"Since raised BP and dyslipidemia frequently coexist to impart a multiplicative impact on CV risk (…), a combined approach of lowering BP and improving lipid profiles is a logical one. The best currently available evidence from clinical trials supports the routine use of such an approach, and consequently several sets of guidelines for the management of hypertension also recommend the routine use of statins for a large proportion of hypertensive patients"

Treating both hypertension and dyslipidemia: a synergistic approach

by N. R. Poulter, *United Kingdom*

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The cardiovascular benefits of lowering blood pressure have been clearly established for decades. More recently, the cardiovascular benefits of lipid lowering with statins among subgroups of hypertensive patients and in specific trials of hypertensive patients have also become clear. Because raised blood pressure and dyslipidemia coexist more frequently than chance would predict, a combined approach to improve both blood pressure and lipid levels in patients with hypertension appears logical. ASCOT-LLA, the lipid-lowering arm of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial) confirmed the logic of such an approach by showing not only the independent and superior benefits of the "A + C" (angiotensin-converting enzyme inhibitor plus calcium channel blocker) combination of antihypertensive agents over the then-standard β-blocker +/- thiazide ("B + D") combination in terms of cardiovascular prevention, but also the benefits of atorvastatin versus placebo. The combined effects of amlodipine +/- perindopril plus atorvastatin in ASCOT-LLA were large and compelling with some suggestion of a real synergy between these two regimens in preventing coronary events. Meanwhile, guidelines for hypertension management based on best current trial data increasingly recommend an "A + C" regimen for optimizing cardiovascular prevention among hypertensive patients and the use of statins for a significant proportion of the hypertensive population. Urgent steps must be taken to implement best practice before the anticipated global increase in the prevalence and absolute numbers affected by hypertension translates into an ever greater cardiovascular burden than that which currently prevails.

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The cardiovascular (CV) benefits of treating severe, moderate, and more mild hypertension were clearly established by the mid-1990s.[1,2,3] Several years later, subgroup analyses of the large statin trials confirmed that those patients with hypertension who were allocated to statins rather than placebo experienced a similar relative risk reduction in CV events as those who were normotensive *(Table I, page 155)*.[4-10] Because those with hypertension are at higher absolute risk of suffering CV events than those who are normotensive, these relative risk reductions translate into greater absolute CV benefits. Furthermore, because CV risk factors tend to cluster in individuals, such that dyslipidemia is more prevalent among hypertensive than normotensive people,[11] there appeared to be a reasonable rationale for using lipid-lowering agents—specifically statins, given their proven efficacy—as part of the routine treatment strategy for those with hypertension, to optimize the reduction of CV events.

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Trial	1°/2°	"Hypertensive" n	"Hypertensive" % reduction*	Total population n	Total population % reduction*
4S[4]	2°	1154	37	4444	34
CARE[5]	2°	1774	23	4159	24
LIPID[6]	2°	3758	15	9014	24
GREACE[7]	2°	686	48	1600	51
HPS†[8]	1°+ 2°	10594	20	20536	24
PROSPER†[9]	1°+ 2°	2212	15	5804	15
AF/TexCAPS[10]	1°	1445	39	6605	37

*All CHD except (†) – CHD + stroke

Table I. *Cardiovascular end point reduction by hypertension status in statin trials.*

Abbreviations: *4S, Scandinavian Simvastatin Survival Study; AF/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE, Cholesterol And Recurrent Events trial; CHD, coronary heart disease; LIPID, Long-term Intervention with Pravastatin in Ischemic heart Disease; GREACE, GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study; HPS, Heart Protection Study; PROSPER, Pravastatin in elderly individuals at risk of vascular disease study.*

