

## Aspirin Resistance among Stable Coronary Artery Disease Patients

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**Background:** Low response to aspirin has been associated with adverse clinical outcome. There is limited data that characterizes patients with stable coronary artery disease (CAD) who are resistant to the anti-platelet effects of aspirin. Our objectives were to identify the prevalence and the characteristics of patients with stable CAD who have reduced anti-platelet response to aspirin treatment.

**Methods:** We evaluated 227 stable patients with CAD who have been treated with aspirin for at least one week. Aspirin resistance was defined by at least 2 of 3 criteria: VerifyNow Aspirin (Accumetrics) score  $\geq 550$ ,  $5\mu\text{M}$  adenosine diphosphate-induced platelet aggregation  $\geq 70\%$  and  $0.5\text{mg/ml}$  arachidonic acid-induced platelet aggregation  $\geq 20\%$ .

**Results:** Of the patients studied 13 (6%) were aspirin resistant. Aspirin resistant patients were more likely to be women and less likely to have hypertension. Other characteristics are shown in the table.

**Conclusions:** A relatively low percentage of patients with stable CAD are resistant to the effect of aspirin. The main clinical feature found in our study is a higher proportion of women among aspirin resistant patients. This finding may contribute to the low benefit of aspirin treatment in women, recently reported in primary prevention trials.

	Aspirin resistant (n=13)	Aspirin sensitive (n=214)
Age (years)	68.8 $\pm$ 9.6	68 $\pm$ 9.7
Gender (women)	38.5%*	13.6%*
Weight (kg)	70.7 $\pm$ 12.8 $\dagger$	77.5 $\pm$ 12.9 $\dagger$
Height (cm)	163.5 $\pm$ 9.1*	169.1 $\pm$ 8.5*
BMI (kg/m <sup>2</sup> )	26.5 $\pm$ 4.6	27 $\pm$ 3.6
Diabetes Mellitus	30.8%	41.5%
Hypertension	38.5% $\dagger$	63.8% $\dagger$
Hypercholesterolemia	84.6%	78.7%
Smoker	22.2%	17%
Family History	58.3%	57.9%
Previous MI	61.5%	58.1%
Previous PCI	84.6%	90.5%
Previous CABG	53.8%	36.9%
Clopidogrel	7.7%	21.1%
Statins	100%	89.5%
Beta Blockers	69.2%	69.3%
ACE Inhibitors	61.5%	58.5%
* $p < 0.05$ , $\dagger p = 0.06$		

## Prevalence of Migraine in Patients with Patent Foramen Ovale

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**Introduction:** Migraine is a common neurological disorder with a prevalence of 11-12% in the general population and a great impact on the quality of life and on social activities. Patent foramen ovale (PFO) is an inter-atrial left-to-right shunt with a prevalence of 25% in the general population. Recent epidemiological data suggest a bidirectional link between PFO and migraine with aura. PFO closure might improve migraine symptoms and serves as an effective treatment modality for migraines. **Objectives:** To investigate the prevalence of migraine with and without aura in a consecutive unselected cohort of young patients with PFO. **Methods:** Patients with PFO between 18-65 years of age were retrieved from database of the echocardiography laboratories at the Meir and Soroka medical centers. Patients were interviewed by phone for headache and migraine using a standard migraine questionnaire and MIDAS questionnaire for quality of life. **Results:** One hundred and eighty-four patients with PFO were included. The prevalence of headache was 51%. Thirty-six percents fulfilled criteria for migraine compared to 12% in the general population ( $p<0.001$ ). Fifty percents of the migraine sufferers had migraine with aura compared to 5-15% in the general population ( $p<0.001$ ). **Conclusions:** Our findings confirm previous observations of higher incidence of migraine with aura in patients with PFO compared to the general population. Echocardiography study should be included in the workup of patients with migraine especially in migraine with aura.

## **High Frequency ECG – a Novel Tool for Improving the Diagnostic Accuracy of Exercise Testing in the Community Setting**

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ECG based detection of exercise-induced myocardial ischemia relies on identifying ST changes, representing the repolarization phase. Recently, a new technology utilizing high-resolution ECG was reported to better identify stress-induced ischemia. This approach quantifies subtle ischemic-induced changes in the depolarization phase using analysis of high frequency QRS components (HFQRS). Our aim was to test the clinical applicability of this novel technique in a large patient population in three community cardiology centers.

**Methods:** High-resolution ECG was acquired (HyperQ™ System, BSP, Israel) during clinically indicated exercise test (ETT) in 1205 consecutive patients (age 57±9 yo, 64% men). The relative intensity change of HFQRS components (HyperQ™) during exercise was used as an index of ischemia. HFQRS data were evaluated automatically using computerized analysis. Patients with evidence of ischemia in exercise ECG or HFQRS data, or those with inconclusive test results were referred for follow-up imaging tests (FIT; stress echocardiography, SPECT perfusion imaging, CT angiography, or angiography, n=172). The follow-up imaging tests were used as the gold standard for presence of IHD.

**Results:** Based on FIT results, addition of HFQRS to ETT significantly improved specificity (74% combined vs. 51% for ETT alone, p<0.005) and enhanced accuracy (76% combined vs. 59% for ETT, p<0.05), although sensitivity was similar. Negative predictive value of HFQRS was > 93% irrespective of ETT result. The positive predictive value for patients with positive ETT and positive HFQRS was 86%. HFQRS was particularly useful in patients with inconclusive ETT.

**Conclusions:** This is the first large scale study to evaluate the utility of the HFQRS technique in a realistic clinical scenario. HFQRS analysis is complementary and additive to conventional ETT. Integrating HFQRS into the clinical decision process could markedly improve the standard of care and decrease unnecessary invasive procedures.

