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Cardiology

UNIVERSITY OF TORONTO

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Scientific Update™

Across the Continuum of Cardiovascular Risk – Evidence for Managing and Treating the Multiple Risk Factor Patient including late-breaking results of the ASCOT-LLA trial

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Experimental and clinical evidence support the additive effects of hypertension and hyperlipidemia on the development and progression of atherosclerosis and, therefore, the risk of adverse cardiovascular (CV) events. Many large randomized trials have demonstrated improved clinical outcomes by lowering cholesterol in individuals at high risk of CV events. However, limited data are available with respect to the potential benefits of cholesterol lowering in the primary prevention of coronary heart disease (CHD) in patients with hypertension who are not conventionally considered hyperlipidemic. The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) is a multicentre trial that was designed to assess the effects of two anti-hypertensive regimens and lipid-lowering on CV clinical outcomes in patients with non-fasting total cholesterol levels ≤ 6 mmol/L. Results of the lipid-lowering arm of ASCOT (ASCOT-LLA) have recently been presented and published. In this issue of *Cardiology Scientific Update*, the background information and rationale behind ASCOT, the results of ASCOT-LLA, as well as their practical implications, will be discussed.

Treating hypertension and dyslipidemia – Evidence for synergistic benefits

Both hypertension and dyslipidemia increase the risk of mortality from CHD. Mortality from CHD has strong, graded relationships with systolic blood pressure (BP) >110 mm Hg and serum cholesterol >4.65 mmol/L, and the impact of each risk factor on CHD mortality is additiive.[1] Patients with hypertension have impaired endothelial function and nitric oxide (NO) synthesis. This abnormality appears to be broad in terms of its mechanisms and is not limited to a specific defect in the muscarinic receptors.[2] Furthermore, increased fat intake acutely impairs coronary endothelial function,[3] which is associated with increased risk of adverse CV events.[4]

Increased oxidative stress is an important process in the development of atherosclerosis and recent studies have shown that NAD(P)H oxidases are major sources of superoxide in vascular cells and myocytes. In response to growth factors and cytokines, they produce superoxide, which is metabolized to hydrogen peroxide, and both of these reactive oxygen species

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Figure 1: Hypertension and dyslipidemia — mechanisms of adverse clinical outcomes

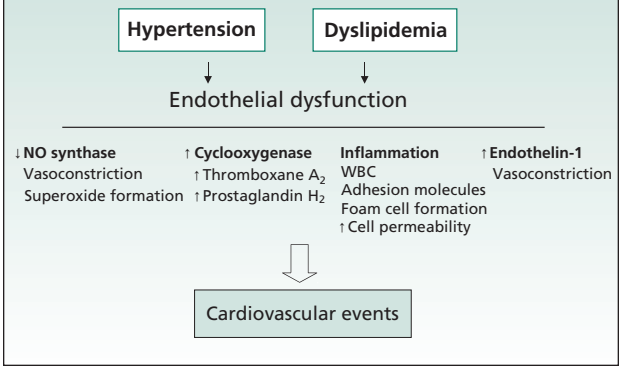
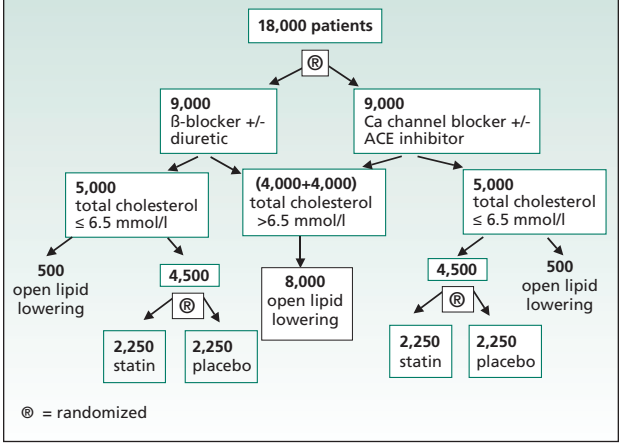