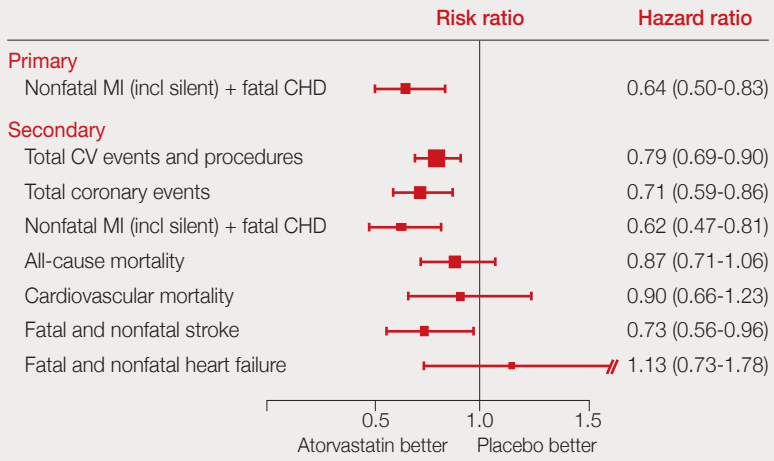

Figure 1. *Effects of atorvastatin and placebo on primary and secondary end points in ASCOT-LLA.*

Abbreviations: *ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction.*

After reference 14: *Sever PS et al.* Lancet. *2003;361:1149-1158. © 2003, Elsevier Ltd.*

Trials of lipid lowering in hypertensive patients

With that background, two trials were designed to incorporate an evaluation of lipid lowering specifically among hypertensive patients.[12,13] Unfortunately, the first trial—ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial)[12]—was designed to compare the effects of pravastatin (a relatively ineffective statin) with usual care, which in the context of the ALLHAT trial population involved significant use of other, and possibly stronger, statins. The net effect was a limited differential effect on low-density lipoprotein (LDL)–cholesterol with a consequently limited effect on CV events between treatment groups.

In contrast, the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial)[13] included as part of a 2 × 2 factorial design, a placebo-controlled evaluation of atorvastatin 10 mg once daily on major CV events. *Figure 1* shows the benefits of atorvastatin on primary and secondary end points in this hypertensive population of 10 305 patients who had a baseline total cholesterol of ≤6.5 mmol/L.[14] This lipid-lowering component of the trial (ASCOT-LLA) was stopped prematurely after a median follow-up period of 3.3 years due to a highly significant reduction (36%; *P*=0.0005) in the primary end point of nonfatal myocardial infarction (MI) and fatal coronary heart disease (CHD).

The ASCOT trial: combining lipid lowering and blood pressure lowering

The blood pressure (BP)–lowering arm of the trial (ASCOT-BPLA), which included 19 257 hypertensive patients at baseline, continued for a further 2 years after the end of ASCOT-LLA. This arm of the trial was also stopped prematurely because of the significantly reduced rates of all-cause mortality and other CV events (notably stroke) among those randomized to receive amlodipine with perindopril added as required to reach BP targets (amlodipine +/– perindopril) compared with those randomized to receive atenolol with bendroflumethiazide added as required (atenolol +/– thiazide).[15]

SELECTED ABBREVIATIONS AND ACRONYMS

ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm
BP	blood pressure
CCB	calcium channel blocker
CHD	coronary heart disease
CV	cardiovascular
GREACE	GREek Atorvastatin and Coronary-heart-disease Evaluation study
LDL	low-density lipoprotein
MI	myocardial infarction

