostasis endoplasmic reticulum protein (CHERP) and cytosolic Ca^{2+} levels (Dhar et al., 2013; Johar et al., 2013). Altered transcriptional activity of SPs also results in an increase in transforming growth factor-I beta-mediated upregulation of calcineurin-induced cardiac hypertrophy and plasminogen activator-inhibitor-I (PAI-I)-
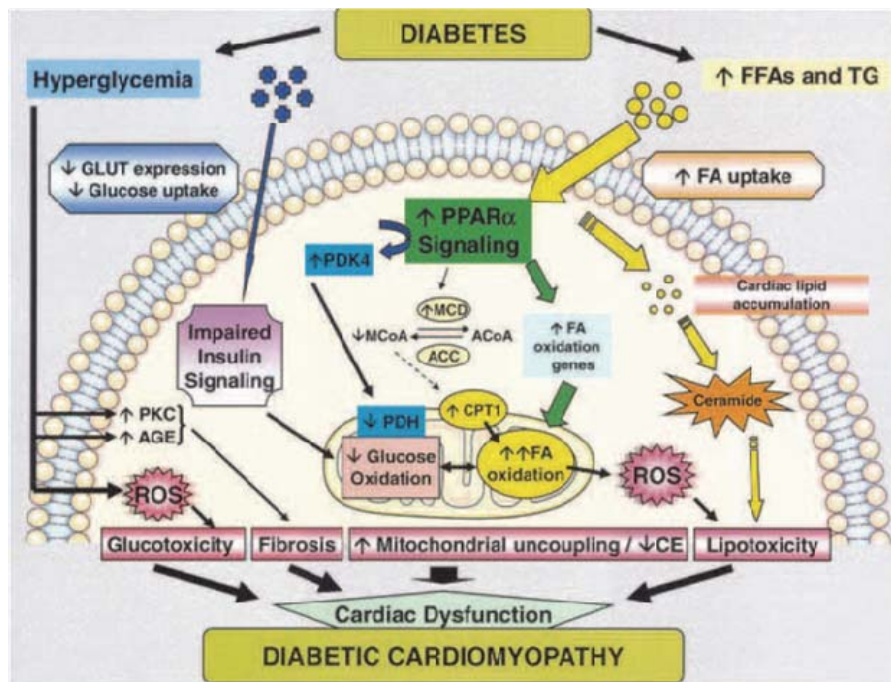
Figure 1: Mitochondrial Dysfunction In Type 2 Diabetes Mellitus Is Associated With Increased Generation of Reactive Oxygen Species (ROS) And Diabetic Cardiomyopathy.

Increased free FA (FFA) activates PPAR- signaling, leading to the increased transcription ofmany genes involved in FA oxidation. Increased FA oxidation leads to the generation ofROS at the level of the electron transport chain. ROS, which also can be generated byextramitochondrial mechanisms such as NADPH oxidase, plays a critical role in severalpathways involved in the pathogenesis of diabetic cardiomyopathy, including central I sympathetic excitation via ROCK II, sympatho-vagal imbalance (Haack et al., 2013), lipotoxicity,cell death, and tissue damage, as well as mitochondrial uncoupling and reduced cardiacefficiency. TG= triglycerides; GLUTs= glucose transporters; PDK4=pyruvate dehydrogenasekinase 4; MCD=malonyl-coenzyme A decarboxylase;MCoA= malonyl-coenzyme A;ACoA=acetyl-coenzyme A; ACC= acetyl coenzyme A carboxylase; CPT1= carnitinepalmitoyl-transferase 1; PDH= pyruvate dehydrogenase; CE= cardiac efficiency; PKC=protein kinase C; and AGE= glycation end products (Adapted from Ojji, 2011)

induced vascular endothelial replicative senescence(Wan et al., 2014; Wilkins and Molkentin, 2004; Brownlee, 2001; Brownlee, 2005: Banting Lecture; Buse, 2006; Fantus et al., 2006). GAPDH and cytochrome c oxidase are highly deregulated in the presence of oxidative stress and leads to decreased ATP levels.

Low cytosolic ATP concentrations impair relaxation of cardiomyocytes

Decreased ATP levels leads to switching off of its allosteric inhibition of cytochrome c release with resultant upregulation of ROS, cytochrome c release and apoptosis (Ramzan et al., 2013) who have noted that GAPDH may be the missing link between glycolysis and mitochondrial oxidative phosphorylation. The lower phosphocreatine content and the switch in substrate preference from glucose to fatty acids may additionally lead to lower levels of ATP in the sarcomeres that cannot be overcome by increased mitochondrial ATP production. Lower cytosolic ATP concentrations are associated with impaired calcium sequestration by the sarcoplasmic reticulum and impaired relaxation of cardiomyocytes (Ojji, 2011).

There is increased interstitial fibrosis in DCM with resultant diastolic (restrictive) and systolic dysfunction. The diabetic heart relies almost solely on free fatty acids (FFA) as metabolic substrate and FFA-induced overproduction of superoxide may lead to uncoupling of endothelial nitric oxide synthase (eNOS) by peroxynitrite (Du et al., 2006; Andersonet al., 2007; Opie and Knuuti, 2009; Bayeva et al., 2013) and oxygen wastage.

