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.

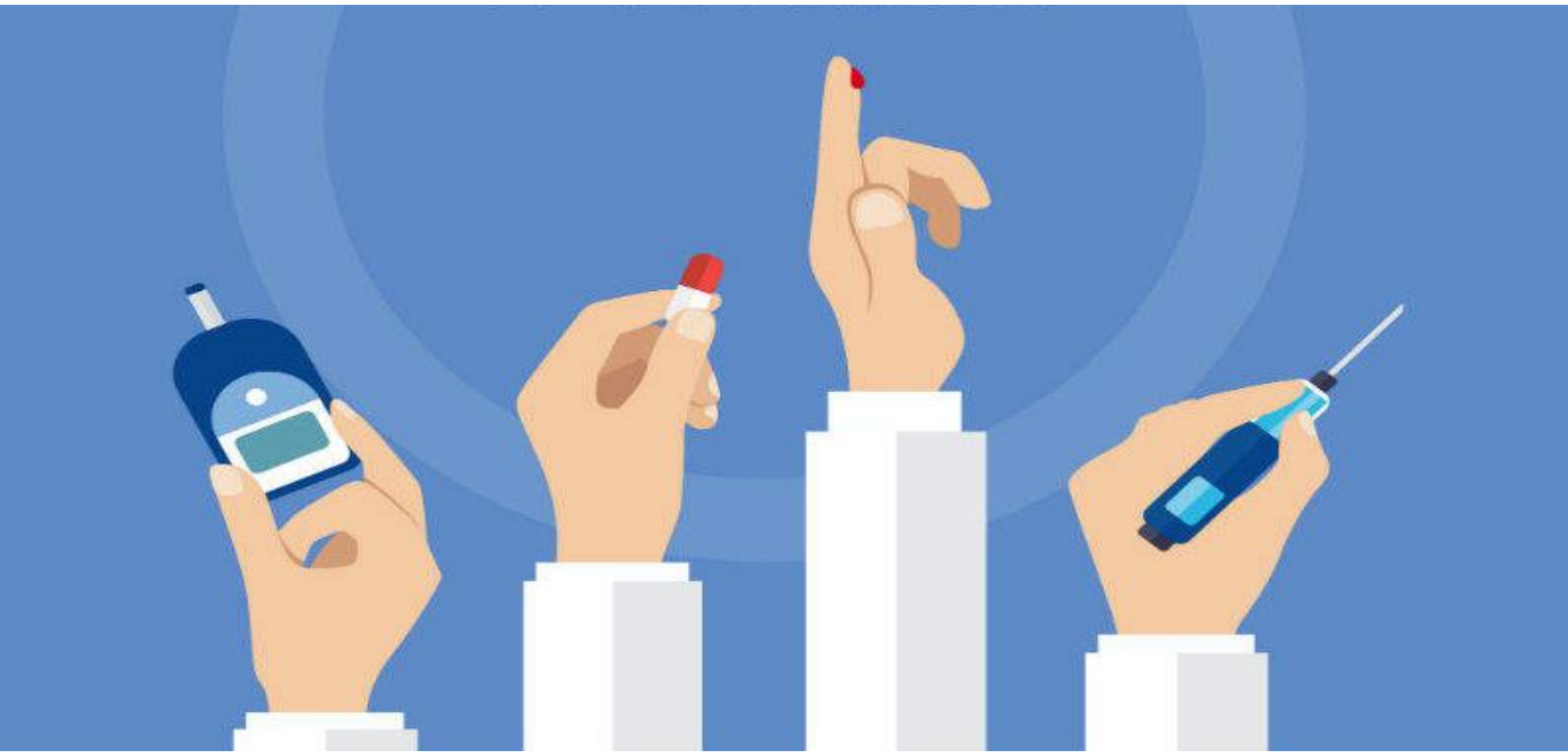
- Interrelationship between Hypoglycemia, CV and Mortality Outcomes in the CAROLINA Trial
- Continuous subcutaneous insulin infusion reduces maternal and neonatal risk in pregnant women with type 1 diabetes
- Association between Admission Hyperglycemia and Culprit Lesion Characteristics in Nondiabetic Patients with Acute MI

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



Interrelationship between Hypoglycemia, CV and Mortality Outcomes in the CAROLINA Trial

Severe hypoglycemia is associated with higher CV and mortality risk. The CAROLINA® trial evaluated the CV safety of linagliptin (LINA) and glimepiride (GLIM) in 6033 subjects with relatively early type 2 diabetes (T2D) and elevated CV risk (mean age 64.0 years, HbA1c 7.2%, median T2D duration 6.3 years) and demonstrated non-inferiority for 3P-MACE and no difference for CV and mortality outcomes.