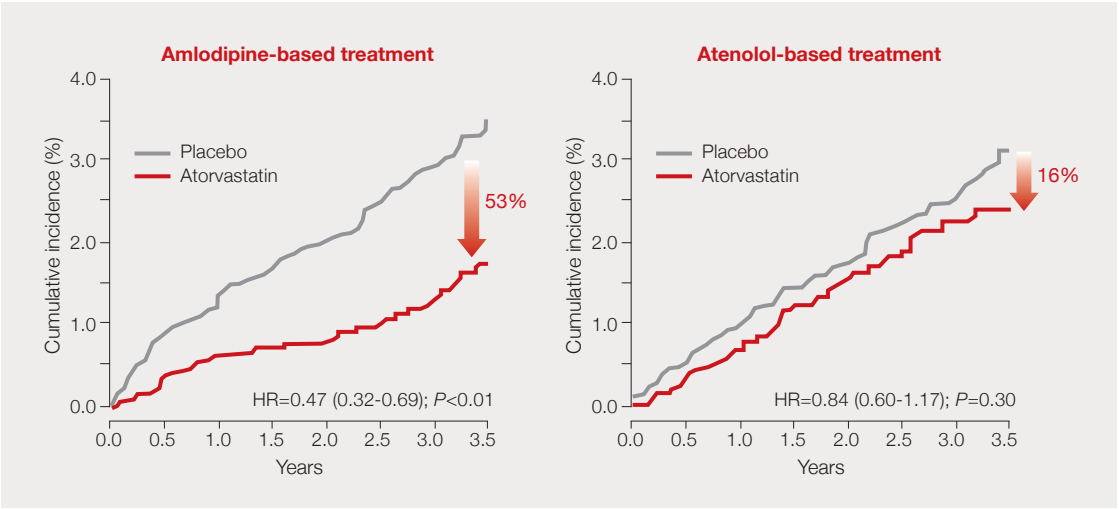

Figure 2. *Cumulative incidence for nonfatal myocardial infarction and fatal coronary heart disease in ASCOT-LLA.*
Abbreviations: *ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; HR, hazard ratio.*
After reference 16: *Sever P et al.* Eur Heart J. *2006;27: 2982-2988. © 2006, European Society of Cardiology.*

One of the tertiary objectives of the ASCOT trial was to evaluate whether there was any interaction between the BP-lowering and lipid-lowering therapies used in the trial in terms of impact on three specified CV events.[13] Consequently, the relevant and appropriate analyses were carried out to evaluate this question and revealed that there was indeed a statistically significant interaction (*P*=0.025) between the use of atorvastatin in the amlodipine +/– perindopril and atenolol +/– thiazide groups in terms of impact on the primary end point of the trial (nonfatal MI and fatal CHD).[16] As shown in *Figure 2,* allocation to atorvastatin was associated with a 53% reduction (*P*<0.001) in the primary end point of the trial among those also allocated to amlodipine +/– perindopril, whereas the equivalent effect on those randomized to atenolol +/– thiazide was a 16% reduction (*P*=0.30). The other two CV end points that were prespecified for evaluation as to whether the impact of statins and the BP-lowering agents in ASCOT would show any sign of interaction in terms of differential effects were nonfatal or fatal stroke (total stroke) and total CV events and procedures (CV mortality, nonfatal MI [symptomatic and silent], unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thrombosis).[13] No such significant effect was observed for either of these two end points (*P*=0.728 and *P*=0.253, respectively) *(Table II).*

The differential effect of statins on coronary events when stratified by BP-lowering regimen was of modest statistical significance given that this was a tertiary objective of the trial.[13] Furthermore, the difference between BP-lowering regimens was to an extent driven by a less-than-expected impact of atorvastatin among those allocated to atenolol +/– thiazide. The possibility that this difference occurred by chance should

End point and blood pressure regimen	Atorvastatin		Placebo		Unadjusted HR 95% CI	*P*-value	Interaction *P*-value
End point	n (%)	Rate*	n (%)	Rate*			
Nonfatal myocardial infarction + fatal CHD							
Amlodipine-based	38 (1.5%)	4.6	80 (3.1%)	9.8	0.47 (0.32-0.69)	0.00007	0.025
Atenolol-based	62 (2.4%)	7.5	74 (2.9%)	9.0	0.84 (0.60-1.17)	0.295	
Totalcardiovascular events and procedures							
Amlodipine-based	173 (6.7%)	21.3	233 (9.1%)	29.4	0.73 (0.60-0.88)	0.001	0.253
Atenolol-based	216 (8.4%)	27.0	253 (9.8%)	31.7	0.85 (0.71-1.02)	0.079	
Fatal and nonfatal stroke							
Amlodipine-based	35 (1.4%)	4.2	50 (2.0%)	6.1	0.69 (0.45-1.06)	0.088	0.728
Atenolol-based	54 (2.1%)	6.5	71 (2.7%)	8.6	0.76 (0.53-1.08)	0.129	

*Per 1000 patient years.

Table II. *The effects of atorvastatin vs placebo for amlodipine-based and atenolol-based treatment for fatal coronary heart disease and nonfatal myocardial infarction, total cardiovascular events and procedures, and fatal and nonfatal stroke.*
Abbreviations: *CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.*
After reference 16: *Sever P et al.* Eur Heart J. *2006;27:2982-2988. © 2006, European Society of Cardiology.*

also not be ignored. Nevertheless, the 53% reduction in coronary events (95% confidence interval, 31-68) observed among those allocated to atorvastatin 10 mg daily and amlodipine +/– perindopril compared with those allocated to placebo and amlodipine +/– perindopril was large and greater than might, on average, have been expected with atorvastatin 10 mg daily.

