Supplementary Material

On re-analysis of the three meta-analyses [9-11] following publication of the ASCOT-BPLA trial[8] , we found an inconsistency amongst trials that were either included or excluded by the respective meta-analyses. Of note none of the analyses took into account blood pressure differences, which is an important omission as may explain discrepancies in the relative risk reduction which could be accounted for by BP differences. We therefore present here a sensitivity analysis using the Lindholm et al.[9], analysis as a baseline, and including first trials that this analysis excluded (VAACS/AASK/CAAP [S1-3]), second by excluding trials from Lindholm et al., where there is non-random allocation to β-blockers[S3-6] , rather random allocation was to the "conventional" drug, where the treating physician was allowed to choose between diuretics or β-blockers and third present an analysis that includes all the randomised studies. All analyses are based on stroke as an outcome, as this was the major factor in informing the change in guidance with respect to pharmacological management of blood pressure. In parallel with these outcome based analyses we also present changes in systolic blood pressure which can account for the differences seen in relative risk of stroke. Trial by trial analyses for stroke and BP are shown in **Supplementary Figure 1**, and these are summarised in **Supplementary Figure 2**.

Supplementary Methods

Meta-analysis

Search Strategies: References within the cited meta-analyses[9-11] were used to extract data from and carry out the meta-analyses, to specifically assess the change in the relative risk estimate of stroke by adding or taking away studies either included or excluded by published meta-analyses. Data extracted included study design (details of

mean follow up, if intention to treat analyse were used, procedures of randomisation), number of patients per arm, outcomes of stroke, myocardial infarction and all cause mortality. Data was extracted by two independent researches (RS and JPC). Blood pressure measures collected were those pre-treatment and those at the end of the trial duration. For ASCOT-BPLA the average BP difference reported over the course of the trial was used for analyses.

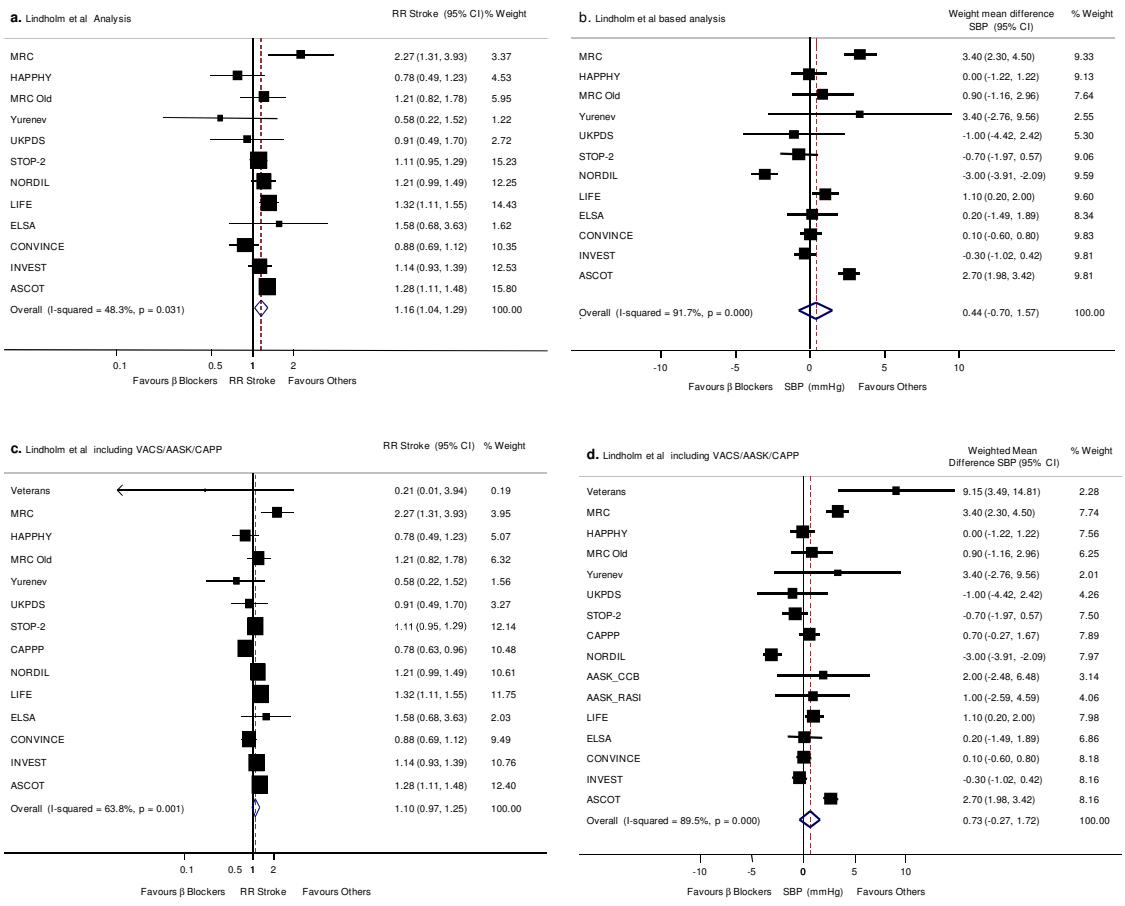
Statistical analysis: The effect of β-blockers on blood pressure was calculated by the difference in the change in mean values between the beta blocker arm and the alternative treatment regime. Blood pressure values and standard deviations (SD) were used for these calculations, where SDs were not given, SDs from the largest study were used. Study specific estimates were weighted by the inverse of the variance and pooled by random effects meta-analysis to generate summary effects. Similarly for outcomes, β-blockers were compared to other treatment regimes and summary relative risks for outcomes of stroke, MI and all cause mortality were estimated using random effects meta-analysis.

