LEFT VENTRICULAR HYPERTROPHY

Dr Danny Myers MD FRCP(C)
Clinical Associate Professor of Medicine, UBC
Consultant in General Internal Medicine, Victoria General Hospital

WHAT IS LVH?

LVH is an increase in LV Mass and a form of cardiac remodeling

LVH is an "adaptive mechanism" caused by chronically increased workload (hypertension most common cause)

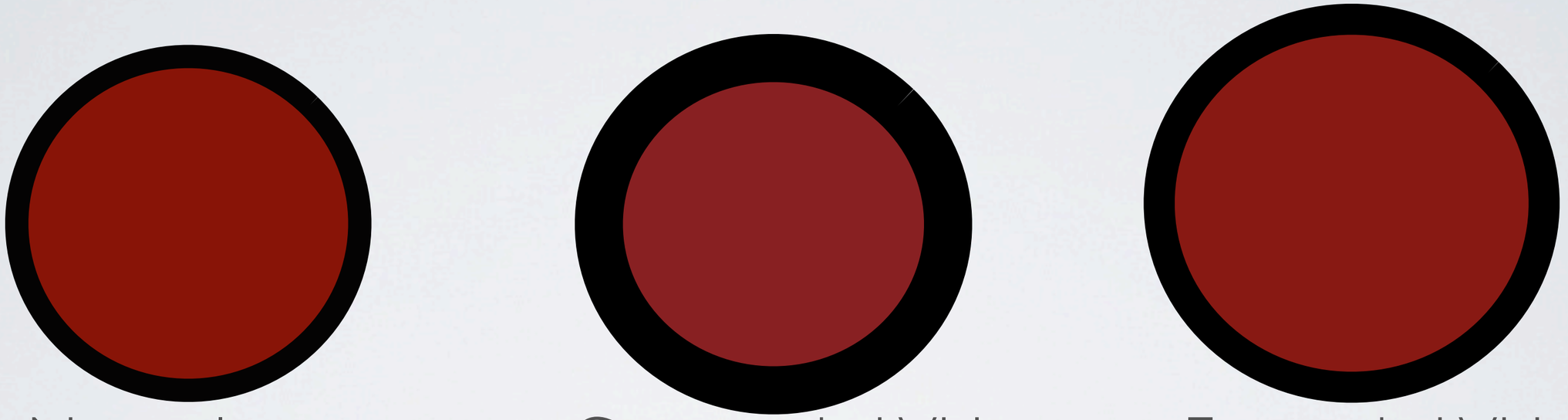
- pathological changes in patients with LVH due to hypertension include:

  1) increase size cardiomyocyte

  2) increase in fibrosis

  3) abnormalities of intra-myocardial coronary vasculature (medial hypertrophy and perivacular fibrosis)

  4) due to mechanical stress as well as effects of neurohormones, growth factors and cytokines (including insulin, angiotensin II)

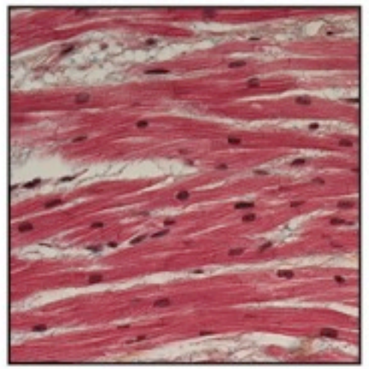


Normal Concentric LVH Eccentric LVH

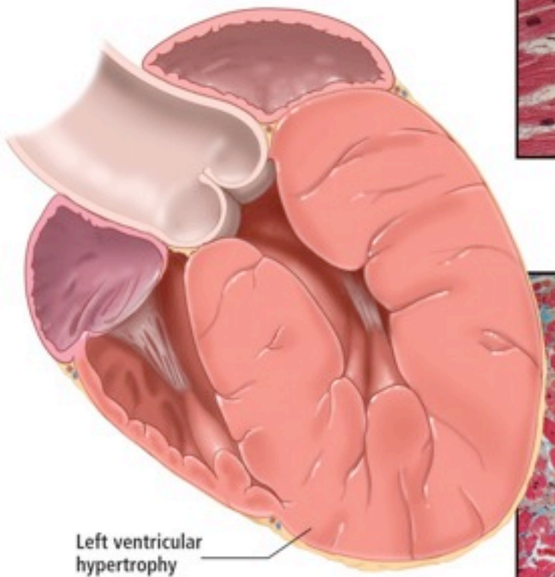
wall thickness more common with pressure overload and chamber dilatation more common with volume overload

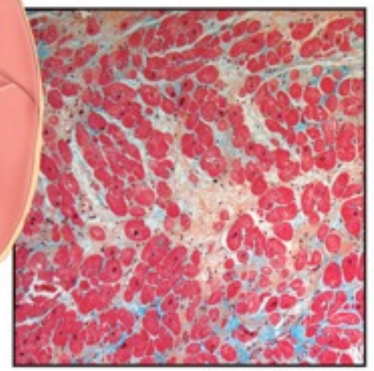
Left ventricular hypertrophy and fibrosis

Left ventricular hypertrophy (LVH) is a response to a chronically increased workload on the heart. A key component is myocardial fibrosis, which has been linked to the renin-angiotensin-aldosterone system. This observation may explain why angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are among the most potent agents for treating LVH.



