

SUPPLEMENTARY DATA

Supplementary Table 1. Baseline demographic data (mean ± SD) in the dose-finding study. The data were calculated after CKD stage reclassification (see the Methods section).

	All patients n = 78	CKD 1 n = 17	CKD 2 n = 11	CKD 3A n = 15	CKD 3B n = 16	CKD 4 n = 13	CKD 5 n = 6	Comparison of the CKD stages (p-value)
Age, years	62.1 ± 10	52.4 ± 12.8	63.8 ± 4.5	65.1 ± 5.9	66.4 ± 9.4	64.3 ± 7.4	63.0 ± 7.2	0.011
Gender, M/F	44/35	11/6	5/6	10/5	10/6	5/8	2/4	—
BMI, kg/m ²	31.5 ± 5.0	30.3 ± 5.5	30.8 ± 4.2	33.7 ± 5.1	30.8 ± 4.1	33.4 ± 4.0	34.8 ± 5.3	0.337
HbA1C, % (mmol/mol)	8.8 ± 2.2 (73.69 ± 24.59)	10.6 ± 2.9 (92.70 ± 33.05)	8.8 ± 2.2 (73.36 ± 24.45)	8.2 ± 1.5 (65.71 ± 16.39)	8.8 ± 1.7 (72.31 ± 18.93)	8.1 ± 1.7 (64.46 ± 18.88)	7.7 ± 1.0 (62.67 ± 9.63)	0.040
Blood glucose, mmol/L	9.8 ± 4.0	11.7 ± 3.8	9.1 ± 3.6	10.6 ± 3.5	9.0 ± 3.0	8.2 ± 5.8	9.23 ± 3.11	0.044
Lactate, mmol/L	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.3	1.2 ± 0.4	1.0 ± 0.5	1.2 ± 0.3	0.7 ± 0.3	0.054
eGFR, mL/min	57.6 ± 37.7	112.6 ± 30.2	78.3 ± 15.6	52.7 ± 5.5	36.2 ± 5.2	22.9 ± 3.8	15.5 ± 4.1*	4.26x10 ⁻¹⁴
Diabetes duration, years	15.4 ± 11.8	2.9 ± 3.6	14.4 ± 8.9	17 ± 12.4	21.1 ± 9.1	20.1 ± 11.1	20.4 ± 11.7	9.13x10 ⁻⁶
Study completion, n	69	15	11	13	13	12	5	—

*Two patients in this group were reclassified from CKD stage 4 to stage 5, which explains the mean value of 15.5 mL/min (corresponding to the upper limit for CKD stage 5).

Supplementary Table 2. Laboratory data in the dose-finding study (mean ± SD (range)). Data are those retained after CKD stage reclassification* (see the Methods section).

