NEWSLETTER OF THE FRIENDS OF THE ISRAEL HEART SOCIETY

Editor's Note: Welcome to the Summer 2010 issue of the FIHS Newsletter. We will be highlighting the cardiology program at the Rabin Medical Center- Beilinson Hospital. We have 2 articles, both from Rabin Medical Center. We will report on the recent Israel Heart Society meeting.

All of our usual features will be included, including our President's message.

Remember, this Newsletter and Society belong to you, the membership. We look forward to enhancing this Society and the connections that we hope to foster between Israeli and non-Israeli cardiologists and their institutions. Please feel free to email us with questions, answers, comments, criticisms, or just to tell us to keep working harder!

Our immediate goal is to try to grow our membership and participation to include any and all cardiologists and fellows that would be interested in supporting this bridging relationship. If you know of any cardiologists or cardiology fellows who we can contact, please email me (my address is on every page hyperlinked). May we continue to grow in size as well as in deeds in the future!

Message from the President

Following our reception at the ACC in March, we had a great flurry of excitement and membership. We thank you all for your support. As our membership grows, we will continue to build upon the programs that have already been initiated. These programs include:

1) Sponsoring Israeli fellows to attend the annual scientific sessions of the AHA or ACC.
2) Assisting in program development and attendance of foreign cardiologists at the annual meetings of the Israel

Heart Society and its allied conferences.

3) Opening avenues of communication with and advocacy for Israeli cardiology.

For those of you who have not had an opportunity to attend a cardiology meeting in Israel, I would encourage you to consider attending one. As a regular attendee at the International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy and the International Meeting on Intensive Cardiac Care, I can tell you that these are extremely high quality meetings with outstanding international faculties. The sessions are fantastic and there is ample opportunity to interact with colleagues and thought leaders in cardiology. Of course, a trip to Israel for a meeting can always be coupled with a visit to its many historical and leisure sites. It is a great way to combine business and pleasure! Some meetings are run on an annual cycle and others on a biannual cycle. We post notices of the meetings in the newsletter and on our website.

We know that we are not yet reaching many of our potential Friends of the Israel Heart Society. Our most successful mode of growth has been from Friends reaching out to other Friends to join the organization. Please let your interested colleagues know about the organization and have them check out our website at http://www.friendsihs.org/index.html. Individuals may join the Friends of the Israel Heart Society on the website or by mailing the brief application to:

FIHS
c/o Debbie Burg
8626 Central Park
Skokie, IL 60076

Thank you for your continued support!

Jeff Goldberger

President, Friends of the Israel Heart Society

Upcoming Meetings in Israel

ICI Meeting 2010-Innovations in Cardiovascular Interventions
Tel Aviv, Israel
December 5-7, 2010

drozenberg@paragon-conventions.com

Emergency and Disaster Preparedness Course 2010 in conjunction with the Israel Health Ministry and the IDF Medical Corps

November 6-11, 2010

www.apfmed.org/apf.php?c=emergencydisaster

58th Annual Congress of the Israel Heart Society in Association with the Israel Society of Cardiothoracic Surgery

May 4-5, 2011

David Intercontinental Hotel, Tel Aviv

Details in our next Newsletter

Israeli cardiology has just received an impressive report card from the European Society of Cardiology, whose prestigious European Heart Journal has found that the death rate of hospitalized heart attack patients in Israel is lower than that in 29 European countries. For more information, see http://www.jpost.com/HealthAndSci-Tech/Health/Article.aspx?id=173948

http://www.jpost.com/HealthAndSci-Tech/Health/Article.aspx?id=173948. If you are interested, we can also forward to you the manuscript from the European Heart Journal.

Israeli cardiology given top marks

By JUDY SIEGEL-ITZKOVICH
26/04/2010 09:59

NEWSLETTER OF THE FRIENDS OF THE ISRAEL HEART SOCIETY

Prestigious journal rates Israeli cardiology better than most of Europe's.

Israeli cardiology has received an impressive report card from the European Society of Cardiology, whose prestigious European Heart Journal has found that the death rate of hospitalized heart attack patients in Israel is lower than that in 29 European countries. In addition, Israeli acute myocardial infarction patients get balloon angioplasty to open clogged coronary arteries faster than in all the others except Germany.

