Major journals

NEW ENGLAND JOURNAL OF MEDICINE

Rosuvastatin reduces CV events in people with elevated CRP levels

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

1 Increased levels of C-reactive protein (CRP) are a predictor of cardiovascular events. The authors of this study hypothesised that benefit might be obtained with statin therapy in people with elevated CRP levels but without hyperlipidaemia.

2 The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study was a double-blind, placebo-controlled randomised controlled trial involving 17 802 "healthy" individuals across 26 countries.

3 The participants were aged 50 years or older (male) or 60 years or older (female), had no history of CVD, had an LDL-cholesterol level <130 mg/dL at initial screening, had a high-sensitivity CRP level ≥2.0 mg/L, and a triglyceride level <500 mg/dL.

4 Participants were randomised to receive placebo or rosuvastatin 20 mg daily, and were followed up until occurrence of the combined primary endpoint of myocardial infarction, stroke, revascularisation, hospitalisation for unstable angina, or death by any cardiovascular cause (median 1.9 years).

5 The results indicate that rosuvastatin reduced high-sensitivity CRP levels by 37%, LDL-cholesterol levels by 50%, and reduced the incidence of death by any cardiovascular cause (P<0.00001). However, there was a significantly higher incidence of physician-reported diabetes in the rosuvastatin group (P=0.01).

Ridker PM, Danielson E, Fonseca FA et al (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med* **359**: 2195–207

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein

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Increasingly, prevention of cardiovascular disease involves drug therapy, particularly statins and the reduction of cholesterol. Statins were first studied in people at high risk of cardiovascular events, with the limits of treatment being expanded to include people at progressively lower risk as exemplified by JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). The investigators enrolled healthy participants with a pre-treatment LDL-cholesterol levels <3.4 mmol/L, and a high-sensitivity C-reactive protein >2.0 mg/dL. This trial of nearly 18 000 individuals was stopped after a median follow up of 1.9 years. Rosuvastatin 20 mg daily reduced LDL-C levels by 50% to 1.4 mmol/L and high-sensitivity C-reactive protein levels by 37%. This was associated with a reduction in cardiovascular events (142 events vs. 251 events in the placebo group); representing a relative risk reduction of 44%. This observation included a 47% relative risk reduction (47 versus 83 events) in the combination of myocardial infarction, stroke and death from cardiovascular causes.

The JUPITER study, therefore, raises important questions about the prevention of cardiovascular disease, particularly in people with diabetes – as none were included in this study, and type 2 diabetes is a condition typically associated with an increase in high-sensitivity C-reactive protein.

Numerous randomised controlled trials enrolling people with diabetes have unequivocally proven that lowering LDL-cholesterol with statin therapy results in a marked reduction in atherosclerotic clinical endpoints. Consequently, current treatment guidelines advocate target LDL-cholesterol levels <2 mmol/L in people with diabetes, which is well below the entry LDL-cholesterol level in the JUPITER study, and also significantly higher than the achieved LDL-cholesterol level following rosuvastatin therapy in the study.

In CARDS (Collaborative Atorvastatin Diabetes Study) of over 2800 individuals with type 2 diabetes and at least one other coronary heart disease (CHD) risk factor, an LDL-cholesterol reduction of 40% and a triglyceride reduction of 19% were associated with a 37% relative risk reduction in major coronary events and a 48% reduction in stroke. If we extrapolate the lipid level changes seen in the JUPITER trial, in which rosuvastatin 20 mg daily resulted in a 50% reduction in LDL-cholesterol and 17% reduction in plasma triglyceride levels, then even greater reductions in coronary events and stroke might be anticipated.

The relative risk reductions seen in JUPITER were highly significant; however, absolute risk reductions are more clinically relevant. The absolute risk of hard cardiovascular endpoints was reduced from 1.8% (157 of 8901 subjects) in the placebo group to 0.9% (83 of 8901 subjects) in the active treatment arm. In other words, 120 participants were treated for 1.9 years to prevent one cardiovascular event. This relatively small absolute risk reduction being a function of the relatively low baseline cardiovascular risk of the study population, people with diabetes are at much greater risk of cardiovascular disease than the JUPITER population, and a recent meta-analysis of lipid-lowering trials in individuals with diabetes has concluded that the number needed to treat to a 1 mmol/L reduction in LDL-cholesterol in order to prevent one CHD event was 13.8 / 4.9 years of secondary prevention and 34.5 / 4.3 years for primary prevention (Cholesterol Treatment Trialists' Collaborators, 2008). Thus, if the results of the JUPITER trial were extrapolated into the population with diabetes then highly significant absolute risk reductions could be envisaged.

