

Diabetes

Lowering blood pressure may prevent the onset of diabetes

Antihypertensive therapy with ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) lowers the risk of developing type 2 diabetes, a meta-analysis has shown.

Data from 22 studies carried out between 1973 and 2008, were obtained by the Blood Pressure Lowering Treatment Trialists' Collaboration in Oxford.

The authors included all primary and secondary prevention trials that used a specific class or classes of antihypertensive drugs versus placebo or other classes of blood pressure lowering drugs that had at least 1,000 person-years of follow-up in each randomly allocated arm.

The individual participant data meta-analysis included 145,939 (60.6% men) randomly assigned participants from 19 trials. Their mean age was 65 years.

After a median follow-up of 4.5 years, 9,883 participants were diagnosed with new onset type 2 diabetes.

A systolic blood pressure reduction of 5 mmHg reduced the risk of type 2 diabetes across all trials by 11%, hazard ratio (HR) 0.89 (95% CI: 0.84-0.95).

The authors further analysed this effect with respect to specific drug class for the five major classes of antihypertensive drugs. Data from 22 trials were used to calculate the relative risk (RR) for drug class comparisons.

Use of ACEI and ARB reduced the RR of new-onset type 2 diabetes compared with placebo.

- ACEI: RR 0.84 (95% CI: 0.76-0.93)
- ARB: RR 0.84 (95% CI: 0.76-0.92)

However, the use of beta blockers and thiazide diuretics appeared to

increase the risk compared with placebo.

- Beta blockers: RR 1.48 (95% CI: 1.27-1.72)
- Thiazide diuretics: RR 1.20 (95% CI: 1.07-1.35)

No effect was found for calcium channel blockers compared with placebo.

- Calcium channel blockers: RR 1.02 (95% CI: 0.92-1.13)

The authors concluded that lowering blood pressure can prevent the onset of type 2 diabetes but the main classes of antihypertensive drugs have different effects with ACEI and ARB having the best outcomes. This could inform drug choices to treat hypertension according to the patient's overall risk of developing diabetes.

The study authors state: 'Using randomised evidence from major pharmacological blood pressure lowering trials, this study has shown consistent evidence to suggest that the preventive effect of blood pressure reduction on type 2 diabetes risk is causal, and therefore reducing blood pressure is likely to prevent new-onset type 2 diabetes.'

'This evidence also supports the indication for selected classes of antihypertensive drugs for the prevention of type 2 diabetes, which could further refine the selection of drug choice according to an individual's risk profile. In particular, ACEI and ARB should be considered as having the most favourable outcomes when clinical risk of diabetes is a concern.'

The authors of an accompanying comment¹ say: 'The absolute risk reduction found in this meta-analysis is modest; however, interventions with small benefits can have an outsized effect when applied to conditions as common as hypertension.'

'It remains unknown to what extent the reduction in diabetes risk is due to blood pressure reduction per se versus RAS (renin aldosterone system) inhibition specifically.'

'Despite its limitations, this meta-analysis provides additional evidence supporting the hypothesis that blood pressure control with specific medications can reduce the risk of diabetes. This study supports the possibility that earlier, more aggressive lowering of blood pressure, with an emphasis on RAS inhibitors, can decrease the incidence of diabetes,' they conclude.

DR PETER SAVILL

Nazarzadeh M, Bidel Z, Canoy D et al. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet* 2021;398:1803-10

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Respiratory disease

Novel model predicts risk factors for mortality in COPD

Heart failure and current smoking were the strongest risk factors for predicting ten-year mortality in COPD patients, a risk prediction model based on primary care data has found.

Data on 37,485 patients with COPD in the Clinical Practice Research Database were analysed. Patients were followed up for ten years. The main outcome was all-cause mortality.

Four types of predictors were examined, demographic and behavioural characteristics (e.g. exercise, smoking status, limitation of physical activity at diagnosis), comorbidities, and COPD severity. Because of the lack of spirometry data COPD severity was based on breathlessness, a history of COPD exacerbations and hospitalisation due to COPD.

The investigators developed and validated a machine learning-based prediction model of ten-year COPD mortality to help risk stratify patients.

Just over half the study population were male (53.1%), 86.2% were 56 years or older. Overall, 14.7% were never smokers, 63.3% former smokers and 22% current smokers. Mean age at COPD diagnosis was 68.

Approximately, a quarter (23.6%)

of patients died within ten years of COPD diagnosis, 57.8% were men.

The mMRC dyspnoea score in the 12 months leading up to diagnosis was recorded in only 61.7% of participants but when it was, there was a strong correlation with the proportion of patients who died: 6.3% when the mMRC dyspnoea score was 0 or 1, 8.5% when the score was 2, and 12.5% when the score was 3 or 4.

