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I declare that I have no conflict of interest.

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Lipid lowering for primary prevention

Three large trials of rosuvastatin to prevent cardiovascular events have been completed.[1–3] Two of these, CORONA and GISSI-HF,[1,2] assessed 10 mg rosuvastatin daily. Substantial reductions in LDL cholesterol, a small increase in HDL cholesterol, and appreciable reductions in high-sensitivity C-reactive protein (hs-CRP) were reported. CORONA enrolled patients with ischaemic heart disease, whereas GISSI-HF included patients with ischaemic (40%), dilated (35%), and hypertensive (18%) causes of heart failure. Because such patients are probably at risk for future ischaemic vascular events, lowering of LDL cholesterol would be expected to reduce cardiovascular death, myocardial infarction, and stroke. Yet in neither trial was there a clear reduction in ischaemic vascular events or cardiovascular mortality (table).

By contrast, in the JUPITER trial,[3] 17 802 apparently healthy people, with LDL cholesterol less than 3·4 mmol/L and CRP concentrations above 2·0 mg/L, received rosuvastatin 20 mg daily. LDL cholesterol decreased by 50% and CRP by 37%. Over 1·9 years, there were substantial and significant reductions in ischaemic vascular events as well as total mortality, which were larger and more rapid than those in previous trials of rosuvastatin or other statins.[4]

How can we explain the apparently contradictory results of JUPITER compared with CORONA and GISSI-HF? In all three trials, CRP was raised, and substantial reductions in both LDL cholesterol and CRP occurred. The duration of the first two trials was much longer than that of JUPITER, and because the benefits of lipid lowering are enhanced by longer

follow-up, the larger and more rapid benefit in JUPITER compared with previous statin trials is a surprise. For example, a 1 mmol/L lowering in LDL cholesterol reduces the risk of vascular events by 10% after 1 year, 25% after 2–3 years, and about 30% after 4 years.[4] The 50% risk reduction in vascular events in JUPITER, after a 1·2 mmol/L drop in LDL cholesterol after 1·9 years, is unexpectedly large and rapid.

	CORONA (n=5011)[1]	GISSI-HF (n=4574)[2]	JUPITER (n=17 802)[3]	Cholesterol Treatment Trialists' (CTT) meta-analysis (n=90 056)[4]*
Background				
Age (years, mean)	73	68	66	62
% women	24%	23%	38%	24%
Major clinical diagnosis	Ischaemic heart failure (NYHA II–IV, LVEF <40%)	Heart failure (40% ischaemic) (NYHA II–IV)	Apparently healthy with high hs-CRP	Vascular disease, diabetes, primary prevention with increased risk factors*
Statin and dose (mg per day)	Rosuvastatin (10)	Rosuvastatin (10)	Rosuvastatin (20)	Simvastatin (20–40); pravastatin (20–40); lovastatin (20–80); fluvastatin (40–80); atorvastatin (10)
Duration of follow-up (years)	2·7	3·9	1·9	4·7
Baseline LDL cholesterol (mmol/L)	3·5	3·1	2·8	3·8
% reduction in LDL cholesterol (placebo subtracted)	45%	32%	50%	29%
Absolute difference in LDL cholesterol (control–active, mmol/L)	1·6	1·0	1·2	1·1
Baseline hs-CRP (mg/L; median, IQR)	3·5 (1·6–7·5)	2·7 (1·2–6·0)†	4·2 (2·8–7·1)	NA
% reduction in hs-CRP (placebo subtracted)	37%	17%	37%	NA
Major outcomes (number of events [event rate per 100 patient-years])‡§				
Composite of cardiovascular death, myocardial infarction, and stroke				
Control	732 (12·3)	550 (6·2)	157 (0·85)	6033 (3·1)
Active	692 (11·4)	553 (6·2)	83 (0·45)	4747 (2·4)
Hazard ratio (95% CI)	0·92 (0·83–1·02)	1·00 (0·89–1·13)¶	0·53 (0·40–0·69)	0·79 (0·76–0·82)
Fatal and non-fatal myocardial infarction				
Control	149 (2·2)	70 (0·8)	68 (0·37)	4420 (2·3)
Active	124 (1·8)	61 (0·7)	31 (0·17)	3337 (1·7)
Hazard ratio (95% CI)	0·82 (0·64–1·04)	0·89 (0·63–1·26)¶	0·46 (0·30–0·70)	0·77 (0·74–0·80)
Fatal and non-fatal stroke				
Control	115 (1·7)	66 (0·7)	64 (0·34)	1617 (0·82)
Active	103 (1·5)	82 (0·9)	33 (0·18)	1340 (0·68)
Hazard ratio (95% CI)	0·88 (0·67–1·16)	1·23 (0·89–1·70)¶	0·52 (0·34–0·79)	0·83 (0·78–0·88)
Cardiovascular death				
Control	593 (9·6)	488 (5·5)	43 (0·25)	2553 (1·3)
Active	581 (9·3)	478 (5·4)	35 (0·21)	2102 (1·0)
Hazard ratio (95% CI)	0·97 (0·87–1·09)	0·96 (0·85–1·09)¶	0·80 (0·52–1·27)	0·83 (0·79–0·87)
Non-cardiovascular mortality (includes deaths of unknown cause)				
Control	166 (2·5)	130 (1·5)	204 (1·21)	1801 (0·89)
Active	147 (2·2)	156 (1·8)	163 (0·96)	1730 (0·85)
Hazard ratio (95% CI)	0·87 (0·69–1·09)	1·19 (0·94–1·50)¶	0·80 (0·65–0·98)	0·95 (0·90–1·01)
All-cause mortality				
Control	759 (12·2)	644 (7·2)	247 (1·25)	4354 (2·2)
Active	728 (11·6)	657 (7·4)	198 (1·00)	3832 (1·9)
Hazard ratio (95% CI)	0·95 (0·86–1·05)	1·00 (0·90–1·12)¶	0·80 (0·97–0·97)	0·88 (0·84–0·91)‖

