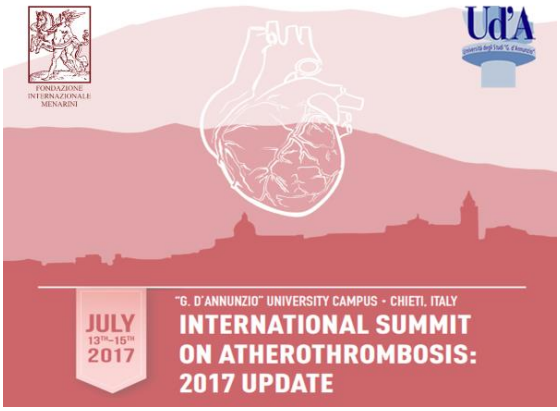
INTERNATIONAL SUMMIT ON ATHEROTHROMBOSIS: 2017 UPDATE

Chieti (IT), July 13-15, 2017

Highlights

Introduction



Prof. De Caterina and Prof. Patrono, chairmen of the symposium, opened the congress and asked for Prof. Miscia introduction. The speaker, the dean of the School of Medicine of the University of Pescara, introduced the congress, by highlighting the high scientific level of this meeting, thanks to the presence of many of the top researchers in Atherothrombosis coming from all the world. The main topics discussed in this symposium were about basic science in Atherothrombosis, pathophysiology, translational research and new therapeutic targets and finally about clinical perspectives leading to new therapies and biomarkers development. The congress has been attended by many of the top researchers of this field coming from all the world and by many young physicians attending the university of Chieti.

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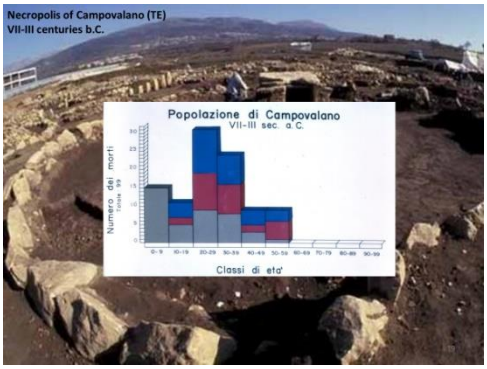
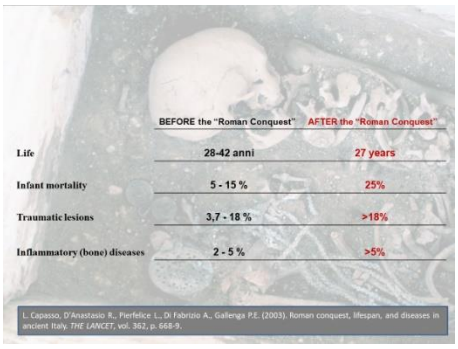
Italics: Life, death and habits of a pre-Roman population in the Abruzzi region

Italics: Life, death and habits of a pre-Roman population in the Abruzzi region, was the topic discussed by Prof. Capasso in his lecture. The speaker, coming from Chieti (IT), went deeper in his talk and presented very interesting data on Italics life. Prof. Capasso, spoke about the Italic populations living in central Italy and presented very interesting data thanks to the presence of archaeological findings. In the main part of his lecture, the speaker talked about the main pale-biological data, related to Italics life span, diet, working activities, diseases, causes of death and finally about medical knowledge and care. Speaking about diet, Prof. Capasso highlighted that the dental analysis performed on archaeological findings, show an annual cyclicity in food production and consumption. From the diseases and cause of death point of view, the speaker presented very interesting data, demonstrating that also at those time many people died from cancer, tuberculosis and traumatic lesions. Finally, Prof. Capasso presented very interesting data on medical care and knowledge, demonstrating that at those times many surgical procedures were practised, like the cranial trepanation and the dental surgery. In conclusion, the speaker pointed out that the passage from the Italics communities to the Roman conquest, dramatically worsened their quality of life, more in particular there was a reduction in life span, a rise in infant mortality and in inflammatory diseases as well as in traumatic lesions.





