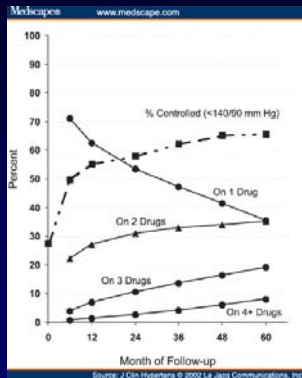
RESISTANT/REFRACTORY HYPERTENSION

SYED ALI ASGHAR,M.D.
DALLAS NEPHROLOGY ASSOCIATES

Control Rates and Medication Use in ALLHAT



Cushman et al.
J Clin Hypertens 2002

JNC VII Classification

BP Classification	SBP mm/Hg		DBP mm/Hg
Normal	<120	and	<80
Pre-Hypertension	120-139	or	80-89
Stage I Hypertension	140-159	or	90-99
Stage II Hypertension	≥160	or	≥100

ASGHAR

JNC 7 report : Key messages

(1) In persons older than 50 years, systolic BP of more than 140 mm Hg is a much more important CVD risk factor than diastolic BP

(2) The risk of CVD, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg.

Individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension

(3) Individuals with a SBP of 120-139 mm Hg or a DBP of 80-89 mm Hg should be considered as prehypertensive and require lifestyle modifications to prevent CVD

JNC 7 report

(4) Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes.

Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (ACE-I, ARBs, beta-blockers, Ca channel blockers)

(5) Most patients with hypertension will require 2 or more antihypertensive medications to achieve goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease)

JNC 7 report

(6) If BP is more than 20/10 mm Hg above goal BP, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a Thiazide-type diuretic

(7) The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with and trust in the clinician.

RESISTANT HYPERTENSION

RESISTANT HYPERTENSION

- What is it ?
- Is there a definition?
- Who is likely to demonstrate refractoriness to optimal therapy?
- What can you do about it?

RESISTANT HYPERTENSION

- Hypertension resistance is defined as blood pressure above goal which is 140/90 in most patients or 130/80 in pts who have diabetes or CKD despite adherence to an appropriate 3 drug regimen including a diuretic.

ETIOLOGY

- Suboptimal therapy
- Volume expansion
- Poor compliance with medical therapy
- Ingestion of drugs that can increase blood pressure
- Secondary Hypertension
- White coat Hypertension
- Pseudohypertension

DIAGNOSIS

- Diagnosis made after blood pressure measurement on 2 different occasions.
- Use of appropriate sized cuff is essential

White coat Hypertension

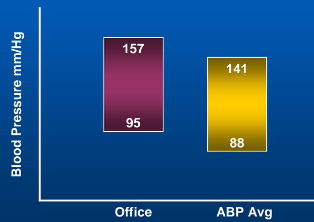
- Defined as office reading >140/90 and out of office averaging 135/85 .
- Mild to moderate elevation in office BP reading should not be diagnosed hypertension unless BP remains high after 3-6 visits.
- 10-20% pts have white coat HTN.
- May develop into HTN later.
- Increased risk of stroke.

Recommendations

- Ambulatory blood pressure monitoring/home blood pressure monitor
- Frequent BP monitoring if not on any meds.
- White coat HTN may also occur in resistant HTN.

Office vs. 24hr ABP in Refractory Hypertension

(Omuir, et al. Blood Pressure. 2003; 12: 211-9)



ASGHAR

Suboptimal therapy

- Single most common correctable cause.
- Lack of administration of more effective drugs.
- Failure to prevent volume expansion with diuretic therapy.
- Failure to increase antihypertensive patient by physicians.

