The Heart Institute Newsletter

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Message from the Head of The Heart Institute

To all our friends

Best wishes for
A Happy and Kosher Passover

Dear friends and supporters,

This spring marks a great milestone, the 60th anniversary of the Independence of The State of Israel. Our vibrant 60-years young state continues to grow and develop, as our Heart Institute continues to grow apace.

This issue of The Heart Institute Newsletter is devoted to the subject of drug-eluting coronary stents, a very important component of interventional cardiology in the last 6 years. With their introduction to the interventional therapy market in 2002, drug-eluting stents were hailed as the revolutionary solution to one of angioplasty's major problems, in-stent restenosis (renewed blockage of the artery, this time within the coronary stent). Experience with and study of the results of widespread use of these stents over these years has taught us a great deal regarding the benefits and limitations of drug-eluting stent implantations.

I wish to extend to you our deepest appreciation of your continuing interest and support, as well as best wishes for a very happy Passover holiday.
As always, we welcome your comments, questions and contributions to our newsletter. You are also warmly invited to visit us virtually on our website, at http://www.hadassah.org.il/English/Eng_SubNavBar/Departments/Medical+departments/Cardiology .

Shalom and Chag Sameach,
Professor Chaim Lotan

News from The Heart Institute: Scientific Congresses

The Hadassah Heart Institute has organized and hosted several important scientific congresses in the past year:

Heart Failure Symposium

The International Heart Failure Symposium, organized by Prof. Andre Keren, was held at Hadassah Ein Kerem in November 2007, with the participation of leading specialists from abroad and Israel in the field of heart failure. The special guest lecturers from abroad were Prof. Philip A. Poole-Wilson of the Imperial College London and past chairman of the European Society of Cardiology, a leading expert in the basic and clinical research of heart failure, and Prof. Dan Atar of the Aker University Hospital University of Oslo and Chairman of the ESC Working Group on Pharmacotherapy. The topics of the meeting spanned from primary to tertiary care management dilemmas, including state of the art lectures on established and developing topics in heart failure management, as well as case presentations and discussions.

ICI Meeting

The annual International meeting “Innovations in Cardiovascular Interventions” meeting, organized by Prof. Chaim Lotan together with Prof. Rafael Beyar of Rambam Hospital, was held in Tel Aviv in December 2007. In addition to live case presentations, lectures by world leaders in the field of interventional cardiology and the field of medical innovation, and presentations by medical start-up companies, the meeting featured as Special Guest Speaker Mr. Shimon Peres, the President of The State of Israel.

Israeli Heart Research Day

The annual meeting of the Israeli Group of Heart Research was held this year at Hadassah Ein Kerem, and was directed by Dr. Ronen Beeri.

The Drug-eluting Stent Controversy:
What is it all about?

Coronary stents are tiny, expandable wire mesh tubes which are inserted into an artery during percutaneous coronary intervention at the site of a coronary lesion, following dilation by balloon. The stent supports the newly reopened artery from within. The introduction of stents to the field of interventional cardiology in the mid 1990's was a major revolution, greatly improving the blood flow in previously obstructed arteries. However, many patients developed restenosis as the result of proliferation of smooth muscle cells which grew in response to the implanted stent, as an overgrowth of scar tissue. The discovery that the drug rapamycin inhibits proliferation in muscle cells and causes cell-cycle arrest led to the development of a new generation of stents, whose polymer coatings contain cell-proliferation-blocking drugs which are gradually released locally within the artery. These drug-eluting stents, which dramatically reduced incidence of in-stent restenosis, quickly took hold in the interventional market.

However, the reduced cell growth caused by the drug also has a drawback - the stent is exposed to the blood for a longer time before it becomes integrated with the arterial wall, which increases the incidence of thrombus formation, or clotting. Stent thrombosis is a serious event that can lead to myocardial infarct or death. Patients following stent implantation are prescribed antiplatelet medication to prevent stent thrombosis, and generally for a longer period if the stent is drug-eluting.

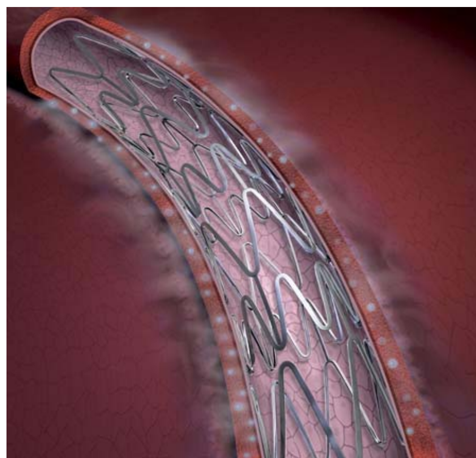
The early studies comparing outcomes of treatment with bare-metal stents (BMS) and drug-eluting stents (DES) showed similar rates of sub-acute and late (up to one year) stent thrombosis. However, the interventional world, and subsequently the public the world over, was shaken when studies presented in the 2nd half of 2006 showed higher rates of very-late (1-3 years) stent thrombosis with DES use.