- Who were the Italics, based on the data presented by the speaker?
- Where and in what period did the Italics live, based on the data presented by the speaker?
- What information do we have today about this ancient population?
- What's about the Italics life span, based on the data presented by the speaker?
- What are the main effects of the Roman conquest on the Italics quality of life, based on the data presented by the speaker

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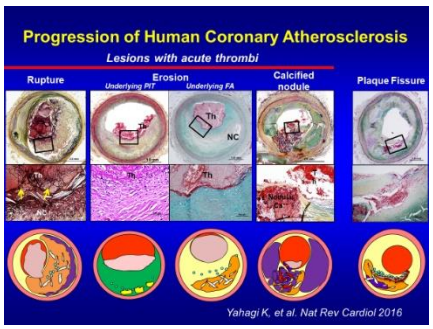
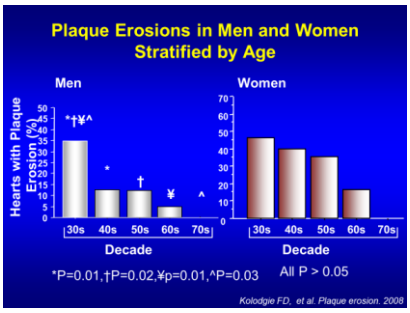
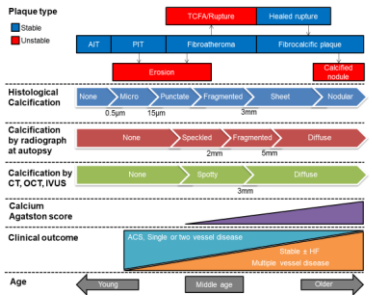
The evolving pathology of atherothrombosis



Prof. Virmani from Washington (USA), spoke about the evolving pathology of Atherothrombosis. Going deeper in her lecture, the speaker presented very interesting data on the AHA classification of Atherosclerosis. In the main part of her lecture, Prof. Virmani spoke about the major causes leading to the coronary thrombosis development and presented very interesting histological data on the progression of the human coronary atherosclerosis. More in particular the speaker talked about the main findings of this process and about the features of the ruptured plaques. Prof. Virmani presented also very interesting data on the differential expression of macrophages and their different subtypes. In the second part of her presentation, the speaker talked about Inflammation and its role in the plaque progression and rupture. In the last part of her talk, Prof. Virmani presented very interesting data on the mechanisms leading to the plaque erosion and its underlying morphology and spoke about the relationship between the presence of intramyocardial emboli and the development of plaque erosion or rupture. Finally, the speaker presented very interesting data on the plaque calcification, its relationship with the sudden coronary death and on the main risk factors for SCD. In conclusion, Prof. Virmani pointed out that the fibrous cap atheroma is the main lesion leading to the plaque fissure, while the thin cap atheroma is highly correlated with the plaque rupture.





- What's about the main processes leading to the progression of the atherosclerotic plaque, based on the data presented by the speaker?
- What are the key topics of the macrophage diversity, based on the data presented by the speaker?
- What are the function of different macrophage subtypes, based on the data presented by the speaker?
- What's about the relationship between angiogenesis and inflammation, based on the data presented by the speaker?
- What's about the incidence of plaque erosion between men and women?
- What is the distribution of the Atherosclerotic Coronary Disease, based on the data presented by the speaker?
- What is the influence of age on coronary thrombosis in men and women, based on the data presented by the speaker?
- What's about the relationship between calcification severity and incidence of plaque rupture, based on the data presented by the speaker?

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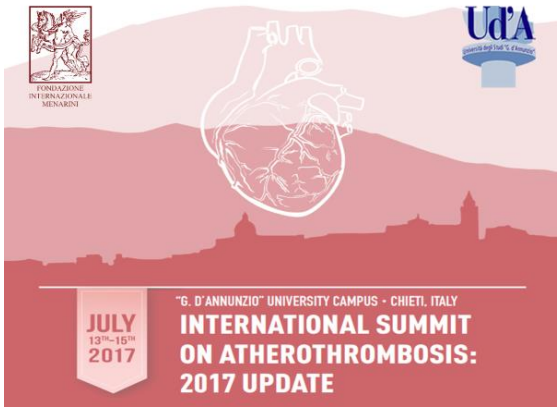
The vulnerable plaque: pitfalls and revisitation