A few years ago, among all diseases cancer was identified as the biggest killer in Israel, surpassing heart disease, whose mortality rates have declined due to improved medical technology, highly trained cardiologists, greater accessibility and better prevention. Accessibility was increased when the Health Ministry required the health funds to give hospitals a rather generous, set amount per procedure instead of the much lower, per diem hospitalization rate.

Experts from 30 countries, from Austria to the UK, were asked to report on their own official national statistics, and Israel was represented by leading cardiologists Profs. Alexander Battler, Basil Lewis and Shlomo Behar.

The just-published scientific paper reported that the number of annual Israeli angioplasties (catheterizations in which a tiny deflated balloon is pushed from the groin or arm into the heart to restore blood flow) is 2,726 per million residents – twice that in the US and higher than France and Italy. Only Germany had a higher rate than Israel's. Just 4.2 percent of patients died in the aftermath of heart attacks in Israeli hospitals, compared to 11.9% in Finland and 13.5% in Italy.

The article also noted that 75% of Israeli heart patients who undergo urgent angioplasties get it immediately rather than the less effective thrombolysis (injection of tPA, which gradually dissolves the clot).

At the same time, the number of new heart attack cases here is similar to the average European rate of 136 per 100,000, the Israel Heart Society reported. The journal showed in its tables that the rate of Israeli residents per catheterization center was 333,500 (there are 22 centers here), which was at an "optimal" level, making this country look good compared to most European countries. Israeli heart attack victims, on average, reach medical care in 90 minutes after the onset of symptoms compared to twice that in Belgium and Greece.

The heart society's president, Prof. Gad Keren, and secretary-general Prof. Doron Zager said they were proud that the mortality rate from heart attacks in Israel is among the lowest in Europe. "It reflects upon years of research and hard work by cardiology departments around the country, as well as the health system's correct investment in catheterization labs. To preserve this achievement for the future and even to improve on it, we must continue to invest many resources in research, manpower and equipment to deal with heart attacks. This investment has proven itself as saving lives," they concluded.

Membership

This is also a reminder regarding membership dues for the Friends of the Israel Heart Society. The basic dues are **$50**. You can register through our website http://friendsihs.org/Register.html or send a check directly to:

Friends of the Israel Heart Society
c/o Debbie Burg
8626 Central Park
Skokie, IL 60076

Please include your email address to assure you do not miss an issue!

We are particularly grateful to those who can be sponsors at any one of the levels indicated below:

$250 Silver member

$500 Gold member

$1,000 Platinum member

$5,000 President's club

Your support enables us to continue growing our programs, including the ACC meeting, support for Israeli fellows to attend the AHA/ACC meetings, and to grow other programs.

For those who are interested in directed donations, we have the following opportunities:

$500 Sponsor an issue of the FIHS newsletter

$1000 Partial sponsorship of an Israeli fellow to attend the AHA meeting

$1000 Partial sponsorship of an Israeli fellow to attend the ACC meeting

$2500 Sponsorship of an Israeli fellow to attend the AHA meeting

$2500 Sponsorship of an Israeli fellow to attend the ACC meeting.

NEWSLETTER OF THE FRIENDS
OF THE ISRAEL HEART SOCIETY

The Cardiology Department of Rabin Medical Center- 2010

This year commemorates 75 years since the establishment of Beilinson Hospital, one of two campuses that constitute Rabin Medical Center. Beilinson Hospital was built in Petah Tikva, a suburb of Tel Aviv, and one of the first Jewish settlements outside of Jerusalem. It soon became the flagship of the largest Health Maintenance Organization in Israel, Kupat Cholim. In 1996, Beilinson Hospital and the smaller Hasharon Hospital, also situated in Petah Tikva and owned by Kupat Cholim, merged under one management. The united hospitals were named Rabin Medical Center, to commemorate the late Prime Minister of Israel, Itzhak Rabin. Kupat Cholim, which was previously owned by the workers' union, Histadrut, subsequently became an independent organization, called Clalit Health Services. Rabin Medical Center, with more than 1000 inpatient beds, remains the largest hospital in Clalit Health Services and the second largest hospital in Israel. Rabin Medical Center is affiliated with Tel Aviv University.

The cardiology departments of both hospitals were united under one management in 1999, when Prof. Alexander Battler was named the Director of Cardiology at Rabin Medical Center. Under one management, the medical staff consists of 40 board-certified cardiologists and 8- 10 fellows. The paramedical staff in both campuses includes approximately 100 nurses,

technicians, secretaries, and other paramedical staff. We take pride that our staff includes 3 full professors, 6 associate professors, 6 senior lecturers, and 8 lecturers and instructors, all of whom contribute significantly to the ongoing activities of the Faculty of Medicine of Tel Aviv University.

