

**DETERMINANTS OF NEW-ONSET DIABETES AMONG 19,257
HYPERTENSIVE PATIENTS RANDOMISED IN THE ASCOT-BPLA
TRIAL AND THE RELATIVE INFLUENCE OF ANTIHYPERTENSIVE
MEDICATION**

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Running Title: Determinants of NOD among hypertensive patients

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ABSTRACT

Objectives: To determine the baseline predictors of new-onset diabetes (NOD) in hypertensive patients, and to develop a risk score to identify those at high risk of NOD.

Research Design and Methods: Among 19257 hypertensive patients in ASCOT-BPLA that were randomised to receive one of two antihypertensive regimens: atenolol ± thiazide or amlodipine ± perindopril, 14120 were 'at risk' of developing diabetes at baseline. Of these, 1366 (9.7%) subsequently developed NOD during median follow-up of 5.5 years. A multivariate Cox model was developed to identify the independent predictors of NOD, and individual risk scores

Results: NOD was significantly associated with increase in baseline fasting plasma glucose (FPG), BMI, serum triglyceride and systolic blood-pressure (SBP). In contrast, amlodipine ± perindopril in comparison with atenolol ± thiazide treatment (HR 0.66 95%CI 0.59 to 0.74), high HDLc, alcohol use and age >55 years were found to be significantly protective factors. FPG was the most powerful predictor with risk increasing by 5.8 times (95%CI 5.23 to 6.43) for each mmol/l rise above 5 mmol/l. Risk of NOD increased steadily with increasing quartile of risk score, with a nineteen-fold increase (95% CI 14.3 to 25.4) among those in the highest compared with those in the lowest quartile. The model showed excellent internal validity and discriminative ability.

Conclusions: Baseline FPG >5mmol/l, BMI and use of an atenolol ± diuretic regimen were among the major determinants of NOD in hypertensive patients. The model developed from these data allows accurate prediction of NOD among hypertensive subjects

Observational data suggest that hypertension is a risk factor for type 2 diabetes¹ and hence the two conditions frequently coexist. The increased propensity of the hypertensive population to develop diabetes is variably affected by different classes of antihypertensive medication. Recently results of a network meta-analysis, using data from 22 clinical trials comprising of 143,153 participants who did not have diabetes at randomisation, suggest that the association between antihypertensive agents and incident diabetes is lowest for angiotensinogen-receptor blockers (ARB) and ACE inhibitors followed by calcium-channel blockers (CCB) and placebo, with beta-blockers and diuretics increasing risk². The diabetogenicity of beta-blockers and diuretics, is consistent with their adverse impact on blood glucose levels, which has been reported for several decades.³⁻⁵ In contrast with the adverse effects of diuretics^{3 6 7} and beta-blockers⁸ on the incidence of NOD in randomised trials, the bulk of trial evidence suggests that drugs which block the renin angiotensin system exert a protective role against the development of NOD.^{2 9 10} These differential effects have influenced recommendations for antihypertensive drug sequencing contained in British guidelines,^{11 12} whilst the extensive use of beta-blockers and diuretics – often in combination - continues worldwide, in part because of controversy regarding whether there is any cardiovascular toll associated with antihypertensive-associated incident diabetes¹³⁻¹⁶. This controversy notwithstanding little is known about the other baseline predictors of NOD in hypertensive populations and the importance of antihypertensive therapy relative to these variables.

Since NOD was a pre-defined tertiary endpoint of the blood-pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA)^{17 18} its database provides an excellent opportunity

to evaluate baseline predictors for development of NOD among a large hypertensive population

RESEARCH DESIGN AND METHODS

Details of the methods used and the main results of the ASCOT-BPLA trial have been described previously^{17 18}. Briefly, 19257 hypertensive patients, aged 40-79 years, with three or more cardiovascular risk factors but without any previous coronary heart disease were randomised using prospective randomised open blinded endpoints design to receive one of two antihypertensive regimens :atenolol adding a thiazide diuretic as required (atenolol-based regimen) or amlodipine adding perindopril as required (amlodipine-based regimen) to reach blood pressure targets. Subsequently these patients were followed-up with fasting blood samples obtained at 6 months, 12 months, and thereafter annually