Causes of Resistant HTN

In tertiary care clinic

Result of 436 chart reviewed,91 pts met criteria for resistant HTN
Most common cause

- Suboptimal medical regimen (39 pts)
- Medicine intolerance (13 pts)
- Undiagnosed secondary hypertension (10 pts)
- Non compliance (9pts)
- Psychiatric causes(7 pts)
- Office resistance(2pts)
- Interfering substances(2 pts)
- Drug interactions(1pts)

Extracellular volume expansion

- Underlying renal insufficiency.
- Sodium retention due to vasodilatory therapy.
- Increased salt diet.
- Recommendation
  Remove fluid even in the absence of edema until
  blood pressure control
  signs/symptoms of volume depletion

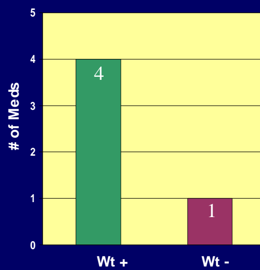
Non adherence to therapy

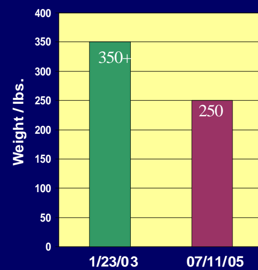
- Inability to afford medication
- Poor access to continuing medical care
- Side effect of therapy
- Non adherent to dietary modification.

Recommendations

- Avoidance of alcohol
- Weight reduction
- Pt education
- Rescheduling missed appointments
- Careful attention of drug side effects
- Simplifying drug regimen

R.D. 47 YOWF





Causes of Secondary Hypertension

- RENAL
  - Renovascular Hypertension (RAS, FMD)
  - Renal Parenchymal disease (GN,ADPKD)
  - Obstructive uropathy
- ENDOCRINE
  - Pheochromocytoma — Hyperparathyroidism
  - Hyperaldosteronism — Hyper-Hypothyroidism
  - Cushing Syndrome — Renin Secreting Tumors
- PHARMACOLOGIC
  - ETOH — NSAID's
  - Corticosteroids — Ephedrine
  - MOA inhibitors — Cocaine
- MISCELLANEOUS
  - Coarctation of aorta — Obstructive Sleep Apnea
  - Pregnancy

Pseudohypertension

- Some elderly people have thickened arteries requiring higher cuff pressure for compression of brachial artery resulting in higher systolic and diastolic blood pressures.
- Treatment with hypertensive meds causes hypoperfusion symptoms.
- Accurate measurement by direct intraarterial pressures or finger BP measurement.

Drugs

- Salt
- Alcohol
- Cocaine
- Amphetamines
- Anabolic steroids
- Oral contraceptives
- Antidepressant
- Calcineurin inhibitors
- Herbal preparations
- NSAIDS
- OTC decongestants

Drug Interactions That May Lead to Resistant Hypertension

Anti-Hypertensive Agents	Interacting Drugs
Hydrochlorothiazide	Cholestyramine
Propranolol	Rifampin
Guanethidine	Tricyclics
ACE Inhibitors	Indomethacin
Diuretics	Indomethacin
All Drugs	Cocaine
	Tricyclics
All Drugs	Phenylpropanolamine

ASGHAR

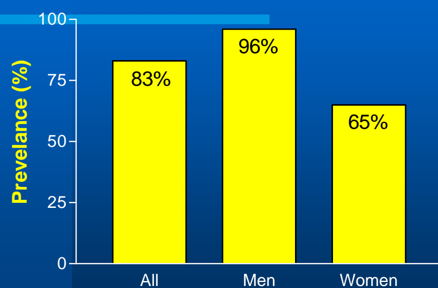
Target Organ Damage/Clinical Cardiovascular Disease

Heart Diseases

- Left ventricular hypertrophy
- Angina/prior myocardial infarction
- Prior coronary revascularization
- Heart failure

Stroke or transient ischemic attack
Nephropathy
Peripheral arterial disease
Retinopathy

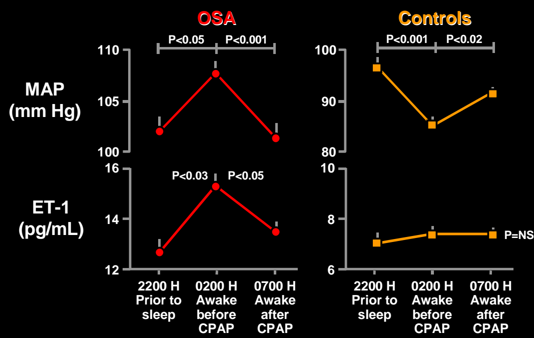
High Prevalence of Unrecognized Obstructive Sleep Apnea in Resistant Hypertension



