MICRO LABS LIMITED

Diabetes Update

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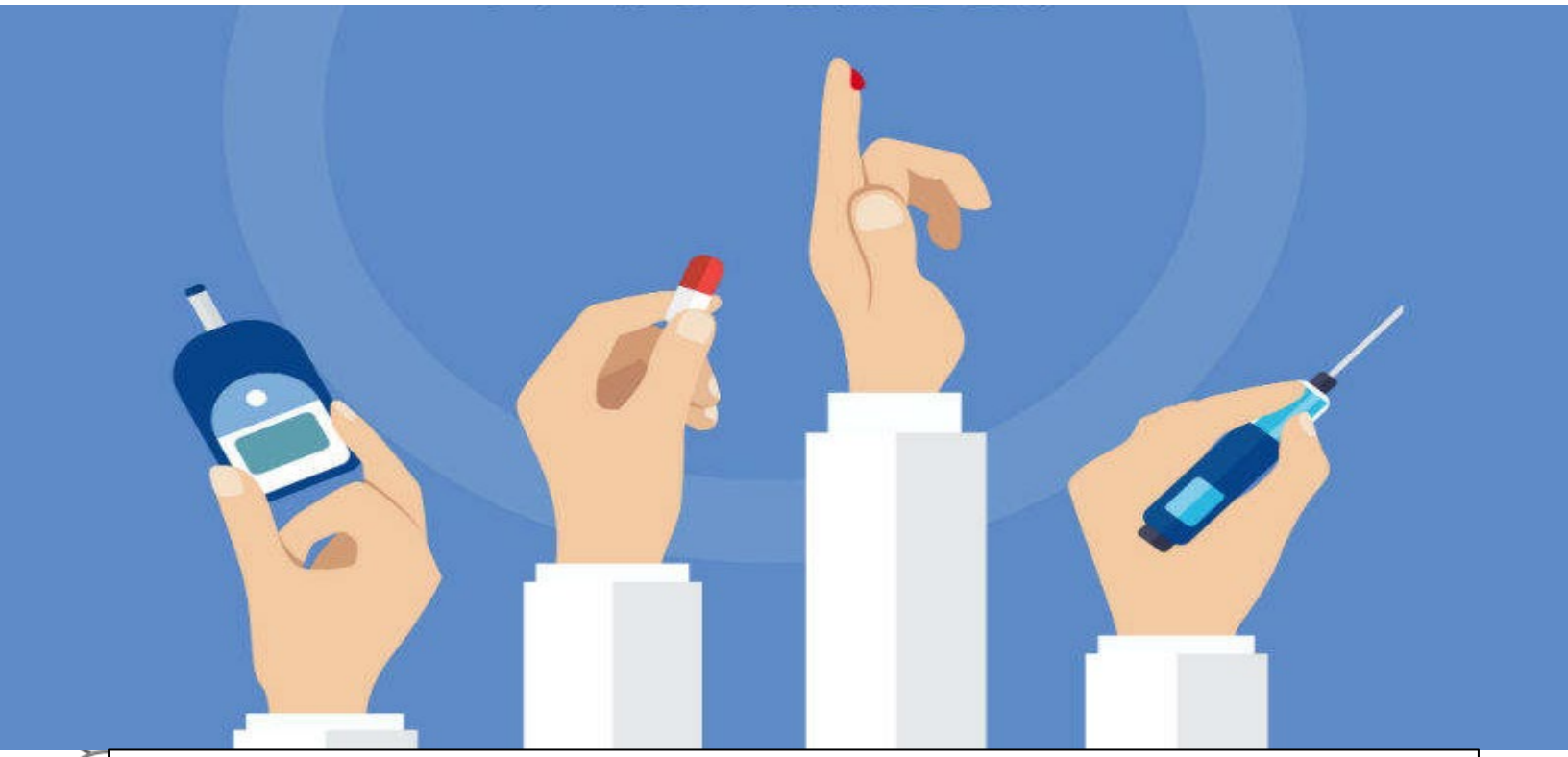

Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Retinopathy predicts stroke in type 2 diabetes
- Ertugliflozin on renal function over 104 weeks of treatment: A post hoc analysis
- "H" for Heterogeneity in Type 2 Diabetes Management

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Limited

Retinopathy predicts stroke in type 2 diabetes

Diabetic retinopathy (DR) is one of the leading cause of vision loss. It is a micro vascular complication. Though it is largely preventable, if affects approximately one third of the patients with diabetes. The aim of this study was to determine whether diabetic retinopathy (DR) and its severity increases stroke and myocardial infarction (MI) risk in a contemporary cohort.

Fremantle Diabetes Study Phase II participants with T2D had DR graded from fundus photography at baseline between 2008 and 2011. Subsequent hospitalizations and mortality for MI or stroke were ascertained through validated data linkage to end-2016. Cox regression modelling identified predictors of first stroke and MI including DR presence and severity. The 1521 participants with T2D and known DR status (mean age 65.6 years, 52.1% males, median diabetes duration 9.0 years) were followed for a mean of 6.6 years.

