Review Article

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# Linagliptin: Perception Vs Reality, More Than A Renal-Friendly Gliptin

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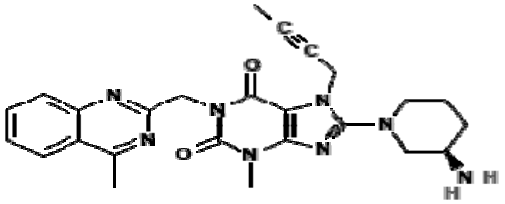
**Introduction:**

Linagliptin belongs to a new chemical class of DPP4 inhibitors based upon a xanthine scaffold structure, which has the molecular formula $C_{25}H_{28}N_8O_2$ and a molecular weight of 472.5 Da.[1]



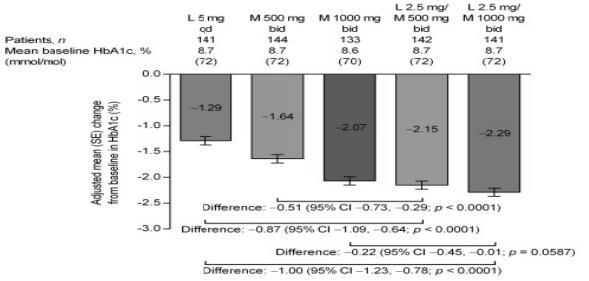
DPP-IV enzyme has been observed to be responsible for degradation of the incretin hormones, e.g. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Consequently, Linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in the glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones have been involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day, and levels rise immediately after meal intake. GLP-1 and GIP are the key factors, which are responsible for insulin incremental biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood-glucose levels. Furthermore, GLP-1 reduces glucagon secretion from pancreatic alpha cells. Hence, reduction in hepatic glucose output.[2] It has excellent selectivity for DPP-4 versus DPP-8 (40,000-fold) and DPP-9 (> 10,000-fold). Linagliptin is having half-life of more than 100 hrs and having same efficacy in 5 mg dose once daily independent of any age group or ethnicity.[1]

**Efficacy of linagliptin in T2DM patients:**

A prospective, observational, post-marketing surveillance study including 2054 patients conducted over 156 weeks with T2DM patients started with linagliptin monotherapy. The mean change in HbA1c from baseline to last observation was - 0.67%.[3]

**Combination of Linagliptin / Metformin:**

The efficacy and safety study of linagliptin/metformin group with different dosing regimen and reduce the HbA1c up to 2.3%.[4] Once-daily linagliptin showed safety and tolerability over 1 year and provided effective add-on therapy leading to significant HbA1c reductions, similar to metformin, over 52 weeks in Japanese patients.[5]Linagliptin add on to insulin also reduces HbA1c significantly up to 0.61%.[6]




*Model includes continuous baseline HbA1c and treatment.
bid, twice daily; CI, confidence interval; HbA1c, glycosylated hemoglobin; L, linagliptin; M, metformin; qd, once daily; SE, standard error.

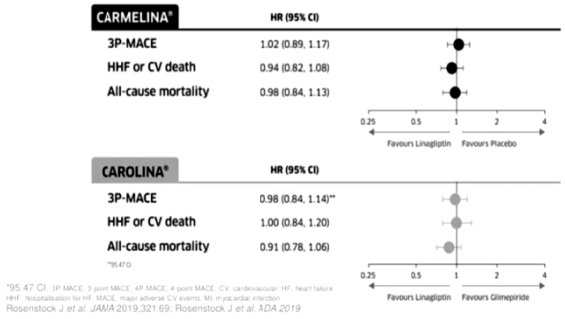
**Combination of Linagliptin/SGLT2 inhibitor:**

Combinations of empagliflozin / linagliptin as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components and were well tolerated.[7]

**Cardiovascular Safety**

Linagliptin decreases aortic PWV as a measure of arterial stiffness and predictor of CV events, in early type 2 diabetes subjects after 26 weeks of treatment. Further studies are needed to assess whether a reduction of aortic PWV sustains on the long-term and translates into an

improvement of CV outcome.[8] Linagliptin is a unique DPP-4 inhibitor with both CV and renal safety profiles. Moreover, it exerts beneficial CV effects beyond glycemic control and beyond class effects. Linagliptin is protective for both macrovascular and microvascular complications of diabetes. Given the role of endothelial-immune cell interactions as one of the key events in the initiation and progression of CVD, linagliptin modulates these cell–cell interactions by affecting two important pathways involving stimulation of NO signaling and potent inhibition of a key immunoregulatory molecule.[9]A study suggests that long-term treatment with linagliptin improves endothelial function and inhibits progression of wall thickness independent of reversal for diabetic status, which may have novel beneficial potentials for residual risk management of complex atherosclerosis in type-2 diabetics.[10]A study including patients with T2DM and CKD concluded that linagliptin when added to metformin and/or insulin demonstrates a functional improvement of CD34+ Endothelial Progenitor Cell migratory function through increased CD34/CXCR4 positivity and concomitant improvement in arterial stiffness parameters along with improvement in lipid profile, podocyte health profile and HbA1C.[11] An international cardiovascular outcome trial (CARMELINA) in participants with type 2 diabetes mellitus and concomitant atherosclerotic cardiovascular disease and/or kidney disease, linagliptin did not affect the risk of hospitalization of heart failure(hHF) or other selected HF-related outcomes, including among participants with and without a history of HF, across the spectrum of kidney disease and independent of previous left ventricular ejection fraction.[12]




Another long CVOT trial (CAROLINA) indicate that among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.[13]

**Renal Safety**

About 5% of linagliptin is eliminated by the kidneys and no dose adjustment is recommended in kidney impairment. Linagliptin in T2DM patients with CKD was able to improve renal progression without significant effect on proteinuria and glucose control. Linagliptin also lowers the risk of microalbuminuria and improves composite microvascular endpoints and proven to be safe in renal transplant patients.[14]

**Linagliptin vs Sitagliptin**

Linagliptin proven to be cardiosafe in broad spectrum suggested from two cardiovascular outcome trials including high risk CV risk and low CV risk patients as well as in heart failure also while for sitaglitpin there is only one CVOT available for high CV risk patients. Linagliptin is safe in high kidney risk and kidney transplant also while the safety of sitagliptin is uncertain. Linagliptin is also proven to be hepatic safe while sitagliptin is safe in the mild to moderate impaired hepatic function.

| Mono therapy | | CVOTs | High CV Risk | Heart Failure | High Kidney Risk | Hepatic Safety |
|---|---|---|---|---|---|---|
| Sitagliptin | ✓ | ✓ | Safe | Safe | Uncertain | Mild to moderate hepatic impairment safe |
| Linagliptin | 3 | 2 | Safe | Safe | Safe | Safe |

**Conclusion:**

Linagliptin simplify T2DM patient care. Linagliptin has long half-life ensuring effective 24 hr glycemic control with once daily dose of 5 mg. Linaglitin can be give independent of any age group, ethnicity, BMI, CV risk, disease duration,

concomitant anti-diabetic medications. With 2 CVOTS, Linaglitin has proven CV safety and kidney safety with no need to adjustment of dose in any stage of CKD.

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