Cholesterol Treatment Trialists' Collaborators (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **371**: 117–25

"... low-dose asprin does not reduce cardiovascular risk in people with type 2 diabetes who have not yet experienced an atherosclerotic event."

NEW ENGLAND JOURNAL OF MEDICINE

Emergent benefits of tight glycaemic control

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

1 The current investigators carried out post-trial monitoring to determine whether the microvascular risk reductions evident with intensive glucose-lowering therapy in the UK Prospective Diabetes Study (UKPDS) persisted. In addition, they aimed to determine whether the original intervention had any long-term macrovascular benefit.

2 Of the original UKPDS population, 3277 people with type 2 diabetes were invited to annual post-trial monitoring clinics for the first 5 years after the end of the study. In years 6–10, participants were assessed by questionnaire.

3 After 1 year, the original between treatment-group differences that existed in HbA_{1c} levels were lost. Compared with those in the conventional therapy (diet alone) group, those who received sulphonylurea or insulin therapy retained a lower risk of microvascular complications and any diabetes-related endpoint after 10 years.

4 Interestingly, relative risk reductions for all-cause mortality and myocardial infarction also emerged in these intensively treated people (13% and 15%, respectively; P=0.007 and P=0.01).

5 In those originally treated with metformin, relative risk reductions for all-cause mortality, myocardial infarction and any diabetes endpoint remained statistically significant (27%, 33% and 21%, respectively; P=0.002, P=0.005 and P=0.01).

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89.

JAMA

Primary prevention with aspirin does not reduce cardiovascular events in T2DM

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

1 The authors of this study, based in Japan, aimed to determine the efficacy of low-dose aspirin for primary prevention of atherosclerotic events in people with type 2 diabetes.

2 This study involved 2539 people with type 2 diabetes at 163 institutions in Japan, and was of a prospective, open-label, blinded, randomised controlled design. Inclusion criteria were: a diagnosis of type 2 diabetes, age between 30 and 85 years, and no history of atherosclerotic disease (cardiovascular disease, stroke, or peripheral vascular disease).

3 Participants were randomised to receive aspirin 81 mg or 100 mg once-daily (n=1262), or no aspirin (n=1277), and followed for a median of 4.37 years. The primary endpoint was any atherosclerotic event, including fatal or nonfatal ischaemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease.

4 Overall, there were a total of 154 atherosclerotic events in the study, 68 in the aspirin group and 86 in the group not taking aspirin. The difference in event rates between the groups was not significant (P=0.16).

5 There was a total of 34 deaths in the aspirin group, compared with 38 in the group not taking aspirin, again this slight difference was not significant (P=0.67).

6 In conclusion, low-dose aspirin does not reduce cardiovascular risk in people with type 2 diabetes who have not yet experienced an atherosclerotic event.

Ogawa H, Nakayama M, Morimoto T et al (2008) Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *J Am Med Assoc* **300**: 2134–41

NEW ENGLAND JOURNAL OF MEDICINE

Blood pressure benefits from intensive therapy are lost if treatment is not maintained

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

1 This study from the post-trial monitoring period of the original UKPDS cohort examined whether the risk reductions in micro- and macrovascular disease achieved in the original study were sustained over time.

2 Among 5102 individuals newly diagnosed with type 2 diabetes, the authors originally randomised 1148 people who had hypertension to tight or less-tight blood-pressure control regimens. Of these, 884 participated in the post-trial monitoring, but did not maintain their previous therapies.

3 Of the initial cohort, 125 of those assigned to less-tight blood pressure control, and 247 of those assigned to tighter blood pressure control completed the 10-year post-trial monitoring period.

4 The differences in blood pressure initially seen between the two groups during the original trial disappeared within 2 years of its end.

