MICRO LABS LIMITED

Diabetes Update

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Dear Doctor,

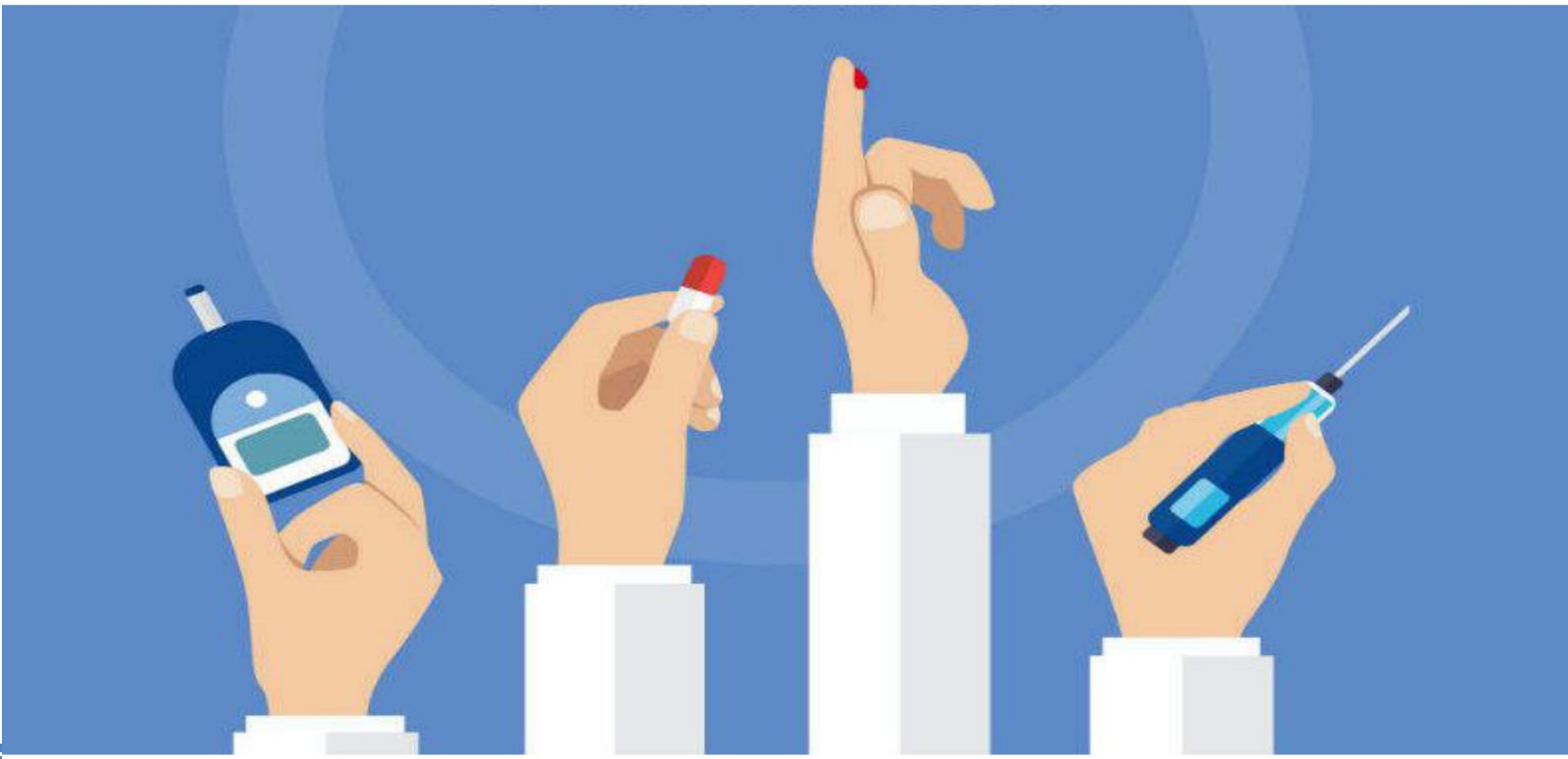
Greetings from Micro Labs Limited. We are happy to bring you **"DIABETES UPDATE"** which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin: The ONSET 9 Trial
- Type 2 Diabetes, Change in Depressive Symptoms Over Time, and Cerebral Small Vessel Diseased Longitudinal Data of the AGES-Reykjavik Study
- Cardiovascular and renal benefits of dapagliflozin: Analysis from the DECLARE-TIMI 58 trial

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



Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin: The ONSET 9 Trial

In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia.

