

# NEWS LETTER

Egyptian Hypertension Society



الجمعية المصرية لارتفاع ضغط الدم

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## THE PRESIDENT'S MESSAGE

### **WHAT IS NEW IN CARDIOLOGY? FROM THE ANNUAL MEETING OF ESC**

This year, the meeting of ESC was held in Munich-Germany during the period August 29th to September 1st. The following is a brief review of some of the recent developments in cardiology. It is impossible to cover all the new information. To choose which session to attend from the large number of simultaneous sessions addressing almost all aspects of CV medicine was not an easy job. My choice was based upon personal interest and I am sure that I missed many important sessions. I will present some of the new information and results of recent clinical trials which I believe will make breakthrough in our patient care.

#### **1. CARDIOVASCULAR PREVENTION**

##### **New Treatment of Obesity, Lipid Disorders and Nicotine Dependence.**

A new agent, the first selective cannabinoid type 1 (CB1) receptor antagonist (rimonabant, 20 mg/d) proved effective in reduction of body weight and waist circumference as well as a substantial increase in HDL-cholesterol and significant reduction in triglyceride levels.

The endocannabinoid system is present in the brain (mainly hypothalamus and mesolimbic system) and peripheral tissues (adipocytes) and is involved in control of energy balance and body weight. Blockade of this system have a significant impact on weight, lipid and glucose metabolism. This was proved in a number of trials: RIO-Lipids, RIO-Europe, RIO-Diabetes. Rimonabant seems to be particularly indicated in patients with the metabolic syndrome. Furthermore, in separate studies STRATUS-US, rimonabant proved effective in helping patients quitting smoking and markedly reduced post-cessation weight gain and was well tolerated. The broad action of rimonabant makes it a potential breakthrough compound for CV multi risk management.

#### **2. CORONARY DISEASE**

##### **1. Management of High Risk Unstable Coronary Syndromes**

A new study-ICTUS trial is changing our approach for management of patients with non-ST elevation ACS who are considered high risk because of elevated plasma troponin level. The recommended approach was an early invasive strategy. The results of the ICTUS trial- invasive versus conservative treatment in unstable coronary syndromes- showed that this policy may not be ideal. Among troponin positive patients with a non-ST elevation ACS, treatment with an early invasive strategy-coronary angio and intervention within 24-28 hours was not associated with a difference in mortality, MI or rehospitalization at 8 months when compared with a more conservative approach of a selective ischemia driven invasive strategy. Both management strategies were equivalent. Recognition of additional risk factors other than elevated troponin levels is needed to identify the patient most likely to benefit from early invasive management e.g. diabetes, old age or ECG changes.

## SCIENTIFIC WISDOMS

Though we are living the era of evidence based medicine, pooled into the international and national guideline updates; yet still one must never forget that embracing clinical practice guidelines does not detract from the importance of individual physician judgment or the variation in patient preferences. We still lack definitive evidence in many situations, as each patient might have a complex array of characteristics that cannot be always captured in such guideline.

*Circulation. 2002;106:1172.*

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## 2. Evaluation of Early vs Delayed Initiation of Simvastatin In Patients With ACS (A to Z, phase Z trial)

Among high risk patients with ACS, treatment with early initiation of high dose statin therapy was not associated with a significant CV event reduction, compared with a more conservative, delayed low-dose one. However, beyond 4 months, a reduction in events was demonstrated in the high dose group. Early, high dose statin treatment is likely to reduce deaths and major cardiac events, but patients careful monitoring for adverse events, is needed.

## 3. New Powerful Antiplatelet Agent: Prasugrel. JUMBO-TIMI 26 Trial

A novel thienopyridine P2Y<sub>12</sub> antagonist, prasugrel, was compared for safety vs clopidogrel among patients undergoing-PCI with in-tended coronary stenting. No difference in bleeding rate between prasugrel compared with clopidogrel but a trend toward lower ischemic event rates, with the new agent, were all observed.

## 4. A New Treatment of Stable Angina

The rationale of the treatment of stable angina should ideally include efficient heart rate reduction. Lowering of heart rate without any other direct cardiac effects offers important advantages compared with B-blockers or calcium channel blockers. Ivabradine is a novel heart rate-lowering agent that selectively and specifically inhibits the cardiac pacemaker current  $I_F$  in the sinus node. Pacemaker activity involves the interplay between several ionic currents that influence the spontaneous diastolic depolarization of the sino atrial node. They include the  $I_F$  current and the calcium currents.  $I_F$  current activation at the termination of actions potential determines the slope of the slow diastolic depolarization, which controls the interval between successive action potentials and, hence, the heart rate.