The larger Beilinson hospital has a cardiac intensive care unit of 10 beds, a stepdown unit of 16 beds, and the option of manning 2 beds for ambulatory heart failure treatments. The smaller Hasharon hospital has a cardiac care unit of 6 beds and a stepdown unit of 2 beds. For both hospitals, on average, there are 6000 cardiac admissions per annum. There are also 50,000 cardiac outpatient visits per annum, and each year approximately 20,000 transthoracic, transesophageal , stress, and intraoperative echocardiograms are performed . We also perform electrocardiographic stress tests and 5000 cardiac nuclear tests. The interventional suites in the Beilinson Hospital include 2 catheterization laboratories and 2 electrophysiology/ pacemaker laboratories, whereas in the Hasharon hospital there is one catheterization/pacemaker laboratory. Each year, we perform over 4000 coronary angiograms, percutaneous coronary interventions and structural heart disease procedures (for example, atrial septal defect, patent ductus arteriosus, and patent foramen ovale closure, coiling of fistulas, and dilation of aortic coarctations), and over 800 pacemaker implantations, AICD implantations, cardiac resynchronization therapy procedures, electrophysiological

studies and ablation procedures (of all kinds of arrhythmias including ventricular tachycardia and atrial fibrillation). In addition we performed in the last 18 months over 30 endovascular aortic valve implantations (TAVI) with both the Corevalve and Sapien devices using the percutaneous and transapical approaches and with zero in- hospital and/or 30 day mortality.

Being a tertiary center, our inpatient services receive referrals from all over the country, especially of complex patients with intractable heart failure, refractory arrhythmias, and complicated cardiac, valvular, or coronary pathologies. Rabin Medical Center is one of three medical centers that offers cardiac transplantation services and one of the four centers that offer assist devices as a bridge to cardiac transplantation or as a destination therapy. As a result, we have become a major referral center for patients with acute or chronic heart failure who need intensive pharmacological, electrical and mechanical assistance, at times culminating in the implantation of assist devices or heart transplantation. At any given time, we have 1-3 patients in our inpatient services awaiting cardiac transplantation and are too sick to wait at home. Other patients with advanced heart failure are followed by our busy outpatient team.

Our department, in close collaboration with Schneider Medical Center, which is the largest children's hospital, is run by Clalit Health Services, and is situated within the Beilinson Campus, also has the largest clinic in Israel of adult patients with congenital heart disease. The clinic follows over 3000 adult patients with over 1200 outpatient visits each year. Whereas in the past, mechanical treatments of congenital defects were restricted to

surgical procedures, over the years percutaneous procedures have evolved that offer excellent alternatives to surgery. Thus, our staff offers percutaneous solutions to suitable patients with ventricular and atrial septal defects, patent formen ovales, ductus arteriosus, and coarctation of aortas. Expanding on this expertise, our staff has applied these techniques for patients with other pathologies, such as patients with prosthetic paravlvular leaks, coronary arterio-venous fistulas and peri-infarction ventricular septal defects.

The cardio-thoracic surgery department at Rabin Medical Center directed by Dr Eyal Porat is one of the largest and busiest in Israel, performing over 1500 coronary, valvular and aortic operations each year. Our department works in close collaboration with our surgical colleagues, with weekly clinical conferences. Our cardiologists assist in assessing patients scheduled for surgery, performing echocardiograms during procedures, and complementing management after complex operations. When the coronary or valvular anatomy is not amenable to pharmacological or percutaneous treatment modalities, patients are considered for surgical solutions. This collaboration is highlighted in cases of transapical aortic valve implantation, where both cardiologists and surgeons take part in the procedure, and in cardiac transplantation procedures, where the cardiologist takes a leading role in pre- and post-transplantation management.

Our staff is actively engaged in translational research. The focus of our clinical research has centered on the management of acute coronary syndromes, diagnosis and treatment of heart failure, diagnosis and

outcomes of valvular heart disease, antithrombotic treatments and novel interventional modalities. Our basic science research activities (see separate section) have centered upon new molecules that promote angiogenesis, activation and inhibition of endothelial progenitor cells, and antiplatelet activities of various drug regimens. These studies have culminated in hundreds of scientific papers over the past 5 years.