NYHA=New York Heart Association class. LVEF=left-ventricular ejection fraction. NA=not applicable. IQR=interquartile range. *Includes four primary prevention trials (including one trial in people with diabetes), six secondary prevention trials, three trials involving mix of primary and secondary prevention, one trial in renal transplant recipients; 42 131 people with pre-existent cardiovascular disease and 47 925 people without pre-existent cardiovascular disease. †In subset of 626 patients. ‡Control=placebo for rosuvastatin trials and for 11 of 14 trials included in CTT meta-analysis; one trial in CTT meta-analysis compared statin with usual care, one used open-label statin vs no treatment, and one compared high-dose with low-dose statin therapy. §Per 1·0 mmol/L reduction in LDL.¶Adjusted for hospitalisation for heart failure in previous year, previous pacemaker, sex, diabetes, pathological Q waves, and use of angiotensin-receptor blockers. ‖A recent network meta-analysis[6] which pooled 20 primary prevention statin trials (n=63 899) found that people treated with statin (lovastatin, pravastatin, fluvastatin, atorvastatin) had relative risks of 0·93 (95% CI 0·87–0·99, p=0·03) for all-cause mortality, 0·89 (0·81–0·98, p=0·01) for cardiovascular death, 0·85 (0·77–0·95, p=0·004) for major vascular events, 0·77 (0·63–0·95, p=0·01) for myocardial infarction, 0·88 (0·78–1·00, p=0·05) for stroke, and 0·84 (0·66–1·08, p=0·18) for revascularisations. These relative risks are similar to those observed in the CTT,[4] and suggest that relative benefits of statins are similar in primary and in secondary prevention.

Table: **Major trials of rosuvastatin in context of other major statin trials**

Although JUPITER explicitly chose healthy people with raised CRP, most people in CORONA and GISSI-HF were likely to also have raised CRP. Moreover, in all three trials, rosuvastatin lowered CRP; yet in CORONA and GISSI-HF little overall benefit was observed. A subgroup analysis from CORONA showed little benefit of rosuvastatin in those with high concentrations of CRP. But a re-analysis[5] suggested a 13% relative risk reduction in those with a CRP concentration of 2·0 mg/L or more, compared with no benefit in those with CRP less than 2·0 mg/L. While subgroup results are intriguing, they suggest a far more modest effect than that observed in JUPITER and, being retrospective, require independent confirmation.

While advanced myocardial disease in individuals in the heart failure trials might explain a lack of effect of rosuvastatin on mortality, specific ischaemic events, such myocardial infarction or stroke, would be expected to be reduced. In CORONA, there were fewer myocardial infarctions and strokes (table), but the benefit was modest and not significant. In GISSI-HF, the reduction of fatal and non-fatal myocardial infarction was also modest and there was no reduction in strokes (table). The benefit of rosuvastatin for specific ischaemic events in the two trials seems to be less than what could be expected on the basis of secondary prevention trials, whereas the large effect in JUPITER was greater than that expected.[6]