In the 70% of patients for whom comorbidities were recorded, asthma, hypertension, and depression were the three most common.

The two risk factors which had the greatest effect on mortality were:

- **Heart failure**

HR 1.92 (95% CI: 1.87-1.96)

- **Current smoker**

HR 1.68 (95% CI: 1.66-1.71)

The other prognostic factors with large effect sizes that were also significant (>20% increased risk of mortality) were:

- **Ischaemic heart disease**

HR 1.49 (95% CI: 1.45-1.54)

- **Former smoker**

HR 1.49 (95% CI: 1.46-1.51)

- **Male gender**

HR 1.26 (95% CI: 1.25-1.27)

- **mMRC dyspnoea score ≥ 3**

HR 1.33 (95% CI: 1.28-1.39)

- **Breathlessness**

HR 1.25 (95% CI: 1.24-1.26)

- **Physical activity limitation**

HR 1.37 (95% CI: 1.33-1.42)

Hypertension, anxiety, a history of pulmonary TB, and depression had more modest effects on mortality.

Although a large and robust study the authors acknowledge that smoking data is often prone to error. They also acknowledge that as primary care data alone were used, hospitalisations may have been missed.

The study authors state: 'While the model developed achieved strong internal validation performance, it is now important to externally validate this model before deploying it in clinical practice.'

The study emphasises that COPD patients with heart failure should be a priority for optimisation of control of both conditions. It offers further evidence for the importance of smoking cessation management in COPD patients and also identifies other adverse prognostic factors that may require action.

DR PETER SAUL

Shah SA, Nwaru BI, Skeikh A et al. Development and validation of a multivariable mortality risk prediction model for COPD in primary care. *NPJ Prim Care Respir Med* 2022;32:21

Gastrointestinal disease

NAFLD associated with raised risk of heart failure

Non-alcoholic fatty liver disease (NAFLD) is associated with a 1.5 times higher risk of new-onset heart failure, independent of the presence of diabetes, hypertension and other common cardiovascular risk factors, a large meta-analysis has found.

The authors searched Scopus, Web of Science and PubMed, from database inception to March 2022, to identify observational cohort studies that assessed the association of NAFLD with risk of new onset heart failure.

Inclusion criteria were the identification of NAFLD through serum biomarkers or scores, ICD codes, imaging techniques or liver histology together with evidence of a primary outcome of new onset heart failure, as assessed mainly by ICD codes.

Eleven studies were identified which provided aggregate data on 11,242,231 individuals (50% women), mean age 55 years, from a range of countries including the UK. A total of 2,944,058 (26.2%) had NAFLD at baseline.

There were 97,716 cases of incident heart failure over a median follow-up of ten years.

The presence of NAFLD was associated with a moderately higher risk of new onset heart failure (11 studies); pooled random-effects hazard ratio (HR) 1.50 (95% CI: 1.34-1.67, $P < 0.0001$; $I^2 = 94.8\%$). This risk was independent of age, gender, ethnicity, adiposity, diabetes, hypertension and other common cardiovascular risk factors. Further analysis did not show

any evidence of significant publication bias.

The risk for new-onset heart failure appeared to be further increased with more advanced liver disease, especially with higher levels of liver fibrosis, as assessed by non-invasive fibrosis biomarkers or histology (two studies); pooled random-effects HR 1.76 (95% CI: 0.75-4.36; $I^2 = 96.9\%$).

It is becoming increasingly clear that NAFLD is part of a multisystem disease with adverse effects not only on the liver but also on extrahepatic organs, including the heart and vasculature. Recent studies have reported an association between NAFLD and the risk of new-onset heart failure. However, the size of the risk, and whether this risk changes with the severity of liver disease, has been uncertain.

Though the study does not prove causality, the significant association between NAFLD and new-onset heart failure supports other findings of increased rates of cardiovascular disease in those with NAFLD, and strengthens guidance that patients found to have NAFLD should be considered for cardiovascular risk assessment in addition to liver investigation and monitoring.¹

The study authors conclude: 'We believe that the results of our meta-analysis further highlight the need for a patient-centred, multidisciplinary and holistic approach to manage both liver disease and cardiovascular risk in people with NAFLD.'

'Future high-quality prospective and mechanistic studies are certainly needed to better elucidate the existing but complex link between NAFLD and risk of new-onset heart failure,' they add.

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Mantovani A, Petracca G, Csermely A et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. *Gut* Published Online First 25 July 2022

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See also *Managing cardiovascular risk key in non-alcoholic fatty liver disease, p11*

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