CKD Stage	1	2	3A	3B	4	5
Step 1 (after 500 mg/day for a week)						
Number	17	11	14	16	12	6
eGFR, mL/min	121.2 ± 20.1 (90 – 150)	77.7 ± 9.7 (59 – 96)	55.9 ± 6 (41 – 65)	37.8 ± 5.4 (30 – 47)	22.6 ± 4.7 (16 – 29)	12.7 ± 1 (11 – 14)
Blood glucose, mmol/l	9.6 ± 3.4 (3.0 – 16.3)	8.8 ± 2.9 (5.6 – 16)	9.9 ± 3.3 (5.2 – 16)	8.8 ± 2.9 (4.8 – 16.7)	8.6 ± 3.8 (3.9 – 16)	9.0 ± 2.1 (6.2 – 12)
Plasma metformin, mg/L	0.23 ± 0.11 (0.10 – 0.44)	0.46 ± 0.26 (0.10 – 1.03)	0.86 ± 0.54 [†] (0.10 – 2.11)	0.97 ± 0.52 (0.33 – 2.0)	1.44 ± 1.13 [‡] (0.29 – 4.17)	1.38 ± 0.57 (0.83 – 2.44)
Erythrocyte metformin, mg/L	0.23 ± 0.11 (0.10 – 0.57)	0.54 ± 0.31 (0.12 – 1.16)	0.65 ± 0.23 (0.40 – 1.09)	0.96 ± 0.76 (0.10 – 3.12)	1.02 ± 0.64 [°] (0.46 – 2.82)	1.43 ± 0.24 (0.80 – 1.38)
Lactate, mmol/L	—	—	1.3 ± 0.6 (0.62 – 2.66)	1.1 ± 0.4 (0.5 – 1.6)	1.2 ± 0.4 (0.7 – 1.97)	0.7 ± 0.5 (0.16 – 1.7)
Step 2 (after 1000 mg/day for a week)						
Number	17	11	14	15	12	5
eGFR, mL/min	123.3 ± 18 (91 – 150)	78.5 ± 11.9 (62 – 96)	53.5 ± 6.2 (39 – 61)	35.7 ± 6.3 (30 – 44)	22.3 ± 5.5 (11 – 32)	11.8 ± 2.6 (8 – 15)
Blood glucose, mmol/l	9.2 ± 3.0 (4.7 – 14.4)	8.3 ± 3.7 (5.6 – 18.7)	8.4 ± 2.0 (5.5 – 12.2)	9.0 ± 2.6 (5 – 14.6)	6.8 ± 3.9 (2 – 15.9)	7.7 ± 1.0 (6.3 – 8.7)
Plasma metformin, mg/L	0.50 ± 0.51 (0.10 – 2.18)	0.66 ± 0.36 (0.32 – 1.45)	1.09 ± 0.51 (0.31 – 1.82)	1.24 ± 0.50 (0.5 – 2.07)	2.28 ± 1.16 (0.89 – 4.9)	1.92 ± 0.95 (1.03 – 3.53)
Erythrocyte metformin, mg/L	0.55 ± 0.40 (0.10 – 1.86)	0.76 ± 0.43 (0.24 – 1.84)	0.96 ± 0.30 (0.59 – 1.49)	1.47 ± 0.68 (0.73 – 3.12)	1.63 ± 0.58 (0.62 – 2.47)	1.20 ± 0.90 (0.10 – 2.44)
Lactate, mmol/L	—	—	1.3 ± 0.7 (0.53 – 3)	1.3 ± 0.6 (0.54 – 2.4)	1.2 ± 0.4 (0.5 – 1.67)	0.4 ± 0.2 (0.2 – 0.61)
Step 3 (after 2000 mg/day for a week)						
Number	15	11	13	13	11	5
eGFR, mL/min	121.7 ± 22.3 (85 – 150)	80.3 ± 7.5 (69 – 96)	55.3 ± 8.1 (42 – 76)	37.3 ± 5.5 (30 – 45)	22.5 ± 3.3 (17 – 27)	12.0 ± 1.2 (10 – 13)
Blood glucose, mmol/l	8.6 ± 3.0 (4.4 – 14.9)	7.9 ± 1.6 (5.1 – 10)	8.7 ± 2.7 (4.2 – 13.2)	7.9 ± 1.7 (5.7 – 11.3)	7.1 ± 3.4 (2.7 – 14.5)	9.6 ± 4.2 (6.7 – 16.6)
Plasma metformin, mg/L	0.49 ± 0.30 (0.10 – 1.1)	0.84 ± 0.62 (0.11 – 2.0)	1.31 ± 0.90 (0.48 – 3.04)	2.07 ± 1.03 (0.76 – 4.06)	3.09 ± 1.58 (1.55 – 7.2)	4.37 ± 1.73 (3.07 – 7.19)

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Erythrocyte metformin, mg/L	0.73 ± 0.27 (0.10 – 1.15)	1.19 ± 0.42 (0.49 – 1.88)	1.48 ± 0.70 (0.83 – 3.34)	2.32 ± 0.90 (0.82 – 4.18)	2.68 ± 0.64 (1.61 – 3.57)	4.54 ± 2.03 (1.56 – 6.74)
Lactate, mmol/L	—	—	1.4 ± 0.6 (0.64 – 2.45)	1.2 ± 0.6 (0.1 – 2.7)	1.5 ± 0.7 (0.74 – 2.7)	0.6 ± 0.1 (0.43 – 0.79)

*The CKD stage was reclassified in 11 cases (CKD1 → CKD2: n=2; CKD2 → CKD1: n=4; CKD3B → CKD3A: n=1; CKD4 → CKD3B: n=2, and → CKD5: n=2)

Supplementary Table 3. Laboratory data at the end of each month during the chronic metformin treatment study (mean ± SD (range)).