The table compares rosuvastatin trials with a meta-analysis of previous primary and secondary prevention trials. This meta-analysis indicates that for about a 1 mmol/L reduction in LDL over 5 years, there is a 21% risk reduction in vascular events, and a 12% risk reduction in mortality. These estimates are similar in primary[6] and secondary prevention trials,[4] and are more modest than that in JUPITER. Furthermore, a recent trial of simvastatin and ezetemibe in mild-to-moderate aortic stenosis[7] showed that a 50% reduction in LDL over 4·4 years led to a 17% decrease in vascular events and no reduction in mortality. Additionally, there was a reduction in non-cardiovascular deaths of about 20% in JUPITER (chiefly due to fewer cancer deaths) that was as large as the reduction in cardiovascular deaths. This finding is not biologically plausible (2 years is too short to influence cancer) and inconsistent with previous trials. Therefore, chance might have exaggerated the apparent benefits in JUPITER (compounded by the trial's early termination). In view of the results of all other statin trials, the real benefits of lowering LDL by 1·2 mmol/L for about 2 years (as in JUPITER) is unlikely to be larger than a 20–30% reduction in relative risk for ischaemic events, and a 10% reduction for total mortality. Both estimates are within the 95% CI of the estimates on specific events observed in JUPITER.

What are the clinical implications of the recent trials? First, rosuvastatin seems safe in the medium term. Whether the excess in diabetes observed in JUPITER is a chance finding or real is unclear, because it has not been observed in other trials of statins. Indeed one trial with pravastatin reported lower rates of diabetes,[8] but it would be prudent to systematically explore this point in all trials. Second, one would expect benefits from rosuvastatin to be proportionate to the degree of lowering of LDL cholesterol and the duration of treatment, so the best estimate on specific ischaemic events might be the weighted average of all trials of rosuvastatin, when viewed in the context of all other previous statin trials.[4,6] Third, because the role of CRP as a predictor of risk remains controversial,[9] its role as a marker of preferential benefits from statins should be evaluated in ongoing trials, and in a meta-analysis of all trials that have stored blood samples suitable for CRP measurement. Fourth, because in those without clinical cardiovascular disease the absolute benefits are likely to be modest in the short term (the absolute risk of events in JUPITER was low, despite use of CRP as a marker of risk), much longer-term trials than those currently completed are needed to discover the full benefits (which may increase over time) and safety of life-long use. Fifth, the effect of statins in several ethnic groups, such as Chinese people and south Asians, needs clarification. In view of the potentially large public-health and economic implications of widespread use of statins in apparently healthy individuals with average risk levels, confirmation of the long-term results of major lowering of LDL cholesterol (as can be safely achieved by rosuvastatin) is needed before potent statins are used widely in average-risk healthy people.

Substantial risk reductions in cardiovascular disease are theoretically possible by combined lowering of blood pressure and LDL cholesterol in those with average levels of both risk factors and no apparent vascular disease, but this promising hypothesis needs assessment.[10,11] Whether biomarkers such as CRP or N-terminal probrain natriuretic peptide[7,12] will be better than simple clinical risk factors in identifying individuals who would benefit from preventive strategies remains unclear. At present, tobacco avoidance, maintenance of optimum weight,

a prudent diet, and regular exercise should remain the foundations for prevention of cardiovascular disease in apparently healthy individuals with average risk factors.

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The responsibilities of the World Medical Association President

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Yoram Blachar's accession to the Presidency of the World Medical Association[1] comes with responsibilities. The World Medical Association was founded to work for the highest possible standards of ethical behaviour and care by physicians at all times. The Israeli Medical Association, of which he is also President, has on its website powerful position statements on health care during conflict[2] and on torture,[3] which deserve strong support. Yet despite these statements, the Israeli Medical Association has been criticised for its reluctance fully to endorse international humanitarian codes.[4] *The Lancet* has recently argued that it is the responsibility of medical professionals, and their professional bodies, explicitly to condemn unethical acts, even when such a challenge might prove unpopular.[5] Blachar's Presidency of the World Medical Association offers the opportunity to restore respect for the Israeli Medical Association from the global medical community, and creates opportunities for doctors to play a vital role in the search for peace.

Israel has a right to act in pursuit of its security, but security might be used as a cover for many authoritarian actions. Some actions of the Israeli General Security Services, under the umbrella of security, have superseded human rights, including the right to health care. Recent events in Gaza have led to widespread distress at the suffering of civilians; international agencies have reported the Israeli Defense Force targeting medical stores and ambulances, and health workers have been killed. There were disturbing reports of the military refusing access to care for the injured, including one of children in a building found clinging to their dead mother 4 days after the house was shelled.[6] Such acts are contrary to the principles stated in the Israeli Medical Association's paper, *Assurance of medical and health services during the Israel-Palestine conflict*,[2] as well as contravening international conventions. Yet the Israeli Medical Association has been disturbingly unforthcoming about these events. Blachar responded to my request for a statement of protest[7] by claiming that Hamas was using medical facilities to store weapons and employing human shields.[8] These reports are unverified and, according to