phan could further augment the vascular actions of bradykinin in patients with CHF on chronic ACE inhibitor therapy.
Methods 10 patients with CHF on chronic ACE inhibitor therapy received an intrabrachial infusion of thiorphan (30 nmol/min) or saline placebo for 3 hours in a randomised, double blind, cross over trial. Thiorphan or placebo was coinfused with Lys-des-Arg^9-bradykinin (B1 kinin receptor agonist; 1 - 10 nmol/min), bradykinin (B2 kinin receptor agonist; 30 - 300 pmol/min), atrial natriuretic peptide (10 -100 pmol/min) and sodium nitroprusside (2 - 8 mcg/min) in random order. Bilateral forearm blood flow (FBF) was recorded using strain gauge plethysmography and plasma t-PA antigen determined using ELISA.
Results There were no changes in heart rate, blood pressure or noninfused FBF or t-PA release during thiorphan or placebo infusion. Bradykinin, atrial natriuretic peptide and sodium nitroprusside caused dose-dependent increases in infused FBF in all studies ($p<0.001$). There were no significant changes in FBF during Lys-des-Arg^9-bradykinin infusion. Bradykinin but not Lys-des-Arg^9-bradykinin or atrial natriuretic peptide caused a dose dependent increase in t-PA antigen and estimated t-PA antigen release in all studies ($p<0.001$). Compared to placebo, thiorphan augmented the increase in infused FBF, t-PA antigen and estimated t-PA antigen release ($p<0.001$, $p=0.076$, $p<0.005$ respectively) to bradykinin but not atrial natriuretic peptide or sodium nitroprusside.
Conclusion In the presence of chronic systemic ACE inhibition, local NEP inhibition potentiates bradykinin mediated vasodilatation and endothelial t-PA release. Given these potential anti-ischaemic benefits, our findings support the hypothesis that combined ACE/NEP inhibition may afford greater cardiovascular protection than ACE inhibition alone.

1012-128 The Long-Term Impact of Initiating Treatment With the Angiotensin-Converting Enzyme Inhibitor Trandolapril After a Myocardial Infarction in Patients With Left Ventricular Dysfunction: A 10- to 12-Year Follow-Up Study

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Background: Following a myocardial infarction (MI), treatment with angiotensin converting enzyme inhibitors reduces mortality and morbidity in patients with left ventricular dysfunction (LVD). However, long-term benefits remain unknown. We conducted a follow-up study on the long-term effects of trandolapril use post-MI in patients with LVD.
Methods: In the Trandolapril Cardiac Evaluation (TRACE) study, 1,749 patients with LVD (ejection fraction <35%) were randomized to trandolapril (n = 876) or placebo (n = 873) 3-7 days post-MI. The study began in 1990 and closed in 1994; on–treatment follow-up ranged from 2-4 years. National registries were used to track all deaths and hospitalizations until the end of 2002. We analyzed mortality with Cox proportional hazard models and hospitalization with Poisson regression models (models adjusted for observation time).
Results: Over 10-12 years of follow-up, a total of 1,281 deaths and 9,192 hospitalizations were registered. Compared with the placebo group, the trandolapril group had a significantly reduced risk of all-cause mortality and significantly reduced rates of all–cause hospitalizations and congestive heart failure (CHF) hospitalizations (table).
Conclusion: In patients with LVD, use of trandolapril shortly after an MI for 2-4 years has long-term benefits. Trandolapril reduces mortality and hospitalization rates for at least 10-12 years. Further follow-up is required to determine the limit of these beneficial effects.

Event	Number of Events	Risk/Rate Ratio*	95% CI	p Value
All-cause death				
Overall 1990-2002	1,281	0.89†	0.80-0.99	0.04
Trial period 1990-1994	675	0.78†	0.67-0.91	0.001
After trial 1994-2002	606	1.03†	0.88-1.21	0.68
All-cause hospitalization				
Overall 1990-2002	9192	0.92‡	0.88-0.96	<0.001
Trial period 1990-1994	4599	0.92‡	0.87-0.98	<0.005
After trial 1994-2002	4593	0.92‡	0.87-0.98	0.005
CHF hospitalization				
Overall 1990-2002	1,628	0.85‡	0.77-0.93	<0.001
Trial period 1990-1994	817	0.76‡	0.67-0.88	<0.001
After trial 1994-2002	811	0.94‡	0.82-1.08	0.82

