

Open Debates in Cardiology

Thiazide Diuretics.
must be used, should not
and can be used.

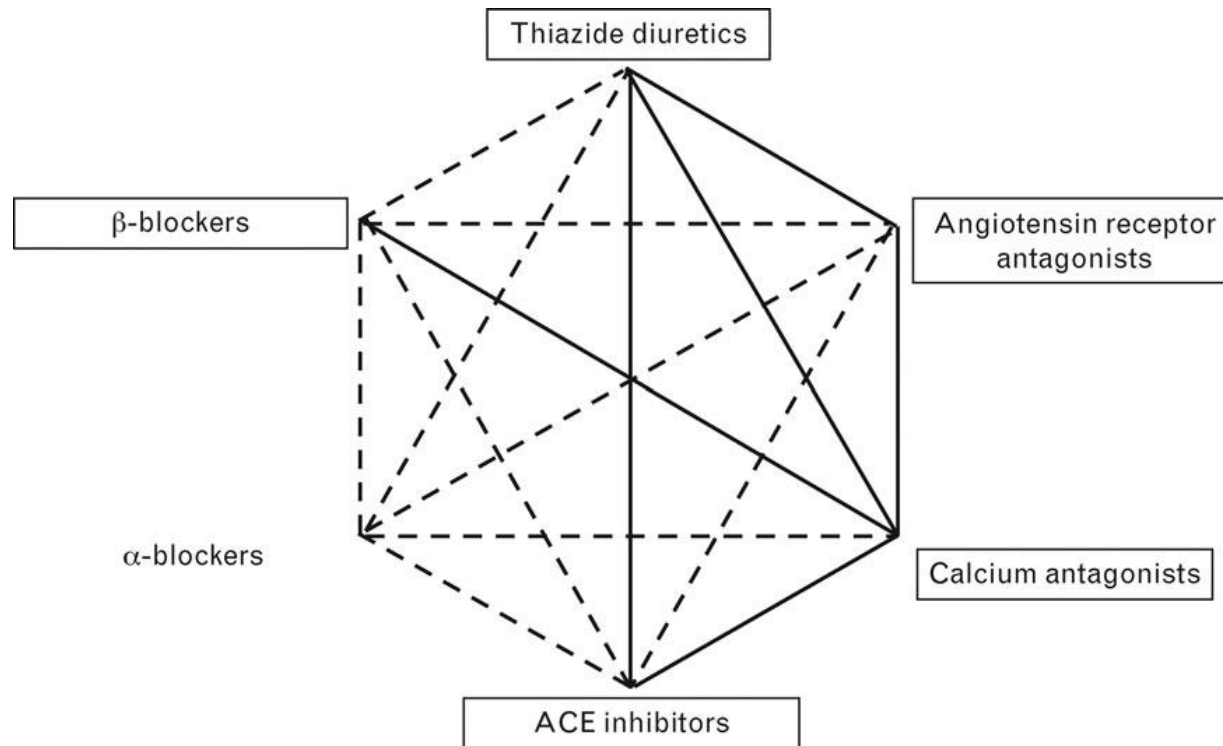
Rafael Ferreira, MD, PhD.
Lisbon

Thiazides in Hypertension

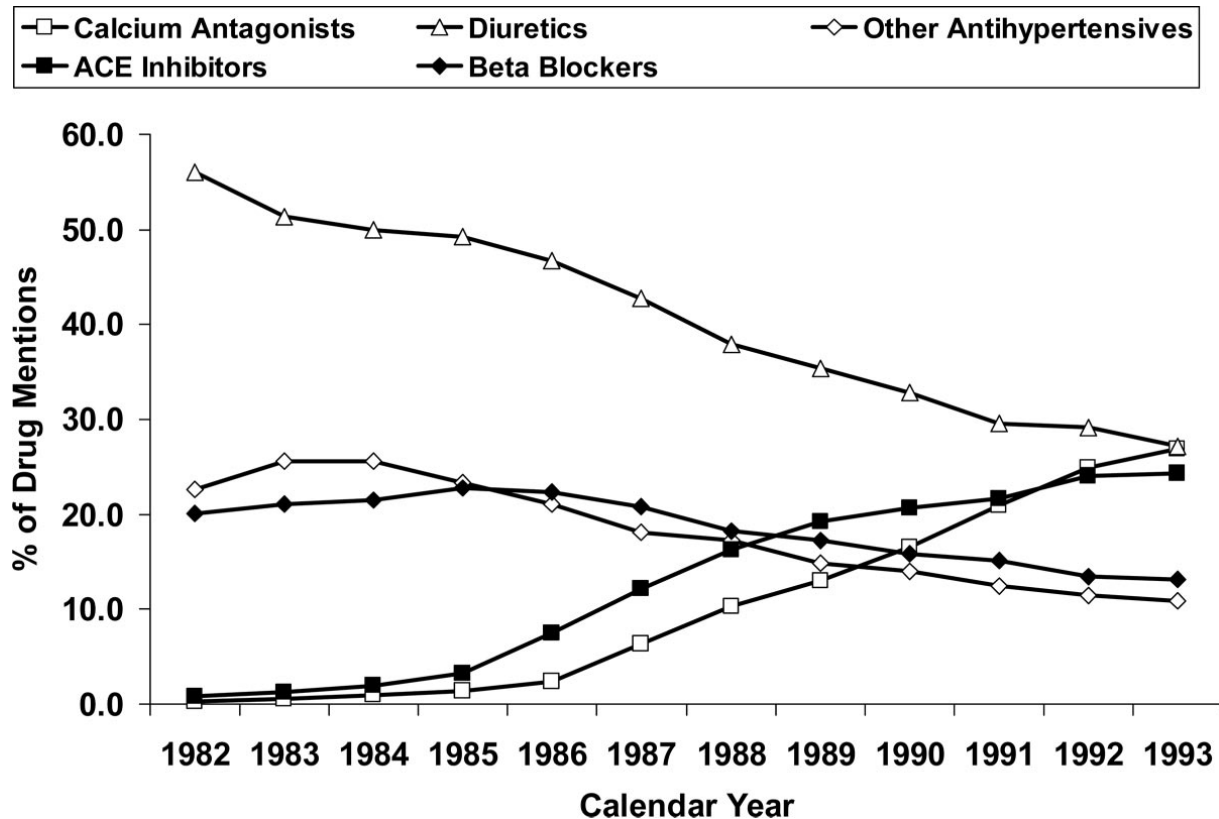
Clinical Pharmacology

1. The onset of action occurs after 2 to 3 hours for most thiazides.
2. Most thiazides have a half-life of 8 to 12 hours, just permitting effective once daily dosing.
3. Chlorthalidone has an elimination half-life of 50 to 60 hours, and is twice as potent as HCTZ.