Logan et al. J Hypertens 2001

Sleep Apnea

- Is OSAH (obstuctive sleep apnea hypopnea) a cause of systemic HTN ?.
- Hypoxia causes increase in sympathetic tone,increase aldosterone level and increase level of endothelin.
- Large studies have confirmed association of OSAH and HTN.
- Whether OSAH cause HTN is uncertain.
  147 pt with OSAH had significantly higher BP than who did not have OSAH
  (Sleep Apnea and HTN, Hla Km,young,T.B ,ann of internal medicine march 1999)
- Treatment of OSAH reduces systemic BP.
  60 Pts with moderate to severe OSAH receive therapeutic or subtherapeutic CPAP therapy.Subtherapeutic had no effect in reducing BP but therapeutic reduced BP.
  (Mayer J, Becker,Bradenburg, cardiology 1991)



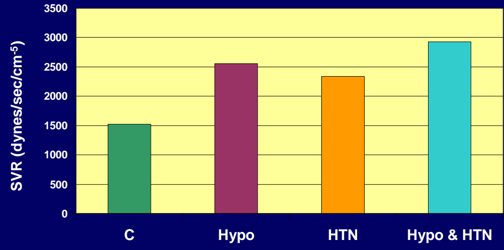
Sleep Apnea

- Should all pts with HTN be evaluated for OSAH?

Consider OSAH if refractory HTN.

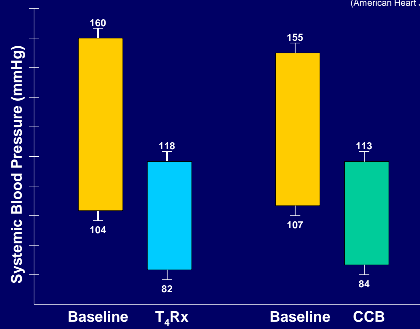
SVR, Thyroid, & HTN

(AHJ 2002; 143: 718)

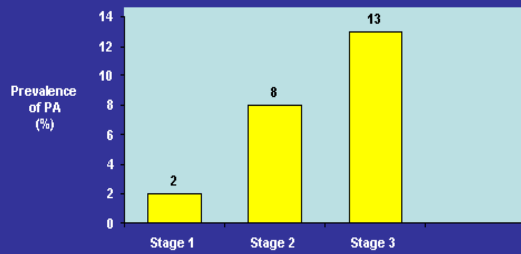


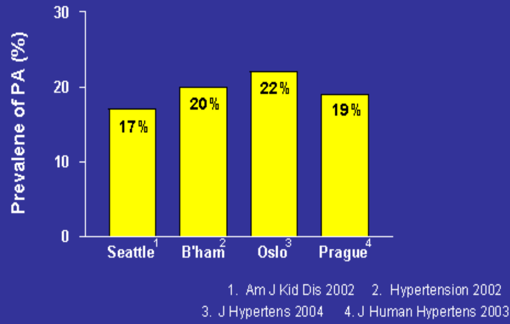
Blood Pressure Response to Thyroxine Therapy or to CCBs

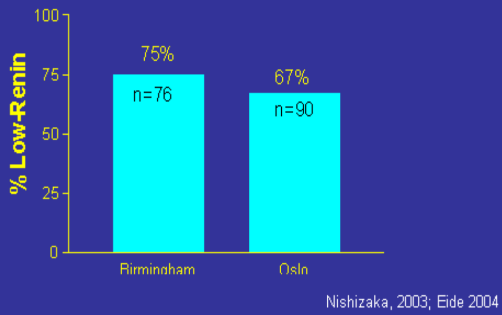
(American Heart J 2002; 143: 718)

