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# Can metformin improve 'the tomorrow' of patients treated for oesophageal cancer?

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**Abstract**

*Introduction*: Recent studies suggest that the use of metformin is associated with reduced cancer incidence and improved prognosis in patients with oesophageal cancer. We explored the relationship between the use of metformin and outcome (pathologic response rate, distant metastasis-free and overall survival) in our mono-institutional cohort of patients treated for oesophageal cancer.
*Material and methods*: Between 2008 and 2014, a total of 196 patients with oesophageal cancer (ages ranged from 37 to 82 years) eligible for curative treatment entered the study. Patients were categorized as non-diabetic (n = 172), diabetic not taking metformin (n = 5) or diabetic taking metformin (n = 19). The majority of patients were treated with trimodality therapy (n = 189). Pathologic response was graded according to Mandard's tumour regression score at the time of surgery. Distant metastasis-free and overall survival were calculated using the Kaplan–Meier method with log rank comparisons performed to determine significance.
*Results*: The overall pathologic complete response rate for the study population was 26%. It was 25% for patients not using metformin and 39% for diabetics taking metformin (p = 0.260). The two-year overall survival rate for the whole group was 59%. Use of metformin was associated with a significantly better distant metastasis-free survival rate (p = 0.040) or overall survival rate (p = 0.012). Multivariate analysis using Cox regression found that metformin treatment significantly prolonged survival (p = 0.043).
*Conclusion*: In our population-based study, the use of metformin was associated with an improved overall and distant metastasis-free survival rate in patients with oesophageal cancer. These data are complementary to one other clinical study and warrant further prospective study.


*Keywords:* Oesophageal cancer; Diabetes; Metformin; Survival

## Introduction

Oesophageal carcinoma is the eighth most common cancer worldwide and is known for its aggressive nature and poor survival rate.[1] Adenocarcinoma of the oesophagogastric junction (AEG) is increasingly common in the Western world and its prevalence now equals or surpasses that of squamous cell carcinoma (SCC).[2] Research has suggested that a high body mass index (BMI) is a major risk factor for the development of AEG.[3] The exact underlying pathomechanism is unclear, but over recent years chronic inflammation accompanying obesity has come to be seen as a crucial contributing factor.[4] The visceral adipose tissue is a sink of a high amount of systemically active cytokines and adipo-cytokines which act as pro-inflammatory mediators, initiating the metaplasia-dysplasia-adenocarcinoma sequence.[5] In addition to high BMI, type 2 diabetes has also become alarmingly common worldwide, sharing the same dual relationship with cancer incidence or mortality.[6]

Metformin (1,1-dimethylbiguanide hydrochloride) belongs to the biguanide class of oral antidiabetic drugs originally derived from galegine (isoamylene guanide), a

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guanidine derivative found in the French lilac Galega officinalis. This drug is typically used in the treatment of people with type 2 diabetes who also have obesity. Long-term use of this drug has been associated with reduced risks for some cancer types and improved cancer prognosis.[7–9]

At the molecular level, the exact mechanism for its anticancer effect is rather complicated and not fully clear. Encouraging results from preclinical data have indicated that metformin may prevent the development of oesophageal cancer.[10] Moreover, emerging clinical data suggests that cancer patients who take metformin have a better treatment response than those who do not.[11,12] Only one retrospective study has addressed the question of whether metformin, in conjunction with a standard neoadjuvant approach, could also improve complete remission and outcome in oesophageal cancer.[12] Therefore, the objective of this single-institution retrospective study was to investigate the effect of metformin on the outcomes in our oesophageal cancer patient cohort.

## Material and methods

### *Patient selection*

Two independent researchers reviewed clinical data about our patients who were treated with curative intent for oesophageal cancer between 2008 and 2014. A total of 196 patients met these criteria, of which 189 (96%) received neoadjuvant chemoradiotherapy (CRT). Only 7 (3%) had clinical stage cT1N0M0 disease and underwent primary surgical treatment.