Normal





Myocardial fibrosis

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Medical illustrator Ross Papalardo; histology images courtesy of E. Rene Rodriguez, MD, and Carmela Tan, MD, Department of Anatomic Pathology, Clevelan

CLINICAL IMPLICATIONS AND PROGNOSIS OF LVH

- LVH associated with an increase incidence of:

i. Diastolic Dysfunction

ii. Heart Failure with normal Systolic Function

iii. Heart Failure with impaired Systolic Function

iv. Atrial and Ventricular Arrhythmias including Sudden Cardiac Death

v. CAD including MI

vi. CVA

PROGRESSION OF HYPERTENSIVE HEART DISEASE

- LVH is an important intermediate step towards progressive Hypertensive Heart Disease

- Hypertension → Concentric Hypertrophy → Dilated Cardiac Failure

  -it is not known the relative % of hypertensive patients **with heart failure** who have preserved vs reduced EF

  -it is not known what role Myocardial Infarction has in Systolic Dysfunction in Hypertensive patients

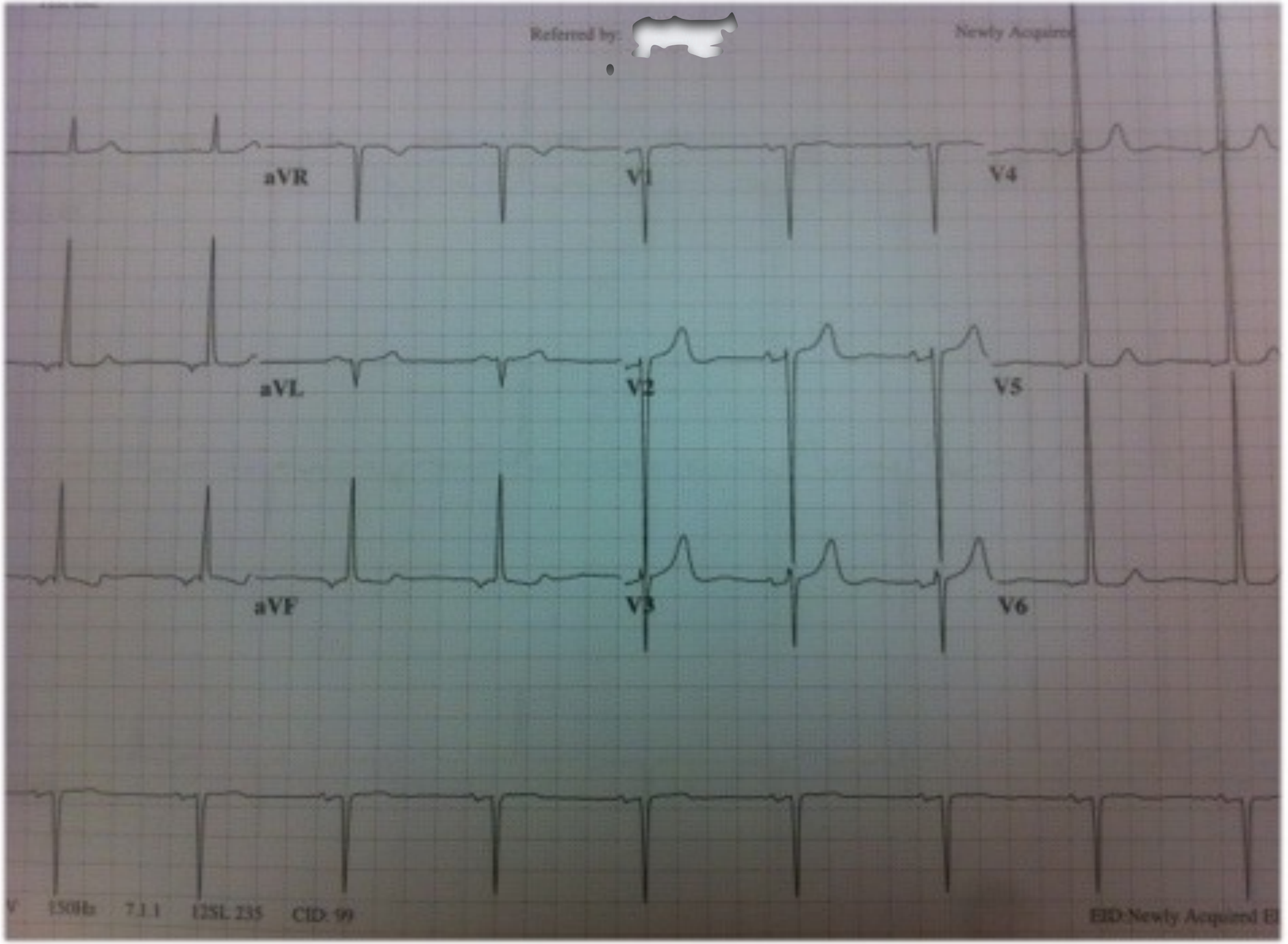
  -risk and progression not well defined and genetic factors may be important in patients who develop complications from LVH

DIASTOLIC DYSFUNCTION AND DIASTOLIC HEART FAILURE

- most common cause hypertension (also seen with CHD without MI, DM and Restrictive CV diseases)
- >40% of CHF patients have normal EF and are more likely to be elderly, female and hypertensive
- poorer prognosis in **asymptomatic** patients with moderate to severe Diastolic Dysfunction
- increase mortality for diastolic dysfunction patients with **symptomatic** CHF that may approach hospitalization and mortality rate of those with systolic dysfunction
- treatment regimens include control BP as well as treat atrial arrhythmias but paucity of data on appropriate medical treatment

EKG DIAGNOSIS

- 1) Cornell Product
- S in V3 and R in AVL >24 mm (men) and 20 mm (women)
- 2) Sokolow-Lyon voltage
- S in V1 and R in V5 or V6 = or > 35 mm
- R in AVL = or > to 11 mm
- (may have repolarization changes such as LV strain and may also have Left axis deviation, LA enlargement, QRS prolongation)
- under-diagnoses LVH occurs commonly in obesity, COPD


