Adverse Outcomes in Patients Treated with Alpha Blockers for Hypertension Analysis of 19,508 Patients

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Background

- Doxazosin is alpha 1 selective antagonist.
- Its main medical use is for the treatment of hypertension and benign prostatic hypertrophy (BPH).
- Doxazosin has significant hypotensive capability and beneficial effect on lipids and glucose metabolism and only minimal effect on renal function.

Background Cont.

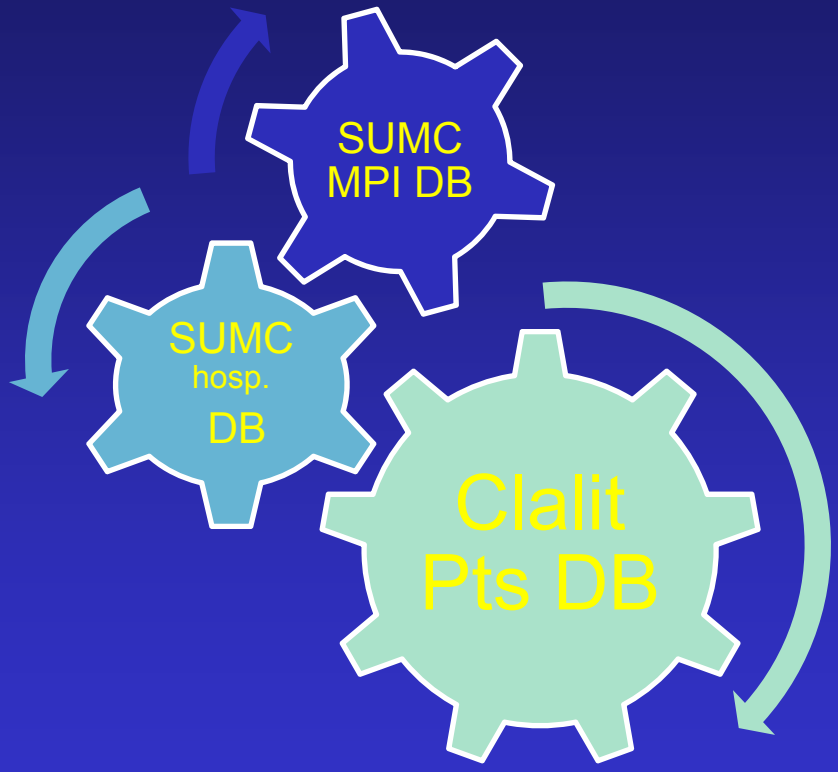
- Yet, in ALLHAT study, Doxazosin was found to be unsafe and.
- The Doxazosin arm was terminated prematurely due to the higher rates of MACE.
- Currently Doxazosin is not recommended as the first line of antihypertensive treatment.
- AB ↔ “J curve” ↔ worsening underlying ischemia.

Aim

- To evaluate the effect of alpha blockers therapy on the outcomes of hypertensive patients who underwent myocardial perfusion imaging (MPI), taking into account the indication for AB treatment and the MPI results.

Methods

Databases



40,502 SPECT MPI studies between the years 1997-2008

Methods
Definitions

- In the current analysis we have included only patients diagnosed with arterial hypertension (HTN) prior to their 1st MPI study.

- HTN was defined as:
  - Computerized diagnosis of HTN in the medical records.

    Or
  - Purchased medications intended for the Rx of HTN.