Decreased compensatory mechanisms in diabetics following myocardial infarction

Following myocardial infarction, the surviving myocardium of non-diabetics becomes hyperkinetic to compensate for non-viable infarcted myocardium in an attempt to maintain cardiac output. However, in diabetic patients, these areas of myocardium cannot achieve this compensatory enhancement in function due to a complex set of intra- and extra-myocardial factors superimposed on an already reduced coronary artery flow reserve (Hayat et al., 2004). There is impaired SERCA 2_A function (Rebsia et al., 2010), increased renin-angiotensin system (RAS) activation which impairs insulin signalling (Muscogiuri et al., 2008), impaired angiogenesis, sympathetic dysfunction and increased arrhythmogenicity in diabetic patients. Chronic adrenergic stimulation in HF increases monoamine oxidases (MAO) which increases ROS (Kaludercic et al., 2011) and uncouples eNOS to increase mitochondrial dysfunction (Kowaltowski et al., 2009; Zou et al., 2002), compromise soluble guanylyl cyclase (Munzel et al., 2005) and upregulate vascular oxidative stress (Davel et al., 2014).

The dysregulated Ca^{2+} homeostasis in CHF may account for the increased arrhythmogenicity which may be made worse by inotropes such as the cardiac glycosides and phosphodiesterase inhibitors. Calcineurin, GSK-3 beta, JNK, p38 MAPK activate nuclear factor of activated T-cells (NFAT) to induce cardiac hypertrophy (Wilkins and Molkentin, 2004). The calcium/calmodulin-dependent phosphatase, calcineurin, which upregulates extracellular matrix proteins via transforming growth factor-beta has been found a sufficient and necessary (Wilkins and Molkentin, 2004) mediator of adult cardiac hypertrophy. GSK-3 beta inhibitors raise heat-shock proteins (HSPs) levels which are low in diabetes and its complications (Hooper, 2007).

The role of mitochondrial dysfunction

There is significant involvement of reactive oxygen species (ROS), endothelial vascular and mitochondrial dysfunction in the mechanisms of pathogenesis of diabetic cardiomyopathy (Duncan, 2011; Joshi et al., 2014). Diabetic cardiomyopathy is the leading cause of heart failure (HF) in diabetic patients and diabetes mellitus is now known to impose stress on the interfibrillar mitochondrial subpopulations (Dabkowski et al., 2009). Mitochondrial dysfunction leads to mitochondria-to-nucleus stress signalling and the retrograde response (Biswas et al., 2005) with its resultant altered expression of genes (Figure 1). It contributes significantly to the increased production of ROS which explains the metabolic dysregulation in diabetes and acceleration of telomere shortening (Passos et al., 2007; Biswas et al., 2005). Depletion of mitochondrial DNA (mtDNA) initiates

the mitochondrial stress signalling which operates through altered Ca^{2+} homeostasis, activating calcineurin and Ca^{2+} responsive factors including PKC and NFAT. Genes for glucose metabolism, oncogenesis, apoptosis, calcium release and storage are also activated in this major adaptive change in global gene expression. Telomere dysfunction activates p53 which in turn binds and represses PGC-I alpha and PGC-I beta promoters (Sahin et al., 2011; Xiong et al., 2013). Overexpression of the catalytic subunit of human telomeres (TERT) counteracts retrograde signalling induced by mitochondrial dysfunction (Biswas et al., 2005) and may reverse the decrease in the anti-oxidative enzymes, catalase and SOD (Wei et al., 2001). Telomerase is credited with the protection of mitochondrial function under oxidative stress (Ahmed et al., 2008).

The place of pharmacotherapy in CHF

CHF is currently treated with a combination of angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers, diuretics and digoxin. However, drug therapy is relatively palliative with cardiac transplantation remaining the only long-term curative treatment (Wilkins and Molkentin, 2004).

B-blockers have been shown convincingly to improve survival and prevent arrhythmia-induced sudden cardiac death after myocardial infarction, in non-ischaemic dilated cardiomyopathy and heart failure (Vora and Kulkarni, 2014). B-blockers but not ACELs and/or ARBs provided additional benefit in African-Americans with HF on isosorbide dinitrate/hydralazine (Ghali et al., 2007). In randomised controlled trials (Carvedilol Prospective Cumulative Survival Study and US Carvedilol Heart Failure Study Group), carvedilol added to standard therapy with ACEIs and diuretics reduced mortality by approximately one-third and risk of hospitalisations by 65%associated with a heart rate reduction (Pacher et al., 2001; 1996; Silke, 2006). In the Carvedilol or Metoprolol European Trial, carvedilol reduced all-cause mortality by 5.7% compared to metoprolol after a 5-year follow-up (Poole-Wilson et al., 2003) and is also associated with reduction in the prevalence of new-onset diabetes by 22% compared with metoprolol (Torp-Pedersen et al., 2005; 2007).

Beneficial actions of beta-blockers in heart failure

i)   Reduce sympathetic tone
ii)   Increase vagal tone
iii)   Reduce renin release
iv)   Reduce endothelin production and release
v)   Increase nor-epinephrine re-uptake
vi)   Reduce inflammatory cytokines

vii)   Anti-oxidant effect
viii)   Antagonize antibodies against β_I-receptors
ix)   Upregulate beta-adrenergic receptor
x)   Normalise high phosphorus energetic imbalance
xi)   Improve force-frequency relationships, increase left ventricular ejection fraction, reduce end- systolic volume and improve ventricular filling time
xii)   Improve myocardial work/oxygen consumption ratio
xiii)   Reduce sub-endocardial ischaemia
xiv)   Increase heart rate variability
xv)   Reduce Q-T dispersion and arrhythmias
xvi)   Reverse chronotropic incompetence by reversing deterioration in heart rate variability
xvii)   Carvedilol and nebivolol increase eNOS and insulin sensitivity
xviii) Carvedilol (El-Kharashi and Abd-El Samad, 2011) reduce post-stroke seizures

