Hypertension and CAD

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Case History 1

AB 82 years female with

- Hypertension 7 yrs treated with ACE inhibitors & Amlodipine, BP fluctuating between 160 – 170 / 80-95 mm Hg.
- Hyperlipidemia > 10 yrs on Statins
- She was not overweight with BMI 27 nor was she diabetic.
- Presented in Emergency room with exertional angina Class II relieved by rest & S/L ISDN
Case History 2

- KKA

- 49 yrs, obese, NIDDM (4 yrs)
- Hyperlipidemia (4 yrs) not on regular treatment
- Hypertension 170 / 100 mm Hg
- Presented with recurrent chest pain at rest & on minimal exertion for 3 days
- Biomarkers
  - Troponin (+)ve
  - Cardiac enzymes – CPK 235 I.U
  - CPK MB 19 I.U
- Echo – Anterolateral & apical hypokinesia, EF = 42%
There is interrelationship between hypertension, dyslipidemia, glucose intolerance, cigarette smoking & LVH.

These 5 primary risk factors are the most important reversible determinants of cardiovascular risk & appears to operate independently of one another.

Risk increases in a multiplicative rather than simply additive fashion.
Hypertension & CAD

• What are the appropriate SBP & DBP targets in patient at high risk of CAD or those with established CAD?

• Are the beneficial effects of treatment simply a function of BP lowering or do particular classes of drugs have uniquely protective actions in addition to lowering BP?
Hypertension & CAD
(Contd....)

• Are there antihypertensive drugs that have shown particular efficacy in the primary & secondary prevention of CAD?

• Which antihypertensive drugs should be used in patients who have established CAD with stable angina, unstable angina, NSTEMI and in those with STEMI?
Hypertension & CAD – Prevalence

- **“PROCAM” STUDY (1986)** – Men 40 to 66 yrs (FU = 4 yrs)
  - HTN + CAD : 14 / 1000
  - HTN + DM : 48 / 1000
  - HTN + DM + HLP : 114 / 1000

- **SECONDARY PREVENTION TRIALS WITH STATINS**
  - “4S” (1994) : 26%
  - “CARE” (1996) : 43%
  - “LIPIDS” (1998) : 41%

Contd…
Hypertension & CAD

• Accelerates the development & progression of atherosclerosis.

• Sustained elevation of BP, destabilize the vascular lesions & precipitate ACS.

• Hypertension by itself can cause myocardial ischemia in the absence of CHD.
Hypertension & CAD: Contributions of “FRAMINGHAM HEART STUDY”
A Journey of 6 decades

- DBP is the stronger predictor of CAD in young people versus SBP in middle aged & elderly people.
- When considered jointly in older age group, SBP was positively associated with CAD risk & DBP was inversely related.
- Pulse pressure (PP) was found to be superior to SBP or DBP as a predictor of CAD in middle aged & elderly Framingham population.
- There was a far greater increase in CAD risk with increments in PP without change in SBP than with increments in SBP without a change in PP.

Contd…
Hypertension & CAD: Contributions of “FRAMINGHAM HEART STUDY”
A Journey of 6 decades

- Consequently, PP as a surrogate measure of arterial stiffness, emerged as the best single BP predictor of risk in older age group.

- In middle aged & elderly subjects, CAD risk increased with lower DBP at any level of SBP ≥ 120 mm Hg, suggesting that wide PP was an important component of risk.
Hypertension & CAD: “FRAMINGHAM HEART STUDY - 2009”

- Only DBP had a quadratic relation to CVD risk so that there was a DBP “J” curve in predicting CVD risk.

- DBP < 70 mm Hg in presence of elevated SBP is a powerful risk factor that is approximately equivalent to a rise of 20 mm Hg in SBP. Supporting the importance of large artery stiffness as a CVD risk factor in elderly age group.
Hypertension & CAD

- Strong but complex association of BP & age.
- Until about 50 yrs of age SBP & DBP rises in tandem.
- After 50 yrs of age SBP continues to rise but DBP tends to fall.
- There is enhanced risk for CV events associated with increased pulse pressure.
Hypertension & CAD

Magnitude of Hypertension & Its impact in the incidence of CAD

“If the risk ratio is 1 for DBP ≤ 80 mm Hg, this ratio increases progressively when DBP is higher, and at least duplicates at value of 94 mm Hg or more”.

