

# A case-series of metformin-associated lactic acidosis in the German spontaneous reporting system – time to remember this serious adverse drug reaction!

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## Background

Metformin is the first-line drug in the treatment of type 2 diabetes mellitus. In Germany, prescriptions have increased substantially since 1990 (Figure 1), with the highest rates of increase in patients > 75 years (Figure 2)<sup>1,2</sup>. An increase of spontaneous reports of metformin-associated lactic acidosis (MALA) since 1990, with a cluster in 2012, has prompted us to reassess reports from recent years (Figure 3).

Figure 1:

Prescriptions [million defined daily doses (DDD)] of metformin reimbursed for outpatient care by German statutory health insurance 1990–2012. Not included are combined products with gliptins, which accounted for about 130 million prescriptions in 2012.

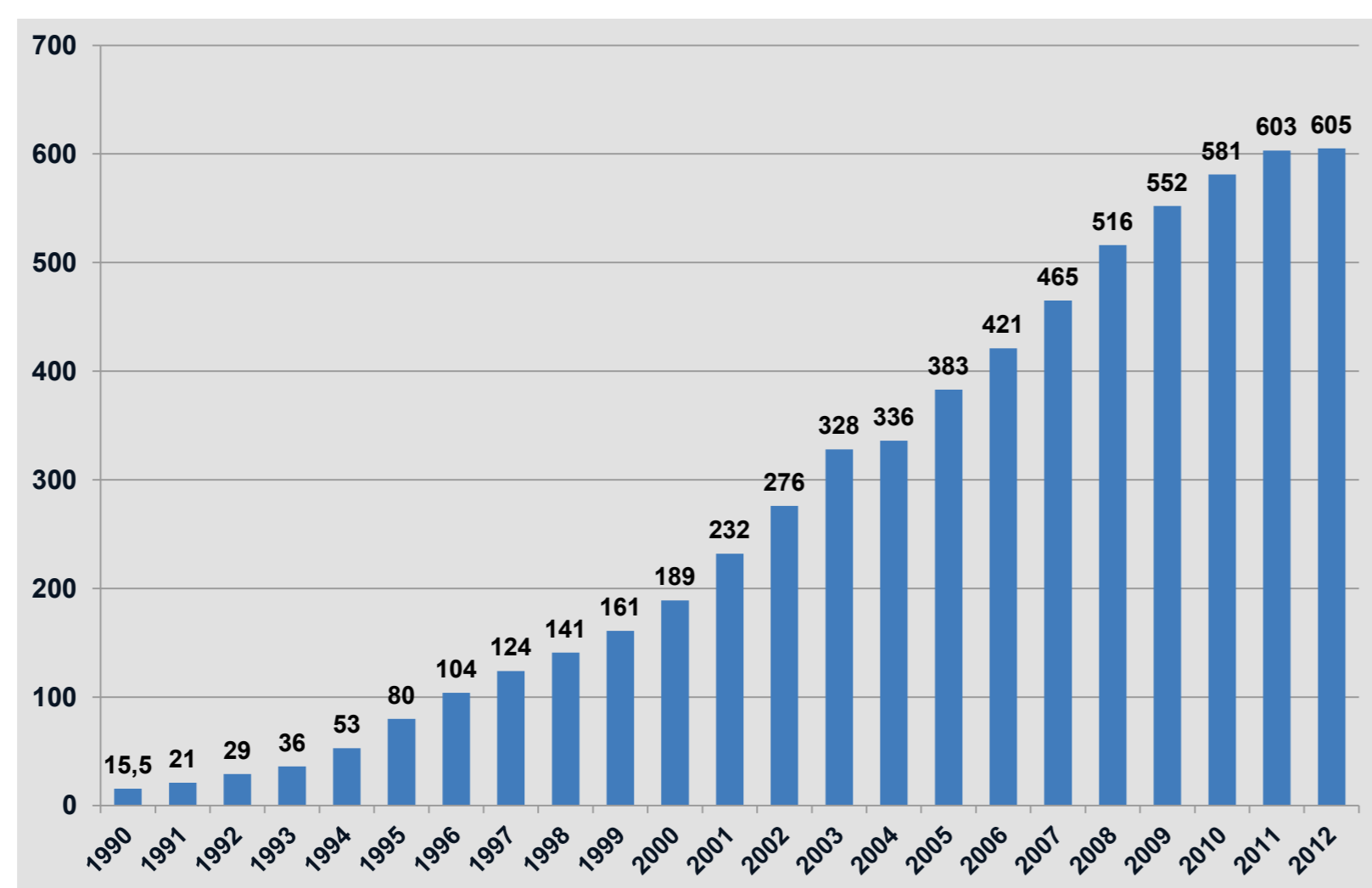


Figure 2:

Metformin prescriptions 2005 (blue columns) and 2010 (red columns) per insurant related to different age groups. The increase of prescriptions refers to patients older than 60 years with the highest increase rates in patients older than 75 years.

