

# SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

The role of ACE inhibitors  
(ACEi) and Angiotensin  
receptor blockers (ARBs)

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# Levels of Evidence

- A: Data derived from multiple randomised clinical trials or metaanalyses.
- B: Data derived from a single randomised clinical trials or non randomised studies.
- C: Consensus of opinion of the experts and/or small studies

# Recommendations Presented as Class I, II or III

**Class I:** Evidence and/or general agreement that a given procedure/treatment is beneficial & effective.

**Class II:** Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the procedure/treatment.

**Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy.

**Class II b:** Usefulness/efficacy is less well established by evidence/opinion.

**Class III:** Evidence or general agreement that the treatment is not useful/effective and, in some cases, may be harmful.

# The "well-known" effects of ACEi

## ➤ Haemodynamic effects

- ACEi decrease total peripheral vascular resistance
- In heart failure ACEi cause arterial and venous dilatation thus reducing capillary wedge pressure and left ventricular pressure
- ACEi reduce cardiac hypertrophy and systemic blood pressure

# The “well-known” effects of ACEi

## ➤ Neurohormonal effects:

After initial administration, ACEi

- Decrease angiotensin-II and aldosterone and increase renin release and angiotensin I
- Reduce epinephrine, norepinephrine and vasopressin in plasma
- Increase the production of bradykinin

# The “well-known” effects of ACEi

**During chronic administration of ACEi:**

Angiotensin-II and aldosterone return to baseline values

ACEi increase NO, kinin and prostacyclin levels

Prevent progression of microalbuminuria and kidney damage in patients with type 2 diabetes and in non diabetic people



# Other effects of ACEi

- ACEi have antiatherogenic properties:
- They reduce migration and proliferation of vascular smooth muscle cells, decrease oxidative stress and activation of inflammatory cells, and also improve endothelial function.

Pitt B. Potential role of angiotensin converting enzyme inhibitors in the treatment of atherosclerosis. Eur Heart J 1995;16:49-54.

Schoelkens BA, Landgraf W. ACE inhibition and atherosclerosis. Can J Physiol Pharmacol 2002;80:354-9.

# Use of ACEi in Heart Failure

## Class I Level A:

- All patients with symptomatic heart failure and reduced left ventricular systolic dysfunction (LVSD), functional class II-IV.
- LVSD with/without symptoms after acute myocardial infarction.
- LVSD (reduced LVEF <40-45%) without symptoms, no previous myocardial infarction.

## Class II a Level C:

- Diastolic failure.

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The task force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004;25:1454-70



# Use of ACEi in Evolving Myocardial Infarction

## Class I Level A:

- Clinical heart failure
- Asymptomatic left ventricular dysfunction (LVEF < 45%)
- Diabetes or other high risk patients

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The task force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004;25:1454-70

# Use of ACE-I in Hypertension

## Class I Level A:

- To control blood pressure in patients with heart failure, systolic left ventricular dysfunction, diabetes, previous myocardial infarction or stroke, and subjects at high coronary disease risk

# Use of ACE-I in Secondary Prevention

➤ Class I Level A:

High risk patients (i.e. Those with evidence of cardiovascular disease or diabetes and one other risk factor)

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The task force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004;25:1454-70

# Use of ACE-I to Prevent Sudden Death

## ➤ Class I Level A:

- Patients with heart failure
- Patients with previous myocardial infarction

## ➤ Class I Level B:

- Patients with dilated cardiomyopathy

# Comparing ACEi with angiotensin receptor blockers

Studies comparing these types of drugs failed to find substantial differences

- **ELITE 2:** Losartan vs captopril - mortality similar in both groups
- **OPTIMAAL:** Losartan vs captopril: mortality similar in both groups
- **VALIANT:** Valsartan vs captopril: no differences between groups regarding mortality or other clinical outcomes

ELITE 2. Lancet 2000;355:1582-7; OPTIMAAL. Lancet 2002; 360: 752-60; VALIANT. N Engl J Med 2003;349:1893-906

# Comparing ACEi with angiotensin receptor blockers

- **CHARM: Candesartan vs placebo, and Candesartan given in addition to ACEi (CHARM added study) improved outcome and mortality in patients with heart failure**

CHARM. Lancet 2003;362:759-66  
CHARM Added. Lancet 2003;362:767-71



# Secondary prevention in patients with diabetes: The ADVANCE Study

The ADVANCE study assessed the effects of the administration of an angiotensin converting enzyme and diuretic combination on serious vascular events in patients with diabetes:

## Results:

- 14% reduction in total mortality
- 18% reduction in cardiovascular mortality
- 14% reduction coronary events
- 21% reduction kidney events

# ACEi versus ARB treatment on mortality and renal outcomes in diabetic nephropathy

- ACEi and ARBs have similar effects on renal outcomes
- ACEi reduce all cause mortality but ARBs do not
- Reliable estimates of the unconfounded relative effects of ACEi compared with ARBs cannot be ascertained from current data due to small sample sizes
- Although the survival benefits of ACEi for patients with diabetic nephropathy are known, the relative effects of ACEi vs. ARBs on survival are unknown owing to the lack of adequate head to head trials

# Use of ACEi in Secondary prevention

## ACC/AHA Update 2006

- Start and continue indefinitely in all patients with LV ejection fraction  $< 40\%$  and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. Class I-A
- Consider for all other patients Class I-B
- Among lower risk patients with normal LV EF in whom cardiovascular risk factors are well controlled and revascularization has been performed use of ACE-I may be considered optional Class II-B

# Use of ACEi in Secondary prevention

## ACC/AHA Update 2006

### Angiotensin receptor blockers:

- Use in patients who are intolerant of ACE-I and have heart failure or have had a myocardial infarction with left ventricular ejection fraction < 40 % - Class I- A
- Consider in other patients who are ACEi intolerant - Class I- B
- Consider use in combination with ACE-I in systolic-dysfunction heart failure - Class IIb- B

# References