4. Initial decreases in BP are attributed to the reductions in extracellular fluid and plasma volumes. The persistent antihypertensive effects are due to an overall reduction in systemic resistance.

Combinations between some classes of antihypertensive drugs



Use of antihypertensive agents, 1982-93



Thiazides in Hypertension

Decline of the use of Diuretics to treat Hypertension

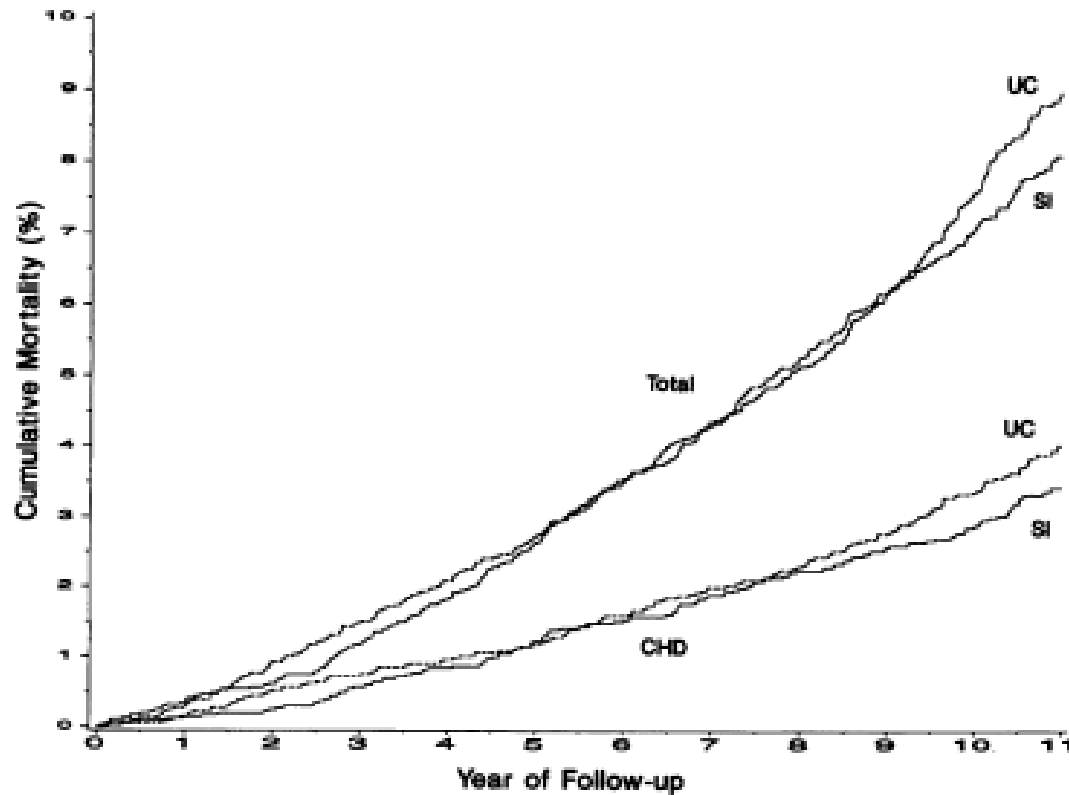
1. Concerns raised regarding metabolic effects
2. Results of trials that used doses of thiazides much higher than in use today
3. Effective marketing of newer patented drugs.