All patients received initial staging with oesophagogastroscopy and biopsies, endoscopic ultrasound and positron emission tomography computed tomography (PET-CT). Staging was done in accordance with the American Joint Committee on Cancer TNM classification, 7th Edition. The standard neoadjuvant approach was to apply radiotherapy to the tumour and draining lymph nodes. Chemoradiotherapy consisted of 50.4 Gy combined with two cycles of cisplatin and 5-FU or 41.4 Gy combined with five cycles of carboplatin and paclitaxel.[13] All patients were treated with external beam radiation, using three-dimensional conformal radiation technique or Volumetric Modulated Arc Therapy (RapidArc). Re-evaluation with PET-CT was planned 6–8 weeks after CRT, followed by en-bloc-oesophagectomy with regional node dissection. Pathologic complete response (pCR) was defined as a tumour regression grade I based on the Mandard classification. In addition, the absence of tumour cells in sampled lymph nodes was necessary to fulfill the definition.

Patients were categorized as non-diabetic ($n = 172$), diabetic not taking metformin ($n = 5$) or diabetic taking metformin ($n = 19$). Classification of diabetes was based on pre-existing diagnosis prior to CRT. From the computer records, we identified all the patients' medical prescriptions. We also did an additional manual search of the patients' pharmacy records or charts to verify our data about the use of any anti-diabetic medications (metformin, sulfonylurea, alfa-glucosidase inhibitors, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors and insulin). We determined the cumulative daily use of metformin from prescription records found in electronic medical records or from self-reported records from the outpatient clinic. Pre-treatment height and weight were used to generate a pre-treatment BMI. Data were censored for analysis on 28 February 2015.

### *Statistics*

All statistical analyses were conducted using SPSS (v.22). Univariate comparisons of patient characteristics between patients with or without metformin use were performed using a Pearson's Chi-square test for comparison of categorical data like sex or T stage and a Student's T-test for continuous data like age and BMI.

Pathologic complete response (pCR), overall survival (OS) and distant metastasis-free survival (DMFS) were the primary endpoints of this study. With respect to pCR, univariate analyses (either Pearson Chi-square or Student's T-test) were performed with the following variables: metformin use, age, BMI, tumour and nodal classification and histopathological subtype. Any variable with a significance of $p \leq 0.1$ was included in the multivariate analysis. Multivariate analysis was performed with logistic regression. All p-values for multivariate analysis are two-sided, with a $p < 0.05$ considered significant.

For DMFS and OS, time-to-event was calculated from the first day of radiation treatment or, when no neoadjuvant treatment was initiated, from the date of surgery until an event occurred or was censored. Event for DMFS was defined as recurrence of disease at distant sites or non-regional lymph nodes. These metastases were identified on computed tomography (with or without positron emission tomography) or chest X-ray. Pathologic confirmation of distant metastasis was not always available when evident. Event for OS was defined as death due to any cause. OS and DMFS were calculated using the Kaplan–Meier statistic, and log rank comparisons were performed to determine significance in univariate analyses for categorical predictors. Univariate analyses for continuous variables were performed using Cox proportional hazards regression. Any variable with a significance of $p \leq 0.1$ was included in the multivariate analysis. Multivariate analysis for DMFS and OS was performed with Cox proportional hazards regression. All p-values for multivariate analyses are two-sided, with a $p < 0.05$ considered significant.

## Results

### *Patient and tumour characteristics*

Of the 196 patients who were eligible for analysis, 10% ($n = 19$) had used metformin before and during their treatment. Detailed characteristics of cases and controls are

Table 1
Baseline characteristics between groups.

| Variable | No metformin | | Metformin | | P-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Number | 177 | 90.3 | 19 | 9.7 | |
| Sex | | | | | 0.772 |
| Female | 35 | 19.8 | 3 | 15.8 | |
| Male | 142 | 80.2 | 16 | 84.2 | |
| Age | | | | | 0.314 |
| Mean (min–max) | 63 (37–82) | | 64 (51–76) | | |
| Type carcinoma | | | | | 0.847 |
| Adenocarcinoma | 137 | 77.4 | 16 | 84.2 | |
| Squamous cell | 36 | 20.3 | 3 | 15.8 | |
| Other | 4 | 2.3 | 0 | 0 | |
| cT stage | | | | | 0.470 |
| T1 | 6 | 3.4 | 1 | 5.3 | |
| T2 | 42 | 23.7 | 7 | 36.8 | |
| T3 | 123 | 69.5 | 11 | 57.9 | |
| T4 | 6 | 3.4 | 0 | 0 | |
| cN stage | | | | | 0.131 |
| N0 | 57 | 32.2 | 10 | 52.6 | |
| N1 | 81 | 45.8 | 8 | 42.1 | |
| N2 | 24 | 13.5 | 1 | 5.3 | |
| N3 | 15 | 8.5 | 0 | 0 | |
| Neoadjuvant CRT | | | | | 0.676 |
| Yes | 171 | 96.8 | 18 | 94.7 | |
| No | 6 | 3.4 | 1 | 5.3 | |
| BMI | | | | | 0.004* |
| Mean (min–max) | 25 (15–40) | | 28 (20–36) | | |
| ≤30 | 152 | 85.9 | 13 | 68.4 | 0.089 |
| >30 | 25 | 14.1 | 6 | 31.6 | |

