

NEWS LETTER

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THE PRESIDENT'S MESSAGE

RAS BLOCKADE IN CARDIOVASCULAR DISEASE THE NEED FOR A POSITION STATEMENT

The introduction of agents that inhibit the renin angiotensin system (RAS) in the early 80s was a breakthrough in CV therapy. Though initially used as antihypertensive agents, their indications rapidly expanded. It was recognized that RAS is not only involved in blood pressure and blood volume hemostasis but also plays an important role in inflammatory processes, tissue repair, immune mechanisms and blood clotting. The link between RAS activation and the development and progression of atherosclerotic plaque was established and the antiatherosclerotic potential of RAS inhibition has been demonstrated in a large number of studies on experimental animals.

Angiotensin II (A II) through its action on cell membrane enzymatic systems can increase the production of reactive oxygen species (oxidative stress). This prooxidant state will activate nuclear transcription factor in cytoplasm namely nuclear factor kappa beta (NF- κ B). When activated, this transcription factor translocates to cell nucleus where it identifies with nucleotide sequences in the promoter (regulatory region) of genes coding for inflammatory proteins e.g. adhesion molecules, cytokines, chemo attractant proteins and growth factors. These proteins play a central role in the initiation and progression of the inflammatory process. Atherosclerosis is now being recognized as an inflammatory process in arterial wall culminating in the development of atherosclerotic plaque. Furthermore, atherosclerotic plaque instability and rupture are also inflammatory in nature leading to the development of acute ischemic syndrome. The development of platelet and fibrin thrombi on the ruptured, ulcerating unstable plaque will result in partial or total occlusion of the involved arterial segment. Spontaneous lysis of these thrombi is achieved through the body's natural anticoagulant and profibrinolytic mechanisms AII has been shown to stimulate the activity of PAI, a factor responsible for persistence and stabilization of fibrin thrombi through interference with plasmin activation (plasmin is the enzyme responsible for fibrin dissolution and lysis of fibrin clots). Also A II stimulates platelet activation and aggregation. Therefore, RAS inhibition has profibrinolytic and antiplatelet potentials.

The previous discussion can explain the mysterious link between RAS inhibitors, atherosclerosis and acute vascular events. Understanding, these various physiologic and molecular mechanisms was the rationale for the wide use of RAS inhibition in an increasing number of cardiovascular disorders. The discovery that ACE-Is were able, in patients with heart failure (HF) to prevent acute coronary events, which came as a surprise to the original investigators, expanded the indications of these agents to the management of patients with CAD.

A GROWING NEED

Globally, there is an increased recognition of the equitable partnership of CV nurses along with other medical professions in improving the related health outcomes of CV diseases i.e. helping in their detection, prevention and management. Consistently, in our health care system, there is a growing need to increase the maturity of such specialized nurses, in terms of their scope of practice and their quality, specially that we are placed under increasing pressure to develop and apply innovative and cost-effective solutions to all our health problems.

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→Cont→

It has been recognized for more than two decades that inappropriate neurohormonal activation is critical for the harmful remodeling process following myocardial injury or damage. Activation of RAS plays a central role in the remodeling process and progression of LV dilatation and HF. The direct vasoconstrictor action of AII in addition to its effect on sympathetic stimulation and aldosterone production will lead to an increase the afterload producing further compromise of LV function in patients with HF. In HF systolic ejection becomes load dependant. RAS inhibition will decrease the afterload, improve LV pumping ability and attenuate the harmful effects of the excessive neurohormonal activation. RAS blockade became recently the corner stone of HF therapy.

The last unexpected discovery of RAS blockade was its value in prevention of diabetes mellitus (DM). In majority of hypertension and HF trials, RAS blockade delayed the onset of DM in the treated groups. RAS inhibition was found to provoke the differentiation of preadipocytes leading to increased number of the large adipocytes and increased ability to store fat in fat cells and improved insulin sensitivity.