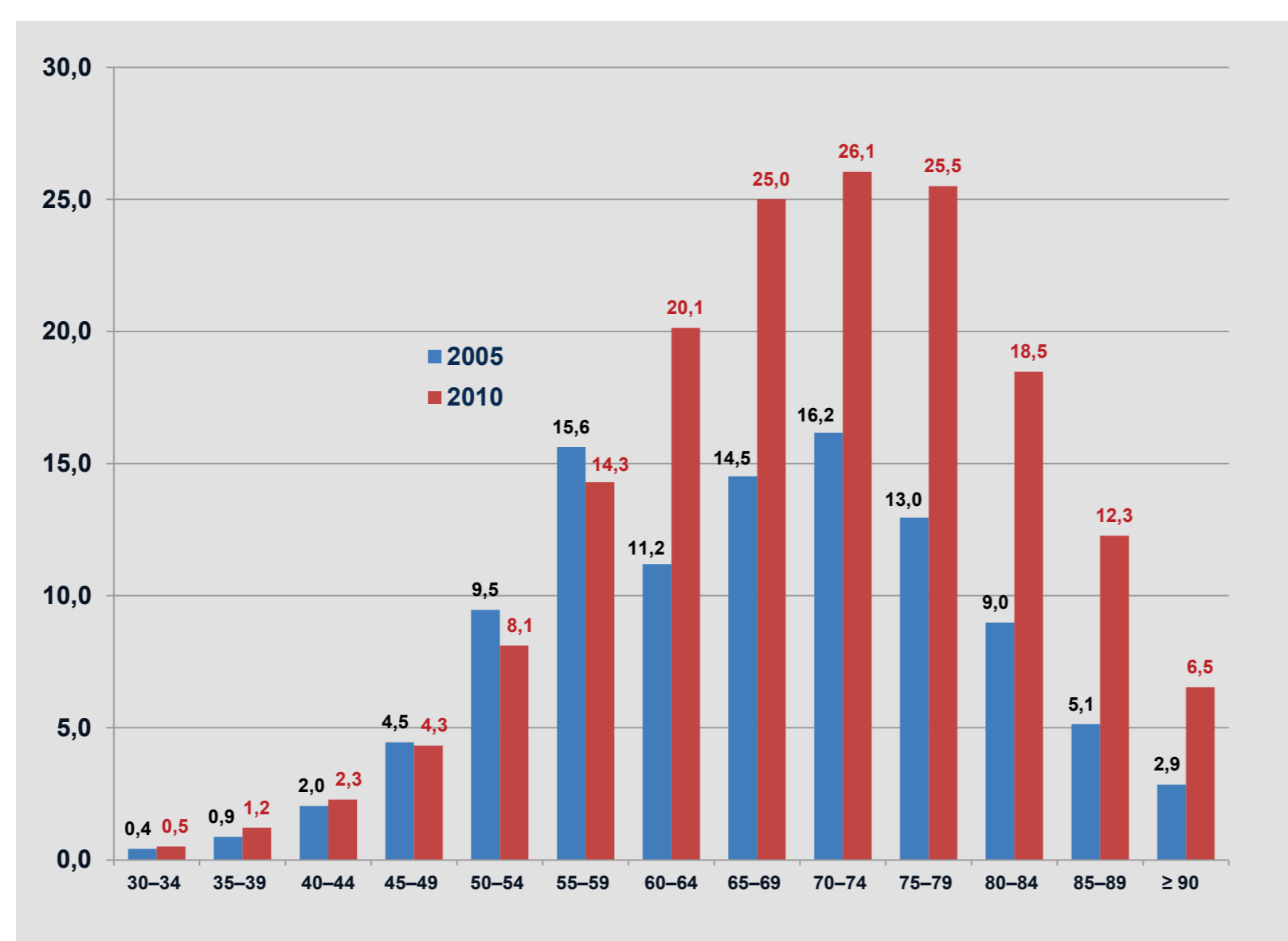