Thiazides in Hypertension

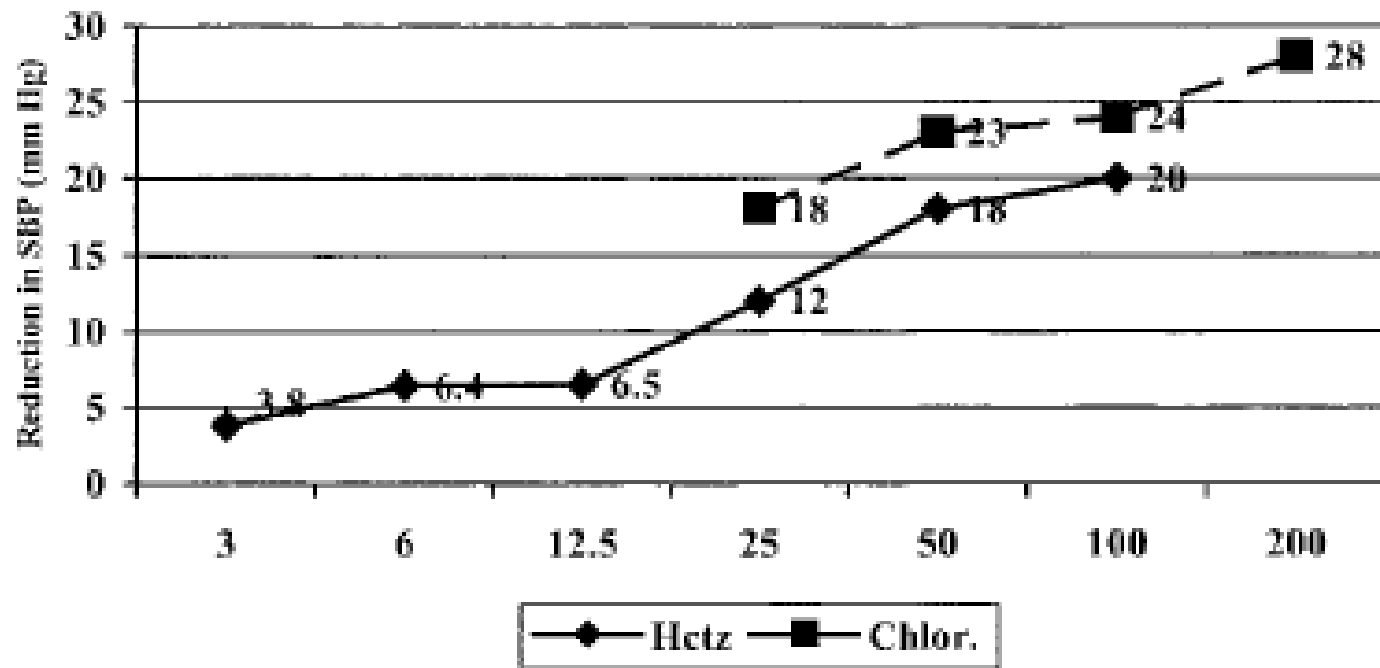
ADVERSE EFFECTS

1. **Hypokalemia**
2. Hyperuricemia
3. **Dysglycemia - Diabetes**
4. Hyponatremia; Hypomagnesemia