MC Mohan: Lancet: 1990
Hypertension & CAD: BP Target (s)

Hypertension & CAD

META ANALYSIS OF 61 TRIALS (N = 1 million)

- BP was related to fatal IHD over BP range of 115 / 75 to 185 / 115 mm Hg.
- Overall, each increase in SBP of 20 mm Hg (or 10 mm Hg DBP) doubles the risk of fatal coronary event.
- Absolute risk of these adverse outcomes also increases with age, such that for any given SBP, the risk of fatal CAD was $\geq 16$ fold higher for person 80-89 yrs of age than those 40 to 49 yrs of age.

Hypertension & CAD – Prevalence

INTERHEART STUDY (2004)

- “HTN conferred a greater adjusted relative risk of AMI than diabetes”.

- “Among individual aged 40 to 90 yrs, each 20 / 10 mm Hg rise in BP doubles the risk of fatal coronary events”.

INTERHEART STUDY (2004)
Hypertension & CAD – Effect of Treatment

• BP lowering produces rapid reduction in cardiovascular risk.

• A 10 mm Hg – lower usual SBP (or a 5 mm Hg lower usual DBP) would predict a 50 to 60% lower risk of death due to CAD or other vascular causes at middle age, benefits that are only slightly less in older people.

  Lewington – Lancet 2000

• Very old individuals, those at least 85 yrs of age the association between high BP and mortality is weaker & lowering the BP in patients older than 80 yrs reduces stroke but not non stroke (including CAD) deaths.

  Bulpitt CJ et al: Circulation 2003
Hypertension & CAD

Ques: What should be the most appropriate BP target (s) in individuals with latent or overt CAD?

Ans: No clinical trials so far, specifically designed to answer this question.
Hypertension & CAD: Treatment Goals

- Current consensus target is < 140 / 90 mm Hg (General)
  < 130 / 90 mm Hg (DM, CKD)

- **CAMELOT** (Comparison of Amlodipine Vs Enalapril to limit occurrence of thrombosis) Trial
  
  - Subject with “normal” BP [≤ 120 / 80 mm Hg] had a mean decrease of atheroma volume of 4.6 mm³
  
  - “Prehypertensive” (120 to 130 / 80 to 89) had no significant change.
  
  - “Hypertensive” (≥ 140 / 90 mm Hg) subjects had a mean increase in atheroma volume of 12.0 mm³

A Very powerful historical trend for lower BP goals, especially in those with target organ damage.

Hypertension & CAD: BP Target (s)

- Target BP for individuals at risk of development of CAD should be lower than that for low risk individuals & a target BP of < 130 / 80 mm Hg is recommended for individuals with demonstrated CAD or CAD risk equivalents (carotid at disease, PVD, AAA) & for high risk patients, (DM, CKD or 10 yrs Framingham risk Score of ≥ 10).

Rosendorff et al: Circulation 2007: 115
Hypertension & CAD: Treatment Goals

• Lowering of either SBP or DBP decreases overall CV risk.

• Lowering of SBP improves cardiac function & outcomes by reduction in cardiac work & improved myocardial oxygen balance.

• Lowering of DBP improves CV outcomes only when coronary perfusion is maintained above the lower limit of coronary auto regulation.
Hypertension & CAD: “J Curve”

• Myocardial perfusion occurs almost exclusively during diastole & therefore DBP is the coronary perfusion pressure.

• Coronary circulation capacity of auto regulation is limited.

• In conscious instrumented dogs, it is about DBP is = 30 mm Hg & shifted upwards to ≈ 15 to 20 mm Hg in LVH.

• We do not have good data on equivalent values for the human circulation.

Roulean et al: Basic Res Cardiol 2002
Hypertension & CAD: Relevance of J Curve

• In presence of occlusive CAD, the hemodynamics is much more complicated.

• Significant CAD will shift the lower auto-regulatory limit upwards

• Myocardial blood flow is heterogeneous & therefore consequences of coronary under perfusion are unpredictable and would depend on:-
  - Intramyocardial wall stress
  - Effect of anti-hypertensive drugs
  - Severity of occlusive disease

Hypertension & CAD: Relevance of J Curve

• **STEWART 1979**
  - N = 169, FUP = 6 YEARS
  - DBP ≤ 90 mm Hg was associated with a five fold greater risk of MI compared to DBP 100 to 109 mm Hg.

