

Quality and characteristics of 4,241 case reports of lactic acidosis in metformin users reported to a large pharmacovigilance database

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Online data supplement

Online Supplementary Table 1. Categorical analysis of key variables according to the recorded dose of metformin.

	Missing data (n=1,544)	Daily metformin dose (mg) category				
		Low (<1,000) (n=388)	Medium (1,000 to 2,000) (n=1,040)	High (2,000 to 2,550) (n=708)	Maximum (2,550 to 3,000) (n=360)	Above maximum (>3,000) (n=201)
Plasma metformin (mg/L)						
Missing	1,308 (84.7)	347 (89.43)	882 (84.81)	572 (80.8)	271 (75.3)	152 (75.6)
Up to 4.99	84 (5.4)	15 (3.87)	29 (2.79)	43 (6.1)	31 (8.6)	26 (12.9)
5 to <20	54 (3.4)	2 (0.52)	32 (3.08)	29 (4.1)	14 (3.9)	6 (3.0)
20 to <50	78 (5.1)	5 (1.29)	27 (2.60)	56 (7.9)	37 (10.3)	12 (6.0)
≥50	20 (1.3)	7 (1.80)	12 (1.15)	8 (1.1)	7 (1.9)	5 (2.5)
Plasma lactate (mmol/L)						
Missing	862 (55.8)	162 (41.8)	396 (38.1)	270 (38.1)	99 (27.5)	73 (36.3)
<2.5 ^a	153 (9.9)	37 (9.5)	115 (11.1)	87 (12.3)	52 (14.4)	53 (26.4)
2.5 to 5.0 ^b	258 (16.7)	56 (14.4)	207 (19.9)	169 (23.9)	128 (35.6)	32 (15.9)
5 to <10 ^c	76 (4.9)	40 (10.3)	110 (10.6)	53 (7.5)	17 (4.7)	12 (6.0)
10 to <20 ^d	144 (9.3)	55 (14.2)	149 (14.3)	96 (13.6)	55 (15.3)	23 (11.4)
≥20 ^e	51 (3.3)	38 (9.8)	63 (6.1)	33 (4.7)	9 (2.5)	8 (4.0)
pH						
Missing	956 (61.92)	229 (59.0)	529 (50.9)	318 (44.9)	109 (30.2)	61 (30.4)
<7.0 ^f	295 (19.1)	93 (24.0)	297 (28.6)	174 (24.6)	107 (29.7)	78 (38.8)
7.0 to <7.35 ^g	8 (0.5)	5 (1.3)	14 (1.4)	5 (0.7)	1 (0.3)	3 (1.5)
7.35 to 7.45 ^h	267 (17.3)	47 (12.11)	172 (16.5)	191 (27.0)	136 (37.8)	51 (25.4)
≥7.45 ⁱ	18 (1.2)	14 (3.6)	28 (2.7)	20 (2.8)	7 (1.9)	8 (4.0)

Categories of plasma lactate: ^aNormal; ^bhyperlactataemia; ^clow lactic acidosis; ^dhigh lactic acidosis; ^eextreme lactic acidosis. Categories of pH: ^fmassive acidosis; ^gacidosis; ^hnormal; ⁱalkalosis. Figures in parentheses are percentages of the corresponding metformin dose category. Metformin dosage categories were determined arbitrarily.

Online Supplementary Table 2. Spearman correlation coefficients (rho, 95% CI) for all correlations between metformin dosage, plasma metformin, plasma lactate, pH and GFR.