The complexity of the system, its wide ramification, expanding indications and increasing importance in CV therapy was a stimulus to invite a group of Egyptian scientists to review the subject and present in a concise monograph the state of the art knowledge as a position statement.

I am sure that clinicians, students and specialists will find this document helpful in their every day management of patients with different cardiovascular disorder.

M. Mohsen Ibrahim, M.D.

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President of The Egyptian Hypertension Society.



REVIZING THE GUIDES ▶

VIII GUIDELINES CHANGE REGARDING β -BLOCKERS ?

Though, the current European hypertension guidelines regard diuretics, CCBs, ACE Is, ARBs and β -blockers as equivalent first-line therapy for uncomplicated hypertension, while the JNC 7 designate thiazide-type diuretics as first-line treatment and the β -blockers, ACE Is, and CCBs as equivalent second choices in hypertension without compelling indications.

Yet these days, there is a call stating that "the era of β -blockers for hypertension is over" on the basis of evidence that "they are inadequate in preventing heart attacks and strokes" and also because of their "subtle and depressing side effects !!!". Such doubts that cast on the utility of these agents are based on meta-analysis of 13 randomized controlled trials involving 105,951 patients. It seems that Committees responsible for producing hypertension guidelines have to revise this and to rethink about their endorsement of β -blockers as "reasonable" first-line treatment for hypertension, especially after "the final blow" provided by the results of the BP-lowering arm of ASCOT (ASCOT-BPLA). However, this does not mean avoiding β -blockers in hypertension altogether, since some patients, especially those with coronary disease, "genuinely do need [them] as their first-line therapy." Which is in accordance still with the current European hypertension guidelines and the JNC 7 designations that enroll β -blockers as first choice in patients at high risk for coronary disease, post MI, or HF.

Lancet. 2005;366:1510-1512.

Lancet. 2005;366:1545-1553.



THERAPEUTIC AWARENESS ▶ DRUGS INDUCING CV RISKS

NSAIDs; It is known that chronic use of **Coxibs** leads to an increased occurrence of thrombotic CV events. This was ascribed to their selective inhibition to COX-2 the isoform responsible for production of prostacyclin from endothelial cells to act as a vasodilator and inhibitor of platelet aggregation. Meanwhile, they do not affect COX-1 nor thromboxane synthase in platelets, thus tipping the haemostatic pattern in favor of thromboxane-mediated atherothrombosis. That is why, they were associated with an increased risk of adverse CV events (MI and stroke) which called for the withdrawal of rofecoxib and valdecoxib a year ago.

But what about **NSAIDs**, do they produce similar hazards???!!! Though by name, these agents non-selectively block both COX isoforms, yet in reality they do so, variably, i.e. having different potentialities to block COX-1:COX-2, to yield a varied continuum of antithrombotic / prothrombotic effects. This was evidenced in current studies clearing a substantial variation in risk between different individual NSAIDs, suggesting a biologically plausible heterogeneity in CV risk. Thus, chronic treatment with some NSAIDs has been associated with a small increased risk of non-fatal MI, which invited a move by FDA to declare that an increased risk of CV events may be a class effect for NSAIDs.

BMC Med. 2005;3:17

Circulation 2005;111:1713-1716

<http://www.fda.gov/cder/drug/advisory/nsaids.htm>

Combination antiretroviral therapy for HIV infection; It has become clear that aside, *host factors* such as age, gender and genetics and *lifestyle factors* such as diet, smoking, anabolic steroids, and leisure drugs or alcohol, the *treatment* by combination antiretroviral therapy - contributes to CV risks in patients with HIV infection. Such antiretroviral combination are prone to induce proatherogenic dyslipidemia, to impair glucose metabolism, that will lead to accumulation of intra-abdominal fat and the development of metabolic syndrome. Accordingly, this has called for symptomatic chemoprophylaxis, by the use of lipid lowering agents, specially statins in such subset of patients, in hope to halt their progression to IHD in HIV-infected individuals.

Clin Infect Dis. 2003;37:613-627.