## Ectatic Coronary Arteries are Associated with Peripheral Vascular Endothelial Dysfunction in Patients with Chest Pain

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**Background:** Endothelial dysfunction is an important prognostic factor in determining atherosclerosis. Prognosis, treatment, and etiology of coronary artery ectasia, abnormal enlargement of coronary arteries, remain unresolved. Current literature suggests that even without the presence of coronary stenosis, ectatic coronary arteries are subject to thrombus formation, vasospasm, and spontaneous dissection.

**Objective:** To evaluate the association of flow-mediated dilation (FMD), assessed by brachial artery vasoreactivity in patients with chest pain and ectatic coronary arteries.

**Methods and Results:** FMD in 40 subjects with chest pain and ectatic coronaries [35 (88%) men, mean age 66±9 years, mean body mass index 28±5 kg/m<sup>2</sup>] was compared to FMD in 40 age- and sex-matched patients with chest pain and normal coronaries. After overnight fasting and discontinuation of all medications for ≥12 hours, percent improvement in endothelium-dependent brachial artery FMD (%FMD) and endothelium-independent nitroglycerin (%NTG)-mediated vasodilatation were assessed using high resolution(15 MHz) linear array ultrasound (Table).

	<b>Ectatic Coronaries (n=40)</b>	<b>Normal Coronaries (n=40)</b>	<b>p-value</b>
Systolic BP (mmHg)	142±22	144±2	0.77
Diastolic BP (mmHg)	82±10	78±9	0.36
Resting heart rate (bpm)	63±9	65±10	0.76
Brachial artery diameter (mm)	6.25±0.93	5.24±0.98	<0.0001
%FMD	7.2±5.0	12.0±5.0	<0.001
%NTG	12.1±4.8	14.3±5.1	0.38

Values are expressed as mean±SD; BP=blood pressure; %FMD, %NTG=% change from baseline in brachial artery diameter caused by FMD and NTG, respectively.

**Conclusions:** Ectatic coronary arteries in patients with chest pain are associated with endothelial dysfunction, compared to normal coronary arteries, suggesting a potential mechanism whereby ectatic coronaries contribute to cardiovascular risk. Long-term follow-up is warranted to further elucidate our findings.

## **Dual Therapy with Statins and Antioxidants is Superior to Statins Alone in Decreasing the Cardiovascular Disease Risk of Individuals with Diabetes Mellitus and the Haptoglobin 2-2 Genotype**

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**Background.** Oxidative stress is an important mediator of DM atherosclerosis. Paradoxically, antioxidants have not been found to provide CVD benefit to DM individuals. The Haptoglobin gene, an antioxidant protein, is polymorphic in man with two classes of alleles denoted 1 and 2. Diabetic individuals with the Haptoglobin 2-2 genotype, have increased CVD risk. These individuals have high oxidative stress and may benefit from antioxidant therapy. We sought to determine if antioxidant therapy could be demonstrated to provide benefit to Haptoglobin 2-2 DM individuals also taking statins which are currently recommended for all DM individuals.

**Methods.** The ICARE was a double blind prospective study in 1434 DM individuals with the Haptoglobin 2-2 genotype randomized to vitamin E or placebo. We showed a 50% decrease in CVD events (MI, stroke, CVD death) with Vitamin E treatment. We present here a secondary analysis of the CVD event rate in ICARE stratified by vitamin E and statin use.

**Results.** The event rate among individuals who did not receive antioxidants or statins was 6.1%. As expected we found that statins reduced the event rate in this population compared to individuals who did not take statins. However, unexpectedly we found that the addition of vitamins to statin treatment dramatically reduced the event rate (4.1% vs. 1.3%,  $p < 0.01$ ), significantly more than statin or vitamin E treatment alone.

**Conclusions.** Dual therapy with antioxidants and statins appears to provide superior cardiovascular protection to Hp 2-2 DM individuals as compared to statins alone.

## Exercise ECG Testing: Low Tech, High Impact

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**Background:** Currently, reliance on noninvasive imaging tests and cardiac catheterization in diagnosing the etiology of chest pain (CP) raises questions about the role of exercise ECG testing (EET) in its evaluation. We assessed the impact of EET on the diagnosis and management of hospitalized pts with CP.

**Methods:** Pts hospitalized with CP without dynamic ECG changes and troponin elevation were referred to treadmill EET. Internal medicine physicians responsible for the pts completed a questionnaire pre and post EET which included a hypothetical question about the management of those pts if EET could not be performed.

**Results:** Physicians filled out the questionnaire for 57 pts, age  $51 \pm 10$  years, 32/57 considered to be of low probability for ischemic heart disease and 25/57 pts of intermediate probability. Based on EET results, physicians confirmed their clinical diagnosis in 68%, modified their diagnosis in 28%, and EET was unhelpful in 4% of the pts. Level of physicians' confidence in their diagnosis at pre-test was 6 (from 1 to 10) and rose to 9 post-test. EET had major impact on the continuing management of the referred pts (Table1) by allowing physicians to discharge 61% (35/57) of the pts who otherwise would have remained hospitalized for additional diagnostic procedures. No major cardiac events were noted as a consequence of the EET study.

**Conclusions:** For many hospitalized pts with CP, EET is a safe procedure that helps physicians to increase their diagnostic rate and diagnostic level of confidence. EET renders significant benefit in the management of these pts by modifying diagnostic strategies, shortening hospitalization, and avoiding inappropriate discharge.

Table1

	PRE-EET		POST-EET. Discharged
<b>Candidate for</b>	Cardiac catheterization	6	5
	Non invasive imaging test	15	12
	In hospital follow-up	9	8
	Discharged	27	26