Definitions. For the purposes of these analyses, patients were considered potentially to have ‘diabetes at baseline’ if they satisfied any one of the following three sets of criteria:

1. FPG ≥ 7 mmol/l or random glucose ≥ 11.1 mmol/l at randomisation or screening visits.
2. Self-reported history of diabetes and receiving drug or dietary therapy for diabetes.
3. Presence of both impaired fasting glucose (>6 mmol/l and <7 mmol/l) and glycosuria at randomisation or screening visits. This criterion was chosen to avoid misclassification of such people as non-diabetic at baseline when full investigation with an oral glucose tolerance test may well have revealed diabetes.

Those included in one or more of these three groups were therefore excluded from the population considered to be ‘at risk’ of developing NOD in these analyses. Development of diabetes (NOD) during follow-up was diagnosed on the basis of the 1999 WHO criteria.¹⁹

Statistical methods. STATA 9 software was used for all statistical analyses. The impact on the development of NOD of demographic, clinical and laboratory data at baseline was assessed using the Cox proportional hazards model. Approximately 10% of subjects at baseline had non-fasting values of either triglyceride or glucose or both, and were excluded for the purpose of our main analysis.

Baseline characteristics among those who developed NOD were compared with those who did not. For each of the baseline characteristics, a univariate Cox model was used to estimate the hazard (risk) ratio and confidence interval for development of NOD.

Multivariate Cox regression models were developed using forward stepwise selection ($p < 0.05$ for inclusion) with age, sex and randomised blood-pressure (BP) treatment group as pre-specified covariates in all models. All baseline variables were considered for inclusion in the multivariate model. Three continuous variables viz. age, FPG and BMI showed some evidence of non-linearity at extreme values. However, these were retained as continuous variables in the model with appropriate cut-off values to account for non-linearity. Three multivariate Cox models were built: model-1 including all 12692 patients with known values (1212 cases of NOD); model-2 including patients with known values who were randomised to the atenolol-based treatment group ($n=6321$, cases=705); model-3 including patients with known values who were randomised to the amlodipine-based group ($n=6371$, cases=507).

Model-1 was taken forward as the primary model to develop a risk score and to test any pre-specified interactions between the treatment groups and other variables. The risk score for each patient was calculated from the primary model by summing the products of the coefficients derived from the primary model, and the actual values of the variables in the model. The distribution of risk scores was then divided into quartiles of

increasing risk, and calibration of the model was evaluated by comparison of the plots of the actual and predicted outcomes. Bootstrap resampling (100 repetitions) was used to assess the internal validity of the primary model.

RESULTS

Out of 19257 hypertensive patients randomised to ASCOT-BPLA, 14120 were considered to be at risk of developing NOD at baseline (fig-1). Of these, 1366 subsequently developed NOD during an accumulated follow-up of 73,425 years (median follow-up 5.5 years; incidence rate of 18.6 per 1000 patient years).

Baseline characteristics. Baseline characteristics in the at-risk population were well-matched among those randomised to the two BP-lowering regimens (Table-1). In each of the two treatment groups compared with those who remained non-diabetic, those who developed diabetes were also much more likely to be younger with higher BMI, FPG, pulse rate, diastolic BP and serum triglyceride levels and lower HDL-cholesterol levels. However some differences were apparent between those who did and did not develop diabetes in each of the two BP-lowering treatment groups e.g. prevalence of current smoking

Risk factors for the development of diabetes. On univariate analysis (appendix table-A), patients allocated to amlodipine-based regimen were 31% less likely to develop NOD compared to those allocated the atenolol-based regimen (HR 0.69 95% CI 0.62 to 0.77) and for each unit rise in HDL-cholesterol or total cholesterol the risk of NOD fell by 61% and 8% respectively. In contrast, for each 5 unit rise in BMI or 10mmHg rise in baseline SBP the risk of NOD increased by 42% and 6% respectively. Presence of micro-albuminuria, >3 cardiovascular risk factors, and higher levels of serum triglyceride, diastolic BP and heart rate at baseline were among other notable and significant risk factors for NOD. However, the largest impact on risk of NOD was that induced by

FPG level which was associated with a greater than 5-fold increase in risk for each 1mmol/l increase.

