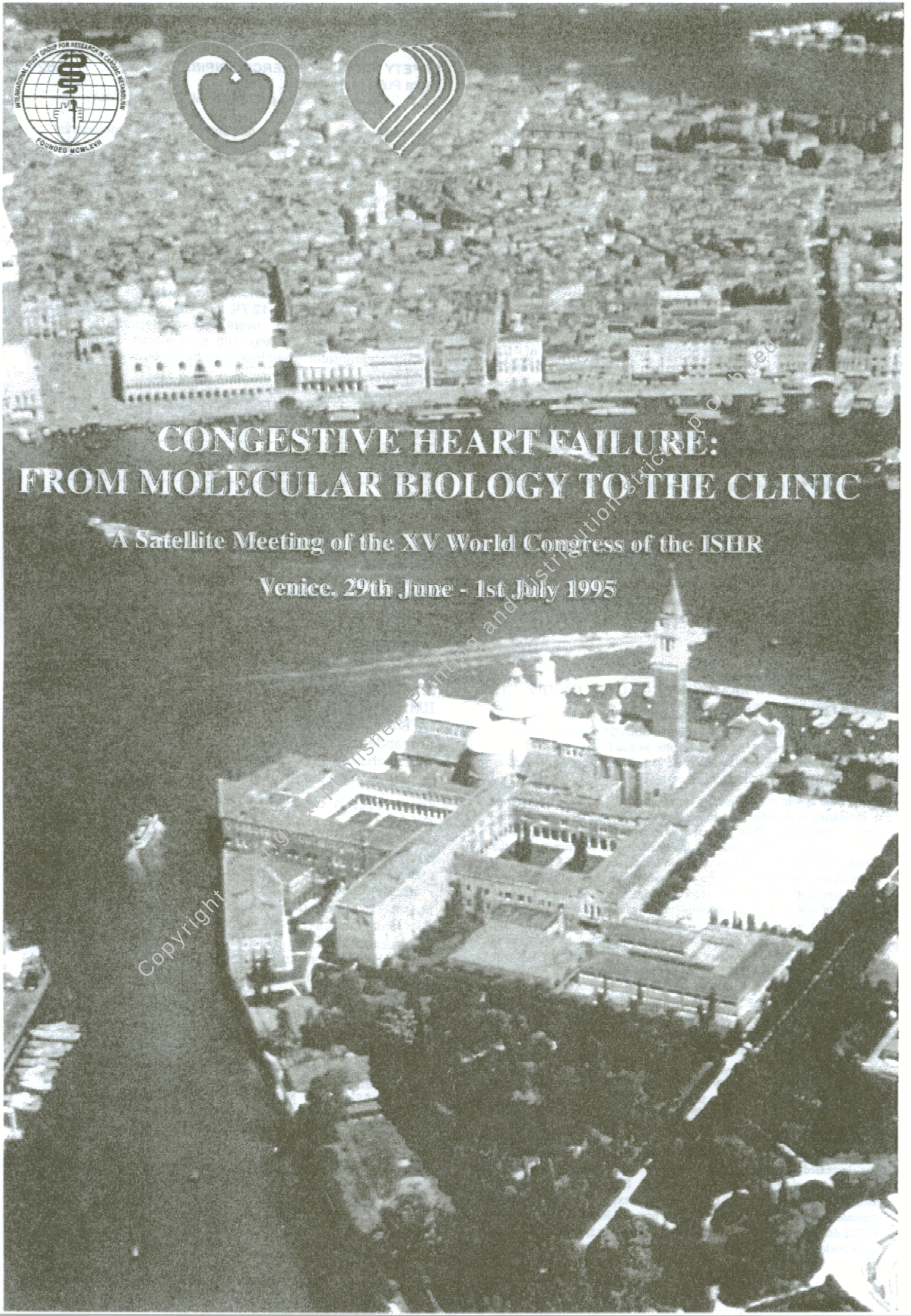

CONGESTIVE HEART FAILURE: FROM MOLECULAR BIOLOGY TO THE CLINIC

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THERAPEUTIC EFFICACY OF TWO DIFFERENT DOSAGES OF LERCANIDIPINE (10 and 20 mg) VERSUS PLACEBO. 161

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Lercanidipine, a new dihydropyridine drug synthesized and developed by Recordati S.p.A., showed a potent and specific calcium blocking activity. Preliminary studies indicate that it has a good and long-acting antihypertensive activity. We analysed all clinical trials with the same study design (double-blind, randomized, parallel groups and controlled versus placebo) in which the primary efficacy end-point was DBP, always measured 24 hours post-dose, after 4 weeks of treatment. This analysis was made on a total of 391 patients (129 treated with 10 mg and 129 with 20 mg o.a.d. of lercanidipine and 133 treated with placebo).
Results: the mean decrease of DBP was respectively of 10, 12 and 5 mmHg with 10 and 20 mg of lercanidipine and placebo. In all studies the statistical analysis showed a high significant difference between lercanidipine and placebo. The percentages of **normalized patients** (DBP ≤ 90 mmHg) were: 53%, 60% and 24% respectively with 10 and 20 mg of lercanidipine and with placebo. While the percentages of **responders patients** (DBP ≤ 90 mmHg or reduced by 10 mmHg at least) were: 61%, 77% and 33% respectively.
The mean decrease of SBP was: 15 and 19 mmHg with 10 and 20 mg of lercanidipine and 5 mmHg with placebo. Heart rate did not show any clinical significant change either when it was measured 4 or 24 hours post-dose.
Conclusion: lercanidipine showed to be an efficacious antihypertensive drug after once daily administration without a clinical significant effect on heart rate.

