

NEWS LETTER

Egyptian Hypertension Society



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THE PRESIDENT'S MESSAGE

CORONARY THERAPEUTIC TARGETS

Clarification of the mechanisms underlying the development of coronary atherosclerosis, its progression and finally the whole spectrum of acute coronary syndromes became possible only in the last two decades. Understanding the pathways leading to the development of ACS helped in the introduction of new therapies and the development of a more rational approach for the management of coronary patients.

Realizing that coronary atherosclerosis is a diffuse inflammatory disorder which runs unpredictable course and the fact that major acute coronary events are the results of rupture or erosion of unstable atherosclerotic plaques introduced new concepts in treatment of coronary disease. An important one is the concept of atherosclerotic plaque stabilization or passivation. Changing unstable, vulnerable plaque, liable to rupture, thrombose and precipitate an acute coronary event into a stable, less active and more benign plaque is a novel therapeutic policy.

The discovery of the presence of systemic proinflammatory and procoagulant states in patients with ACS and the persistence of this procoagulant state months after the acute event provided a rationale for prolonged anticoagulant, antiplatelet and antithrombotic therapy.

Our concept of atherosclerosis has changed and instead of being considered a degenerative, inevitable and irreversible process, now we know that it is inflammatory, preventable and reversible. It is possible through drug therapy to induce regression of atherosclerotic plaque. Also, it is possible through pharmacologic therapy to attenuate and even correct the adverse myocardial changes and damage following coronary occlusion and myocyte necrosis.

Therapeutic Targets

The first target is the ASO plaque which is responsible for the majority of clinical manifestations of CAD. Pharmacologic therapy has two goals:

1. Regress or prevent further progression of ASO plaque.
2. Stabilize or passivate the ASO plaque i.e. make it less liable to rupture and, thrombose. This will prevent acute coronary events.

The best available approach at this stage is aggressive lipid lowering. If therapy fails to stabilize the vulnerable plaque and if the plaque is disrupted or eroded, there is subsequent formation of intracoronary thrombus which is the second target of therapy. The objectives of therapy are to dissolve the thrombus if it occludes completely the coronary artery or prevent its progression if there is partial occlusion and prevent its reoccurrence.

PRESCRIBING VARIATIONS !!!

Many reasons exist for the considerable international variation in antihypertensive prescribing patterns among many countries. Among the outstanding explanations was the promotion and marketing considerations by pharmaceutical companies to "seed trials" after drug approval with an objective to "seed" the use of their drug among physicians as one of the driving force behind the prescribing of newer expensive drugs. This is being antagonised by the promotion of less-expensive drugs by non-industry pharmaceutical advisors who influence prescribing behaviour by developing local guides, super-vising prescription feedbacks and conducting outreach visits to disseminate more cost awareness. Another explanation was the difference in physicians' attitudes some being conservative and slow implementers versus others who are early adopters and rapid implementers.

BMC Health Services Research 2005, 5:21

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→Cont→

The third target is the systemic milieu in patients with CAD particularly in ACS. In this situation there are generalized proinflammatory and prothrombotic states. The proinflammatory state will invite progression, activation, instability and rupture of the ASO plaque.

The prothrombotic state will help development and will favour the persistence and progression of the intracoronary thrombus. The goals here are to attenuate the inflammatory activity and the prothrombotic state.

The myocardium is the last therapeutic target. Failure to stabilize the plaque and failure to prevent coronary thrombus formation or maintain adequate coronary perfusion will result in myocardial ischemia and myocyte loss. If necrosis is extensive cardiac remodeling and deterioration of LV function develops. Therapy at this stage aims at minimizing the effects of ischemia, protecting cardiac myocytes, prevent or attenuate cardiac remodeling.

Pharmacologic therapy, when achieving, the previous therapeutic goals will help relieving symptoms and prevent complications of coronary atherosclerosis namely MI, deterioration in LV function and sudden death. Modern pharmacologic therapy can improve quality of life and prolong survival.

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President of The Egyptian Hypertension Society.