CKD Stage	3A	3B	4
1st month			
Number	12	12	15
eGFR, mL/min	50.00 ± 4.22 (42 – 58)	34.92 ± 6.67 (25 – 46)	24.47 ± 5.28 (14 – 32)
Blood glucose, mmol/L	10.03 ± 3.86 (4.50 – 17.50)	11.88 ± 4.12 (7.90 – 22.70)	10.91 ± 5.21 (4.40 – 24.60)
HbA1c, % [mmol/mol]	7.76 ± 0.94 (6.90 – 10.00) [61.30 ± 10.26] [(52 – 86)]	8.42 ± 2.05 (6.30 – 13.70) [68.45 ± 22.40] [(45 – 126)]	8.07 ± 1.17 (6.30 – 10.20) [64.54 ± 12.90] [(45 – 88)]
Plasma metformin, mg/L	1.93 ± 0.75 (0.95 – 3.16)	1.47 ± 1.00 (0.23 – 3.54)	0.81 ± 0.86 (0.10 – 3.47)
Erythrocyte metformin, mg/L	1.49 ± 0.37 (1.02 – 2.34)	1.34 ± 0.49 (0.47 – 2.22)	0.83 ± 0.51 (0.29 – 2.27)
Lactate, mmol/L	1.68 ± 0.68 (0.61 – 2.84)	1.48 ± 0.69 (0.98 – 3.37)	1.13 ± 0.61 (0.51 – 2.57)
2nd month			
Number	12	12	15
eGFR, mL/min	50.08 ± 7.12 (40 – 64)	34.17 ± 7.59 (27 – 49)	25.00 ± 6.13 (13 – 37)
Blood glucose, mmol/L	13.41 ± 8.68 (5.5 – 38.60)	11.71 ± 2.91 (7.60 – 16.80)	9.29 ± 3.01 (5.50 – 15.80)
HbA1c, % [mmol/mol]	7.94 ± 1.34 (6.50 – 10.80) [63.42 ± 14.64] [(48 – 95)]	8.33 ± 1.96 (6.60 – 13.60) [67.54 ± 21.36] [(49 – 125)]	8.13 ± 1.18 (6.50 – 10.30) [65.27 ± 12.81] [(48 – 89)]
Plasma metformin, mg/L	1.41 ± 0.86 (0.10 – 2.82)	1.50 ± 0.83 (0.15 – 2.86)	0.75 ± 0.81 (0.10 – 3.13)
Erythrocyte metformin, mg/L	1.34 ± 0.43 (0.50 – 1.93)	1.41 ± 0.72 (0.54 – 3.26)	0.99 ± 0.50 (0.26 – 2.21)
Lactate, mmol/L	1.56 ± 0.72 (0.96 – 3.34)	1.53 ± 0.68 (0.69 – 3.25)	1.15 ± 0.50 (0.65 – 2.42)
3rd month			
Number	9	11	14
eGFR, mL/min	46.67 ± 5.29 (40 – 53)	33.45 ± 5.43 (27 – 44)	24.21 ± 4.58 (13 – 32)
Blood glucose, mmol/L	12.53 ± 7.86 (6.20 – 32.00)	11.77 ± 5.23 (5.70 – 24.60)	9.68 ± 4.41 (5.90 – 20.20)
HbA1c, % [mmol/mol]	7.92 ± 1.16 (6.30 – 10.00) [63.09 ± 12.65] [(45 – 86)]	7.94 ± 0.91 (6.60 – 9.40) [63.18 ± 9.85] [(49 – 79)]	7.9 ± 1.32 (6.20 – 10.60) [62.94 ± 14.43] [(44 – 92)]
Plasma metformin, mg/L	1.65 ± 0.68 (0.67 – 2.94)	1.48 ± 0.91 (0.23 – 2.97)	0.57 ± 0.34 (0.10 – 1.25)
Erythrocyte metformin, mg/L	1.54 ± 0.52 (0.82 – 2.05)	1.62 ± 0.67 (0.73 – 2.55)	1.00 ± 0.42 (0.40 – 1.74)
Lactate, mmol/L	1.31 ± 0.52 (0.59 – 2.17)	1.44 ± 0.44 (0.94 – 2.17)	1.06 ± 0.62 (0.60 – 2.84)
4th month			
Number	10	11	14
eGFR, mL/min	50.10 ± 6.24 (41 – 60)	34.55 ± 5.48 (28 – 47)	23.21 ± 5.45 (11 – 32)
Blood glucose, mmol/L	10.79 ± 2.46 (7.40 – 15.50)	11.93 ± 3.92 (7.70 – 22.00)	10.52 ± 4.70 (6.20 – 22.50)
HbA1c, % [mmol/mol]	7.84 ± 1.47 (6.10 – 11.30) [62.27 ± 16.31] [(43 – 100)]	7.80 ± 0.88 (6.60 – 9.30) [61.82 ± 9.61] [(49 – 78)]	7.87 ± 1.49 (6.00 – 10.90) [62.36 ± 16.48] [(42 – 96)]
Plasma metformin, mg/L	1.53 ± 0.83	1.55 ± 0.75	0.85 ± 0.77

