

Determinants of new onset diabetes among hypertensive patients randomised in the ASCOT-BPLA Trial

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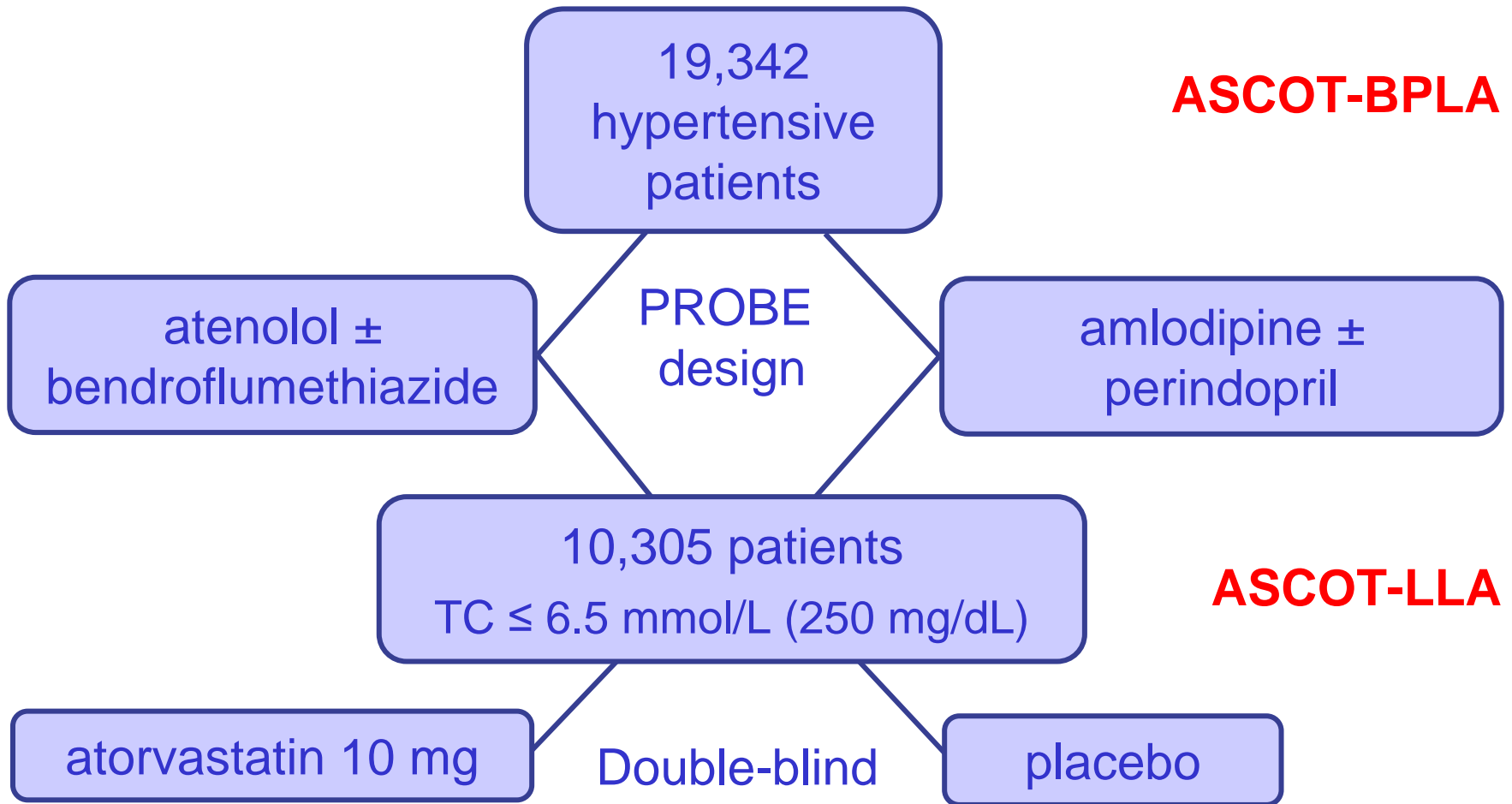
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London

