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Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis

Bruckert E, Labreuche J, Amarenco P.

Atherosclerosis 2009 Dec 21

OBJECTIVE: High-density lipoprotein cholesterol (HDL-C) concentration is a strong predictor of cardiovascular events in both naïve and statin-treated patients. Nicotinic acid is an attractive option for decreasing residual risk in statin-treated or statin-intolerant patients since it increases HDL-C by up to 20% and decreases low-density lipoprotein cholesterol and lipoprotein(a) plasma concentrations. METHODS: We performed a computerized PubMed literature search that focused on clinical trials evaluating niacin, alone or in combination with other lipid-lowering drugs, published between January 1966 and August 2008. RESULTS: Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. Overall 11 randomized controlled trials enrolled 2682 patients in the active group and 3934 in the control group. In primary analysis, niacin significantly reduced major coronary events (relative odds reduction=25%, 95% CI 13, 35), stroke (26%, 95% CI=8, 41) and any cardiovascular events (27%, 95% CI=15, 37). Except for stroke, the pooled between-group difference remained significant in sensitivity analysis excluding the largest trial. In comparison with the non-niacin group, more patients in the niacin group had regression of coronary atherosclerosis (relative increase=92%, 95% CI=39, 67) whereas the rate of patients with progression decreased by 41%, 95% CI=25, 53. Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of -17mum/year (95% CI=-22, -12). CONCLUSIONS: Although the studies were conducted before statin therapy become standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1-3g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution.

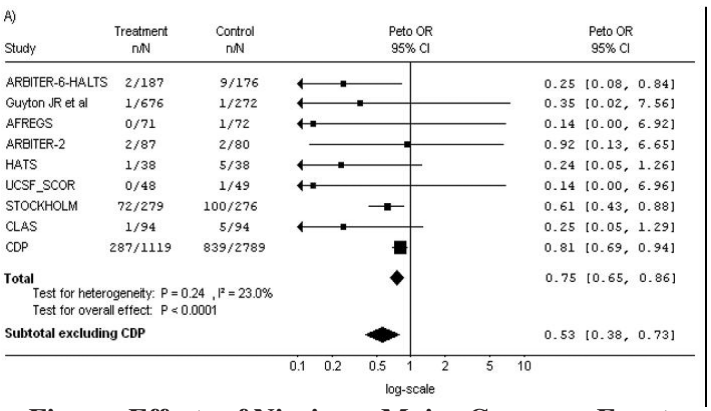

Figure: Effects of Niacin on Major Coronary Events

Editorial comment

Currently, nicotinic acid is the most potent lipid lowering agent capable to achieve the triple task of raising HDL-C levels and lowering both triglycerides and LDL-C. Previous clinical trials (like the Coronary Drug Project - CDP) have demonstrated that niacin therapy significantly reduces the threat of future cardiovascular events in high risk subjects. In addition it should be pointed out that a number of recent well-designed studies provided direct and impressive evidence that niacin effectively reduces carotid atherosclerosis in statin-treated patients (ARBITER-6-HALTS, N Engl J Med. 2009;361:2113-22, Lee et al J Am Coll Cardiol 2009;54:1787-94).

However, niacin is not very commonly used due to its significant side effects (especially flushing). Laropiprant is a potent selective antagonist of PGD2-receptor subtype-1 and can thus reduce niacin-induced flushing. Although the addition of laropiprant will considerably reduce flushing frequency, it will not completely eliminate this side effect. Laropiprant does not change niacin beneficial influence on lipids or other side effects of niacin (i.e. gastro-intestinal problems, glucose elevation). The combination of niacin with laropiprant may therefore enable use of niacin at higher doses and therefore exploit the full potential of the drug. Endpoint studies that will be published over the next few years will show whether this treatment modality is also reflected in the clinical outcome of patients treated with statins: the triple combination therapy of simvastatin/ER niacin/laropiprant may reduce flushing side effects and facilitate a more comprehensive treatment for patients with mixed dyslipidemia. An additional large outcome trial is underway: the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study will assess a new combination therapy containing extended-release nicotinic acid and laropiprant (projected completion in 2013).

