The Cardiovascular Drug Therapy Newsletter

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Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive Type 2 diabetic patients with microalbuminuria: DIAL Study (Diabete, Ipertensione, Albuminuria, Lercanidipina)

M. Dalla Vestra*, G. Pozza, A. Mosca, V. Grazioli, A. Lapolla, P. Fioretto, G. Crepaldi.
Diab Nutr Metab 2004;17:259-266
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Abstract: Microalbuminuria and hypertension are risk factors for diabetic nephropathy in Type 2 diabetic patients. Recent data suggest that blockade of the renin-angiotensin system slows the progression of diabetic nephropathy; in contrast, the results on the renoprotective effect of calcium channel antagonists are conflicting. We evaluated the effectiveness of lercanidipine, in comparison with ramipril, on the reduction in albumin excretion rate (AER) and blood pressure in mild-to-moderate hypertensive patients with Type 2 diabetes and persistent microalbuminuria. A total of 277 patients were enrolled in a multicentric, randomized, double-blind, active-controlled, parallel-group trial; 180 were randomized to receive 10-20 mg/day of lercanidipine or 5-10 mg/day of ramipril and followed up for 9-12 months. The primary outcome was the change in AER from baseline. After 9-12 months of follow up, a reduction in AER of -17.4+/-65 microg/min ($p<0.05$) and -19.7+/-52.5 ($p<0.05$) in the lercanidipine and ramipril group, respectively, was observed, without differences between the groups. A significant reduction in systolic and diastolic blood pressure was observed in both the lercanidipine and ramipril-based treatment groups ($p<0.0001$ for both). This study demonstrated that treatment with lercanidipine 10-20 mg/day does not worsen albuminuria in microalbuminuric Type 2 diabetic patients with hypertension. Indeed, both lercanidipine and ramipril treatments resulted in a significant reduction in AER without a statistically significant difference between the two groups.

Editorial comment: *It is well established that calcium antagonists lower blood pressure mainly through vasodilation and reduction of peripheral resistance. They maintain blood flow to vital organs, and are safe in patients with renal impairment. Unlike diuretics and beta-blockers, they do not impair glucose metabolism or lipid profile and may even attenuate the development of arteriosclerotic lesions. In long-term follow-up, patients treated with calcium antagonists develop less overt diabetes mellitus than those who were treated with diuretics and beta-blockers. Moreover, calcium antagonists are able to reduce left ventricular mass. Recent prospective randomized studies attested to the beneficial effects of calcium antagonists in hypertensive patients. In comparison with placebo, calcium antagonist-based therapy reduced major cardiovascular events and cardiovascular death significantly in elderly hypertensive patients and in diabetic patients (Grossman E, Messerli FH, Prog Cardiovasc Dis 2004;47:34-57). In contrast to these recognized features, the renoprotective effects of these drugs*

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Efficacy and Safety of Ezetimibe Co-Administered With Simvastatin Compared With Atorvastatin in Adults With Hypercholesterolemia