Further analysis has indicated that adverse events are somewhat more prevalent in DES use, compared with BMS, in cases of "off-label use". "Off-label" use is use of the device in cases other than what is specified in the manufacturer's specifications, which list the scope of use which has been approved by the governmental regulatory body (FDA, EMEA etc). Regulatory laws forbid the manufacturer to recommend a drug or device for any but the approved indications, however physicians are free to prescribe off-label (*although this is not known to much of the general public*) on the assumption that such a decision has scientific/medical basis; this is a wide-spread practice. The FDA states, in one of its information sheets: "If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects." In the case of DES, approved use, which was based on stringently limited clinical study groups, is limited to treatment of de novo lesions in a specific size range in native coronary arteries, and excludes patients in high-risk groups. However, it is estimated that at least 50% of DES use is "off-label", as the beneficial effect of restenosis-reduction is much less significant in cases of "simple" lesions in low-risk patients, and clinical studies since the initial regulatory approval have shown that extrapolation of the indications to a larger patient cohort is appropriate. It is commonly accepted that DES may be indicated in such "off-label" cases as diabetic patients, very long lesions, small arteries etc.

The only independent factor related to late and very-late stent thrombosis in the main body of analyses of DES real-world data is early cessation of anti-platelet therapy. These data show high patient compliance with dual-antiplatelet therapy in the first few months following stent implantation, but the rate of compliance declined sharply well before the end of the recommended 12 month (at least) treatment period. While there is still controversy as to DES safety in this regard, most of the experts agree that the benefit of the reduction in restenosis rates for certain subsets of patients outweighs the minimal risk of stent thrombosis. All agree, however, on the importance of the anti-platelet therapy, and that it is imperative that the interventionalist makes certain in advance that the patient understands this and will be willing and able to comply with the treatment regimen. “Patients should receive appropriate antiplatelet therapy according to existing practice guidelines wherever possible,” said Raymond J. Gibbons, M.D., American Heart Association president. “This will usually require patients taking both aspirin and a thienopyridine (most commonly clopidogrel) for periods of up to at least one year after stenting and aspirin indefinitely. Patients should not discontinue either aspirin or the thienopyridine within the first year without consulting their treating cardiologist.”

One of the major reasons for early cessation of the dual-antiplatelet therapy is preparation for an invasive or surgical procedure. The medication must be stopped or switched before the procedure, in order to avoid excessive bleeding during the procedure. Elective procedures that carry a risk of bleeding should be delayed until after the patient has completed an appropriate course of thienopyridine treatment – if this is not feasible, a bare metal stent or balloon angioplasty with a provisional stent should be considered instead of using DES. Healthcare providers who perform invasive or surgical procedures should be made aware of the potentially catastrophic risks of prematurely stopping thienopyridine therapy, and should contact the patient’s cardiologist to discuss optimal patient management.

The DES controversy is far from settled, but a large body of interventionalists agrees that, provided that physicians use good professional judgment in deciding which patients should have DES implantation – as opposed to an earlier tendency towards very liberal use – and assure a high likelihood that the patient will follow through with appropriate antiplatelet therapy, drug-eluting stents “do more good than harm”.



?? Questions and Answers : ??

Drug-eluting coronary stents

Q: What is the composition of a drug-eluting stent?
A: The drug-eluting stent has 3 components: the stent body (a “regular” stent), the coating (usually a polymer) that carries the drug, and the cell proliferation-blocking drug itself.

Q: For what types of patients are drug-eluting stents not suitable?
A: Although DES are suitable for use in many cases which are “off-label”, they should not be implanted in patients with surgery planned or patients on long-term anti-coagulant therapy, and they are not recommended for use where the expected restenosis rate is relatively low.

Q: Are drug-eluting stents cost effective?
A: Drug-eluting stents are more expensive than bare-metal stents. However, in the larger picture this cost is offset by the reduced expense of repeat stenting procedures for cases of restenosis prevented.

Q: What advances are being made regarding drug-eluting stents to make them safer?
A: Researchers and medical device companies are of course constantly seeking to improve upon current technology. Numerous variations, called collectively “next generation stent technology”, are being developed and tested.
One technology currently being tested incorporates hundreds of small reservoirs, each acting as a depot into which drug-polymer compositions are loaded. This is designed to enhances control of the rate and direction of drug delivery.
Another new technology with early trial results is a drug-coated angioplasty balloon, which in early testing appears to be more effective than a DES in treating the unwanted build-up of tissue inside a bare-metal coronary stent. "This drug-eluting balloon clearly qualifies for consideration as an alternative to DES for the treatment of restenosis inside bare-metal stents," said Martin Unverdorben, MD, PhD, an associate professor of medicine at the University of Frankfurt/Main, Germany. "However, two to three years' more data are required before making a definitive statement."
This drug-eluting balloon is coated with paclitaxel, the same medication that coats the Taxus™ stent. The balloon is inflated for about 30 seconds inside the narrowed artery, and the paclitaxel - which has a natural attraction to cells - quickly moves from the surface of the balloon into the arterial cells.
Not only does the drug-eluting balloon avoid a second layer of metal inside the artery, the carrier that is used to bind paclitaxel to the balloon is iopromide, a commonly used contrast agent. This avoids concerns about the artery's reaction to the polymers used to bind the anti-restenosis medications in DES.
Other innovations in development and testing include biodegradable polymer stents, microstents, new materials developed through nanotechnology, healing therapy utilizing progenitor endothelial cells, and passive stent coatings.