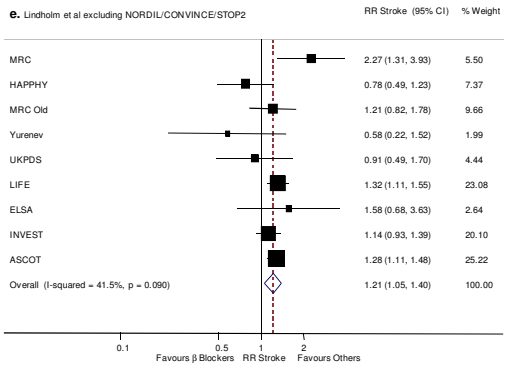
Overlapping distributions: Reported means and SD from the ASCOT-BPLA trial were used to generate overlapping distribution curves, to assess the difference in the actual levels of glucose in both treatment arms and to calculate an odds ratio from this. Post treatment glucose levels were calculated from addition of the change from baseline to final visit to the baseline levels. Standard deviations of the post treatment glucose were not reported, and therefore pre-treatment SDs were used and were assumed to be equal (SD=2.12 was used for calculations). Distributions were assumed to be normal. These summary data (means and SDs) were then used to construct normal distributions of

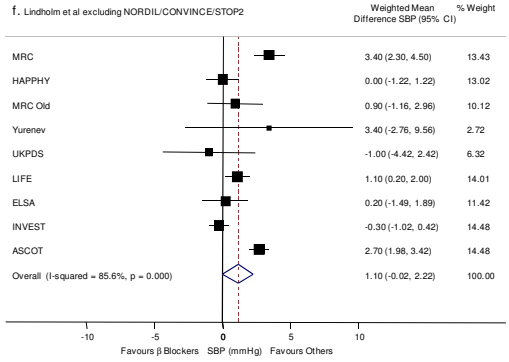
glucose for those treated with the amlodipine based regime and those treated with the beta blocker based regime. Odds ratios were estimated as described in Wald NJ et al 1999[(S7).] In brief, taking 7 mmol/ l as the cut off for diagnosis of diabetes, the proportion of individuals over this level was calculated using standard one tailed z tables. Odds of those affected compared to those unaffected for each treatment group was compared and were then used to generate odds of developing diabetes in those treated with the atenolol based regime compared to those treated with amlodipine based regime.