Selected papers from Israel published recently in leading medical journals.

Patient characteristics and cell source determine the number of isolated human cardiac progenitor cells.

Itzhaki-Alfia A, Leor J, Raanani E, Sternik L, Spiegelstein D, Netser S, Holbova R, Pevsner-Fischer M, Lavee J, Barbash IM.

Circulation. 2009 Dec 22;120(25):2559-66

Neufeld Cardiac Research Institute, Sheba Medical Center, Tel-Hashomer, Israel

The authors developed a novel isolation method that produced viable cells (7 x 10(6)+/-6.53 x 10(5)/g) from various tissue samples obtained during heart surgery or endomyocardial biopsies (113 samples from 94 patients 23 to 80 years of age). The isolated cardiac cells were grown in culture with a stem cell expansion medium. According to fluorescence-activated cell sorting analysis, cultured cells derived from the right atrium generated higher amounts of c-kit(+) (24+/-2.5%) and Islet-1(+) cells (7%) in culture (mean of passages 1, 2, and 3) than did cultured cells from the left atrium (7.3+/-3.5%), right ventricle (4.1+/-1.6%), and left ventricle (9.7+/-3%; P=0.001). According to multivariable analysis, the right atrium as the cell source and female sex were associated with a higher number of c-kit(+) cells. There was no overlap between c-kit(+) and Islet-1 expression. In vitro assays of differentiation into osteoblasts, adipocytes, and myogenic lineage showed that the isolated human cardiac progenitor cells were multipotent. Finally, the cells were transplanted into infarcted myocardium of rats and generated myocardial grafts. CONCLUSIONS: Our results show that the right atrium is the best source for c-kit(+) and Islet-1 progenitors, with higher percentages of c-kit(+) cells being produced by women.

Long-term effects of peroxisome proliferator-activated receptor ligand bezafibrate on N-terminal pro-B type natriuretic peptide in patients with advanced functional capacity impairment.

Node K, Inoue T, Boyko V, Goldberg I, Fisman EZ, Adler Y, Schwammenthal E, Matas Z, Behar S, Tenenbaum A.

Cardiovasc Diabetol. 2009;8:5.

Cardiac Rehabilitation Institute, Sheba Medical Center, Tel-Hashomer, Israel and Department of Cardiovascular and Renal Medicine, Saga University Faculty of Medicine, Saga, Japan.

BACKGROUND: The effects of pan-peroxisome proliferator-activated receptor (PPAR) ligand bezafibrate on N-terminal pro-B type natriuretic peptide (ProBNP) level in patients with coronary artery disease (CAD) is unknown. The current study aimed to investigate the long-term effects of bezafibrate on ProBNP level in patients with pre-existing CAD and advanced functional capacity impairment. METHODS: Metabolic and inflammatory parameters were analyzed from stored frozen serum samples obtained from 108 patients enrolled in the Bezafibrate Infarction Prevention (BIP) Study. They presented with New York Heart Association (NYHA) functional class III, comprising 58 patients in the bezafibrate group and 50 in the placebo groups, and completed a 2-year prospective, double-blind, placebo-controlled follow-up. RESULTS: During follow-up ProBNP level did not change significantly in the placebo group, whereas it increased slightly in the bezafibrate group, which was older and with lower baseline ProBNP values. No significant differences between the groups were found for ProBNP levels after 2 year of follow-up. Analysis-of-covariance (ANCOVA) -taking into account age and baseline ProBNP level- showed that bezafibrate was not associated with longitudinal ProBNP changes during the follow-up period (p = 0.3). CONCLUSION: Long-term treatment by bezafibrate was not associated with longitudinal ProBNP changes in patients with pre-existing CAD and advanced functional capacity impairment.