Our department also takes active part in the education of medical students, nursing staff, medical residents and cardiology fellows, and the continued medical education of cardiologists. In the past three years, members of our staff were responsible for the preparation and expedition of the board exams in cardiology. These physicians were also responsible for planning and carrying out a 3-day annual course for advanced cardiology fellows.

Although our medical staff has assumed a central role in the leadership of cardiology in Israel, it has also gained the attention of the international community. Members of our staff are frequently invited as speakers and chairmen in international meetings. Our staff has contributed significantly to the European Society of Cardiology, including a board member, members in the congress committee of the annual scientific meeting, and a member in the clinical practice guidelines committee. Our staff members are also active nucleus members in various working groups of the European Society of Cardiology

Translational Research at the Cardiology Department, Rabin Medical Center, Israel.

The laboratory of vascular biology (director- Prof Battler, chief investigator- Dr Eli Lev) at the Felsenstein Medical Research Center

situated within the Rabin Medical Center area, has focused in recent years on research of progenitor stem cells – mainly endothelial progenitor cells (EPCs). EPCs are bone marrow-derived cells that are mobilized to the circulation in response to tissue ischemia and/or vascular injury and incorporate into sites of neovascularization and vascular repair. EPCs co-express CD133, CD34 and vascular endothelial growth factor receptor 2 antigens on their surface and have the potential to proliferate and differentiate into mature endothelial cells. Their role in vascular repair has been elucidated from various animal models of arterial injury. In humans low levels of peripheral blood circulating EPCs have been correlated with poor outcomes in various cardiovascular diseases.

We have previously performed, and are currently conducting, several projects involving EPCs. We examined the levels and function of EPCs in patients who have experienced coronary stent thrombosis. Stent thrombosis is a rare but potentially fatal complication of coronary stenting. Late stent thrombosis (occurring at least a month after stent implantation) has been related to impaired endothelialization of stents (mainly drug eluting stents) as well as other factors, such as discontinuation of anti-platelet treatment. Since EPCs appear to have a central role in stent re-endothelialization, we hypothesized that patients who develop late stent thrombosis may have reduced levels or dysfunctional EPCs. We, therefore, compared EPC level and function in patients who have experienced stent thrombosis vs. a matched control group of patients who underwent stenting and did not develop this complication.

In another project we are examining the profile of EPCs in patients with

"uncontrolled" diabetes, and are evaluating the effect of tight metabolic control on EPCs. Vascular injury is a central process in the development of diabetic complications, and EPCs have been shown to have an important role in the process of repair following injury. Patients with diabetes have been previously shown to have significantly reduced EPC levels and highly dysfunctional cells. We are, therefore, examining whether tight glycemic and metabolic control for several months, can improve the profile of EPCs in patients with initially uncontrolled diabetes.

An additional project examines the profile of EPCs in subjects with bicuspid aortic valves. Bicuspid aortic valve is the most common cardiovascular malformation in humans (prevalence of 0.5-2%). Interestingly, some subjects with bicuspid aortic valves develop over the years severe dysfunction of the valve (regurgitation and\or stenosis), attributed to wear and tear of the cusps, while others of comparable ages have relatively normal functioning valves. The factors which lead some individuals with bicuspid aortic valve to develop severely dysfunctional valves (in contrast to others) are not clear. Since EPCs are involved in repair of the endothelium lining blood vessels, valves etc. we hypothesized that attenuation in EPC level or function may be involved in the development of dysfunctional bicuspid valves. We are, therefore, examining the level and function of EPCs in patients with bicuspid valves with severe dysfunction (regurgitation and\or stenosis) vs. matched subjects with bicuspid valves without dysfunction.

From a more basic perspective, we are investigating the mechanisms of the interaction between platelets and EPCs. Platelets and EPCs have been shown to directly interact, mainly via

P-selectin - P-selectin glycoprotein ligand-1 (PSGL-1) binding. This interaction appears to be central to the homing process of EPCs to the site of an acute vascular injury, whereby platelets "attract" EPCs to the injury site. Furthermore, we and others have shown that platelets promote functional aspects of EPCs, such as migration, proliferation, colony formation and the ability to differentiate to cells of endothelial lineage. The mechanism of this effect is not clear (e.g. direct contact or paracrine effect, which platelet factors are involved etc.). We are conducting *in-vitro* experiments (co-culture of EPCs with platelets) to elucidate the mechanisms by which platelets enhance EPC function. We hope that such experiments, as well as the translational research described above, will help to find ways to augment EPC level and function in specific patient populations.