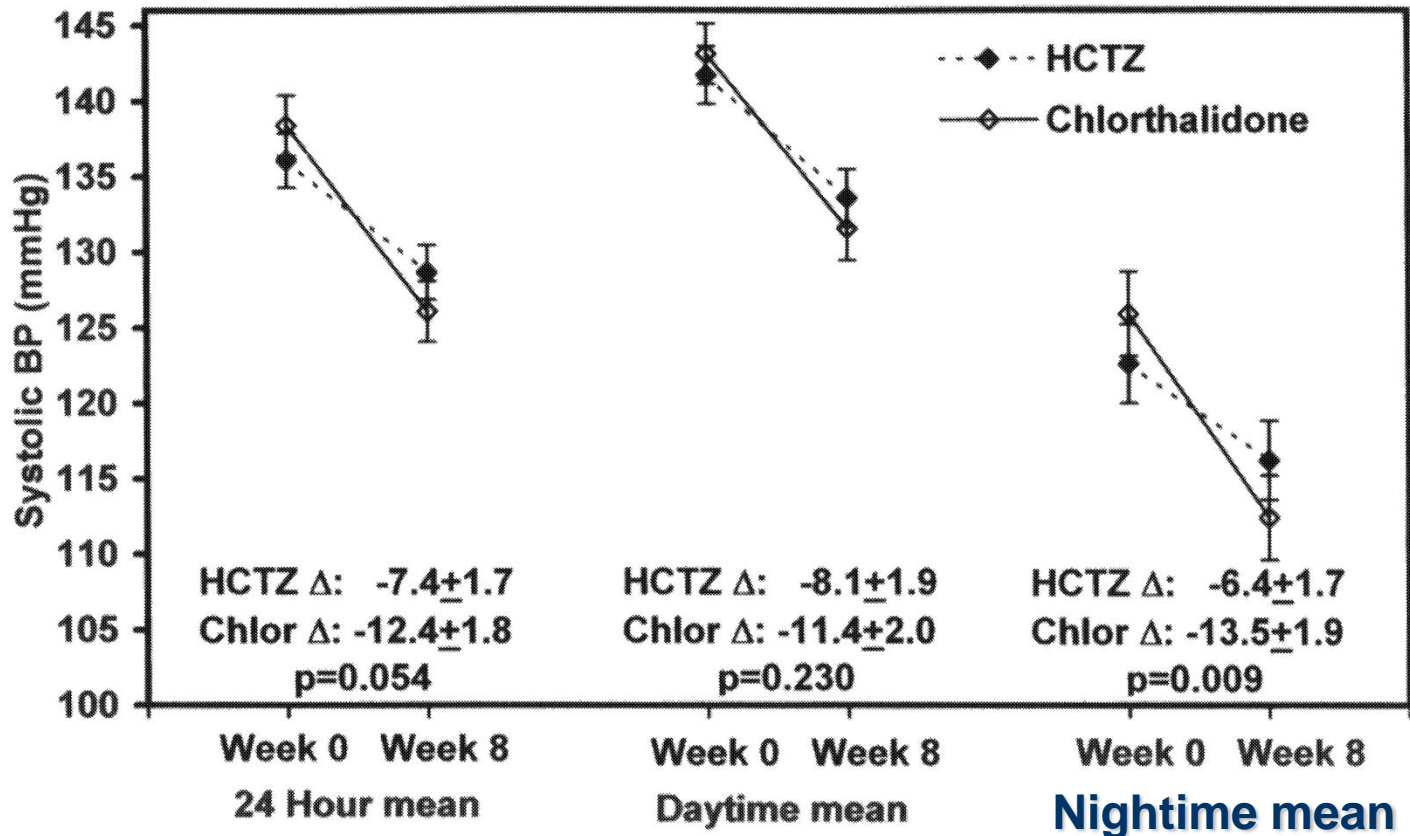
MRFIT - Mortality after 10 1/2 years



HCTZ versus Chlorthalidone



AntiHT effects of HCTZ and Chlorthalidone - ABPM



Thiazides in Hypertension

ALLHAT Trial

Ace-In, Ca CB versus diuretic in HT patients

- Feb.1994 to March 2002; - 33357 pts aged 55y or older.
- **Chlorthalidone** 12,5 to 25 mg/d (n-15255); **Amlodipine** 2,5 to 10mg/d (n-9048); **Lisinopril** 10 to 40mg/d (n-9054).

Main outcome- combined fatal CHD or nonfatal MI. Mean F-up - 4.9y.

Primary outcome - 11,5% for Chlorth; 11,3% for amlod; 11,4% for Lisin.

Amlodipine-more HF; Lisinopril-more CVD, stroke and HF.

Thiazides in Hypertension

ALLHAT Trial

Conclusion

Thiazide-type diuretics are superior in preventing one or more major forms of Cardiovascular Disease.

Thiazides in Hypertension

Second Australian National BP Study

6083 patients - 65 to 84 years - Follow-up - 4.1y

ACE-In versus **HCTZ**

BP decrease to a similar extent in both groups

The rates of nonfatal CV events and MI decrease with ACE-In.

A similar number of strokes occurred in each group.

Conclusion - ACE-In are better than diuretics, despite similar reduction of BP.