5 Furthermore, the significant relative risk reductions found during the trial for any diabetes-related endpoint, death, microvascular disease, and stroke in the group receiving tight blood-pressure control were not sustained during the post-trial follow-up period.

6 These data clearly indicate that, while tight blood pressure control provides significant benefits, it must be maintained in order for the benefits to be sustained.

Holman RR, Paul SK, Bethel MA et al (2008) Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* **359**: 1565–76

ARCHIVES OF INTERNAL MEDICINE

Rosiglitazone increases risk of ischaemic CV events compared with pioglitazone

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

1 The authors of this US-based inception cohort study compared cardiovascular (CV) outcomes and mortality rates between people initiating pioglitazone or rosiglitazone, to determine whether or not rosiglitazone increases the risk of ischaemic CV events.

2 The inception cohort was aged over 65 years on the baseline date of 1 January 2000, had diabetes, and was initiated on either rosiglitazone or pioglitazone between the baseline date and 31 December 2005.

3 Study outcomes included all-cause mortality, myocardial infarction, stroke, and hospitalisation for congestive heart failure.

4 Of the 28 361 individuals studied, 50.3% began treatment with pioglitazone in the study period, and 49.7% initiated rosiglitazone. Baseline characteristics were similar for both groups.

5 During more than 29 000 patient-years of follow-up, 1869 people died.

6 The results indicate that, in those who began rosiglitazone, there was a 15% greater mortality compared with in those on pioglitazone, and a 13% greater risk of congestive heart failure. No differences were seen in rates of myocardial infarction or stroke.

7 The authors conclude that these results confirm the concerns regarding the safety of rosiglitazone.

Winkelmayer WC, Setoguchi S, Levin R, Solomon DH (2008) Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med* **168**: 2368–75

NEW ENGLAND JOURNAL OF MEDICINE

Telmisartan after stroke does not reduce rates of major CV events

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

1 This study was undertaken to ascertain the benefits of adding a renin–angiotensin system inhibitor to other blood pressure lowering medication following a stroke.

2 The authors randomised 10 146 individuals who had recently had an ischaemic stroke to telmisartan, an angiotensin-receptor blocker, and another 10 186 people to placebo.

3 The primary endpoint for the study was recurrent stroke. Secondary outcomes were major cardiovascular (CV) events (a composite of death from CV causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes.

4 During a mean follow-up of 2.5 years, the mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group than in the placebo group. A total of 880 individuals (8.7%) receiving telmisartan, and 934 (9.2%) receiving placebo, had a subsequent stroke. The difference was not significant.

5 Major CV events occurred in 1367 individuals (13.5%) in the telmisartan group and 1463 (14.4%) in the placebo group, and new-onset diabetes occurred in 1.7% of the telmisartan group and 2.1% of the placebo group. Again, none of these differences were significant.

6 The authors conclude that additional treatment with telmisartan following ischaemic stroke does not prevent recurrence of major CV events.

Yusuf S, Diener HC, Sacco RL et al (2008) Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* **359**: 1225–37

ARCHIVES OF INTERNAL MEDICINE

Intensive glycaemic control reduces risk of developing hypertension in type 1 diabetes

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

1 In this study, the authors examined the effects of intensive insulin therapy and hyperglycaemia on the development of hypertension in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications) study.

2 Participants were enrolled between 23 August 1983 and 30 June 1989. During a median follow-up of 15.8 years, 630 of 1441 individuals developed hypertension (defined as two consecutive study visits with a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medications to treat high blood pressure).

3 During the DCCT, incidence of hypertension was similar between those on intensive or conventional glucose-lowering therapy. However, intensive therapy reduced the risk of incident hypertension by 24% during the follow-up EDIC study. Overall, this translated to an overall reduction in incidence of 20% (P=0.006).

4 A higher HbA_{1c} was associated with an increased risk of hypertension at baseline, or through the follow-up period.

5 Older age, male sex, family history of hypertension, greater baseline BMI, weight gain, and greater albumin excretion rate were also associated with increased risk of hypertension.

6 In conclusion, intensive glycaemic control reduces long-term risk of developing hypertension.

de Boer IH, Kestenbaum B, Rue TC et al (2008) Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. *Arch Intern Med* **168**: 1867–73

"... intensive glycaemic control reduces long-term risk of developing hypertension."