Referred by:
Newly Acquired
aVR
V1
V4
aVL
V2
V5
aVF
V3
V6
V 150Hz 7.1 1 12SL 235 CID: 99
EID:Newly Acquired E

EKG'S IN LVH

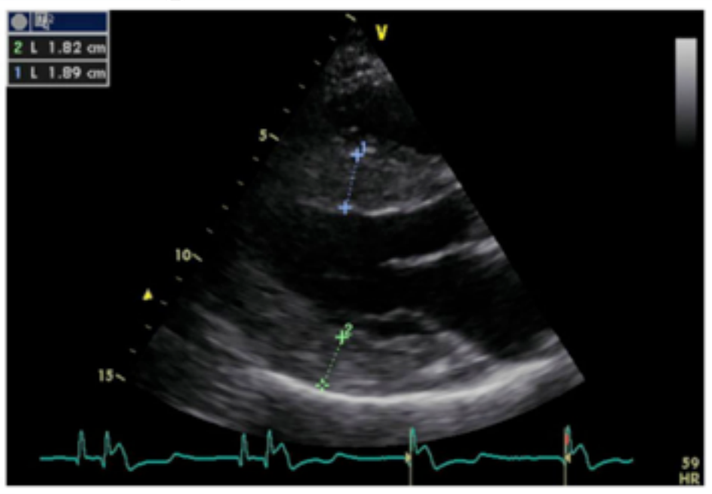
- Correlation with LV Mass is poor
- Sensitivity for diagnosis of LVH relatively low but variable depending on degree of LVH and patient characteristics (obesity, COPD)
- Specificity better in 80 to 90% range
- however EKG's are inexpensive, accessible, and in higher risk patients can also assess for arrhythmias, LBBB, and presence of Q waves

LVH IMAGING

1. Echocardiography

- correlation with Cardiac MRI variable but Echocardiography is procedure of choice for diagnosis of LVH

- advantage of 2D Echo: can assess diastolic dysfunction, Systolic function, valves and LA size

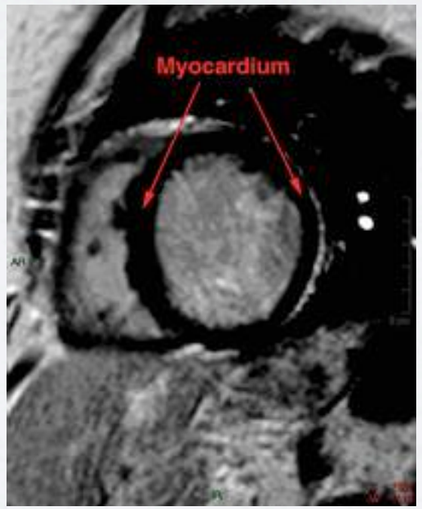


- Real Time 3D Echo better correlation with Cardiac MRI but evolving technique and not widely available

LVH IMAGING

2. Cardiac MRI

- gold standard for measurement of LV mass and volume and highly reproducible
- no radiation nor iodine contrast
- can assess LA, valves, and ventricular function as well as determine other causes of LVH, and provide prognostic information
- limited access



LVH APPROACH

Identify higher risk patients:

- -Hypertension (SBP>DBP)
- -DM
- -Obesity
- Age
- -OSA ?
- -rule out other causes i.e. Athlete's heart, Aortic Stenosis, Congenital Hypertrophic Cardiomyopathy, Infiltrative Cardiac Disorders such as Amyloidosis or Sarcoidosis

LVH IN DIABETICS

- Diabetes associated with LVH, CAD, Diastolic Dysfunction and Systolic Dysfunction
- LVH without underlying hypertension or CAD common in Diabetics
- prevalence of LVH depends on mode of detection and baseline characteristics of those studied
- EKG diagnosis low sensitivity (due to obesity?)
- NT proBNP low accuracy for LVH
- Echocardiography should be considered on a case by case basis

LVH IN OBSTRUCTIVE SLEEP APNEA

- complications of OSA include CHF, MI, CVA, Arrhythmias, hypertension, pulmonary hypertension
- Age, Obesity and Hypertension common in OSA patients
- conflicting data in literature re OSA and LVH/Left Ventricular Mass

LVH IN HYPERTENSION-CHEP GUIDELINES 2013

- "Routine echocardiographic evaluations of all hypertensive patients is not recommended " (grade D)
- "An echocardiogram for assessment of LVH is useful in selected cases to help define the future risk of CV events" (Grade C)
- "Echocardiographic assessment of LV mass as well as systolic and diastolic ventricular function is recommended for hypertensive patients suspected to have LV dysfunction or CAD" (Grade D)
- "Patients with hypertension and evidence of CHF should have an objective assessment of LV Ejection Function, either by Echocardiography or Nuclear Imaging" (Grade D)

DIAGNOSIS - WHICH PATIENTS SHOULD HAVE ECHO/MRI?

- Symptoms (dyspnea, pre-syncope, chest pain)
- Signs (murmur, CHF)
- borderline BP (borderline indication for treatment and presence of LVH would confirm anti-hypertensive treatment required)
- concerns of Congenital Hypertrophic Cardiomyopathy
- risk factors for LVH ?
- moderate to severe hypertension ?
- EKG criteria of LVH ?