Thiazides in Hypertension

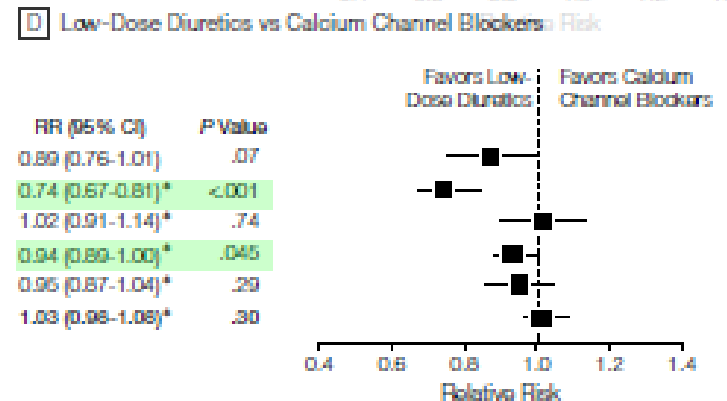
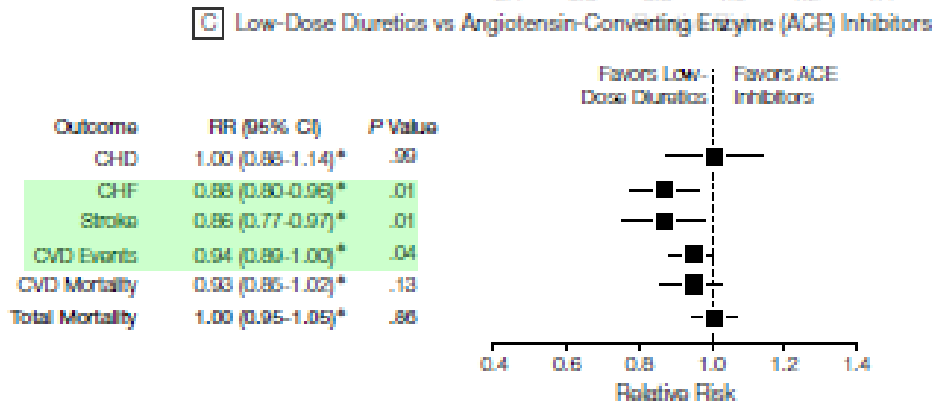
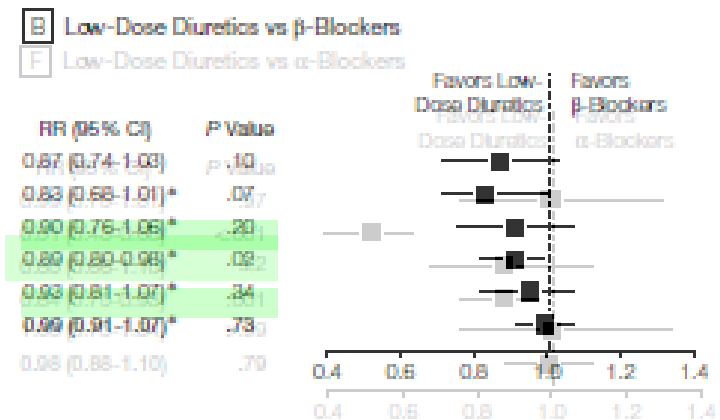
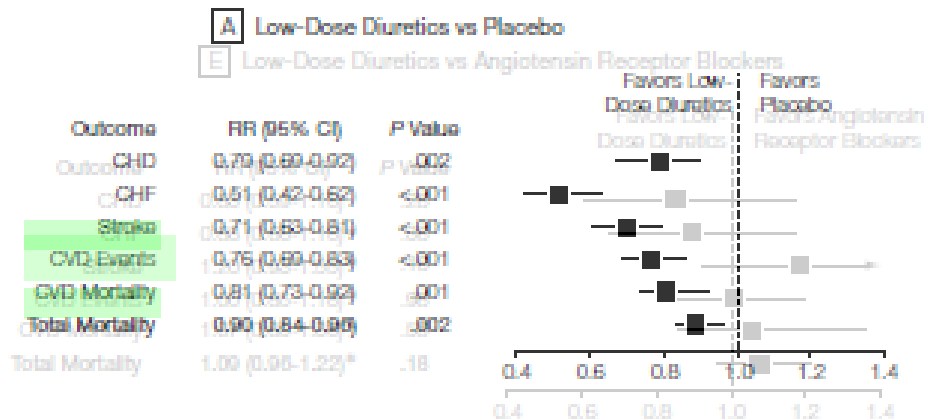
EDITORIALS



Treating Hypertension — What Are We to Believe?

Edward D. Frohlich, M.D.

