Memo: Carvedilol for Blood Pressure Control in Metabolic Syndrome and Type 2 Diabetes

The compensatory hyperinsulinemia associated with metabolic syndrome and type2 diabetes provides an activating stimulus to brain sympathetic centers (which evidently maintain their sensitivity to insulin), leading to a chronic up-regulation of sympathetic tone.[1, 2] This is a key cause of the blood pressure elevation typically seen in these syndromes. An increase in sympathetic tone promotes increases in heart rate, cardiac inotropy, renin secretion, renal sodium retention, and vascular resistance - all of which interact to elevate blood pressure.[2] (Hyperinsulinemia also acts directly on the kidney – which likewise maintains its insulin responsiveness in metabolic syndrome – to promote sodium reabsorption.[3]) Moreover, the increase in global mortality associated with an increased resting heart rate suggests that chronic elevation of sympathetic activity increases risk not only for cardiovascular events and heart failure but for cancer mortality as well, likely reflecting the presence of beta2 receptors on many pre-neoplastic and neoplastic tissues.[4-9] Hence, increased sympathetic tone may be a key mediator of the increased cardiovascular and cancer risk associated with metabolic syndrome and type 2 diabetes.[10, 11]

For this reason, the vasodilating beta-blocker carvedilol, which inhibits alpha1 as well as beta1 and beta2 adrenergic receptors, has the potential to strike to the root of the contribution of metabolic syndrome to hypertension, and to lessen the adverse impact of this syndrome on overall health and survival. Studies of carvedilol in metabolic syndrome and type 2 diabetes indicate that it is an effective and reasonably well tolerated agent for blood pressure control.[12-14] The randomized, double-blind GEMINI trial, targeting hypertensive type 2 diabetics already receiving renin-angiotensin system inhibitors, found that, as contrasted to the non-vasodilating beta blocker metoprolol, (a beta1-selective agent which does not inhibit alpha1 receptors), carvedilol tends to have a favorable impact on insulin sensitivity, glycemic control, and lipid values; moreover, its use is associated with fewer diabetic symptoms, lower risk for weight gain, and a lesser tendency for normoalbuminuria to progress to microalbuminuria, .[15-18] These findings suggest that alpha1 stimulation promotes and exacerbates metabolic syndrome – as further demonstrated by the favorable metabolic impact of pure alpha1 antagonists such as doxazosin.[19] Carvedilol also has the further merit of direct antioxidant activity[20-23] – of interest in light of the prominent contribution of oxidative stress to the complications of metabolic syndrome and diabetes.

These considerations do not gainsay the utility of other pharmaceutical strategies – angiotensin and calcium antagonists, diuretics – for controlling blood pressure in patients with metabolic syndrome or type 2 diabetes; telemisartan, an AT1 receptors antagonist, is of particular interest in this regard in light of its partial PPARgamma agonism.[24] Many patients will require combination regimens for optimal blood pressure control. However, there is reason to suspect that antihypertensive protocols which include carvedilol may have a better impact on long term health outcomes in such patients – a proposition that hopefully will be tested in future research.

References

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