*Risk/rate ratio <1.0 favors trandolapril over placebo

†Risk ratio; ‡Rate ratio; CI, conficence interval

1012-129 Dual Angiotensin-II Suppression With Angiotensin-Converting Enzyme Inhibitor and Irbesartan Improves Submaximal Exercise Time Without Changes in Exercise-Induced Neurohumoral Response in Patients With Congestive Heart Failure

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Background: The combination of an angiotensin-II receptor blocker (ARB) with an ACE inhibitor (ACEi) provides benefits on clinical events and LV remodelling in patients with congestive heart failure (CHF). The primary objective of this study was to investigate the effects of Irbesartan versus placebo on submaximal exercise duration in patients with CHF. The secondary objective was to assess the impact of such treatment on catecholamines and angiotensin-II (A-II) levels at rest, at 6 minutes, and at peak exercise during a submaximal exercise test. Methods: Thirty-three patients with NYHA II or III CHF aged 56±12 years (mean±SD), LVEF 25.5±7.2%, and with exercise limited by dyspnea were prospectively studied. Patients were blindly randomized to receive either Irbesartan 150 mg o.d. (n=22) or a placebo (n=11) for 6 months (m) in addition to optimal dose of ACEi and beta-blockers. Maximal exercise capacity was evaluated using a Ramp protocol. Submaximal exercise duration was assessed using a constant load protocol prescribed at the level of the anaerobic threshold. Gas exchange was measured continuously during both protocols. Results: (See Table). Conclusions: Dual A-II suppression with Irbesartan and ACEi therapy improves submaximal exercise time by 23% without significant changes in neurohumoral response at rest or during stress.

	VO_2 Peak ml/kg/min		Duration Max (sec)		Duration Submax (sec)		A-II (pg/ml) (6 m)	
	Bsl	6 m	Bsl	6 m	Bsl	6 m	Rest	Peak Ex
Irbe (n=22)	19.1±4.9	19.6 ±4.3	554±127	578± 123	1043±507	1360* ±725	286±211	262±180
Placebo (n=11)	21.3±6.4	20.5 ±6.6	630±140	647± 15	1581±664	1697 ±743	239±118	310±272

Mean±SD; Irbe=Irbesartan: Bsl=baseline; Ex=exercise; *p=0.018 vs Bsl by Wilcoxon.

1012-130 Long-Term Effect of Statin on Exercise Tolerance, Cardiac Function and Clinical Outcome in Patients With Ischemic Chronic Heart Failure

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Background: Statins have pleiotropic effects such as anti-inflammatory and vascular protective effects, which would be beneficial for patients with chronic heart failure (CHF). We sought to investigate the long-term effect of statins on exercise tolerance, cardiac function and prognosis in patients with ischemic CHF.
Methods: We prospectively followed-up 66 consecutive ischemic CHF outpatients with radionuclide left ventricular ejection fraction (RI-LVEF) < 40% for three years. At the entry, we measured six minute walk distance (6MWD), left ventricular end-diastolic dimension (LVDd) in echocardiography, RI-LVEF and plasma concentration of atrial natriuretic peptide (ANP), and thereafter these measurements were repeated at least every year.
Results: There were no significant differences in age, gender, NYHA class, 6MWD, LVDd or RI-LVEF at the entry between patients with (n=27) and without statins (n=39). After the follow-up period of 2.8±0.5 years, patients with statins had a significant increase in 6MWD and RI-LVEF and a decrease in LVDd and plasma level of ANP, while there were no significant changes in these parameters in patients without statins. Furthermore, during the follow-up period, the cardiac events were significantly ($p=0.004$) infrequently observed in patients with (0%) than without statins (26%).
Conclusion: Long-term statin treatment might improve exercise tolerance and cardiac function, resulting in an improvement in clinical outcome in patients with ischemic CHF.

	With statins		Without statins		p Value
	at entry	follow-up	at entry	follow-up	(ANOVA)
6MWD (m)	363±73	392±68	374±88	363±100	0.008
RI-LVEF (%)	28.9±6.6	35.5±10.9	30.3±7.6	31.4±11.5	0.012
LVDd (mm)	58.3±5.4	56.4±6.7	60.5±7.4	61.6±7.7	0.02
ANP (pg/ml)	55.9±51.3	33.3±24.7	62.8±53.2	80.3±100.5	0.04