Health outcomes with antiHT therapies

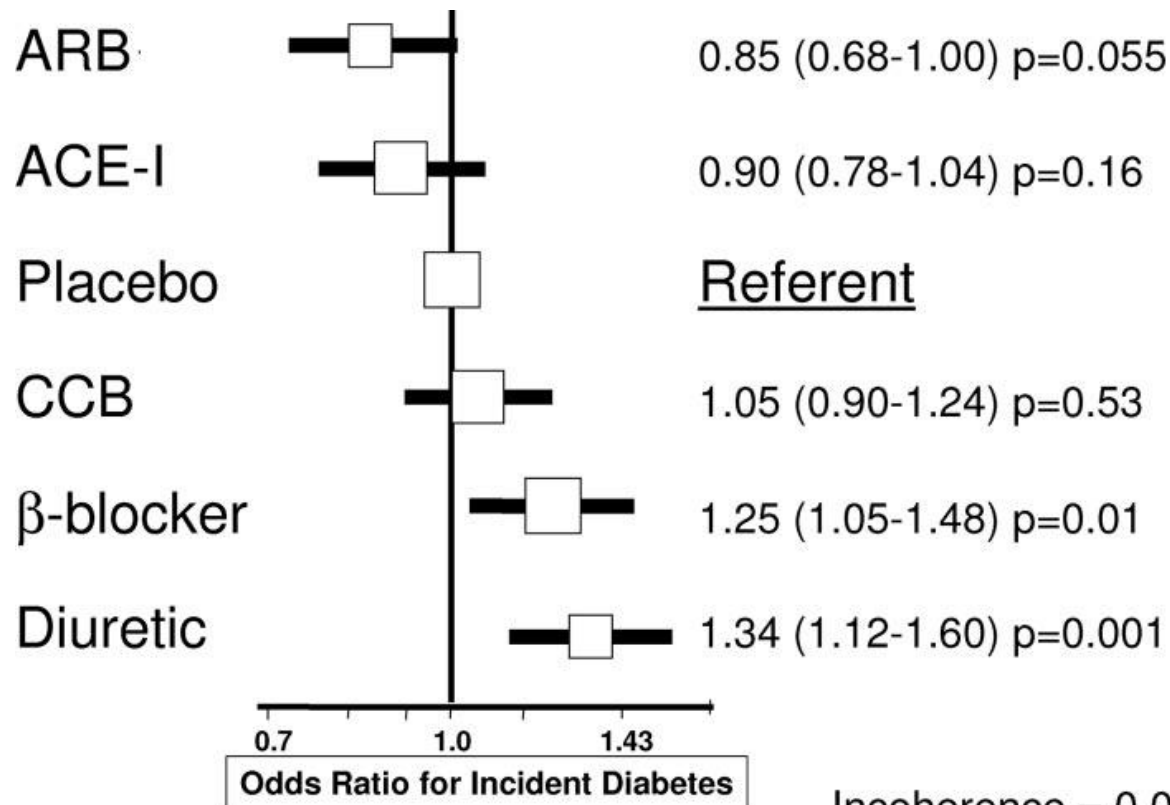


Thiazides in Hypertension

New-Onset DB with Thiazides

1. ALLHAT study – 2002
10% of all patients developed NOD throughout the 5y of the study – 18% to 40% higher in patients in the chlorthalidone arm. No more CV events at 4-6y follow-up.
2. ALPINE study – 2003
After 1 year, 18 patients in the diuretic group developed metabolic syndrome, and 9 had NOD.
3. META-ANALYSIS – Messerli et al – 2008
Diuretics – 32% increase risk of NOD.
4. SHEP study – 2005
No significant increase in CV events in patients with DB + chlorthalidone therapy.

Risk of NOD with antiHT treatment



Incoherence = 0.054

Thiazides in Hypertension

NEW ONSET DIABETES WITH THIAZIDES

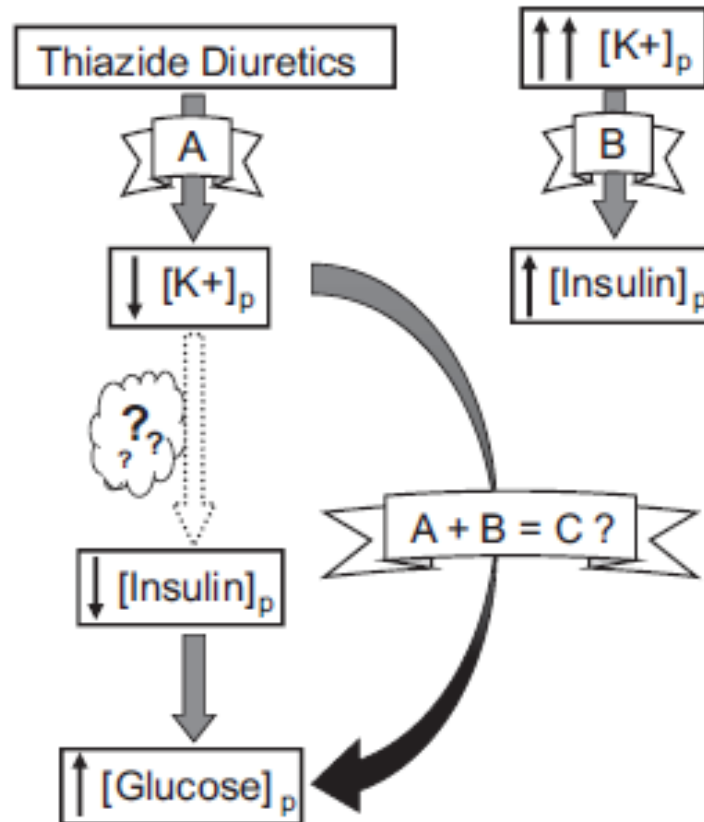
NOD associated with diuretics may be reversible on the discontinuation of diuretic. Thus treatment withdrawal could potentially separate the drug-induced NOD from spontaneously occurring new onset diabetes.