• **CRUISHANK 1987**
  - N = 902 Moderate to severe hypertension
  - A strong J-Curve relationship between death & MI and treated DBP only in patient with CAD
  - Nadir of “J” Curve in DBP was at 85 – 90 mm Hg with an increased mortality from MI on either side of this range
Schematic depiction of J-curve: The chart on the left shows an increase in events below a critical pressure level: the J-curve relationship. The chart on the right shows a continuous positive relationship of diastolic pressure achieved on treatment and events.
Hypertension & CAD: Relevance of J Curve

Hypertension & CAD: Relevance of “J” Curve

FARNETT et al

- Consistent J-shaped relationship for cardiac events & DBP but not between treated BP & stroke or SBP and cardiac event.

Organ Specific effect of low DBP

“This might leave a clinician with the uncomfortable choice of whether to prevent stroke or renal disease at the expense of coronary heart disease or vice versa”.

JAMA 1991: 265
Interaction of the J-Curve with Coronary Revascularization
<table>
<thead>
<tr>
<th>First Author/Study Name (Ref. #)</th>
<th>Year</th>
<th>Subjects (n)</th>
<th>Mean Age (yrs)</th>
<th>Mean Entry DBP (mm Hg)</th>
<th>Includes Subjects With CVD</th>
<th>Mean Follow-Up (yrs)</th>
<th>J-Curve Relationship for DBP and Event</th>
<th>Total Mortality or Non-CV Events</th>
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</table>
Incidence of MI & Stroke stratified by diastolic BP in the Invest Study
Hypertension & CAD

Hypertension Optimal Treatment (HOT) Trial

• An additional lowering of BP below minimum value, does not produce a further reduction in events, but it is not harmful.

• There was no evidence of a “J-Curve” for the relation of major CV events, all MI, stroke & CV mortality with achieved BP at least in the ranges observed in the study (down to 70 mm DBP & 120 mm Hg SBP).

• This was also true in the subgroup of > 3000 patients with signs or H/o IHD at randomization.

Lancet 1998: 351
Mechanism(s) of “J” Curve Phenomenon

A) Over aggressive anti-hypertensive therapy could lead to too-low DBP & thus hypo perfusion of coronaries resulting in coronary events.

B) Low DBP could be caused by an increased Pulse pressure reflecting advanced vascular disease & stiffened large arteries.

C) Low DBP could be an epiphenomenon to coexisting or underlying poor health or chronic illness leading to increased morbidity & mortality (Reverse Causality)
Hypertension & CAD: Reverse Causality

EPESE (Established Populations for Epidemiologic Studies of the Elderly)

- N = 10,000, FUP 5 yrs
- At 2 years, SBP showed a J-Curve relationship with all cause mortality
- All cause mortality, CVD and cancer mortality were highest in low DBP group (< 75 mm Hg).

Co-morbidities such as cancer & low weight & hypotension were confounding factors that obscured the true relationship of BP & mortality.
Hypertension & CAD: “J Curve”

META ANALYSIS - Boutitie F et al 2002

• N = 40,233 Hypertensive from 7 Randomized trial
• Positive J Curve relationship between DBP as well as SBP & both fatal cardiovascular & non cardiovascular mortalities.
• J Curve relationship is attributed to poor health, because it was independent of either treatment or type of events.

Ann Intern Med 2002
“The association between BP level & Cardiovascular disease (CVD) risk was generally linear; specifically, there was no evidence of a “J-shaped relationship”.

Yet again, on closer scrutiny, a J-shaped relationship between DBP & MI is observed with a nadir at \( \leq 69 \) mm Hg. Additionally, a similar relationship was observed between DBP & risk of death in all 4902 subjects”.