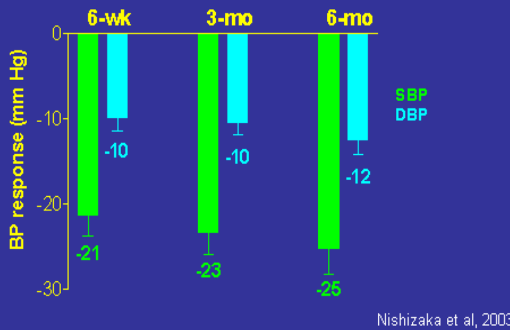


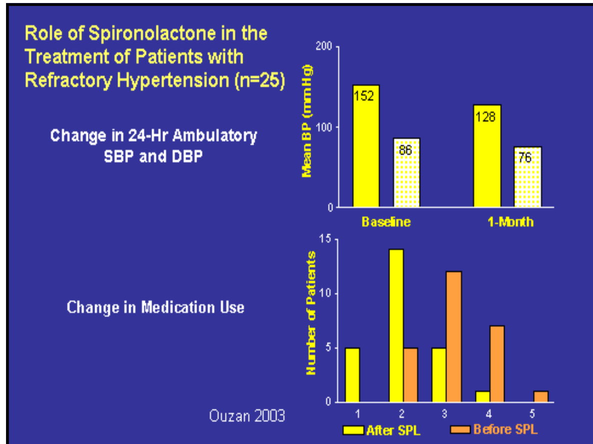
Prevalence of Primary Aldosteronism Hypertensive Subjects




Prevalence of PA in Subjects with Resistant Hypertension
Prevalene of PA (%)
30
20
10
0
17%
20%
22%
19%
Seattle[1]
B'ham[2]
Oslo[3]
Prague[4]
1. Am J Kid Dis 2002 2. Hypertension 2002
3. J Hypertens 2004 4. J Human Hypertens 2003


Prevalence of Low-Renin Levels Among Subjects with Resistant Hypertension
% Low-Renin
100
75
50
25
0
75%
n=76
67%
n=90
Birmingham
Oslo
Nishizaka, 2003; Eide 2004


BP Response to Spironolactone in Subjects with Resistant Hypertension
BP response (mm Hg)
6-wk
3-mo
6-mo
0
-10
-20
-30
-21
-10
-23
-10
-25
-12
SBP
DBP
Nishizaka et al, 2003



Resistant Hypertension and Aldosterone Blockade

- Aldosterone blockade broadly effective as add-on antihypertensive therapy in patients with resistant hypertension including in the setting of diuretic use and RAAS blockade.
- Aldosteronism associated with increased cardiovascular risk including higher ambulatory blood pressure levels, impaired endothelial dysfunction, and greater LVH.
- Aldosterone blockade improves cardiovascular risk both through reducing blood pressure and improving associated risk factors such as endothelial function and reversing LV fibrosis and hypertrophy.

Case 1 56 YOWF

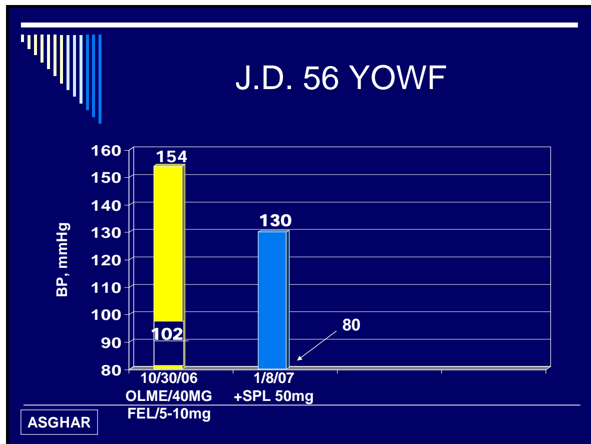
10/30/2006 BP 150/100; 150/102

On: Olmesartan 40 mg
Felodipine 5mg/10mg
Start SPL 25 mg b.i.d.

1/8/2007 BP 132/84; 130/80

On: The above Rx (including SPL)

ASGHAR



An Alternate Approach

- Recent clinical trial shows 35%pt did not reach blood pressure goal.
- Persistence of resistant hypertension is a major clinical problem.
- Failure to achieve the goal by traditional approach.
- Pts who fail traditional therapy may benefit with change in approach.