Ivabradine anti-anginal and anti-ischemic efficacy has also been demonstrated, being as effective as atenolol in improving exercise capacity and reducing angina attack frequency. It is given in a dose of 510 mg twice daily. It represents an alternative to B-blockers with the advantage of freedom from side effects.

## 3. ARRHYTHMIAS Dronedaron: a new ant arrhythmic agent

Amiodarone is a first choice drug in management of most tachyarrhythmias, being effective in maintenance of sinus rhythm and prevention of recurrence of atrial fibrillation (AF) and atrial flutter (AFL). However, it has many side effects and organ toxicity when used for a long time. Dronedaron; is a derivative of amiodarone without the iodine component. When its safety and efficacy was compared with placebo among patients with AF or AFL in two trials (EURIDIS and ADONIS) followed for one year, dronedaron proved to be safe and effective. There was a reduction in time to recurrent AF-AFL with no evidence to toxicity. It is hoped that dronedaron will offer the advantages of both safety and efficacy over cordarone.

## 4. HEART FAILURE

$\beta$ -blockers have an established role in management of heart failure due to poor LV systolic function. It improves morbidity and mortality in all grades of its severity. However, information about the role of  $\beta$ -blockade in elderly HF patients is not available, since the majority of clinical trials excluded old patients. The SENIORS trial is the first trial of  $\beta$ -blockade in elderly patients with HF. Its objective was to study the effects of  $\beta$ -blockade (Nebivolol) on outcomes and rehospitalization in seniors with HF. Nebivolol was given for 40 months to elderly patients with HF. The results were a reduction in mortality and rehospitalization for CV events compared with placebo.  $\beta$ -blockers (nebivolol) can be given safely to elderly patients with heart failure.

**M. Mohsen Ibrahim, M.D.**

Prof. of Cardiovascular Medicine–Cairo University.  
President of The Egyptian Hypertension Society.



## LOOKING UP IN THE GUIDES ►

4<sup>th</sup> report on diagnosis, evaluation, and treatment of high blood pressure [BP] in children and adolescents sponsored by the National Heart, Lung, and Blood Institute (NHLBI) has recommended that regular BP measurement in children should begin at age 3 years, and earlier in preterm infants and that the preferred method of measurement is auscultation.

They added the 50th and 99th percentiles to the 90th and 95th percentiles. The 50th percentile defines the midpoint of the normal BP range, and the 99th percentile allows for more precise staging of hypertension, which is defined as beginning at the 95th percentile.

Thus hypertension in this age is defined as a (SBP) and/or (DBP)  $\geq$  95th percentile for age, gender, and height measured on at least 3 separate occasions. They declared that "White coat hypertension" exists in children if they have BP  $>$  95th percentile in the physician's office or clinic but  $<$  90th percentile outside the clinical setting.

With respect to management, it is suggested that in a prehypertensive child, introduction of physical activity, and counseling for the overweight should be "instituted or strongly encouraged" while drug therapy is reserved only if there are compelling indications such as renal disease, diabetes, or LVH.

In a hypertensive child, lifestyle changes should be emphasized in concomitance with initiation of drug therapy in stage 1 or 2, unless there is a dramatic response to lifestyle changes. One should begin with a single drug at the lowest recommended dose, increasing it until the target BP is reached. A second drug may be added if BP is not controlled at the highest recommended dose or if the child experiences side effects. Suitable drugs may include ACE inhibitors, ARBs,  $\beta$ -blockers, CCBs, or diuretics. Specific classes of drugs may be used preferentially in children with specific underlying or concurrent medical conditions, following that reported in JNC7.

Associated risk factors for CV disease, as obesity, lipid disorders, glucose metabolism abnormalities including familial history of diabetes, and sleep disorders should be identified.

Target organ damage is recommended to be evaluated of which an echocardiogram for LVH should be a part

*Pediatrics 2004;114 (suppl):555-576*

# WHAT'S NEW!!!

## HYPERTENSION RISK, DATES TO PRESCHOOL

In a 1215 predominantly 3-to-4-year-old minority children, obese preschoolers had approximately three times the risk of having high SBP and twice the risk of low HDL compared with nonobese children. Ethnicity seemed to play a role, as this was evident in white and Hispanic children, where environmental interactions strongly contribute. In Blacks, the increased risk was only in link to the elevated BP whereby genetic factors are the likely players while lipid profile was found favorable. These data indicate that at-risk populations can be early identified and that primary prevention can begin at such a young age.