ASCOT-LLA: impact on guidelines

The large relative reductions in risk among those randomized to atorvastatin compared with placebo are clear *(Figure 1)* and argue forcibly for the routine use of statins among the hypertensive population. Indeed, hypertension guidelines[17,18] produced after the results of ASCOT-LLA were published[14] supported such a position, including the following statement for patients with hypertension in the context of primary prevention:

> "In view of the results of the ASCOT trial and other currently available trial data, it seems reasonable, in the interests of simplicity, to treat with a statin, all those patients at least up to the age of 80 years with a total cholesterol >3.5mmol/L who have an estimated 10-year cardiovascular disease risk of 20% or more. In reality, this would mean considering statin therapy in most hypertensive patients (especially men) over the age of 50 years. As resources allow, a rationale for lowering this threshold could be made on the basis of trial evidence." [17,18]

Furthermore, support for the use of statins in the context of hypertensive patients arose from cost-effectiveness analyses based on the ASCOT-LLA data.[19] These data showed that the cost per life-year gained using atorvastatin 10 mg daily in hypertensive adults was about €10 000, and based on these findings, it was concluded that the use of atorvastatin in hypertensive patients at modest CV risk but who have not suffered a prior MI was a cost-effective strategy. It is important to add that since these health economic analyses were performed, atorvastatin has become generic and so any residual cost-based reservations regarding the use of atorvastatin in hypertensive patients appear to have no basis. Finally, the CV benefits of lipid lowering with atorvastatin 10 mg in ASCOT-LLA would reasonably be expected to be enhanced by higher doses of atorvastatin and by use among those with more adverse lipid profiles (inclusion in ASCOT-LLA was restricted to those with a total cholesterol of ≤6.5 mmol/L [≤250 mg/dL]).

Statistical synergy between lipid-lowering and blood pressure lowering in ASCOT: possible mechanisms

The apparently greater preventive effect on coronary events of atorvastatin when used in combination with amlodipine +/– perindopril compared with atenolol +/– thiazide *(Figure 2)* may have occurred as a result of differential BP-lowering or lipid-lowering effects induced by atorvastatin in the two BP treatment groups. While statins do cause a small BP-lowering effect,[20] no differential effect was noted in ASCOT (unpublished data). Furthermore, the effect of atorvastatin compared with placebo on LDL-cholesterol, high-density lipoprotein (HDL)–cholesterol, and triglycerides was essentially the same once stratified by BP-lowering group,[16] and if anything, what minor differences that did exist favored the atenolol +/– thiazide group.

More generally, angiotensin-converting enzyme (ACE) inhibition has been reportedly associated with reductions in CHD events beyond BP-associated benefits[21,22] and in both experimental[23] and clinical situations,[24,25] dihydropyridine calcium channel blockers (CCBs) have been reported to have antiatherosclerotic actions. Furthermore, a hypothesis based on studies of a cellular and molecular interaction between amlodipine and atorvastatin has been proposed.[26,27] Based on Mason's report that electrochemical bonding between amlodipine and atorvastatin occurs in the lipid bilayer of vascular smooth muscle membranes,[27] it is hypothesized that, while the functionality of L-type calcium channels in vascular smooth muscle cells is normally lost during the migration of these cells in the atherosclerotic process, the effect of atorvastatin is to induce arrest of growth and differentiation of the smooth muscle cells and restoration of their responsiveness to CCBs.

In addition, it is argued that atherosclerotic plaques are stabilized due to the reduced apoptosis and destruction of vascular smooth muscle cells, a reduction in the release of matrix metalloproteinases, and preservation of the intracellular matrix. The findings of bonding between amlodipine and atorvastatin have not been replicated using other statins and other antihypertensive agents and hence makes any such interaction, if true, product-specific.