On multivariable analysis (model 1; n =12692), higher levels of FPG, BMI, serum triglyceride, SBP and concomitant use of non-cardiovascular medication were found to be significant risk factors for NOD at baseline. In contrast, amlodipine-based treatment (HR 0.66 95%CI 0.59 to 0.74), higher total and HDL-cholesterol levels, alcohol use, and age >55 were found to be significantly protective factors. FPG was again the most powerful predictor with risk increasing by 5.8 times (95%CI 5.23 to 6.43) for each 1mmol/l rise above 5 mmol/l. Risk increased by 49% and 12% for each 5 unit increase in BMI (up to 35kg/m²) and 1 mmol/l increase in serum triglyceride levels respectively, whereas randomisation to amlodipine-based treatment and increase in baseline HDL by 1 mmol/l reduced the risk by 34% and 28% respectively.(Table-2).

On multivariable analysis based on treatment allocation, the predictors for NOD among those randomised to atenolol-based (model 2) and amlodipine-based (model 3) treatment groups were essentially similar to that of the primary model, however some differences were apparent (table-B). For example whilst FPG, BMI, total cholesterol, SBP, and age were significant predictors in both BP treatment groups, raised serum triglycerides was a major predictor only among those randomised to the atenolol-based regimen (HR1.24, 95%CI 1.17 to 1.32). Conversely raised HDL-cholesterol (HR 0.55, 95% CI 0.51 to 0.75), alcohol intake, baseline heart rate and smoking were significant predictors only among those randomised to the amlodipine-based regimen. However when these differences between the two treatment groups were evaluated in the primary Cox model, there was no strong evidence of a significant interaction between allocated drug treatment and baseline triglyceride (p=0.09, after excluding an outlier), smoking (p=0.09), HDL-cholesterol (p=0.75), alcohol intake(p=0.25), and baseline heart rate

(p=0.13). Of note, among these potential interactions only that between treatment allocation and serum triglyceride was pre-specified in the statistical analysis plan.

Risk Scores. The β -coefficients, Z-scores and p-values of each of the baseline variables used in the risk score are shown in table-2. Larger values of the Z score (irrespective of the sign) indicate the strength of the variables as a predictor. Fig 2a illustrates the increasing risk of NOD with an increase in risk quartile using Kaplan-Meier plots. Compared to the lowest risk quartile, patients in the highest quartile had a nineteen-fold increase in risk of NOD (HR 19.04, 95%CI 14.27 to 25.41). There was no evidence of an interaction between risk quartile and antihypertensive treatment group when the risk score was calculated without allocated treatment. Fig-2b shows that allocation to the amlodipine-based regimen reduced the risk to the same extent in each risk quartile. The model had an excellent internal validity and reasonably strong discriminative ability (Harrell's c-index of 0.80) (appendix figure-A)

DISCUSSION

These analyses of baseline measures among over 14000 hypertensive patients considered free of diabetes at the start of the ASCOT-BPLA trial¹⁷ indicate that randomisation to antihypertensive treatment, low HDL-cholesterol and raised BMI, serum triglyceride, systolic BP, and particularly FPG are important determinants of NOD. The relative importance of each of the determinants of incident diabetes is implied by increase in Z-score regardless of its sign (Table-2).The risk model thus developed allows the accurate prediction of NOD over a 5 year period for an individual. The more than 5-fold increase in risk of NOD for each mmol/l rise in FPG reported in this paper is larger than observed in most⁸¹⁰but not all²⁰ earlier reports. In contrast to some earlier studies⁸ the exclusive use of fasting glucose, and unambiguous, robust definitions may have contributed to the large effect size observed. The putative

effects of FPG were linear and apparent from 5mmol/l onwards - a threshold for incremental risk which has previously been identified.²¹ The risk attenuated progressively through the trial with the effect reducing from a hazard ratio of 9.72 (95% CI, 8.06 to 11.72) during the first year to 1.88 (95% CI 1.25 to 2.83) after 5 or more years of follow-up. This trend may reflect the attrition of subjects susceptible to developing NOD.