The progressive deterioration of b-cell function in type 2 diabetes requires the intensification of treatment over time. The aim of the ONSET 9 trial was to confirm the effect in terms of glycemic control of treatment with faster aspart compared with IAsp, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal bolus regimen. The trial also aimed to test superiority in terms of PPG regulation while evaluating the safety profile of both treatments. This was the first trial with faster as part to recruit only participants with long-standing (>10 years) type 2 diabetes treated with intensive (basal-bolus) insulin therapy for>1 year.

The trial was designed to quantify a population average effect for participants with type 2 diabetes irrespective of adherence to randomized treatment and use of ancillary treatment. The primary objective was to estimate the effect based on difference in HbA1c from baseline to 16 weeks under these circumstances. This multicenter, double-blind, treat-to-target trial randomized participants to faster aspart (n = 546) or IAsp (n = 545). All available information, regardless of treatment discontinuation or use of ancillary treatment, was used for evaluation of effect.

Noninferiority for the change from baseline in HbA1c 16 weeks after randomization (primary end point) was confirmed for faster aspart versus IAsp (estimated treatment difference [ETD] -0.04% [95% CI -0.11; 0.03]; -0.39 mmol/mol [-1.15; 0.37]; P < 0.001). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD -0.40 mmol/L [-0.66; -0.14]; -7.23 mg/dL [-11.92; -2.55]; P = 0.001 for superiority). Change from baseline in self-measured 1-h PPG increment for the mean over all meals favored faster aspart (ETD -0.25 mmol/L [-0.42; -0.09]); -4.58 mg/dL [-7.59; -1.57]; P = 0.003). The overall rate of treatment-emergent severe or blood glucose (BG)-confirmed hypoglycemia was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]).

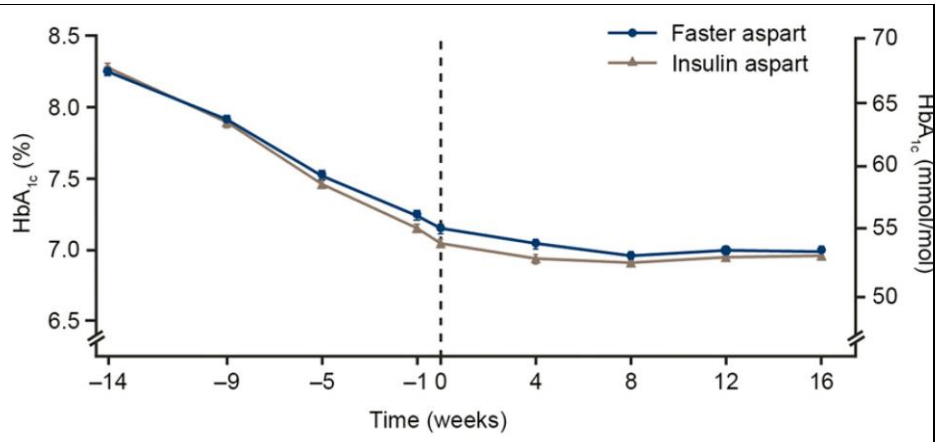


Figure 1—Mean HbA1c over time.

Error bars: SE (mean). All available information regardless of treatment discontinuation or use of ancillary treatment was used. ETD after 16 weeks for the change in HbA1c from baseline was20.04% (95% CI20.11; 0.03);20.39 mmol/mol (21.15; 0.37). Noninferiority confirmed at 0.4% level (P value from the one-sided test for noninferiority evaluated at the 2.5% level: P , 0.001).

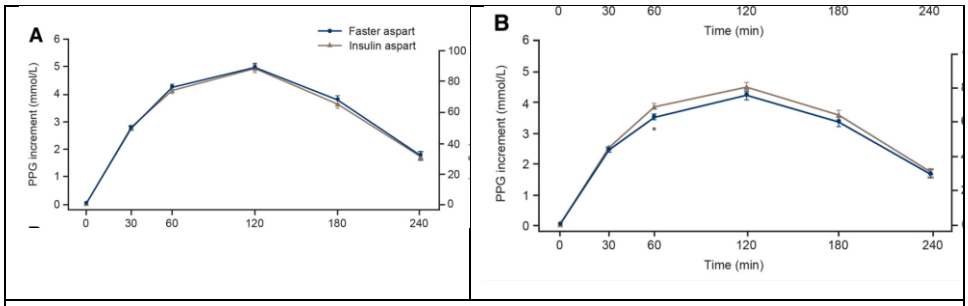


Figure 2—PPG increment after a meal test at baseline (A) and week 16 (B).