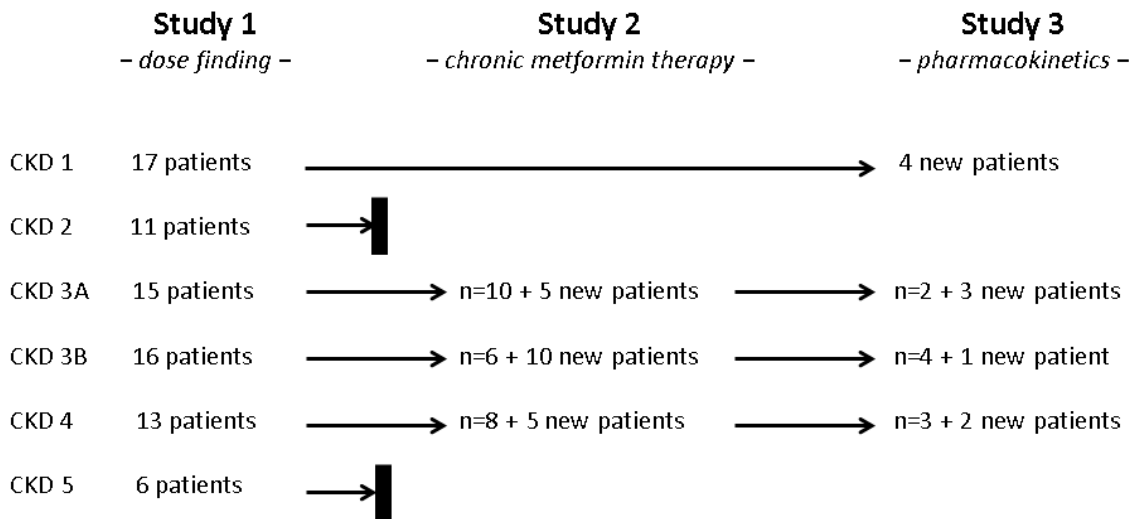
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	(0.10 – 3.21)	(0.35 – 2.82)	(0.10 – 2.34)
Erythrocyte metformin, mg/L	1.25 ± 0.46 (0.34 – 1.92)	1.58 ± 0.48 (0.92 – 2.31)	1.04 ± 0.58 (0.26 – 2.09)
Lactate, mmol/L	1.34 ± 0.46 (0.80 – 1.95)	1.40 ± 0.28 (1.00 – 2.02)	1.19 ± 0.65 (0.51 – 2.92)

Supplementary Table 4. Details of the patients who participated in the PK study.

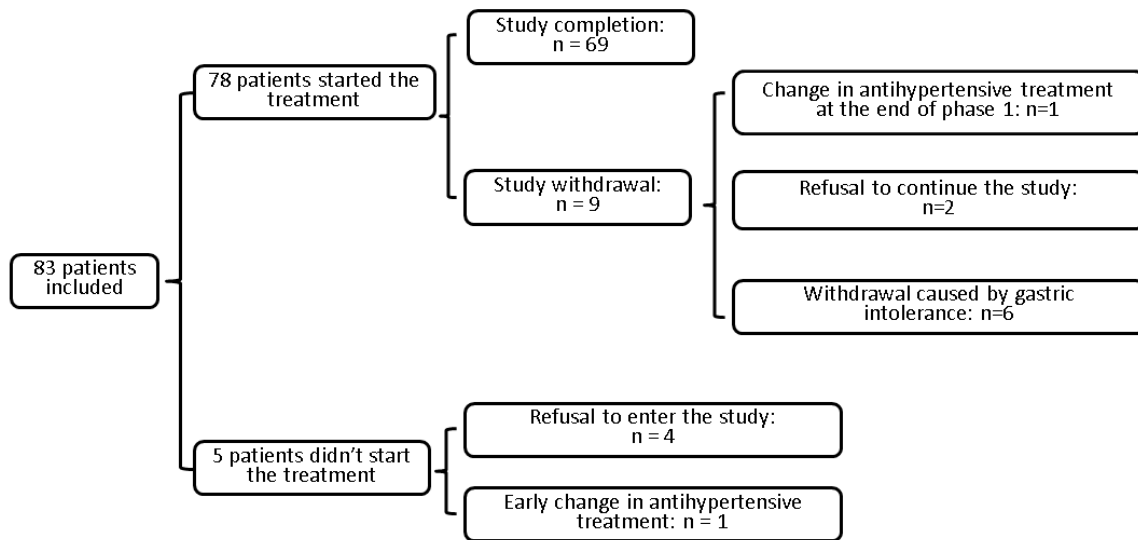
Patients studied at the end of the chronic (4-month) metformin treatment study (see Methods for metformin doses)		Patients not having participated to the chronic metformin treatment study but with at least 1 month of metformin treatment
CKD3A n = 5	n=2	n=3 (1 treated with 1500 mg/d and 2 others treated with 1000 mg/d)
CKD3B n = 5	n=4	n=1 (treated with 1000 mg/d)
CKD4 n = 5	n=3	n=2 (1 treated with 1000 mg/d and the other treated with 500 mg/d)