*$p < 0.05$.

summarized in Table 1. Thirteen patients had a daily intake of more than 850 mg of metformin, compared to six patients with an intake less than or equal to 850 mg.

The mean age of the whole patient population was 63 years (range 37–82 years). The majority of patients were diagnosed with adenocarcinoma (78%), clinical stage T3 (68%) and N0–N1 stage (80%). Only BMI, measured as a continuous variable, was significantly different for both treatment groups ($p = 0.004$).

### *Pathologic complete response*

Of the 189 patients who received neoadjuvant CRT, 50 (26%) were found to have a pCR at the time of surgical resection (Table 2). A pCR was reached for 18 out of 38 patients with SCC (47%) while for adenocarcinoma this percentage was considerably lower (21% or 31 out of 148 patients).

For the metformin group, this percentage was 39% and for the non-metformin group it was 25%. The univariate analysis of our study cohort revealed that metformin treatment did not result in a significantly increased pCR rate ($p = 0.260$). Tumour characteristics that did significantly influence pCR rate were N stage ($p = 0.026$) or N category (N0/1 vs N2/3, $p = 0.010$) and SCC ($p = 0.004$). Controlling for these three factors, the pCR effect was only significant in favour of SCC ($p = 0.001$; HR 0.393; 95% CI 0.133–0.620) but not for metformin ($p = 0.139$; HR 0.546; 95% CI 0.769–6.538).

### *Distant metastasis-free survival*

We report a 30-month median follow-up for DMFS (95% CI 24–35 months). One-, two- and five-year DMFS for the whole group were 84.5%, 72.1% and 71%, respectively (Table 2). Median DMFS was not reached for the whole group and both subgroups. One- and two-year DMFS for the non-metformin patients were 82.1% and 69.6%, respectively, compared to 100% and 93.3% for the metformin group ($p = 0.040$; Fig. 1). On a multivariate analysis, metformin use was no longer significantly associated with improved DMFS ($p = 0.082$, HR 1.014; 95% CI 0.024–1.253).

### *Survival outcomes*

Median follow-up for OS in our patient cohort was 51 months (95% CI 44–57 months). Median OS for the whole study population was 34 months (95% CI 18.6–49.3 months (Table 2). One-, two- and five-year OS rates for the whole patient cohort were 78.7%, 59.1% and 44.8%, respectively. They were 77%, 56.5% and 41%, respectively,

Table 2
Impact of metformin on outcome.

| | All patients (n = 196) | No metformin (n = 177) | Metformin (n = 19) | Univariate analysis p-value |
|---|---|---|---|---|
| pCR | | | | |
| n events (%)[a] | 50 (26)[a] | 43 (25)[a] | 7 (39)[a] | 0.260[a] |
| DMFS | | | | |
| n events | 45 | 44 | 1 | |
| median, months | NR | NR | NR | 0.040 |
| 12-month DMFS, % | 84.5 | 82.1 | 100 | |
| 24-month DMFS, % | 72.1 | 69.6 | 93.3 | |
| 60-months DMFS, % | 71 | 68.2 | 93.3 | |
| OS | | | | |
| n deaths | 93 | 89 | 4 | |
| median, months | 34 | 32 | NR | 0.012 |
| 12-month OS,% | 78.7 | 77 | 94.7 | |
| 24 month OS, % | 59.1 | 56.5 | 82.9 | |
| 60-month OS, % | 44.8 | 41 | 74.6 | |

Abbreviations: pCR = pathologic complete response, DMFS = distant metastasis-free survival, OS = overall survival, n = number, NR = not reached.
[a] pCR was calculated for patients treated with neoadjuvant chemoradiotherapy (n = 189) without (n = 171) or with (n = 18) metformin.

for the non-metformin group and 94.7%, 82.9% and 74.6%, respectively, for the metformin group. In the non-metformin group, median OS was 32 months (95% CI 18–46 months). In the metformin group, median OS had not been reached at the time of analysis.