Antibodies to oxidized LDL as predictors of morbidity and mortality in patients with chronic heart failure.

Charach G, George J, Afek A, Wexler D, Sheps D, Keren G, Rubinstein A.

J Card Fail. 2009;15:770-4.

Department of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

BACKGROUND: Oxidative stress appears to play a significant role in the pathogenesis of heart failure (HF). Antibodies to oxidized low-density lipoprotein (Ox LDL Abs) reflect an immune response to LDL over a prolonged period and may thus represent oxidative stress over an extended time. Ox LDL Abs have been shown to correlate with clinical control in HF patients. We evaluated the predictive power of Ox LDL Abs on the outcome in patients with HF. METHODS AND RESULTS: Baseline levels of Ox LDL Abs were determined by enzyme-linked immunosorbent assay in 284 consecutive outpatients with severe chronic HF who were being treated in the cardiology services of our medical center. Their mean New York Heart Association (NYHA) Class was 2.8. The mean follow-up for the group was 3.7 years, during which 107 (37%) died. The mean time from symptom onset to first hospital admission from HF was 25.8 months. Ox LDL Abs were found to predict morbidity and mortality as evaluated by a Cox multivariate regression analysis with a hazard ration of 1.013 (P < .013), whereas N-terminal pro-B-type natriuretic peptide (NT pro-BNP) levels achieved a HR of 1.028 (P < .099). CONCLUSIONS: Ox LDL Abs level maybe a useful parameter for monitoring and planning better management of patients with HF. It was superior to pro-BNP as a predictor of clinical course as expressed by time to hospitalization.

Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation.

Lev EI, Solodky A, Harel N, Mager A, Brosh D, Assali A, Roller M, Battler A, Kleiman NS, Kornowski R.
J Am Coll Cardiol. 2010;55:114-21.

Cardiology Department, Rabin Medical Center, Petah Tikva, Israel.

Patients (n = 485) with stable coronary artery disease taking low-dose aspirin (75 to 162 mg) for at least 1 week were screened for aspirin response with the VerifyNow Aspirin assay (Accumetrics, San Diego, California). Further testing was performed by platelet aggregation. Aspirin resistance was defined by > or =2 of 3 criteria: VerifyNow score > or =550, 0.5-mg/ml AA-induced aggregation > or =20%, and 10-micromol/l adenosine diphosphate (ADP)-induced aggregation > or =70%. Thirty patients (6.2%) were found to be aspirin resistant and randomized to receive either low-dose aspirin + omega-3 fatty acids (4 capsules daily) or aspirin 325 mg daily. After 30 days of treatment patients were re-tested. RESULTS: Both groups (n = 15 each) had similar clinical characteristics. After treatment significant reductions in AA- and ADP-induced aggregation and the VerifyNow score were observed in both groups. Plasma levels of thromboxane B2 were also reduced in both groups (56.8% reduction in the omega-3 fatty acids group, and 39.6% decrease in the aspirin group). Twelve patients (80%) who received omega-3 fatty acids and 11 patients (73%) who received aspirin 325 mg were no longer aspirin resistant after treatment. CONCLUSIONS: Treatment of aspirin-resistant patients by adding omega-3 fatty acids or increasing the aspirin dose seems to improve response to aspirin and effectively reduces platelet reactivity.

Increased insulin resistance and risk of incident cerebrovascular events in patients with pre-existing atherothrombotic disease.

Tanne D, Tenenbaum A, Boyko V, Benderly M, Fisman EZ, Matas Z, Adler Y, Behar S.
Eur J Neurol. 2009;16:1217-23.