C.M. Ballantyne, M.A. Blazing, T.R. King, W. E. Brady, J. Palmisano. ***Am J Cardiol*** 2004; 93:1487–1494
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Abstract: This study compared the efficacy and safety of coadministered ezetimibe-simvastatin with atorvastatin monotherapy in adults with ypercholesterolemia. Seven hundred eighty-eight patients were randomized 1:1:1 to 3 treatment groups; each group was force-titrated over four 6-week treatment periods: (1) 10 mg of atorvastatin as the initial dose was titrated to 20, 40, and 80 mg; (2) coadministration of 10 mg of ezetimibe and 10 mg of simvastatin (10/10 mg) was titrated to 10/20, 10/40, and 10/80 mg of ezetimibe-simvastatin; and (3) coadministration of 10/20 mg of ezetimibe-simvastatin was titrated to 10/40 mg (for 2 treatment periods) and 10/80 mg of ezetimibe-simvastatin. Key efficacy measures included percent changes in ow-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) from baseline to the ends of (1) treatment periods 1 and 2 (for LDL cholesterol) comparing coadministration of 10/20 mg and 10/10 mg of ezetimibe-simvastatin with 10 mg of atorvastatin and (2) treatment period 4 (for LDL cholesterol and HDL cholesterol) comparing co-administration of 10/80 mg of ezetimibe-simvastatin with 80 mg of atorvastatin. Baseline LDL and HDL cholesterol levels were comparable between treatment groups. At the end of treatment period 1, the mean decrease of LDL cholesterol was significantly ($p<0.001$) greater for co-administration of 10/10 mg and 10/20 mg of ezetimibe-simvastatin than for 10 mg of atorvastatin. At the end of treatment period 4 and after comparing maximum doses, coadministration of 10/80 mg of ezetimibe-simvastatin was superior to 80 mg of atorvastatin in the percent LDL cholesterol decrease (-59.4% vs -52.5%, $p<0.001$) and HDL cholesterol increase (12.3% vs 6.5%; $p<0.001$). All treatments were well tolerated. Thus, a greater LDL cholesterol decrease and HDL cholesterol increase were attained by treating patients with co-administration of ezetimibe and simvastatin than with atorvastatin.

Editorial comment: *Ezetimibe is a cholesterol-lowering agent inhibiting absorption of dietary and biliary cholesterol across the intestinal wall without affecting absorption of bile acids, fatty acids, fat-soluble vitamins, or triglycerides. It has a complementary mechanism of action to the statins, which inhibit cholesterol synthesis in the liver. The coadministration of ezetimibe and statins provides inhibition of both sources of cholesterol, leading to greater reductions in low-density lipoprotein cholesterol (LDL-C) than with either agent alone. Previous studies have shown that this coadministration is effective and well tolerated. In this study, a titration design was used to compare coadministration of ezetimibe + simvastatin with atorvastatin across their respective dose ranges. The combination showed significantly greater efficacy in decreasing levels of LDL cholesterol, non-HDL cholesterol, apolipoprotein B, and total cholesterol compared with atorvastatin at all time points during the titration periods. Focusing on LDL-C reduction, the study also showed that the LDL-C reduction of the maximum dose of Atorvastatin (80 mg) at the end of the study (after 24 weeks) and the LDL-C reduction of EZETROL/simvastatin 10/20 mg at the beginning of the study (after 6 weeks) were very similar (52.5%*

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were not yet thoroughly studied; the DIAL trial is an important step in this direction. The present randomized, double-blind, active-controlled study was specifically focused in diabetic hypertensive patients with nephropathy, comparing lercanidipine with ramipril in a parallel trial. This well-designed study showed that lercanidipine yielded a significant reduction in albumin excretion rate (AER) at completion of the study, when compared with baseline values. Furthermore, both drugs were equipotent in their reduction of AER. These findings are in keeping with the ZAFRA study (Robles NR et al: Lercanidipine in patients with chronic renal failure: the ZAFRA study. Ren Fail 2005;27:73-80). The ZAFRA study aimed to establish whether, on top of ACE or angiotensin receptor blocker (ARB) inhibition, the addition of lercanidipine could be of benefit in chronic kidney disease. Lercanidipine presents both high lipophilicity and vascular selectivity, yielding so a smooth and prolonged effect. The study demonstrates that lercanidipine is a safe and effective antihypertensive drug in this type of patients. In addition, it showed that when associated to ACE or ARB inhibitors, lercanidipine had lead to an additional improvement of renal function and a lowering of proteinuria. These trials support the likelihood that lercanidipine presents specific renoprotective activity beyond its antihypertensive effects. The drug dilates both the afferent and efferent arterioles, and this could be the mechanism for kidney protection.

...Continued from page 1 **- Efficacy and Safety of Ezetimibe...**

versus 50%). In addition, significantly greater decreases in these atherogenic lipoproteins were observed for ezetimibe + simvastatin compared with atorvastatin when averaged across the entire dose range. It should be pointed out that the he combined treatment was well tolerated and did not increase the risk of clinically significant increases in muscle or liver enzymes compared with atorvastatin, and there were no differences in clinical drug-related adverse events or study discontinuations due to drug-related adverse events between the reatment groups.