Psay BM et al: Arch Intern Med 2001
Summary of Clinical Studies Reporting No Clear Association Between Low DBP and Adverse End Points But Upon Further Inspection of Data Pointing to Existence of a J-Curve

<table>
<thead>
<tr>
<th>First Author/Study Name (Ref. #)</th>
<th>Year</th>
<th>Subjects (n)</th>
<th>Mean Age (yrs)</th>
<th>Mean Entry DBP (mm Hg)</th>
<th>Include Subjects With CAD</th>
<th>Mean Follow-Up (yrs)</th>
<th>MI</th>
<th>Stroke</th>
<th>Total Mortality or Non-CV Events</th>
<th>J-Point DBP (mm Hg)</th>
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<td>Hansson (20)</td>
<td>1998</td>
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</table>
Hypertension & CAD: Relevance of “J” Curve

TREATING TO NEW TARGET (TNT) Trial 2010
(N=10001 CHD patients)

- Higher CV event rate seen in group with lowest BP than with SBP 130 – 140 & DBP 70 – 80 mm Hg
- There was much greater risk in group with BP levels of 110 – 120 & 60 – 70 mm Hg

ON-TARGET STUDY (2009) – 75% of patients with CHD

- CV mortality & MI increased for systolic BP value below 126 – 130 mm Hg.
Hypertension & CAD: Relevance of “J” Curve

SMART TRIAL 2012 (N = 5788)

- Patients with manifest CHD, stroke or PVD
- Tried to relate baseline SBP, DBP & PP with the occurrence of vascular events & all cause mortality.
- There was a “J” curve with a nadir of 143/82 mm Hg & claimed that BP above or below this level could be considered an independent risk factor for CV events.

Hypertension & CAD

J Curve “Alive & Threatening”

“The problem is the need to intensify anti-hypertensive therapy to control persistently high systolic BP, which can increase coronary risk through a parallel fall in diastolic BP, especially in the elderly with ISH, who are more likely to have CHD”.

Kaplan NM Hypertension 2011
“We suggest a cautious, individualized approach to treatment, particularly in hypertensive patients with CHD or high risk for impaired Coronary blood flow (elderly & those with LVH). In these patients, we advise against systolic BP levels below 120 – 125 mm Hg & particularly diastolic BP below 70-75 mm Hg”.

Nogueira Jose Rev Port Cardiol 2013: 32
Hypertension & CAD: Relevance of J Curve

- J Curve is found in physiologic range at level of DBP below 70 to 80 mm Hg.

- At the same reduced DBP level, there is little if any evidence of J Curve as regards to other target organs viz. kidney & brain.

- Careful scrutiny of available data shows a J Shaped relationship between DBP & CAD in high risk patients:
  - Elderly
  - LVH & For CAD
  - Wide Pulse pressure
Management of Hypertension in patients with various subset of CAD

The target BP is < 130/80 mm Hg. If ventricular dysfunction is present, consideration should be given to lowering the BP even further, to < 120 /80 mm Hg. In patients with CAD, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (< 60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia (Class II a; LOE B)

Circulation 2007: 115: 2761-88
Hypertension & CAD: Pharmacotherapy

• The most important strategy for lowering the burden of atherosclerotic disease is fastidious BP control.

• BP Lowering is more important than the choice of drug class in the primary prevention of the complication of hypertension.

• Effective combination anti-hypertensive therapy is required to achieve & sustain effective long term BP control.

• The question of which class of agents to use first in hypertension is essentially moot.
Hypertension & CAD: Pharmacotherapy (contd…)

- There are class effects for thiazide-type diuretics, ACE inhibitors & ARBs due to high degree of homogeneity in mechanism of action & side effects.

- Major differences between drugs within more heterogeneous classes of agents such as B-blockers & CCBs.
Hypertension & CAD: Thiazide Diuretics

• Highly effective in reducing BP & preventing cerebrovascular events
  - VAS 1970
  - MRC Trial 1985
  - SHEP 1991
  - ALLHAT 2003

• Concern – Thiazide induced hyperglycemia & diabetes mellitus contributes to long term IHD risk not measured during study interval.

Verdecchio P et al: Hypertension 2004
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

33,357 patients with HTN and ≥1 CHD risk factor randomized to chlorthalidone, amlodipine, or lisinopril for 5 years

There is similar efficacy among BP lowering agents

BP=Blood pressure, CHD=Coronary heart disease, HTN=Hypertension, MI=Myocardial infarction
### β-blocker Evidence: Secondary Prevention