Methods

Definitions

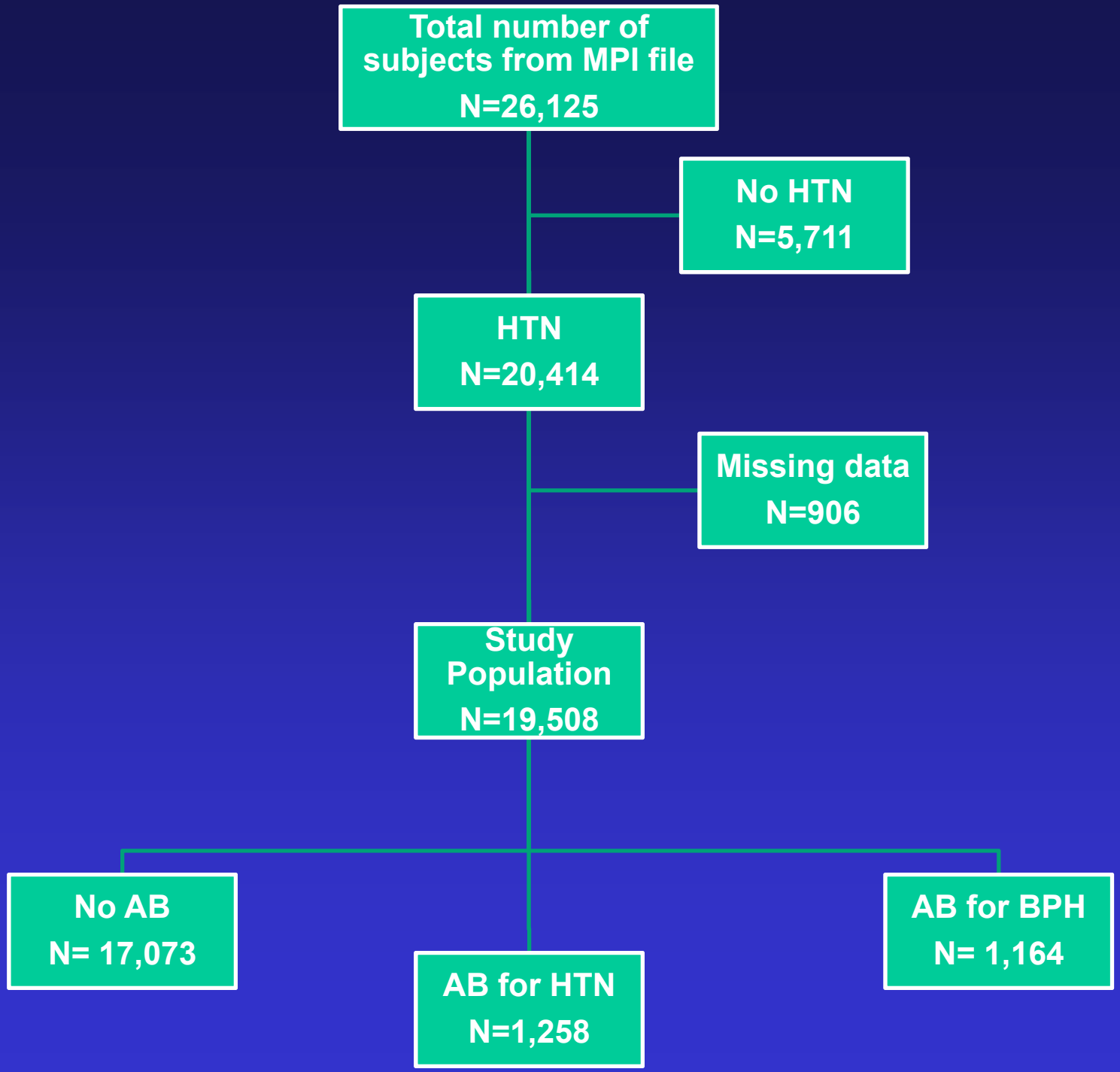
- Family history of coronary artery disease (CAD) was defined as a CAD event occurring in a first degree relative (M<55 F<65 y/o).

- Dyslipidemia was defined as a documented diagnosis of dyslipidemia in the patient's file and/or use of a lipid-lowering medication.

- An established diagnosis of diabetes mellitus and/or insulin or oral hypoglycemic agent treatment defined the presence of diabetes.

Methods
Definitions

- Obesity was defined as a body mass index (BMI) above 30 kg/m^2.
- CAD was defined as a previous MI, PCI, CABG, or documented coronary artery disease by coronary angiography prior to the index MPI date.
- CHF was defined as documented diagnosis in the computerized database


Total number of subjects from MPI file
N=26,125
No HTN
N=5,711
HTN
N=20,414
Missing data
N=906
Study Population
N=19,508
No AB
N= 17,073
AB for HTN
N=1,258
AB for BPH
N= 1,164

Methods

SPECT – Protocols and Analysis

- Standard protocols were used to trigger ischemia and perform the MPI study.

- The stress and rest images were divided into 10 segments - anterior Basal, anterior mid, anterior lateral anterior septal, posterior basal, posterior lateral, inferior, apical, inferior apical.

Methods

SPECT – Protocols and Analysis

- Uptake in each segment was graded using a 4-point scale (3 = severely diminished or absents uptake; 2 = moderately diminished uptake; 1 = mildly diminished uptake; 0 = normal uptake).