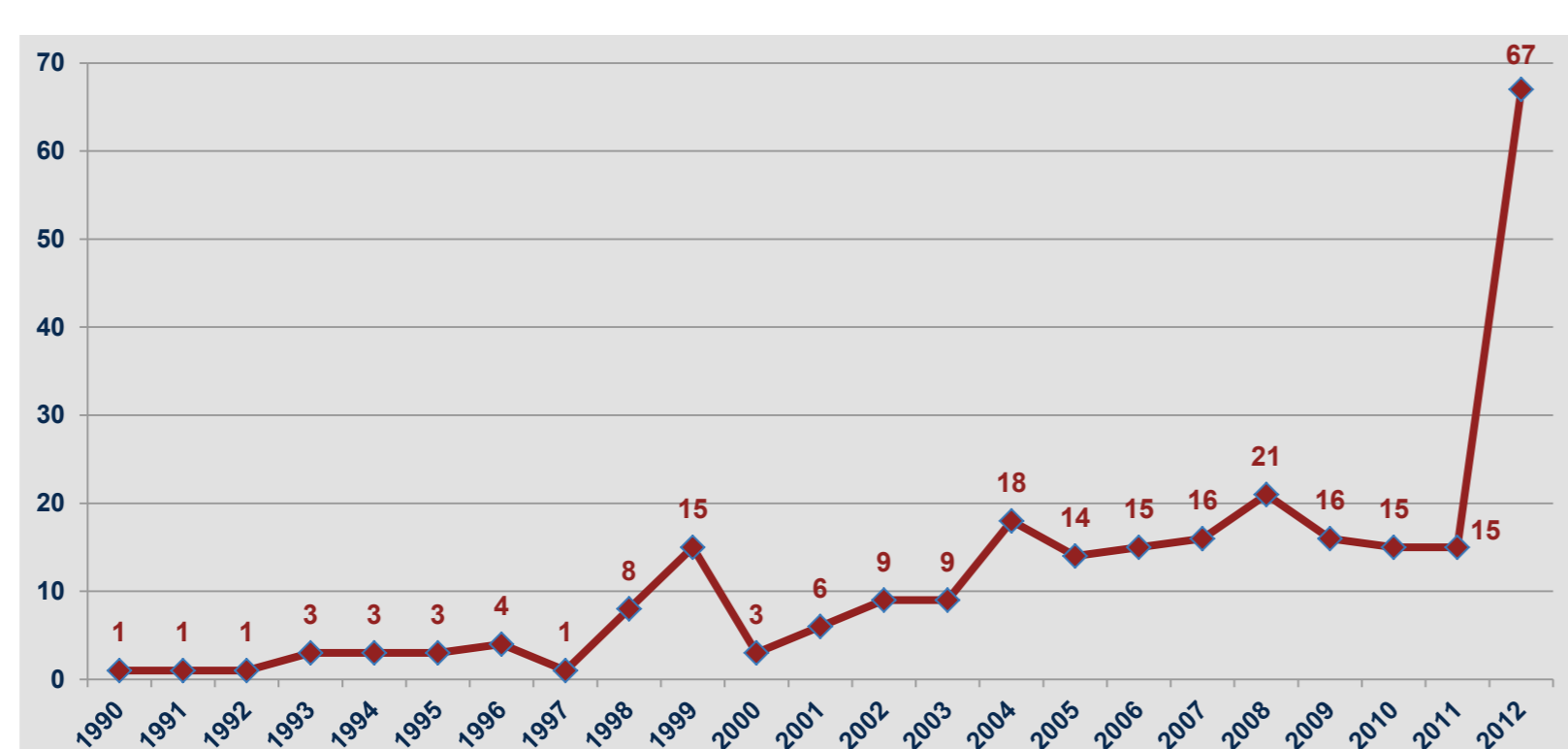


