**762 5-AMINOLEVULINIC ACID-DERIVED PROTOPORPHYRIN IX MEDIATED FLUORESCENCE DIAGNOSIS AND PHOTODYNAMIC THERAPY OF MACROPHAGES WITHIN THE Atherosclerotic PLAQUE**


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**Introduction:** 5-aminolevulinic acid-derived protoporphyrin IX (ALA-PpIX) has shown great potential in detection and treatment of cancer. Immunofluorescent staining of plaque macrophages and SMCs was performed to locate ALA-PpIX. Plaque burden was evaluated by Hematoxylin and eosin (H&E) staining. Plaque macrophages and SMCs content was determined by immunohistochemical staining.

**Results:** PpIX was found accumulated in the cytoplasm of THP-1 macrophages. In the plaque fresh-frozen sections, the fluorescence of ALA-PpIX was detected which was amplified by immunofluorescent staining. Compared with the control group, the plaque area was reduced by 59% (P < 0.001) at 1 week after PDT, the plaque macrophages content decreased by 56% (P < 0.001) at 1 week and 64% (P < 0.001) at 4 week respectively.

**Conclusion:** ALA-PpIX is preferentially accumulated in the macrophages of plaque and ALA-PpIX mediated PDT significantly decreases macrophages content, indicating a promising strategy of atherosclerotic plaque macrophages diagnosis and therapy.

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**763 EFFECT OF MIPOMERSEN ON LP(a) IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA; RESULTS FROM TWO PHASE 3 STUDIES**


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**Background and Aim:** Lp(a) is considered an independent risk factor for coronary artery disease (CAD). The EAS consensus panel has recommended screening and treatment of elevated Lp(a). We evaluated effects of mipomersen (MIPO), an antisense apo B synthesis inhibitor, on Lp(a) in two Phase 3 studies in which patients with HeFH with CAD or severe HeFH (LDL-C > 5.1 mmol/L with CAD/equivalent or >7.8 mmol/L) (n = 124 and 58, respectively) were randomized (1:2) to placebo (PBO) or MIPO 200 mg/week subcutaneous in addition to ongoing maximally tolerated statin and other hypolipidemic therapies for 26 weeks. The primary endpoint was change in LDL-C from baseline to week 26 of 2 and 2% or the last dose. Significant (P < 0.001) reductions in LDL-C were seen with MIPO (~28% and ~36%) vs PBO (5.2% and +13%), reported elsewhere.

**Results for Lp(a):** Most patients had elevated Lp(a) levels (>20 mg/dL) at baseline (71% and 62%). Median % reductions in Lp(a) were 21% and 39% for MIPO vs 0% and 5% for PBO (P < 0.001). 21.5% of MIPO-treated patients achieved Lp(a) reductions of ≥50%. Common AEs included injection-site reactions (MIPO: 93% and 90% vs PBO: 42% and 32%) and flu-like symptoms (MIPO: 49% and 46% vs PBO: 32% and 21%). Persistent ALT elevations >3×ULN on consecutive measure at least 7 days apart were observed in MIPO patients (6% and 15%) without clinically significant elevations in bilirubin. These results suggest that mipomersen as a potential add-on therapy for reducing elevated Lp(a) and LDL-C in patients with HeFH.

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**764 OCCURRENCE OF CORONARY HEART DISEASE IN A COHORT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIC PATIENTS IN NORWAY**

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**Introduction:** Heterozygous familial hypercholesterolemia (HeFH) is an inherited autosomal dominant disorder in the LDL-receptor (LDL-R) gene, causing non-functional LDL-receptors on the cell surface, resulting in reduced LDL-cholesterol uptake in cells, increased serum LDL-cholesterol levels and increased risk of developing coronary heart disease (CHD).

**Material and Methods:** In 2006, we provided data on 545 HeFH patients with a genetically confirmed diagnosis, without diabetes mellitus before a CHD event. “Event tables” with regard to occurrence of first clinically manifested coronary heart disease event were constructed. A Cox Proportional Hazard model was applied to the data with stratification for gender and smoking status.

**Results:** Seventy-four events were recorded, with roughly half the number of events recorded for female smokers (10 events) than the other three groups (21–22 events per group), the majority of these events occurring between the ages of 30 and 55. The estimated hazard ratio for men vs. women was 1.72 (95% CI 1.07–2.76) and for smoking vs. non-smoking was 1.40 (95% CI 0.87–2.19).

**Discussion/conclusion:** In FH patients the risk of having a coronary disease event is high, even in 2006 when statin treatment had been available for more than 15 years. Moreover, even with a relatively small number of events recorded, there is clear support for the expectation that being male and smoking increases risk of CHD.

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**765 NITRIC OXIDE-DONATING STATINS EXERT BENEFICIAL EFFECTS ON ACUTE VASCULAR INFLAMMATION IN NORMOCHELOEROLEMIC RABBITS**

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**Introduction:** Evidence has emerged suggesting that polymorphonuclear leucocytes before initiation of LA, the first event occurred at a far earlier inflammatory event compared to placebo (PBO) or MIPO 200 mg/week subcutaneous in addition to ongoing maximally tolerated statin and other hypolipidemic therapies for 26 weeks. The primary endpoint was change in LDL-C from baseline to week 26 of 2 and 2% or the last dose. Significant (P < 0.001) reductions in LDL-C were seen with MIPO (~28% and ~36%) vs PBO (5.2% and +13%), reported elsewhere.

**Methods:** Chow-fed rabbits (n = 10/group) received a daily oral dose of vehicle or experimental compounds (equivalent to 5 mg/kg/day atorvastatin) for 6 days. Collars were implanted after the last dose of treatment. Twenty-four hours later arteries were removed, immunostained for PMA, and measured by image analysis.

**Results:** Collared carotids from the control group had a high content of PMN. Unlike atorvastatin, which did not influence the average value of PMN-positive-area compared to control, both the NO-donating statins NCX 616 and NCX 656, which retain the inhibitor activity of atorvastatin on HMG-CoA reductase and release bioactive NO, reduced PMN infiltration of about 40% (p < 0.05) and 35% vs. control, respectively.

**Conclusions:** NO-donating derivatives of atorvastatin exert, in addition to the effect of statin, additional beneficial effects on vascular inflammation, thus supporting a pharmacological rationale for their clinical development.

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**766 LONG TERM COURSE IN PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA UNDERGOING LIPID-APHERESIS**

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**Introduction:** Homozygous familial hypercholesterolemia (FH) leads to several fold elevated LDL-cholesterol and early cardiovascular disease (CVD). As lipid-lowering medication is not sufficiently effective patients need lipid apheresis (LA) to reduce LDL-cholesterol and slow the course of CVD.

**Method:** In 16 homzygous FH patients (9 males, 14 females) clinical manifestations of CVD were documented before and since initiation of LA. Data are available from 1977 until 2010.

**Results:** 9 of the patients had CVD (9 aortic valve disease, 5 coronary artery disease) before initiation of LA. The first event occurred at a far earlier inflammatory event compared to placebo (PBO) or MIPO 200 mg/week subcutaneous in addition to ongoing maximally tolerated statin and other hypolipidemic therapies for 26 weeks. The primary endpoint was change in LDL-C from baseline to week 26 of 2 and 2% or the last dose. Significant (P < 0.001) reductions in LDL-C were seen with MIPO (~28% and ~36%) vs PBO (5.2% and +13%), reported elsewhere.

**Conclusion:** Long-term lipid-apheresis in patients with homzygous familial hypercholesterolemia slows atherosclerotic disease progression or can prevent the development of CVD, especially if initiated early and optimally before the first CVD event.