Presented on behalf of the ASCOT Investigators

Background

- Hypertension and diabetes are common co-morbid conditions, and have complex inter-relationships
- Hypertension is an independent risk factor for diabetes development, and increases risk by 2-3 times
- Recent studies have shown that antihypertensive drugs - particularly beta-blockers and diuretics - variably potentiate this enhanced risk
- Controversy still persists because of methodological criticisms of these studies, and lack of robust evidence for increased cardiovascular risk associated with new-onset diabetes

Study design



**Investigator-lead, multinational
randomised controlled trial**

ascot

Objectives

- To determine the predictors of new onset diabetes* (NOD) among hypertensive patients in ASCOT-BPLA
- To develop a risk score to identify those at high risk

* New onset diabetes was a pre-specified outcome in ASCOT

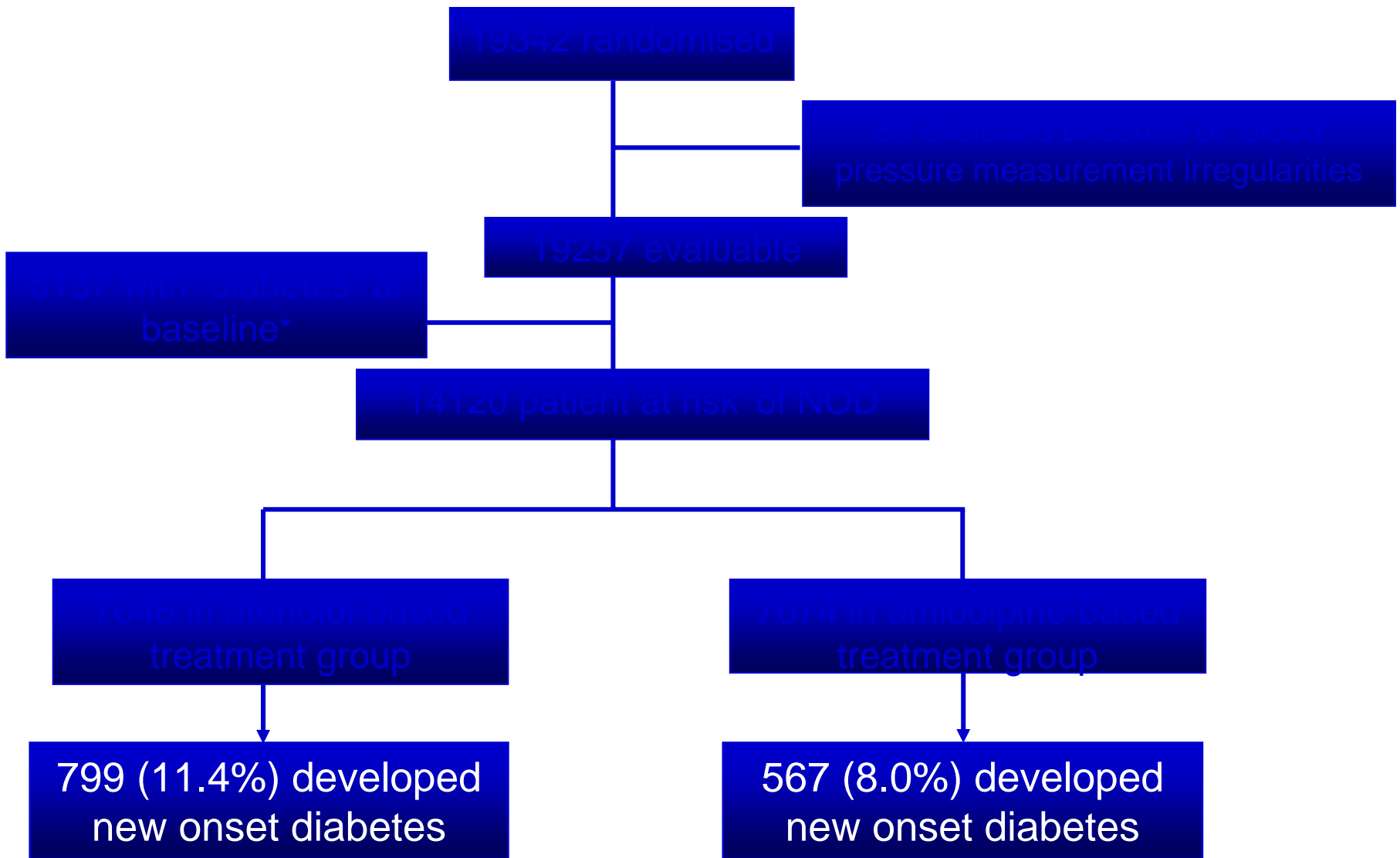
Outcome definitions

- **Baseline diabetes : Presence of one or more of the following criterion**
 1. **FPG ≥ 7 mmol/l and/or random glucose ≥ 11.1 mmol/l**
 2. **Self reported diabetes and receiving dietary or drug therapy**
 3. **Presence of both IFG (≥ 6 mmol/l) and glucosuria in absence of above two criteria** (*endpoint committee exclusion definition*)
- **New onset diabetes : according to WHO 1999 definition**

Methods

