GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Meeting report

The unstable plaque: From molecules to the community: Aswan Heart Centre Science and Practice Series, El Gouna, Egypt, February 1-3, 2013

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ABSTRACT

The symposium "The Unstable Plaque: From Molecules to the Community" was sponsored by The Aswan Heart Centre in El Gouna, Egypt, on February 1–3, 2013, as the third installment of the Centre's Science and Practice series. This 3-day symposium delved into the pathophysiology, prevention, and treatment of acute coronary syndromes, bringing together leading international experts who bridged the spectrum of epidemiology, molecular mechanisms, clinical trials, and clinical practice.

http://dx.doi.org/10.5339/gcsp.2013.40

Submitted: 01 December 2013
Accepted: 09 December 2013

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Cite this article as: Bonow RO, Yacoub MH. The unstable plaque: From molecules to the community: Aswan Heart Centre Science and Practice Series, El Gouna, Egypt, February 1-3, 2013, *Global Cardiology Science and Practice* **2013:40** http://dx.doi.org/10.5339/gcsp.2013.40

The third installment of the Aswan Heart Centre Science and Practice Series was held in El Gouna, Egypt, on February 1–3, 2013, at the beautiful satellite campus of the Technische Universität Berlin. This 3-day symposium (Figure 1) focused on the unstable coronary plaque and acute coronary syndromes, bringing together leading international experts who bridged the spectrum of epidemiology, molecular mechanisms, clinical trials, and clinical practice. The program was designed to allow maximal interaction between the audience and the national and international faculty, and the topics were chosen to stimulate interaction between clinicians and basic scientists with the purpose of offering the very best to our patients. The venue had advanced audiovisual technology, allowing for recording of all of the presentations, which are now available online at the Aswan Heart Centre website (See http://aswanheartcentre.com/2013-04-11-00-47-42/2013), and the setting was stunning and relaxing (Figure 2).

The first session of the symposium consisted of elegant discussions dedicated to the global epidemiology of coronary artery disease and acute coronary syndromes. Stuart Spencer, executive editor of *The Lancet*, discussed the Global Burden of Disease project that was highlighted in his journal in December 2012 and summarized earlier this year in his excellent review in Global Cardiology Science and Practice.[1–3] In addition to the clear demonstration that chronic diseases are the leading causes of death worldwide, stemming from evolving risk factors in both developed and developing nations, Dr. Spencer displayed the amazing interactive program that is available on the *Lancet* website that provides in-depth information about current and future disease trends globally and regionally.

Professor Peter Wilson from Emory University, who is a former investigator at the Framingham Heart Study, was a strong contributor to this meeting. As a cardiologist and endocrinologist, he provided an important overview of the impact of diabetes and cardiovascular diseases as well as practical information on glycemic management in patients presenting with acute coronary syndromes. Dr. Wilson also discussed the lessons learned from the Framingham Heart Study and other large databases over the last several decades; importantly, epidemiologic research is moving beyond the standard risk factors to evaluate genetic and epigenetic determinants of disease.

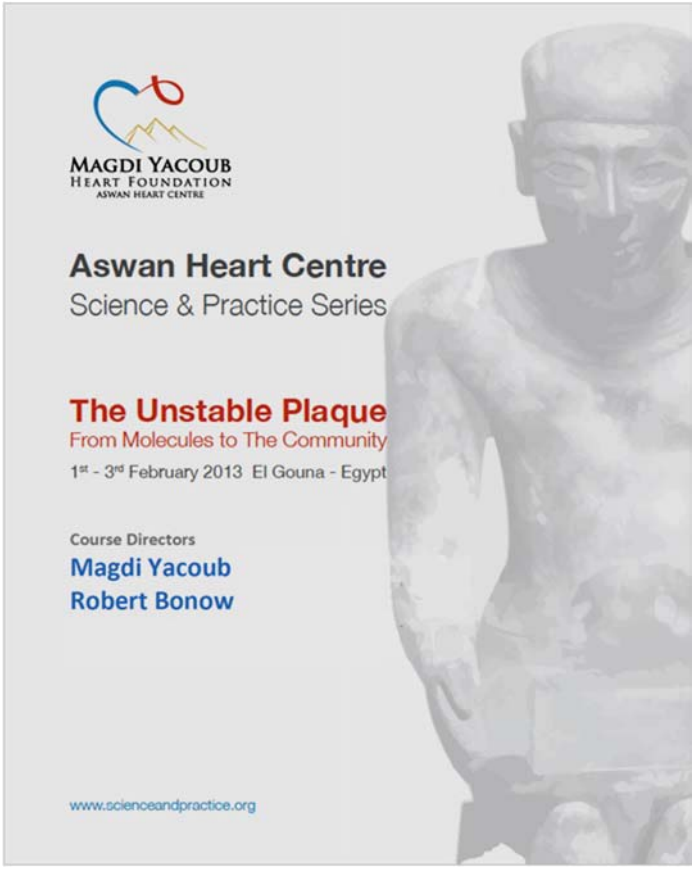

Figure 1. The cover of the program book: The Unstable Plaque: From Molecules to the Community.