TREATMENT - LVH REGRESSION

- Regression of LVH can occur with anti-hypertensive drugs over months to several years
- meta-analysis 2003 of 80 trials: reduction in LV mass ARB -13%, CCB -11%, ACE -10%, diuretics -8% and B Blockers -6%
- LIFE trial showed improved diastolic dysfunction at one year in LVH patients
- Reduction in CV risk? based on reduction LV mass
- insufficient data to recommend following LV mass (LVH) as treatment goal

HOPE LVH SUB-STUDY

- HOPE trial assessed Ramipril vs Placebo in patients with CV disease or combination of DM and one additional risk factor

- Risk of Cardiac Death, MI or Stroke in the **HOPE trial** was 14% in Ramipril arm vs 17.8% in the placebo arm after 4.5 years

- **HOPE LVH sub-study** included patients who were also randomized to Ramipril or Placebo with 4.5 year followup and EKG's performed at baseline and study end

LVH status in ramipril vs placebo patients

LVH status	Ramipril (N=4135)	Placebo (N=4146)	RR (95% CI) for ramipril/ placebo
LVH development/ persistence	336 (8.1%)	406 (9.8%)	0.83 (0.72-0.95)
LVH regression/ prevention	3799 (91.9%)	3740 (90.2%)	1.02 (1.01-1.03)

Mathew J et al. *Circulation* 2001; 104(14):1615-21.

LVH status and CV risk

Outcome	LVH regression/ prevention (N=7539)	LVH development/ persistence (N=742)	p value
Predefined primary outcome	925 (12.3%)	117 (15.8%)	0.006
CHF	697 (9.3%)	114 (15.4%)	<0.0001

Mathew J et al. *Circulation* 2001; 104(14):1615-21.

BP reduction with anti-hypertensive agents reduces clinical event rates but are there differences between different classes of drugs?

LIFE: Study Design

Patients with hypertension (blood pressure 160-200/ 95-115 mm Hg) and left ventricular hypertrophy

Losartan
Angiotensin II antagonist
Dose titrated to BP <140/90 mm Hg

(n=4,605)

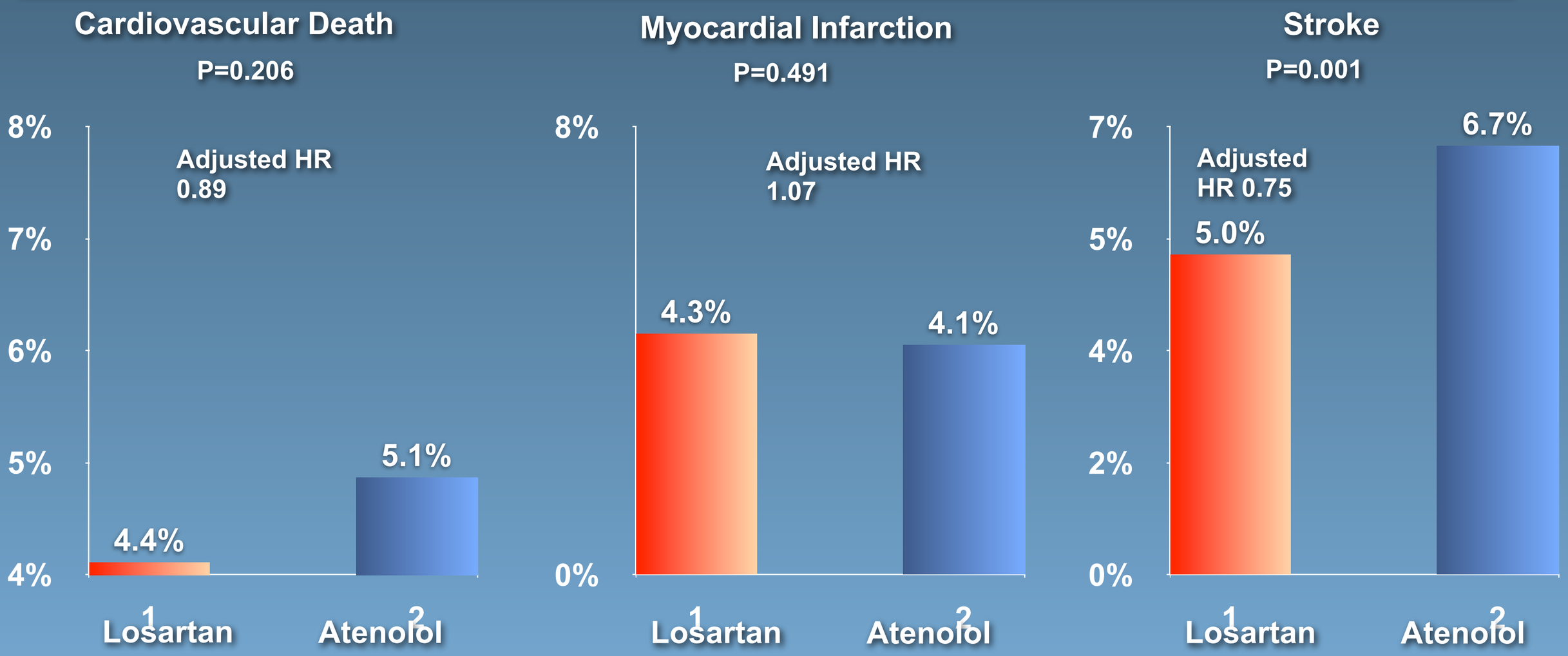
Atenolol
Beta-blocker
Dose titrated to BP <140/90 mm Hg

(n=4,588)