12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005

WHAT'S NEW

LIFE STYLE MODALITIES

◆ *Decreasing CV risks*

* **Several cups of flavanol-rich cocoa** each day (which equates to 600-900g of flavanol oligomers called procyanidins) was associated with elevation in levels of circulating nitric oxide, enhanced flow-mediated dilation of conduit arteries and relaxation of precontracted aortic rings. This is a new avenue to a dietary intervention aiming at improving CV health.

PNAS 2006: Early edition

* **Aerobic physical activity and resistance exercise training** offsets the development of metabolic syndrome; as shown in a study, where by muscular strength was inversely associated with the disease incidence, independent of age and body size. This is because with exercise the the slow twitch insulin sensitive muscle fibres increase compared to the fast twitch insulin resistant fibres, thus protecting against insulin resistance.

Clin Invest 2005;115:451-8

Sci Sports Exerc. 2005;37:1849-1855

◆ *Increasing CV risks*

* **High-carbohydrate diets** was proved to cause modest rise in BP compared to a diet high in cis-monounsaturated fats. The most plausible mechanism for this rise, is an increase in BP and HR secondary to an accentuation of hyperinsulinemia.

Diabetes Care 2005;28:2607-2612.

* **Noise level** is associated with a risk for myocardial infarction (MI), according to the results of a case-control study which declared that the increase appears more closely associated with actual sound levels rather than with subjective annoyance.

Eur Heart J. on line 24th Nov 2005

* When climate-related changes in BP were probed, it was found that living in **hot weather** increases systolic readings at night, particularly in elderly people with hypertension, though their daytime BP gets reduced. The bearing of becoming non-dippers to CV risks hazards is definitely known.

Hypertension 2006; 47: 1-7

A MOLECULAR STANDPOINT;

ENDOTHELIAL PROGENITOR CELLS; Their relevance to hypertension.

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

Because the endothelial cells (ECs) lie at the interface between the circulating blood and the rest of the vessel layers, they are primary concerned in pertaining the functional and structural integrity of our vasculature. However they are always posed under continuous threat of becoming defective, that is why repair mechanisms in them must be continuously active.

The replacement of defective cells was previously attributed only to the migration and proliferation of neighboring ECs. However recently, homing of circulating endothelial progenitor cells [EPCs] whether of bone marrow (haemangioblasts or mesenchymal) or non-bone marrow origin; seem to be the main contributors that enhance regeneration (in low grade dysfunction) or reendothelization (in loss of discontinuity). With more injury and subsequent repair, the telomere within EPCs shortens, till it reaches a critical threshold, EPCs then become senescent. This means that these cells have a finite capacity for repair, and that this competence diminishes naturally with age [as part of the overall diminish in intrinsic repair capacity of individual]. EPCs also decrease in number and function when risk factors breaches the integrity of our endothelium and call on them along our life span. This will exhaust their repair capacity, ending up in diseases such as atherosclerosis and hypertension. Studies have shown that levels of circulating EPCs are related directly to the degree of hypertension. Not only this, but there is a relationship between engraftment capacity of EPCs and the eNOS level, the expression of which decrease with increased hypertension (a clear gene dose effect exists). This highlights that not only in number but also the function of EPCs to home and start regeneration is impaired, denoting that systemic hypertension, at least in part is due to the loss of competent EPCs.

In an era of cell therapy, the use of exogenous EPCs to home and reendothelize damaged vasculature has been partly successful in localized atherosclerotic vessels (though no influence on plaque composition) or after PCI. But can their therapeutic use, repair the whole endothelium in a systemic disease like hypertension is an open question left to so many challenges. A more intuitive sense is to enhance the native repair mechanisms by agents that can enhance EPCs number and function by pertaining their proliferation and mobilization, and preventing their senescence and apoptosis, as by statins and estrogens,...etc. These agents achieve this via activation of PI3K/Akt survival pathway. This will present a novel approach for management of hypertension, through enhancing vascular regeneration by EPCs.