A recently published paper (Sager PT et al: Effects of tezetimibe coadministered with simvastatin on C-reactive protein ina a large cohort of hypercholesterolemic patients. Atherosclerosis 2005:179:361-7) enlightens an additional interesting feature of the combined therapy. It is well established that the formation and progression of an atherosclerotic plaque frequently involves an inflammatory process. C-reactive protein (CRP), an inflammatory biomarker, has been shown to predict morbidity and mortality from coronary heart disease. This study evaluates the pooled data from more than 1000 subjects participating in two nearly identical multicenter, randomized, double-blind, placebo controlled trials evaluating simvastatin, ezetimibe, or the coadministration of ezetimibe and simvastatin in patients with primary hypercholesterolemia. The rsults demonstrate that this coadministration leads to significant further hs-CRP reductions, and thus this therapeutic approach may potentiate the vascular protective effects of simvastatin.

Selected papers from Israel published recently in leading medical journals

The involvement of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in atherosclerosis.

Michowitz Y, Goldstein E, Roth A, Afek A, Abashidze A, Ben Gal Y, Keren G, George J.
J Am Coll Cardiol 2005;45:1018-24
Department of Cardiology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

BACKGROUND: Inflammation is associated with the pathogenesis of atherosclerosis. The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)/APO-2L, a member of the TNF superfamily, has a role in apoptosis induction and is recognized for its immunomodulatory properties. METHODS: Stable and vulnerable atherosclerotic human plaques and aortas from atherosclerotic mice were assayed for the presence of TRAIL, and its inducibility was assayed by immunoblot and real-time polymerase chain reaction on peripheral mononuclear cells incubated with oxidized low-density lipoprotein (oxLDL). Enzyme-linked immunosorbent assay was used for the determination of soluble TRAIL levels in atherosclerotic patients. RESULTS: Tumor necrosis factor-related apoptosis-inducing ligand is present in stable atherosclerotic lesions, is increased in vulnerable plaques, and is found to colocalize with CD3 cells and oxLDL. The TNF-related apoptosis-inducing ligand messenger ribonucleic acid (mRNA) and protein expression was up-regulated in peripheral blood mononuclear cells after incubation with oxLDL. Serum levels of soluble TRAIL but not TNF-alpha or Fas-ligand were reduced significantly in patients with unstable angina as compared with patients with stable atherosclerotic disease and healthy subjects. A negative correlation was demonstrated between soluble TRAIL and C-reactive protein levels but not with levels of mRNA of TRAIL in peripheral blood mononuclear cells. CONCLUSIONS: Tumor necrosis f actor-related apoptosis-inducing ligand is expressed in plaque-infiltrating CD3 cells and induced by oxLDL, whereas levels of soluble TRAIL are reduced in patients with acute coronary syndromes and negatively correlate with C-reactive protein levels.

Editorial comment: *These results support the significance of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) in atherosclerotic vascular disease.*

Does current treatment of cardiogenic shock complicating the acute coronary syndromes comply with guidelines?

Iakobishvili Z, Behar S, Boyko V, Battler A, Hasdai D. ***Am Heart J*** 2005;149:98-103
Department of Cardiology, Rabin Medical Center, Petah Tikva, Israel.