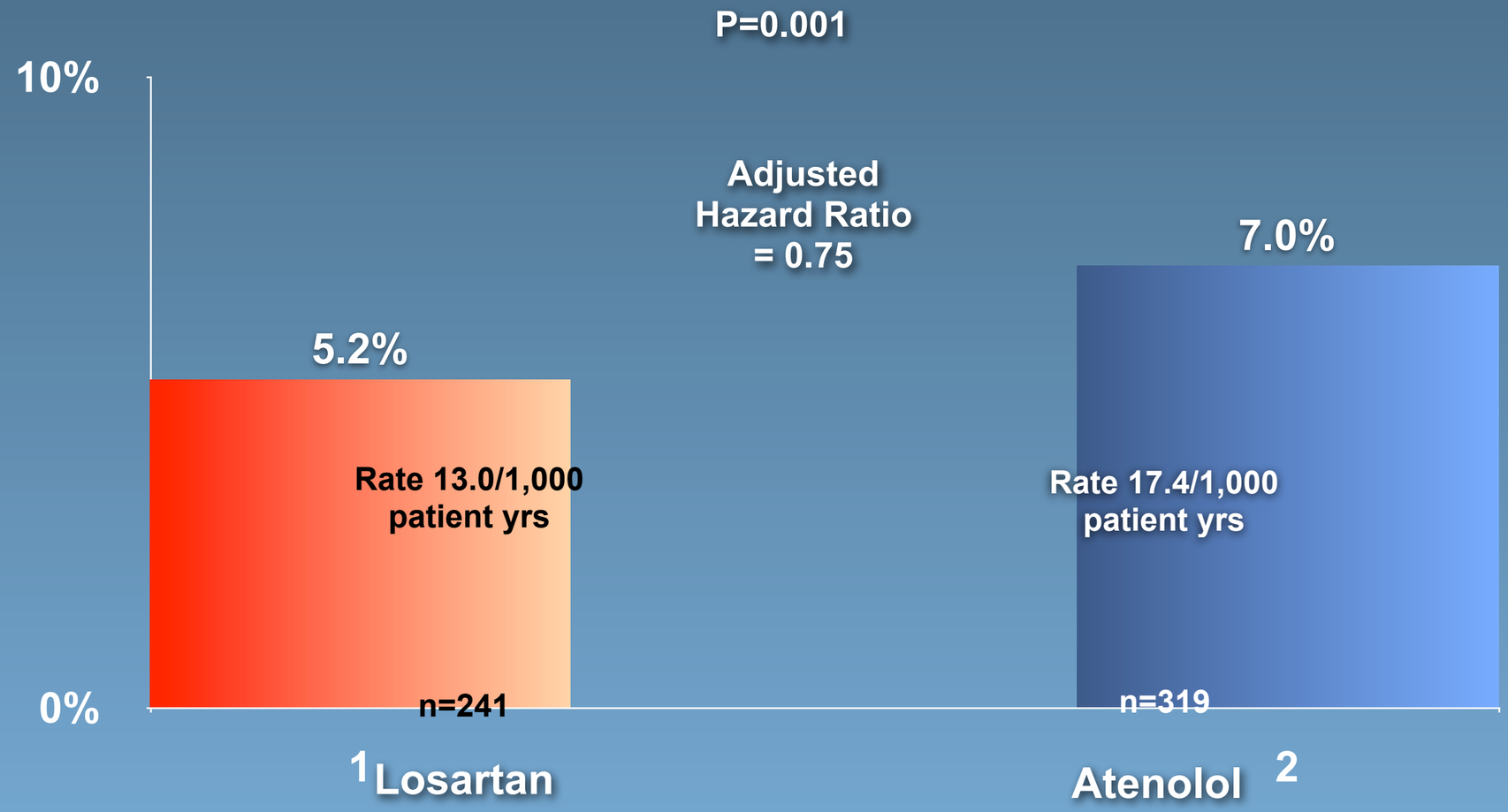
Followed for ≥4 years - Mean follow-up 4.8 years

Cardiovascular death, MI, stroke

LIFE: Individual Endpoint Results



LIFE: New-onset diabetes



LIFE STUDY AND A-FIB

- those with in-treatment regression or continued absence of EKG LVH new onset A-fib occurred in 14.9 vs 19.0 per 1000 patient years (12.4% lower)
- this was independent of BP lowering and treatment modality
- suggests that BP lowering treatment with prevention or regression of EKG LVH may reduce incidence of new onset A-Fib
- other smaller trials suggest similar findings

LIFE LVH ECHOCARDIOGRAPHY SUBSTUDY

- **What is the value of performing Echocardiography in asymptomatic hypertensive patients with EKG LVH?**
- 960 patients with EKG LVH on screening EKG treated with atenolol vs losartan
- no change primary endpoint CV death, MI or Stroke
- secondary endpoint 4X higher risk hospitalization for CHF over 5 years IN THOSE WITH EKG and ECHO EVIDENCE OF LVH despite BP control comparable in both groups

QUESTIONS

1. Is Hypertension present?

   -rule out secondary causes of hypertension when appropriate

   -identify presence of absence of end organ damage

2. what is the target BP?

3. identify presence or absence of other CV risk factors

4. which agent(s) are preferable for treatment?

REMEMBER

- NaCl restriction and weight loss can facilitate regression of LVH
- Majority of patients require more than one anti-hypertensive agent
- Reaching BP target more important than type of agent used
- choose agents based on presence or absence of co-morbidities and efficacy
- some agents are more effective than others

B BLOCKERS 2013

- Question: what role do B Blockers have in the management of Hypertension in 2013?