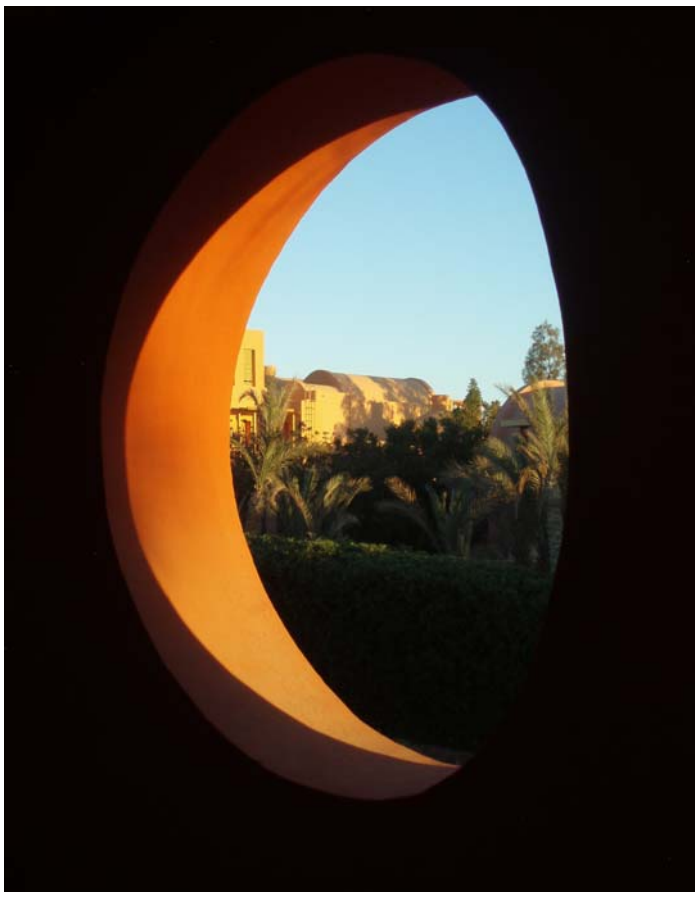

Figure 2. View of El Gouna.

Professor Jaspar Kooner from Imperial College, London, discussed the LOLIPOP Study, which is providing detailed information about cardiovascular disease in the South Asian population, particularly as they immigrate to Western cultures. This study has shown, for example, that South Asians have twice the prevalence of coronary artery disease and four times the prevalence diabetes compared to Caucasians living in the same community.[4] LOLIPOP has also been engaged in important genetic studies that initially demonstrated no clear differences in the genetic determinants of cardiovascular disease between Caucasians and South Asians. This has lead to current advanced genetic studies designed to identify genetic clues that are unique to the South Asians that may explain not only their tendency to develop cardiovascular disease but also the gene-environment interaction that is triggered when they immigrate to Western cultures.

The first session concluded with an exquisite discussion by Elio Riboli, Professor at Imperial College and Director of Qatar Biobank, on the behavioral and dietary determinants of chronic disease. Prof. Riboli has been working primarily in the field of oncology, but is now also investigating the epidemiologic intersections of cancer, cardiovascular disease and other chronic diseases. His lecture presaged his publication in the *New England Journal of Medicine* several months later in 2013.[5]

The second session was initiated with a keynote address by Dr. Adel Allam, who discussed the HORUS Study of atherosclerosis detected by computed tomography (CT) in ancient Egyptian mummies, many of whom had advance atherosclerotic disease. HORUS indicates that atherosclerosis is not necessarily a disease of modern man, but occurred even in young people in the ancient world. HORUS was the cover story of *JACC Cardiovascular Imaging* in April 2011.[6]

This was followed by excellent presentations of the pathophysiology and molecular mechanisms of plaque instability and acute coronary syndromes. Professor Erling Falk from Aarhus University in Denmark, who has been among the leading investigators in plaque inflammation, gave an elegant description of the mechanisms of plaque rupture, the leading cause of acute coronary syndromes, and also pointed out that plaque erosion and calcified nodules contribute importantly in some patients.

