

Role of ACE Inhibitors in Managing Diabetes

Abstract

Type 2 diabetes accounts for 90% of all diabetes and currently affects at least 5% of adults worldwide and is rapidly rising in prevalence. Affected people are at high risk of serious eye, kidney, nerve and vascular diseases which can lead to premature mortality. Dietary and physical activity changes can prevent diabetes in high-risk individuals with impaired glucose tolerance. Several large CV outcome trials have also shown that RAS inhibition with ACE Inhibitors or ARBs may prevent diabetes.

Ramipril is an angiotensin-converting enzyme inhibitor (ACE-I) drug that clearly prevents cardiovascular events in high-risk people, including those with diabetes. The DREAM trial was a large, international, multicentre trial testing whether ramipril and/or rosiglitazone prevents type 2 diabetes. 5269 people age 30 or older (mean age 55; 59% women, mean weight 85 kg) with impaired fasting glucose alone (14%), impaired glucose tolerance alone (57.5%) or both abnormalities (28.5%) were recruited in 191 clinical centres located in 21 countries. They were randomly allocated to ramipril 8 mg/day or placebo and/or rosiglitazone 15 mg/day or placebo, and followed for a median of 3 years. The primary outcome was the development of either diabetes or death. Ramipril and rosiglitazone had independent effects on the study outcomes and are therefore analyzed separately.

Ramipril was associated with a nonsignificant 9% reduction in the primary outcome. However, it increased regression from high to normal glucose levels with 42.6% in the ramipril group versus 38.3% in the placebo group achieving a normal fasting (<6.1 mmol/L) and 2 hour glucose (<7.8 mmol/L) level (HR 1.16; 95% CI 1.07-1.27; P=0.001). It also reduced 2 hour glucose, blood pressure levels and liver enzyme (ALT) levels.

These findings are consistent with other studies suggesting that RAS inhibition has favourable glucometabolic benefits, and these may contribute to the well known clinical benefits of ACE-Is related to reducing cardiovascular events, renal disease, CV death, and blood pressure in both diabetic and nondiabetic individuals.

ACE-Is Reduce CV Events Ambulatory People at High CV Risk

	Death	MI	Stroke	CHF Hosp
HOPE	0.83 (0.73-0.95)	0.77 (0.65-0.9)	0.68 (0.55-0.84)	0.88 (0.70-1.11)
EUROPA	0.89 (0.77-1.02)	0.78 (0.67-0.9)	0.96 (0.73-1.27)	0.61 (0.44-0.83)
PEACE	0.89 (0.76-1.04)	1.00 (0.83-1.2)	0.76 (0.56-1.04)	0.77 (0.60-1.00)
Total	0.86 (0.79-0.94)	0.82 (0.75-0.91)	0.77 (0.67-0.89)	0.77 (0.67-0.90)

Dagenais et al; Lancet Aug 2006
Sept 29, 2006

DREAM

ACE-I & Reduced DM (2ndary Outcome)

Study	N (no DM)	Active	Control	RRR
HOPE	5720	Ramipril 10 OD	Placebo	34%
PEACE	6174	Trandolapril	Placebo	17%
EUROPA	10716	Perindopril 8 mg	Placebo	3%
D-SOLVD	291	Enalapril	Placebo	74%
ALLHAT	14816	Lisinopril	Amlodipine	21.6%
ALLHAT	14816	Lisinopril	Chlorthalidone	39.6%
CAPP	10413	Captopril 100 BID	B blocker/Thiazide	14%
STOP 2	5893	Enala/Lisino 10/d	B block/Thiazide/CCB	3%
INVEST 2006	16176	Trandola + Verapa	HCTZ + Atenolol	15%

DREAM

ACE-I & Reduced DM (2ndary Outcome)

Study	N (no DM)	Active	Control	RRR
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Overall Effect (HOPE, EUROPA, PEACE):
0.86 (0.78-0.95)

Dagenais et al. Lancet 2006;368:581

DREAM

ARBs & Reduced DM (2ndary Outcome)

Study	N (no DM)	Active	Control	RRR
SCOPE	4368	Candesartan 16/d	Placebo	20%
CHARM	5436	Candesartan 4-32/d	Placebo	24%
VALUE	~10420	Valsartan 80-160/d	Amlodipine 5-10/d	23%
ALPINE	392	Candesartan 16/d	HCTZ 25/d	88%
LIFE	7998	Losartan 50-100/d	Atenolol	25%

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Do ACE-Is Prevent DM?

Limitations of Previous Reports

- Glucose tolerance tests **not** done at baseline or end...
 - would have missed prevalent DM at baseline
 - would have missed incident cases on follow-up
 - no ability to detect regression
 - possibility of ascertainment bias
 - incident cases included both: a) new ascertainment of prior DM, & b) truly incident DM
- Variable definitions of incident DM were used (1 FPG, 2 FPGs, self-report etc) with varying analytic approaches
- Participants were at high CV risk & intermediate DM risk; DM incidence rate was ~ 2%/yr
- None designed to prospectively test if ACE-I prevented DM

Effect on Glucose Category: Ramipril