Classification of beta-blockers

1st group: non-selective without ancillary properties like propranolol and timolol. Propranolol has the greatest inverse agonism of the β-blockers and is associated with significant negative chronotropic and inotropic effects (Vanderhoff and Ruppel, 1998)

2nd group: selective without ancillary properties. Examples include metoprolol, bisoprolol and atenolol

3rd group: non-selective, vasodilating. Examples are labetalol, nebivolol, carvedilol and bucindolol. Carvedilol and labetalol cause vasodilation through α_I-receptor blockade (Pedersen and Cockcroft, 2007) which may lead to endothelium-dependent NO-mediated vasodilation (Kamper et al., 2005). Atenolol is not vasodilating and, therefore, does not reduce stroke and cardiovascular mortality. Prognosis for HF patients has remained poor despite reduced mortality resulting from the addition of ACEIs (Vanderhoff and Ruppel, 1998) probably due to the fact ACEIs have no anti-arrhythmogenic effect (Gilat et al., 1998) and may not inhibit angiotensin II produced through chymase-dependent mechanisms (Park et al., 2013; Harrison-Bernard et al., 2013). There is a switch from renal vascular ACE-dependent to chymase-dependent Ang II production and increased endothelin conversion in diabetic kidney.

Carvedilol, nebivolol, bucindolol and metoprolol are devoid of intrinsic sympathomimetic activity in human myocardium

As it were, the beta-adrenergic receptor blockers display considerable haemodynamic and pharmacodynamics heterogeneity. B-blockers with intrinsic sympathomimetic effects (ISA) like xamoterol are contraindicated in HF because of their detrimental increase in heart rate

(Brixius et al., 2001). Carvedilol and nebivolol, apart from lacking ISA, do not display inverse agonism which metoprolol possesses to cause receptor upregulation. Inverse agonism is more pronounced at beta2- receptors than at beta I-receptors (Taira et al., 2008).

Carvedilol has advantage in diabetic cardiomyopathy compared to other β-blockers

Carvedilol improves left ventricular ejection fraction which is reduced in DCM with systolic heart failure and reduces mortality (Bristow et al., 1996). There was no overall reduction in mortality with bisoprolol in the Cardiac Insufficiency Bisoprolol Study (CIBIS) or with metoprolol in the Metoprolol in Dilated Cardiomyopathy Trial (MDC). Bucindolol (Brixius et al., 2001) improves symptoms but not outcome in heart failure patients.

Carvedilol in CHF is more advantageous than the other beta-blockers in improving glucose and lipid metabolism, in reducing lipid peroxidation (Ferrua et al., 2005; Bhatt et al., 2007; Jacob and Hennksen, www.medscape.com). Carvedilol in patients with CHF results in significant reduction in free fatty acid use and relative increase in glucose utilisation (Wallhaus et al., 2001; Kessler and Friedman, 1998) thus reducing free radical generation and oxygen wastage. Carvedilol has the most evidence for reducing mortality and morbidity in HF and post-myocardial infarction (DiNicolantonio et al., 2015; Yang et al., 2003). Micro-albuminuria, a surrogate marker of endothelial dysfunction, is less likely with carvedilol (Ritz, 2005) than with metoprolol. While metoprolol and atenolol decrease insulin sensitivity, carvedilol increases insulin sensitivity and HDL cholesterol while decreasing plasma triglycerides (DiNicolantonio et al., 2015; Kveiborg et al., 2010; Giugliano et al., 1997; Jacob et al., 1996). Metoprolol, though more effective than atenolol in HF and reduces risk of re-infarction, may increase risk of cardiogenic shock and mortality in DCM. Bisoprolol reduces mortality more than placebo but increases risk of stroke. Carvedilol is comparable to captopril in reducing serum lipids (Hauf-Zachariou et al., 1993) but captopril may increase fatal and non-fatal strokes. Amlodipine may also reduce risk of diabetes mellitus but calcium channel blockers do not improve outcome in diabetic heart failure (PRAISE 2 Study: Packer et al., 2013).

The anti-oxidant carvedilol is a biased agonist at β_I-adrenoceptors

Carvedilol, like nebivolol, are not classical beta-blockers (Erickson et al., 2013). Carvedilol is a biased agonist at β_I-and β_2-adrenoceptors (Violin and Lefkowitz, 2007; Wisler et al., 2007) that is independent of G-protein and involves G-protein- coupled receptor kinase 5 and

6(GRK)/β-arrestin signalling with downstream activation of the epidermal growth factor receptor (EGFR) and extra-cellular signal-regulated kinase (ERK) to enhance Akt-mediated cardioprotection, anti-apoptosis and eNOS genneneration. $β_I$-arrestin transactivation of EGFRcounteracts the effects ofcatecholamine toxicity, a process partlymediated via inhibition of central (GTPase) Rho_A and its associated coiled-coil containing protein kinase (ROCK II) signalling. Attenuation of ROS-mediated upregulation of the Rho/ROCK pathway (Sun et al., 2008; Ying et al., 2009) leads to decrease of central sympathetic activation and baroreceptor imbalance while attenuating eNOS mRNA destabilisation (Haack et al., 2013; Noma et al., 2007). Increased superoxide generation from FFA- and shear stress mediated uncoupling of eNOS, hyperglycaemic stress, endothelin-I (ET-I) activation and AT I_A-R upregulation may mediate an increase in sympathetic outflow by central neurons in congestive heart failure (Zucker, 2006; Campese et al., 2004; Hsieh et al., 2014). Inhibition of ROS generation by carvedilol also blocks transforming growth factor-beta (TGF-β)-mediated calcineurin phosphatase activity and decrease extracellular matrix (ECM) accumulation (Gooch et al., 2004) and cardiac hypertrophy (Wilkins and Molkentin, 2004). Biased ligands block GPCR-dependent harmful signalling but increase β-arrestin dependent signalling to offer cardioprotection (Patel et al., 2008; Kim et al., 2008; Tilley, 2011) and regulate microRNA processing (Kim et al., 2014; Zhu et al., 2013).