	All cases	LA subpopulation ^a	MaLA subpopulation ^b	Metformin dose ≤3000 mg ^c	Metformin dose >3000 mg ^c
Metformin dose x plasma metformin	0.29 (0.2, 0.38)	0.26 (0.14, 0.38)	0.19 (0.05, 0.32)	0.26 (0.17, 0.34)	0.39 (0.1, 0.6)
Metformin dose x plasma lactate	0.22 (0.18, 0.27)	0.13 (0.06, 0.19)	0.17 (0.04, 0.3)	0.19 (0.14, 0.23)	0.28 (0.11, 0.43)
Metformin dose x pH	-0.17 (-0.22, -0.12)	-0.14 (-0.2, -0.08)	-0.15 (-0.27, -0.04)	-0.22 (-0.28, -0.17)	-0.12 (-0.29, 0.06)
Plasma metformin x plasma lactate	0.35 (0.27, 0.43)	0.25 (0.16, 0.34)	0.26 (0.17, 0.36)	0.3 (0.19, 0.4)	0.63 (0.4, 0.78)
Plasma metformin x pH	-0.45 (-0.52, -0.37)	-0.4 (-0.47, -0.32)	-0.35 (-0.43, -0.26)	-0.43 (-0.52, -0.34)	-0.63 (-0.78, -0.41)
Plasma lactate x pH	-0.57 (-0.61, -0.54)	-0.52 (-0.56, -0.48)	-0.47 (-0.55, -0.39)	-0.61 (-0.65, -0.56)	-0.57 (-0.69, -0.41)
Metformin dose x GFR	-0.23 (-0.28, -0.18)	-0.16 (-0.24, -0.08)	-0.02 (-0.17, 0.14)	-0.32 (-0.37, -0.26)	0.42 (0.22, 0.59)
Plasma metformin x GFR	-0.32 (-0.4, -0.23)	-0.29 (-0.4, -0.18)	-0.14 (-0.27, -0.01)	-0.42 (-0.51, -0.31)	0.06 (-0.29, 0.43)
Plasma lactate x GFR	-0.2 (-0.25, -0.15)	-0.08 (-0.15, -0.02)	0.03 (-0.09, 0.16)	-0.27 (-0.33, -0.21)	-0.11 (-0.35, 0.14)
pH x GFR	0.25 (0.2, 0.3)	0.21 (0.15, 0.28)	0.13 (0.01, 0.25)	0.3 (0.24, 0.36)	0.12 (-0.12, 0.34)

Subpopulations (see Methods): ^asufficient data presented to correctly diagnose lactic acidosis (LA); ^bsufficient data presented to correctly diagnose metformin-associated LA (MaLA); ^cRecorded metformin dose at prior to the acidotic event. Table cells where rho exceeds an arbitrarily defined value of 0.3 and 0.4 are shaded to aid visibility.

Online Supplementary Table 3. Univariate predictors of mortality.

a) All cases with sufficient data

Plasma metformin (mg/L)	OR (95% CI)	p
<2.5	Reference	–
2.5–4.99	1.73 (0.87, 3.44)	0.12
5– <10	0.92 (0.44, 1.88)	0.83
10– <20	1.20 (0.66, 2.21)	0.55
20– <50	0.73 (0.43, 1.24)	0.24
≥50	1.29 (0.75, 2.23)	0.36

Metformin dose (mg)	OR (95% CI)	p
<1,000	Reference	–
1,000–2,000	1.16 (0.88, 1.55)	0.30
2,000–2,550	1.12 (0.83, 1.51)	0.47
2,550–3,000	0.90 (0.63, 1.29)	0.57
>3,000	0.65 (0.41, 1.03)	0.07
–		

Plasma lactate (mmol/L)	OR (95% CI)	p
<2.5 mmol/L	Reference	–
2.5– <5.0	0.91 (0.43, 2.02)	0.81
5.0– <10.0	1.90 (1.01, 3.89)	0.06
10.0– <20.0	4.74 (2.64, 9.43)	<0.001
20.0–50.0	6.99 (3.85, 14.02)	<0.001
>50	6.91 (2.81, 17.40)	<0.001

pH	OR (95% CI)	p
7.35– 7.45	Reference	–
≥7.45	3.05 (1.49, 7.35)	0.0053
7–7.35	2.03 (0.56, 6.82)	0.2555
<7	5.56 (2.73, 13.38)	<0.001

b) The LA subpopulation

Plasma metformin (mg/L)	OR (95% CI)	p
<2.5	Reference	–
2.5–4.99	3.40 (1.20, 10.09)	0.0228
5– <10	1.61 (0.63, 4.17)	0.3203
10– <20	1.33 (0.57, 3.14)	0.5159
20– <50	0.66 (0.32, 1.38)	0.2530
≥50	1.13 (0.55, 2.42)	0.7408