Figure 2: ASCOT — Entire study design



(ROS) serve as secondary messengers to activate multiple intracellular signaling pathways. As well, ROS inactivates NO directly and moreover, can convert it into cytotoxic products. The vascular NAD(P)H oxidases appear to be essential in the physiological response of vascular cells, including growth, migration, and modification of the extracellular matrix. They have also been linked to hypertension and atherosclerosis, a process characterized by uncontrolled neointimal growth and inflammation.[5,6] Endothelial dysfunction has been reported in patients with hypercholesterolemia and recently, an association of the latter with increased vascular superoxide production was described.[7] Native and oxidized low-density lipoproteins inhibit NO generation. The lipoproteins decrease the uptake of L-arginine, which in turn deranges NO synthesis favouring overproduction of superoxide.[8] Lowering cholesterol and administering the anti-oxidant probucol have been demonstrated to improve coronary endothelial function.[9] In summary, hypertension and dyslipidemia both induce endothelial dysfunction, which activates numerous pathologic mechanisms that ultimately result in adverse clinical outcomes. These mechanisms explain, in part, the combined adverse effects of hypertension and dyslipidemia on CV outcomes and provide a rationale for aggressive treatment of both conditions (Figure 1).

Dyslipidemia in patients with hypertension – the need for multiple risk factor intervention

The *World Health Report 2002*[10] has recently quantified the major contributions of smoking, alcohol consumption, high BP, high cholesterol, low intake of fruit and vegetables, physical inactivity, and high body-mass index to the global burden of disease, and of CV disease in particular.[11] Improved data on degree of exposure and detailed assessments of the magnitude of hazards, have led to the appreciation that high BP and high cholesterol have a much greater influence on population health than previously thought.[12] About two-thirds of strokes and close to one-half of cases of CHD can be attributed to systolic BP >115 mm Hg. On the other hand, 18% of strokes and 55% of the cases of CHD globally can be accounted for by total cholesterol >3.8 mmol/L.[13] An elevated low-density lipoprotein-cholesterol (LDL-C) level appears to be the primary risk factor for CHD as some degree of elevation of LDL-C seems to be necessary for the development of coronary atherosclerosis.[14]

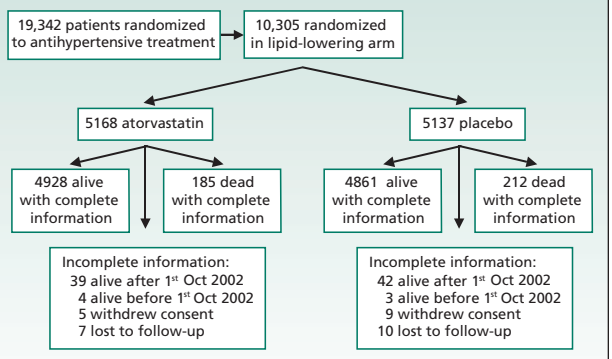
The Framingham Heart Study demonstrated that the major risk factors are additive in predictive power for the development of CHD.[15] For example, a 55-year-old male nonsmoker with SBP of 155 mm Hg and total cholesterol of 4.4 mmol/L, in the absence of diabetes, has a 7% 10-year absolute risk for developing CHD. On the other hand, another subject with the same risk factors except for total cholesterol of 6.2 mmol/L has a 13% 10-year absolute risk. These findings underscore the usefulness of assessing global risk of patients and the need for multiple risk factor intervention.

ASCOT: The benefits of lipid lowering in a hypertensive population

Background and study design

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a multicentre, international trial that involves two treatment comparisons in a factorial design.[16]

Figure 3: ASCOT LLA — Study profile and follow-up status[22]



The first design is a prospective, randomized, open, blinded endpoint (PROBE) design comparing "old" versus "new" antihypertensive regimens. The second design, in a subgroup of the hypertensives, is a double-blind placebo-controlled trial of a lipid-lowering agent (Figure 2).