*Prev Cardiol 7(3):116-121, 2004.*

## WARNING SIGNS OF HYPERTENSION;

**Erectile dysfunction** is assumed to antedate the development of hypertension. This has been clarified in laboratory researches showing that erectile tissue is at the front line of development of endothelial dysfunction and tissue remodeling compared to vascular tissue. This seems secondary to functional disturbances of the collagenous network due the striking and consistent changes in the distribution of collagen types I, III, and V. In humans, about 8% to 10% of untreated male patients have ED at the time of their hypertension diagnosis. If confirmed by more research, the penis will represent an early target end organ in hypertensives.

*Medscape Cardiology, 09/14/2004*

**Retinal microvascular signs** may be used to identify individuals at risk for development of clinically severe hypertension, (grade 2 or 3) within 5 years. Though this will not be clinically applied unless better automated methods to measure arteriolar caliber are available, yet they point out that these structural signs could be a more stable measure of risk than functional measures, such as BP, which vary over time.

*Ann Intern Med. 2004;140:248-255.*

## MOLECULAR REASONINGS;

### HOW FLOW DYNAMICS RESTRUCTURE VESSELS IN HYPERTENSION!

**Omnia Nayel, Ph.D.** *Prof, Pharmacol, Alex. University, Editor of EHS Newsletter.*

BP is literally the property of liquid in a conduit. The conduit, is the diverse blood vessel network with different calibers, varied structures, branching, bifurcating, narrowing, curving and kinking, that is unique in its elasticity and distensibility,... While the liquid, is the pulsatile blood ejected by the pumping heart that does not obey Newtonian laws because of its cellular components. Yet as it flows, it exerts different constrains on the vessels, that template their functional behavior and their structuring. Of such mechanical constrains is a friction force acting on the interface between flowing blood & vessel wall, due to the drag between the thin stationary layer of fluid adjacent to the luminal endothelial surface and the outer layers of moving blood, which propagates along the longitudinal axes of the vessel and is termed shear stress [SS]. Another, is the rhythmic distension and expansion of arteries per cardiac cycle and exerts a tensile strain [stretch] imposed circumferentially at right angles to flowing blood and is termed cyclic stretch [CS].

Normally with each ejection, an aortic pressure wave [APW], is created at systole and travels down stream along the capacitant to the conduit vessels passing through resistant arteries, arterioles, then capillaries to maintain blood flowing to the peripheral tissues. The rate at which it travels is known as pulse wave velocity [PWV]. Down stream, part of the propagated wave reflects back upstream as reflection wave [RW] to reach the aorta by diastole. In doing so, it pertains optimum diastolic pressure and maintains sufficient coronary blood flow.

Along its flow journey, SS will be sensed by luminal integrin mechanosensors [ $\alpha_1\beta_1$ ,  $\alpha_5\beta_1$ ] at caveoli and will be transduced rapidly into intracellular messages [PI<sub>3</sub>, DAG, Ca, Gproteins..] to trigger the release of a spurt of NO, PGI<sub>2</sub>...to pertain a balanced vasomotor tone especially at the level of muscular arteries ensuring forward progression of PW distally to nourish the tissues. Both the CS and SS will further activate ubluminal integrin mechanosensors [ $\alpha_{\infty}\beta_3$ ] to propagate the mechanical signals via the cytoskeleton to the nucleus [activating SSRE to express ADMs, cytokines, growth factors] to help endothelial cells, to reorganize its alignment and its surface stiffness to stand the posed constrains. The mechanical signals are also propagated via the adhesive glycoproteins to the underlying fibrillar network and vSMCs to restructure the vessel in proportion to the brunt of constrain set upon it, as what happens vividly in hypertension. This will finally culminate in an increase in collagen deposition, muscle hyperplasia and hypertrophy in capacitant vessels ending up in fracture and fragmentation of their elastic lamellae and stiffness. In the same essence, this will end up by the hypertrophic or eutrophic remodeling of conduit arteries characteristic to hypertension.