Metformin dose (mg)	OR (95% CI)	p
<1,000	Reference	–
1,000–2,000	0.86 (0.54, 1.39)	0.524
2,000–2,550	0.82 (0.51, 1.35)	0.431
2,550–3,000	0.60 (0.35, 1.02)	0.056
>3,000	0.29 (0.14, 0.60)	0.001

Plasma lactate (mmol/L)	OR (95% CI)	p
<2.5 mmol/L	–	–
2.5– <5.0	–	–
5.0– <10.0	Reference	–
10.0– <20.0	2.51 (1.73, 3.72)	<0.001
20.0–50.0	4.38 (2.97, 6.58)	<0.001
>50	3.19 (1.31, 7.30)	0.0075

pH	OR (95% CI)	p
7.35–7.45	–	–
≥7.45	–	–
7–7.35	Reference	–
<7	1.52 (1.19, 1.93)	<0.001

c) The MaLA subpopulation

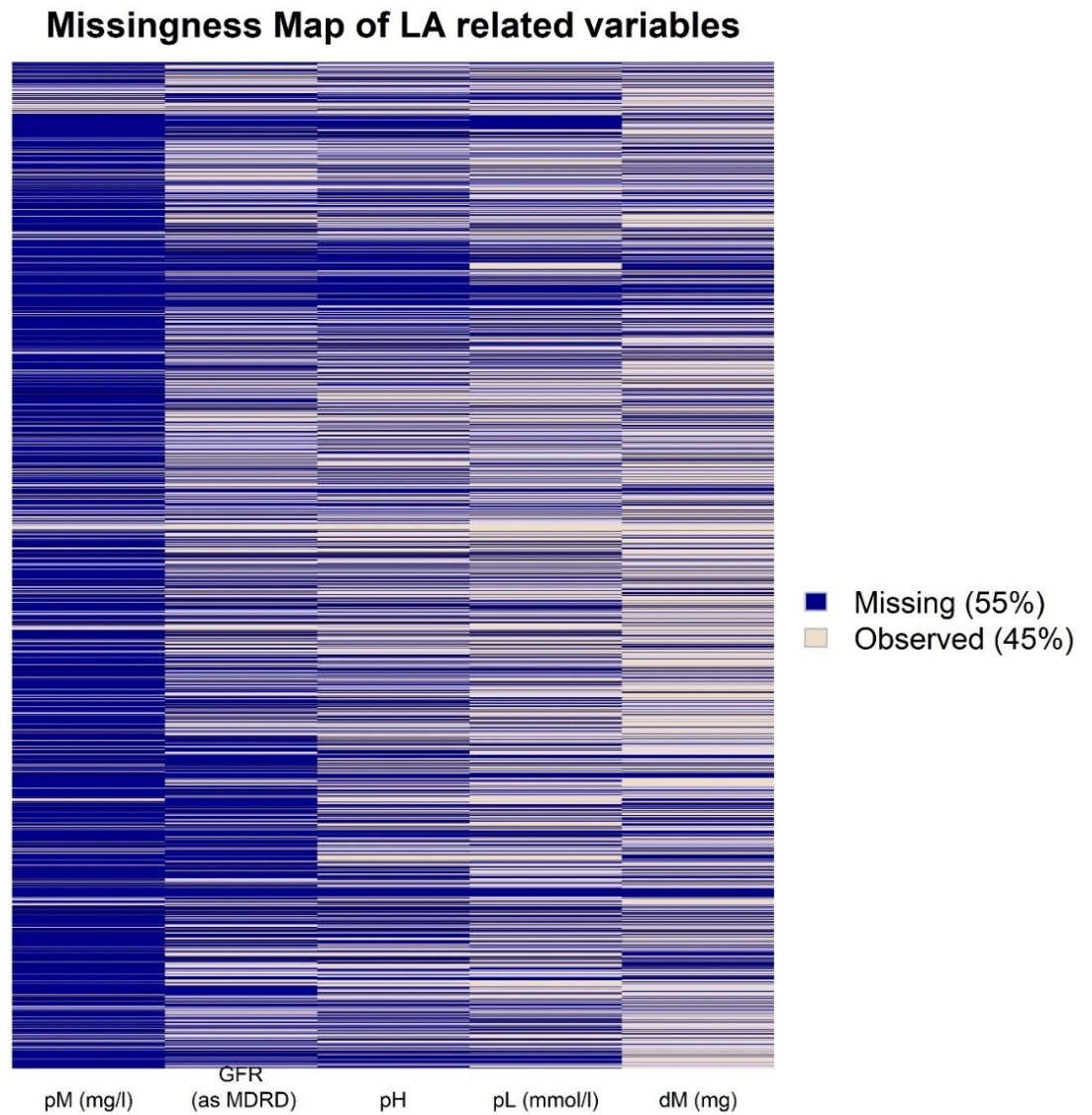
Plasma metformin (mg/L)	OR (95% CI)	p
<2.5	–	–
2.5–4.99	–	–
5–<10	Reference	–
10–<20	0.89 (0.35, 2.27)	0.806
20–<50	0.44 (0.20, 1.01)	0.047
≥50	0.76 (0.34, 1.77)	0.515

