

**Supplementary Table 2.** Anthropometric, clinical, metabolic, and neurological characteristics of patients with T2DM according to the CAN state

| Characteristic                                   | No CAN (n=109)                  | Early CAN (n=16)              | Confirmed CAN (n=15) | P value               |
|--|---------------------------------|-------------------------------|----------------------|-----------------------|
| Sex, males:females                               | 69:40                           | 12:4                          | 12:3                 | 0.304                 |
| Age, yr  | 65.0 (58.0–69.0)                | 64.5 (57.0–69.0)              | 61.0 (53.2–64.5)     | 0.208                 |
| Disease duration, yr                             | 9.0 (5.0–15.0)                  | 16.0 (4.0–26.5)               | 12.0 (5.2–21.5)      | 0.312                 |
| BMI, kg/m <sup>2</sup>                           | 28.7 (25.6–31.5)                | 29.6 (28.8–33.8)              | 27.8 (23.5–34.4)     | 0.174                 |
| HbA1c, %   | 6.7 (6.1–7.3)                   | 7.2 (6.5–7.6)                 | 8.4 (7.0–9.6)        | 0.002 <sup>ab</sup>   |
| HbA1c, mmol/mol                                  | 50.0 (44.0–56.0)                | 55.0 (48.0–59.0)              | 68.0 (53.0–81.0)     | 0.002 <sup>ab</sup>   |
| Total cholesterol, mg/dL                         | 169.0 (138.2–190.0)             | 164.0 (132.0–194.0)           | 188.0 (145.7–220.0)  | 0.337                 |
| LDL cholesterol, mg/dL                           | 89.4 (68.0–113.0)               | 97.8 (65.2–126.4)             | 83.5 (61.0–115.3)    | 0.817                 |
| HDL cholesterol, mg/dL                           | 45.0 (37.0–55.0)                | 37.0 (31.2–49.0)              | 51.0 (35.0–57.2)     | 0.278                 |
| Triglycerides, mg/dL                             | 107.0 (91.2–150.5) <sup>d</sup> | 172.5 (116.0–203.0)           | 136.0 (88.2–178.7)   | 0.302 <sup>b</sup>    |
| With retinopathy, % <sup>e</sup>                 | 18/103 (17.5)                   | 5/15 (33.3)                   | 9/14 (64.3)          | 0.001 <sup>a</sup>    |
| With microalbuminuria, % <sup>h</sup>            | 14/98 (14.3)                    | 5/13 (23.1)                   | 4/11 (36.4)          | 0.050                 |
| eGFR, mL/min/1.73 m <sup>2</sup>                 | 85.9 (69.2–97.5)                | 85.0 (79.7–103.2)             | 81.0 (66.4–98.9)     | 0.408                 |
| With chronic kidney disease, % <sup>h</sup>      | 23/98 (23.5)                    | 5/13 (23.1)                   | 5/11 (41.7)          | 0.206                 |
| Casual systolic BP, mm Hg                        | 132.5±18.8 <sup>c</sup>         | 142.8±20.7 <sup>f</sup>       | 126.3±16.6           | 0.232 <sup>b</sup>    |
| Casual diastolic BP, mm Hg                       | 76.6±10.5                       | 79.2±7.6                      | 75.7±10.5            | 0.144                 |
| With hypertension, %                             | 84 (77.1)                       | 13 (81.2)                     | 10 (66.7)            | 0.974                 |
| With cardiovascular disease, %                   | 23 (21.1)                       | 6 (37.5)                      | 5 (33.3)             | 0.270                 |
| With peripheral vascular disease, % <sup>i</sup> | 17/107 (15.9)                   | 7/15 (46.7)                   | 5 (33.3)             | 0.019 <sup>a</sup>    |
| Alcohol consumption, %                           | 24/107 (22.4)                   | 5 (31.2)                      | 1 (6.7)              | 0.185                 |
| Current smokers, %                               | 17 (15.6)                       | 5 (31.2)                      | 4 (26.7)             | 0.254                 |
| Regular physical activity, % <sup>j</sup>        | 45/107 (42.0)                   | 5 (31.2)                      | 2/14 (17.8)          | 0.086                 |
| CARTs score                                      | 0.0 (0–1.0) <sup>e</sup>        | 3.0 (2.0–4.0)                 | 5.0 (4.0–6.0)        | <0.0001 <sup>ab</sup> |
| Expiration:inspiration ratio                     | 1.22 (1.15–1.32) <sup>d</sup>   | 1.12 (1.10–1.18) <sup>f</sup> | 1.07 (1.05–1.09)     | <0.0001 <sup>ab</sup> |
| 30:15 ratio                                      | 1.12 (1.08–1.17) <sup>d</sup>   | 1.07 (1.02–1.12) <sup>f</sup> | 1.03 (1.00–1.04)     | <0.0001 <sup>ab</sup> |
| Valsalva ratio                                   | 1.46 (1.32–1.62) <sup>e</sup>   | 1.20 (1.14–1.26)              | 1.13 (1.11–1.18)     | <0.0001 <sup>ab</sup> |
| Orthostatic hypotension, mm Hg                   | 10.0 (5.0–15.0) <sup>c</sup>    | 16.0 (10.0–21.0)              | 15.0 (11.2–37.2)     | 0.001 <sup>ab</sup>   |
| With DPN, %                                      | 55 (50.4)                       | 13 (81.2)                     | 13 (86.7)            | 0.002 <sup>a</sup>    |
| MNSI   | 2.0 (0–4.0) <sup>c</sup>        | 5.0 (1.2–6.0)                 | 6.0 (3.0–8.0)        | 0.005 <sup>ab</sup>   |
| MDNS   | 3.0 (2.0–6.0) <sup>d</sup>      | 7.0 (3.0–9.0)                 | 10.0 (5.0–13.0)      | 0.002 <sup>ab</sup>   |
| VPT hallux, V                                    | 20.7 (14.0–31.2) <sup>d</sup>   | 37.3 (28.8–47.3)              | 35.0 (24.0–45.2)     | 0.022 <sup>ab</sup>   |
| Warm perception threshold, °C                    | 34.6 (33.1–38.0) <sup>c</sup>   | 38.6 (34.6–39.3)              | 41.4 (34.8–45.9)     | 0.010 <sup>ab</sup>   |
| Cold perception threshold, °C                    | 30.5 (28.6–31.5)                | 29.2 (26.6–31.1)              | 27.0 (19.8–28.5)     | 0.002 <sup>ab</sup>   |