The rationale for the first design is very similar to that of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[17] reviewed in recent issues of *Cardiology Scientific Update* because, at the inception of ASCOT and ALLHAT, there was uncertainty on the relative benefit of "old" versus "new" antihypertensive agents on clinical outcomes. The rationale for the second design stemmed from two concepts. First, as reviewed earlier, hypertension and dyslipidemia exert additive effects on the risk of CV events. Subgroup analyses of studies of cholesterol lowering have suggested that the relative CV benefit with this strategy is similar in hypertensive and normo-tensive subjects.[18-20] Secondly, a significant number of CV events attributable to hypertension and dyslipidemia occurred among subjects with BP and lipid levels that were deemed to be "normal."[21] The benefit of lipid-lowering in subjects with reasonably controlled BP and normal, or only mildly raised, serum cholesterol, remains to be determined. Therefore, the primary objectives of ASCOT were:

- To compare the effects on the combined endpoint of nonfatal myocardial infarction (MI) and fatal CHD of a ß-blocker, atenolol (+ a diuretic, if necessary) with a calcium channel blocker (CCB) (+ an angiotensin-converting enzyme (ACE) inhibitor, if necessary).

Figure 4: ASCOT — baseline characteristics[22]

Characteristics	Atorvastatin (n = 5168)	Placebo (n = 5137)
Age* (years)	63.1 ± 8.5	63.2 ± 8.6
Male (%)	81.1	81.3
Caucasian (%)	94.6	94.7
SBP* (mm Hg)	164.2 ± 17.7	164.2 ± 18.0
DBP* (mm Hg)	95.0 ± 10.3	95.0 ± 10.3
TC* (mmol/L [mg/dL])	5.5 ± 0.8 (213 ± 31)	5.5 ± 0.8 (213 ± 31)
LDL-C* (mmol/L [mg/dL])	3.4 ± 0.7 (131 ± 27)	3.4 ± 0.7 (131 ± 27)
TG* (mmol/L [mg/dL])	1.7 ± 0.9 (150 ± 80)	1.6 ± 0.9 (142 ± 80)
HDL-C* (mmol/L [mg/dL])	1.3 ± 0.4 (50 ± 27)	1.3 ± 0.4 (50 ± 27)
Number of risk factors*	3.7 ± 0.9	3.7 ± 0.9

*Mean ± SD

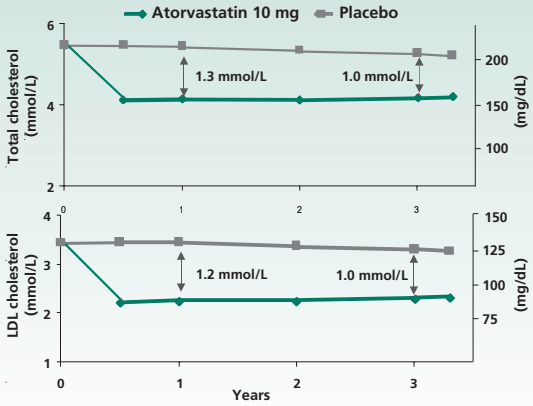
- To compare the effect on the same outcome of a statin, atorvastatin (starting dose 10 mg daily, not titrated) with that of placebo, among hypertensive patients with total cholesterol ≤ 6.5 mmol/L.

Patients eligible for inclusion in the lipid-lowering arm of ASCOT were men and women aged between 40 and 79 years, with either untreated hypertension (defined as systolic BP of ≥160 mm Hg, diastolic BP of ≥100 mm Hg, or both), or treated hypertension with systolic BP of ≥140 mm Hg, diastolic BP ≥ 90 mm Hg, or both. Patients had to be eligible for the BP-lowering arm, have total cholesterol concentrations of ≤ 6.5 mmol/L, and could not be on a statin or a fibrate. In addition, the study population was required to have at least 3 of the following risk factors for CV events:

- left-ventricular hypertrophy
- other specified abnormalities on electrocardiogram
- type 2 diabetes
- peripheral arterial disease
- previous stroke or transient ischemic attack
- male sex
- age ≥ 55 years
- microalbuminuria or proteinuria
- smoking
- ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher
- a family history of premature CHD.