These results are coherent with most other analyses of trials using antihypertensive agents – in finding that a regimen based on a calcium channel blocker to which an ACE inhibitor was added, was associated with significantly less NOD than a regimen based on a beta-blocker to which a diuretic was usually added.^{3 9} Indeed the randomisation to amlodipine-based regimen emerged as the strongest protective factor of those variables evaluated. The finding that the differential risk of NOD between the two antihypertensive regimens remained the same irrespective of baseline risk (Fig 2b), contrasts with results in the CAPPP Trial¹⁰ but is in keeping with findings in the LIFE trial.⁸

Increasing age was an independent protective factor for the development of diabetes which contrasts with some¹⁰ but not all trial results²² and is consistent with several observational studies^{23 24} which have show that while the prevalence continues to increase with age, the incidence of diabetes plateaus in the elderly.

Our study is consistent with several other observational studies in finding alcohol intake to be protective^{25 26} and raised triglycerides to be a putative risk factor for NOD.^{27 28} Somewhat counter-intuitively raised total cholesterol appeared to be protective in these analyses, although this too has been reported in other trials.^{8 10} The increased risk associated with concomitant use of one or more of non-cardiovascular medications, including some that are known to be diabetogenic, may reflect or be a marker of chronic ill health.

The conduct of several previous analyses relating to NOD have been subject to methodological criticism^{9 29} such as being post-hoc, using different definitions of NOD and use of non-fasting and/or whole blood glucose values, but most of these criticisms do not apply to the current study design and analyses. This study demonstrates the relative importance of antihypertensive therapy—after FPG and BMI—and, suggests that their judicious use will benefit all regardless of risk category. These analyses allowed the development of a relatively simple risk score for predicting NOD. This score appears to have excellent internal validity and pending further external validation, could be potentially useful in routine clinical practice to guide not just prescribing of antihypertensive medication, but other interventions aimed at preventing NOD.

Given evidence from previous trials^{2 9 30} it seems likely that the differential effect of the two antihypertensive regimens used in ASCOT-BPLA on NOD is a composite of the adverse effects on risk produced by the atenolol and thiazide, plus the protective effects of perindopril, with amlodipine probably playing a neutral role. However recent analyses of the DREAM trial³¹ in contrast to the HOPE trial³² did not show a significant protective effect of ramipril against NOD. Nevertheless, 2-hour glucose levels were significantly improved among those taking ramipril in the DREAM trial which, allied to the 9% non-significant reduction in NOD, suggest that the apparently ‘negative’ findings in DREAM may reflect inadequate power to detect an effect in too short a time.

Although those studied in the ASCOT trial were more representative of the general hypertensive population than those in several other recent trials,^{6-8 20 30 32} the population was largely Caucasian and male from the UK, Ireland, and Nordic countries. Whether and to what extent the findings relate to other ethnic groups requires evaluation in other studies. Furthermore, given the large sample size and hence power

of these analyses, the clinical relevance of some of the less significant relationships needs to be considered when interpreting the results.

Further analyses evaluating the effects of changes in baseline variables (e.g. body weight, BP etc) throughout the trial are in progress, as are analyses evaluating whether worsening dysglycaemia and NOD are associated with worsening cardiovascular outcomes are in progress. Whilst these analyses may inform policy decisions on prescribing for hypertensive patients, the limited power of such analyses with relatively limited follow-up hampers appropriate interpretation of such data, and possibly explains earlier conflicting results¹⁴⁻¹⁶

In summary, the present analyses provide robust evidence that treating hypertensive patients with regimen based on amlodipine and perindopril in comparison to a regimen based on atenolol and thiazide diuretic significantly reduces the risk of NOD such that the number needed to treat of 30 patients for just over 5 years is required to prevent one case of NOD