TURNING CONCEPTS

CENTRALLY ACTING ANTIHYPERTENSIVES

The last three decades have witnessed an increased refrain from the use of central acting antihypertensives in control of essential hypertension due to their central, metabolic ...etc. side effects. Thus, guanethidine, clonidine, α -methyldopa, ..etc. no longer appeared in the guides, except for sporadic indications as the use of α -methyldopa in pregnant hypertensives; for instance in pre-eclampsia. Their need was further obliterated through the decades by the introduction of many antihypertensives that would go beyond BP control to encompass the functional [metabolic, humoral, paracrine & autocrine derangements] and the structural [remodeling changes] that deleteriously end up in target organ failure in hypertensives.

Recently, the concept has been changed with the newer version of centrally acting drugs [rilmenidine, moxonidine,...etc.] that are agonists at the I_1 imidazoline receptor (I_1R) 40 times > than at α_2AR whether in the medulla oblongata [so no central sedation occurs] or in the kidney [so naturis issues] and in liver & endocrine pancreas[so a favourable metabolic profile is achieved].

The merits are evident when these drugs are used in patients with metabolic syndrome, as they improve glucose tolerance, restore fasting levels of insulin and reduce triglycerides, cholesterol, and FFA. This may be through acting on I_1R in β -cells to restore early phase of insulin secretion & by directly acting in the liver to increase expression and tyrosine phosphorylation of insulin receptor and their substrates. Their role on adipocytokines is debatable. Yet the gene candidate of I_1R share several motifs with cytokine receptors and their signaling pathway overlaps those of cytokine receptors; thus favouring the potentiality that these imidazoline agonists can halt the deleterious loop that links obesity, insulin resistance & hypertension within th context of metabolic syndrome.

JPET 2003; 307:1104-1111

Endocrine Reviews 2003; 24: 278-301



LOOKING UP IN THE GUIDES → HYPERTENSIVE DIABETICS

In patients with hypertension and diabetes, the BP goal is <130/80 mmHg. Achieving such target with one drug is rather difficult and a combination of two or more drugs are usually needed to achieve such goals.

According to the JNC VII: thiazide diuretics, BBs, ACEIs, ARBs, and CCBs are beneficial in reducing CVD and stroke incidence in patients with diabetes. While ACEI- or ARB-based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce progression to macroalbuminuria.

In the **Canadian Guidelines:** ACE-inhibitors or ARBs were recommended as **first line therapy** in all subgroups of diabetic patients with hypertension based on considerations of the diabetic subgroup analysis of LIFE, as well as the established renoprotective effect of ARBs (i.e., RENAAL & IDNT). **Second line therapy** in *those with nephropathy* is the addition of one or more of thiazide diuretics, cardioselective BB, long-acting CCBs or an ARB/ACE inhibitor combination, while in *those without nephropathy*, combination of 1st line drugs, or addition of cardioselective BB &/or long acting dihydropyridine CCBs becomes the alternative. If the serum creatinine level is >150 mmol/L, loop diuretic should replace low-dose thiazide diuretic if volume control is required.

In both guides, adoption of a healthy lifestyles by all persons is critical for the prevention and is an indispensable part of the management, specially in diabetics. Physical activity (regular aerobics such as brisk walking at least 30 min per day, most days of the week), weight reduction (by reducing at least 10% of existing weight.), dietary Na restriction no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride) are all indicated. This aside the consumption of diet rich in fruits, vegetables, complex CHO, fibers, some nuts.... but low in fat dairy products in content of saturated and total fat ,in sweets and sugar containing beverages,...will all be of help.

J Nutrition 2001; 31:132-146.

Can J Cardiol 2002; 18(6): 591-603.

Medscape Gen Med 2005: 7(2).

WHAT'S NEW!!!

PULMONARY HYPERTENSION

Pulmonary arterial hypertension [PAH] is a rare blood vessel disorder characterized by increased pressure in the PA. Symptoms of PAH, such as shortness of breath, fatigue, chest pain, dizzy spells, and fainting, are similar to those of pulmonary vascular disease and make diagnosing the condition extremely difficult. Management of the condition is particularly important, given that it can cause an increased afterload that, if left untreated, can lead to heart failure [HF] and subsequent death.

Standard therapy for HF can improve PH, however many new specialized modalities have been advocated to refractory cases either for control or as a bridge prior to open heart transplant [OHT].

Thus one must distinguish reversible from "fixed" PH, preoperative evaluations include high-flow 100% O₂ or NO inhalation; sublingual, oral or **IV vasodilators**; **PGI₂, PGE₁ or Na nitroprusside** and/or **inotropic** challenge with **dobutamine** or an **inodilator PDE III inhibitor**; **milrinone**.