The vulnerable plaque: pitfalls and revisitation, was the topic Prof. Libby spoke about in his lecture. The speaker coming from Boston (USA), presented very interesting data on the main characteristics of the pathophysiology of the fibro-cap atheroma and spoke about the validity of the vulnerable plaque concept, by highlighting that only the 5% of thin-cap fibroatheroma cause events. Going deeper in his lecture, Prof. Libby, presented very interesting data on the different composition of the human plaques thanks to the use of statins, leading to the development of plaques less rich in fats. The speaker highlighted that this change in composition is the main cause of the shifts in clinical presentation and in the underlying mechanisms of the atherosclerotic processes. In the main part of his lecture, Prof. Libby talked about the changes also in the clinical presentation of ACD, by highlighting that today the NSTEMI disease is more correlated with erosion than rupture. In the second part of his lecture, Prof. Libby presented very interesting in vitro data on the hyaluronidase fragments involvement in the development of the superficial erosion processes and on the multiple physiopathological processes involved. Prof. Libby talked also about the in vivo studies performed by his team of researchers, demonstrating the presence of the same in vitro processes. Finally, the speaker presented very interesting data on the role played by neutrophils, TLR2 and disturbed flow in the development of the plaque erosion and highlighted that, thanks to these data, it is the time to rewrite the plaque erosion theory.

- What's about the implication of the engagement of the innate immune receptor TLR2 in the plaque superficial erosion, based on the data presented by the speaker?
- What's about the hyaluronan activation in human cells, based on the data presented by the speaker?
- What are the effects of the intensive statin treatment on human atherosclerotic plaques, based on the data presented by the speaker?
- What are the effects of the disturbed flow on the development of the erosion processes at the plaque level, based on the data presented by the speaker?
- Is the vulnerable plaque a valid concept today on 2017, from the speaker point of view?
- What is the relationship between neutrophil and the erosion plaque processes development, based on the data presented by the speaker?

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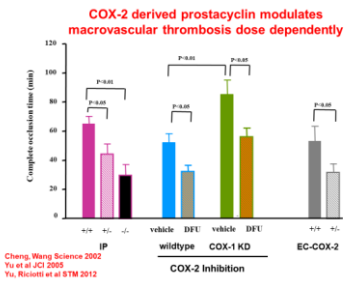
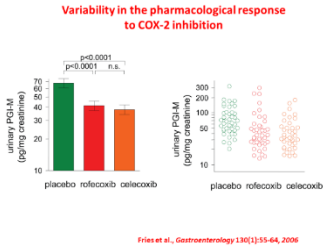
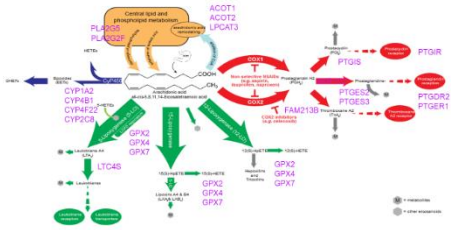
Eicosanoid modulation and atherothrombosis



Eicosanoid modulation and atherothrombosis, was the topic discussed by Prof. FitzGerald. The speaker, coming from Philadelphia (USA), spoke about the cyclooxygenase (COX) pathway and about its complex regulatory network. Going deeper in his lecture, Prof. FitzGerald presented very interesting data on the two CX pathway, their promoters and controlling mechanisms. In the main part of his lecture, the speaker talked about the relationship between the COX-2 derived prostacyclin and the macrovascular thrombosis and presented very interesting experimental data on the effects of the main COX-2 inhibitors on thrombogenesis. More in particular Prof. FitzGerald talked about the variability of the pharmacological response to COX-2 inhibition and on the COX expression variability, based on data given by experiments running in immortalized human B-cells. Finally,





the speaker presented very interesting data on the relationship between COX-2 inhibitors pharmacokinetic and microbiota and on the hypotensive effect of aspirin in mice. In conclusion, the speaker pointed out that it is necessary to apply for network, structure and dynamic based approaches to modelling in order to develop predictive paradigms of CV risk that can be prospectively tested in trials.

- Why do we have two COX pathways, based on the data presented by the speaker?
- What is the effect on platelets of the selective inhibitors of PGHS-2, based on the data presented by the speaker?
- What are the main effects of the COXIBS on the major cardiovascular events, based on the data presented by the speaker?
- What's about the limitations of large RCTs performed on the main COX-2 inhibitors, based on the data presented by the speaker?
- What's about the Personalized NSAID Therapeutic Consortium presented by the speaker?