(95%CI 23 to 42). It further describes a robust, discriminative model, which helps to determine accurately the risk of NOD in hypertensive patients, and highlights the relative importance of various other independent predictors such as FPG, BMI, SBP, serum HDL-cholesterol and triglycerides, in the development of NOD. Pending further definitive evidence related to cardiovascular morbidity and mortality with antihypertensive-associated incident diabetes, it seems at best unwise, except where compelling indications apply, to use beta-blockers and diuretics in combination in preference to other combinations such as CCB plus an ACE inhibitor, particularly since the latter agents have been shown to be more cost-effective.¹¹

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LEGENDS

Table 1. Baseline characteristics in the at risk population (n=14120) by treatment group and development of new onset diabetes (percent / mean± SD)

*Comparison between those who developed diabetes and those who remained non-diabetic on each of the antihypertensive-treatment group at the end of follow-up: Chi square test or t-test, whichever is applicable

† Including those who smoked within 1 year

‡ Out of 14210 at risk patients, 1428 (10.1%) patients in all had non-fasting values of either triglycerides (n=1392:atenolol-based treatment (n=705) & amlodipine-based treatment (n=687)) or FPG(n=1427:atenolol-based treatment (n=725) & amlodipine-based treatment (n=702) or both

Abbreviations: SD: Standard deviation, H/O: History of, CAD: Coronary artery disease, TIA: Transient ischaemic attack, TC: Total Cholesterol, TG: Triglyceride, PVD: Peripheral vascular disease, LVH: Left Ventricular hypertrophy, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Primary multivariate Cox proportional hazard regression model for the development of new-onset diabetes (Model 1).

* Irrespective of sign, it indicates strength of association, and relative influence. Those with negative signs indicates protective influence in this model

† All those with FBS≤5 mmol/l were given the same risk; hazard ratio is for every subsequent 1 mmol/l rise

‡ All those with BMI ≥35kg/m² were given the same risk BMI=35 kg/m²; hazard ratio is for every 5 kg/m² rise in those with BMI ≤35 at baseline

§ Compared with those on atenolol-based regimen

** Hazard ratio for every 10mm of Hg rise in SBP

†† All those with age ≤55 were given the same risk; hazard ratio is for every subsequent 5 year increase

Figure 1. New onset diabetes development according to the randomised treatment group in ASCOT-BPLA Trial-

Figure 2a. Kaplan –Meier graphs of incidence of NOD stratified by quartiles of risk score with the uppermost quartile divided equally into two as 4a and 4b (cut off at 5-year follow-up)

* Hazard Ratios and 95% confidence interval for each of the risk quartile with 1st quartile as the reference group: 2nd quartile HR=2.5(1.8, 3.5); 3rd quartile HR=5.0 (3.7, 6.9); 4th quartile HR= 19.0 (14.3, 25.4) [4b quartile HR= 9.72 (7.14, 13.25);4a quartile HR= 30.31 (22.64, 40.57)].

Corresponding risk scores for each of the quartile groups: 1st quartile = (<10.26); 2nd quartile = (10.26 – 10.85); 3rd quartile = (10.86 – 11.62); 4th quartile = (≥11.63) [4b quartile = (11.63 – 12.29; 4a quartile = (≥12.30)]

Figure 2b. Kaplan-Meier graph of incidence of NOD stratified by quartile of risk score* and the BP lowering treatment (cut off at 5-year follow-up)

Atenolol-based treatment =solid; Amlodipine-based treatment=dash

TABLE 1. Baseline characteristics in the at risk population (n=14120) by treatment group and development of new onset diabetes (percent / mean± SD)