Article in cleveland clinic journal in june 2007 by Hirsch

An Alternate Approach

- An individualised hemodynamic approach in which volume,cardiac output and SVR are measured has been proven to be effective.
- Failure to prescribe diuretics.
- Failure of vasodilators to control BP.

An Alternate Approach

Physical exam

- **Excess volume**(edema,rales,JVD)
- Loop diuretics,thiazide diuretics.
- Add spironolactone if potassium < 4,proteinuria or systolic dysfunction
- **Catecholamine excess**(heart rate >84)
- add or increase B-blockers
- If B-blockers contraindicated use nondihydropyridines calcium channel blockers.
- **High SVR**(heart rate <84,no edema)
- Use ACEI,ARB or other vasodilators.

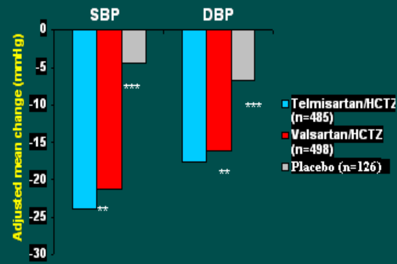
CASE

- 68 yr male with office BP of 136/76 h/o BPH
- Medication HCTZ/Lisinopril 12.5/20 mg poqd
- Toprol 100 mg po qd,nifedipine 60 mg po qd
- Self monitored BP 170-180/90 in a.m and 140/80 in afternoon.
- Physical exam obese,no rales,trace peripheral edema.
- Lab exam ,renal function,UA nml.EKG tall R waves,no ST changes
- ABP daytime 142/72,evening 130/84 and early am 160/100.

CASE

- Medication regimen changed to telmisartan/HCTZ 80/25 mg po qd,continue same dose of metoprolol and nifedipine.added doxazosin 2 mg po qhs.
- Self monitoring BP 130-135/75-80 mmHg in a.m and 120-130/80 mm Hg in afternoon ,confirmed by ABP monitoring .
- Doubling dose of thiazide diuretics help.

Does it help to use higher doses of the thiazides?



**P < 0.01 vs telmisartan/HCTZ

*** P < 0.001 vs telmisartan/HCTZ

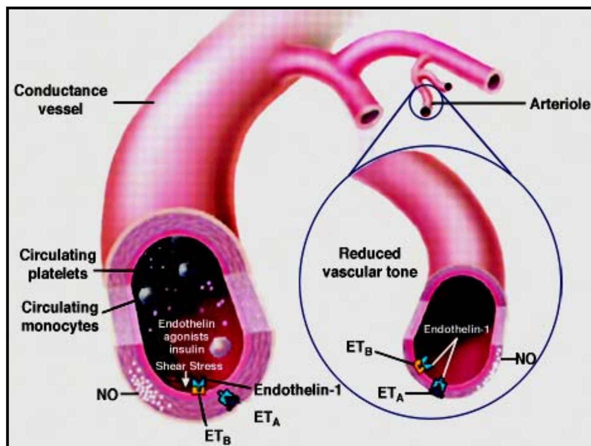
White WB et al. *Presented as ASH 2005*

REFRACTORY HYPERTENSION

- Direct vasodilators
- Concomitant diuretic therapy – which one
- Adjunctive therapy

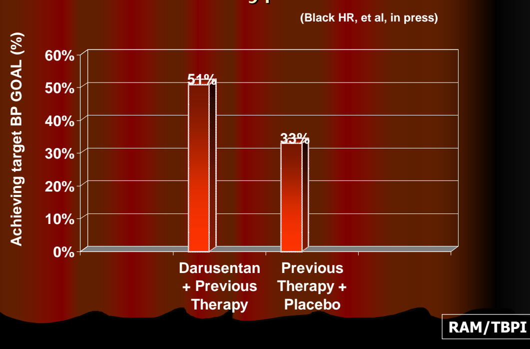
- Transdermal clonidine
- Aldosterone antagonists
- ?Endothelin antagonists
- ?Mechanical (Cartoid impulse firing)