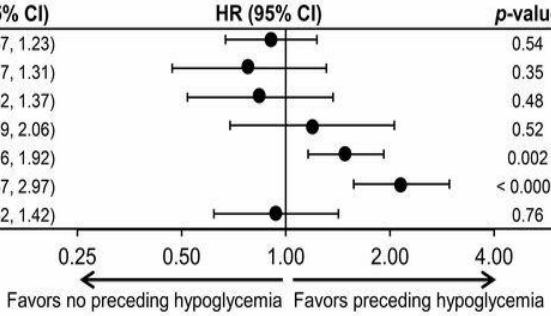
However, a significant lower risk of hypoglycemia was observed with LINA vs. GLIM regardless of severity classification. We assessed, in 6014 participants, the associations between severe hypoglycemia and/or documented hypoglycemia (BG <54 mg/dl), which occurred in 109/3014 (3.6%) and 537/3000 (17.9%) in the LINA and GLIM groups, respectively (HR 0.19 [95% CI 0.15, 0.23]), and CV and mortality outcomes using Cox regression models.

Hypoglycemia events preceded CV outcomes in 0.0-3.6% of all events with LINA and in 8.0-26.2% events with GLIM. Of note, even when multivariably adjusted, occurrence of hypoglycemia was associated only with higher risk for all-cause mortality (HR 1.49 [1.16, 1.92]), and non-CV mortality (HR 2.16 [1.57, 2.97]) (Fig A). The relative effect of LINA vs. GLIM on any CV or mortality outcome (Fig B) was not influenced by antecedent hypoglycemia.

The preceding hypoglycemia was associated with higher risk for all-cause and non-CV mortality

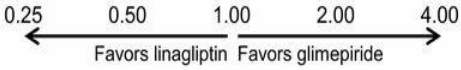
A

	HR (95% CI)	p-value
3P-MACE	0.91 (0.67, 1.23)	0.54
TIA or F/NF stroke	0.78 (0.47, 1.31)	0.35
Fatal/non-fatal MI	0.84 (0.52, 1.37)	0.48
HHF	1.20 (0.69, 2.06)	0.52
All-cause mortality	1.49 (1.16, 1.92)	0.002
Non-CV death	2.16 (1.57, 2.97)	< 0.0001
CV death	0.94 (0.62, 1.42)	0.76



B

	HR (95% CI)	p-value
3P-MACE		
Primary analysis	0.98 (0.84, 1.13)	0.76
Adjusted for time-dependent occurrence of hypoglycemia	0.97 (0.84, 1.13)	
TIA or F/NF stroke		
Primary analysis	0.82 (0.65, 1.04)	0.10
Adjusted for time-dependent occurrence of hypoglycemia	0.80 (0.63, 1.02)	
F/NF MI		
Primary analysis	1.03 (0.82, 1.29)	0.82
Adjusted for time-dependent occurrence of hypoglycemia	1.01 (0.80, 1.27)	
HHF		
Primary analysis	1.21 (0.92, 1.59)	0.18
Adjusted for time-dependent occurrence of hypoglycemia	1.22 (0.92, 1.62)	
All-cause mortality		
Primary analysis	0.91 (0.78, 1.06)	0.23
Adjusted for time-dependent occurrence of hypoglycemia	0.96 (0.82, 1.13)	
Non-CV mortality		
Primary analysis	0.82 (0.66, 1.03)	0.08
Adjusted for time-dependent occurrence of hypoglycemia	0.92 (0.73, 1.16)	
CV death		
Primary analysis	1.00 (0.81, 1.24)	0.99
Adjusted for time-dependent occurrence of hypoglycemia	1.00 (0.80, 1.24)	



A: Association between occurrence of any hypoglycemia with BG <54 mg/dl, or a severe (requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions) hypoglycemic event, and outcomes. Model included terms for treatment, baseline factors region, age, sex, risk group A (history of vascular disease), albuminuria at baseline, time since diagnosis of diabetes, eGFR, HbA1c, prior intake of SU or glinide, BMI, heart failure, smoking status, and atrial fibrillation, and time-varying covariate for hypoglycemic event.
B: Effects on outcomes adjusting for time-dependent occurrence of hypoglycemia. Primary analysis based on 6033 participants while the model with time-dependent hypoglycemia covariate analysis on 6014 participants. HR based on Cox regression model. 3P-MACE, 3-point major adverse cardiovascular events; HR, hazard ratio; TIA, transient ischemic attack; F, fatal; NF, non-fatal; MI, myocardial infarction; CV, cardiovascular; BG, blood glucose. Hypoglycemia defined as any BG <54 mg/dl, or a severe hypoglycemic event.

The preceding hypoglycemia was associated with higher risk for all-cause and non-CV mortality, but not with any other outcomes in a relatively early T2D population at elevated CV risk.