This discussion was then amplified by Professor Andrew Newby, BHF Chair of Vascular Cell Biology at the University of Bristol, who provided an intricate and detailed discussion of the mechanisms of plaque inflammation, including the role of proteinases and the regulation of several important transcription factors, such as NF$\kappa\beta$, mitogen-activated protein kinase (MAP kinase) and interferon gamma (INFγ). Prof. Newby also pointed out that it is not necessarily the number of macrophages that are triggered in the inflammatory response but rather the phenotype of the macrophages, which become much more aggressive as they permeate the hypoxic milieu of the vulnerable plaque and do their dirty work in causing plaque instability and disruption of the fibrous cap.

Following this, Dr. Adrian Chester of the Imperial College London and The Royal Brompton & Harefield NHS Foundation Trust discussed the importance of flow dynamics in arteries, why flow separation can lead to areas of high sheer stress and low sheer stress, and how cellular signaling in those low sheer stress areas may trigger some of the molecular mechanisms that Prof. Newby had discussed previously. Thus, plaque vulnerability may be the result of the combination of flow disturbances, sheer stress and cell signaling that trigger that inflammatory cascade.

Finally, Professor Raad Mohiaddin, also from Imperial College London and The Royal Brompton Hospital and National Heart and Lung Institute, discussed how these processes could be studied with advance imaging techniques, primarily CT, to assess plaque characterization and plaque calcification.

The third session was a discussion by our Egyptian colleagues on how the epidemiology and pathophysiology of plaque vulnerability apply to the many patients in Egypt now presenting with acute coronary syndromes. The distinguished leaders of our host country pointed out the unique characteristics of the Egyptian patients that distinguish them from those in many other places in the world: young age, heavy smoking, and high prevalence of diabetes, indicating that lifestyle issues are very important factors. Professor Ashraf Reda from Menoufiya University discussed the Egyptian Cardiovascular Risk Factor Project, which has identified the dyslipidemic profile of Egyptian population and the remarkable rate of risk factors in those with acute coronary syndromes, even among young individuals, including obesity and diabetes. Professor Magdy Rashwan from Alexandria discussed vascular imaging and plaque characterization among Egyptians, including participation in the international Big Picture Study,[7] involving over 5000 patients in 14 countries. The number of patients in Egypt undergoing imaging who have extensive coronary disease, including coronary occlusions, was higher than that of patients included in this same registry from other parts of the world, indicating either that Egyptian patients have more extensive disease, or perhaps that imaging is being used more appropriately in his country to identify the highest risk patients. Thus, imaging may be used more selectively and appropriately than other countries, such as the U.S., where imaging may be used less selectively and more indiscriminately, such as for screening of asymptomatic individuals.

Professor Mohamed Sohby from Alexandria then discussed the state of the art of primary PCI in Egypt, including participation in the ACCESS Registry, which provides an important look at the management of acute coronary syndromes in developing countries,[8] thus creating the foundation on which a primary PCI network can be developed in Egypt. Prof. Sohby's presentation highlighted not only (again) the young age of Egyptian patients enrolled in this registry compared to other countries of the world, but also the striking lack of reperfusion therapies, whether mechanical or thrombolytic. Roughly half of the Egyptian patients received no form of reperfusion therapy, indicating the great opportunity to develop and implement processes of care, such as the Stent for Life program,[9] that would lead to better outcomes for patients in this country.

The second day of the symposium opened with the fourth session, which focused attention on cardiovascular imaging, with Professors Bonow and DiMario (Northwestern University and Imperial College, respectively) discussing the application of advanced imaging tools. In the U.S. there are ongoing controversies about the appropriate use of these tools in the appropriate patients. These issues have led to Appropriate Use Criteria documents from the American College of Cardiology. Does imaging result in better patient outcomes? How does one apply imaging in a manner that is cost effective? In addition to noninvasive imaging, the work of many investigators using intravascular ultrasound and optical coherence tomography, summarized by Prof. DiMario, identifies the opportunity to exquisitely visualize the vascular wall and the composition of the atherosclerotic plaque and, in some patients, even guide therapy during the course of intravascular intervention. This discussion was followed by an interesting to-and-fro between Professor Roxy Senior, Imperial College and Royal Brompton Hospital, and Dr. Ahmed ElGuindy from the Aswan Heart Centre regarding the importance of the coronary microcirculation in health and disease, an often overlooked subject, and whether

microcirculatory function can be assessed accurately by noninvasive and invasive methodologies. Prof. Senior discussed his seminal work on the use of contrast echocardiography as a tool for assessing the microcirculation,[10] and Dr. ElGuindy discussed the use of the innovative intracoronary microcirculatory resistance (IMR) index as a potential tool to unravel the complexities of the microcirculation in patients with epicardial coronary artery disease and those with cardiomyopathies without epicardial vascular disease.