The study has, in addition to the primary endpoint, multiple secondary and tertiary endpoints. In the lipid-lowering arm (LLA) that included over 10,000 patients, the study had >90% power with a significance level of 1% to

Figure 5: ASCOT — Reductions in total and LDL-cholesterol[22]



detect a 30% relative reduction in coronary events by atorvastatin versus placebo.

Results

The LLA of ASCOT was terminated early based on a benefit observed in the atorvastatin over the placebo group on the primary endpoint. The hypertension arm of ASCOT is still ongoing. The results of the LLA of ASCOT have recently been presented and published.[22] The study profile, including the final sample size and the status of follow-up, is shown in Figure 3. Most patients were followed to the end of the study with very few lost to follow-up. The key baseline characteristics are shown in Figure 4. The two groups were comparable in baseline demographics. After 3 years of follow-up, 87% of patients assigned to atorvastatin were still taking a statin and 9% assigned to placebo had been prescribed open-label statins. BP control was similar for both groups, with identical mean values of 138/80 mm Hg for both groups at the end of the LLA follow-up. Total cholesterol and LDL-C were both reduced by 1 mmol/L at the end of follow-up (Figure 5).

Results of the primary endpoint, the time to first nonfatal MI and fatal CHD, are shown in Figure 6. Compared to placebo, atorvastatin produced a 36% relative reduction in the combined endpoint over approximately 3.5 years. The effect of atorvastain on the primary endpoint, together with the secondary and tertiary endpoints, expressed as hazard ratios (HR), is shown in

Figure 6: ASCOT — primary endpoint: nonfatal MI and fatal CHD[22]

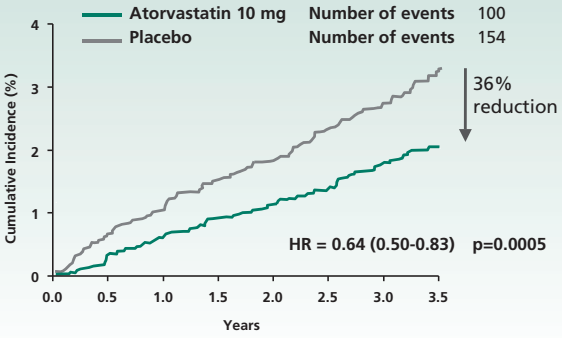
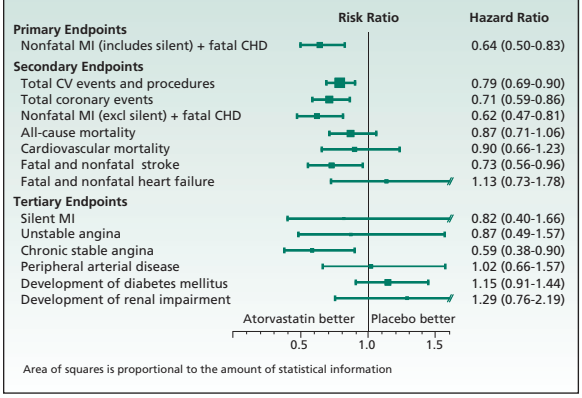


Figure 7. In addition to the beneficial effect on the primary endpoint, the risks for secondary endpoints – total CV events and procedures, total coronary events, nonfatal MI (excluding silent MI) and fatal CHD, as well as fatal and nonfatal stroke (Figure 8) – were all significantly reduced. Also, a non-significant trend favoured atorvastatin for all-cause mortality and CV mortality. The effects on the tertiary endpoints are more difficult to interpret due to the wide confidence intervals. Analysis according to predefined subgroups indicates that the benefit of atorvastatin on the primary outcome is consistent, regardless of the presence or absence at baseline of diabetes, smoking, obesity, left ventricular hypertrophy, age over 60, previous vascular disease, renal dysfunction, and metabolic syndrome. Also, the benefit of atorvastatin is similar for a broad spectrum of baseline total cholesterol levels: total cholesterol < 5.0 mmol/L (HR 0.628, $p = 0.098$); total cholesterol 5.0-5.9 mmol/L (HR 0.615, $p < 0.011$); total cholesterol ≥ 6.0 mmol/L (HR 0.689, $p = 0.084$). The number of adverse events, including fatal cancer and liver enzyme abnormalities, did not differ between study groups.

