Combination therapy in The Management of Diabetic Hypertensives

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Prevalence of Comorbid Diabetes and Hypertension
Patients with type 2 diabetes

Up to 60% have concomitant hypertension

Comorbidity appears to increase risk of cardiovascular disease twofold*

*Versus patients with hypertension but not diabetes
Risk reduction in patients with diabetes (n=1,501) with target value for diastolic blood pressure ≤80 mmHg

Hypertension Optimal Treatment (HOT) randomized trial
Adapted from Hansson L et al. Lancet 1998;351:1755–62

Effects of intensified blood pressure lowering on cardiovascular events in patients with versus patients without diabetes (Syst-Eur study)

JNC 7 2003

- For patients with uncomplicated hypertension, the goal blood pressure is < 140/90 mm Hg.

- In patients with comorbidities such as diabetes or chronic kidney disease, a goal blood pressure of < 130/80 mm Hg is recommended.

- Monotherapy has been the traditional route to control of hypertension for many years.

- The treatment of hypertension remains a difficult task.

- This is especially true since the current goal of treatment is the normalization of both SBP and DBP.

- Thus, perhaps because of the highly heterogeneous character of essential hypertension, monotherapy often proves insufficient to normalize blood pressure.
Given the multifactorial nature of hypertension, the approach that makes the most therapeutic sense will be treatment with more than 1 agent or, more importantly, more than 1 class of agent.

By combining medications that act by different mechanisms, it is possible to gain considerably in terms of antihypertensive efficacy because of synergistic impacts on the cardiovascular system.

Combination therapy allows the use of lower doses of each antihypertensive agent, meaning that compensatory stimulation may be diminished, and, conceivably, the second component of combination may counteract this stimulation.

Furthermore, lower doses of antihypertensive agents are generally sufficient when used in combination, which accounts for the excellent tolerability of combination products.
Fixed-dose Therapy

- One of the important recommendations of the JNC 7 guidelines applies to those patients who are initially diagnosed with blood pressure levels more than 20/10 mm Hg above goal.

- For these patients, or those whose levels increase to these elevations, the guidelines recommend that consideration should be given to initiating therapy with 2 drugs, either as separate prescriptions "or in fixed-dose combinations."

Antihypertensive Therapy in Diabetics

Treatment guidelines recommend a blocker of the RAAS system as first choice.

Adapted from Guidelines Committee J Hypertens 2003;21:1011–1053.
Practical Approach For Management of Hypertension in Diabetics   ADA guidelines 2005

- BP Goal < 130/80 mmHg
- Goal not achieved
- Lifestyle therapy For 3 months
- Pharmacological therapy
  - ACE inhibitor or ARB
    - Add low-dose thiazide diuretic
      - Add B-blocker
      - Add CCB
      - Add other agents

Type 1
- Albuminuria
  - Add B-blocker
  - Add CCB
  - Add other agents

Type 2
- Microalbuminuria
- Macroalbuminuria
  - ACE inhibitor
  - ARB

ESC / EASD Recommendations for the Management of Diabetes and CVD

February 14, 2007
Eur Heart J.
Diabetes increases the risk for cerebrovascular disease by 3- to 5-fold.

Treatment of hypertension with a renin-angiotensin-system inhibitor may afford an augmented reduction in the risk for stroke among diabetic patients.

Blood pressure should be lowered to less than 130/80 mm Hg among patients with diabetes. Treatment should include a renin-angiotensin-system inhibitor.

June 2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of (ESH) and (ESC)
Antihypertensive treatment in diabetics

• Intense non-pharmacological measures should be encouraged in all diabetic patients, with particular attention to weight loss and reduction of salt intake in type 2 diabetes.

• Goal BP should be <130/80mmHg

• To lower BP, all effective and well tolerated drugs can be used.

• A combination of two or more drugs is frequently needed.

Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage.

Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).
A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.

ADA

Summary of Revisions for the 2008 Clinical Practice Recommendations

- **Hypertension/blood pressure control section:** the number of treatment recommendations has been reduced to emphasize use of angiotensin converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).
Which one we use
ACE Inhibitors or ARBs?

- ACE inhibitors and ARBs had similar efficacy for blood pressure control, with no significant differences in benefits or harms (strength of evidence: high).

- Quality-of-life measures and adherence were similar for ACE inhibitors and ARBs.

- There were no consistent differential effects seen for death and cardiovascular events.
Both classes of medication had similar effects on lipid levels, left ventricular mass, and risk for dysglycemia or renal dysfunction.

Adverse effects of headache and dizziness were similar for the 2 classes.

Cough as an adverse effect was 3 times more common with ACE inhibitors.

The number needed to treat to cause 1 case of chronic cough for ACE inhibitors was 15.

Monotherapy with ACE inhibitors or ARBs reduced proteinuria to a similar degree but less than combination therapy.

Mean reduction in proteinuria with combination vs ARB monotherapy in 5- to 12-month studies was 0.75 vs 0.82 (ratio of means) with ACE inhibitors

Monotherapy with ARBs reduced proteinuria vs placebo, with a ratio of means of 0.57 in 1 to 4 months and 0.69 in 5 to 12 months.

Results were similar for ACE inhibitors and ARBs vs calcium-channel blockers.
April 1, 2008 (Chicago) — ARB telmisartan was "noninferior" to ACE inhibitor ramipril in patients with vascular disease or high-risk diabetes in the landmark Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET).

However, the combination of the two drugs was associated with more adverse events without an increase in benefit.

The results of the trial were presented at the ACC 2008 and published simultaneously online in the New England Journal of Medicine.

**Investigators of the trial said:**

"Our data show that, in patients who have vascular disease or high-risk diabetes but do not have heart failure, telmisartan is an equally effective alternative to ramipril,"

And "the choice between the two agents will depend on the preferences of patients and physicians and the individual patient's susceptibility to specific adverse events."
They add: "There is no additional advantage (and there is some harm) from the combination of telmisartan and ramipril used in full doses in this population, as compared with ramipril alone," and they say the lack of additional benefit of the combination despite a substantial lowering of blood pressure is "puzzling."

Public Awareness

Survey on 2,000 People with Diabetes

Findings:
- 68% do not consider cardiovascular disease to be complication of diabetes
- 50%+ don’t feel risk for heart condition or stroke
- 60% don’t feel at risk for high blood pressure or cholesterol
- Awareness lowest among elderly, minorities
**Beware of Your Blood Pressure**

High blood pressure raises your risk for heart attack, stroke, eye problems and kidney disease.

Get your blood pressure checked at every visit.

*Target BP = less than 130/80*

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**Key Steps for Lowering Blood Pressure**

- Eat more fruits and vegetables!
- Reduce the amount of salt in diet.
- Lose weight.
- Lower alcohol intake.
- Quit smoking.
- Take blood pressure pills.
- Many people require more than one pill