- Summed stress, rest and difference scores (SSS, SRS, SDS) were calculated .

- SDS groups: none or mild reversible perfusion defect (PD) 0-2, moderate PD 3-6, severe PD >6

Results

Results

- The median follow-up time was 83 months (IQR 55-118).
- The mean age was 65±11.1 years
- Male gender proportion was 55.2%.

Baseline Clinical Characteristics

Variables	No AB N=17,073	AB for BPH N=1,164	AB for HTN N=1,258	P Value
Age (M±S.D)	64.25±11.11	70.97±8.44	69.50±9.43	<0.001
Male N(%)	8,712(51)	1,164(100)	891(70.8)	<0.001
Dysl N(%)	9,969(58.4)	735(63.1)	693(55.1)	0.001
Current smoker N(%)	2,288(13.4)	150(12.9)	111(8.8)	<0.001
DM N(%)	6,381(37.4)	431(37)	544 (43.2)	<0.001
Sys BP mmHg (M±S.D)	147.28±30.14	144.96±23.54	155.51±24.49	<0.001

Myocardial Perfusion Imaging Characteristics

Variables	No AB N=17,073	AB for BPH N=1,164	AB for HTN N=1,258	P Value
SSS (M±S.D)	3.45±5.30	4.81±5.69	4.07±5.27	<0.001
SRS (M±S.D)	1.69±3.76	2.35±4.27	1.82±3.58	<0.001
SDS (M±S.D)	1.71±3.30	2.40±3.67	2.16±3.51	<0.001
SDS 0-2	11,094(69.1%)	646(57.9%)	722(61.2%)	<0.001
SDS 3-6	3,584(22.3%)	327(29.3%)	332(28.1%)	
SDS > 6	1,384(8.6%)	142(12.7%)	126(10.7%)	

Baseline Medical Treatment

Variables	No AB N=17,073	AB for BPH N=1,164	AB for HTN N=1,258	P Value
DM drugs N(%)	4,660(27.3)	304(26.1)	441(35.1)	<0.001
Anti PLT N(%)	11,183(65.5)	753(64.7)	836(66.5)	0.656
BB N(%)	10,199(59.7)	509(43.7)	811(64.5)	<0.001
Statins N(%)	9,341(54.7)	632(54.3)	718(57.1)	0.248
RAS N(%)	9,671(56.6)	607(52.1)	880(70)	<0.001
Number of HTN drug families (median + IQR)	2(1-2)	1(1-2)	3(2-3)	<0.001

Kaplan-Meier Rates of Composite Cardiac Death and AMI

Years	No AB N=17,073	AB for BPH N=1,164	AB for HTN N=1,258	P Value
1	1.9%	3.3%	2.9%	0.01
3	4.6%	7%	6.4%	<0.001
5	6.7%	9.6%	10.5%	<0.001
8	8.9%	11.3%	14.1%	<0.001

