**EC5**

## Intravitreal Bevacizumab (Avastin) and Cardiovascular Adverse Events - More Than Meets the Eye

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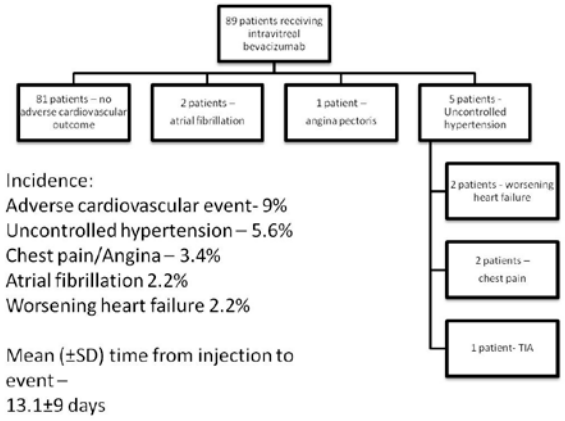
Introduction: Neovascular age-related macular degeneration (AMD) is the leading cause of legal blindness in the elderly population worldwide. Bevacizumab (Avastin, Genetech) is an anti vascular endothelial growth factor antibody, primarily known for its use in malignancies. When Bevacizumab is administered intravitrealy, it has been shown to improve visual acuity in patients with AMD. Although cardiovascular side effects have been described in a large trial, their significance remained questionable.
Methods: We conducted a retrospective analysis of a patient cohort receiving intravitreal Bevacizumab in our institution. We sought to determine the incidence and specific types of adverse cardiovascular events related to these injections. All consecutive patients receiving this therapy during the period 1/2008 until 6/2011 were considered. Cardiovascular adverse events were defined as any cardiovascular symptom or sign developing within a month of the injection.
Results: A total of 89 patients were included in this study. 8 adverse cardiovascular events occurred, yielding an incidence of 9%. These events included 5 patients with uncontrolled hypertension, 2 patients with recurrence of atrial fibrillation, and one patient with worsening angina pectoris. Uncontrolled hypertension was complicated by worsening heart failure in 2 patients, chest pain in 2 patients, and a TIA in one patient. The mean time (±SD) from injection to the adverse event was 13.1±9 days. An unexpected finding was that Bevacizumab therapy was mentioned only in 2 of the patients with these complications.




Conclusions: Intravitreal Bevacizumab injections may be associated with adverse cardiovascular events. These include uncontrolled hypertension, worsening angina or heart failure, atrial fibrillation, and TIA. A focused ophthalmologic history might aid in identifying a previously unrecognized precipitating factor for these common events and possibly prevent recurrence in the future.

**Association Between Neighborhood Socioeconomic Context and Recurrent Coronary Events After MI**

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Longitudinal data linking area-level socioeconomic status (SES) to repeated coronary events are limited. Using multiple failure-time data, the authors examined the association between neighborhood SES and acute coronary syndromes (ACS) in a cohort of myocardial infarction (MI) survivors. Consecutive patients aged ≤65 years released from 8 hospitals in central Israel after first MI in 1992-3 were followed through 2005. Recurrent MI and unstable angina pectoris (UAP) leading to hospitalization were recorded. Neighborhood SES was assessed through a composite census-derived index. Different variance-corrected proportional hazards models were used to account for multiple recurrent events: Andersen-Gill (AG), Wei-Lin-Weissfeld (WLW) and Prentice-Williams-Peterson (PWP). During follow-up, 531 recurrent MIs and 1,584 UAP episodes occurred among 1,164 patients. Estimates of recurrent ACS by neighborhood SES tertiles are shown in the Figure. Adjusting for known prognostic factors and individual SES using the AG model, higher estimated hazards were associated with poor neighborood SES (HR = 1.55, 95% CI: 1.13, 2.14 for recurrent MI; and 1.48, 95% CI: 1.22, 1.79 for UAP; in the 5th vs. 95th percentiles). The WLW and PWP models yielded similar results. When the two outcomes were combined, the WLW-derived HR was 1.64 (95% CI: 1.39, 1.93). Thus, MI survivors living in a deprived neighborhood are at higher risk of repeated hospital admissions due to ACS.

