

# Mortality and Death Statistics Related to Metformin

## Introduction

While metformin is generally considered a safe medication for the treatment of type 2 diabetes, it is associated with a rare but potentially fatal adverse effect known as metformin-associated lactic acidosis (MALA). This section examines the mortality rates associated with metformin use, with particular focus on MALA, and compares these rates with other diabetes medications when possible.

## Metformin-Associated Lactic Acidosis (MALA) Mortality

Metformin-associated lactic acidosis is a rare but serious adverse event characterized by elevated blood lactate levels, decreased blood pH, and a history of metformin administration. Despite its rarity, MALA carries a significant mortality risk that has been well-documented in medical literature.

A comprehensive review of MALA mortality data from the 1960s to recent years by Kajbaf and Lalau (2014) revealed a notable trend in mortality rates. According to their analysis of 12 published series and a large pharmacovigilance database containing 722 case reports with specified outcomes, the overall mortality rate for MALA was approximately 50% during the period 1960-2000. However, this rate has since declined to around 25% in more recent years. This improvement likely reflects advances in critical care medicine, earlier recognition of the condition, and more effective treatment protocols.

More recent studies have reported similar findings. Van Berlo-van de Laar et al. (2020) noted that MALA continues to be associated with a high mortality rate of 30-50%. Their research focused on identifying clinical parameters that could help recognize MALA early in emergency department settings, as timely intervention may reduce morbidity and mortality.

A 2022 observational study by Thammavaranucupt et al. examined factors associated with 30-day mortality among 105 MALA patients. They reported a 30-day mortality rate of 36.2%, with the majority of deaths (60.5%) occurring within 5 days after diagnosis. This study also found that early dialysis treatment (within 6 hours after admission) and hemodialysis (versus other forms of renal replacement therapy) were independently associated with lower 30-day mortality.

Other recent research by Rivera (2023) confirmed that mortality from MALA continues to range from 25% to 50%, making it one of the most serious complications of metformin therapy. Similarly, Gautier (2024) reported mortality rates of up to 35% in cases of lactic acidosis with metformin accumulation.

The incidence of MALA itself is relatively low, estimated at between 2 and 9 cases per 100,000 patient-years according to Tong (2024). However, this incidence may be increasing due to the growing number of type 2 diabetes patients using metformin and recent changes in prescribing guidelines that no longer contraindicate metformin use in patients with more severe renal failure.

## Factors Affecting MALA Mortality

Several factors have been identified as influencing mortality risk in patients with MALA:

1. **Severity of acidosis:** Lower arterial pH at presentation is associated with higher mortality rates. In the literature series reviewed by Kajbaf and Lalau, the mean pH varied widely from 6.89 to 7.20, with more severe acidosis correlating with poorer outcomes.
2. **Timing of intervention:** Early recognition and treatment of MALA appear crucial for survival. Thammavaranucupt et al. found that dialysis treatment within 6 hours of admission was associated with significantly lower 30-day mortality (hazard ratio = 0.31; 95% CI, 0.14–0.69;  $p = 0.004$ ).
3. **Mode of renal replacement therapy:** Hemodialysis appears to be more effective than other forms of renal replacement therapy, with Thammavaranucupt et al. reporting an association between hemodialysis and lower 30-day mortality (hazard ratio = 0.20; 95% CI, 0.06–0.67;  $p = 0.010$ ).
4. **Disease severity:** Higher APACHE II scores (indicating greater disease severity) were associated with increased mortality risk. Conversely, lower APACHE II scores were associated with improved survival (hazard ratio = 0.95; 95% CI, 0.91–0.99;  $p = 0.038$ ).
5. **Comorbidities:** The presence of acute kidney injury, particularly stage 3 according to KDIGO 2012 definition, was common among MALA patients (95.2% in the Thammavaranucupt study), suggesting that renal impairment is a significant risk factor for both developing MALA and for poor outcomes.

# Historical Trends in MALA Mortality

The decline in MALA mortality rates from approximately 50% in the 1960-2000 period to around 25-36% in more recent years represents a significant improvement. This trend may be attributed to several factors:

1. **Improved critical care:** Advances in intensive care medicine have enhanced the management of critically ill patients with metabolic disturbances.
2. **Earlier recognition:** Increased awareness of MALA among healthcare providers has likely led to earlier diagnosis and intervention.
3. **More effective renal replacement therapies:** Modern dialysis techniques may be more efficient at removing metformin and lactate from circulation.
4. **Better supportive care:** Improvements in managing complications such as hypotension, respiratory failure, and multi-organ dysfunction have likely contributed to better outcomes.

Despite these improvements, the mortality rate for MALA remains substantial, underscoring the importance of prevention, early recognition, and prompt treatment.

## Comparison with Other Diabetes Medications

Direct comparisons of mortality rates between metformin and other diabetes medications are limited in the literature. However, some contextual information is available:

1. **Sulfonylureas:** These medications are associated with a higher risk of hypoglycemia compared to metformin, which can lead to serious adverse events including death, particularly in elderly patients. However, specific comparative mortality statistics are sparse.
2. **Thiazolidinediones:** Rosiglitazone has been associated with increased cardiovascular mortality risk, leading to restrictions on its use in many countries. Pioglitazone has a more favorable cardiovascular profile but has been associated with increased risk of bladder cancer in some studies.
3. **SGLT2 inhibitors:** These newer agents have shown cardiovascular and renal benefits in clinical trials, with some studies suggesting reduced all-cause mortality compared to other diabetes medications. However, they can cause euglycemic diabetic ketoacidosis, which carries its own mortality risk.

4. **GLP-1 receptor agonists:** These medications have demonstrated cardiovascular benefits and potential reduction in all-cause mortality in high-risk patients with type 2 diabetes.
5. **Insulin:** While essential for many patients, insulin therapy carries risks of hypoglycemia, which can be fatal, particularly in vulnerable populations such as the elderly or those with impaired hypoglycemia awareness.

It's important to note that direct mortality comparisons between these medications are complicated by differences in patient populations, comorbidities, and study methodologies. Additionally, the rare but serious nature of MALA makes it difficult to compare directly with more common adverse effects of other medications.

## Overall Mortality Risk with Metformin

Despite the serious nature of MALA, the overall mortality risk associated with metformin therapy is considered low due to the rarity of this complication. The incidence of MALA ranges from 2 to 9 cases per 100,000 patient-years, making it an uncommon adverse event.

Furthermore, multiple studies have suggested that metformin may be associated with reduced all-cause mortality and cardiovascular mortality in patients with type 2 diabetes compared to other glucose-lowering agents. This potential mortality benefit must be weighed against the rare but serious risk of MALA when considering metformin therapy.

## Conclusion

Metformin-associated lactic acidosis remains a rare but potentially fatal complication of metformin therapy, with mortality rates that have improved from approximately 50% to 25-36% over recent decades. Early recognition, prompt intervention (particularly early dialysis), and appropriate critical care management appear to be key factors in improving survival. Despite this serious adverse effect, the overall mortality risk associated with metformin therapy is considered low due to the rarity of MALA, and metformin continues to be recommended as a first-line therapy for type 2 diabetes due to its established efficacy and generally favorable safety profile.

## References

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