Metformin dose (mg)	OR (95% CI)	p
<1,000	Reference	–
1,000–2,000	0.36 (0.08, 1.48)	0.154
2,000–2,550	0.31 (0.07, 1.29)	0.106
2,550–3,000	0.41 (0.09, 1.70)	0.217
>3,000	0.18 (0.03, 0.89)	0.037

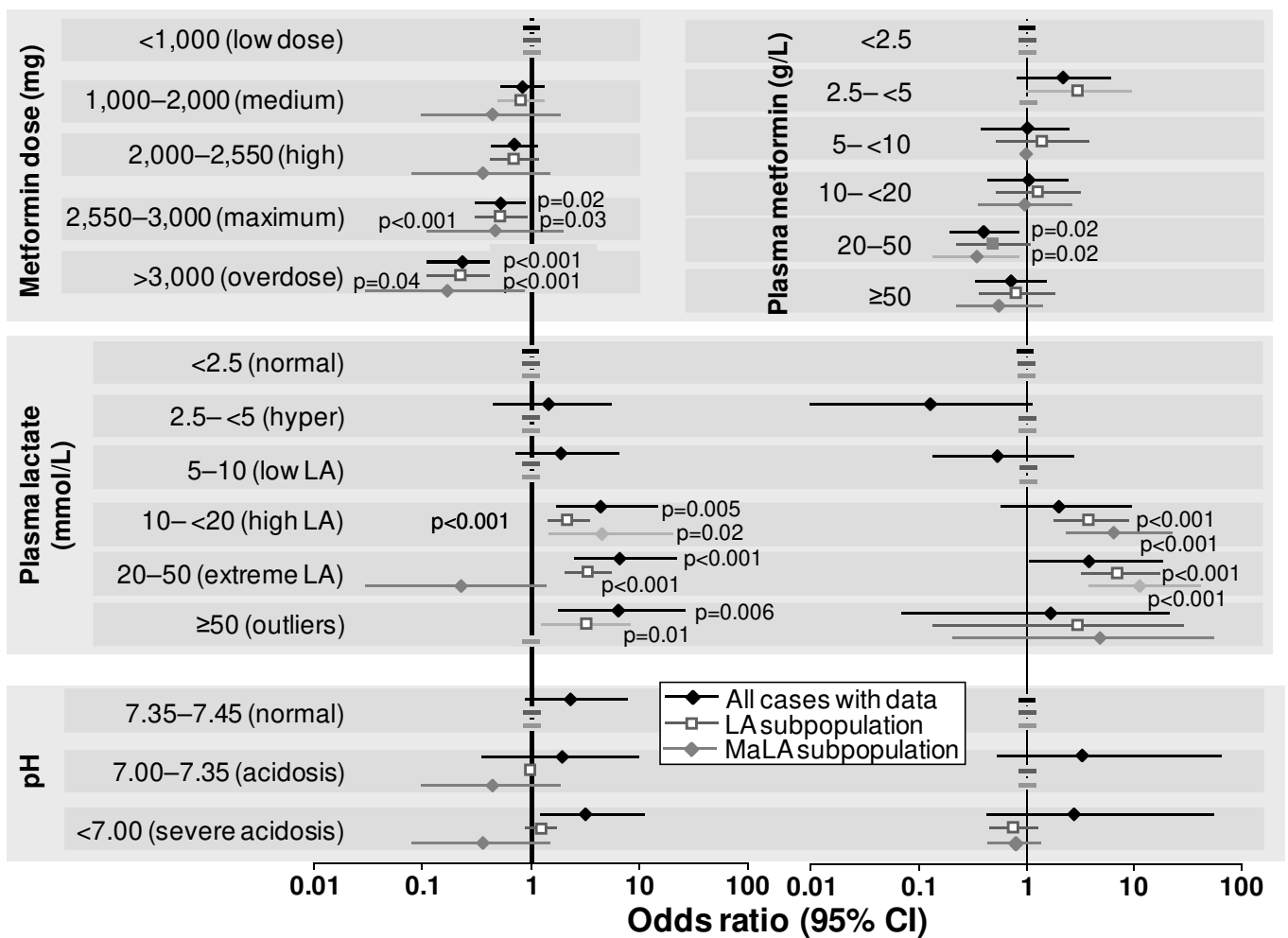
Plasma lactate (mmol/L)	OR (95% CI)	p
<2.5 mmol/L	–	–
2.5–<5.0	–	–
5.0–<10.0	Reference	–
10.0–<20.0	4.77 (1.83, 16.38)	0.0042
20.0–50.0	7.54 (2.85, 26.11)	<0.001
>50	4.08 (0.18, 42.19)	0.2666

pH	OR (95% CI)	p
7.35–7.45	–	–
≥7.45	–	–
7–7.35	Reference	–
<7	1.17 (0.73, 1.89)	0.53

Online Supplementary Fig. 1. Missingness map for laboratory variables related to the diagnosis of lactic acidosis or metformin-associated lactic acidosis.



Online Supplementary Fig. 2. Odds ratios for death from logistic regression models adjusted on key variables related to lactic acidosis (LA) or metformin-associated lactic acidosis (MaLA) as per index of exposure.



Figures on the left were adjusted on metformin dose, plasma lactate and pH; Figures on the right were adjusted on plasma metformin, plasma lactate and pH. Null values (–) were either excluded from subpopulations due to their entry criteria for pH, plasma metformin or plasma lactate (see text) or due to insufficient data. Numbers of cases based on metformin dose were 1,222 (all available records), 966 (all records based on metformin plasma level), 435 (LA subpopulation), and 312 (MaLA subpopulation). Numbers of cases based on metformin plasma level were 996 (all available records), 435 (all records based on metformin plasma level), 312 (LA subpopulation), and 312 (MaLA subpopulation). For respective reference comparison groups, please refer to Online Supplementary Table 3. Some ORs have wide confidence intervals due to low number of cases and should be interpreted with caution.