In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

Source: Lane WS et al. Diabetes Care. 2020 Aug;43(8):1710-1716. doi: 10.2337/dc19-2232

Type 2 Diabetes, Change in Depressive Symptoms Over Time, and Cerebral Small Vessel Diseased Longitudinal Data of the AGES-Reykjavik Study

Type 2 diabetes has been associated with depression. However, the underlying pathophysiological mechanisms remain unknown. Cerebral small vessel disease, a consequence of diabetes, may lead to depression. Therefore, we evaluated whether cerebral small vessel disease mediates the association between type 2 diabetes and higher depressive symptoms.

This study used longitudinal data from the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, with examinations from 2002 to 2006 and 5 years later. Type 2 diabetes was defined as self-reported history of type 2 diabetes, use of blood glucose–lowering drugs, or fasting blood glucose level ≥7.0 mmol/L. Cerebral small vessel disease load was quantified in a composite score based on MRI-defined presence of high white matter hyperintensity volume, low total brain parenchyma volume, and subcortical infarcts, cerebral microbleeds, and large perivascular spaces. The 5-year change in the 15-item Geriatric Depression Scale score (GDS-15) was measured between baseline and follow-up.

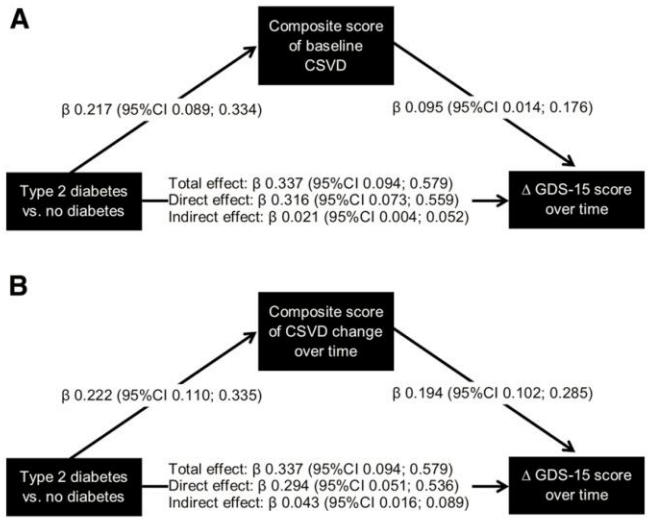


Figure 1—Association between type 2 diabetes at baseline and change in the GDS-15 score, and the mediating effect by the composite score of baseline cerebral small vessel disease (CVSD) (A) and the composite score of cerebral small vessel disease change (B). Total effect is the association between type 2 diabetes at baseline and change in the GDS-15 score without adjustment for the composite score, direct effect is the association between type 2 diabetes and change in the GDS-15 score after adjustment for the composite score, and indirect effect is the explained or mediated effect by the composite score. Associations are given as regression coefficients (b) and corresponding 95% CIs. All associations are adjusted for age, sex,

Type 2 diabetes is associated with a greater increase in depressive symptoms score over 5 years, and cerebral small vessel disease partly explains this association..

education level, alcohol use, smoking history, BMI, hypertension, and total cholesterol-to-HDL cholesterol ratio

	Model	Change in the GDS-15 score over time β (95% CI)	Composite score of baseline β (95% CI)	Composite score of change over time β (95% CI)
Type 2 diabetes vs. no diabetes at baseline	1	0.339 (0.099; 0.579)	0.219 (0.093; 0.345)	0.205 (0.094; 0.316)
	2	0.337 (0.094; 0.579)	0.217 (0.089; 0.344)	0.222 (0.110; 0.335)
Composite score of baseline	1	0.094 (0.013; 0.175)	--	--
	2	0.095 (0.014; 0.176)	--	--
Composite score of change	1	0.198 (0.107; 0.290)	--	--
	2	0.194 (0.102; 0.285)	--	--

The study included were 2,135 individuals without dementia and baseline depression (baseline age 74.5 [SD 4.6] years, 1,245 women [58.3%], and 197 [9.2%] with diabetes). The GDS-15 score increased 0.4 (SD 1.6) points over time. Baseline diabetes was associated with a greater increase in the GDS-15 score (β = 0.337; 95% CI 0.094; 0.579), adjusted for age, sex, education, and cardiovascular risk factors. Baseline cerebral small vessel disease and change of cerebral small vessel disease statistically significantly mediated a part of this association. Type 2 diabetes is associated with a greater increase in depressive symptoms score over 5 years, and cerebral small vessel disease partly explains this association.