Carvedilol possesses enhanced survival advantages

Carvedilol has dose-related beneficial effects in survival in heart failure (Yang et al., 2003): a) through its anti-oxidant mechanisms, it may couple eNOS to induce vaso-relaxation, b) it displays anti-inflammatory effect throughupregulating interleukin-10 and downregulating interleukin-18 , an independent risk marker for cardiovascular morbidity (Watanabe et al., 2011), c) it has anti-proliferative effect and decreases neo-intima formation (Feuerstein et al., 1996), d) it displays significant anti-arrhythmic effects via inhibition of a number of cationic channels in the cardiomyocyte including the HERG-associated potassium channel, the L-type calcium channel and the rapid depolarising sodium channel (Nacarelli et al., 2005; Gilbert et al., 1996). Carvedilol is the only beta-blocker that reduces the open duration of the cardiac ryanodine receptor by suppressing store-overload induced calcium release (Zhou et al., 2011) in order to suppress arrhythmogenesis. e) it possesses $α_I$-adrenoceptor blocking effect to enhance vaso-relaxation (Pedersen and Cockcroft, 2007, f) it enhances PI3K- Akt- PGC-I alpha signalling which is anti-apoptotic and gerosuppressant (Hsiung et al., 2005; Povsicet al., 2003; Hayat et al., 2004; Gomez-Arroyo et

al., 2011; Xiong et al., 2013). This action of carvedilol may be mediated via increasing the concentration of hydrogen sulphide (H_2S) in the heart (Wilinski et al., 2011; King et al., 2014; Lefer, 2007). Vasodilating effects of nitric oxide and H_2S are mutually dependent and H_2S deficiency limits Akt activation, g) Carvedilol is a biased agonist at $β_I$-adrenoceptors which acts downstream of $β_I$-arrestin to transactivate EGFR and enhance EGFR - ERK signalling. It thus counteracts the effects of catecholamine by inhibiting apoptosis, enhancing cardiac cytoskeletal re-organisation and Akt-mediated cardioprotection (Tilley, 2011; Luttrell et al., 2015); h) in tandem with the above, carvedilol reverses cardiac hypertrophy and haemodynamic deficiency by normalising cardiac calcineurin and calcium/calmodulin dependent protein kinase II (CaMkII) (Li et al., 2014; MacDonnel et al., 2009). CaMkII overexpression may contribute to arrhythmogenesis (Sag et al., 2009). Carvedilol thus has survival advantages over other beta-adrenoceptor antagonists (Wisler et al., 2007).

By comparison, metoprolol may only prevent left ventricular dilatation but not hypertrophy after acute myocardial infarction (AMI) (Yang et al., 2003). Furthermore, carvedilol, not metoprolol, reduces the calcium-dependent augmentation of mitochondrial oxygen consumption (mvO_2) and ROS production upon complex I injury (Kametani et al., 2006). It also prevents mitochondrial permeability transition (MPT) (Carreira et al., 2006), attenuates doxorubicin-induced cardio-myopathy (Santos et al., 2002; Pereira et al., 2015) and decreases mitochondria-to-nucleus stress signaling. Not the least, carvedilol decreases autoantibodies against the beta (I), beta (2) and alpha (I) receptors (Chen et al., 2005), reduces the severity of atherosclerosis (Shimada et al., 2012) and may be protective against diabetic nephropathy (Abdel-Raheem et al., 2015). Bell (2004) observed that carvedilol may be the ideal beta-blocker for patients with diabetes mellitus.

Administration and pharmacokinetics of carvedilol

Carvedilol is rapidly and extensively absorbed and needs to be taken with food to lessen orthostatic hypotension. Both R (+) and S (-) enantiomers are extensively metabolised by ring oxidation and glucuronidation during first-pass in the liver by the P450 enzymes CYP2D6 and CYP2C9. The metabolites are excreted primarily via the bile into the faeces. Carvedilol is subject to the effects of genetic polymorphism with poor metabolisers of debrisoquin exhibiting higher plasma concentrations of R (+)- carvedilol compared to extensive metabolisers. 3 active metabolites have β-receptor blocking activity. Less than 2% of carvedilol is excreted unchanged by the kidneys. The absolute bioavailability is 25-30%. The half-life of carvedilol is 7-10 hours (Neugebauer and Neubert,

1991). The volume of distribution is 115 L, clearance is 500-700 ml/min and it is more than 98% bound to albumin.

It is safer to start treatment with low doses of carvediol (3.125 mg twice a day) and then increase to 6.25 mg twice a day. Based on tolerability, this is increased to 12.5 mg twice a day after a week. This can later be increased to the target dose of 25 mg twice a day after 5 days (Nikolic et al., 2013). Total daily dose should not exceed 50 mg (www.drug.com).

Drug interactions: Since carvedilol is metabolised by the liver P 450 enzymes, its metabolism is influenced by inhibitors or inducers of the liver P 450 microsomal enzymes. Thus, cimetidine may increase the plasma concentration of carvedilol. Carvedilol may increase the plasma concentration of digoxin by about 15%.