#### Placebo-Controlled Post-MI Trials* Using Oral β-Blockers

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Treatment Groups</th>
<th>Duration of Follow-Up</th>
<th>Effect on Mortality</th>
<th>Effect on Reinfarction</th>
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<td>Göteborg Study†</td>
<td>1,395</td>
<td>Metoprolol tartrate</td>
<td>3 months</td>
<td>↓ 36% (P&lt;.03)</td>
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<td>Timolol Trial (Norwegian)</td>
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<td>b-blocker Heart Attack Trial</td>
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<td>25 months</td>
<td>↓ 26% (P&lt;.005)</td>
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<td>CAPRICORN Trial</td>
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<td>15 months</td>
<td>↓ 23% (P=.03)</td>
<td>↓ 40% (P=.01)</td>
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MI=Myocardial infarction, NA=Not applicable, NS=Not significant

*Includes the largest trials performed to date
†Patients received IV followed by oral metoprolol
## β-blocker Evidence: Secondary Prevention

### Summary of Secondary Prevention Trials of β-blocker Therapy

<table>
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<tr>
<th>Phase of Treatment</th>
<th>Total # Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment</td>
<td>28,970</td>
<td>0.87 (0.77-0.98)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>24,298</td>
<td>0.77 (0.70-0.84)</td>
</tr>
<tr>
<td>Overall</td>
<td>53,268</td>
<td>0.81 (0.75-0.87)</td>
</tr>
</tbody>
</table>

CI=Confidence interval, RR=Relative risk

### β-blocker Evidence: Secondary Prevention

Hypertension & CAD: Betablockers

• A heterogeneous class of anti-hypertensive drugs

• B-blockers administration remains a standard of care in patients with angina, MI & with LV dysfunction with or without HF symptoms unless contraindicated.

• The use of B-blockers for secondary prevention in all but the lowest risk patient is a (Class I, LOE-A) indication.

• Even for the lowest risk patients weight of evidence favours their use (Class II a, LOE-B)
Hypertension & CAD: Beta Blockers

- Patients who do not have symptomatic CAD
  - have not had an MI
  - do not have HF

- Evidence for B-Blocker Cardio protection is weak, especially in elderly.


- Relative lack of benefit on cerebrovascular, renal disease endpoints.

  LIFE: Lancet 2002
  Wright et al: JAMA 2002
Hypertension & CAD: Calcium Channel Blockers

- Forms a heterogeneous class of agents with similar BP effects but differing action on cardiac conduction & contractility.

- **ALLHAT (JAMA 2002)**
  - Primary prevention of CV event with dihydropyridine CCB
  - Amlodipine was equivalent to that produced by Diuretics or ACE inhibitor based therapy

- **ASCOT (Lancet 2005)**
  - Superiority of CCB over Betablockers
Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA)

19,342 high-risk hypertensive patients with 3 additional CV risk factors randomized to amlodipine (10 mg) & perindopril (8 mg) or atenolol (100 mg) & bendroflumethiazide (2.5 mg) for 5.5 years

There is similar efficacy with both BP lowering regimens

BP=Blood pressure, CV=Cardiovascular, CHD=Coronary heart disease, MI=Myocardial infarction

Hypertension & CAD: Calcium Channel Blockers

- **CAMELOT (2004) – Amlodipine Vs Enalapril**
  - BP reduction was similar in two groups
  - Adverse CV event occurs less frequently in Amlodipine group than in Enalapril group
  - **INTRAVASCULAR ULTRASOUND SUBSTUDY**
    - Progression of atherosclerosis in placebo group
    - A trend towards progression in Enalapril group
    - No progression in Amlodipine group

- Amlodipine may have pleiotropic effects beyond BP lowering that favours atherosclerotic plaque stabilization

Nisson et al: JAMA 2004
Mason et al: Atherosclerosis 2002
Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) Trial

1,991 patients with CAD and a DBP <100 mmHg randomized to amlodipine (10 mg), enalapril (20 mg), or placebo for 2 years

*Includes CV death, myocardial infarction, cardiac arrest, coronary revascularization, hospitalization for heart failure or angina pectoris, stroke, transient ischemic attack, development of peripheral arterial disease

A BP <130/80 mmHg is associated with fewer CV events*

*Includes CV death, myocardial infarction, cardiac arrest, coronary revascularization, hospitalization for heart failure or angina pectoris, stroke, transient ischemic attack, development of peripheral arterial disease

BP=Blood pressure, CAD=Coronary artery disease, CV=Cardiovascular, DBP=Diastolic BP

Nissen S et al. JAMA 2004;292:2217-26
Hypertension & CAD: Calcium Channel Blockers