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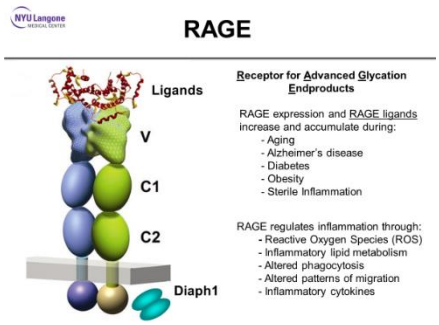
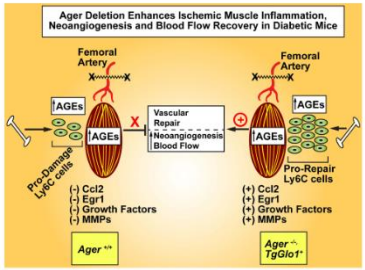
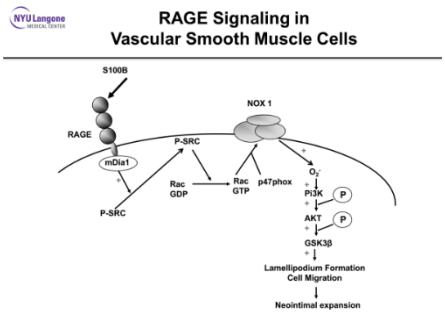
Understanding diabetic vascular disease



Understanding diabetic vascular disease, was the topic discussed by Prof. Schmidt in her lecture. The speaker, coming from New York (USA), talked about RAGE that is the Receptor for Advanced Glycation Endproducts project. Going deeper in her lecture, Prof. Schmidt presented very interesting experimental data on the relationship between RAGE and the diabetic cardiovascular disease, by highlighting that the receptor is highly expressed in human diabetes patients. In the main part of her lecture, the speaker talked about the relationship between RAGE and the accelerated atherosclerosis in diabetes thanks to the development of mouse models. Prof. Schmidt talked also about the relationship between RAGE and the peripherical vascular disease and presented very interesting experimental animal data on the effect of the deletion of RAGE on the blood flow recovery, on the angiogenesis and on the macrophages content in skeletal mice muscles. In the second part of her lecture, the speaker talked about the relationship between RAGE, high glucose levels and the loss of macrophage anti-inflammatory activity and presented very interesting data on the identification of specific genes involved in the anti-inflammatory macrophage activities and on the effects of the suppression of their expression. Finally, Prof. Schmidt presented a huge amount of experimental data in the effects of the RAGE/DIAPH1 connection, by highlighting the central role played by this domain in the development of atherosclerosis in presence of high blood glucose levels. In conclusion, the speaker, pointed out that small molecule antagonists of RAGE-DAPH1 may form the foundation for a novel class of Rage inhibitors.





- What's about the relationship between RAGE expression and aging, based on the data presented by the speaker?
- What's about the relationship between RAGE and high glucose levels on macrophage properties, based on the data presented by the speaker?
- What are the effects of Ager deletion in diabetic mice presented by the speaker?
- What are the key points of RAGE signaling in the vascular muscles cells, presented by the speaker?
- What are the effects of RAGE diverse ligands on specific domains, based on the data presented by the speaker?

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Low-density lipoproteins receptors and associated molecules

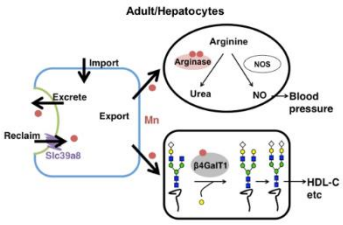
Directionality of *SLC39A8* and associated traits

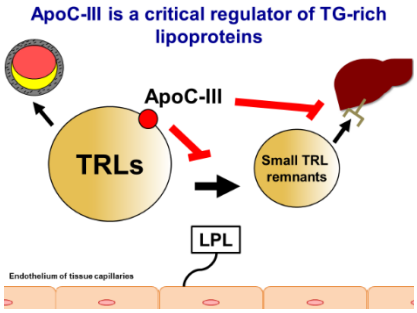
Locus	Lead SNP	Trait	Effect size	P value	Ref.
SLC39A8	rs13107325	SBP	- 0.981 mmHg	3.3E-14	Ehret et al., 2011
SLC39A8	rs13107325	SBP	- 0.837 mmHg	4.7E-11	Ehret et al., 2016
SLC39A8	rs13107325	DBP	- 0.684 mmHg	2.3E-17	Ehret et al., 2011
SLC39A8	rs13107325	DBP	- 0.602 mmHg	1.6E-14	Ehret et al., 2016
SLC39A8	rs13107325	Hypertension	- 0.105	4.9E-7	Ehret et al., 2011
SLC39A8	rs13107325	HDL-C	- 0.84 mg/dl	7.0E-11	Teslovich et al., 2010
SLC39A8	rs13107325	HDL-C	- 0.071 s.d.	1.0E-15	Willer et al., 2013
SLC39A8	rs13107325	BMI	+ 0.19 kg/m²	1.5E-13	Speliotes et al., 2010
SLC39A8	rs13107325	Schizophrenia	Odds ratio 1.17	5.3E-15	Li et al., 2015