BACKGROUND: The purpose of this study was to evaluate the implementation of guidelines for the treatment of cardiogenic shock (CS) complicating the acute coronary syndromes (ACS). METHODS AND RESULTS: Of the 10 136 patients in the Euro-Heart-Survey-ACS with complete data, CS occurred in 549 (5.4%), of whom 28.6% had CS upon presentation. We examined the use of coronary angiography (CA), percutaneous (PCI) and surgical (CABG) revascularization, and intra-aortic balloon counterpulsation (IABP) among ACS patients with and without CS. During the hospital course, there were no significant differences between patients with and without CS in referral to CA (52.4% vs 53.3%, respectively) or CABG (4.4% vs 4.5%), but CS patients were more likely to undergo IABP (17.7% vs 0.8%, P < .001) and PCI (40.8% vs 31.8%, P < .001), especially younger (<75 years) patients (52.2% vs 31.8%, P < .001). A similar trend was observed when comparing ST-elevation-ACS patients with (368 [8.5%]) and without CS (3945): CA (58.1% vs 56.2%), CABG (3.6% vs 3.3%), IABP (20.0% vs 0.9%, P < .01), and PCI (47.3% vs 40.6%, P < .01; 54.4% vs. 44.6% for patients <75 years, P < .003). Of the 94 ST-elevation-ACS patients presenting with CS, only 39 (41.4%) received any reperfusion treatment, more often fibrinolysis (64.1%). The in-hospital mortality was 52.1% for all CS pts vs 2.0% for all others (P < .001). CONCLUSIONS: Our contemporary survey demonstrates prohibitively-high mortality rates among ACS patients complicated by CS and poor implementation of recent guidelines advocating an aggressive invasive approach, including low rates of revascularization and IABP.

Editorial comment: *Improved adherence to the guidelines pertaining to ACS patients developing cardiogenic shock may expectantly improve outcomes*

Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study.

Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, Markiewicz W, Aronson D.
Circulation 2005;111:754-60.

Department of Cardiology, Rambam Medical Center, and the Bruce Rappaport Faculty of Medicine, Haifa, Israel.

BACKGROUND: Stress hyperglycemia in patients with acute myocardial infarction has been associated with increased mortality. Most studies looked at the relationship between admission glucose (AG) and outcome; limited information is available about the clinical significance of fasting glucose (FG). METHODS AND RESULTS: We prospectively studied the relationship between FG and 30-day mortality in 735 nondiabetic patients with acute myocardial infarction. FG (> or =8-hour fast within 24 hours of admission) and AG were measured in each patient. At 30 days, 9 deaths (2%) occurred in patients with normal FG, and 11 (10%), 14 (13%), and 31 (29%) deaths occurred in the first, second, and third tertiles of elevated FG, respectively. Compared with normal FG (<110 mg/dL), the adjusted OR for 30-day mortality progressively increased with higher tertiles of elevated FG (first tertile, 4.6; 95% CI, 1.7 to 12.7; P=0.003; second tertile, 6.4; 95% CI, 2.5 to 16.6; P<0.0001; third tertile, 11.5; 95% CI, 4.7 to 20.0; P<0.0001). Compared with patients categorized as having normal AG (<140 mg/d), the adjusted ORs for tertiles of elevated AG were as follows: first tertile, 1.4 (95% CI, 0.5 to 3.8 ; P=0.54); second tertile, 3.0 (95% CI, 1.3 to 7.0; P=0.01); and third tertile, 4.4 (95% CI, 2.0 to 9.7; P<0.0001). Compared with patients with normal FG and AG, the adjusted ORs for 30-day mortality were 0.71 (95% CI, 0.15 to 3.4; P=0.67) in patients with elevated AG and normal FG, 3.4 (95% CI, 1.1 to 10.4; P=0.03) for patients with normal AG glucose and elevated FG, and 9.6 (95% CI, 3.5 to 26.0; P<0.0001) for patients with both elevated FG and AG. Comparing nested models showed that including AG failed to improve the prediction of the model based on FG (chi2=5.4, 3 df, P=0.15). In contrast, the addition of FG classes to the model based on AG improved model prediction (chi2=22.4, 3 df, P<0.0001). CONCLUSIONS: There is a graded relation between elevated FG and AG and 30-day mortality in patients with acute myocardial infarction.

Editorial comment: *Fasting glucose is superior to admission glucose in the assessment of short-term risk.*

Impact of short-term intermittent intravenous dobutamine therapy on endothelial function in patients with severe chronic heart failure.

Freimark D, Feinberg MS, Matezky S, Hochberg N, Shechter M.
Am Heart J 2004;148:878-82

Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel.