Figure 3:

Number of reported cases of metformin-associated lactic acidosis in Germany 1990 to 2012 (n = 264).



## Objective

To investigate patient characteristics, outcome and possible risk factors in spontaneous reports of MALA.

## Methods

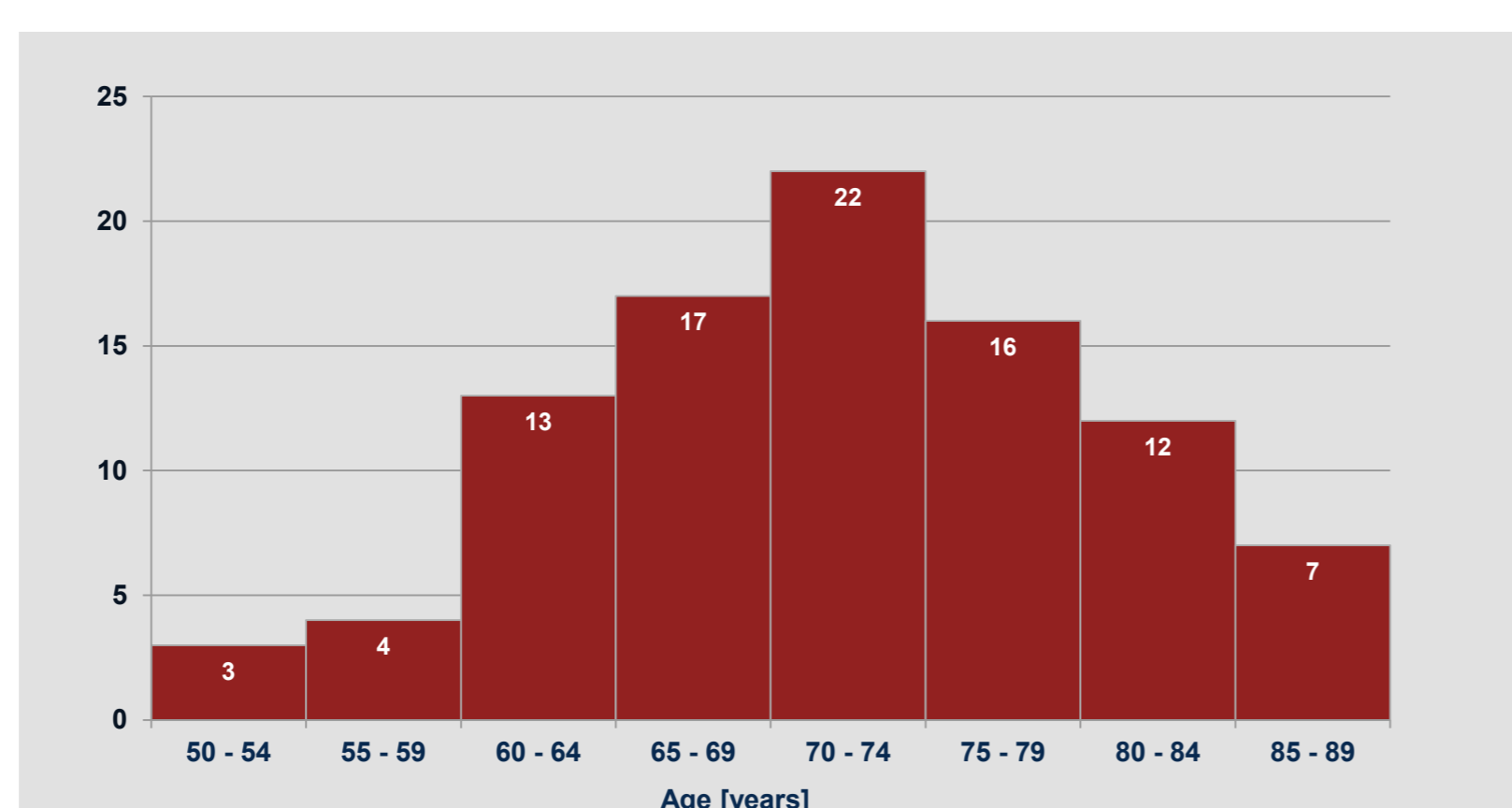
We included cases from the German spontaneous reporting database from 2001–2012 with available original reporting documents (report form, medical letters, laboratory findings). We reviewed data on patient characteristics, medical history, laboratory findings and outcome.