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; s.d.: standard deviation

Low-density lipoproteins receptors and associated molecules, was the topic of Prof. Rader presentation. The speaker, coming from Philadelphia, (USA), talked about the leveraging of human genetics for biological discovery, precision medicine and human health. Going deeper in his lecture, Prof. Rader presented very interesting data on the GWS lipid loci discovered since the 2010. More in particular the speaker talked about the involvement of the SLC39A8 locus with multiple cardiometabolic traits and presented very interesting experimental animal data given by studies running in specific mouse models. In the main part of his lecture, Prof. Rader presented very interesting data on the manganese metabolism in liver and on the tight correlation between Mn levels and its main dependent enzymes like arginase that influences the availability of arginine and the production of nitric oxide. More in particular the speaker talked about the relationship between Mn, arginase, arginine, NO and blood pressure, by highlighting that the genetically reduction of the Slc39a8 function may lower blood pressure. In the second part of his lecture, Prof. Rader talked about precision medicine applied to LDL-C and CAD and presented very interesting data on the effects of the PCSK9 inhibitors on LDL-C and on the emerging risk factors for cardiovascular disease like TG-rich lipoproteins. More in particular the speaker talked about the correlation between LPL and the cardiovascular risk and about the correlation between ApoC-III and the TRL remnants levels. In the last part of his lecture, Prof. Rader presented very interesting data on ApoC-III knock-out individuals, their correlation with post-prandial Triglycerides and the pathway through A43T influences the APO C-III expression. Finally, the speaker talked about a model explaining the protective mechanism of ApoC-III A43T variant on TRL remnants and about the new possibilities that human genetics may offer for the development of new very effective drugs for CAD treatment.

SLC39A8/ZIP8 influences complex traits by regulating whole body Mn metabolism





- What is the biological basis of the strong association of the SLC39A8 locus in chromosome 4 with multiple cardiometabolic traits, based on the data presented by the speaker?
- What's about the correlation between SLc3a8 deletion and manganese levels, based on the data presented by the speaker?
- What is the potential mechanism of the influence of Slc39a8 on blood pressure, based on the data presented by the speaker?
- What's about the correlation between TG-rich lipoprotein and CHD, based on the data presented by the speaker?
- How many genomic loci are associated with CAD, based on the data presented by the speaker?

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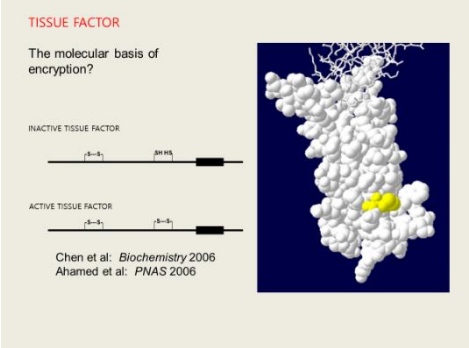
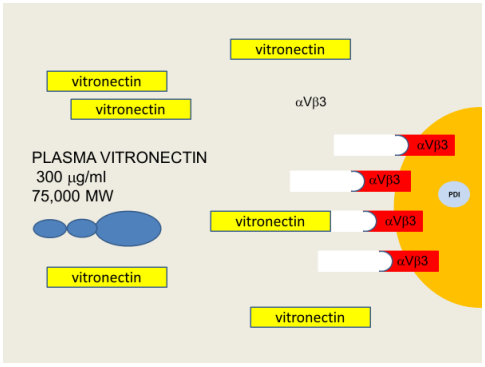
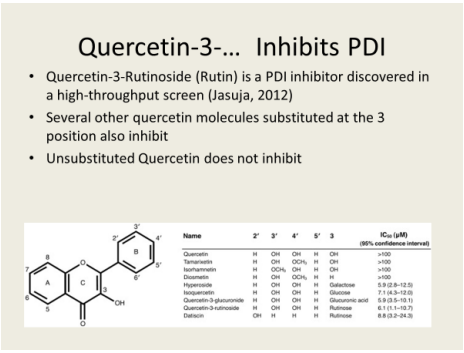
Regulation of thrombosis by protein disulfide isomerase: the Master Switch Hypothesis



