



Session 11: Clinical studies update

Endothelin receptor antagonists in clinical research — Lessons learned

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Endothelin receptor antagonists are approved for the treatment of pulmonary hypertension. The efforts to approve this class of drugs for renal indications, however, failed so far. Preclinical studies were promising. Transgenic overexpression of ET-1 or ET-2 in rodents causes chronic renal failure in a blood pressure independent manner. Blocking in particular the ETA receptor was effective in the treatment of rodent models of renal failure such as rats with 5/6 nephrectomy, L-NAME induced renal failure and diabetic nephropathy. On the other hand, various animal studies indicate that blocking the renal tubular ETA and ETB receptor may cause water and salt retention partially mediated via the epithelial sodium transporter (ENaC) in tubular cells. Endothelin receptor antagonists were successfully tested clinically in renal indications in phase 2 trials for the treatment of diabetic nephropathy. They showed efficacy in terms of reducing albumin excretion in patients with diabetic nephropathy on top of guideline based background therapy (angiotensin II receptor blockade). However, these promising results could not be translated to successful phase III trials so far. The spectrum of serious adverse events was similar to other phase III trials using endothelin receptor antagonists. We will discuss potential underlying reasons for these failures and what could be done in the future. The lessons learned in renal indications are also important for other potential indications of endothelin receptor antagonists like cancer and heart failure.

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Endothelin receptor antagonism versus combined ECE/NEP inhibition in patients with type 2 diabetes and nephropathy

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Endothelin receptor antagonists have been used in clinical trials to test their renoprotection properties in patients with type 2 diabetes who do not invariably respond to angiotensin II blockers. Thus, combined treatment with ET-1 antagonists on top of angiotensin II blockers could represent an effective tool to reduce blood pressure and ameliorating renal function. Here we tested the effect of combined treatment with daglutril, a combined endothelin-converting-enzyme and neutral endopeptidase (MME) inhibitor on top of losartan (100 mg/day) in patients with type 2 diabetes. The randomised, crossover trial was held in two hospitals in Italy. Eligibility criteria were: age 18 years or older, urinary

albumin excretion 20–999 µg/min, systolic blood pressure (BP) less than 140 mm Hg, and diastolic BP less than 90 mm Hg. Patients were randomly assigned (1:1) with a computer-generated randomized sequence to receive either daglutril (300 mg/day) then placebo for 8 weeks each or vice versa, with a 4-week washout period. The primary endpoint was 24-h urinary albumin excretion in the intention-to-treat population. Secondary endpoints were median office and ambulatory (24 h, daytime, and night-time) BP, renal haemodynamics and sieving function, and metabolic and laboratory test results. This study is registered with ClinicalTrials.gov, number [NCT00160225](https://clinicaltrials.gov/ct2/show/study/NCT00160225). 58 patients were screened, of whom 45 were enrolled (22 assigned to daglutril then placebo, 23 to placebo then daglutril) and 42 (20 vs 22) were included in the primary analysis. Daglutril did not significantly affect 24-h urinary albumin excretion compared with placebo ($p = 0.559$). 34 patients had complete 24-h BP readings; compared with placebo, daglutril significantly reduced ambulatory systolic ($p = 0.0013$), diastolic ($p = 0.015$), pulse ($p = 0.019$), and mean ($p = 0.003$) BP, as well as all night-time BP readings and daytime systolic, pulse, and mean BP, but not diastolic BP. Compared with placebo, daglutril also significantly reduced office systolic BP ($p = 0.028$), but not diastolic, pulse, or mean BP, and increase big endothelin serum concentration. Three patients taking placebo and six patients taking daglutril had mild treatment-related adverse events — the most common was facial or peripheral oedema (in four patients taking daglutril). Our data suggest that daglutril improved control of BP in hypertensive patients with type 2 diabetes and nephropathy particularly as for systolic hypertension, that in patients with diabetes and renal involvement is often resistant to treatment. The treatment effect of daglutril was larger during night time, which is of major clinical relevance, since night time hypertension is a strong cardiovascular risk factor in this patient population. We also found that daglutril on top of full dose losartan had a very good safety profile.

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The selective type A endothelin antagonist atrasentan reduces residual albuminuria in patients with type 2 diabetes and nephropathy

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Introduction and Aims: Patients with type 2 diabetes and albuminuria have high cardiorenal morbidity and mortality. We evaluated whether atrasentan, a selective endothelin receptor A antagonist, could reduce albuminuria in use with renin angiotensin system inhibitors (RASi). **Methods:** 211 subjects with type 2 diabetes, macroalbuminuria,