Source: Rensma SP et al. Diabetes Care 2020 Aug; 43(8): 1781-1787. https://doi.org/10.2337/dc19-2437

Cardiovascular and renal benefits of dapagliflozin: Analysis from the DECLARE-TIMI 58 trial

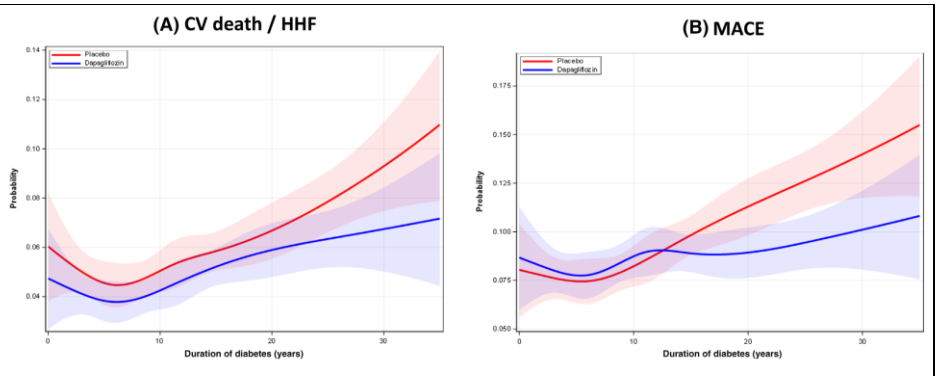
Long-standing diabetes is associated with an increasing risk of diabetes complications, including heart failure, and microvascular and macrovascular complications. Post hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial revealed an independent association of diabetes duration with microvascular and macrovascular complications. Moreover, in the population-based coronary artery risk development in young adults (CARDIA) study, duration of diabetes and prediabetes during early adulthood was independently associated with subclinical atherosclerosis as well a with measures of systolic and diastolic dysfunction later in life.

This post hoc analysis studied the dual primary efficacy endpoints, a composite of cardiovascular death or hospitalization for heart failure (CVD/HHF) and major adverse cardiovascular events (MACE; CVD, myocardial infarction [MI], ischaemic stroke) by diabetes duration. Of the 17 160 patients, 3836 had diabetes duration of ≤5 years, 4731 >5-10 years, 3952 >10-15 years, 2433 >15-20 years and 2206 >20 years. Dapagliflozin reduced the risk of CVD/HHF by a similar amount across diabetes duration subgroups, ranging from HR 0.79 (0.58-1.06) in patients with diabetes duration of ≤5 years to 0.75 (0.55-1.03) in those patients with diabetes duration of >20 years (interaction trend P-value 0.76).

Dapagliflozin reduced the risk of CVD/HHF consistently, regardless of diabetes duration.

Hazard ratios (HRs) for MACE ranged from 1.08 (0.87-1.35) in patients with diabetes duration of ≤5 years to 0.67 (0.52-0.86) in those patients with diabetes duration of >20 years (interaction trend P-value 0.004). This was driven by greater reductions in the risk of MI and ischaemic stroke with dapagliflozin in patients with long-standing diabetes (interaction trend P-values 0.019 and 0.015, respectively). The duration-based MACE heterogeneity was apparent in those with or without a history of prior MI and in those with multiple risk factors. The renal-specific outcome was reduced with dapagliflozin with HRs ranging from 0.79 (0.47-1.34) in patients with diabetes duration of ≤5 years to 0.42 (0.25-0.72) in those patients with diabetes duration of >20 years (interaction trend P-value 0.084).

Dapagliflozin reduced the risk of CVD/HHF consistently, regardless of diabetes duration, whereas the treatment effect for MACE differed by duration subgroups, with significant reductions with dapagliflozin in patients with long-standing diabetes.



