ACE-Inhibitors and new-onset diabetes

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1 - Epidemiology

Type 2 diabetes is a major risk factor for cardiovascular mortality and morbidity. The prevalence of diabetes is increasing worldwide causing tremendous social economic burden to patients and health care providers.

Effective strategies for the prevention of diabetes include **diet and exercise in order to reduce insulin-resistant fatty tissue and improve insulin sensitivity** 1. Randomised trials have convincingly demonstrated that **lifestyle changes are associated with a convincing reduction in the progression to diabetes 1. However, the implementation of lifestyle modifications is challenging and therefore, new strategies for the prevention of diabetes are warranted**.

2 - Preventive Treatment

Peroxisome-proliferator-activated receptor (PPAR) agonists which are known to improve insulin sensitivity and metformin have been shown to reduce the incidence of diabetes 2.

In addition, **various clinical trials in more than 66,608 patients with coronary artery disease, hypertension, or heart failure have demonstrated a delay and/or prevention of new-onset diabetes with substances directed to inhibit the renin-angiotensin system** (RAS) 3-6. **However**, in all these studies, the incidence of diabetes was not the primary endpoint and in most of the studies **results were obtained from post-hoc analyses**. In addition, **glucose levels were not systematically reviewed**. Since inhibition of the RAS is an effective and widely used method for reducing mortality and morbidity in patients with cardiovascular disease, additional positive effects on plasma glucose levels would be intriguing.

3 - The Dream Trial

In order to further elucidate the effect of inhibitors of the RAS and the incidence of diabetes the Diabetes Reduction Assessment of Ramipril and Rosiglitazone Medications (DREAM) trial was performed 7.

5269 patients without cardiovascular disease were recruited to this double blind, randomized clinical trial with a two-by-two factorial design.
Table 1 DREAM trial : Main inclusion criteria

- Impaired fasting glucose levels of at least 110mg/dl (6.1mmol/l) but less than 126mg/dl (7.0mmol/l)

- or
- Impaired glucose tolerance 2 hours after an oral glucose load of at least 140mg/dl (7.8mmol/l) but less than 200mg/dl (11.1mmol/l)

Eligible patients were randomized to receive the angiotensin converting enzyme inhibitor (ACE-I) **ramipril or placebo** (and rosiglitazone or placebo).

Ramipril was started at a dose of 5mg/day for 2 months, increased to 10mg/d and finally 15 mg/d after 2 and 12 months, respectively.

Patients were followed for a median of 3 years. **At the 2-year and the final study visits, a glucose tolerance test was performed**. The primary endpoint of the study was a new onset of diabetes or death. Secondary outcomes included a composite endpoint of cardiac and renal events, glucose levels and regression to normal glucose levels. Patient groups did not differ in their baseline characteristics.

At the end of the study, about 70% of the patients were still taking their medication and this was similar in both groups. **Ramipril effectively reduced blood pressure** (8.2mmHg vs 3.9mmHg in mean systolic blood pressure) **but had no effect on creatinine levels**. With ramipril, slightly fewer patients met the primary endpoint criteria of diabetes or death but the difference with placebo was non significant. (table 2).

Table 2 : DREAM trial : Study results

	Ramipril N=2623	Placebo N=2623	Hazard ratio 95% CI	P-value
Primary Enpoint Diabetes and Death	475 (18.1%)	517 (19.5%)	0.91 (0.81 – 1.03)	0.015
Diabetes	449 (17.1)	489 (18.5%)	0.91 (0.80 – 1.03)	
Death	31 (1.2%)	32 (1.2%)	0.98 (0.60 – 1.60)	
Regression to Normoglycemia	1116 (42.5%)	1012 (38.2%)	1.16 (1.07 – 1.27)	0.001

475 patients (18.1%) met the criteria of the primary endpoint diabetes or death in the ramipril group vs. 517 patients (19.5%) in the placebo treated group (with 31 and 32 deaths, respectively). 17.1% of patients on ACE-I treatment developed diabetes vs. 18.5% in the placebo group. This difference was not statistically significant (p=0.15).

Regression analysis correcting for the use of drugs known to increase the incidence of diabetes (e.g. diuretics, betablockers) or angiotensin-receptor blockers (ARB) did not change the results for the primary endpoint.

Median fasting plasma glucose levels were not different between the ramipril and placebo. However, the median glucose level, two hours after load, was significantly reduced in the ramipril group compared to control; also the regression to normal glucose levels was enhanced with ramipril.

The two-by-two factorial design additionally evaluated the effect of rosiglitazone on the incidence of diabetes and death. These results published previously demonstrated a significant reduction in the incidence of death or diabetes (Hazard ratio 0.40; 95% confidence interval 0.35-0.46; $p<0.001$) in rosiglitazone treated patients 8. There was no significant interaction detectable between rosiglitazone and ramipril with respect to the primary endpoint.

4 - Conclusion

The DREAM trial 7 demonstrates that the ACE-I ramipril at a maximal dose of 15mg/day cannot significantly reduce the incidence of diabetes and death in non-diabetic patients without cardiovascular disease and impaired fasting glucose or glucose tolerance. The observation that patients receiving ramipril showed a higher regression to normoglycemia and significantly lower 2 hour glucose plasma levels after an oral glucose load suggests **a beneficial role of ACE-inhibition in pre-diabetic patients**.

Why are the results of the DREAM trial so discrepant to the previously published studies? Potentially various factors have to be taken into account. None of the published studies had a primary endpoint which was defined as the incidence of new-onset diabetes. None of the studies consistently measured glucose levels or performed oral glucose tolerance tests. Different patient groups were evaluated including patients with coronary artery disease, hypertension, and heart failure. In contrast the DREAM trial investigated patients without any evidence of cardiovascular disease. Meta-analysis suggest the incidence of diabetes may be more important in higher risk patients for type 2 diabetes. Unfortunately, subgroup analyses stratifying this population for impaired fasting glucose versus normal glucose levels do not exist 3.

Taken together ramipril is currently not the drug of choice for the prevention of type 2 diabetes 7;9. Patients already on ACE-I due to hypertension, congestive heart failure, or high-risk for cardiovascular events may potentially benefit from a positive effect on glucose metabolism. Further studies such as the ONTARGET trial may provide deeper insights into the role of RAS inhibition and new-onset diabetes.

The content of this article reflects the personal opinion of the author/s and is not necessarily the official position of the European Society of Cardiology.

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