**Assessment of a Frailty Index in a Cohort of Myocardial Infarction Survivors**

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Background: Frailty describes the heterogeneity of vulnerability in older people and has been shown to predict mortality in the general population. Little is known about the clinical relevance of frailty in survivors of myocardial infarction (MI), who are at increased risk of mortality and adverse events. We adapted the Rockwood frailty index (FI), based on accumulation of deficits, in a cohort of post-MI survivors and examined its predictive value for mortality and hospital admissions.
Methods: Participants were 885 patients aged ≤65 years admitted to one of 8 hospitals in central Israel with first acute MI in 1992-1993. An FI was developed comprising 32 variables collected during initial hospitalization, and 10-13 years after MI, including functional limitations (e.g. activities of daily living), mobility (e.g. climbing stairs), health attitudes (e.g. self-rated health) and comorbidity (e.g. diabetes, stroke).
Results: Baseline frailty scores ranged from 0-0.38 with a mean of 0.09 (SD 0.07). After 10-13 years, frailty scores in survivors were higher, as expected, with a range of 0.02-0.64 and a mean of 0.22 (SD 0.12). A moderate correlation was evident between FI calculated at the two time-points (rho=0.39). With baseline frailty score dichotomized below and above the median (0.08), mortality rates were significantly higher in the high frailty compared to the low frailty group (28 vs. 11 deaths per 1000 person-years, $p<0.001$). Frailer patients additionally had a higher rate of hospitalization during follow-up (833 vs. 523 per 1000 person-years, $p<0.001$).
Conclusion: Frailty score calculated via an index of deficits was significantly associated with mortality and hospitalizations following MI. This index facilitates identification of the most vulnerable post-MI patients and forecasts healthcare use. Beyond predictive value, accurate identification of frailty may indicate which individuals will benefit from preventive interventions.

**Statin Adherence is Associated with Reduced Incidence of Venous Thromboembolism**

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Background: The association between statin use and venous thromboembolism (VTE) prevention has been repeatedly shown in multiple reports. Since patient adherence to medications is poor, their applicability in a real-life setting is questionable.

Objectives: Investigate the association between the use of statins and incidence of VTE.

Methods: A retrospective cohort study in a large healthcare maintenance organization (HMO) population. Prescription drug purchase data was analyzed in order to evaluate the association between statin use and adherence and between VTE prevention. Included were statin initiators aged 30 years or older since 2003 who did not have a statin prescription for at least 4 years before that and had at least 18 months follow up. End of follow up was defined as the first of the following: leaving MHS, death, VTE or October 27, 2010.

Results: The study population included 159,109 subjects (79,194 females). The follow-up period comprised of 752,538 patient years (PY), and included 815 and 1139 VTE cases and 5-year cumulative incidence rates of 1.09% and 1.49%, among man and women, respectively. Cox regression analysis demonstrated a significantly lower VTE risk of up to 30% for males, in more adherent patients compared to the risk for the lowest adherence group. A similar analysis for females was not found. In both genders, several atherosclerotic risk factors were associated with higher VTE risk.

Conclusion: In a real life HMO setting, better adherence to statins is associated with a reduced risk of first ever VTE events in males.

**Catheter-Based Renal Sympathetic Denervation (RDN) for Resistant Hypertension: Initial Experience**

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Background: Based on Semplicity-1 and Semplicity-2 studies, catheter-based Renal sympathetic Denervation (RDN) is proved as an effective and safe treatment for resistant hypertension.
Aim: To evaluate early and late effects of RDN on BP in patients with resistant HTN in our initial experience.
Methodes:Eleven patients with resistant HTN were treated by RDN.
Inclusion Criteria: Office SBP ≥160 mmHg (≥150 mmHg in type II-DM), On 3+ more anti-HTN medications, Renal artery diameter ≥4mm and ≥20 mm length and eGFR of ≥45. Exclusion Criteria: Significant renal artery abnormalities, Type I-DM, and MI, unstable angina or CVA in the prior 6 months, ICD or pacemaker or pregnancy.
Results: Eleven patients (7males), age 47-67 years, 3 with type II-DM, 5 with hyperlipidemia, 4 smokers, 4 CAD and 1 PVD, eGFR 89±25, Mean number of antihypertension medications 3.75, all on diuretics & ACEI and/or ARB, 8 on Beta blockers, 7 on Ca Channel Blockers and 2 on clonidine. RDN was successfully done in 10, in one patient RDN catheter could not be introduced due to unfavorable vascular anatomy.
Procedure Detail & Safety: RDN procedure time was 70-120 -median 87- minutes, 100-200ml 1:2 diluted contrast, 5-7 ablations per artery were done. Intravenous narcotics & sedatives used to during RF ablations. RDN was completed successfully in all 10 patients. No catheter or generator malfunctions, no vascular abnormalities at any site of RF delivery. No early or late major or minor complication, No electrolyte disturbances or change in renal function.

Baseline BP was 168 ±21/84±9 decreased significantly to 150±21 / 81±6 and 142±12 / 76±9, one and 3 months after RDN, respectively.

<IMAGE04> Figure 1: Systolic BP after RDN
Conclusions: Catheter-based renal denervation is safe and effeciant,was done successfully in 10 patients with treatment-resistant essential hypertension, resulted in significant reductions in BP. The technique was applied without minor or major complications.