Chaim Sheba Medical Center, Tel-Hashomer, Israel

Patients with stable coronary heart disease included in a secondary prevention trial were followed up for a mean of 6.2 years. Crude rates of incident cerebrovascular events rose from 5.0% for HOMA-IR at the bottom tertile to 5.7% at the middle tertile, and 7.0% at the top tertile (P = 0.07). HOMA-IR at the top versus bottom tertile was associated with an unadjusted hazard ratio (HR) of 1.37 (95%CI, 0.94-1.98) and a 1-unit increase in the ln HOMA-IR was associated with a HR of 1.14 (95%CI, 0.97-1.35). In further analyses adjusting for potential confounders, or categorizing baseline HOMA-IR into quartiles, or excluding diabetic patients, we did not identify an increased risk for incident cerebrovascular events conferred by the top category. CONCLUSIONS: Increased insulin resistance did not predict incident cerebrovascular events amongst patients with pre-existing atherothrombotic disease.

Impact of diastolic dysfunction on the development of heart failure in diabetic patients after acute myocardial infarction.

Aronson D, Musallam A, Lessick J, Dabbah S, Carasso S, Hammerman H, Reisner S, Agmon Y, Mutlak D.
Circ Heart Fail. 2010;3:125-31.

Department of Cardiology, Rambam Medical Center, Haifa, Israel.
daronson@tx.technion.ac.il

A total of 1513 patients with acute myocardial infarction (417 diabetic) underwent echocardiographic examination during the index hospitalization. The primary end points of the study were readmission for HF and all-cause mortality. The frequency of RFP was higher in patients with diabetes (20 versus 14%; P=0.005). During a median follow-up of 17 months (range, 8 to 39 months), 52 (12.5%) and 62 (5.7%) HF events occurred in patients with and without diabetes, respectively (P<0.001). There was a significant interaction between diabetes and RFP (P=0.04) such that HF events among diabetic patients occurred mainly in those with RFP. The adjusted hazard ratio for HF was 2.77 (95%, CI 1.41 to 5.46) in diabetic patients with RFP and 1.21 (95% CI, 0.75 to 1.55) in diabetic patients without RFP. A borderline interaction (P=0.059) was present with regard to mortality (adjusted hazard ratio, 3.39 [95% CI, 1.57 to 7.34] versus 1.61 [95% CI, 1.04 to 2.51] in diabetic patients with and without RFP, respectively). CONCLUSIONS: Severe diastolic dysfunction is more common among diabetic patients after acute myocardial infarction and portends adverse outcome. HF and mortality in diabetic patients occur predominantly in those with concomitant RFP.

Vascular endothelial function predicts mortality risk in patients with advanced ischaemic chronic heart failure.

Shechter M, Matetzky S, Arad M, Feinberg MS, Freimark D.
Eur J Heart Fail. 2009;11:588-93

Heart Institute, Chaim Sheba Medical Center, 52621 Tel Hashomer, Israel.

We prospectively assessed brachial flow-mediated dilation (FMD) in 82 consecutive New York Heart Association class IV ischaemic ACHF patients with a mean left ventricular ejection fraction (LVEF) of 22 +/- 3%. Following overnight fasting and discontinuation of all medications for > or = 12 h, percent increase in FMD (%FMD) and nitroglycerin-mediated vasodilation were assessed using linear array ultrasound. All patients were followed for 14 +/- 2 months for adverse cardiovascular events, including death, hospitalization for CHF exacerbation, or myocardial infarction. During follow-up, 22 (53.6%) patients with FMD lesser than or equal to the median had composite adverse cardiovascular events compared with only eight patients (19.5%) with FMD above the median (P < 0.01). Furthermore, fiver deaths (12.1%) occurred in patients with FMD lesser than or equal to the median, compared with no deaths in patients with FMD above the median (P < 0.03). Cox regression analyses revealed that FMD was an independent predictor for these events. CONCLUSION: Flow-mediated dilation is associated with increased mortality risk in ischaemic ACHF patients.

Circumferential and Longitudinal Strain in 3 Myocardial Layers in Normal Subjects and in Patients with Regional Left Ventricular Dysfunction.