• NORDIL (Nordic Diltiazem Study)
  - Overall cardiovascular event rates were similar for Diltiazem & a combination of Diuretics & Betablockers

Hypertension & CAD: Calcium Channel Blockers

- INVEST (2003)
  - N = > 22000 hypertensives with chronic CAD
  - Verapamil or Atenolol

24 months Follow up, ACE INHIBITOR TRANDOLAPRIL required in:
  - 63% of Verapamil group
  - 52% of Atenolol group

- Hydrochlorothiazide
  - 44% of Verapamil group
  - 60% of Atenolol group

No difference between groups in the composite endpoints of death, MI or stroke over a mean follow up of 2.7 years.

Pepine et al: JAMA 2003: 290
Blood Pressure Evidence: Secondary Prevention

International Verapamil-Trandolapril Study (INVEST)

22,576 patients with HTN and CAD randomized to a BP lowering strategy with verapamil SR (240 mg) or atenolol (50 mg) for 2.7 years

There is comparable efficacy with a CAS or NCAS

RR=0.98, P=0.57

Blood Pressure Evidence: Secondary Prevention

International Verapamil-Trandolapril Study (INVEST)

22,576 patients with HTN and CAD randomized to a BP lowering strategy with verapamil SR (240 mg) or atenolol (50 mg) for 2.7 years

There is comparable efficacy with a CAS or NCAS

Incidence of death, MI, or stroke

Months

RR=0.98, P=0.57

Calcium antagonist strategy (CAS)*

Non-calcium antagonist strategy (NCAS)*

Pepine CJ et al. JAMA 2003;290:2805-2816

*Trandolapril (up to 4 mg) was added in those with DM, chronic kidney disease, or heart failure.
Hypertension & CAD: Calcium Channel Blockers

VALUE Randomized Trial (2004) – n = 15245

“Outcome in hypertensive patients at high cardiovascular risk treated with regimen based on Valsartan or Amlodipine”.

- 46% of patients in both group had CAD
- Mean FUP 4.2 yearske in Valsartan group

- No difference between groups in primary composite endpoints of cardiac morbidity & mortality.

- Risk of MI was lower in Amlodipine group, whereas risk of new onset DM was lower in Valsartan group.

- Amlodipine was more effective in reducing BP

- Strong trend for an excessive risk of stroke in Valsartan group

Julins et al: Lancet 2004
Hypertension & CAD: Calcium Channel Blockers in ACS

• **DAVIT (DANISH Verapamil Infarction Trial – 1997) – n = 3447**
  - A trend in reducing the outcomes of death or non fatal MI in patients with suspected ACS

• **DRS (Diltiazem Reinfarction Study) – 1986**
  - n = 576 treated with Diltiazem or Placebo 24 to 72 hours after onset of non Q MI
  - There was significant reduction in reinfarction rate & refractory angina at 14 days.
Hypertension & CAD: Calcium Channel Blockers

- **DAVIT & MDPIT (Retrospective Analysis)**
  
  - Verapamail or Diltiazem in patients with ACE who have LV dysfunction has an overall detrimental effect on mortality

- Not recommended for secondary cardiac protection because of the relative inability of this class of drug to prevent ventricular dilatation & HF especially compared to ACE inhibitors or ARBs

*Gold Stein et al: Circulation 1991: 83*
Hypertension & CAD : Calcium Channel Blockers

- CCBs are added to or substituted for B-Blockers
  - When BP remains elevated
  - When angina persists
  - When drug side effects or contraindication mandate:

- CCBs are useful in management of angina, there is no consensus about their role in preventing cardiovascular events in established CAD.

Hypertension & CAD: ACE Inhibitors

- A relatively homogeneous class of antihypertensive agent
  - Effective in reducing initial IHD events
  - Proven to forestall & treat HF and kidney failure
  - Reduce the incidence of recurrent stroke when combined with Diuretics

Lancet 2001

NEJM 1991: 325
NEJM 1992: 327
Hypertension & CAD: ACE Inhibitors

- **HOPE (Yusuf et al: NEJM 2000) – N = 9297**
  - Patient 55 yrs or older with evidence of DM or vascular disease plus one other CV risk factors
  - Ramipril Vs Placebo
  - FUP – Mean 5 years
  - 47% were hypertensive, 8.4% EKG – LVH

- 22% reduction in the composite endpoint of CV death, MI & stroke
  - Magnitude of reduction in endpoints were similar in patients with & without hypertension
  - Significant reduction in rate of revascularization, HF, worsening angina & control all cause mortality.
Heart Outcomes Prevention and Evaluation (HOPE) Study

9,297 patients with DM or vascular disease plus an additional CV risk factor, but without HF or known LVSD randomized to ramipril (10 mg) or placebo for 5 years.