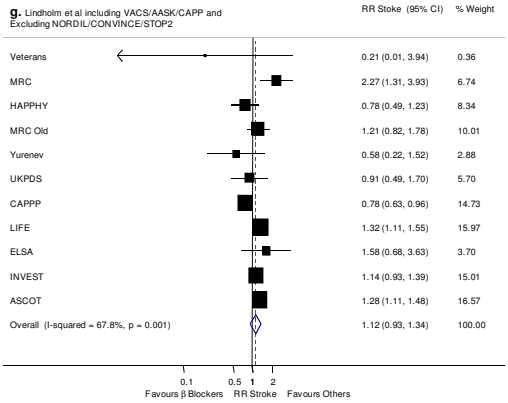
Supplementary Figure 1

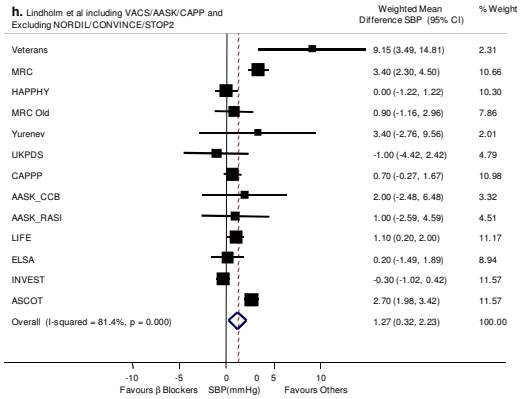
The left hand panel of forest plots shows relative risk of stroke, the right hand panel shows weighted mean difference in Systolic blood pressure in the same studies, an analysis which was not included in previously published meta-analyses. The baseline analysis considered here is the Lindholm et al analysis, which is shown in Figures 1a and b, sensitivity analyses are then performed based on this as a baseline, first to include studies that were excluded in Lindholm et al (VACS, AASK, CAPP) Figures 1c and d; second, based on Lindholm et al but excluding studies where treatment allocation was non randomised (NORDIL/ CONVINCE and STOP2) in Figures 1 e and f, and finally randomised studies in one analysis Figures 1g and 1h.







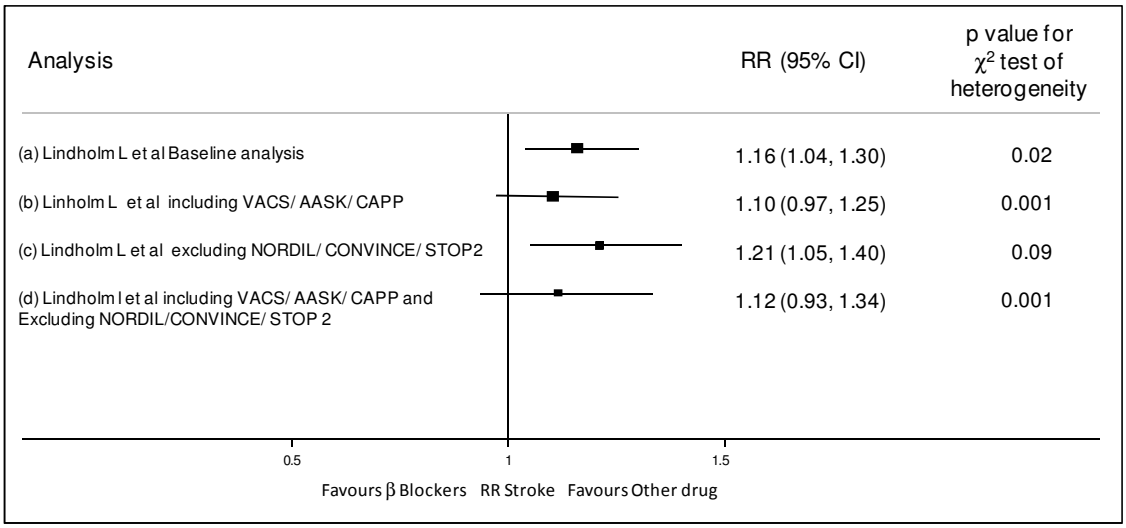




AASK African American Study of Kidney Disease and Hypertension, CAPPP Captopril Prevention Project, NORDIL Nordic Diltiazem Study, CONVINCE Controlled Onset Verapamil Investigation of Cardiovascular Endpoints, STOP2 Swedish Trial in Old Patients with Hypertension, VACS Veterans Administration Cooperative Study