Statin/CCB interaction: supportive data

◆ *Internal consistency from ASCOT*

The possible mechanisms underlying the superiority of amlodipine +/– perindopril over atenolol +/– thiazide in ASCOT-BPLA were evaluated and published along with the main final results.[28] The authors concluded that it was likely that some as-yet-unidentified mechanisms—other than those identified in this publication, and certainly beyond the mean BP differences achieved—might have contributed to the differential CV event rates. One such possibility might involve a positive interaction between atorvastatin and amlodipine among those in the amlodipine +/– perindopril group (half of whom were on atorvastatin). However, more recently, the differential effects of the two BP-lowering regimens on BP variability appear to have explained away most of the CV differences observed.[29,30]

Other examples of synergy between atorvastatin and amlodipine +/– perindopril have also been observed in analyses of two subgroups from among the ASCOT participants. In the first one, Manisty and colleagues described a statistically significant interaction between the lipid-lowering and BP-lowering regimens in terms of their impact on carotid systolic BP in a subgroup of ASCOT patients.[31] Systolic BP was found to be significantly lower among those randomized to atorvastatin

and the amlodipine +/– perindopril combination than in those treated with atorvastatin and atenolol +/– thiazide. In the second example, analysis of the subgroup of diabetic patients in ASCOT demonstrated a significant interaction favoring the atorvastatin, amlodipine +/– perindopril combination in terms of a beneficial effect on estimated glomerular filtration rate (eGFR), which was not observed between the two BP-lowering groups randomized to placebo.[32]

◆ *External consistency from other studies*

In the GREACE trial (GREek Atorvastatin and Coronary-heart-disease Evaluation) a synergistic effect between atorvastatin and ACE inhibitors was reported among patients with established CHD.[33]

Statin/CCB interaction: conflicting data

In the Prospective Pravastatin Pooling Project, the impact of pravastatin on CHD events among hypertensive patients was significantly less than among nonhypertensives (14% vs 33%, heterogeneity; *P*=0.003).[34] However, the authors were unable to attribute this apparent difference to any specific antihypertensive agents. To be compatible with the ASCOT-BPLA findings, a predominance of β-blocker use and limited CCB use among the hypertensive population of the pooling project would have been required.

In the Heart Protection Study,[35] the effect of simvastatin on CHD events did not differ between those receiving or not receiving antihypertensive medication. Furthermore, no differential CCB-specific effect on events was apparent in this large trial.[35]

In the meta-analysis carried out on behalf of the Cholesterol Treatment Trialists (CTT) collaboration,[36] the presence or absence of hypertension at baseline in the 14 trials included did not affect the impact of statins on CHD event rates, or indeed any other event rates.

Conclusion

Whether the apparent synergy between atorvastatin and the amlodipine +/– perindopril regimen shown in *Figure 2* was the result of chance or not, when the results of ASCOT-BPLA and ASCOT-LLA are viewed together, it is quite clear that of the four possible means of preventing CV events incorporated in the ASCOT trial design *(Table III),* those allocated to the newer antihypertensive regimen (amlodipine +/– perindopril) and atorvastatin (a) were less likely to suffer any of the major CV end points evaluated in this trial than those allocated to any of the other three possible treatment combinations (b, c, or d). By contrast, those allocated to receive atenolol +/– thiazide and placebo (d) were more like to suffer any of the major CV end points evaluated than those allocated to any of the other possible treatment combinations (a, b, or c). Those allocated to either of the other two possible combinations (b and c in *Table III*) were neither 'best' nor 'worst' in terms of prevention of whatever CV end point was considered.

		BPLA	
		Amlodipine ± perindopril	Atenolol ± thiazide
LLA	Atorvastatin	a	b
	Placebo	c	d

Table III. *ASCOT trial design: blood pressure–lowering arm and lipid-lowering arm combined.*
Abbreviations: *ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BPLA, blood pressure–lowering arm; LLA, lipid-lowering arm.*
Data from reference 16: *Sever P et al.* Eur Heart J. *2006;27:2982-2988.*

End point	Amlodipine ± perindopril + atorvastatin	Atenolol ± thiazide + placebo	Relative risk reduction
Nonfatal MI and fatal CHD	4.8	9.2	48%
Fatal and nonfatal stroke	4.6	8.2	44%

Table IV. *ASCOT blood pressure–lowering arm and lipid-lowering arm combined: insight into optimal cardiovascular prevention.*
Abbreviations: *ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CHD, coronary heart disease; MI, myocardial infarction.*
Data from reference 16: *Sever P et al.* Eur Heart J. *2006;27:2982-2988.*

The absolute event rates of the primary end point of the trial (nonfatal MI and fatal CHD) and all strokes (fatal and nonfatal) suffered by those allocated to the "best" and "worst" therapy combination (respectively, a and d in *Table III*) are shown in *Table IV.*

Summary

As recently stated in the most recent NICE guidelines on hypertension management, "The prime motivation for treatment in hypertension, as an asymptomatic condition, is the prevention of mortality and morbidity."[37] Similarly, the purpose of using statins is to reduce the huge burden to global health that CV disease currently causes.