Cox Model for the Composite Outcome of Cardiac Death and MI

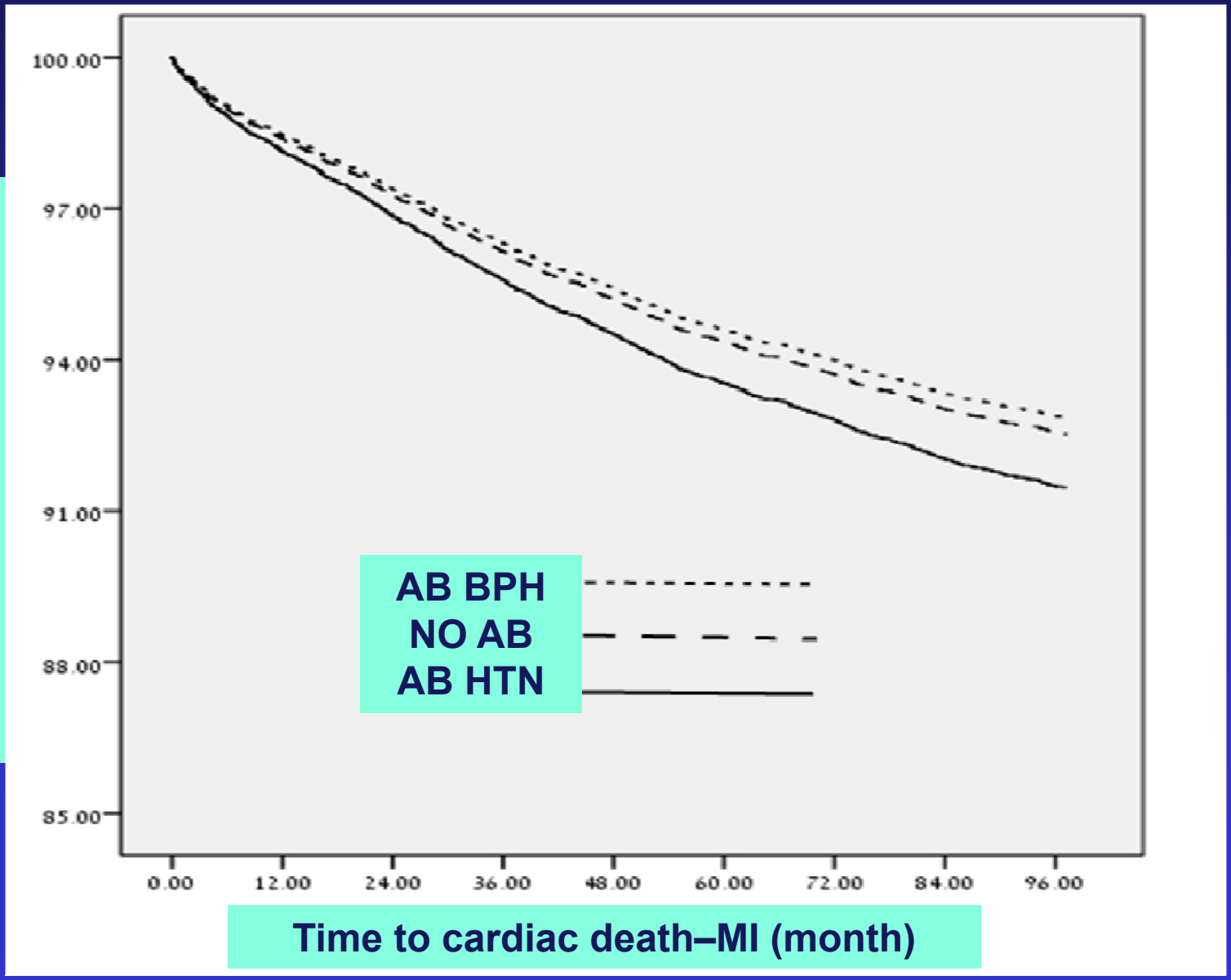
	HR	95% CI Low	95% CI Up	P Value
No AB	1			
AB BPH	0.95	0.78	1.16	0.65
AB HTN	1.14	0.95	1.38	0.14
Sys BP	1.08	1.01	1.15	0.02
Male	1.25	1.11	1.41	<0.001
Age	1.02	1.01	1.02	<0.001
SDS divided	1.18	1.10	1.27	<0.001
Increased LU	1.36	1.20	1.53	<0.001
# HTN drugs	1.08	1.02	1.14	<0.001
CHF	5.09	4.54	5.71	<0.001
Smoking	1.18	1.02	1.36	<0.001
Statins	0.84	0.76	0.93	<0.001
IHD	1.28	1.10	1.49	<0.001

*systolic blood pressure- divided to: ≤139; 140-159;160+

#SDS- divided to : 0=-0-2; 1=3-6; 2≥6

$ number of HTN drugs including: beta blockers, angiotensin converting enzyme inhibitors, angiotensin recptor blocker inhibitors, calcium channel blockers, diuretics