## Results

99 of 221 reports of MALA were eligible. 5 reports were excluded because neither pH nor serum lactate was documented, or pH was > 7.35. Table 1 displays the clinical characteristics of the remaining 94 cases. The distribution of the reports to different age groups is shown in Figure 4.

Figure 4:

Distribution of patients in the reports of MALA to different age groups.



The reported data on duration of metformin medication to diagnosis of lactic acidosis were highly variable ranging from a few days to several years. In roughly half of the cases the initiation of metformin administration is unknown.

Table 1: Clinical characteristics of patients in spontaneous reports of suspected metformin-associated lactic acidosis. (ACEB: ace blockers, ARB: angiotensin receptor blockers)

<b>No. of cases</b>	94
<b>Sex</b>	34 m/ 60 f
<b>Mean age (range)</b>	71.7 years (50–87)
<b>Mean BMI (range)</b>	30.3 (16–67)
<b>Medical history</b>	Arterial hypertension 63 (67.0 %) Coronary artery disease 20 (21.3 %) Cerebrovascular disease 10 (10.6 %) Peripheral artery disease 8 (8.5 %) Chronic heart failure 24 (25.5 %) Chronic renal failure 26 (27.7 %)
<b>Mean daily dose of metformin (range)</b>	1700 mg (500–3000)
<b>Additional antidiabetic medication</b>	28 (29.8 %)
<b>Other concomitant drugs</b>	ACEB or ARB 34 (36.2 %) diuretics 33 (35.1 %)
<b>Fatal outcome</b>	44 (46.8 %)

78 (83 %) patients had acute renal failure (ARF) at diagnosis of MALA (mean serum creatinine 7.7 mg/dl, Figure 5); most commonly (n = 25) caused by dehydration due to gastrointestinal symptoms (vomiting, diarrhea). In 47 patients (50 %) concomitant cardiovascular diseases other than hypertension were reported (Table 1). 28 patients (29.8 %) also took other anti-diabetes drugs including sulfonylurea (9), insulin (7), gliptins (5) and exenatide (1). Mean serum pH was 6.93 (range 6.5–7.35, Figure 6), serum lactate 15.7 mmol/l (2.3–32, Figure 7). In 22 cases serum metformin concentration was available and highly elevated (mean 38.4 mg/l, therapeutic range 0.1–1.3 mg/l, Figure 8). Renal replacement therapy was performed in 59 (63 %) cases. 44 patients (46.8 %) died.