ASGHAR



Change in Blood Pressure after ETA Darusentan Therapy

Effects of ETA Darusentan in Resistant Hypertension



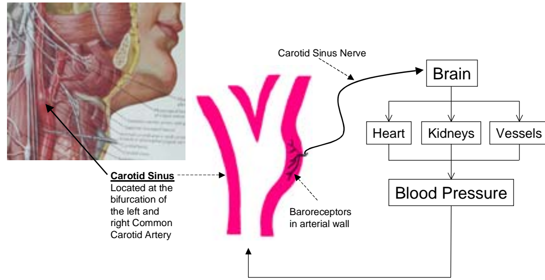
Darusentan Study - Conclusions

" Darusentan appears to provide additional BP lowering benefit as an add-on anti-hypertensive therapy in resistant hypertension."

RAM/TBPI

Baroreceptor Control of Blood Pressure

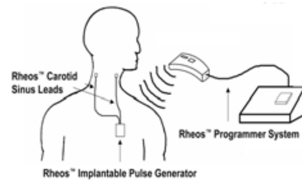
Baroreceptors regulate blood pressure and sympathetic nervous system activity



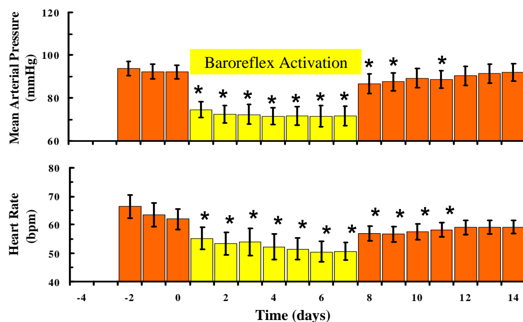
Mechanism of Blood Pressure Control

Implantable medical device electrically activates the baroreflex

- Simulates a rise in blood pressure that the brain works to counteract
- Reflexively reduces excessive blood pressure
  - Heart: Reduced heart rate
  - Vessels: Relaxation
  - Kidneys: Fluid release
- Achieves system-wide therapy by acting via the central nervous system



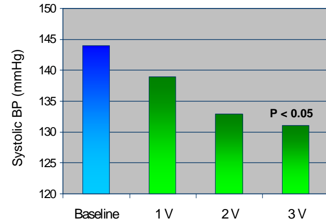
Normotensive Canines: Effect of Baroreflex Activation



Lohmeier, et al., Hypertension 2004;43(pt2):306-311.

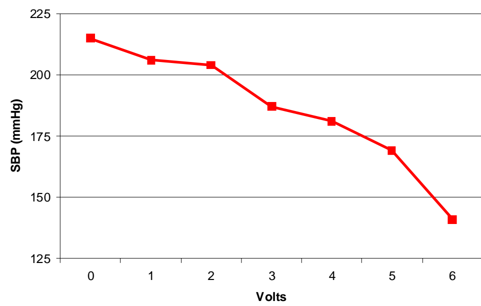
Acute Human Evaluation

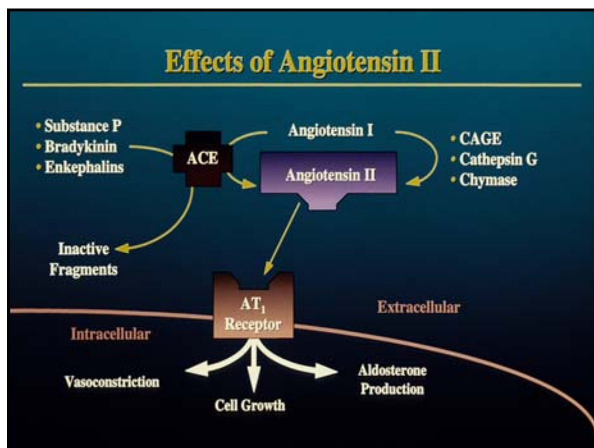
- Objectives
  - Human proof of concept
  - Technology validation
  - Temporary device application to carotid sinus
- 11 Patients Studied
  - Hemodynamic response demonstrated
  - No adverse events
  - No tissue / patient reaction