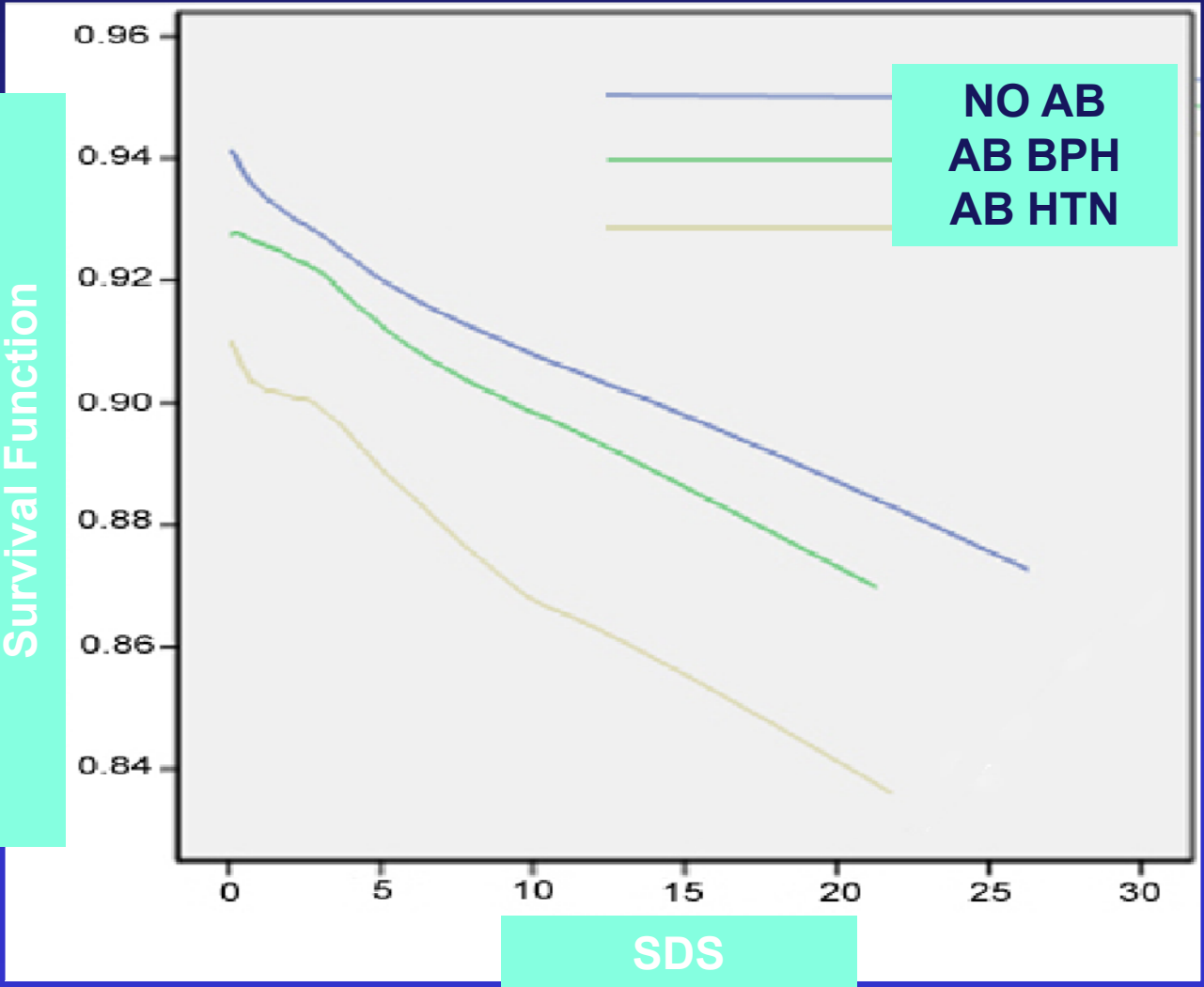
Cox Model for the Composite Outcome of Cardiac Death and MI



Sensitivity Analysis: Interaction with Perfusion Defect

	No AB	AB for BPH	AB for HTN
None or mild rev. PD	1	0.96(0.73-1.26)	0.92 (0.69-1.21)
Moderate rev. PD	1	0.97(0.67-1.41)	1.35 (0.99-1.85)
Severe rev. PD	1	0.89(0.53-1.50)	1.64 (1.04-2.58)

Adjusted Composite Outcome Probabilities (LOWESS) by SDS



Ischemia in Adverse Cardiac Outcome in AB Treated HTN Patients.

	SDS 0-2 N=12,471	SDS 3-6 N= 4,244	SDS >6 N=1,655
Cardiac death and MI (95% CI)	0.92 (0.69-1.21)	1.35 (0.99-1.85)	1.64 (1.04-2.58)
Cardiac death (95% CI)	1.08 (0.76-1.56)	1.47 (0.93-2.17)	1.92 (1.06-3.48)
MI (95% CI)	0.78 (0.53-1.15)	1.27 (0.83-1.94)	1.46 (0.77-2.76)
All death (95% CI)	1.17 (0.97-1.41)	1.08 (0.83-1.40)	1.24 (0.83-1.84)

Conclusion

- Alpha blockers for the treatment of HTN and alpha blockers for the treatment of BPH are not associated with increased morbidity and mortality in all patients groups except for patients with severe reversible perfusion defect (ischemia).


Thank you