Original Research

Observational study

Mortality due to cirrhosis and liver cancer in the United States, 1999-2016

Tapper EB, Parikh ND

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Study question How has the mortality due to cirrhosis and hepatocellular carcinoma changed over time in the US?

Methods The authors analysed mortality due to liver disease in Americans during 1999-2016 using national death record data from the Vital Statistics Cooperative and demographic data from the US Census Bureau. Mortality was described by age group, sex, race, cause of liver disease, and geographical area of residence.

Study answer and limitations Mortality due to cirrhosis and liver cancer increased substantially during 1999-2016. While the age adjusted death rate due to liver cancer rose annually by 2.1% (95% confidence interval 1.9% to 2.3%), deaths due to cirrhosis did not increase and then began increasing during 2009-16 by 3.4% (3.1% to 3.8%). Deaths due to cirrhosis were driven primarily by alcohol related liver disease, with the highest average annual increase experienced by people aged 25-34 years (10.5%, 8.9% to 12.2%) during 2009-16. Only one state, Maryland, showed improvements in mortality (–1.2%, –1.7% to –0.7% per year), while many, concentrated in the south and west observed disproportionate annual increases. These included Kentucky, New Mexico, Arkansas, Indiana, and Alabama. No state had improvements in deaths from hepatocellular carcinoma, and Arizona and Kansas experienced the most severe annual increases. These data were abstracted from deidentified death certificates, so they cannot be assessed for their sensitivity or specificity.

What this study adds Mortality due to advanced liver disease is increasing in the US. Interventions to improve outcomes for young people with alcohol use disorder and further research to elucidate the reasons behind the demographic and geographical disparities are indicated.

Funding, competing interests, data sharing EBT received funding from the Michigan Institute for Clinical and Health Research. No competing interests are declared. The dataset is publicly available.
Sulfonylureas for type 2 diabetes

ORIGINAL RESEARCH  Population based cohort study

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events

Douroa A, Dell'Aniello S, Yu OHY, et al

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Methods Data from the UK Clinical Practice Research Datalink were used to form a population based cohort of patients with type 2 diabetes initiating metformin monotherapy between 1998 and 2013. The prevalent new user cohort design was used to match 1:1 patients adding or switching to sulfonylureas with those continuing metformin monotherapy on high dimensional propensity score, haemoglobin A1c, and number of previous metformin prescriptions.

Study question Is adding or switching to sulfonylureas associated with an increased risk of myocardial infarction, ischaemic stroke, cardiovascular death, all cause mortality, and severe hypoglycaemia, compared with continuing metformin monotherapy in patients with type 2 diabetes?

During a mean treatment duration of 1.1 years, sulfonylureas were associated with an increased risk of myocardial infarction (hazard ratio 1.26, 95% confidence interval 1.01 to1.56), all cause mortality (1.28, 1.15 to 1.44), and severe hypoglycaemia (7.60, 4.64 to 12.44) compared with continuing metformin monotherapy. There was a trend towards increased risks of ischaemic stroke (1.24, 0.99 to 1.56) and cardiovascular death (1.18, 0.98 to 1.43).

What this study adds Sulfonylureas as second line drugs are associated with an increased risk in the risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with continuing metformin monotherapy.

Matching characteristics included date of study entry, number of metformin prescriptions (surrogate for diabetes duration), HbA1c level (surrogate for diabetes severity), and a high dimensional propensity score, built considering 500 covariates that represent possible confounders.

The resultant participants resembled those commonly seen in clinical practice—average age 64 years, 43% women, and 53% with an HbA1c level >8% (63.9 mmol/mol). Sulfonylurea use (switching and adding combined) was associated with an increased risk of myocardial infarction, all cause mortality, and hypoglycaemia. Compared with similar participants who continued taking metformin, switching to a sulfonylurea was associated with a greater risk of myocardial infarction, cardiovascular death, and all cause mortality than adding a sulfonylurea.

The results of the UK Prospective Diabetes Study (UKPDS) in 1998 left unanswered questions about whether a sulfonylurea is harmful or metformin is beneficial. Douros and colleagues’ study supports the beneficial effects of metformin, by showing that the increased risk from sulfonylurea use was primarily among those who switched, and completely stopped metformin.

Adding a sulfonylurea to ongoing metformin treatment was not associated with a statistically significant increase in cardiovascular and hypoglycaemic events.

