Major journals

Metformin for secondary prevention of CVD?

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Metformin remains the first-line pharmacological treatment for type 2 diabetes. Historical concerns about the increased risk of lactic acidosis in people with cardiac failure, renal failure and in older people remain in our therapeutic consciousness when using metformin (Inzucchi, 2005).

Roussel et al (2010; summarised alongside) have published a reassuring analysis from the REACH (Reduction of Atherothrombosis for Continued Health) registry. The diabetes subgroup consisted of 19 691 people (aged ≥45 years) with established coronary artery disease, cerebrovascular disease, or peripheral vascular disease or with three or more atherothrombosis risk factors. Metformin use was confirmed in 7457 (39%) participants, with the authors implying that many of the other 61% may not have had metformin prescribed due to existing cardiovascular disease (CVD) or renal disease.

The 2-year mortality rate was 6.3% (95% confidence interval [CI], 5.2–7.4%) in the metformin group, versus 9.8% (95% CI, 8.4–11.2%) in the non-metformin group. The adjusted risk reduction was 24%. This reduction was consistent across all the main subgroups: cardiac failure, 31%; aged >65 years, 23%; estimated glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m^2, 36%. It is particularly important to note that the mortality reduction remained following adjustment for thiazolidinedione, insulin or sulfonylurea use.

The mechanism of action for metformin's CVD protective effect remains uncertain. The agent's impact on hepatic insulin resistance, LDL-cholesterol and plasminogen activator-inhibitor levels have all been suggested as possible causes.

We can conclude that metformin may be safe for use in people with T2D and manifest CVD and renal disease (eGFR >30 mL/min/1.73 m^2) and indeed may have a role in secondary prevention of CVD. In light of this evidence, clinicians can be even more persistent in prescribing metformin. Among people who are metformin intolerant the slow-release formulation or the dispersible formulation should be considered.

Inzucchi SE (2005) Metformin and heart failure: innocent until proven guilty. *Diabetes Care* **28**: 2585–7

ARCHIVES OF INTERNAL MEDICINE

Intensive exercise strategy improves HbA_{1c} and CV risk

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The effect of an intensive exercise intervention strategy on HbA_{1c} and modifiable cardiovascular (CV) risk factors was determined in 606 sedentary people with T2D and the metabolic syndrome.

2 Participants were randomised to aerobic exercise and resistance training twice a week with exercise counselling (exercise group, n=303) or to counselling alone (control group, n=303) for 1 year; outcome measures were HbA_{1c} and other CV risk factors.

3 Compared with the control group, supervised exercise significantly improved fitness, HbA_{1c}, blood pressure, HDL- and LDL-cholesterol, BMI, insulin resistance and risk scores (all $P \leq 0.03$).

4 The intensive exercise intervention strategy improved HbA_{1c} and CV risk. Counseling alone was successful in achieving recommended amount of activity but of limited efficacy on CV risk factors, which the authors suggested indicates the need for a larger volume of activity to modify risk in those people who are at high CV risk.

Balducci S, Zanuso S, Nicolucci A et al (2010) Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus. *Arch Intern Med* **170**: 1794–803

ARCHIVES OF INTERNAL MEDICINE

Metformin use may decrease mortality in people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Studies have shown that metformin use in people with T2D who are overweight reduces mortality.

2 Although metformin could be beneficial in the primary prevention of cardiovascular disease (CVD), concerns about metformin-associated lactic acidosis have resulted in conservative metformin use in patients with CVD.

3 In order to determine the potential risks and benefits associated with metformin use as a secondary measure of prevention of CVD, the authors assessed whether metformin use was associated with a difference in mortality in people with T2D and atherothrombosis.

4 In total, 19 691 people with atherothrombosis and T2D treated with and without metformin were enrolled; the main outcome measure was mortality at 2-year follow-up.

5 People in the metformin group tended to be younger and were more frequently overweight or obese; overall CV risk was lower in this group.

6 Mortality rates were 6.3% (95% confidence interval [CI], 5.2–7.4%) with metformin and 9.8% (95% CI, 8.4–11.2%) without metformin (adjusted hazard ratio, 0.76; 95% CI, 0.65–0.89; P<0.001).

7 Lower mortality was consistent among subgroups, including people in whom metformin use is not recommended.

8 The authors concluded that metformin use may decrease mortality rates in people with T2D when used as a secondary prevention.

Roussel R, Travert F, Pasquet B et al (2010) Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med* **170**: 1892–9

JAMA

Diet with physical activity significantly reduces weight

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Although the prevalence of severe obesity is increasing, few studies have examined the effects of treating this condition.