Baseline Characteristics	Atenolol-based regimen			Amlodipine-based regimen		
	Total (n=7046)	Developed diabetes (n=799)		Total (n =7074)	Developed diabetes (n=567)	
	Percent/mean±SD	Percent/mean±SD	p-value*	Percent/mean±SD	Percent/mean±SD	p-value
Age (years)	62.8±8.6	61.5±8.3	<0.001	62.9±8.5	61.9±8.2	0.006
Male sex (%)	77.9	79.9	0.156	78.2	81.8	0.028
Europeans (%)	96.6	97.1	0.589	96.6	95.9	0.569
BMI (kg/m ²)	28.2±4.3	30.3±4.5	<0.001	28.2±4.4	30.1±4.6	<0.001
Current smoker † (%)	69.7	71.1	0.354	70.1	75.5	0.003
Alcohol intake‡ (units/wk)	8.3±11.9	8.2±11.3	0.72	8.4±11.8	8.1±10.7	0.445
Family H/O early CAD (%)	30.8	33.2	0.123	30.7	28.9	0.338
H/O previous stroke or TIA(%)	11.8	8.9	0.006	11.6	11.5	0.904
H/O previous PVD (%)	6.3	6.4	0.962	6.2	6.0	0.841
Presence of LVH (%)	22.8	20.4	0.083	22.7	22.1	0.697
Presence of microalbuminuria (%)	61.8	66.7	0.002	61.2	64.6	0.084
TC/HDL ratio ≥ 6(%)	24.3	31.2	<0.001	24.6	28.8	0.017
Total cholesterol (mmol/l)	6.0±1.1	5.9±1.1	0.06	6.0±1.1	5.9±1.1	0.03
HDL(mmol/l)	1.3±0.4	1.2±0.3	<0.001	1.3±0.4	1.2±0.3	<0.001
Triglyceride ‡ (mmol/l)	1.8±0.9	2.2±1.1	<0.001	1.8±1.0	2.1±1.1	<0.001
FPG‡ (mmol/l)	5.4±0.7	5.9±0.6	<0.001	5.4±0.7	5.9±0.7	<0.001
Number of cardiovascular risk factors (cf 3 risk factors)						
4 risk factors (%)	31.2	32.8	0.008	31.1	33.5	0.016
>4 risk factors (%)	12.8	15.6		12.5	15.3	
H/O previous anti-HT drug (%)	79.8	80.4	0.66	79.2	79.7	0.754
Non CAD concomitant medication (%)	57.7	61.8	0.012	55.8	57.9	0.295
SBP (mm Hg)	163.6±18.0	164.6±18.3	0.107	163.8±18.0	165.5±18.3	0.017
DBP (mm Hg)	95.4±10.3	96.2±10.8	0.019	95.5±10.3	96.7±10.6	0.007
Heart rate (beats per minute)	70.9±12.3	72.5±12.5	<0.001	71.1±12.5	73.5±13.4	<0.001

*Comparison between those who developed diabetes and those who remained non-diabetic on each of the antihypertensive-treatment group at the end of follow-up: Chi square test or t-test, whichever is applicable

† Including those who smoked within 1 year

‡ Out of 14210 at risk patients, 1428 (10.1%) patients in all had non-fasting values of either triglycerides (n=1392:atenolol-based treatment (n=705) & amiodipine-based treatment (n=687)) or FPG(n=1427:atenolol-based treatment (n=725) & amiodipine-based treatment (n=702) or both

Abbreviations: SD: Standard deviation, H/O: History of, CAD: Coronary artery disease, TIA: Transient ischaemic attack, TC: Total Cholesterol, TG: Triglyceride, PVD: Peripheral vascular disease, LVH: Left Ventricular hypertrophy, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

TABLE 2. Primary multivariate Cox proportional hazard regression model for the development of new-onset diabetes (Model 1).