Leitman M, Lysiansky M, Lysyansky P, Friedman Z, Tyomkin V, Fuchs T, Adam D, Krakover R, Vered Z.

J Am Soc Echocardiogr. 2010;23:64-70.

Department of Cardiology, Assaf Harofeh Medical Center, Zerifin, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. Twenty normal subjects and 21 patients with LV dysfunction underwent echocardiography. Short-axis (for circumferential) and apical (for longitudinal strain) views were analyzed using modified speckle-tracking software enabling the analysis of strain in 3 myocardial layers. RESULTS: In normal subjects, longitudinal and circumferential strain was highest in the endocardium and lowest in the epicardium. Longitudinal endocardial and mid layer strain was highest in the apex and lowest in the base. Epicardial longitudinal strain was homogenous over the left ventricle. Circumferential 3-layer strain was highest in the apex and lowest in the base. In patients with LV dysfunction, strain was lower, with late diastolic or double peak. CONCLUSIONS: Three-layer analysis of circumferential and longitudinal strain using speckle-tracking imaging can be performed on a clinical basis and may become an important method for the assessment of real-time, quantitative global and regional LV function.

Safety and effectiveness of the endeavor zotarolimus-eluting stent in real-world clinical practice 12-month data from the e-five registry.

Lotan C, Meredith IT, Mauri L, Liu M, Rothman MT; E-Five Investigators.

JACC Cardiovasc Interv. 2009;2:1227-35.

Heart Institute, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. The E-Five registry is a prospective, nonrandomized, multicenter global registry conducted at 188 centers worldwide. Adult patients (n = 8,314) with coronary artery disease who underwent single-vessel or multivessel percutaneous coronary intervention were enrolled. The primary end point was the rate of major adverse cardiac events (MACE) at 12 months. A secondary analysis stratified patients by standard versus extended-use clinical and lesion characteristics. RESULTS: Overall 12-month outcome rates were MACE 7.5%; cardiac death 1.7%; myocardial infarction (all) 1.6%; target lesion revascularization 4.5%; and stent thrombosis (Academic Research Consortium definite and probable) 1.1%. The 12-month MACE rates were 4.3% and 8.6% for standard- and extended-use patients, respectively ($p < 0.001$). CONCLUSIONS: This large, international multicenter registry provides important information regarding the long-term safety and efficacy of the Endeavor ZES across standard and extended-use patients in the real-world setting. Rates of MACE and measures of safety including cardiac death, myocardial infarction, and stent thrombosis were low and consistent with pooled results of clinical trials. (E-Five Registry: A World-Wide Registry With The Endeavor Zotarolimus Eluting Coronary Stent.

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

The recent meeting of our Working Group took place on February 8 2010 at Derby Restaurant, Tel-Aviv, and it was dedicated to two interrelated topics: 1) the etiology, pathology, prevalence and clinical characteristics of the fatty liver, and 2) the possible safety concerns regarding hepatic function in patients on statin therapy. The invited speaker, Prof. Ran Oren – head of the Hepatology Unit at Ichilov Hospital - brought an updated and authoritative review of this essential issue. The main ìtake home messagesî were that NFLD (nonalcoholic fatty liver disease) is a rather common finding, affecting more of 25% of obese individuals. It ranges from simple steatosis to eventually severe steatohepatitis. It presents a strong positive correlation with obesity and insulin resistance; thus, it may be considered as the hepatic expression of the metabolic syndrome. In addition, as a general rule, the several types of statin medication do not negatively affect hepatic function. The presentation was followed by a friendly panel discussion. The meeting was sponsored by Pfizer Israel.

Dr. Ilan Hay and Prof. Alexander Tenenbaum during the Working Group meeting

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Editorial Adress: Cardiac Rehabilitation Institute, the Chaim Sheba Medical Center, Tel-Hashomer, affiliated with the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, 52621 Israel

Editor-in-Chief: Prof. A.Tenenbaum

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