From the univariate analysis, we found that the following characteristics influence OS: metformin use ($p = 0.012$; Fig. 2), cN stage ($p = 0.044$), Mandard tumour regression grade ($p = 0.001$) and BMI as a continuous variable ($p = 0.012$). Patients whose BMI was 30 or higher had a better OS rate ($p = 0.041$). We performed multivariate Cox regression analysis to evaluate the influence of these variables and found metformin was the only prognostic factor for OS ($p = 0.043$; HR 0.352; 95 CI 0.128–0.969).

## Discussion

The renewed interest in the Warburg effect and cancer energetics emphasizes the dependence of many cancers on glycolysis for energy.[14] Metformin, a first-line diabetes drug, inhibits gluconeogenesis and increases glucose uptake and peripheral glycolysis. Several epidemiological studies explored the role of metformin as a chemopreventive agent to decrease the risk of various types of cancer.[8] Metformin may not only reduce cancer incidence, but may also alter the behaviour of present cancer cells. In our opinion, the possibility that metformin use hampers neoplastic proliferation and thereby improves outcome for oesophageal cancer patients deserved further consideration.

To our knowledge, this study is the first to assess the survival benefit of metformin intake in oesophageal cancer patients. Both univariate and multivariate analysis confirmed that survival was significantly better for patients using metformin. Exposure to this biguanide was also associated with an improved DMFS, but did not affect the results of the multivariate analysis. Although pCR was not statistically significantly better among metformin users, there was a trend towards higher pCR rates in favour of metformin intake. The only factor influencing pCR rate was squamous

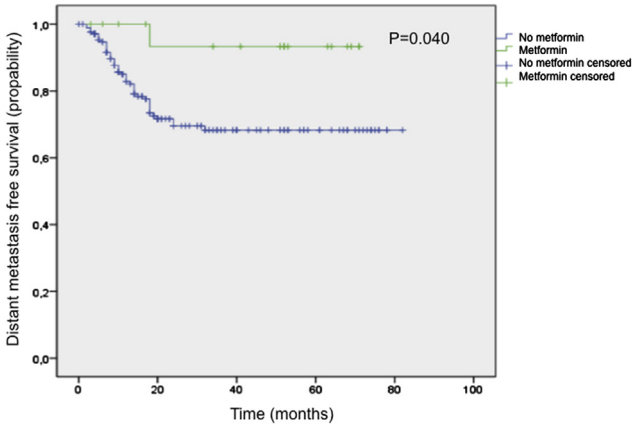


Figure 1. Kaplan–Meier distant metastasis-free survival curves comparing patients treated with metformin versus without metformin.

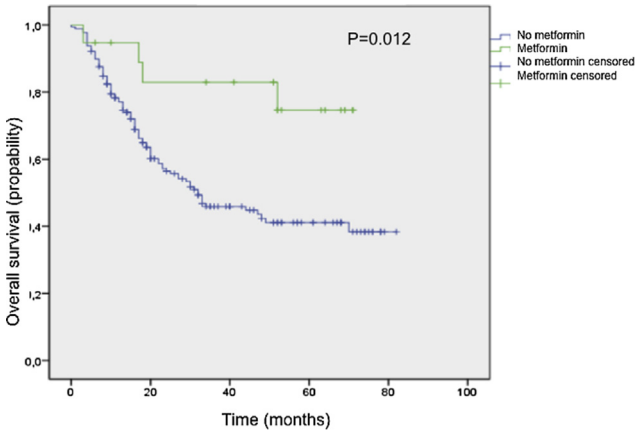


Figure 2. Survival analysis Kaplan-Meier plots comparing patients treated with metformin versus without metformin.