After excluding those with prior MI/stroke, there were 126 incident MIs among 1393 eligible participants and 53 incident strokes in 1473 eligible participants, respectively. Moderate non-proliferative DR (NPDR) or worse was significantly and independently associated with an increased risk of incident stroke (adjusted hazard ratio 2.55 (95% CI 1.19, 5.47), p = 0.016). Retinopathy presence and severity increased the risk of incident MI in unadjusted models ($p \leq 0.001$), but these associations were no longer statistically significant after adjusting for other risk factors. Moderate DR is an independent risk factor for stroke but not MI in people with T2D. The retinal microvasculature is readily observable and its appearances should be considered when CVD and especially stroke risk management is planned in T2D.

Baseline variable	Model A		Model B	
	Cox model, HR (95% CI)	p-value	Cox model, HR (95% CI)	p-value
HbA1c (per 1% increase)	1.24 (1.03, 1.51)	0.027	1.21 (0.99, 1.47)	0.062
Atrial fibrillation	3.20 (1.50, 6.84)	0.003	3.50 (1.62, 7.56)	0.001
Ln (urinary albumin:creatinine)	1.34 (1.12, 1.61)	0.002	1.30 (1.08, 1.56)	0.006
Moderate NPDR or worse			2.55 (1.19, 5.47)	0.016

Moderate Diabetic Retinopathy is an independent risk factor for stroke in patients with Diabetes.

Source: Drinkwater et al. Cardiovasc Diabetol 2020 March. 19 (43): 1-11

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Ertugliflozin on renal function over 104 weeks of treatment: A post hoc analysis

In this post hoc, exploratory analysis, data from two RCTs (VERTIS MET and VERTIS SU that evaluated ertugliflozin vs glimepiride or placebo/glimepiride (non-ertugliflozin) in patients with type 2 diabetes mellitus were combined to to evaluate the effects of ertugliflozin on eGFR (using the Modification of Diet in Renal Disease study equation) and albuminuria (UACR, geometric mean of change from baseline) in the overall population and by baseline UACR category over 104 weeks. The renal safety profile of ertugliflozin was assessed in the overall population.

Overall, mean (SD) baseline eGFR was 88.2 (18.8) ml min^{-1} (1.73 $m)^{-2}$ and geometric mean (95% CI) of baseline UACR was 1.31 mg/mmol (1.23, 1.38). At week 6, the changes in eGFR from baseline were −2.3, −2.7 and −0.7 ml min^{-1} (1.73 $m)^{-2}$ for the ertugliflozin 5 mg, ertugliflozin 15 mg and non-ertugliflozin groups, respectively. Mean eGFR in the ertugliflozin groups increased over time thereafter, while it decreased in the non-ertugliflozin group. Week 104 changes in eGFR from baseline were −0.2, 0.1 and −2.0 ml min^{-1} (1.73 $m)^{-2}$ for the ertugliflozin 5 mg, ertugliflozin 15 mg and non-ertugliflozin groups, respectively. Among 415 patients (21.4% of the cohort) with albuminuria at baseline, the ertugliflozin groups had greater reductions in UACR at all measured time points up to week 104. At week 104, the non-ertugliflozin-corrected difference in UACR (95% CI) was −29.5% (−44.8, −9.8; $p < 0.01$) for ertugliflozin 5 mg and −37.6% (−51.8, −19.2; $p < 0.001$) for

eGFR values returned to baseline and were higher with ertugliflozin compared with non-ertugliflozin