BACKGROUND: Intermittent intravenous dobutamine therapy is used to treat patients with decompensated end-stage chronic heart failure (CHF), in whom the vascular endothelium is usually impaired. The impact of short-term intermittent intravenous dobutamine therapy on flow-mediated dilation (FMD) in patients with severe decompensated end-stage chronic CHF has not been assessed. METHODS: We prospectively assessed the impact of intermittent intravenous low-dose dobutamine therapy on endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin (NTG)-mediated vasodilation using high resolution ultrasound scanning in 20 consecutive male patients with severe CHF and ischemic cardiomyopathy (New York Heart Association functional class IV), at baseline and after 4 months, and compared them to 20 age- and sex-matched control subjects. The cardiac index (CI), stroke index (SI), and systemic vascular resistance (SVR) were assessed non-invasively with a thoracic electrical bioimpedance device before and after intravenous dobutamine therapy. RESULTS: Intermittent intravenous dobutamine therapy resulted in significant improvement in post-intervention FMD compared with baseline (7.7% +/- 2.4% vs 1.1% +/- 2.6%; P = .001), a finding not evident in control subjects (1.3% +/- 2.6% vs 1.2% +/- 2.1%; P = .78). There was no significant effect of dobutamine treatment compared with control subjects on NTG-induced vasodilation (7.6% +/- 5.5% vs 7.5% +/- 8.8%, P = .979). Short-term dobutamine therapy also significantly improved SVR (1797 +/- 926 dyne sec/cm5 vs 2172 +/- 1133 dyne sec/cm5, P = .05), CI (2.4+/- 0.6 L/min/m2 vs 1.9 +/- 0.6 L/min/m2, P = .01), and SI (33.5 +/- 11.7 mL/m(2) vs 27.2 +/- 12.4 mL/m2, P = .02). CONCLUSIONS: Short-term intermittent intravenous low-dose dobutamine therapy significantly improved vascular endothelial function, perhaps demonstrating an additional mechanism for improved SVR, CI, and SI in patients with severe CHF.

Editorial comment: *Modification of endothelial dysfunction by low-dose dobutamine therapy may be of significant short-term therapeutic benefit.*

Macrovascular complications of metabolic syndrome: an early intervention is imperative.

Tenenbaum A, Motro M, Schwammenthal E, Fisman EZ
Int J Cardiol 2004;97:167-72

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The metabolic syndrome is a widespread clinical condition and an important cluster of atherothrombotic disease risk factors. The inclusion of this syndrome in the recently published Adult Treatment Panel III (ATP III) guidelines focused the attention of the physicians on this entity. Abdominal obesity, PPAR modulation, insulin resistance (with or without glucose intolerance), atherogenic dyslipidemia, elevated blood pressure, prothrombotic and proinflammatory states are the principal factors of this multifaceted syndrome. There are two major pathways of metabolic syndrome progress: (1) With preserved pancreatic beta cells function and insulin hypersecretion, which can recompense for insulin resistance. This pathway leads mostly to the macrovascular complications of metabolic syndrome. (2) With substantial injure of pancreatic beta cells leading to gradually reduced insulin secretion and to hyperglycemia (e.g. overt type 2 diabetes). This pathway leads to both microvascular and macrovascular complications. Since central obesity (accompanied by insulin resistance even in the absence of hyperglycemia) is the key factor leading to development of metabolic syndrome and its future macrovascular complications, we assume that next logical step is the recognition of central obesity itself as a major risk factor for cardiovascular diseases.