Messerli FH, et al
Circulation, 2008

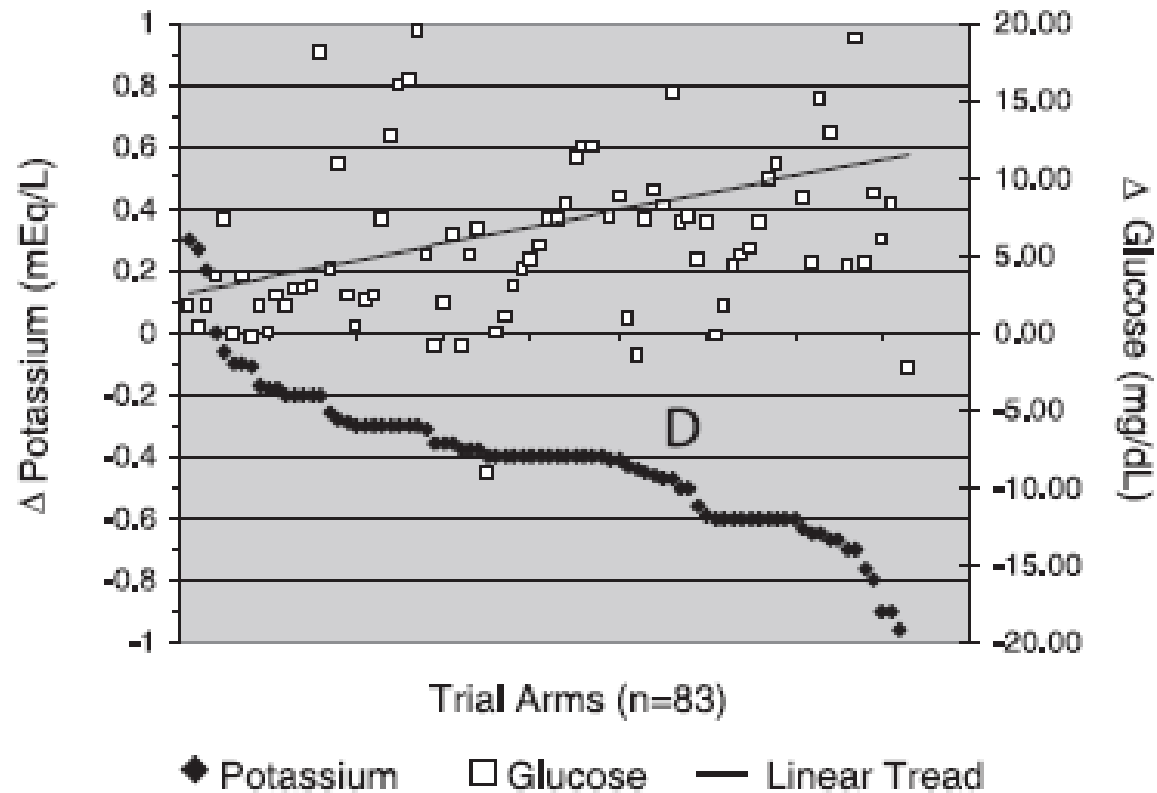
The cause of the Diabetes epidemic is increasing overweight/obesity and physical inactivity. Most NOD in diuretic treated patients is not diuretic induced. Cases that are can likely be prevented by avoiding significant potassium depletion.

Cutler JA, Davis BR
Circulation, 2008

Relationship between Thiazide induced hyperglycemia and hypokalemia



Thiazides, Potassium and NOD



Thiazides in Hypertension

ACCOMPLISH Trial

Benazepril plus amlodipine or HCTZ for HT

Methods - 11,506 HT patients with high risk for CV events

Primary endpoint - death from CV causes, nonfatal MI.