Nat Med. 2000; 6: 1004-1010 - J Clin Invest. 2001; 108: 399-405 - N Engl J Med 2003;

348: 593-600 - Nat Med 2003; 9: 1370-1376 - Circulation Research. 2004;95:343.

A PROGNOSTIC INDICATOR

BP reactivity; might provide a useful prognostic information about future coronary artery risk beyond traditional risk factors. This was proved in healthy participants, aged [20 to 35 years] whom were subjected to tasks designed to induce psychological stress. Their BP and HR were measured to index CV reactivity. While a computed tomography was performed to gauge the prevalence of calcified coronary lesions. It was found that for each 10-mmHg change in SBP during psychological stress, there was a 24% increase in the likelihood of having calcified lesions latter at follow-up. The HR reactivity followed the same patterns i.e was associated with subsequent coronary calcifications, but only in Black participants. This is the first time a prognostic correlation is reported between BP reactivity to a stressor and the prediction of coronary artery calcification.

Hypertension 2006; 47: 391



LATE-BREAKING TRIALS ▶ OmniHeart –

Optimal Macronutrient Intake Trial to Prevent Heart Disease

Although a widespread consensus on Dietary Approaches to Stop Hypertension “DASH diet” do exist, yet a look for further improvements, still hold. The partial replacement of dietary carbohydrate with protein (about half from plant sources) or with unsaturated fat (mostly monounsaturated) can further lower BP, improve lipid profiles, and reduce estimated coronary heart disease risk, in people with hypertension or prehypertension. This has been recently concluded from results of *OmniHeart Trial*. This study, provides convincing evidence that the amount of carbohydrates, protein and fat people eat, influences CV risks and highlight the merits of shifting calories from carbohydrates. However, the most alarming observation reported from this trial, is that on the protein diet, there was a reduction in HDL, which must be taken in consideration, before policy makers consider making changes in dietary recommendations and guidelines.

JAMA. 2005;294:2455-2464.

Late Breaking Clinical Trials III: coverage from AHA Scientific Sessions 2005; November 13-16, 2005; Dallas, Texas.



* EHS is due to hold its 10th annual meeting next April. On this occasion, the society tends to release several publications. One, concerns a “Positional Statement on RAS Inhibition” The second manuscript, will tackle the “ Low HDL-Cholesterol and Related Disorders. The third will enroll, “Guidliness of the Egyptian Cardiovascular Prevention Program:Delta-C”.

* EHS is planning to organize a full day scientific activity for the physicians as well as a campagne for public awarness, the coming 13th of May, on the occasion of the “*WORLD HYPERTENSION DAY*”.



CALENDAR:

LOCAL MEETINGS		
33 rd Annual Meeting of the Egyptian Society of Cardiology	Intercontinental Heliopolis Hotel, Cairo, Egypt. 21-24 February 2006	Secretary; Mrs. Fathia El Said Tel (202) 403 9020 - Fax (202) 260 585
The 10 th Annual Meeting of EHS and WHL Regional Meeting	Marriot Hotel , Cairo, Egypt April 5-7, 2006	Secretary; Mrs Rehab Mohamed Tel (202) 794-8877 - Fax (202) 794-8879
INTERNATIONAL MEETINGS		
Royal College of Physicians: Hypertension and CVD	London, UK 7th March 2006	11 St Andrews Place, Regent's Park, NW1 4LE, UK. Tel +44 2079351174 - Fax +44 2074875218 Link http://www.rcplondon.ac.uk/event
ACC 55 th Annual Scientific Session	Atlanta, GA, USA 11- 14 March 2006	Heart House, Bethesda MD 20814-1699, USA Tel +1 301 897 5400 – Fax +1 301 897 9745 Email: resource@acc.org
1 st International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention	Paris, France 30 th March - 1 st April, 2006.	Kenes International, , PO Box 1726, Geneva 1, CH-1211, Switzerland Tel +41 22 908 0488 – Fax +41 22 732 2850 Email: strokeprevention@kenes.com

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