Probability (95% CI) of **(A)** cardiovascular death (CVD)/hospitalization for heart failure (HHF) and **(B)** major adverse cardiovascular events (MACE) with dapagliflozin versus placebo at 1440 days by diabetes duration

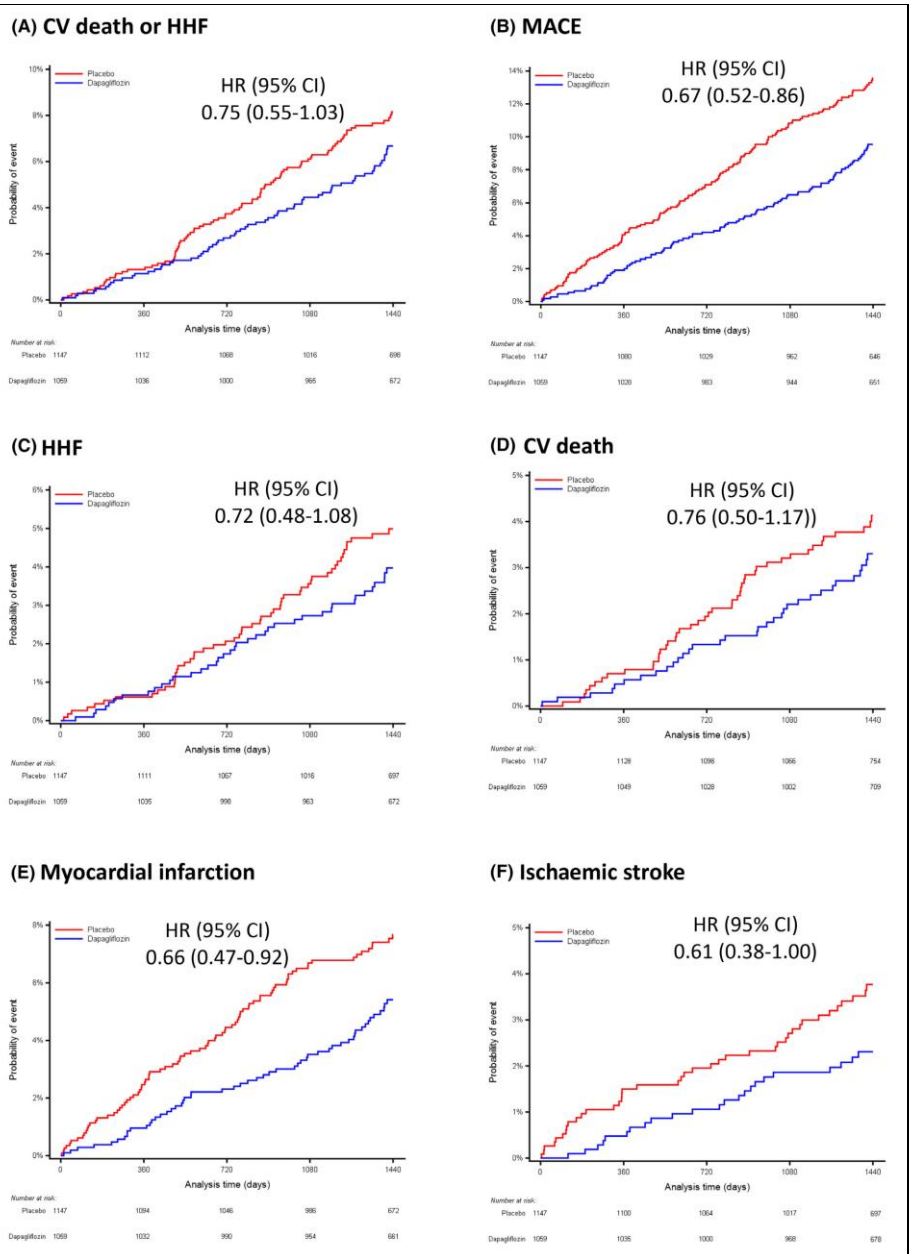


FIGURE: Dual primary outcomes and their components with dapagliflozin versus placebo in patients with diabetes duration of >20 years: (A) cardiovascular death (CVD)/hospitalization for heart failure (HHF); (B) major adverse cardiovascular events (MACE); (C) HHF; (D) CVD; (E) myocardial infarction; (F) ischaemic stroke

The current study shows that dapagliflozin reduced the risk of CVD/HHF consistently, regardless of diabetes duration, whereas the treatment effect for MACE differed by diabetes duration subgroup, with significant benefit with dapagliflozin in patients with long-standing diabetes, because of reductions in MI and ischaemic stroke.

Source: Bajaj HS et al Diabetes Obes Metab. 2020 Jul;22(7):1122-1131.

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