Baseline characteristics	Hazard ratio	95%confidence Interval	β -coefficient	z-score*	p- value	Contribution to risk score
FPG † (per mmol/l above 5 mmol/l)	5.8	5.24-6.43	1.758	33.55	<0.001	If FPG \leq 5 mmol/l add 8.79 to the score , for FPG >5 mmol/l multiply the value with coefficient , and add
BMI ‡ (per 5 unit)	1.49	1.38-1.62	0.399	9.73	<0.001	If BMI <35 kg/m ² multiply the β -coefficient with BMI/5 and add, & for those with BMI \geq 35 add 2.814
Amlodipine-based regimen §	0.66	0.59-0.74	-0.412	-7.05	<0.001	Subtract β -coefficient if yes
Triglyceride (per mmol/l)	1.12	1.07-1.17	0.109	4.70	<0.001	Multiply β -coefficient with the value of triglyceride, and add
SBP ** (per 10 mm Hg)	1.07	1.04-1.1	0.067	4.19	<0.001	Multiply the coefficient with SBP/10, and add
Total cholesterol (per mmol/l)	0.89	0.84-0.94	-0.118	-3.97	<0.001	Multiply the coefficient with total cholesterol value and subtract
Use of non CAD medication (Yes/No)	1.25	1.11-1.40	0.22	3.69	<0.001	Add β -coefficient if yes
HDL Cholesterol (per mmol/l)	0.72	0.58-0.89	-0.329	-3.07	0.002	Multiply the β -coefficient with HDL value and subtract
Age >55 (per 5 year) ††	0.94	0.90-0.98	-0.061	-2.77	0.006	if Age \leq 55 subtract 0.671 from score, and If Age> 55 multiply β -coefficient by Age/11, and subtract
Alcohol intake (unit/wk)	0.99	0.99-1.00	-0.006	-2.38	0.017	Multiply β -coefficient with units/wk, and subtract
Male sex	0.98	0.84-1.14	-0.025	-0.31	0.75	Subtract β -coefficient if yes

* Irrespective of sign, it indicates strength of association, and relative influence. Those with negative signs indicates protective influence in this model

† All those with FBS \leq 5 mmol/l were given the same risk; hazard ratio is fro every subsequent 1 mmol/l rise

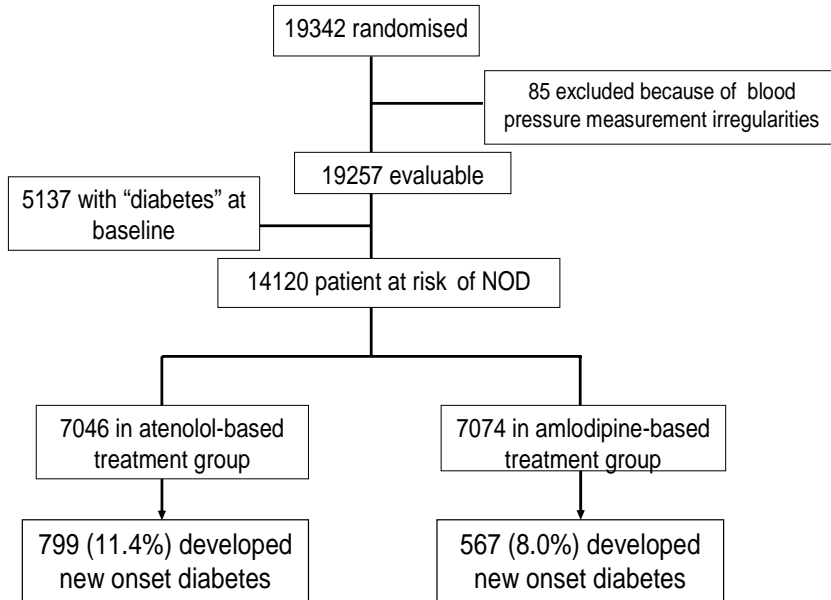
‡ All those with BMI \geq 35kg/m² were given the same risk BMI=35 kg/m²; hazard ratio is for every 5 kg/m² rise in those with BMI \leq 35 at baseline

§ Compared with those on atenolol-based regimen

** Hazard ratio for every 10mm of Hg rise in SBP

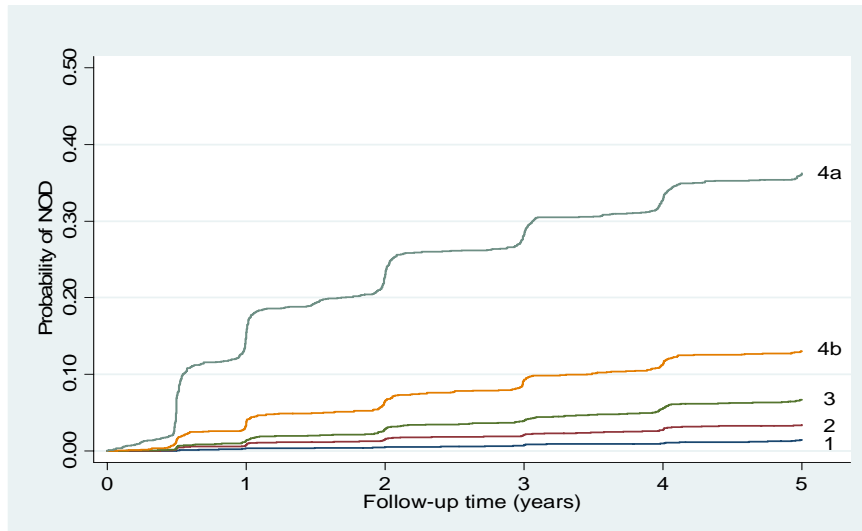
†† All those with age \leq 55 were given the same risk; hazard ratio is for every subsequent 5 year increase