EFFECTS OF B BLOCKERS

- B Blockers can reduce HDL and increase TG levels though cardio-selective B Blockers can reduce LDL
- increase blood sugars may occur in patients treated with B Blockers
- vasodilatory B Blockers such as Carvedilol and Labetolol may be less detrimental than other B Blockers

B BLOCKERS AND HYPERTENSION

- B Blockers reduce BP similar to other meds
- atenolol most frequently studied B Blocker
- increase risk of CVA with B Blocker Hypertensive trials compared to other meds (> 60 years old)
- no change overall CV mortality, CHF or MI in meta-analysis of B Blockers versus other anti-hypertensive drugs
- recent trials such as LIFE and ASCOT(BPLA) demonstrated inferiority of B Blockers vs CCB and ACE or ARB

APPROPRIATE USE OF B BLOCKERS

It is appropriate to use B Blockers in the following patients:

1. CAD in those symptomatic with angina
2. patients with atrial fibrillation for rate control
3. patients with Systolic Dysfunction/CHF (carvedilol, bisoprolol or metoprolol XL)
4. other indications such as Migraine prophylaxis, Portal Hypertension with esophageal varicies, thyrotoxicosis, benign essential tremor

REACH TRIAL JAMA 2012

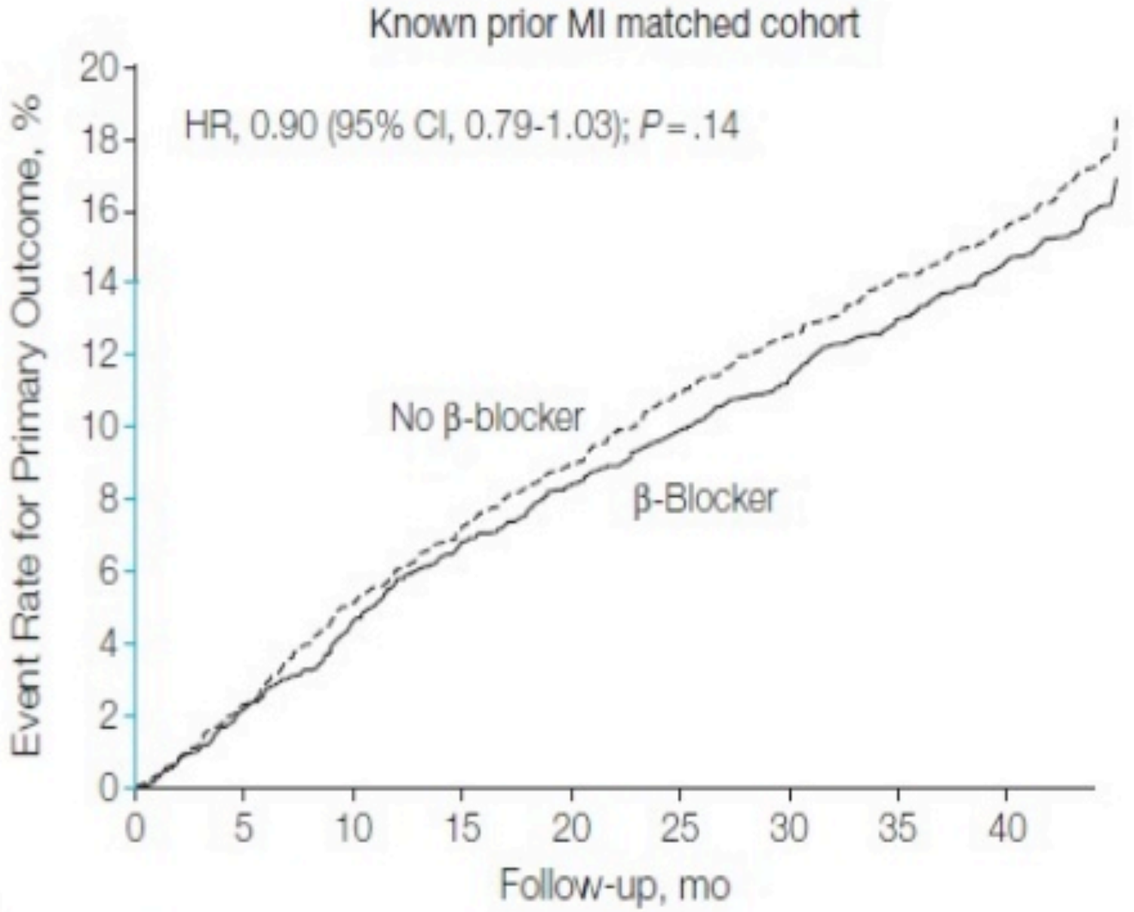
- question: observational trial to determine the benefit of B Blockers in reducing CV events in stable patients with remote history of MI defined as > 1 year ago, in those with CAD but no history of MI, and in those with only risk factors for CV disease

- Conclusion: In 44,708 patients, B Blocker use was not associated with a lower incidence of CV events among patients with prior history of MI, prior history of PCI/CABG or CAD without MI, or those with 3 or more risk factors for CAD

- previous evidence for B Blocker use based on old Post MI trials which occurred prior to modern re-perfusion treatment, and modern medical treatment for CAD and Heart Failure