- A multivariable Cox proportional hazard regression model was developed using forward stepwise selection ($p < 0.05$) with age, sex and blood pressure treatment group as covariates. The model was assessed for internal validity and discriminative ability
- Based on the Cox model, risk scores for individuals were estimated by summing of the product of the beta-coefficient and the variable value
- Risk scores were divided into quartiles and model calibration was evaluated by comparing the observed outcomes with the predicted outcomes

ASCOT-BPLA: Trial Profile



Baseline characteristics

	At risk population (n=14120)	
	Remain non-diabetic (n=12754)	Develop diabetes (n=1366)
	Percent/mean±SD	Percent/mean±SD
Atenolol-based group (%)	49.0	58.5
Age (yrs)	63.0 ± 8.5	61.6 ± 8.3
Male (%)	77.8	80.7
BMI (kg/m ²)	27.9 ± 4.3	30.2 ± 4.5
Current smoker (%)	69.5	72.9
TC/HDL ratio	4.8	5.1
Total cholesterol (mmol/l)	6.0 ±1.1	5.9 ±1.1
HDL (mmol/l)	1.34 ±0.4	1.23 ±0.3

Baseline characteristics

	At risk population (n=14120)	
	Remain non-diabetic (n=12754)	Develop diabetes (n=1366)
TG (mmol/l)	1.73 ± 0.9	2.11 ± 1.1
FPG (mmol/l)	5.3 ± 0.6	5.9 ± 0.7
>4 risk factors (%)	12.3	15.5
H/O previous anti-HT drug (%)	79.4	80.1
Use of non CAD concomitant medication (%)	56.4	60.2
Previous aspirin (%)	18.9	18.4
Previous lipid lowering drugs (%)	9.0	10.1
SBP (mm Hg)	163.6 ± 17.9	165.0 ± 18.3
DBP (mm Hg)	95.3 ± 10.2	96.4 ± 10.7
HR (beats per minute)	70.8 ± 12.3	72.9 ± 12.9