Figure1: New onset diabetes development according to the randomised treatment group in ASCOT-BPLA Trial-



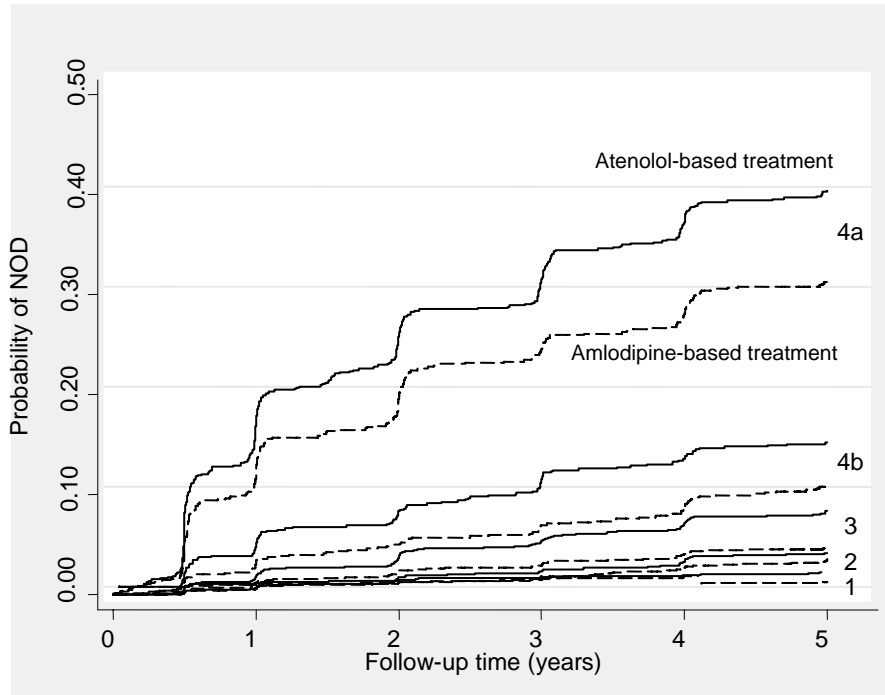
*

Figure2a. Kaplan –Meier graphs of incidence of NOD stratified by quartiles of risk score with the uppermost quartile divided equally into two as 4a and 4b (cut off at 5-year follow-up).



* Hazard Ratios and 95% confidence interval for each of the risk quartile with 1st quartile as the reference group: 2nd quartile HR=2.5(1.8, 3.5); 3rd quartile HR=5.0 (3.7, 6.9); 4th quartile HR= 19.0 (14.3, 25.4) [4b quartile HR= 9.72 (7.14, 13.25);4a quartile HR= 30.31 (22.64, 40.57)].
 Corresponding risk scores for each of the quartile groups: 1st quartile = (<10.26); 2nd quartile = (10.26 – 10.85); 3rd quartile = (10.86 – 11.62); 4th quartile = (≥11.63) [4b quartile = (11.63 – 12.29; 4a quartile = (≥12.30)]

Figure 2b : Kaplan-Meier graph of incidence of NOD stratified by quartile of risk score* and the BP lowering treatment (cut off at 5-year follow-up)



Atenolol-based treatment =solid; Amlodipine-based treatment=dash

* Treatment adjusted for but excluded in the calculation of risk score