Side-effects: Side-effects of carvedilol therapy include dizziness, fatigue, low blood pressure, diarrhea, bradycardia and weight gain.

In subjects with normal renal function, therapeutic doses decrease renal vascular resistance with no change in glomerular filtration rate.

Contraindications to carvedilol

Contraindications (Watanabe et al., 2011) to carvedilol include bronchial asthma, decompensated NYHA functional Class IV HF requiring intravenous inotropic therapy, severe liver impairment, second- or third-degree A/V block, sick sinus syndrome, cardiogenic shock, severe bradycardia and hypersensitivity to carvedilol.

Perspectives

Drugs that may prevent diabetic microvascular and macrovascular complications are based on the new paradigm of a unifying mechanism for the pathogenesis of diabetic complications (Brownlee, 2005: Banting Lecture 2004). These drugs would include: a) transketolase activators such as benfotiamine which decrease fructose-6-phosphate and glyceraldehyde-6-phosphate, two major glycolytic intermediates; b) PARP inhibitors which would block the four major pathways of hyperglycaemic damage, (PARP mediates structural alterations in DCM (Chiu et al., 2008) and c) catalytic anti-oxidants such as catalase- or peroxidase-mimetics (for example, metalloporphyrin) that would upregulate eNOS and prostacyclin synthase attenuated by hyperglycaemia, FFA and shear stress-induced increase in ROS production (Day, 2009; Hsieh et al., 2014). Nitric oxide exerts a tonic inhibitory control of sympathetic nervous system activity (Campese et al., 2004).

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-I(GLP-I) agonists may be combined for cardioprotection (Hausenloy et al., 2013). The DPP-4

inhibitor sitagliptin is a GLP-I enhancer and promotes cardioprotection via GLP-I in type 2 diabetic hearts primarily by limiting hyperglycaemia and hyperlipidaemia (Picatoste et al., 2013). GLP-I and its insulinotropic-inactive metabolite, GLP-I (9-36), may possess cell-autonomous cardioprotective action. GLP-receptor signalling may be linked to PPAR-δ activation. Metformin may also exhibit anti-apoptotic/anti-necrotic and anti-fibrotic direct effects in cardiac cells (Picatoste et al., 2013). Trimetazidine may be used to inhibit FFA oxidation (Opie and Knuuti, 2009) and decrease uncoupling of eNOS, while ranolazine which inhibits the late sodium inward channel is under investigation. Similarly, activators of protein kinase C epsilon may have a role in preventing DCM as they may inhibit the negative chronotropic properties of chronic hyperglycaemia (Malhotra et al., 2005).

Similarly, ghrelin which reverses sympatho-vagal imbalance in HF, protects from HF-induced myocardial infarction, improves exercise capacity, ameliorates diabetic cachexia and improves ventricular and endothelial function is being investigated for cardioprotection (Khatid et al., 2014; Qi et al., 2010).

Differential diagnosis of clinical diabetic cardiomyopathy with heart failure

Advanced glycation end products in diabetes mellitus may give rise to both dilated and restrictive phenotypes of clinical diabetic cardiomyopathy (Seferovic et al., 2015). Patients with unexplained dilated cardiomyopathy may be 75% more likely to have diabetes than age-matched controls (Poornima et al., 2006). The differentials of a dilated phenotype with heart failure and reduced ejection fraction are listed below. The diagnosis of diabetic cardiomyopathy relies on clinical data correlated with a long history of diabetes mellitus and, if possible, pathological and echocardiographic findings (Liu et al., 2007).

Differential diagnosis of dilated cardiomyopathy (Figure 2)

a) Restrictive cardiomyopathy and heart failure with preserved ejection fraction (diastolic dysfunction). In this, there is coronary microvascular endothelial dysfunction and restrictive filling in diastole. Causes include amyloidosis and endomyocardial fibrosis and may be more prevalent in obese type 2 diabetics (Seferovic and Paulus, 2015; Ojji, 2011). Ejection fraction may be normal or preserved.
b) Hypertrophic cardiomyopathy where ejection fraction may be more than 75%.
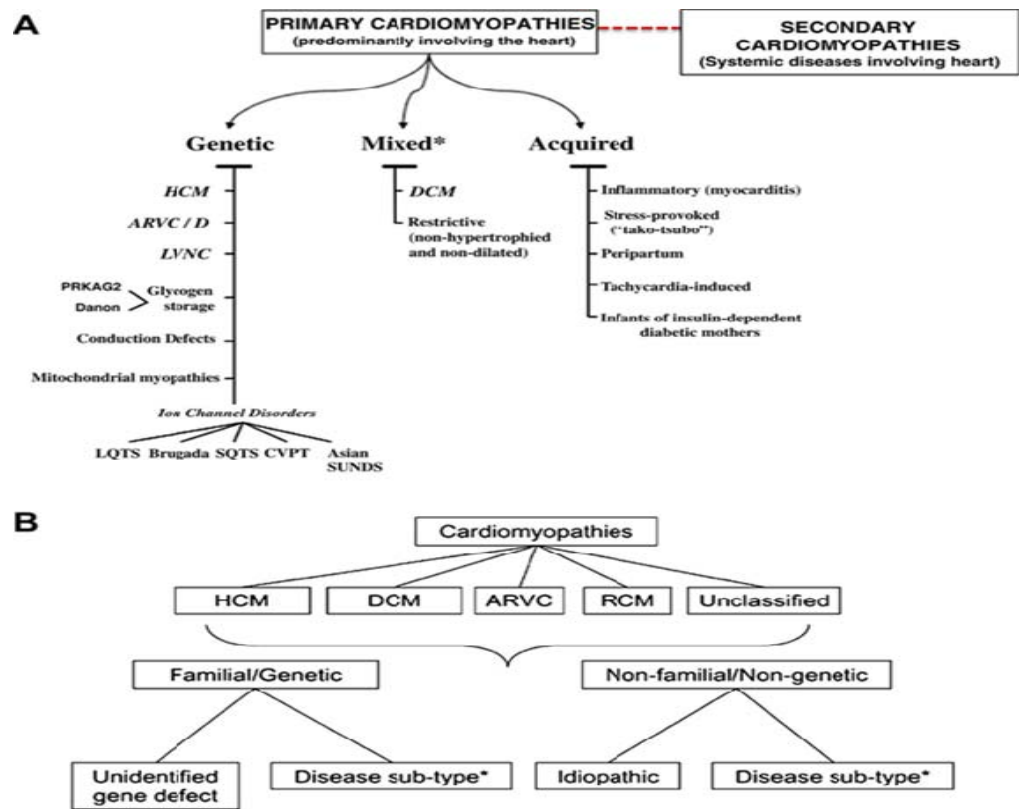c) Arrhythmogenic right ventricular cardiomyopathy/ dysplasia