Source: Rosenstock J et al. Diabetes 2020 Jun; 69(Supplement 1): -.https://doi.org/10.2337/db20-162-OR

Continuous subcutaneous insulin infusion reduces maternal and neonatal risk in pregnant women with type 1 diabetes

Despite therapeutic progress, type 1 diabetes (T1D) in pregnant women remains a potential high-risk condition for maternal, fetal and neonatal complications. Continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) are both effective approaches in pregnancy.

While CSII offer many potential advantages over MDI in terms of flexibility of bolusing, there is insufficient evidence to recommend one method over the other in type 1 diabetic pregnant women. In a recent prespecified analysis of the CONCEPTT trial, researchers observed better glycemic outcomes, less neonatal hypoglycemia, and fewer neonatal intensive care admissions with MDI versus CSII.

In light of these observations, the aim of the study was to compare metabolic, obstetric and fetal neonatal data of singleton pregnancies (n= 122) from 53 T1D women treated with CSII with those of 37 T1D women treated with MDI. All women, followed up in our Diabetes Unit, delivered in Papa Giovanni XXIII Hospital of Bergamo between January 2006 and December 2015. In all women, blood glucose control was performed by capillary self-glucose monitoring. Data are shown as mean +/- SD, unless otherwise stated. Categorical variables were compared by two-tailed chi-square test, while unpaired T-test was used to compare continuous variables.

CSII-therapy could be the therapeutic option in pregnant women with T1D of long duration

Retrospective studies not involving drugs do not require registration at ClinicalTrials.gov in our Institution. CSII group had at baseline significantly higher maternal mean age, longer diabetes duration and higher prevalence of diabetic complications (Table 1). Although A1c was not significantly different at baseline between groups, it was higher in CSII group than in MDI group during second and third trimesters of pregnancy (Table 1). Both

therapies promoted statistically significant decrease of mean A1c at the end of pregnancy, with comparable insulin doses.

Table 1: Comparison between CSII-therapy and MDI-therapy groups about metabolic, obstetric and neonatal outcomes (data are shown as mean ± SD, unless otherwise stated).

Singleton pregnancies (n)	CSII (53 patients) 72	MDI (37 patients) 50	p-value*
Metabolic data			
Maternal mean age (years)	33,5 ± 3,6	30,5 ± 4,7	< 0,01
Mean diabetes duration (years)	17,2 ± 7,1	9,4 ± 7	< 0,01
Retinopathy (n)†	23	4	< 0,01
Nephropathy (n)‡	8	1	0,05
Mean A1c (I trimester) (mmol/mol)	53,2 ± 8,4	49,5 ± 14	0,07
Mean A1c (II trimester) (mmol/mol)	45,5 ± 7,1	40,6 ± 6,7	< 0,01
Mean A1c (III trimester) (mmol/mol)	46,4 ± 6,9	41,5 ± 6,4	< 0,01
Δ A1c between I and III trimester (mmol/mol)	6,8 ± 1,5	8,0 ± 7,6	0,19
Obstetric and neonatal outcomes			
Gestational age at delivery (wks)	37,4 ± 1,1	37,5 ± 1,9	0,71
Preterm delivery (< 37w) (%)	17,6	8	0,23
Vaginal delivery (%)	45	62	0,15
Urgent caesarean section (%)	17,6	14	0,67
Elective caesarean section (%)	37,2	24	0,21
Pre-eclampsia (%)	11,7	4	0,34
Large-for-gestational age (%)	41,2	32	0,42
Neonatal hypoglycemia (%)§	36	28	0,41
Admission to neonatal intensive care unit (%)	16	8	0,23

* p-value was calculated between CSII and MDI group , † all patients had background retinopathy
‡ all patients had normal eGFR with microalbuminuria, .define as at least one episode of hypoglycemia < 45 mg/dl

Despite the significant differences in glucose control, no differences in maternal outcomes were found between the two treatment groups (Table 1), in particular about large-for-gestational age, neonatal hypoglycaemia and admission to Neonatal Intensive Care Unit (table 1).

The main limitation of this relative small retrospective study is the selection bias: CSII therapy was mainly offered to older women with T1D of longer duration and higher prevalence of diabetic complications.

The study findings highlights that, at the beginning of pregnancy, CSII-therapy could be the best therapeutic option in pregnant women with T1D of long duration with sub-optimal glycemic control because it may help to achieve comparable maternal and neonatal outcomes as MDI-therapy in lower risk T1D women. Ad-hoc prospective studies are warranted to confirm our advice and to clarify the reason for CSII better efficacy in pregnant women with T1D.

Source: Dodesini AR et al J Diabetes. 2020 June. https://doi.org/10.1111/1753-0407.13080.