SAFETY PROFILE OF LERCANIDIPINE 162

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Lercanidipine is a new 1,4-dihydropyridine Ca^{++}-antagonist synthesized and developed by Recordati S.p.A. for the treatment of patients with essential hypertension. The dose interval of 2,5-40 mg/day was investigated but phase III trials have shown that the 10 mg o.a.d. dosage is appropriate both for efficacy and tolerability. By means of a standardized methodology, the safety of lercanidipine was evaluated on 1016 hypertensive patients treated with 10 mg, 502 treated with 20 mg and 182 treated with placebo in single daily administration.
Results: pooled data have shown a low incidence of adverse events: 5,6% lerc. 10 mg, 12,7% lerc. 20 mg, 8,8% placebo. Most of the adverse events were typical of the pharmacological class, being mild to moderate in intensity and usually transient. Their incidence by dose was:

Adverse event	lerc. 10 mg oad n = 1016	lerc. 20 mg oad n = 502	placebo n = 182
headache	2,5 %	2,8 %	2,2 %
flushing	1,2 %	3,0 %	2,2 %
periph. oedema	1,1 %	3,0 %	1,7 %
tachycardia	0,7 %	5,4 %	0,6 %
dizziness	0,3 %	0,2 %	1,1 %

Also the incidence and severity of laboratory test changes after treatment were similar in lercanidipine and placebo groups (0,8% and 0,6% respectively, out of a total of over 45.000 tests performed).
Conclusion: among the dihydropyridine derivatives, lercanidipine showed a low incidence of untoward effects, particularly for peripheral oedemas, and an overall favourable safety profile in therapeutic use.

EFFECT OF A NEW BRADYCARDIC AGENT ON THE ISOLATED PERFUSED RABBIT HEART 163

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Bradycardic agents could limit the consequences of myocardial ischemia by decreasing myocardial oxygen demand (MVO2) and by increasing diastolic coronary flow. Thus, reduction in heart rate (HR) could possibly prevent ischemia or reduce ischemic injury. **Methods:** We investigated the effects of pharmacologic HR reduction on hemodynamics of 8 isolated, saline-perfused rabbit hearts, using a new bradycardic agent of the benzazepinone type (DK-AH 269) that reportedly acts solely on the sinus node. Duration of systole (tsys) and diastole (tdia) was derived from HR. Stroke volume (SV) was calculated from aortic flow and HR. LVPmax and dP/dtmax were assessed as systolic measures and dP/dtmin as parameter of early relaxation. Global coronary flow per beat (CF/beat) was assessed, and coloured microspheres were used to determine the ratio (R) between endo- and epicardial regional flow. MVO2 was calculated from arterio-venous oxygen difference and coronary flow. Variables during control (C) and after administration of DK-AH 269 at 3 increasing concentrations (D1: 10^{-8} M; D2: 10^{-7} M; D3: 10^{-6} M) are presented at comparable preloading conditions. **Results:** mean±SEM

	HR [min-1]	tdia [ms]	SV [ml]	LVPmax [mmHg]	dP/dtmax [mmHg/s]	dP/dtmin [mmHg/s]	CF/beat [ml]	R	MVO2 [ml/min]
C	206±25	133±46	0.25±0.09	126±8	1679±277	1126±215	0.30±0.06	1.28±0.09	10.4±2.5
D1	195±30	162±56	0.22±0.09	119±23	1594±338	1056±207	0.29±0.07		9.6±2.5
D2	177±40	182±74	0.23±0.13	116±25	1490±453	1049±178	0.29±0.09		8.8±2.6
D3	154±48	265±144	0.27±0.17	115±32	1290±361	973±224	0.29±0.09	1.28±0.08	7.9±2.3

Summary: DK-AH 269 reduced HR dose-dependently. In parallel, tdia was increased at maintained duration of tsys. With SV essentially unchanged, aortic flow was slightly reduced. Both the impaired systolic function and early relaxation can possibly be explained via the negative staircase phenomenon. Coronary flow per beat and R remained unchanged. MVO2 decreased dose-dependently. **Conclusion:** The specific bradycardic agent could be useful in treating ischemic myocardial disease.

EFFECTS OF CALCIUM ANTAGONISTS ON RENAL SODIUM AND WATER TRANSPORT IN CONGESTIVE HEART FAILURE /CHF/ 164

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Renal action of single oral intake of nifedipine /Nf/ 20 mg, and nisoldipine /Ns/ 10 mg, was studied in 62 patients with mild to moderate CHF. Both Nf and Ns increased renal excretion of sodium /Na/ by 24-72%, mainly via suppression of Na reabsorption in the proximal tubule. Thic action seems to occur due to effect on calcium-dependent components of Na transport and intrarenal hemodynamic shifts. Nf /but not Ns/ also reduced Na reabsorption in diluting segment distal to the loop of Henle by 6.8-9.4% /$p<0.05$/. Contrary to Nf, Ns altered renal hydruretic function directly. It caused a significant /$p<0.05$/ drop in Uosm/Posm ratio and elevated renal free water excretion. Ns-induced water diuresis usually was observed 20-30 min after Ns administration and persisted during 25-50 min. This previously unknown effect of Ns seems to take place via direct interference into calcium-calmodulin-dependent mechanisms of transcellular water transport in collecting ducts.
The ability of calcium antagonists to promote a slight elevation in renal Na excretion might also warrant the use of these drugs in the treatment of mild to moderate CHF.