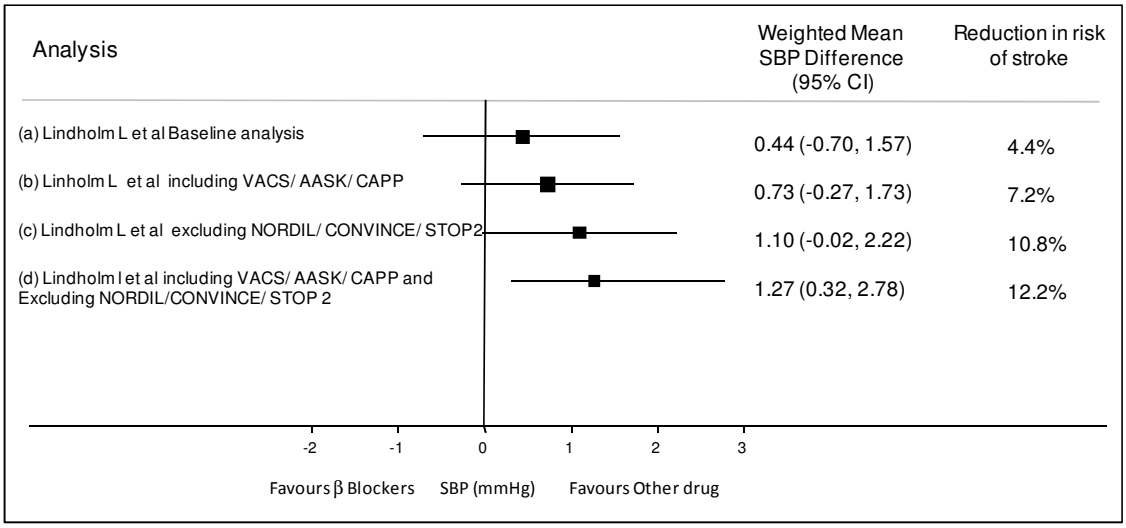
Supplementary Figure 2a

Summary plots of the pooled risk ratio for stroke in trials of beta-blockers varies depending on the trials included/ excluded in the analyses