Prof. Furie coming from St. Louis (USA) spoke about Regulation of thrombosis by protein disulfide isomerase: the Master Switch Hypothesis and presented very interesting data on the activation of the hemostatic system. Going deeper in his lecture, the speaker talked about the regulation of the blood coagulation through the tissue factor pathway inhibitor, the protein pathway and the antithrombin III pathway. In the main part of his lecture, Prof. Furie presented very interesting data on the mechanisms leading to the suppression of the thrombus initiation and to the release of this suppression for allowing the initiation of the thrombus formation and more in particular on the tissue factor. The speaker talked also about the protein disulphide isomerase (PDI) family, its expression during thrombus formation and the ways PDI is able to modify the vascular substrates for the activation of those process supporting the thrombus formation. More in particular Prof. Furie presented a huge amount of experimental data on the vascular substrates that are PDI targets and on Vitronectin, its modification due to the PDI activity, the way the modified vitronectin binds the vessel wall after injury, the cell activation and finally the way the modified fibronectin acts in the thrombus formation. In the last part of his lecture, the speaker talked about Rutin as a potential PDI inhibitor to be applied for the suppression of the thrombus formation. In conclusion. Prof. Furie pointed out that the PDI inhibitors may represent a valuable option for the control of those processes which lead to the thrombus formation.





- What are the key steps of the regulation of the blood coagulation through the tissue factor pathway inhibitor, based on the data presented by the speaker?
- What does suppress the initiation of thrombus formation and release this suppression to allow initiation, based on the data presented by the speaker?
- How does PDI modify the vascular substrates, based on the data presented by the speaker?
- How does substrate activation support thrombus formation?
- What is the role played by vitronectin in the thrombus formation?
- What's about quercetin 3 and PDI based on the data presented by the speaker?

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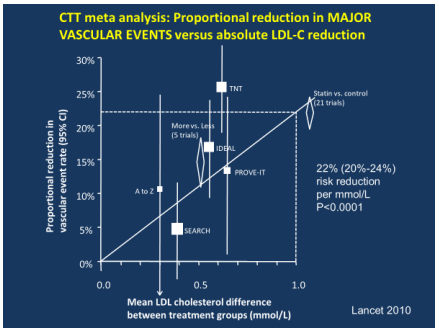
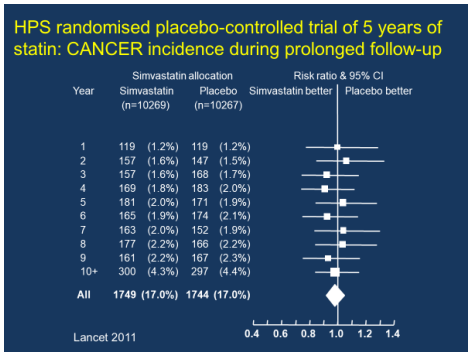
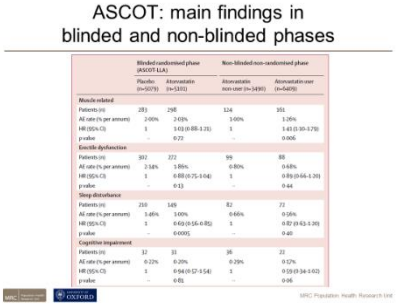
Who should take a statin, and are they safe?



Prof. Baigent from Oxford (UK), spoke about "Who should take a statin, and are they safe?" and presented very interesting data starting from the relation between the proportional reduction in major cardiovascular events and the mean absolute LDL-C reduction at 1 years in 14 statin trials. Going deeper in his lecture, Prof. Baigent talked about the CTT meta-analysis performed on more than 200 trials on the main effects on major cardiovascular events per mmol/L LDL-C reduction. In the main part of his lecture, the speaker presented other very interesting data on the statin proportional effects on cause-specific mortality and highlighted that on haemorrhagic stroke statins have less beneficial effects and that in general they do not prevent non-coronary cardiac death. Speaking about the absolute benefit of statins in major vascular event reduction, Prof. Baigent highlighted that higher is the LDL-C reduction more effective the statins are. In the second part of his lecture, the speaker presented very interesting data on statin safety and more in particular he spoke about the relationship between statins and the risk for diabetes. Prof. Baigent talked also about other issue on statin safety, more in particular on the relationship between statins and memory loss, cognitive impairment, cancer mortality and cataract. Finally, Prof. Baigent presented very interesting data on the main adverse events of statins related to muscle disorders, given by the ODYSSEY ALTERNATIVE and the ASCOT-LLA trials. In conclusion, the speaker pointed out that known hazards of statins are far outweighed by known benefits, even in low-risk patients.