Multivariable Cox proportional hazard model

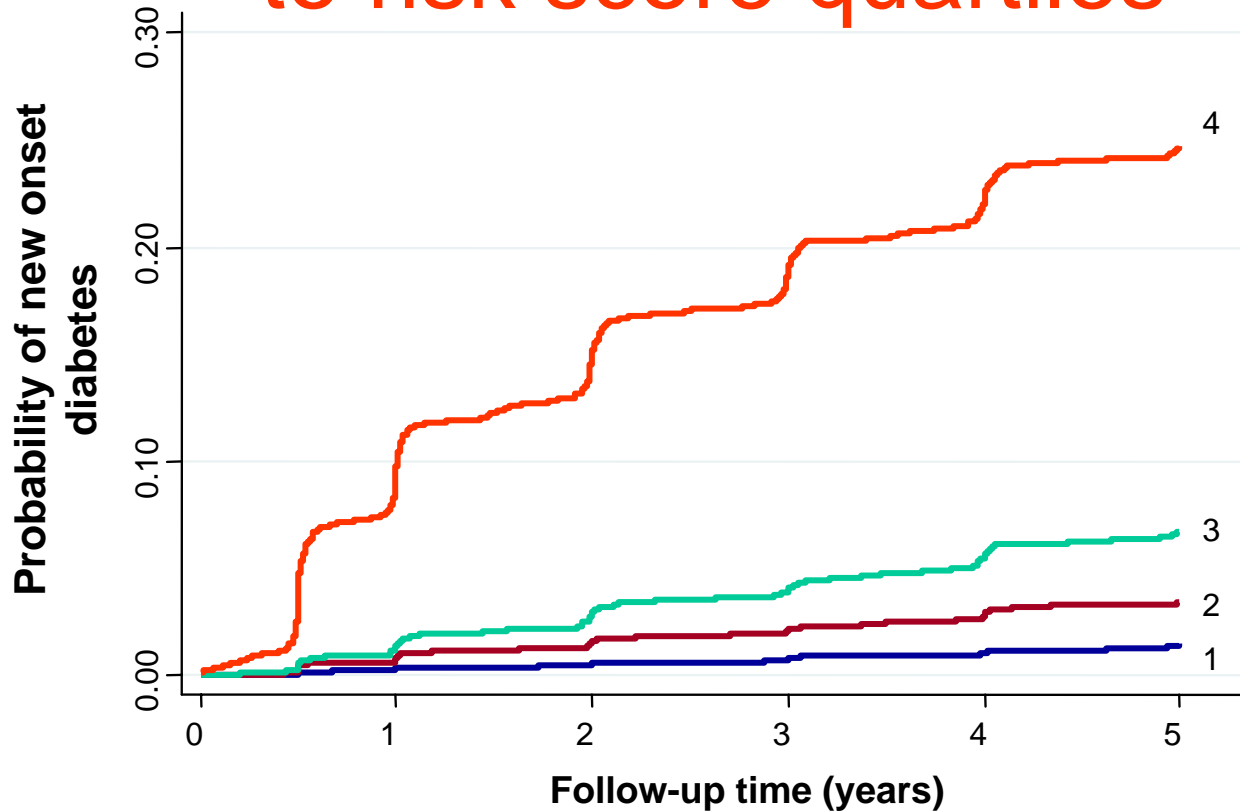
(Primary Cox model n=12692; cases=1212)

	Hazard ratio	95% confidence interval	p-value
Age>55 (per 5 year)	0.94	0.90-0.98	0.006
FBS* (per mmol/l above 5 mmol/l)	5.80	5.24-6.43	<0.001
Male sex	0.98	0.84-1.14	0.750
BMI** (per 5 units increase)	1.49	1.38-1.62	<0.001
SBP (per 10 mmHg)	1.07	1.04-1.10	<0.001
Amlodipine ± Perindopril	0.66	0.59-0.74	<0.001
HDL Cholesterol (per mmol/l)	0.72	0.58-0.89	0.002
Triglyceride (per mmol/l)	1.12	1.07-1.17	<0.001
Total cholesterol (per mmol/l)	0.89	0.84-0.94	<0.001
Use of non CAD medication (Y/N)	1.25	1.11-1.40	<0.001
Alcohol intake (unit/wk)	0.99	0.99-1.00	0.017