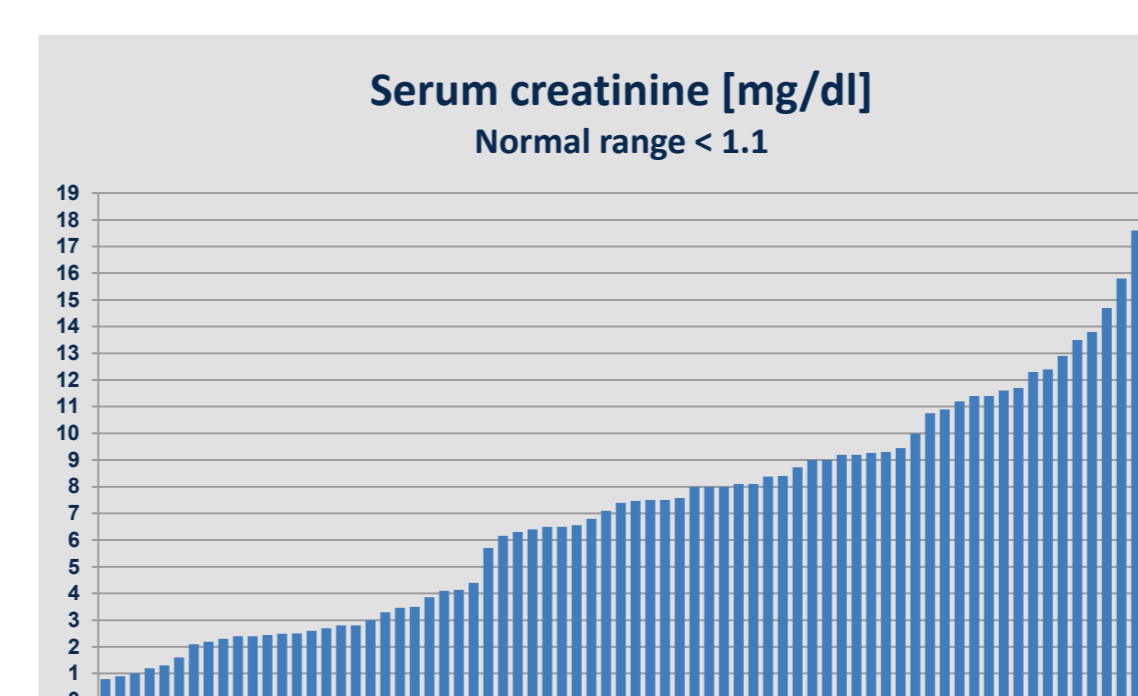


Figure 5: Serum creatinine in 71 of 94 cases (not reported in 23 cases).