Sulfonylureas have a consistent association with a higher risk of cardiovascular disease and hypoglycaemia compared with metformin. Despite this increased risk they remain the second most common initial treatment for diabetes and when combined with metformin, the most common combination regimen. Many people who are initially prescribed metformin either add or switch to a sulfonylurea owing to increased HbA1c levels. Clinicians and patients have for many years focused on HbA1c, perhaps rightly, even though it remains a surrogate marker for diabetes outcomes and death. Whether a patient should add a drug, switch to a different regimen, or simply continue with metformin monotherapy for a slightly increased HbA1c level remains an important clinical question.

To answer this question, Douros and colleagues conducted an observational study comparing key macrovascular clinical outcomes for people with type 2 diabetes who continue metformin monotherapy compared with those who either add or switch to sulfonylureas.

Close match The authors defined time based on exposure sets and computed propensity scores to closely match participants who either added or switched to a sulfonylurea (the new users) with those who continued treatment with metformin alone (the prevalent users).

These data suggest that adding a sulfonylurea to metformin treatment is preferable to switching to sulfonylurea monotherapy.

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events

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Funding, competing interests, data sharing Funded by the Canadian Institutes of Health Research, the Canadian Foundation for Innovation, and Boehringer Ingelheim. See bmj.com for competing interests. No additional data available.

COMMENTARY New evidence helps individualise treatment decisions and minimise harm

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in macrovascular events, including cardiovascular death (8.1 per 1000 person years for metformin alone v 6.3 per 1000 for adding a sulfonylurea; adjusted hazard ratio 0.95, 95% confidence interval 0.75 to 1.20). Event rates were highest (18.3 cardiovascular deaths per 1000 person years) among those who switched to a sulfonylurea.

The observed difference in risk between adding and switching could be driven by the possibility that higher doses of sulfonylureas are needed by those who switched, and this deserves further study.

It is hard to define clinical practice based on an observational study, as patients using different treatments may differ in ways that are unmeasured. This study, however, is well designed and the relations appear strong and consistent when examining several important macrovascular clinical outcomes. The results were also robust to sensitivity analyses, which varied the definitions of the patient’s exposure and tested the sensitivity to unmeasured confounders.

These data suggest that adding a sulfonylurea to metformin treatment is preferable to switching to sulfonylurea monotherapy. It also suggests that continuing metformin alone and accepting higher HbA1c targets is preferable to switching to sulfonylureas when considering both macrovascular outcomes and hypoglycaemia.

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Subacromial decompression versus diagnostic arthroscopy for shoulder impingement

Paavola M, Malmivaara A, Taimela S, for the Finnish Shoulder Impingement Arthroscopy Controlled Trial (FIMPACT) Investigators

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Study question
Is arthroscopic subacromial decompression superior to diagnostic arthroscopy, a placebo surgical intervention, in the treatment of shoulder impingement syndrome?

Methods
FIMPACT was a multicentre, three group, randomised, sham controlled trial. Eligible patients were aged 35-65 years, had symptoms (for more than three months) and clinical and imaging findings consistent with shoulder impingement syndrome, and were unresponsive to conventional conservative treatment. Patients (n=210) were randomised to arthroscopic subacromial decompression (ASD), diagnostic arthroscopy (placebo surgery control), or exercise therapy. Primary outcomes were shoulder pain at rest and on arm activity (visual analogue scale from 0 to 100), at 24 months. The threshold for minimal clinically important difference was set at 15. Patients, outcome assessors, statistician, and people interpreting the principal findings were blinded to the treatment assignment for ASD versus diagnostic arthroscopy.

Study answer and limitations
ASD provided no clinically relevant benefit over diagnostic arthroscopy in patients with shoulder impingement syndrome. In the secondary comparison between ASD and exercise therapy, statistically significant differences were found in favour of ASD in the two primary outcomes at 24 months, but the mean differences between groups did not exceed the prespecified minimal clinically important difference. This comparison was confounded by lack of blinding and likely to be biased in favour of ASD owing to selective removal of patients with likely poor outcome from the ASD group.

What this study adds
These findings challenge the current practice of performing arthroscopic subacromial decompression in patients with shoulder impingement syndrome.

Funding, competing interests, data sharing
The FIMPACT trial was supported by the Sigrid Juselius Foundation, the state funding for university level health research (Tampere and Helsinki University Hospitals), the Academy of Finland, and the Jane and Aatos Erkko Foundation.

Trial registration
Clinicaltrials.gov NCT00428870.