* All those having FBS≤5 mmol/l were given baseline risk

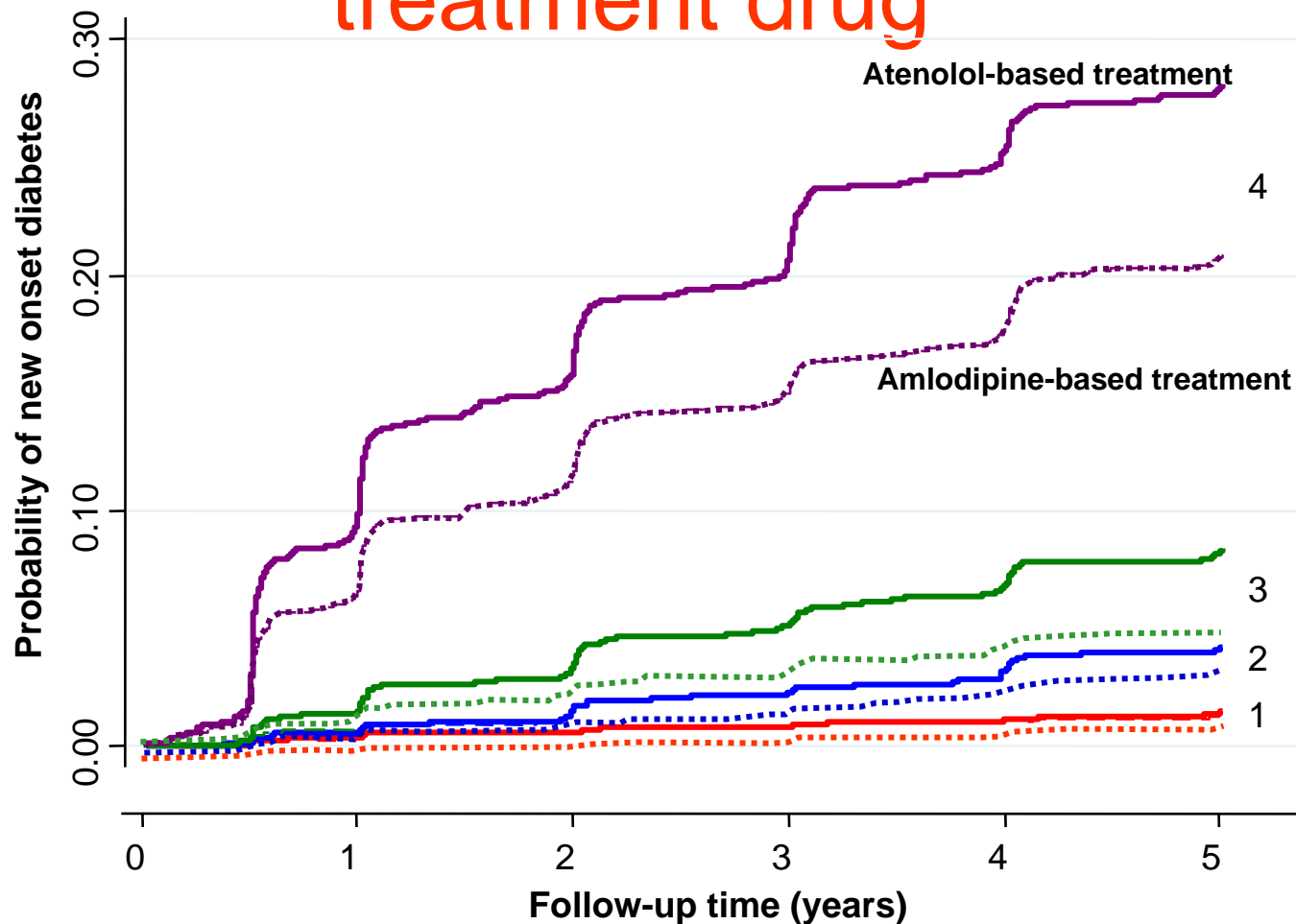
** All those with BMI >35 kg/m² were given similar risk, hazard ratio for every 5 unit rise from baseline

New onset diabetes according to risk score quartiles



Risk quartile	1 st Quartile	2 nd Quartile	3 rd Quartile	4 th Quartile
Hazard Ratio (95% CI)	1	2.5 (1.8-3.5)	5.0 (3.7-6.8)	19.0 (14.3-25.4)

Probability of development of diabetes stratified by quartile of risk score and the treatment drug