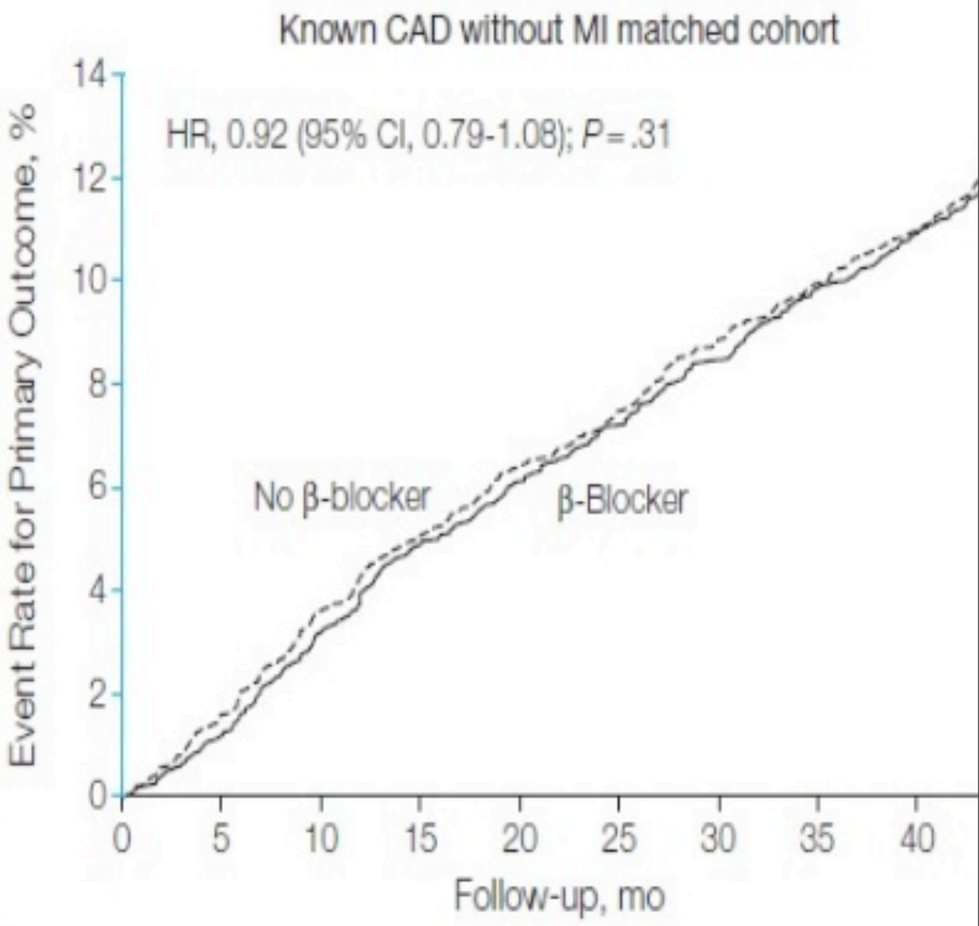
- B Blockers should be continued in those with CHF and Systolic Dysfunction as well as those immediately post MI but duration of treatment in latter group not known