2 The authors conducted a single-blind, randomised trial to evaluate the effectiveness of an intensive lifestyle intervention on weight loss in severely obese adults over 1 year.

3 In total, 130 severely obese (BMI, ≥35 kg/m^2) adults were randomised to either diet and physical activity for 1 year (initial-activity group, n=67) or to diet and physical activity delayed for 6 months (delayed-activity group, n=63).

4 Both intervention groups lost a significant amount of weight at 6 months; however, the initial-activity group lost significantly more weight in the first 6 months (mean –10.9 kg; 95% confidence interval (CI), 9.1–12.7) than the delayed-activity group (mean –8.2 kg; 95% CI, 6.4–9.9; P=0.02 for group × time interaction).

5 Weight loss at 1 year was similar in both groups; the initial-activity group lost a mean of 12.1 kg (95% CI, 10.0–14.2) and the delayed-activity group 9.9 kg (95% CI, 8.0–11.7; P=0.25 for group × time interaction).

6 The addition of physical activity to diet caused greater reductions in waist circumference and hepatic fat content.

7 An intensive lifestyle intervention involving diet combined with initial or delayed physical activity caused clinically significant weight loss as well as improvements in cardiometabolic risk factors in severely obese adults.

8 The authors concluded that this non-surgical approach offers an effective treatment for severe obesity in adults.

Goodpaster BH, DeLany JP, Otto AD et al (2010) Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults. *JAMA* **304**: 1795–802

ANNALS OF INTERNAL MEDICINE

Animal-based low-carbohydrate diet increases mortality

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 To examine the association of low-carbohydrate diets on mortality, 85 168 women and 44 548 men without heart disease, cancer or diabetes were followed-up for 26 years in women and 20 years in men.

2 Type of diet was ascertained by food questionnaire; diets were divided into animal-based and vegetable-based low-carbohydrate diets, determined by their main constituent proteins and fats.

3 During follow-up, 12 555 women and 8678 men died.

4 An animal-based low-carbohydrate diet was associated with higher all-cause mortality, cardiovascular mortality and cancer mortality; a vegetable-based low-carbohydrate diet was associated with lower all-cause mortality and cardiovascular mortality.

Fung TT, van Dam RM, Hankinson SE et al (2010) Low-carbohydrate diets and all-cause and cause-specific mortality. *Ann Intern Med* **153**: 289–98

AMERICAN JOURNAL OF MEDICINE

High serum uric acid levels increase future risk of T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Prospective data from the Framingham Heart Study were analysed to determine the association between serum uric acid levels and the future risk of developing T2D.

2 The original cohort comprised 2690 women and 2193 men and the offspring cohort comprised 2243 women and 2049 men without T2D at baseline.

3 Cox proportional hazard models were used to estimate the relative risk of incident T2D in both groups, adjusting for variables.

4 There were 641 and 497 cases of incident T2D in the original and offspring cohorts, respectively.

5 The incident rates of diabetes per 1000 person-years for serum uric acid levels <5.0, 5.0–5.9, 6.0–6.9, 7.0–7.9 and ≥8.0 mg/dL were 3.3, 6.1, 8.7, 11.5 and 15.9 in the original cohort and 2.9, 5.0, 6.6, 8.7 and 10.9 in the offspring cohort, respectively (P<0.001).

6 Higher levels of serum uric acid were associated with an increased risk of T2D, independent of other risk factors.

Bhole V, Choi JWJ, Kim SW et al (2010) Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med* **123**: 957–61

BMJ

Risk factors high for non-communicable disease in rural India

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The Indian Migration Study investigated the effect of rural–urban migration; the authors performed a secondary analysis of data on rural participants to examine the prevalence of non-communicable disease risk factors by age, sex, socioeconomic position and geographic location.

2 Rural participants (1375 men, 608 women) were aged 20–69 years.

3 The prevalence of most risk factors was generally high across a range of sociodemographic groups, and tended to increase with age.

4 Notably tobacco use in men was more common in lower socioeconomic groups, whereas obesity in women was more prevalent in the higher socioeconomic groups.

Kinra S, Bowen LJ, Lyngdoh T et al (2010) Sociodemographic patterning of non-communicable disease risk factors in rural India. *BMJ* **341**: c4974

"An intensive lifestyle intervention involving diet combined with initial or delayed physical activity caused clinically significant weight loss as well as improvements in cardiometabolic risk factors in severely obese adults."