Figure 2: Classification of cardiomyopathies.

Current Classifications Of Cardiomyopathies: The 2006 American Heart Association classification proposes genetics-based classification (A). On the other hand, the 2008 European Society of Cardiology classification suggests first the morphofunctional phenotype and then the addition of inheritance information (B). ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CVPT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular noncompaction; LQTS = long QT syndrome; RCM = restrictive cardiomyopathy; SQTS = short QT syndrome; SUNDS = sudden unexplained nocturnal death syndrome.
Source: The Morpho-functional, Organ-System involvement, Genetic, Etiological annotation, Stage (MOGE(S)) Classification for a Phenotype–Genotype Nomenclature of Cardiomyopathy: Endorsed by the World Heart Federation (Arbustini et al., 2013).

d) Cardiac tamponade
e) Myocarditis
f) Acute pericarditis
g) Hyperthyroidism
h) Heavy metal toxicity
i) Thiamine deficiency
j) Amphetamine toxicity and cocaine-related cardiomyopathy

Classification of heart failure

American College of Cardiology/American Heart Association system:
Stage A: (high risk for developing heart failure): hypertension, coronary artery disease, diabetes mellitus, family history of cardiomyopathy

Stage B: (asymptomatic heart failure): previous myocardial infarction, left ventricular systolic dysfunction, asymptomatic valvular disease.
Stage C: (symptomatic heart failure): structural heart disease, dyspnea, fatigue, reduced exertion tolerance.
Stage D: (refractory end-stage heart failure): marked symptoms at rest despite maximal medical therapy, recurrent hospitalisations.

Present drugs for heart failure

Angiotensin converting enzyme inhibitors (ACEIs)
Angiotensin receptor blockers (ARBs)
B-blockers
Cardiac glycosides
Diuretics
Vasodilators

Anti-arrhythmics
Human B-type natriuretic peptide
Inotropic agents
Inodilators (for example, levosimendan which is under clinical trial)

CASE REPORT

A 62 year-old male patient was seen January, 2014 at Oseghale Oriaifo Medical Centre, Idumebo-Ekpoma with clinical diagnosis of diabetes-induced CHF. Patient has had diabetes mellitus for more than 11 years. He presented with moderate tachypnea, dyspnea on exertion, limitation of physical activity and cough. There was finger clubbing, severe pedal oedema and hepatomegaly. There was pulmonary oedema with wheezes. Heart examination revealed right ventricular heave, apical presystolic pulse and systolic mitral murmur. He had no fever but was very pale with PCV of 12%. The total WBC count revealed no eosinophilia and this ruled out loeffler's syndrome. Otherwise, the serum electrolytes/urea and total WBC revealed no significant abnormality. Pulse was 105/min, regular but of poor volume. Fasting blood sugar was 326 mg/dl. Patient was also hypertensive (BP of 170/115 in the supine position). Chest X-ray showed cardiomegaly which was confirmed by ultra-sound examination. Chest X-ray showed marked unfolding of the aorta, increased cardio-thoracic ratio with prominent vascular markings of the upper lung fields. There was pleural effusion on the right side. In fact, the heart appeared boot-shaped as found in endomyocardial fibrosis (EMF) which affects children and young adults in the tropics. Ultra-sound showed hepatomegaly with tortuosity of hepatic vessels.

Echocardiography in M-mode showed diastolic left ventricular dimension > 65 mm. There was septal wall thickness of 12 mm. Electrocardiography showed non-specific ST elevation,a Q wave and left ventricular hypertrophy with chamber enlargement. Echocardiography showed patient's ejection fraction to be reduced (39±2%) consistent with heart failure and cardiomegaly. Normal ejection fraction is 55-70%. There were premature ventricular complexes. He confirmed he has not been compliant with his medications (which included metoprolol, furosemide and digoxin) due to finance. Diagnosis of DCM-induced HF (American Heart Association Stage C) was made.

The first priority was to resuscitate and transfuse with a pint of packed cells under the cover of furosemide 100 mg intravenously and digoxin tablet orally, in order to fore-stall acute decompensation, a known sequel of drug non-compliance/lack of efficacy. He was also administered aminophylline slowly intravenously during the transfusion procedure. The pint of packed cells ran very slowly for over 5 hours under direct supervision by author. With absolute precautions, he tolerated the transfusion with lessening of the orthopnea and regained strength.