nulative Incidence Curve for the Risk of Primary Outcome by β-Blocker Use



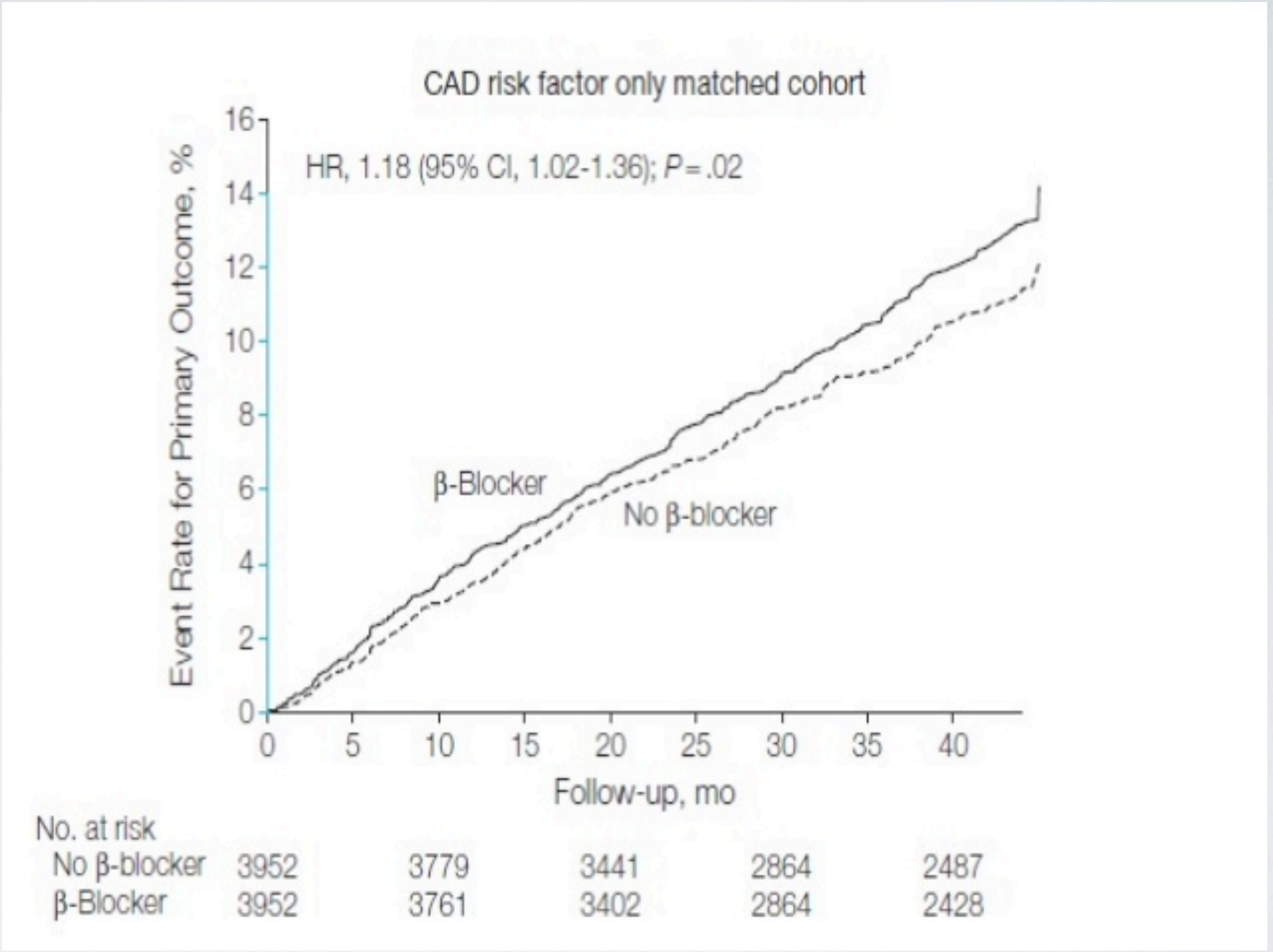
No. at risk

No β-blocker	3379	3165	2850	2357	2029
β-Blocker	3379	3178	2899	2424	2061



No. at risk

No β-blocker	3599	3420	3105	2615	2270
β-Blocker	3599	3447	3148	2634	2251


CAD risk factor only matched cohort
HR, 1.18 (95% CI, 1.02-1.36); P = .02
Event Rate for Primary Outcome, %
16
14
12
10
8
6
4
2
0
β-Blocker
No β-blocker
0
5
10
15
20
25
30
35
40
Follow-up, mo
No. at risk
No β-blocker 3952 3779 3441 2864 2487
β-Blocker 3952 3761 3402 2864 2428

CONCLUSIONS

- LVH is common and associated with increase morbidity and mortality
- EKG criteria poorly sensitive though mod specific but inexpensive screening tool
- select subset of patients whom Echocardiography (or MRI) may be useful
- treat all CV risk factors simultaneously
- BP reduction via lifestyle and medication single most important factor but choice of medication also important based on co-morbidities as well as evidence of most effective agents
- B Blockers are not considered first or second line therapy for hypertension in the absence of other indications for treatment

The following slides are not part of the presentation but for interest only as they highlight some (though not all) of the more important clinical trials

HCTZ VS CHLORTHALIDONE

- controversy whether chlorthalidone is superior to HCTZ in hypertension management
- MRFIT trial men age 35 to 57 years of age in 1973
- both drugs better than placebo
- chlorthalidone recommended in 1980 by advisory board as CHD mortality in special intervention clinics using HCTZ was 44% higher
- review of database recently also showed reduced Cardiovascular Events in chlorthalidone group

SHEP

SYSTOLIC HYPERTENSION IN THE ELDERLY

- patients > age 60 with SBP (ave age 72)
- chlorthalidone step 1 with atenolol step 2 compared to placebo
- BP 155 placebo vs 143 treatment arm
- 5 year stroke risk 5.2 per 100 vs 8.2 per 100
- 36% reduction in rate of fatal and non fatal stroke

ALLHAT

- study to determine whether CHD in higher risk hypertensive patients is affected by treatment with amlodipine, lisinopril, doxazosin (alpha blocker) each compared to chlorthalidone diuretic
- doxazosin arm discontinued as higher rate of CHF and stroke
- concluded that no change in treatment arms for CHD and less CHF in diuretic arm but note study design may account for this, and risk DM higher in diuretic arm
- can one conclude that diuretic is BETTER than ACE inhibitor or CCB or equivalent?

ASCOT

- 2 trials, lipid lowering agent and Blood Pressure Lowering Agent
- BP trial 2 arms, amlodipine + - Peridinopril versus Atenolol + - thiazide diuretic BP target
- mod BP elevation or failed target BP with other risk factors (LVH, DM, CVADx, PVDx)
- study stopped early due to higher death rate in atenolol assigned group
- no change primary outcome of non fatal MI and fatal Coronary Heart Disease after 5 years
- significant difference in secondary outcomes of fatal and non fatal stroke -23%, major CV events -16% and in DM -30%
- CONCLUSION: ASCOT supports the use of "newer" antihypertensive drugs in combination when necessary compared to use of B Blockers and diuretics

HOPE AND ON-TARGET TRIAL

1. HOPE trial included patients with PHx CV disease or DM with one additional CV risk factor

- trial prematurely stopped at 4.5 years
- primary endpoint CV death, MI or stroke 14% versus 17.8% (RR .78)
- controversy whether some of the benefit due to BP improvement

2. ON-Target looked at Ramipril vs Telmisartan (and combination treatment) in patients with DM or vascular disease.

- No difference in primary outcome of death from CV causes, MI, CVA or hospitalization for CHF

ACCOMPLISH TRIAL

- trial of patients with systolic hypertension mean age 68 with nearly 50% PHx CV disease, 13% CVA and 60% DM
- compared ACE inhibitor (benazepril) and amlodipine vs benazepril with HCTZ
- at 36 months 3/4 of patients had BP <140/90
- ACE and CCB had 20% lower risk major fatal and non fatal CV events

HYVET TRIAL

- treatment of hypertension in patients >80 years old is inconclusive
- HYVET trial patients mean age 84 with sustained SBP >160
- indapamide SR vs placebo (can add perindorpril to indapamide arm if required)
- target BP <150/80
- primary endpoint CVA and secondary endpoint CV and total mortality
- primary end point 2.6 vs 3.6% P value .06
- secondary end point all cause mortality 10.1 vs 12.3 % (NNT 45)
- fatal/non fatal HF and 1.1 vs 3.0% (NNT 52)

ACCORD BP TRIAL

- Age 40 to 79 with DM average 10 years with pre-existing CV disease, subclinical CV disease or at least 2 CV risk factors in addition to DM
- determine whether SBP <120 vs 140 lowers CV risk (non fatal CVA or MI or CV death) but not specific drug class
- Average SBP was 119 in intensive vs 134 in standard arm
- no change in CV rate between intensive vs standard treatment after ave 5 year followup (1.9 vs 2.1%)
- however NNT over 5 years to reduce 1 stroke was 89 though intensive arm higher risk syncope, postural hypotension and hypokalemia