- What are the main effects of statins on the major vascular events in low-risk people, based on the data presented by the speaker?
- What's about the effects of statins by age, based on the data presented by the speaker?
- Can observational data replace randomized trials, based on the data presented by the speaker?
- What are the main statin adverse events related to statins based on the ODYSSEY trial, based on the data presented by the speaker?
- What are the main characteristics of the CTT project, based on the data presented by the speaker?

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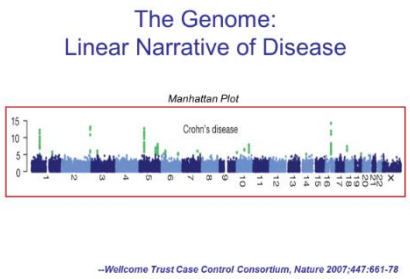
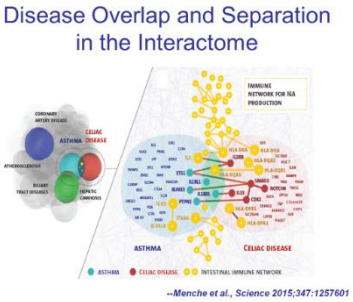
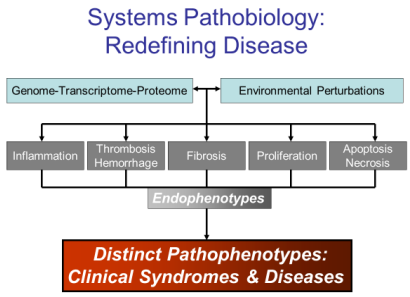
Endophenotype networks and atherothrombosis



Prof. Loscalzo from Boston (USA), spoke about Endophenotype networks and atherothrombosis. More in particular, the speaker talked about genomics and disease, network medicine and disease definition, endophenotype networks and disease and more in particular on the correlation between endophenotype and Atherothrombosis. Going deeper in his lecture, Prof. Loscalzo presented very interesting data on the importance of the genomic context for a better definition and management of disease. More in particular the speaker talked about the differences between essential vs disease genes and highlighted that the disease genes are largely nonessential and do not encode hubs. Prof. Loscalzo, presented also other very interesting data on the genome-proteome relationship, where genome implies phenotypes, but proteome is phenotype. In the second part of his lecture, the speaker talked about the disease modules taking part of the interactome and about the different disease overlap and separation present in the interactome.



Finally, Prof. Loscalzo presented very interesting data on inflammation as a common endophenotype and talked about a model of system pathobiology, applied in the diseases redefinition, with the genome-transcriptome-proteome and the environmental perturbations at the basis of the model, that influence the endophenotypes characterized by inflammation, thrombosis and others. The endophenotypes are the determinant of distinct pathophenotypes characterized by the clinical syndromes and diseases.



- Do diseases genes cluster in discrete modules in the interactome, based on the data presented by the speaker?
- What's about the importance of the genomic context, based on the data presented by the speaker?
- Can molecular networks give unique insight into disease pathogenesis and therapy, from the speaker point of view?
- What's about the relationship between essential vs disease genes, based on the data presented by the speaker?
- What are the key points of the genome-proteome relationship, based on the data presented by the speaker?

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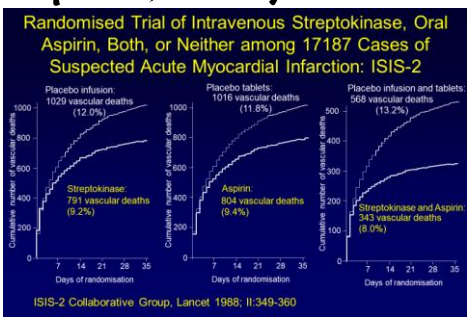
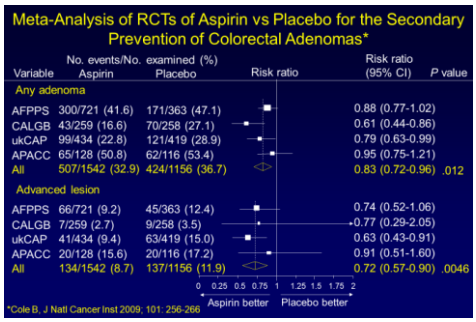
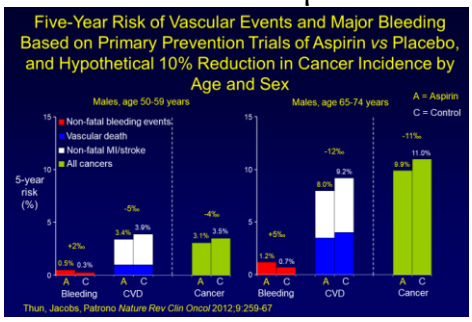
Aspirin, 120 years later