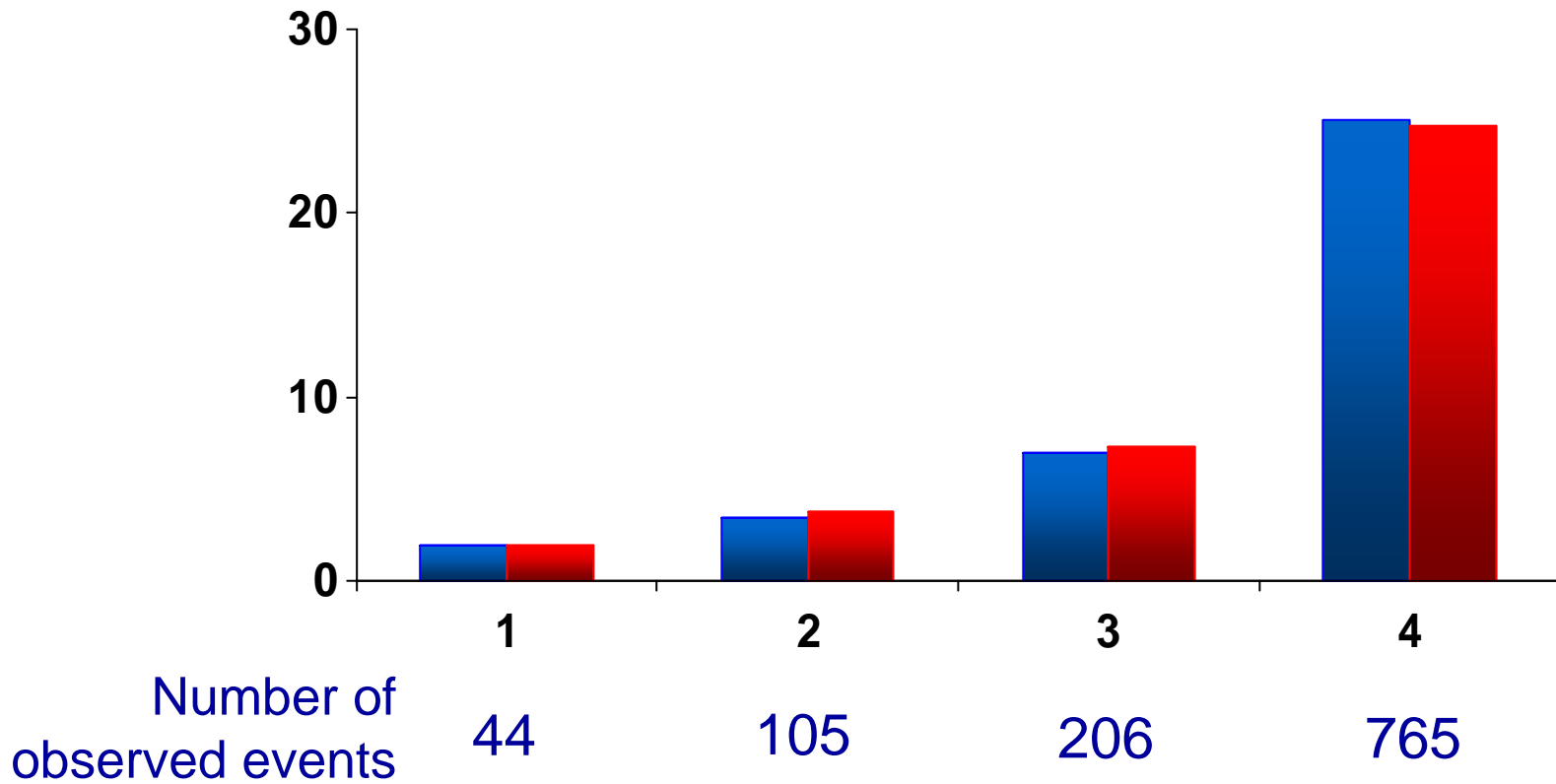
Atenolol ± thiazide =solid; Amlodipine± perindopril=dash



NB: risk score re-calculated by adjusting for treatment but excluded it in risk score calculation

Observed and expected probabilities of the development of diabetes by quartile of risk score in ASCOT

■ Observed ■ Predicted



Summary & conclusions

- FPG, BMI, antihypertensive therapy, HDL-c and triglyceride level are important baseline predictors for development of diabetes
- Compared with use of atenolol \pm thiazide, the use of amlodipine \pm perindopril is associated with 34% reduction in risk of NOD, and this decrease is irrespective of the baseline risk category
- Risk model developed is robust, has an excellent discriminative ability, and potentially could play an important role in clinical practice

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