Since raised BP and dyslipidemia frequently coexist to impart a multiplicative impact on CV risk (ie, if for example, raised BP doubles CV risk and abnormal lipids trebles risk, the combined effect is to increase risk six-fold), a combined approach of lowering BP and improving lipid profiles is a logical one. The best currently available evidence from clinical trials supports the routine use of such an approach, and consequently several sets of guidelines for the management of hypertension also recommend the routine use of statins for a large proportion of hypertensive patients.[17,18]

Some data suggest that specific combinations of BP-lowering drugs and statins may interact to generate synergistic benefit on CHD events,[16] but even without synergy, the ASCOT trial clearly shows large beneficial effects on all CV events as-

sociated with the use of amlodipine +/– perindopril with atorvastatin *(Table IV)*. It seems likely that, for patients with hypertension, the routine use of the combination of an "A" drug (ACE-inhibitor or ARB) plus a "C" drug (CCB) as recommended in the NICE guidelines of 2011,[37] along with a cost-effective statin (eg, atorvastatin), would result in a dramatic reduction in the dreadful CV burden currently caused by raised BP and, on the basis of best currently available evidence, should probably form the cornerstone of standard hypertension management. ■

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UNE APPROCHE SYNERGIQUE POUR TRAITER À LA FOIS L'HYPERTENSION ET LA DYSLIPIDÉMIE

Les bénéfices sur le plan cardiovasculaire d'une diminution de la pression artérielle sont clairement établis depuis des années. Plus récemment, c'est également devenu le cas pour les bénéfices cardiovasculaires d'une diminution des lipides par les statines dans le cadre d'études spécifiques menées chez des patients hypertendus et dans des sous-groupes de patients hypertendus. Etant donné qu'une pression artérielle élevée et une dyslipidémie sont plus fréquemment concomitantes que ne le voudrait le hasard, il semble logique d'associer chez les patients hypertendus l'amélioration de la pression artérielle à celle des taux de lipides sanguins. L'étude ASCOT-LLA, le bras hypolipémiant de l'étude ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) *a confirmé la logique d'une telle approche : non seulement l'association d'antihypertenseurs A+C (inhibiteur de l'enzyme de conversion + inhibiteur calcique) s'est montrée indépendante et supérieure en termes de bénéfices sur la prévention cardiovasculaire à l'association standard B+D (bêtabloquant +/- diurétique thiazidique), mais les effets supérieurs de l'atorvastatine par rapport au placebo ont également été démontrés. Les effets combinés de l'amlodipine +/-périndopril plus atorvastatine dans l'étude ASCOT-LLA sont importants et incontestables et suggèrent une réelle synergie entre ces deux traitements dans la prévention des événements coronaires. Par ailleurs, les recommandations dans la prise en charge de l'hypertension, basées sur les meilleures données actuelles, sont de plus en plus en faveur d'une association A+C, afin d'optimiser la prévention cardiovasculaire chez les hypertendus, et de l'utilisation des statines pour une proportion significative des hypertendus. Il est urgent de prendre des mesures pour mettre en œuvre de meilleures pratiques, avant que l'augmentation globale et attendue de la prévalence et du nombre absolu d'hypertendus ne se traduise par un fardeau cardiovasculaire encore plus lourd qu'il ne l'est actuellement.*

Treating both hypertension and dyslipidemia: a synergistic approach

A COMMENTARY
SIX YEARS LATER!

by N. R. Poulter, *United Kingdom*

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Most of the reported results, on which the 2013 article was based, remain valid despite the new information that has arisen in the last 6 years. However, one fundamental change since 2013 is the newly-proposed definition of hypertension, which arose because, in the 2017 American guidelines,[1] hypertension is defined as a systolic blood pressure (SBP) ≥130 mm Hg or a diastolic blood pressure (DBP) ≥80 mm Hg. Importantly, the more recent European guidelines[2] have not supported this proposal, leaving the definition of hypertension as ≥140 mm Hg and/or ≥90 mm Hg.