Supplementary Figure 1. Flow chart indicating the patients' participation in the various studies.

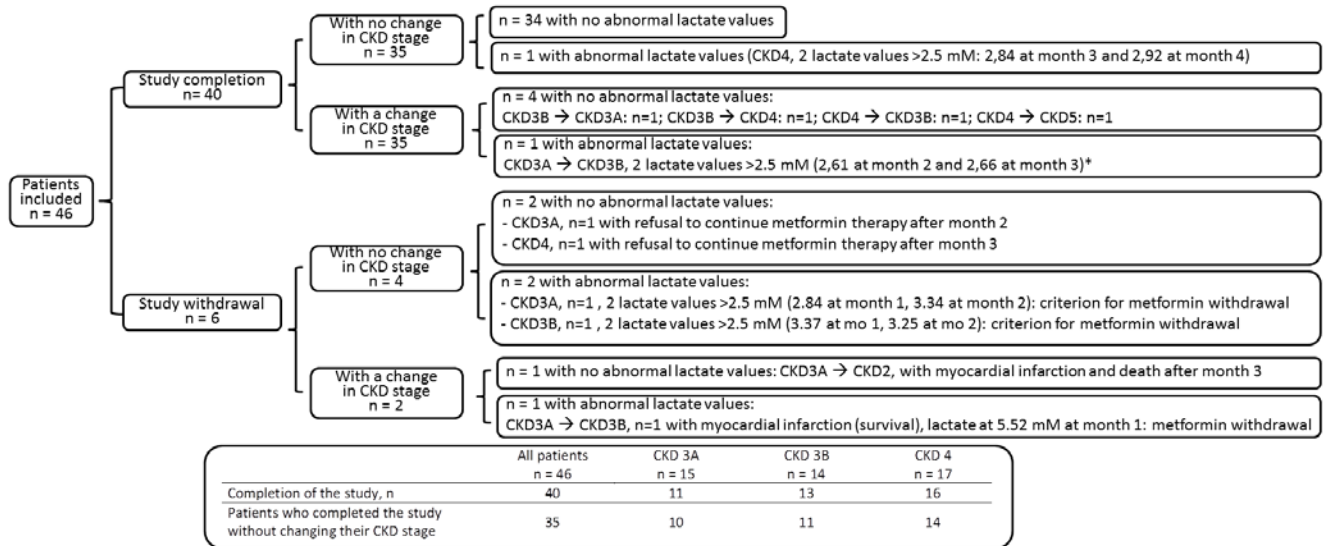


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Supplementary Figure 2. Patient flow chart for study 1.



Supplementary Figure 3. Patient flow chart for study 2.



	All patients n = 46	CKD 3A n = 15	CKD 3B n = 14	CKD 4 n = 17
Completion of the study, n	40	11	13	16
Patients who completed the study without changing their CKD stage	35	10	11	14

* i.e. criterion for metformin withdrawal. Metformin therapy was continued because (i) the increase in lactate values was small, (ii) the metformin concentrations was not abnormally elevated (1.8 mg/l), and (iii) other antidiabetic agents were not tolerated. The lactate concentration was 2.34 mM at month 4.

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Supplementary Figure 4. Time-course of metformin concentrations in plasma (top) and in erythrocytes (bottom) after the administration of a single, oral dose of 500 mg of metformin in steady-state diabetic patients with CKD 3A, 3B, and 4.