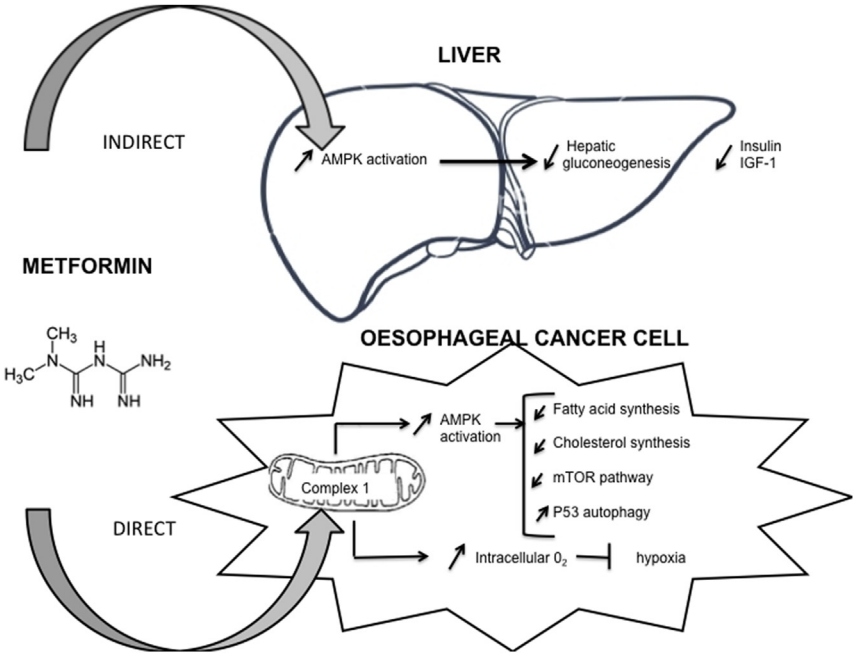


Figure 3. Potential dual anti-cancer effects of metformin: Indirect by reduced hepatic gluconeogenesis with lower circulating insulin levels. Direct by activation of AMPK through inhibition of complex I of the mitochondrial respiratory chain. Other cell cycle mediators may also be intracellular targets of metformin independent of AMPK activation.

cell cancer, which was in line with the observation of Van Hagen et al.[13] A remarkable finding in this study was the observation that a higher BMI correlates with an improved OS rate on univariate analysis. In the literature, the influence of a high BMI on long-term survival has been investigated with contradictory results. Some authors have described an improved overall and disease-free survival rate in obese patients, while others have reported no marked differences compared to patients with a normal BMI.[15–17] Since we do not exactly know which molecular pathways dominate the promotion of obesity-related oesophageal cancer, a variety of questions still remain unanswered.

In the literature, there is only one other retrospective observational study investigating the effect of metformin in oesophageal cancer: Skinner et al.[12] looked at patients with oesophageal adenocarcinoma treated with neoadjuvant CRT. They found that metformin use was associated with an increased pCR rate compared to non-users of metformin. This may be explained by the fact that metformin together with 5-fluorouracil can cause a synergistic reduction in tumour growth by targeting cancer stem cells and the components of the mammalian target of rapamycin (mTOR) pathway (Fig. 3).[18] The mTOR protein is a key protein that regulates processes of cell growth and angiogenesis, and promotes cell division and protein synthesis.[19] Other studies have also suggested immunological or anti-inflammatory actions.[20] As these mechanisms may affect both local and distant response to anti-cancer treatments, these mechanisms could clarify the improved pCR rate found by Skinner et al.[12] as well as the improved overall survival rate found in our study.

Consistent with our results, recent population studies reinforced the use of metformin to reduce cancer-related mortality in different types of cancer: head and neck cancer,[21,22] lung cancer,[23–25] breast cancer,[26,27] gastrointestinal cancer,[28–31] gynaecological cancer[32,33] and prostate cancer.[34,35] Other retrospective studies report less encouraging results and only tentative conclusions of the true effect of metformin can be drawn.[36–38]

The strength of our study is that we were able to study a large number of patients with oesophageal cancer in a well-established primary care database of high quality and completeness. Comparing other clinical studies of metformin use in cancer patients, their percentage of metformin intake is in the same range as our reported institutional rate (10%). When combined with the results from Skinner et al.[12] our clinical data suggest the need for a prospective trial to evaluate the effect of metformin on outcome.