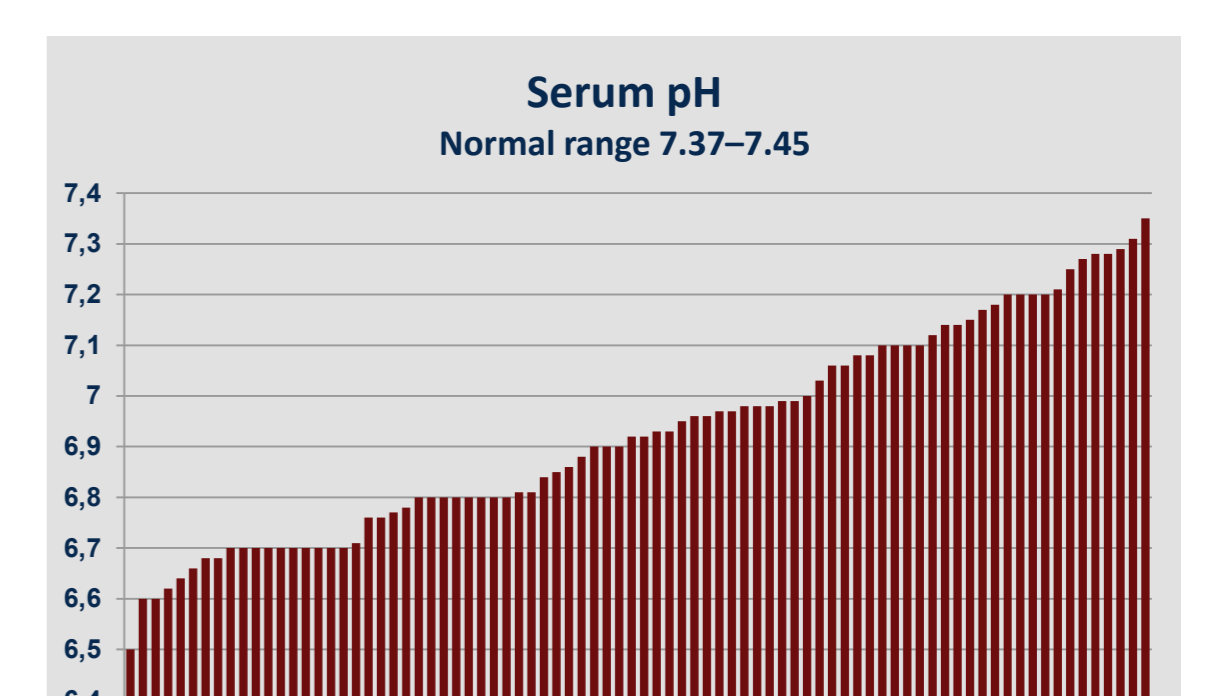


Figure 6: Serum pH in 82 of 94 cases (not reported in 12 cases).

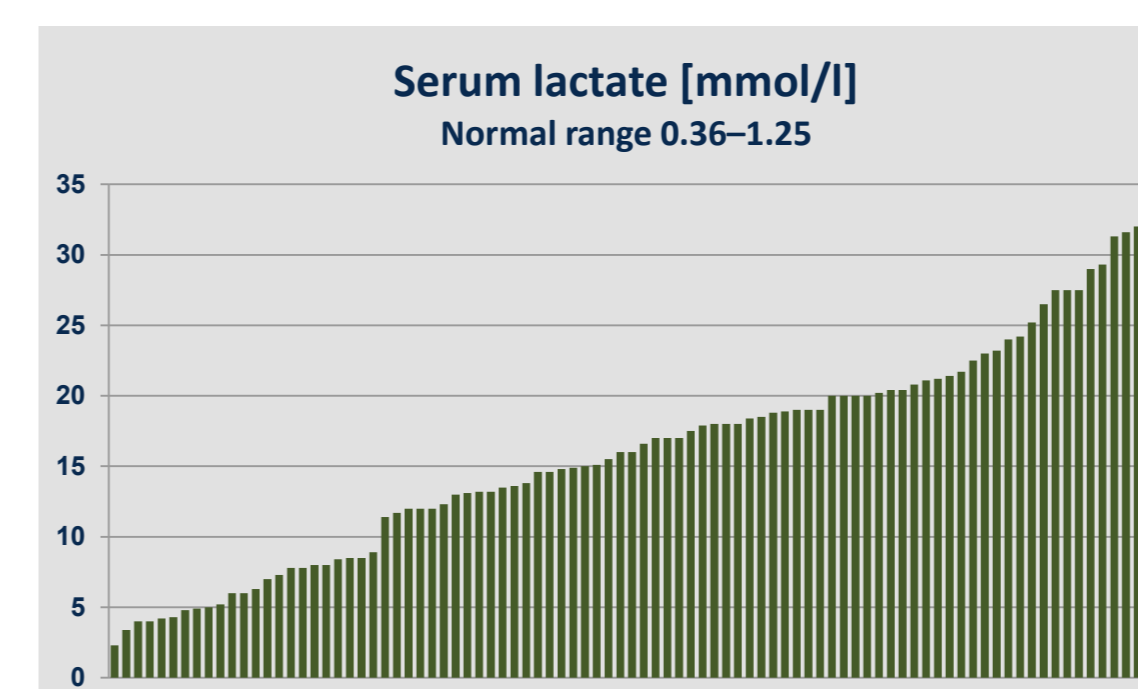


Figure 7: Serum lactate in 88 of 94 cases (not reported in 6 cases).