From the clinical research center to the scientific literature

The e-Cypher Registry, a multi-center, international internet-based registry, was initiated in April 2002 to assess safety and efficacy in “real-world use” of the Cypher® Sirolimus-eluting Stent in treating coronary lesions, after several closely monitored randomized trials showed sirolimus-eluting stents to be highly effective in lowering rates of coronary artery restenosis and target-lesion revascularization compared with bare metal stents up to at least 3 years. Short-term results and 1-year follow-up reports of the registry, presented at scientific meetings worldwide and published in the scientific literature, have shown the stent to be safe and closely correlate results of the randomized trials.

Prof. Chaim Lotan, one of the Principle Investigators worldwide of this registry, and Dr. David (Dudu) Planer of our Heart Institute have just published the long-term (>3 years) results of the Israeli arm of the e-Cypher Registry in the April 1, 2008 issue of The American Journal of Cardiology. Between July 2002 and October 2003, 488 patients from 8 medical centers in Israel were enrolled in the e-Cypher registry. 63% of the cases were “off-label” use. Long-term follow-up was completed for 98% of the eligible patients.

The length of follow-up was a median of 3.4 years. During this follow-up there were only 76 cases (16.3%) of major adverse cardiac events (MACE): a composite of death, myocardial infarction and target lesion revascularization (repeat angioplasty in the same coronary lesion) – a relatively low rate compared with studies of bare metal stent use. During > 3 years of follow-up, stent thrombosis was observed at a rate of 0.5% per year. This is a very notable finding, in light of the concerns that the long-term results might be not as good as those of the early (one-year) data.

Additional results and longer follow-up from this and other studies will help us establish a clearer picture of the safety and efficacy of these stents.

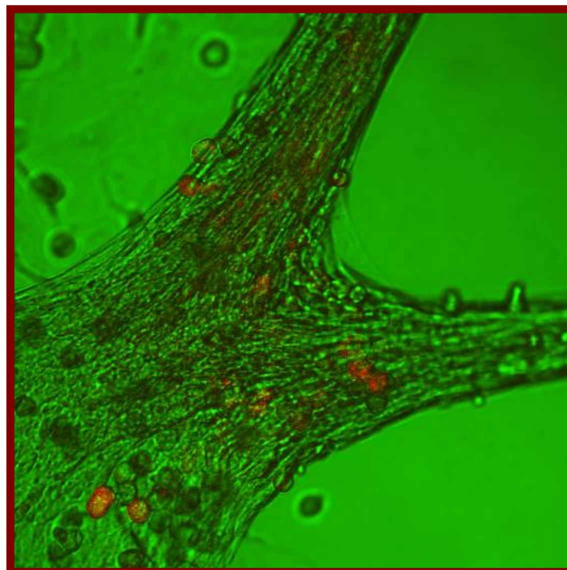
Reference: Planer D, Beyar R, Lotan C et al. Long-term (>3 years) outcome and predictors of clinical events after insertion of Sirolimus-eluting stent in one or more native coronary arteries (from the Israeli arm of the e-Cypher registry. American Journal of Cardiology 2008;101(7): 953-959

News from our Cardiovascular Research Center

New approaches to repair of the injured heart

Heart failure is fast becoming an epidemic in the industrialized world. Presently, physicians struggle to prevent loss of cardiac muscle using medications, but no one has been able to actually repair or replace the cells that have been lost. Many experimental approaches have been tried, including implanting cells from bone marrow or stem cells from limb muscles, with no major success.

It has become apparent, lately, that in contrary to prior belief, the heart does contain some cells that retain the capability to divide and make new heart tissue. In The Cardiovascular Research Center we have succeeded, in an unprecedented finding, to grow cells in culture from a piece of a left atrium (which is often removed during open-heart surgery). These cells have the characteristics of cardiac stem cells (orange stain in the photograph)



Dr Ronen Beeri, director of the Cardiovascular Research Center, will gladly answer any question you may have by email at: rbeeri@hadassah.org.il.

To All Our Friends and Supporters

The entire Heart Institute staff
Wishes you a very Happy and Kosher Passover

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