ACE-I reduce CV events in high-risk individuals

ACE-I=Angiotensin converting enzyme inhibitors, DM=Diabetes mellitus, CV=Cardiovascular, HF=Heart failure, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction

HOPE Investigators. NEJM 2000;342:145-153
Comparative effects of Ranipril on Ambulatory & office blood pressure

A HOPE Substudy Hypertension 2001: 38

“A marked reduction in 24 hours Ambulatory BP with ACE Inhibitors that was missed in the main trial that measured only office BPs”.
Hypertension & CAD: ACE Inhibitors

EUROPA – N = 12218 (FUP = 4.2 Yrs) Parindopril Vs Placebo

- Perindopril therapy was associated with a 20% relative risk reduction in the primary endpoints, a composite of CV death, MI.
- The benefit of active treatment with Perindopril was similar for patients with & without hypertension.

Fox et al: Lancet 2003
ACE Inhibitor Evidence: Secondary Prevention

European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)

12,218 patients with CAD and presumed normal LV function randomized to perindopril (8 mg) or placebo for 4 years

Cardiovascular death (0.86; 0.72-1.03)
Non-fatal MI (0.78; 0.20-0.90)
Cardiac arrest (0.54; 0.20-1.47)
Combined endpoint (0.80; 0.71-0.91)

ACE-I reduce CV events in intermediate-risk individuals

ACE-I=Angiotensin converting enzyme inhibitors,
CAD=Coronary artery disease, CV=Cardiovascular,
MI=Myocardial infarction

Hypertension & CAD : ACE Inhibitors

Prevention of Events with Angiotensin Converting Enzyme Inhibitors (PEACE) Trail

- Trandoparil Vs Placebo
- Stable CAD, Normal or Slightly reduced EF
- FUP 4.8 years
- No difference in incidence of primary composite & point of CV death, MI or coronary revascularization

ACE Inhibitors might not be necessary as routine therapy in low risk CAD patients with preserved LV function

Braunwald et al: NEJM 2004
Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial

8,290 patients with stable CAD and normal LV function randomized to trandolapril (4 mg) or placebo for 5 years

ACE-I do not reduce CV events in lower-risk individuals

*Includes death from cardiovascular causes, myocardial infarction, or coronary revascularization

The PEACE Trial Investigators. *NEJM* 2004;351:2058-68
Second Australian National Blood Pressure Study Group (ANBP – 2)

- Patient 65 – 84 years with hypertension
- In man but not in women, better CV outcome with ACE inhibitors than with Diuretics despite similar reduction in BP.

Wing et al: NEJM 2003
## ACE Inhibitor Evidence: Secondary Prevention

### Meta-Analysis of the HOPE, EUROPA, and PEACE Trials*

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>N</th>
<th>Deaths</th>
<th>RR of Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>9,297</td>
<td>1051</td>
<td>HR=0.84 P=0.005</td>
</tr>
<tr>
<td>EUROPA</td>
<td>12,218</td>
<td>795</td>
<td>HR=0.89 P=0.10</td>
</tr>
<tr>
<td>PEACE</td>
<td>8,290</td>
<td>633</td>
<td>HR=0.89 P=0.13</td>
</tr>
<tr>
<td>All Trials</td>
<td>33,960</td>
<td>&gt;3000</td>
<td>HR=0.86 P&lt;0.001</td>
</tr>
</tbody>
</table>

*7 RCTs, 33,960 randomized patients, and 4.4 years of mean follow-up. Other findings include a CVD HR=0.81, MI HR=0.82, and stroke HR=0.77

ACE-I=Angiotensin converting enzyme inhibitors,
CVD=Cardiovascular disease, MI=Myocardial infarction

ACE Inhibitor Evidence: Secondary Prevention

ACE-I provide substantial benefit in post-MI LVSD

ACE-I=Angiotensin converting enzyme inhibitors, EF=Ejection fraction, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction, OR=Odds ratio

Hypertension & CAD: ARBs

- ARBs are highly uniform in their CV effects

- **VALUE STUDY**
  - Primary protection against CV events similar to that produced by a calcium antagonist (Amlodipine)

- **VALIANT TRIAL (2003)**
  - ARB therapy was similar to ACE inhibitions in reducing CV endpoints.