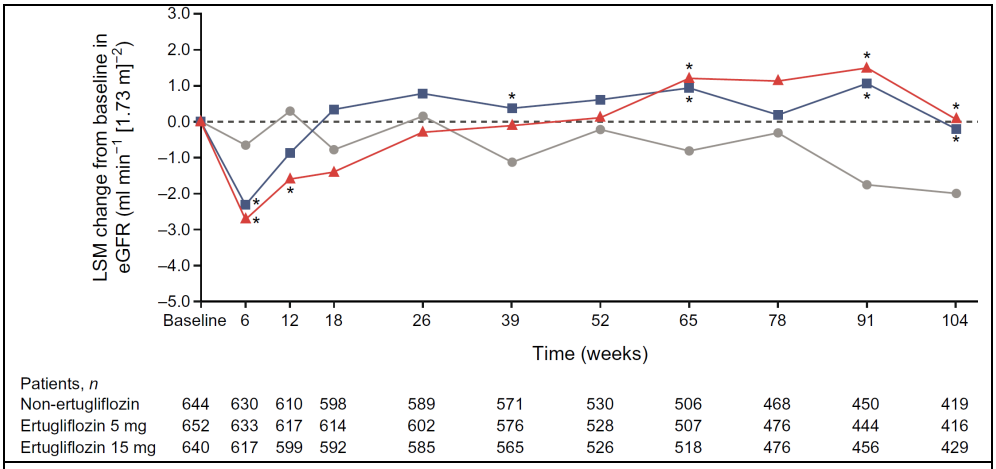

Fig.: Change from baseline in eGFR over 104 weeks

ertugliflozin 15 mg. Least squares mean changes from baseline in HbA1c (mmol/mol [95% CI]) at week 104 were similar between treatment groups: −6.84 (−7.64, −6.03), −7.74 (−8.54, −6.94) and −6.84 (−7.65, −6.03) in the ertugliflozin 5 mg, ertugliflozin 15 mg and non-ertugliflozin groups, respectively. Least squares mean changes from baseline in HbA1c (% [95% CI]) at week 104 were: −0.63 (−0.70, −0.55), −0.71 (−0.78, −0.64) and −0.63 (−0.70, −0.55) in the ertugliflozin 5 mg, ertugliflozin 15 mg and non-ertugliflozin groups, respectively. Over 104 weeks, eGFR values returned to baseline and were higher with ertugliflozin compared with non-ertugliflozin treatment, even though changes in HbA1c did not differ between the groups.

Source: David Z et al. Diabetologia. [onine ahead of print] https://doi.org/10.1007/s00125-020-05133-4

"H" for Heterogeneity in Type 2 Diabetes Management

The complexity of type 2 diabetes (T2D) management has previously prompted the formulation of an algorithm to facilitate practitioners when planning the correct therapeutic strategy. In this regard, “ABCDEFG” has been one of the first and easy to recall algorithms addressing the clinical complexity of type 2 diabetes. Indeed, Age, Body weight, presence of Complications, Duration of disease, Empowerment Economics, degree of Frailty and Geography are features that may differ considerably among subjects with diabetes and influence clinical outcomes.

Genetic, socioeconomic and clinical features vary considerably among individuals with type 2 diabetes (T2D) influencing disease development, progression and response to therapy. Although a patient-centred approach to pharmacologic therapy of T2D is widely recommended, patients are often treated similarly, irrespective of the differences that may affect therapeutic response. Addressing the heterogeneity of T2D is a major task of diabetes research to lower the high rate of treatment failure as well as to reduce the risk of long-term complications.

Although a patient-centred approach to pharmacologic therapy of T2D is widely recommended, patients are often treated similarly, irrespective of the differences that might affect therapeutic response. This is mainly due to the inability to

differentiate subgroups of patients with similar metabolic impairments within the heterogenous T2D population. The path towards an effective clustering of diabetes requires the presence of effective disease biomarkers leading to the identification of subgroups of patients potentially differing for their response to treatment [Fig. 1]. The experience from the studies suggests that only a pathophysiology-based clustering system may help in the stratification of diabetes in terms of complication risk and response to treatment. There are at least eight different metabolic pathways leading to diabetes, plus the eventual presence of pancreatic autoimmunity. However, at present, only the measurement of insulin-resistance, insulin secretion, and only in a few clinical settings, of autoimmunity are implemented in clinical practice to differentiate between T2D patients. As the prevalence of T2D increases, the heterogeneity of the T2D population will also increase.

Source: Silvia P et al. Curr Diab Rep. 2020;20(5):14.

As the prevalence of T2D increases, the heterogeneity of the T2D population will also increase treatment

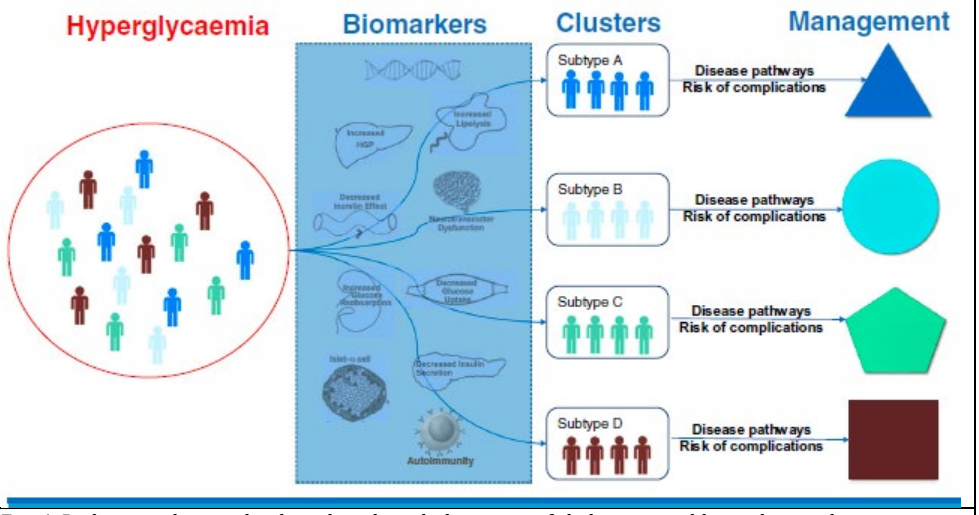

Fig. 1 Path towards a pathophysiology-based clustering of diabetes to address disease heterogeneity. Hyperglycaemia equates individuals differing in genetic predisposition, environmental exposure and pathological pathways. Biomarkers of such differences are necessary to recognize the appropriate diabetes cluster informing about treatment strategy based on the affected disease pathway and the risk of complications