For therapy; **IV milrinone/IV nitroprusside** are effective at reducing LV filling pressures and pulmonary vascular resistance [PVR], PV reactivity testing and as bridge to OHT. They are useful and also inhaled NO in post-cardiac surgery/OHT with PH/RV failure.

On the contrary, chronic administration of **CCBs** except for **amlodipine** and also treatment with oral PDE III inhibitors [increase cAMP] in high dose without a beta-blockers worsen outcomes in systolic HF. Mortality studies are underway with lower doses of PDE III inhibitor; **enoximone**.

Oral **PDE-V inhibitors**; **sildenafil** [increase cGMP]; does not increase pulmonary capillary wedge pressure [PCWP] and is shown to acutely decrease PVR

IV nesiritide; a **recombinant BNP** [increase cGMP] decrease PCWP and PVR acutely and is useful as bridge to OHT

Endothelin receptor antagonists exert beneficial effects on acute hemodynamics (reduces PVR) while chronically **enrasentan** worsened outcomes in **systolic HF** and **bosentan** had no effect on morbidity or mortality but increased fluid retention in **systolic HF**

Medscape Cardiology 2005; 9 (1)

MOLECULAR REASONINGS;

INSULIN; A NEWLY COINED VASODILATOR

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

No body can deny that macrovascular complications [hypertension, CAD, PVD, stroke & IHD] present 60-80% of the morbidity & mortality outcomes of diabetes - that they can date back [6-10 years], before a patient becomes even coined as a diabetic - that they are not proportionally halted by tight glycaemic control as cleared by UKPDS. Meanwhile, the simultaneous findings that CV therapeutics [ACE inhibitors or ARBs] did halt diabetes progression, while drugs controlling hyperglycaemia [TZDs or metformin] were vasculoprotective, all raised the possibility of an existing direct link between insulin and vascular function.

Indeed, this has been appraised these days, where by insulin in itself was found to be a transcription regulator of eNOS; the enzyme responsible for generation of NO by the endothelial cells. It also stabilizes the t_{1/2} of its mRNA over 20 hours, so as to pertain ample NO production over time. Moreover, insulin receptors co-localize with eNOS in invaginated flask shape microdomains called caveolae, present on luminal surface of endothelial cell membranes, where both act in synchrony. The scenario starts by insulin, in the context of glucose transport, it tyrosine phosphorylates its receptor, docks & activates its insulin receptor substrate [IRS-1], to escalate a series of protein kinase phosphorylation: starting by PI3-K & one of its ends being PKB [called Akt]. This latter activates GLUT-4 transporter -to move up to caveolae, influxing glucose and simultaneously phosphorylating the eNOS co-localized there, thus producing NO. This increases local vasopermeability to allow for macromolecular extravasation of glucose at a) *skeletal muscles & adipocytes*; to ensure glucose disposal b) *pancreatic β-cells*; to pertain insulin production & β-cell survival via this Akt vasodilatory pathway [thus mediating an insulinotropic & an antiapoptotic growth response there].

Recognizing the synchronized vasodilatory-metabolic-insulinotropic potentiality of insulin, is apt to explain how with obesity [in the context of metabolic syndrome], FFA & adipocytokins come to inhibit insulin signaling along the IRS-1/PI3-K/Akt- pathway, to impair its NO vasodilatory potentiality [leading to macrovascular complications], its metabolic activity [leading to insulin resistance] and finally its insulinotropic propensity [marking β-cell functional maladaptation (impaired glucose tolerance) then failure (frank diabetes) over time]. It also explains how halting this FFAs & adipocytokine inhibitory roles whether by TZDs, ACE Is, ARBs, or even statins all of which interact at different sites of this vasodilatory, metabolic, insulinotropic pathway, will set it back better functioning, to encompass the macrovascular & metabolic derangements in pre-diabetics and to share in control of the hyperglycaemic & its subsidiary microvascular complications thereafter.