Pfeffer et al: NEJM: 2003
Valsartan in Acute Myocardial Infarction Trial (VALIANT)

14,703 patients with post-MI HF or LVSD (EF <0.40) randomized to captopril (50 mg tid), valsartan (160 mg bid), or captopril (50 mg tid) plus valsartan (80 mg bid) for 2 years.

**Figure:**

- **Red line:** Captopril
- **Black line:** Valsartan
- **Green line:** Valsartan + Captopril

- **Valsartan vs. Captopril:** HR = 1.00; P = 0.982
- **Valsartan + Captopril vs. Captopril:** HR = 0.98; P = 0.726

**Graph:**

All Cause Mortality

0.0 0.1 0.2 0.3 0.4

0 6 12 18 24 30 36

**Months**

**ARB Evidence: Secondary Prevention**

**ARB** provide similar efficacy to ACE-I in Post-MI LVSD.

ACE-I=Angiotensin converting enzyme inhibitors,
ARB=Angiotensin receptor blockers, EF=Ejection fraction, LVSD=Left ventricular systolic dysfunction

Pfeffer M et al. NEJM 2003;349:1893-1906
Hypertension & CAD: Pharmacotherapy

**Primary Prevention:**

- Amount of BP reduction rather than the choice of anti-hypertensive drug, is the major determinant of reduction of CV risk.

- ACEI, ARB, CCB or Diuretics as first line of therapy, supplemented by a second drug if BP control is not achieved.

- In asymptomatic post MI patient, a B-blocker is more appropriate choice (Class I / A).
Hypertension & CAD: Pharmacotherapy

CAD with Stable Angina

- B-blocker in patient with H/o MI.
- ACEI / ARB in DM and or LV systolic dysfunction & a thiazide diuretics (Class I / c)
- Combination of B-blocker, ACE inhibitors or ARB, and a thiazide diuretics should also be considered in absence of a prior MI, DM or LV dysfunction (Class II a / B).
Hypertension & CAD: Pharmacotherapy

Chronic Stable angina

- If betablockers are contraindicated or produces intolerable side effects. Nondihydropyridine CCBs (Diltiazem / Verapamil) can be substituted, but not if there is LV dysfunction (Class IIa / B).

- If angina or hypertension remains uncontrolled, a long acting dihydropyridine CCB can be added to the basic regime of B-blocker, ACEI & thiazide diuretics (Class IIa / B)
Hypertension & CAD: Pharmacotherapy

**Acute Coronary Syndrome**

- Initial therapy of hypertension short acting $B_1$ selective B-blocker without ISA (usually IV) &

- Oral Betablocker can be substituted later (Class II a, LOE B)

- Oral betablocker can be started promptly without prior use of I/V [Class I (A)]
Hypertension & CAD: Pharmacotherapy (contd…)

**Acute Coronary Syndrome**

A) - Nondihydropyridine CCBs (Diltiazem / Verapamil) may be substituted, but not in case of LV dysfunction

- If BP is not controlled with B-blocker alone then long acting dihydropyridine CCB / Diuretics can be added (Class I / B).

B) If patient is hemodynamically stable

- ACE Inhibitor (Class I / A) or
- ARBs (Class I / B) should be added if
  - Patient has Anterior MI
  - Hypertension persists
  - LV dysfunction or HF
  - Diabetes mellitus
Acute Coronary Syndrome

C) Aldosterone Antagonist

- helpful in STEMI with LV dysfunction & HF

- have additive BP lowering effects (class I / A)
Hypertension & CAD

• CAD is the most common outcome of hypertension.

• The CV risk attributed to hypertension can be reduced by optimal BP control.

• The target BP in hypertensive patients with CAD is < 130 / 80 mm Hg with caution in lowering the DBP below 60 mm Hg.

• To achieve & sustain the target effective combination antihypertensive drug therapy is required.

• The overall goal of therapy is to reduce morbidity & mortality associated with both hypertension & CAD.