Values are presented as median (interquartile range), number (%), or mean ± standard deviation. Analysis of variance (parametric) and Kruskal-Wallis test (non-parametric) as tests of significance for means with *post hoc* Bonferroni correction and Dunn's test and the chi-square test for categorical variables were used.

T2DM, type 2 diabetes mellitus; CAN, cardiovascular autonomic neuropathy; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; BP, blood pressure; CART, cardiovascular autonomic reflex test; DPN, diabetic polyneuropathy; MNSI, Michigan Neuropathy Screening Instrument; MDNS, Michigan Diabetic Neuropathy Score; VPT, vibration perception threshold.

<sup>a</sup>Significant P value; <sup>b</sup>No CAN vs. confirmed CAN: corrected P; No CAN vs. early CAN: <sup>c</sup>corrected P<0.05, <sup>d</sup>corrected P<0.01, <sup>e</sup>corrected P<0.0001;

<sup>f</sup>Early CAN vs. confirmed CAN: corrected P<0.05; Missing data for <sup>g</sup>no CAN patients (n=6), early CAN (n=1) and confirmed CAN (n=1) patient,

<sup>h</sup>no CAN patients (n=11), early CAN (n=3) and confirmed CAN (n=4) patient, <sup>i</sup>no CAN (n=2) patients and confirmed CAN (n=1) patient, <sup>j</sup>no CAN patients (n=2).