Implications of the results of ASCOT-LLA on clinical recommendations and practice

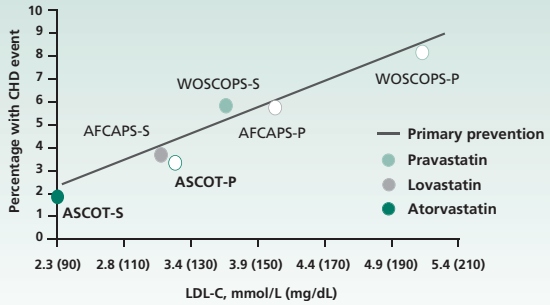
ASCOT-LLA demonstrates that in hypertensive patients at modest risk of CHD: Treatment with atorvastatin 10 mg daily is associated with a significant 36% reduction in the primary endpoint of CHD, accompanied by significant reductions in the secondary endpoints of stroke, all CV events and procedures, and total coronary

Figure 7: All predefined endpoints[22]



Area of squares is proportional to the amount of statistical information

Figure 9: ASCOT in context of other landmark statin trials — LDL-C levels vs CHD events

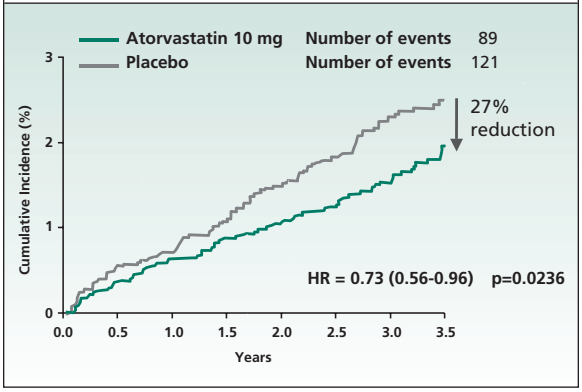


S = statin treated; P = placebo treated, ASCOT data extrapolated to 5 years

events. Benefits are observed across pre-specified subgroups. Risk reductions in CHD events are unrelated to baseline cholesterol and are consistent across the whole range of cholesterol levels. Benefits are accrued in the absence of any increased risk of non-CV disease, including fatal cancer and liver function abnormalities.

The benefits of atorvastatin appear to emerge early. Furthermore, the reductions in major CV events are large given the short follow-up time and they occurred earlier than in many other statin trials. Indeed, by extrapolation, the relative risk reduction may have reached 50% had the follow-up been carried to 5 years as planned. It is useful to place the results of ASCOT-LLA in the context of other landmark trials of statins (Figure 9). The CHD event rates are plotted against the end-of-trial LDL-C levels for each treatment group in landmark primary prevention trials, thereby enabling a comparison of the relation between relative risk reduction in CHD event and proportional reduction of LDL-C among trials.[19,22,23] Taking the results of all of the landmark treatment trials together, a linear relation between CHD event and LDL-C is observed, similar to that observed in previous observational studies.[21] More importantly, these results suggest that the lower the LDL-C, the lower the event rate for CHD. This is further exemplified by the ALLHAT study, where an insufficient (9%) lowering of total cholesterol by pravastatin (due to open-label use) likely explains the lack of benefit of pravastatin in that study.[24] Recent international surveys on patients with CHD continue to demonstrate a lack of improvement in BP management and failure to achieve the cholesterol goal of < 5 mmol/L.[25,26] The results of ASCOT-LLA, together with other recently published statin trials such as the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study[27] and the Heart Protection Study (HPS),[18] are likely to have an important impact on the existing recommendations for the primary and secondary prevention of CHD.[28-30]

Figure 8: ASCOT — Secondary endpoint: fatal and nonfatal stroke



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