Senior staff members of Cardiology Department (partial list):

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http://www.thejewishweek.com/editorial_opinion/letters/fighting_obesity

Fighting Obesity

Tuesday, May 18, 2010
Dr. Morton Leibowitz

I congratulate The Jewish Week on your article, “Childhood Obesity Hits Israel” (Healthcare, May 7).
The Israel Heart Fund promotes programs to prevent heart disease. In 1999 we initiated a partnership with The Childhood Obesity center at Meir Hospital in Kfar Saba, Israel.

The program, headed by pediatricians Alon Eliakim and Dan Nemet, reported in 2002 in the European Journal of Pediatrics, favorable short-term results in treating obesity in hundreds of Israeli children and adolescents.

In 2005, Pediatrics, the leading journal in the field, published Eliakim and Nemet’s impressive success in maintaining those results over the long term.

In 2005, we initiated a small pilot program in kindergartens in an Israeli community. Our findings showed that 22 percent of children at this age level were obese. At the end of the school year, our kindergarten-based program had reduced obesity in these same kindergartens to 8 percent.

With the encouragement of the Israeli Ministry of Education the kindergarten program has been implemented in hundreds of kindergartens.

Our studies show exceptional success in kindergartens across Israel, including in disadvantaged communities. We are currently proposing long-term follow up of these children to see if the lifestyle training given in kindergarten has long-term success.

These extraordinary efforts were carried out with the support of Carlos Lindenfeld Fund of the San Diego Jewish Communal Fund and The Rosalinde and Albert Gilbert Foundation and the Israel Heart Fund.

President, Israel Heart Fund

Featured Research- both from Rabin Medical Center

Basic Research

J Vasc Res. 2010 Feb 6;47(5):399-411. [Epub ahead of print]

Activation of GRP78 on Endothelial Cell Membranes by an ADAM15-Derived Peptide Induces Angiogenesis.
Raiter A, Weiss C, Bechor Z, Ben-Dor I, Battler A, Kaplan B, Hardy B.
Felsenstein Medical Research Center, Tel-Aviv University School of Medicine, Rabin Medical Center, Beilinson Campus, Petach-Tikva, Israel.

Abstract
Impaired angiogenesis is one of the features of ischemic diseases. We have previously identified, by screening a phage display peptide library, a peptide that induces angiogenesis in endothelial cells under hypoxic conditions by binding the cell's membrane heat shock protein GRP78. Protein data base search identified 4 amino acids (HWRR) of that synthetic peptide present on the ADAM15 metalloprotease domain, a protein considered to be involved in neovascularization. Three peptides were synthesized according to the ADAM15 sequence placing HWRR at different positions. Peptide ADoPep1 exhibited significant angiogenic properties under hypoxic conditions as determined by cell proliferation, migration and tube formation. In a mouse hind limb ischemia model, a single injection of the peptide restored blood perfusion. The identified peptide was found to activate GRP78 on endothelial cell membrane and siRNA directed against the GRP78 mRNA interfered with induction of angiogenesis by the peptide. The peptide binding induced a decrease in heat shock protein GRP78 that is overexpressed under hypoxic conditions. The mechanism of peptide-induced angiogenic activity involves inhibition of apoptosis as well as increased Akt phosphorylation and ERK 1/2 activation. The peptide did not induce VEGF receptor-2 protein synthesis and phosphorylation, suggesting a VEGF-independent mechanism of angiogenesis. Copyright © 2010 S. Karger AG, Basel.

Clinical Research

Treatment of Aspirin-Resistant Patients With Omega-3 Fatty Acids Versus Aspirin Dose Escalation

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Petah Tikva and Tel-Aviv, Israel; and Houston, Texas

Objectives **The aim of this study was to**

evaluate whether addition of omega-3 fatty acids or increase in aspirin dose improves response to low-dose aspirin among patients who are aspirin resistant.

Background
Low response to aspirin has been associated with adverse cardiovascular events. However, there is no estab- lished therapeutic approach to overcome aspirin resistance. Omega-3 fatty acids decrease the availability of platelet arachidonic acid (AA) and indirectly thromboxane A2 formation.