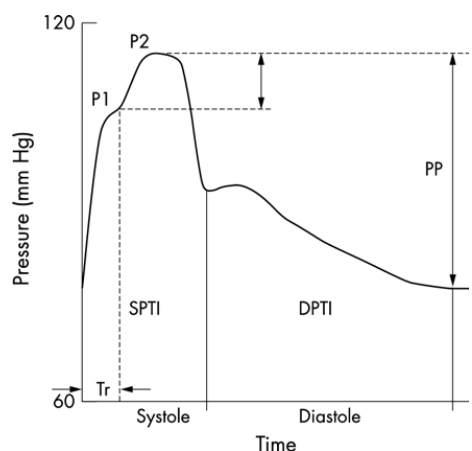
This structural derangement in hypertension, will perpetuate more disturbance in flow dynamics and more constrain. Thus, the loss of the buffering within capacitant vessels, will permit PWs to travel more rapidly downwards increasing their PWV. In consequence, RW will propagate back more earlier and more upstream than it should have been, being confronted by a disturbed vasomotor tone in remodeled muscular arteries, that will also increase its amplitude. The premature arrival of RW in systoli will summate with the APW leading to a net increase in central peak systolic pressure and increase work load on LV ending up in LVH. This extra summation when divided by the pulse pressure creates an index known as augmentation index [AIx] that reflects the extent of arterial stiffness and loss of compliance. This index is becoming one of the surrogate end points deemed to be quantified in clinic trials assessing efficacy of antihypertensives in halting the structural derangements and improving the arterial compliance.

*Q J Med 1999; 92: 595-600.*

*Circulation Research. 2000;87:683.*

*Circ. Res., July 25, 2003; 93(2): 155 - 161.*

## DIAGNOSTIC CONSIDERATIONS; AUGMENTATION INDEX [AIx] PREDICTS ARTERIAL STIFFNESS



**AIx**; is the difference between 1st & 2nd systolic pressure [SP] expressed as % of PP. It is attributable to reflection wave[RW] and thus index arterial stiffness. It is obtained by pulse wave analysis [PWA] of the arterial pressure waveform using a recently-developed computerized, portable simple-to-use device named [SphygmoCor]. This is achieved by recording of radial, carotid, femoral ... waveform by using an applanation tonometry; The latter is composed of a hand-held pencil type probe incorporating a high fidelity strain-gauge transducer at the tip of which is a small pressure sensitive ceramic sensor area. It should be applied by gentle pressure at max pulsating area against underlying bone for 10 consecutive beats to cover a respiratory cycle. It is negative in young, zero at 35years and positive thereafter. It reveals the extent of endothelial dysfunction and measures the additional load imposed on LV due to RW which correlates with LVM. It partly depends on PWV which is inversely proportion to dispensability and compliance. It is partly dependent on EF and its duration and on amount and site of RW (m. art. / arterioles). It is higher in short stature and in women, because RW returns earlier. This is believed to explain why short stature [ $>$ RW] is a risk to CVD. *Annals of the Rheumatic Diseases 2003;62:414-418.*



\* Egyptian hypertension society cardiovascular protection forum in collaborative scientific program with Servier held its July 16, 2004 at Sheraton El-Montazah Hotel – Alexandria. It was centered on hypertension in diabetics and potentialities of targetting RAS especially in such category of patients. Appropriate measurement techniques and pitfalls, relevant clinical and laboratory evaluation and optimal office management of hypertension were all tackled.

\* A separate arabic corner for the public and patients updated every 3 months will be issued in the EHS web site. It will include medical information about hypertension, cardiovascular risk factors, life style modification and what's new in cardiovascular diseases. A dynamic medical consultation in the form of 'Questions & Answers' has been constructed in collaboration with the EHS expert professors to evaluate and assess e-mailing case problems.



### CALENDAR:

LOCAL MEETINGS		
7 <sup>th</sup> meeting of EHS Cardiovascular Protection Forum; in reference to "Prevention of hypertension"	Conrad Hotel, Cairo, Egypt, 22 <sup>th</sup> October, 2004.	Secretary; Miss Rehab Mohamed Tel (202) 794-8877 - Fax (202) 794-8879
INTERNATIONAL MEETINGS		
77 <sup>th</sup> Scientific Sessions of the American Heart Association	New Orleans, Louisiana USA, 7 – 10 November, 2004,	Barbara Charbonneau, 7272 Greenville Ave. Dallas, TX Phone: (214) 706-1425 Fax: (214) 706-1517 <b>Email:</b> barbara.charbonneau@heart.org

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