- *FASEB J. 2001;15:2099-111* -*Diabetes 2003; 52:29-37.* -*J. Biol. Chem 2003; 278(3), 28359-6.* -*Endocrine Reviews 24 (3): 278-301* - *Diabetes Care 2004 27:813-823.* - *Biochem Pharmacol. 2005;69(5):781-90.*

DIAGNOSTIC CONSIDERATIONS;

ECHOCARDIOGRAPHY FOR HYPERTENSIVES

ECHO is the most accurate non-invasive procedure to evaluate the cardiac effects of systemic hypertension. It is superior to radiography and electrocardiography in detection and quantification of LVH but not for its follow-up. It is not used routine but is indicated if symptoms or signs of CVD or ECG abnormalities prevail. It can influence the decision to initiate therapy when LVH is detected in borderline hypertensive patients. Its cost-effectiveness is questionable and its only limitation is that it is operator dependent i.e. training and experience are required for precise measurements of internal chamber dimensions and wall thickness.

From EHS Guidelines



LATE-BREAKING ALERTS ► COXIBs

Debates never ceased ever since Merck voluntarily withdrew rofecoxib (Vioxx) from the market, in fall last year, based on preliminary results from the Adenomatous Polyp Prevention On Vioxx (APPROVe) study that showed an increase in myocardial infarction and stroke in patients who took it. Such negative findings stressed researchers, regulators, and clinicians to scrutinize them not only in relevance to other available COX-2 inhibitors but even to some standard NSAIDs. While others view that the notorious publicity has escalated things to a point where it may be based more on emotion than science!!!

It is known that COX-1 mediates platelet aggregation and COX-2 mediates endothelial anti-aggregatory functions. Upon use of anti-COX-2, aggregation tendencies overweigh, while NSAIDs variably block both COXs, that is why they seemed for life time, neutral, although this is now being re-checked. This leaves only aspirin, with a favorable antiplatelet profile, being more of a COX-1 inhibitor. That is why at present it is the NSAIDs to be recommended with at most safety in those with CVDs.

Read more → *Circulation*. 2004 ;22;109(24):3000-6 *BMJ* 2004;329:31-34 - *Pharmacol Rev* 2004; 56:387-437. *JAMA* 2004; 292(2): 2647-50.



* The 9th Annual Meeting of EHS in collaboration with the WHL Regional Meeting, was held at Marriot Hotel, Cairo, Egypt from 6-9th April, 2005. *The WHL discussed "Contemporary issues of hypertension"* throughout the 1st day. At he evening, an extraordinary opening ceremony was arranged by Prof. Dr. Aziz Madkour; the chairman of the Organizing Committee, where by the blend of culture (Mohamed Salmawy's Talk "Egypt: Crossroad to civilization") and fine arts (Salah Taher's Exhibition "Color Symphony") added a third depth to the meeting. Though young investigator award was nominated to Dr. Amr A. El-Husseini, from Mansoura Urology and Nephrology Center, Mansoura University, Egypt, yet for the first time all accepted abstracts were also rewarded.

* The EHS has arranged a "World Hypertension Day" as part of the activity of the Hypertension Society CARDIOVASCULAR PROTECTION FORUM. This was held on Thursday 14th April, 2005 at Cairo Conrad Hotel. Discussions covered methods to evaluate hypertension and tackled approaches to manage hypertension in special groups.



CALENDAR:

LOCAL MEETINGS		
CARDIOALEX 2005; Summer Meeting of E S C - Ann. Conf. Pan Arab SIC - Ann. Conf. EWG Electrophys. & Pacing	Bibliotheca Alexandrina, Alex., Egypt 29 June to 1 July 2005	International Center for Organization & Marketing Tel. (203) 4204849 - Fax (203) 4204849 E-mail: icom@dataxprs.com.eg
EHS CME courses	Damietta 2 nd June 2005.	Secretary; Mrs Amany Kandeel Tel (202) 794-8877 - Fax (202) 794-8879
PANARAB MEETINGS		
5 th Conference of the Pan Arab Hypertension Society	Tunis 15-17 th September, 2005	Secretary; Dept Int Med. Charles Nichole Hosp. Tel (216) 71562670 - Fax (216) 71560280
INTERNATIONAL MEETINGS		
20 th Ann. Sci. Meeting & Exposition of American Soc. of Hypertension	San Francisco, California, USA 14 th – 18 th May , 2005	ASH; 148 Madison Avenue, NY10016, USA . Email: ash@ash-us.org Tel +1 212 696 9099 -
14th European Stroke Conference	Bologna, Italy 25th-28th May 2005	Admin. Secret. Basel, CH-4005, Switzerland Tel +41 61 686 77 11 – Fax +41 61 686 77 88

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