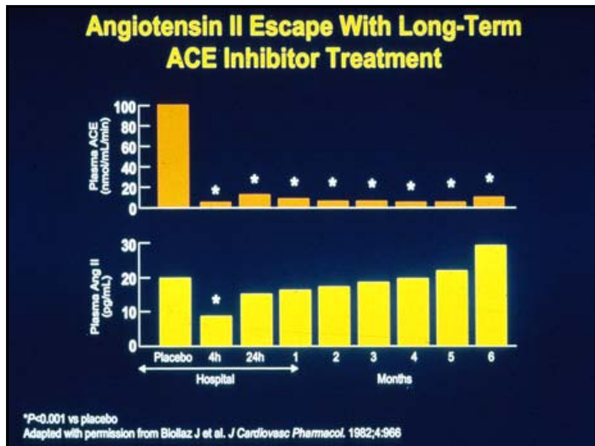


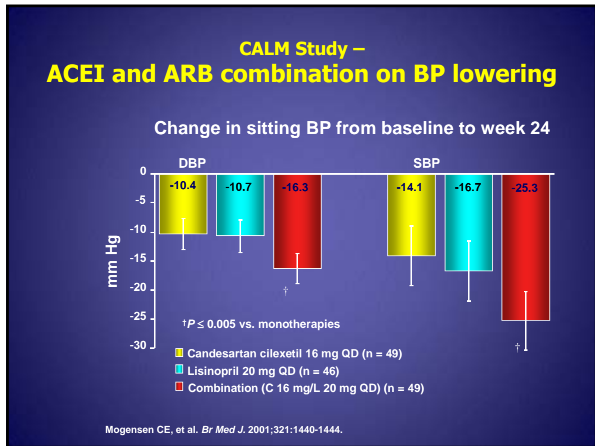
Schmidli, et al., J Hypertension 2004; 22(Suppl 2):S252

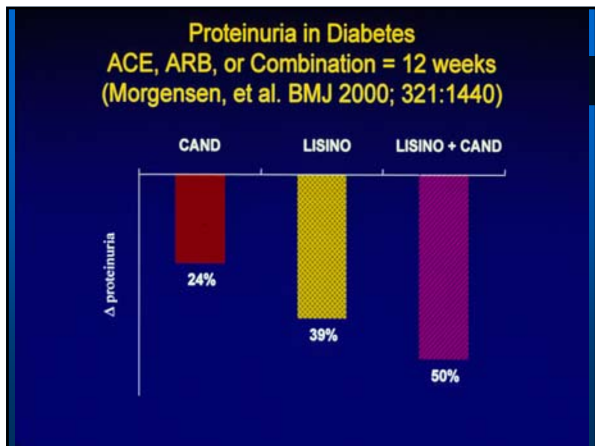
Dose Response to Permanently Implanted Baroreflex Activating System






Angiotensin II Escape With Long-Term ACE Inhibitor Treatment
Plasma ACE (nmol/mL/min)
Plasma Ang II (pg/mL)
Placebo
4h
24h
1
2
3
4
5
6
Hospital
Months
*P<0.001 vs placebo
Adapted with permission from Biollaz J et al. J Cardiovasc Pharmacol. 1982;4:966


CALM Study –
ACEI and ARB combination on BP lowering
Change in sitting BP from baseline to week 24
DBP
SBP
mm Hg
-10.4
-10.7
-16.3
-14.1
-16.7
-25.3
†P ≤ 0.005 vs. monotherapies
Candesartan cilexetil 16 mg QD (n = 49)
Lisinopril 20 mg QD (n = 46)
Combination (C 16 mg/L 20 mg QD) (n = 49)
Mogensen CE, et al. Br Med J. 2001;321:1440-1444.


Proteinuria in Diabetes
ACE, ARB, or Combination = 12 weeks
(Morgensen, et al. BMJ 2000; 321:1440)
CAND
LISINO
LISINO + CAND
Δ proteinuria
24%
39%
50%

Refractory Hypertension

Management Summary

- Compliance
- Salt Intake
- Weight
- Titrate the meds
- Close Follow-up
- Clonidine Patch/ Aldosterone Antagonist
- ACEi + ARB
- Hydralazine/Minoxidil
- Secondary Causes

ASGHAR