**Haptoglobin Phenotype Does not Predict Coronary Artery Calcification in Diabetic Subjects**

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Background: Haptoglobin (Hp) 2-2 phenotype predicts increased cardiovascular events in diabetes mellitus compared to Hp phenotypes 1-1 and 1-2. We postulated that diabetics with the Hp 2-2 phenotype would have a higher coronary calcium score than diabetics with other phenotypes.
Methods: Coronary calcium scores were measured by 64-slice computed tomography in 196 subjects with type-2 diabetes and no known heart disease. Haptoglobin phenotype was correlated with calcium scores.
Results: Coronary artery calcification was detected in 79% of the subjects (Agatston score >100 in 46%). Haptoglobin phenotype was 1-1 in 13%, 1-2 in 44% and 2-2 in 43% of the subjects. On multivariate analysis, predictors of coronary calcium score >100 AU were heavy smoking (OR 2.6, 95% CI 1.02-6.8), male sex (OR 2.2, 95% CI 1.2-4.1), statin therapy (OR 2.2, 95% CI 1.1-4.4) and longstanding diabetes (OR 2.0, 95% CI 1.7-3.6). Haptoglobin phenotype did not predict coronary artery calcification .
Conclusions: Coronary artery calcification was associated with with the presence of atherosclerotic risk factors but not with Hp phenotype. The findings suggest that the adverse cardiovascular outcomes in Hp 2-2 diabetics are not related to increased plaque burden. Increased plaque vulnerability in these subjects may underlie their increased risk for cardiovascular events.

**Barriers to Comply with Preventive Medications in Patients with Acute Cardiac or Cerebrovascular Events**

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Background: Poor compliance to preventive medications (meds) is associated with increased morbidity, mortality and higher costs for the health care system. We therefore evaluated the compliance and barriers of compliance in pts hospitalized with acute cardiac or cerebrovascular event.
Methods: All patients hospitalized in Neurology and Cardiology departments during March-December 2010 with acute cardiovascular or cerebrovascular event were included. Pts must have taken at least 1 preventive meds during the month before hospitalization. Pts were asked to answer two questionnaires: during index hospitalization and a telephonic questionnaire 3 months after discharge. We evaluated the differences in compliance between pts with cardiovascular and cerebrovascular event, as well as between pts with first and recurrent event.
Results: 253 pts, mean age 64 (68.8% men). Overall compliance increased from 65.9% before admission to 91.2% after 3 months. The lowest compliance was to lipid lowering drugs and anti-platelets (72.3% and 77.4%, respectively). Pts with recurrent event had better compliance to these medications (p=0.073, OR=1.93; p=0.079, OR=1.96). Pts with cardiac event had better compliance to diuretics (p=0.042, OR=13.84). Main barriers to compliance were inability to read the print on the container/instruction sheet (35.3%), lack of clear instructions on the meds (37.1%), lack of a defined method for remembering meds' intake (44.7%) and cost of meds (46.7%). Taking meds is a burden to 46.2% of pts and 34.5% of them sometimes skip a dose out of choice. 15% of pts stopped taking at least one of the meds on their own decision.
Conclusions: We found a high rate of poor compliance to lipid-lowering and anti-platelet meds prior to hospitalization with acute cardiac and cerebrovascular event. Measures should be taken to preserve the high compliance after hospitalization. Our findings should be considered when planning interventions to improve compliance.

**_IRS1_ Gene Variations Modify Insulin Resistance Response to Various Diet Types (DIRECT Study)**

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Background: In the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT) study, participants were randomized to low-fat, Mediterranean, or low-carbohydrate diets and followed up for metabolic parameters. It is currently unknown whether genetic variants influence insulin resistance dietary response. Common genetic variants in the Insulin receptor substrate 1 (*IRS1*) gene have been recently associated with insulin resistance and hyperinsulinemia. We examined whether the best-associated variant of IRS1 modifies the long-term changes in insulin resistance and body weight among participants of the DIRECT study.

Methods and Results: We genotyped *IRS1* rs2943641 in 263 overweight adults randomly assigned to either low fat, low carbohydrate or Mediterranean diets. We assessed the progress in fasting insulin, insulin resistance (HOMA-IR) and weight loss by genotypes. There was significant interactions between *IRS1* rs2943641 genotype and dietary intervention on changes in fasting insulin (P=0.004 for interaction) and HOMA-IR (P=0.013 for interaction) at 2 years. For example: participants with CC genotype had greater decreases in insulin resistance (HOMA-IR) than those without this genotype in the low-fat diet group, while an opposite effect was observed on the non-wild type allele carriers (CT+TT) (P=0.01). No such interaction was seen on body weight. Our results recapitulated the recently published results of the Pound Loss cohort. [1]

Conclusions: There is a genetic predisposition affecting insulin levels and insulin resistance after dietary intervention. This is demonstrated by different response to various types of diet among carriers of the wild type and non-wild type *IRS1* rs2943641 allele.

1. Qi, Q., et al., Insulin Receptor Substrate 1 Gene Variation Modifies Insulin Resistance Response to Weight-Loss Diets in a 2-Year Randomized Trial: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial. Circulation, 2011. 124(5): p. 563-71.