Session 5 provided a discussion of patient management including secondary prevention and the use of biomarkers from Professors Bonow, Yacoub and Wilson. This was followed by a scholarly and provocative keynote address from Professor Attilio Maseri on the revival of clinical research, and how our research hypotheses are driven by our observations in patients, especially those patients who are the "outliers" and do not fit the existing clinical paradigms. Why, for example, do patients with no risk factors have acute coronary syndromes while many with extensive multiple risk factor burden have no events? These observations not only provide the basis for research hypotheses but also the foundations for the research careers of young investigators. As always, Prof. Maseri instilled important take-home messages for fellows and both junior and senior faculty.

The final session of the second day focused on the implementation of primary angioplasty programs in Egypt, the Region, and developing countries worldwide, which is one of the greatest hurdles facing many countries as they face the expanding number of patients with acute coronary syndromes. Dr. David Antonucci, Director of the Division of Cardiology, Careggi Hospital, Florence, Italy, discussed the necessary ingredients in setting up a primary PCI program. Dr. Antonucci, a prominent leader in Europe who was instrumental in developing this program in Aswan, discussed solutions to the many obstacles, including logistical issues, setting up local emergency medical services (EMS), the communications between EMS and the catheterization laboratory team, and the development of telemetry systems to reduce the time from onset of symptoms to the open artery while also reducing the number of false alarms. Professor Di Mario amplified the details of creating primary PCI programs, pointing out that one of the key components of primary PCI success is not only the volume of the program and the door-to-balloon time, but also the skill of the operator and the cohesiveness of the team. Dr. Abdurrazzak Gehani, from the Heart Hospital at the Hamad Medical Corporation in Doha, explained the challenges that he and his colleagues have overcome in establishing a nation-wide primary PCI program in Qatar,[11] which is now operational. In the setting of a high volume interventional program and skilled operators, there were nonetheless issues that needed to surmounted with respect to EMS systems and timely delivery of patients to the appropriate receiving hospital, placing them in the hands of the team that is most equipped to provide the most optimal care. This discussions were followed by a more in-depth discussion by Dr. Sohby of the ACCESS Registry and the transition from this registry to the Stent For Life Program,[8,9] with particular emphasis on the many levels of complexity including the patients, the doctors, the hospital, the system, and the economics. Clearly, developing the resources to provide ongoing primary PCI programs in Egypt will be challenging. This pertains not only to the primary PCI procedure itself but the follow-up care and secondary prevention measures that will insure clinical success. The plan is to implement primary PCI in selected hospitals, using them as the test sites, and then slowly moving forward to expand to other institutions in a wider scale network. This plan appears to be cogent. There will challenges in implementing the plan, but the opportunity to improve the outcomes of patients is very clear and compelling. Dr. Amr ElFaramawy discussed how this model is being used successfully at the Aswan Heart Centre, where the appropriate patients are sent to state-of-the-art facilities for high quality care.

The final day of the symposium was a series of intriguing case presentations of treatment of complex patients with acute coronary syndromes in Egypt, which demonstrated the high technical skill of the local cardiologists in angiography, PCI, rheolytic therapies and thrombus aspiration. The physicians not only presented excellent cases but took care of very sick patients with a high degree of clinical acumen and technical proficiency.

What have we learned from this unique symposium? We have learned that we in the medical community, despite differences in cultures and resources, share many things in common with respect to the challenges we face in treating the growing number of patients with acute coronary syndromes. These include our aging populations with advanced risk factors, access to care and medications, and resource utilization. Although these problems play out differently if different places in the world, they are the same problems. Sharing our experiences and best practices will result in better outcomes for all of our patients. We have also learned that our hearts are lighter as a result of our productive

Figure 3. The judgment of Ani. Judgment scene from the Book of the Dead. Discovered in the tomb of a man named Ani. This scene is painted on papyrus around 1275 BC, showing Anubis measuring the heart against the feather of Ma'at. From the British Museaum.

interactions, and having a lighter heart in Egypt takes on particular importance. If the concept is correct, that our afterlife is determined by whether our heart is light or heavy as measured by Anubis (Figure 3), then a lighter heart is an important gift. More important is a pure heart, as we are told, because Anubis would often help those who led a good life to adjust the scale to be certain that one's heart weighs less than the feather of Ma'at. The knowledge shared among all of us at the Aswan Heart Centre Science and Practice meeting in El Gouna has left us with the understanding that our hearts are light and pure, and our patients' hearts will also be healthier as a result.

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