He was started on metformin (Glucophage), after confirming that the plasma creatinine was 1.40 mg/dl, at a dose of 1,500 mg/day. For the DCM-induced HF, he continued with intravenous furosemide (60 mg/day) for a week before changing to the tablets at 40 mg daily per oral. Also, low-dose digoxin was started orally and discontinued after 15 days. Losartan was also commenced. Adjunctive carvedilol was commenced at a dose of 3.125 mg twice daily which was increased to 6.25 mg twice daily after 5 days ("starting low and going slow"). This was increased to 12.5 mg twice a dayafter for two weeks before changing to the maximal dose of 25 mg twice daily.

After a week on metformin and dietary restriction, his blood sugar dropped to 150 mg/dl and BP reduced to 150/105 mm Hg. With the combination treatment for HF, there was improvement in exercise tolerance after a week and his pedal oedema and hepatomegaly greatly reduced. His easy fatigability on moderate exertion disappeared after three weeks and repeat scans showed gradual decrease in the cardiomegaly and liver enlargement. With echocardiography, the ejection increased to 45±4% after three months. His score on the Geriatric Depression Scale (GDS), administered as a structured face-to-face interview, which was 14.20±5 at beginning of treatment reflecting mild depression (Wikipedia.org) fell significantly to 8.50±4 after 3 months (normal: 0-9). He has continued to maintain improvement and was counselled on need for calorie restriction with the *Oriaifo diet* and moderate exercise training.

DISCUSSION

Diabetes affects 10-30% of patients with heart failure (Solang et al., 1999) and, especially in women, the presence of diabetes increases the risk of death by 50% in patients with heart failure (Gustafsson et al., 2004). Simultaneous control of glycaemia, hypertension and dyslipidaemia are reported (Miki et al., 2013) to significantly reduce cardiovascular events and mortality in type 2 diabetes mellitus patients. Case-report illustrates successful management of DCM-induced HF with adjunctive carvedilol, furosemide, losartan and metformin in an elderly male Nigerian patient. Clinical outcomes in diabetic patients with heart failure are better in patients treated with metformin (Eurich et al., 2005; Aguilar et al., 2011; Miki et al., 2013). Metformin is known to be useful in management of type 2 diabetes mellitus and may exhibit enhanced cardioprotective effects when combined with DPP-4 inhibitors (Hamdani et al., 2014) that possess GLP-I enhancing effects such as sitagliptin (Picatoste et al., 2013) which may partially upregulate the cGMP-PKG pathway to decrease left ventricular passive stiffness. We have previously reported that the combination of

metformin and calorie restriction was more effective in the prevention of adverse cardiovascular events and mortality amongst patients with type 2 diabetes mellitus than metformin alone, sulphonylureas and insulin (Oriaifo et al., 2015). While rosiglitazone accentuated lipid accumulation and decreased eNOS in the spontaneously hypertensive, insulin resistant (SHHR) rat, the biguanide metformin upregulated eNOS and hydrogen sulphide whileattenuating left ventricular remodelling, wall stress, perivascular fibrosis and cardiac lipid accumulation (Cittadini et al., 2010; Wilsinski et al., 2013). Age- and hypertension-related decline in nitric oxide and hydrogen sulphide bioavailability may be corrected by calorie restriction and exercise training (Smith et al., 2006; Predmore et al., 2010; Gu et al., 2012). Generation of hydrogen sulphide (H_2S) by exercise training, calorie restriction, carvedilol and metformin may in concert enhance mitochondrial function and rescue eNOS from peroxynitrite-induced uncoupling (Gu et al., 2012; Predmore et al., 2010; Al-Magableh et al., 2013; Guo et al., 2012).

The nitric oxide- and hydrogen sulphide-dependent vasodilator and β_l-adrenoceptor biased agonist, carvedilol, exhibits beneficial actions in hypertension, heart failure and acute myocardial infarction (Verma et al., 2004; Leonetti and Egan, 2012; DiNicolantonio et al., 2015, Kveiborg et al., 2007) and may be combined with losartan for enhanced effects (Yang et al., 2003). Low dose carvedilol may be effective in reducing areas of myocardial fibrosis and stiffness (Watanabe et al., 2000; Masutani et al., 2008) important in contributing to a restrictive left ventricular filling pattern and mitral regurgitation which is frequent in dilated cardiomyopathy (Palazzuolli et al., 2004; Capomolla et al., 2000). Restricted left ventricular filling pattern assessed by Doppler echocardiography is a powerful indicator of increased mortality risk in CHF and may signal need for additional vasodilator therapy (Atherton et al., 1998) or heart transplant (Pinamonti et al., 1993). Increased hydrogen sulphide consumption by hyperglycaemic cells causes hydrogen sulphide deficiency implicated in dampening Akt-mediated cardioprotection (Szabo, 2012; King et al., 2014).

Compared to metoprolol which may increase coronary sinus norepinephrine levels and β-receptor density, carvedilol selectively lowered coronary sinus norepinephrine levels and do not change cardiac β-receptor density (Gilbert et al., 1996). This may be an additional advantage for carvedilol since norepinephrine stimulates apoptosis in adult ventricular myocytes by activation of the β-adrenergic pathway (Communal et al., 1998).