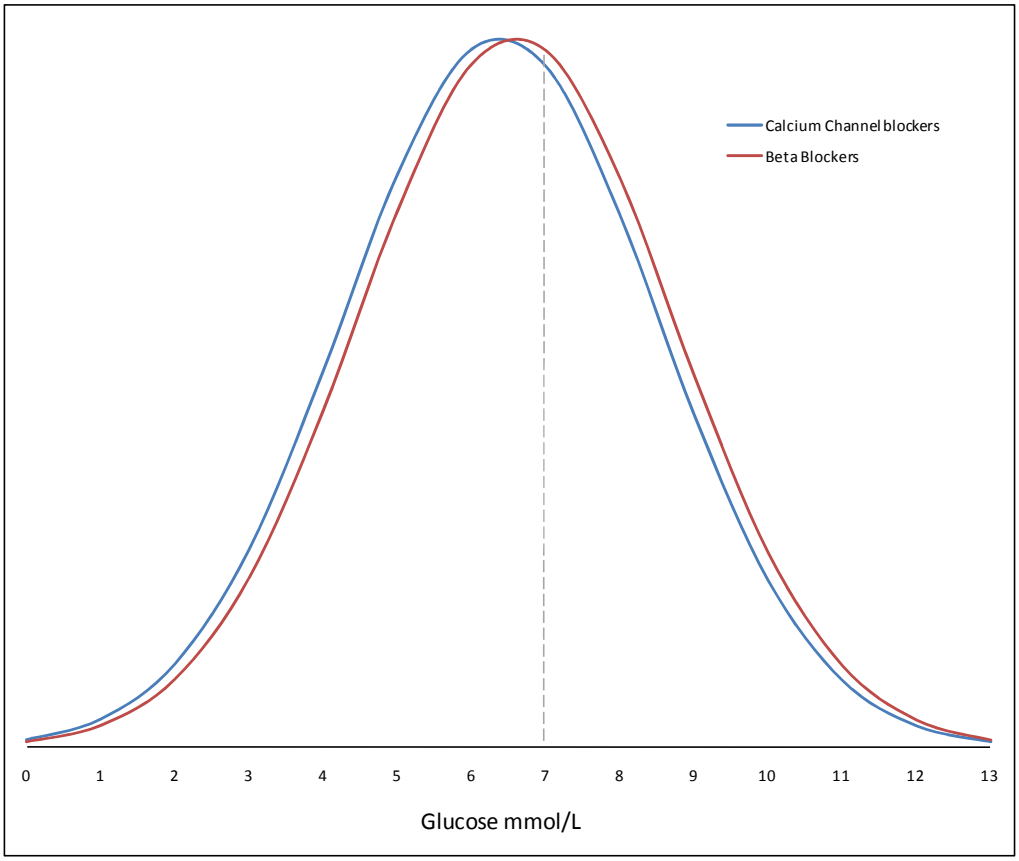
Supplementary Figure 2b

Summary plot of the difference in systolic blood pressure (SBP (mmHg) corresponding to the stroke end-point analysis reported in Figure 2a. In all scenarios, the BP difference favours the comparator drug over β-blockers. Percentage reduction in stroke risk is calculated from what is expected from the calculated blood pressure difference (see Staesson et al 2005, Reference 13 in main manuscript)



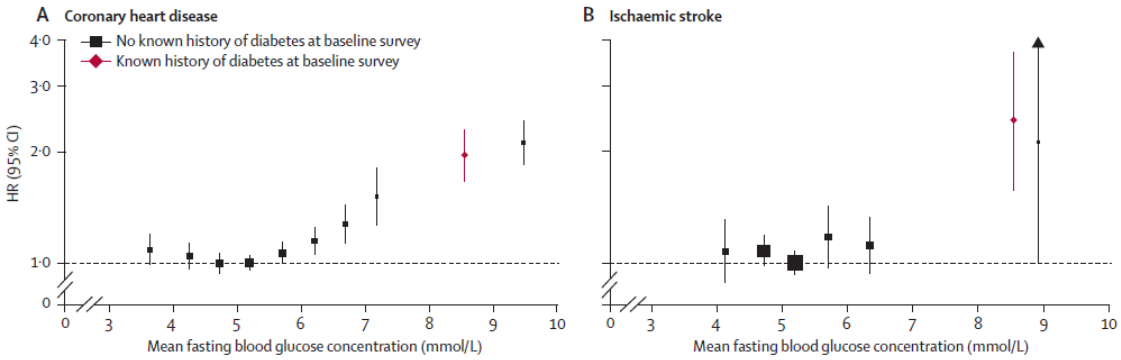
Supplementary Figure 3

Estimated distribution of on treatment blood glucose values in patients randomised to amlodipine and atenolol in the ASCOT-BPLA trial based reported mean (SD)[8] . The relative odds ratio of diabetes in those taking β-blockers *vs* amlodipine, using a cut off of 7 mmol/l glucose for the diagnosis of diabetes is 1.18. The reported relative risk for diabetes was 0.70 (95% CI 0.63, 0.78) in favour of the amlodipine based regime.



Supplementary Figure 4

Non-linear relationship between mean fasting blood glucose and risk of CHD or stroke from the Emerging Risk Factors Collaboration[21]



Supplementary references:

S1 Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *Jama* 1982;248(16):2004-11

S2 Wright JT, Jr., Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *Jama* 2002;288(19):2421-31.

S3 Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353(9153):611-6.

S4 Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *Jama* 2003;289(16):2073-82.

S5 Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;356(9227):359-65.

S6 Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354(9192):1751-6.

S7 Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *Bmj* 1999;319(7224):1562-5.