Editorial comment: *Because macrovascular complications of insulin resistance state precede the onset of hyperglycemia, early intervention in patients with metabolic syndrome is particularly important.*

Meeting of the Working Group on Cardiovascular Pharmacology and Drug Therapy of the Israel Heart Society

A meeting of this Working Group was held on February 2, 2005 at Merkaz Azrieli, Tel-Aviv. The main scientific issue of the meeting was the management of hyperlipidemia. The invited speaker, Dror Harats, talked about "The treatment of hyperlipidemia: current aspects". The conference was followed by a panel discussion on "Current evidence-based medicine: moderate or intensive lipid lowering?"
Elections for the Working Group took place after completion of the scientific program. Zvi Fisman and Itzhak Shapira were elected Chairman and Secretary, respectively, instead of Michael Motro and Alexander Tenenbaum, who finished their tenure. Doron Aronson, Michael Motro, Leonardo Reisin and Alexander Tenenbaum are the members of the new board.
The meeting was sponsored by Neopharm.

Professors Michael Motro, Zvi Fisman and Zvi Vered during the panel discussion (February 2, 2005)

Dear colleagues!

The Editorial Board cordially invites you to inform us by e-mail regarding **your newly published papers** related to cardiovascular pharmacology and drug treatment!
We will be pleased to update our readers in the forthcoming editions of *The Newsletter*. E-mail for updating:
altenen@post.tau.ac.il

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Thrombocytopenia, immunoglobulin treatment, and acute myocardial infarction-a case report.

Amit G, Yermiyahu T, Gilutz H, Ilia R, Zahger D.

Angiology 2005;56:229-31

Department of Cardiology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel.

Platelets play a pivotal role in the pathophysiology of the acute coronary syndromes, and platelet inhibition is a cornerstone in the management of these patients. Patients with profound thrombocytopenia who present with an acute coronary syndrome present a difficult challenge. The authors report a patient with immune thrombocytopenic purpura who presented with acute myocardial infarction despite a very low platelet count and who sustained recurrent infarction after receiving immune globulin treatment. The best management of thrombocytopenic patients with acute coronary syndromes is uncertain, but extreme caution is needed before efforts are made to raise the platelet count in order to allow conventional treatment.

Editorial comment: *An interesting case report underscoring the need of a better and evidence-based therapy in these cases, in which current therapeutic approach is blurred.*

The 52nd Annual Meeting of the Israel Heart Society

The 52nd Annual Meeting of the Israel Heart Society (IHS) together with the Israel Society of Cardiothoracic Surgery was held on April 13-14, 2005, at David Intercontinental Hotel, Tel-Aviv, in a warm and friendly atmosphere.

Above 1300 participants attended the meeting. These included a number of renowned guests and invited speakers who have honored us with their presence. Amongst them the world distinguished cardiologist Eugene Braunwald, the senior cardiac surgeon Stephen Westaby from Oxford, UK, the current president of European Society of Cardiology Michal Tendera, the former president of the American College of Cardiology Michael Wolk, Amir Lerman from Mayo College of Medicine, Alec Vahanian from Bichat University Hospital, Paris, Maurice Enriquez-Sarano from Mayo Clinic at Rochester, Alain Berrebi from Paris, members of AFICARDIO (Association Franco-Israelienne de Cardiologie) and other prominent scientific pesonalities. In addition, an honorary IHS membership was awarded to William Ganz from Los Angeles, co-creator of the well-known Swan-Ganz catheter. Several esteemed awards were granted during the Congress. The Henry Neufeld Award for original research was granted to Avishag Farkash, and for the outstanding publication to Shlomi Matetzky. The Jan Kellermann Young's Investigator Awards were received by Dalit May (1st Prize), Itzhak Kehat (2nd Prize) and Ayelet Itzhaki (3rd Prize). Zvi Vered was awarded with the Michael Mirowski Prize for Excellence in Cardiology. The Ami Cohen Young Investigator Award in Cardiac Surgery was received by Anat Zivi. Finally, the MSD Fellowship and the Mayo Clinic Fellowship were awarded to Ashraf Hamdan and Shahar Lavi, respectively.

Congratulations to the winners!

Prof. Dan Tzivoni was elected President of the IHS and initiated his tenure; Dr. Michael Glikson was reelected General Secretary. Prof. Basil Lewis is the new President Elect

Professor Solomon Behar and Ms. Batia Ziv, Executive Secretary of the IHS, during the Congress (April 14, 2005)