Methods 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). Fur- ther testing was performed by platelet aggregation. Aspirin resistance was defined by □2 of 3 criteria: VerifyNow score □550, 0.5-mg/ml AA-induced aggregation □20%, and 10-□mol/l adenosine diphosphate (ADP)-induced aggre- gation □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. (J Am Coll Cardiol 2010;55:114–21) © 2010 by the American College of Cardiology Foundation

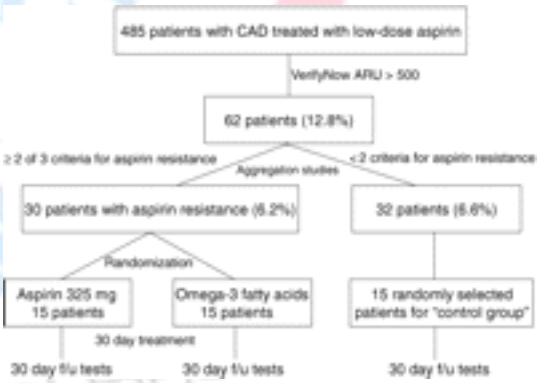

Figure 1 Algorithm of the Study
We aimed to identify 30 patients with aspirin resistance. Patients with stable coronary artery disease (CAD) (n = 485) were screened for resistance by the VerifyNow Aspirin assay (Accumetrics). Sixty-two patients (12.8%) had an aspirin reaction unit (ARU) score >500 and underwent further testing by platelet aggregation. Thirty patients (6.2%) were found to be resistant and were randomized to 1 of the 2 treatment groups. They were re-tested after 30 days of treatment. f/u = follow-up.

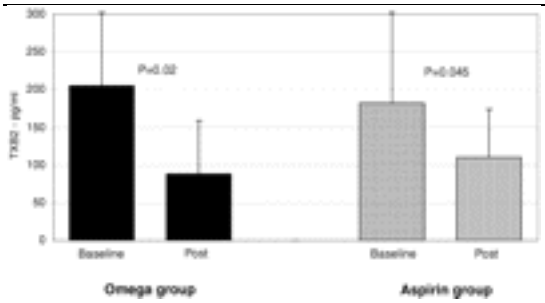

Figure 2 Plasma TXB2 Levels at Baseline and After 30 Days of Treatment
Plasma thromboxane B2 (TXB2) levels at baseline and after 30 days of treatment with omega-3 fatty acids (omega group) or 325 mg of aspirin (aspirin group). In both groups a significant reduction was noted from baseline after 30 days of treatment (57% relative reduction with p = 0.02 in the omega group, and 40% relative reduction with a p = 0.045 in the aspirin group). There were no significant differences between the groups at baseline or after treatment.

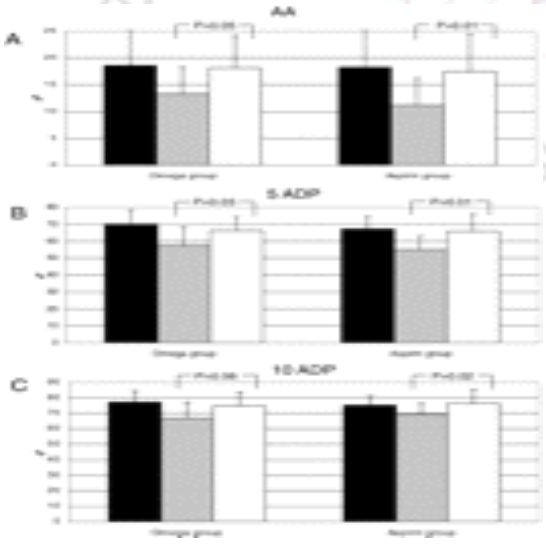

Figure 4 Platelet Aggregation at Baseline, After Treatment, and During Follow-Up

Platelet aggregation in response to arachidonic acid (AA) and adenosine diphosphate (ADP) in the omega and aspirin groups (12 patients in each group) at 3 time points: **(A)** baseline—low-dose aspirin **(solid bars)**; **(B)** after 30 days of treatment with the corresponding regimen—omega-3 fatty acids or high-dose aspirin **(gray bars)**; and **(C)** low-dose aspirin—after discontinuing the corresponding treatment regimens for at least 1 week (**open bars**—follow-up phase). In both groups, aggregation decreased after treatment and increased back to levels similar to the baseline levels after discontinuing the treatment regimens (p values for **B** vs. **C** time points).

That's all for this issue. Have a great summer wherever you are! Remember, for us to succeed we need active members willing to take the lead in creating a bond between Israeli cardiology and her sisters abroad. Please help! Join us in our task!