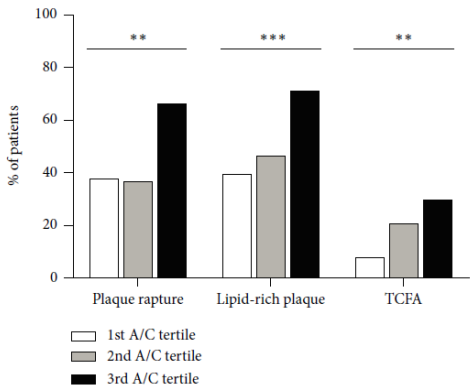
Association between Admission Hyperglycemia and Culprit Lesion Characteristics in Nondiabetic Patients with Acute MI

Diabetes mellitus (DM) in general increases vascular complications, including coronary heart disease, ischemic stroke, and vascular deaths. DM patients have a high prevalence of multivessel disease and an accelerated atherosclerotic progression related to the glucose level. Optical coherence tomography (OCT) allows accurate evaluation of coronary atherosclerotic plaques in vivo. Although a pilot study including 63 participants with coronary artery diseases (CAD) found no significant difference in plaque characteristics between the DM group and the non-DM group, recent studies reported conflicting results that diabetic individuals with CAD may have more calcification or lipid-rich plaques. Additionally, individuals with hemoglobin A1c (HbA1c) ≥8% had the highest prevalence of thin-cap fibroatheroma (TCFA). These results indicate that the glucose level has an impact on coronary plaque characteristics.

Hyperglycemia is frequently observed in acute myocardial infarction (AMI). Diabetes mellitus (DM) patients and non-DM patients have different culprit lesion phenotypes and few data are available on non-DM patients with admission hyperglycemia. Therefore, this study aimed to investigate the association between admission hyperglycemia and culprit lesion characteristics using optical coherence tomography (OCT) in AMI patients.

Zhou et al. consecutively enrolled 434 patients with AMI, and 277 patients were included in analysis: 65.7% (N=182) non-DM patients and 34.3% (N=95) DM patients. We measured acute blood glucose (ABG) and hemoglobin A1c to calculate the acute-to-chronic glycemic ratio (A/C). Then, we grouped non-DM patients into tertiles of A/C. OCT-based culprit lesion characteristics were compared across A/C tertiles in non-DM patients and between DM and non-DM patients. Non-DM patients had fewer lipid-rich plaques (52.7% versus 68.4%, P=0.012) and thin-cap fibroatheroma (TCFA) (19.8% versus 34.7%, P=0.006) than DM patients but similar prevalence of plaque rupture (47.3% versus 56.8%, P=0.0130). Non-DM patients with the highest A/C tertile had the highest prevalence of plaque rupture (P=0.002), lipid-rich plaque (P=0.001), and TCFA (P=0.003). A1c> 1.22 but not ABG > 140 mg/dl predicted a high prevalence of plaque rupture, lipid-rich plaque, and TCFA in non-DM patient.

In AMI patients without DM, admission hyperglycemia is associated with vulnerable culprit lesion characteristics



Comparison of vulnerable culprit lesion characteristics among A/C tertiles in nondiabetic patients with AMI, n = 182. White bars:first A/C tertile, n = 60; grey bars: second A/C tertile, n = 62; black bars: third A/C tertile, n = 60. **pfor trend ≤ 0:01, ***pfor trend ≤ 0:001.

Table: Association between optical coherence tomography measurements and metabolic variables of the study population.

	ABG	HbA1c	A/C	TC	TG	HDL-C	LDL-C	Lp (a)	Hs-CRP	eGFR
Non-DM group										
FCT, $n = 182$	-0.149*	0.091	-0.206†	-0.138	-0.045	-0.019	-0.122	0.097	0.143	0.065
Lipid arc, $n = 84$‡	-0.038	0.006	-0.019	0.193	-0.026	0.092	0.228*	0.136	-0.137	0.226*
MLA, $n = 182$	0.050	0.007	0.034	-0.082	0.028	0.112	-0.164*	0.035	0.025	-0.229†
DM group										
FCT, $n = 95$	0.157	0.158	-0.029	-0.216*	0.012	0.031	-0.252*	0.194	0.154	0.108
Lipid arc, $n = 38$‡	-0.022	0.011	0.071	0.073	-0.116	0.059	0.079	-0.096	0.014	-0.105
MLA, $n = 95$	0.040	0.072	0.005	-0.018	0.045	-0.039	-0.049	-0.130	0.062	0.072

*$p < 0.05$; †$p < 0.01$. ‡Individuals with lipid arc = 360° were excluded, as truncated data is refused by Spearman's correlations. DM: diabetes mellitus.

In AMI patients without DM, admission hyperglycemia is associated with vulnerable culprit lesion characteristics, and A1C is a better predictor for vulnerable culprit plaque characteristics than ABG. These results call for a tailored evaluation and management of glucose metabolism in nondiabetic AMI patients.

Source: Zhou J *et al.* J Diab Res. 2020 June; 1763567: 1-12. https://doi.org/10.1155/2020/1763567