Angiotensin II is correlated with hyperglycaemia-induced oxidative stress and cardiac myocyte apoptosis δ fibrosis. Hyperglycaemia activates the intra-cellular renin-angiotensin system in cardiac fibroblasts (Singh et al., 2008$_A$) and increases intracellular levels of angiotensin II

(Ang II) in cardiac myocytes and kidneys from diabetic hearts. This intracellular synthesis of Ang II is not blocked by ACE inhibitors (Singh et al., 2008b; Park et al., 2013). Furthermore, the sole use of ACE I or ARB may be associated with Ang II and aldosterone escape and increase in plasma renin activity (Badheka et al., 2012). Importantly, carvedilol markedly suppresses the increase in active renin observed with time despite angiotensin converting enzyme inhibition and also decreases angiotensin converting enzyme activity (Solal et al., 2004).

Carvedilol and aerobic exercise training may represent better prognostic power in life-long treatment of diabetic HF. Exercise training stands to enhance the effect of carvedilol in improving baroreflex function and reducing sympathetic nerve activity by decreasing ROS-mediated activation of the Rho/ROCK pathway (Campese et al., 2004, Sun et al., 2008; Ying et al., 2009) and attenuating angiotensin II and angiotensin receptors in the CNS (Mousa et al., 2008). Both aerobic exercise training and carvedilol reduce mortality, increase exercise tolerance (Vanzelli et al., 2013) and mitochondrial biogenesis (Steiner et al., 1985; Pereira et al., 2011). Both re-establish left ventricular contractility and lead to a ventricular reverse re-modeling. Both prevent ventricular lipid peroxidation and alter expression levels of proteins involved in Ca^{2+} handling. Combined treatment is noted to significantly increase $SERCA_2$ expression. Exercise training is the most potent stimulus to increase skeletal muscle GLUT 4 expression (Richter and Hargreaves, 2013) even in conditions of insulin resistance (Stanford and Goodyear, 2014; Hawley and Lessard, 2008) and may synergise with carvedilol that also increases insulin sensitivity in HF (Torp-Pedersen et al., 2005; Ferrua et al., 2005; Kveiborg et al., 2007; 2010).Exercise mediates muscle GLUT 4-dependent glucose uptake independent of AMPK via Ca^{2+}/calmodulin-dependent protein kinases, Akt substrate of 160 KD_A (AS160), atypical protein kinase Cs and the Rho family of GTPase Rac_l (Stanford and Goodyear, 2014).

Carvedilol may attenuate the age-related decline (Lowe et al., 2000)in GAPDH levels via its inhibition of PARP (Strosznaider and Dziewulska, 2005; Habon et al., 2001) and its induced decrease in TGFB-I/GAPDH ratio (Okumura et al., 2015).Carvedilol-induced decrease in ADP-ribosylation of GAPDH and resultant enhanced GAPDH levels stand to downregulate the pathways important in pathobiology of diabetic complications (Brownlee, 2005; Fantus et al., 2006): attenuation of the polyol pathway-mediated decrease in NADPH and glutathione levels, decrease in AGEs biosynthesis, attenuation of PKC activation and decrease of the hesoxamine biosynthesis pathway.

Importantly, carvedilol's upregulation of mitochondrial biogenesis may upregulate neurotrophic factors and stands to impact positively on parameters of cardiovascular psychiatry and neurology, a protégé of

the heart-brain connection (Ritz et al., 2013; Manev, 2009; Oriaifo et al., 2015). This is important when we consider that other potential advantages of carvedilol include the suppression of seizures which may be more common in diabetic and stroke patients (Kirchner et al., 2006; Schwechter et al., 2003; El-kharashi and El-Samad, 2011; Goel and Goel, 2013). Carvedilol is more potent than amlodipine in preventing cytotoxicity in cortical neurons from stroke-prone states (Yamagata et al.,   2004).Carvedilol's   inhibition   of   acid sphingomyelinase (Reddy et al., 2014) leads to inhibition of ceramide production (Beckmann et al., 2014) and this may likely contribute to   beneficial effects in insulin resistance (Smith et al., 2006; Hansen et al., 2014), status epilepticus (Mikati et al., 2003; Schauwecke, 2012), Alzheimer's disease, bipolar disorder and depression which may be co-morbid with DCM (Arrieta-Cruz et al., 2010; Schwarz et al., 2008; Singh et al., 2002). Score in the GDS became normal after 3 months in this patient. In fact, carvedilol may help prevent Alzheimer's disease (Wang et al., 2011) and depression (Chen et al., 2013) partly through hydrogen sulphide which upregulates nitric oxide production (Wilinski et al., 2011), an effect that may be enhanced by metformin which also increases brain H_2S (Wilinskiet al. 2013). Carvedilol alone via its vasodilator and anti-oxidant mechanisms (Cotter and Cameron, 1995) or in combination with metformin may produce enhanced anti-hyperglycaemic   effects   which   may   reverse hyperglycaemia-induced schwann cell de-differentiation like aldose reductase inhibitors such as epalrestat and could be beneficial in diabetic neuropathy (Hao et al., 2015).

Diabetes   mellitus   causes   bone   marrow microangiopathy,   hypoperfusion   and   depletion   of haematopoietic cells (Oikawa et al., 2010) and this may explain the severe anaemia in this patient which necessitated blood transfusion. Carvedilol via its anti-oxidant mechanism also prevents red blood cell membrane damage due to free radicals (Habon et al., 2001) and could contribute to prevention of diabetes-induced anaemia.

CONCLUSION

The vasodilator, anti-oxidant and β-arrestin$_l$-biased β$_l$-adrenergic receptor agonist, carvedilol seems to possess significant survival benefits in diabetes-induced dilated cardiomyopathy with heart failure and its effect may be enhanced by exercise training. Carvedilol, which may partly explain the link between cardiometabolic and neuropsychiatric disorders, deserves to be more frequently   prescribed   for   patients   with   diabetic cardiomyopathy and heart failure.

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