In the abstract of the 2013 article, the use of "A+C" BP–lowering agents (ie, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs]+ calcium channel blockers [CCB]) was described as being increasingly recommended in the guidelines. While true at the time, the latest 2018 ESC/ESH guidelines[2] recommended "A+C" or A+D" (D=diuretic) as alternative optimal combinations of therapy while the US guidelines[1] recommend any two of five different classes of agents (excluding ACE inhibitors plus ARBs) as possible combinations.

The major changes in practice to take place or at least that have been recommended since 2013 might be summarized as "more of the same" in that both BP and lipid lowering has become more assertive. In terms of BP lowering, the trend is for lower BP thresholds for treatments (especially in the American guidelines[1]) and lower BP targets.[1,2] As for lipid lowering, the quotes from the British and European guidelines in relation to the use of statins in the hypertensive population were made in 2004 and 2003, respectively, and were largely based on the results of the ASCOT-LLA trial (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm).

Since then, the NICE guidelines on lipid lowering from 2014[3] recommended the use of statins for those with an estimated 10-year cardiovascular risk of >10%. This risk threshold has halved since the 2003 and 2004 guidelines and, furthermore, the baseline daily dose of atorvastatin recommended for primary prevention is 20 mg – twice the dose used in the ASCOT-LLA trial! As mentioned in the 2013 article, the absolute benefits of atorvastatin in the hypertensive population would likely be even bigger than those observed by using higher doses of atorvastatin (more than the 10 mg used in ASCOT) and by administering the drug to those with worse lipid profiles than those included in ASCOT-LLA (those with a total cholesterol >6.5 mmol/L [>250 mg/dL] were excluded). As outlined in the 2018 ESC/ESH guidelines,[2] more recent trial data (JUPITER [Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin] and HOPE-3 [Heart Outcomes Pre-

vention Evaluation]) justify using statins in patients at moderate-to-high cardiovascular risk, but without established disease. Furthermore, lower target low-density lipoprotein cholesterol (LDL-C) levels are now recommended depending on initial risk status and baseline LDL-C.

The possibility of a real synergistic beneficial effect of amlodipine and atorvastatin on preventing coronary events remains valid, although I am unaware of any further data that confirms or refutes the work of Preston Mason, which provided a potential mechanism for this interaction.[4] In 2013, I suggested that the mechanism whereby amlodipine±perindopril produced superior cardiovascular protection over atenolol±bendroflumethiazide in the BP–lowering arm (BPLA) of the ASCOT trial (over and above a marginally higher BP reduction) appeared to be attributed to differential effects of the two combinations on long-term BP variability.

However, that link with BP variability is rarely referred to, whereas the differential effects of the two combinations on central BP, as reported in the CAFÉ study (Conduit Artery Function Endpoint)[5] is frequently quoted as providing good evidence of the differential impact of central BP on cardiovascular outcomes in the two BP–lowering groups in ASCOT. In fact, unlike the BP variability data, there was no such direct evidence in ASCOT-BPLA.

In the year following the ASCOT trial, there was a cadre of physicians reluctant to abandon β-blockers as one of the first-line agents for BP lowering. Their argument – frequently voiced all over the world – was that the newer generation β-blockers would have performed better than atenolol and therefore these newer agents should be retained as first-line treatments for hypertension. The counter argument, which I favor, is that while the various β-blockers do differ in several ways, there is no randomized trial evidence to support the use of any of the new β-blockers in the management of hypertension. The other frequently quoted belief that β-blockers should be used preferentially in the context of hypertension associated with a tachycardia had already been seriously challenged by the data arising from ASCOT.

In the summary of the earlier paper, I quoted the 2011 NICE guidelines[6] by highlighting that the "prime motivation for treatment in hypertension as an asymptomatic condition, is the prevention of mortality and morbidity." This statement remains equally true in 2019 and it should be remembered by those who would focus their BP management on the impact of their agents on various degrees of proteinuria.

Finally, the concluding paragraph of the summary reiterates that "A+C" plus a statin should be the routine "cornerstone of standard hypertension management." This statement remains a reasonable and tenable position, 6 years later. What has received increasing emphasis in that time, particularly in the latest European[2] and US[1] guidelines, is that, for hypertension (using the ≥140/90 mm Hg definition), two drugs should probably be used initially for most hypertensive patients and ideally as a single-pill combination. ■

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