Results - The trial was terminated after a mean F-up of 36 months

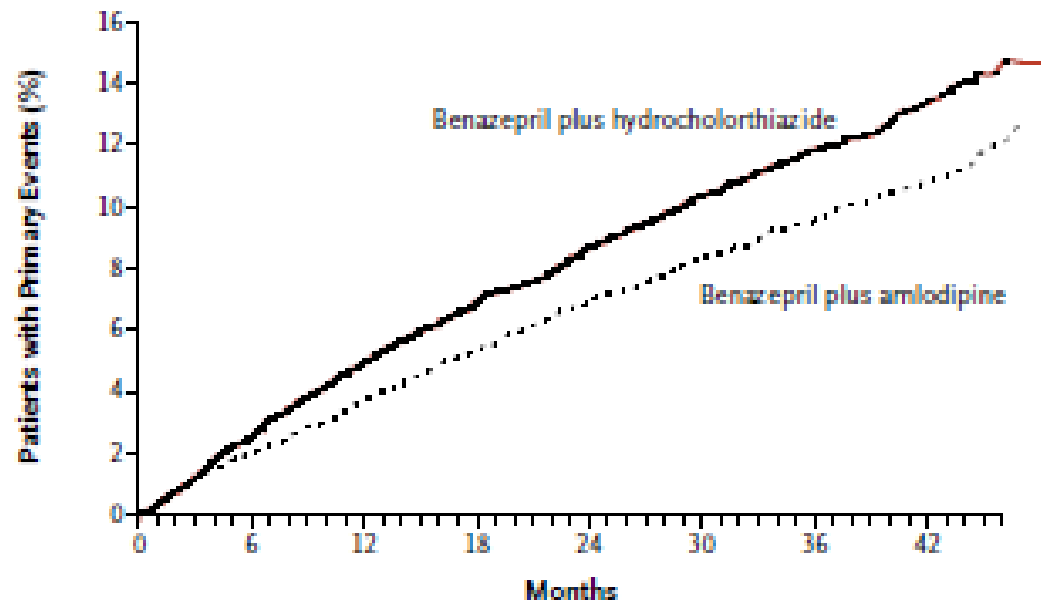
Primary outcome 

- ACE-In plus Amlodipine - 9,6%
- ACE-In plus HCTZ - 11,8%

Relative risk reduction - 19,6%

ACCOMPLISH Trial

Time to first primary composite endpoint

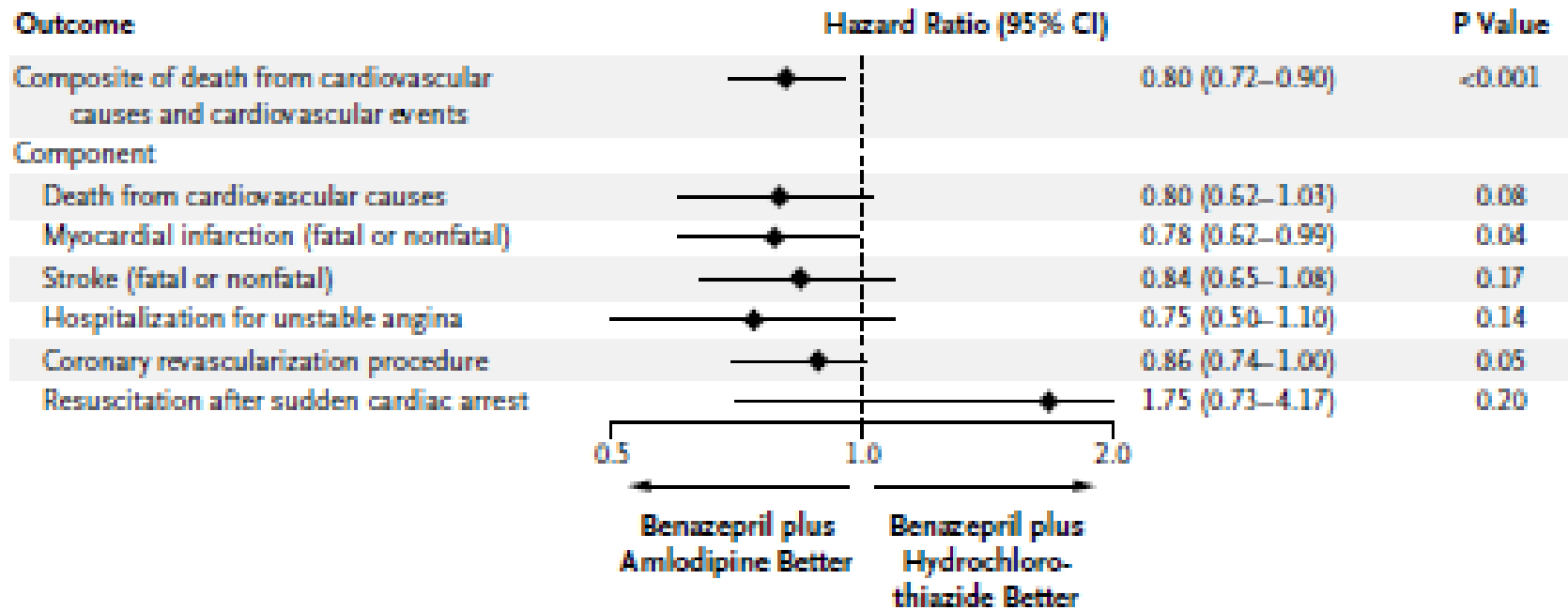


No. at Risk

Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

ACCOMPLISH Trial

Primary outcome hazard ratio



Thiazides in Hypertension

ACCOMPLISH Trial

Conclusion

ACE-In + Ca CB was
superior to ACE-In + HCTZ in
reducing CV events in HTpatients.

Thiazides in Hypertension

KEY ISSUES

1. The preference for diuretics in the management of HT has been challenged in light of the results of the ACCOMPLISH Trial.
2. The advantage of Chlorthalidone over other BP agents was shown by additional analysis of ALLHAT Trial.
3. The best explanation for the paradoxical results of ALLHAT and ACCOMPLISH trials is the use of different diuretics-HCTZ and Chlorthalidone.
4. Chlorthalidone is more potent and has a longer duration of action than HCTZ, and should be preferred, alone or in combination, for the management of HT.

Thiazides in Hypertension

ALLHAT - 10 year follow-up

1. Amlodipine and lisinopril-based treatments were not superior to chlorthalidone-based treatment in preventing major cardiovascular events.
2. Thiazide-type diuretics should still be preferred as first step treatment.

Thiazides in Hypertension

Use of BP Lowering drugs in the prevention of CVD

Meta-analysis of 147 RCT

1. All the classes of BP lowering drugs had a similar effect in reducing CHD events and stroke for a given reduction of BP.
2. Exclusion of pleiotropic effects-cardioprotection.
3. The reduction in CVD events was the same regardless of pretreatment BP.
4. The results indicate the importance of lowering BP in everyone over a certain age.

Thiazides in Hypertension

Choice of AntiHypertensive Drugs

1. The main benefits of antihypertensive therapy are due to lowering of BP *per se*, regardless of how it is obtained
2. Major antihypertensive drugs classes do not differ significantly for their ability to reduce BP.
3. Each drug class has contra-indications as well as favorable effects in specific clinical settings. The choice of drugs should be made according to this evidence.

Thiazides in Hypertension

CONCLUSION

Appropriate use of diuretics can still be a safe and effective way to treat hypertension.

Kaplan, NM

Hypertension, 2009