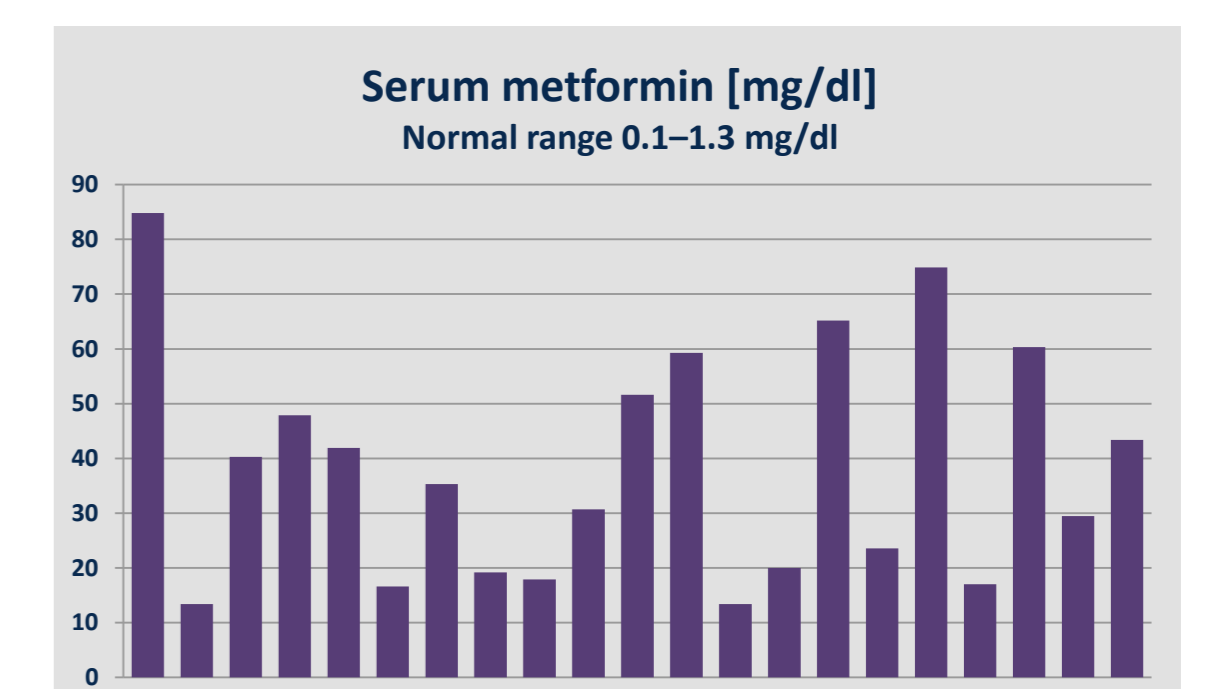


Figure 8: Serum metformin concentration in 21 of 94 cases.

## Discussion

Our data suggest that an age above 70 years and concomitant cardiovascular or renal disease are risk factors for MALA. Since metformin is prescribed increasingly for older patients, this might in part explain the observed increase of reports in Germany. Acute renal failure (ARF) was identified as the possible trigger for MALA in the majority of our cases. However, we cannot clearly distinguish between vomiting/diarrhea as a cause for dehydration and ARF inducing MALA or a symptom of beginning lactic acidosis. Nevertheless, gastroenteritis in elderly patients treated with metformin should be considered as a potential risk factor for MALA. Regular monitoring and informing of patients and caregivers about the risks of metformin in acute illness seems crucial, especially in patients at high risk of renal function deterioration. The benefit-risk profile of metformin in elderly patients requires further studies.

## References

- Schwabe U, Paffrath D (ed): Arzneiverordnungs-Report (German Drug Report) 2012. Berlin, Heidelberg, Springer Medizin Verlag, 2012.
- GKV-Arzneimittelindex (German Drug Index; data not published). Wissenschaftliches Institut der AOK – WIdO (Research Institute of the Local Health Care Fund). Berlin, September 17th, 2012.