

Comparing the effects of tofogliflozin and pioglitazone in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus (ToPiND study): A randomized, prospective, open-label, controlled trial

Online-Only Supplemental Material

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Supplemental Table S1. Inclusion and exclusion criteria

Inclusion criteria

- Both men and women aged 20–74 years
- Type 2 diabetes patients who had undergone diet and exercise therapies
- Patients with HbA1c $\geq 6.5\%$ (48 mmol/mol) within 90 days of primary registration
- Patients diagnosed with non-alcoholic fatty liver disease
- Patients with ALT levels beyond the institutional standard levels (42 IU/L for men and 23 IU/L for women) within 90 days of primary registration

Exclusion criteria

- Patients with drinking habits (men, more than 30 g/day; women, more than 20 g/day converted to ethanol)
- Patients diagnosed with viral hepatitis (including patients under treatment and carriers)
- Patients with other types of hepatitis or liver disorder (e.g., drug-induced, autoimmune)
- Patients diagnosed with liver cirrhosis
- Patients with serious liver dysfunction (Child-Pugh B or C)
- Patients with PLT $< 150 \times 10^3 / \mu\text{L}$ within 90 days of primary registration
- Patients with BMI $< 22 \text{ kg/m}^2$ within 90 days of primary registration
- Patients with ALT ≥ 5 times the upper limit of the standard value within 90 days of primary registration
- Patients with serious renal dysfunction or with eGFR $< 60 \text{ mL/min/1.73 m}^2$ within 90 days of primary registration
- Patients with type 1 diabetes mellitus or with HbA1c $\geq 9.0\%$ (75 mmol/mol) within 90 days of primary registration
- Patients using SGLT2 inhibitor, pioglitazone, insulin, or GLP-1 receptor agonists
- Patients taking vitamin E
- Patients with any contraindications to MRI (e.g., pacemaker)
- Patients unable to undergo MRI (e.g., cannot hold breath, patients with excessive iron deposition)
- Patients with heart failure of more than NYHA III at present or in the past

Abbreviations: ALT: alanine transaminase, BMI: body mass index, eGFR: estimated glomerular filtration rate, GLP-1: glucagon-like peptide-1, MRI: magnetic resonance imaging, NYHA: New York Heart Association, PLT: platelet count, SGLT2: sodium-glucose cotransporter

Supplemental Table S2. Study endpoints**Primary endpoint**

Change in hepatic steatosis measured by MRI-PDFF after 24 weeks of medication (compared between two groups)

Key secondary endpoint

Change in ALT levels after 24 weeks of medication (compared between two groups)

Other endpoints

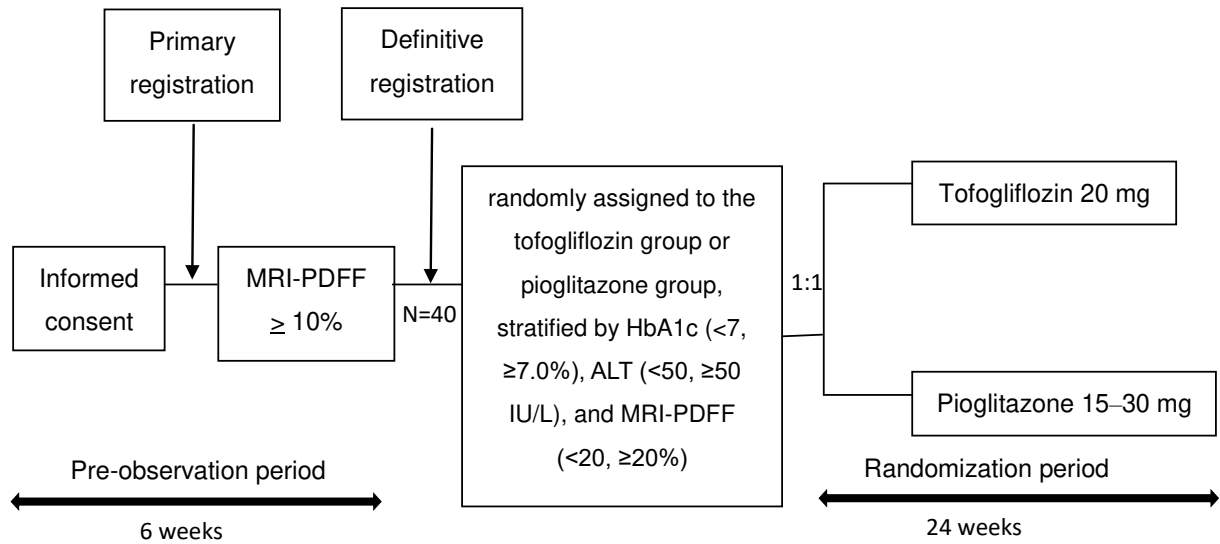
1. Changes in liver stiffness measurements by MR Elastography (MRE-LSM)
2. Changes in HbA1c and fasting plasma glucose levels
3. Changes in weight and BMI
4. Changes in AST, GGT, and ALP levels
5. Changes in the levels of WFA⁺-M2BP, type IV collagen 7S, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, uric acid, high sensitivity CRP, urine 8-OHdG, adiponectin, ketone fraction, and CK18 fragment M30 antigen

Abbreviations: 8-OHdG: 8-hydroxy-2'-deoxyguanosine, ALT: alanine transaminase, ALP: alkaline phosphatase, AST: aspartate transaminase, BMI: body mass index, CHE: cholinesterase, CK-18: cytokeratin 18, CRP: C-reactive protein, GGT: γ -glutamyl transpeptidase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MRI: magnetic resonance imaging, PDFF: proton density fat fraction, WFA⁺-M2BP: *Wisteria floribunda* agglutinin-positive Mac-2 binding protein glycosylation isomer.

Supplemental Table 3. Adverse events

	Pioglitazone (n=19)	Tofogliflozin (n=21)
Deaths	0	0
Serious adverse events	0	0
Heart failure	0	0
Acute kidney disease	0	0
Hepatic failure	0	0
Discontinuation because of adverse events	1 (5.3%)	0
Adverse events		
Edema	2 (10.5%)	0
Weight gain (>3%)	6 (31.6%)	0
(>5%)	3 (15.8%)	0
Urinary tract infection	0	1(4.8%)

Supplemental Figure S1. Study schedule



The flow chart of the study

Abbreviations: MRI-PDFF: magnetic resonance imaging (MRI) for estimating the proton density of the fat fraction (PDFF) of the liver, ALT: Alanine transaminase