Our study had several limitations. One is its retrospective nature and the fact that we had no insight into the strict drug-compliance and the severity of patients' type 2 diabetes. We did not examine a dose-effect and treatment duration relationship for metformin as our sample size was too small.[39] Other potential chemopreventive medications which are associated with a reduced risk of oesophageal cancer e.g. nonsteroidal anti-inflammatory drugs or statins were not co-investigated.[40] Locoregional controle rate was not assessed because the lack of objective and accurate information of the anastomotic site e.g. endoscopy and biopsy.

As the genetic make-up of oesophageal cancer patients is expected to be different in different geographic treatment

populations, our results may not be applicable to other populations.[18] It is for example known that the anti-tumour effects or enhanced radiosensitivity of metformin may be limited to tumours with tumour protein 53 (p53) gene mutations. Although the loss of p53 confers a selective growth advantage to cancer cells, it impairs their ability to respond to metabolic changes induced by metformin and to survive when there is glucose limitation.[41,42]

Fig. 3 summarizes the anticancer effects of metformin in oesophageal tumour cells. One mechanism may be indirect where metformin alters the endocrine-metabolic milieu of the host in a way that may influence oesophageal cancer. The drug gets into the liver and prevents gluconeogenesis. Consequently, levels of mitogens like insulin and insulin growth factors are decreased with less activation of the phosphatidylinositol 3-kinase (PI3K) pathway to support cancer growth.[19]

A second presumed effect is that the organic cation transporters can allow metformin to accumulate directly in cancer cells, which then stops the cells from proliferating. This could be arranged by inhibiting several targets in the mitochondria (e.g. complex I of oxidative phosphorylation). In vitro studies point to its activation of a molecular regulator of cell metabolism called 5′ adenosine monophosphate-activated protein kinase (AMPK) with consequent downstream inhibition of mTOR signalling in both oesophageal squamous cells and oesophageal adenocarcinoma cell lines in vitro.[18] Other AMPK-related downstream effects are suppression of the fatty acid and cholesterol synthesis which is necessary for tumour survival.[19] There are also alternative pathways by which metformin downregulates mTOR independent of AMPK or reduces cellular oxygen consumption by inhibiting the mitochondrial respiratory chain.[43] This metformin-induced tumour re-oxygenation could improve radiation-induced tumour growth delay.[44]

Less studied direct anticancer effects of metformin include the reduction of cyclines D1 and E, increased ubiquitin-specific-processing protease 7 (USP7), cell cycle arrest, increased autophagy and effects on $CD8^+$ tumour-infiltrating lymphocytes and cancer stem cells.[4,20]

Given the low cost, general availability and low side effects of this drug, investigating the role of metformin on a broad scale is justified. Numerous preclinical findings have encouraged more than 100 registered clinical trials on the effect of metformin in cancer patients, including prevention, adjuvant treatment and palliative treatment (cfr. on the NIH ClinicalTrials.gov web site).[45] Until now, no prospective study about its use in the secondary prevention in oesophageal cancer has been registered. The right clinical trial in oesophageal cancer would include a high number of patients from different geographic regions, an exact knowledge of insulin levels, the insulin receptor, organic cation transporters status, pharmacokinetic study and a signature of mitochrondrial and glycolytic metabolic functions on biopsy. The increasing use of (18)F-2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) in cancer evaluation will consequently raise a number of questions about the possible modulation of metformin on FDG distribution. The effect of metformin on FDG-PET image intensity is difficult to predict, as drugs with antiproliferative activity generally decrease FDG uptake, but agents capable of activating AMPK in tumors would be expected to increase FDG uptake.[46] Collecting prospective data in this setting will help to verify whether FDG-PET can be a valid tool to assess the anticancer effect of this new therapeutic approach.[47] All this information could help us understand the complex working mechanism of metformin on oesophageal cancer cells and select those patients who could potentially benefit from its use.

In summary, although the association between metformin use and oesophageal cancer outcome remains uncertain and the exact underlying molecular mechanism is yet to be revealed, our study provides arguments in favour of further research on metformin and its impact on prognosis. The good safety profile of this drug creates a window of opportunity for selecting metformin for drug repurposing especially in a growing elderly population.

## Disclosure statement

The authors have nothing to disclose.

## Conflict of interest

None declared.

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