Prof. Patrono from Rome (IT), presented very interesting data on Aspirin, 120 years later. More in particular the speaker talked about the main data of the randomized trials running in patients treated with low-dose aspirin and about the results of the meta-analyses of the aspirin trials in high-risk patients. Going deeper in his lecture, Prof. Patrono presented very interesting data on the altered pharmacodynamics of low-dose aspirin in type 2 diabetes compared to healthy people. In the main part of his lecture, the speaker talked about the ADAPTABLE trial comparing low-dose to regular-dose aspirin in preventing heart attacks in heart disease patients and presented very interesting data on the determinants of the rate of recovery od platelet COX-1 patients treated with low-dose aspirin. In the second part of his lecture, Prof. Patrono talked about a chemopreventive effect of aspirin against gastrointestinal cancers, like gastric and colorectal cancer and presented very interesting data given by observational, RC trials and meta-analyses where the beneficial effect of aspirin is remarkable. The speaker presented also other data given by a clinical study running in patients undergoing CRC screening, by highlighting that low-dose aspirin is able to reduce the rectal mucosal PGE2 production. Finally, the speaker presented very interesting data given by a meta-analysis on the cancer incidence of low-dose aspirin in primary prevention of vascular events. In conclusion, Prof. Patrono pointed out that for the first time the US preventive services task force recommendation statements, stated that in adults aged 50 to 59 years, the use of low-dose aspirin is recommended for the primary prevention of cardiovascular disease and colorectal cancer.





- What are the main determinants of the rate of recovery pf platelet COX-1 in patients treated with low-dose aspirin, based on the data presented by the speaker?
- What' s about the sources of evidence supporting a chemopreventive effect of aspirin against gastrointestinal cancers, based on the data presented by the speaker?
- What are the main features of the chemopreventive effect of aspirin against colorectal cancer, based on the data presented by the speaker?
- What are the potential cellular targets of low-dose aspirin, based on the data presented by the speaker?

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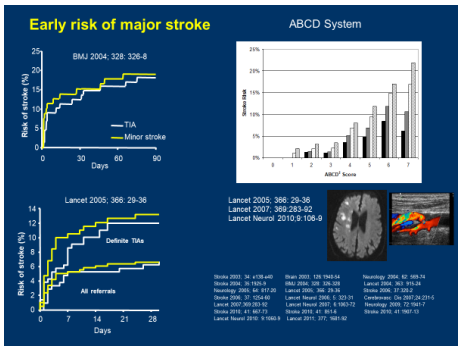
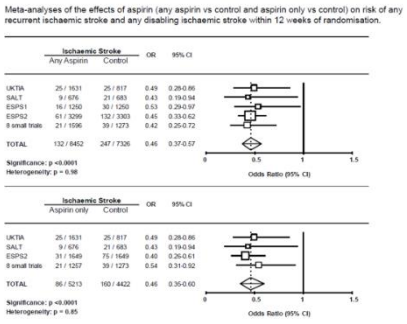
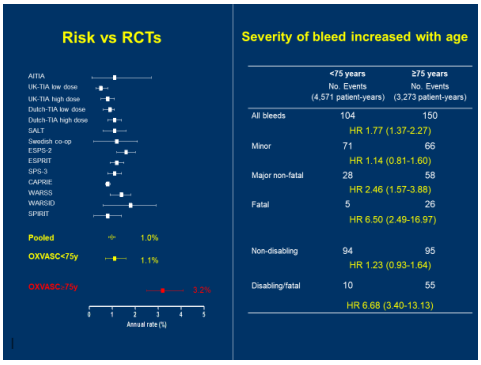
Early vs late mechanisms of stroke progression and recurrence



Early vs late mechanisms of stroke progression and recurrence was the topic of Prof. Rothwell presentation. The speaker, coming from Oxford (UK), presented very interesting data starting from the 20-years of fatal colorectal cancer on long-term follow-up of aspirin vs control. Going deeper in his lecture, Prof. Rothwell talked about the effect of aspirin on MI and ischaemic stroke incidence and presented very interesting data given by many clinical trials running in high risk patients. In the main part of his lecture, the speaker talked about the recurrent risk of stroke after TIA and presented very interesting data given by the OXVASC and the EXPRESS studies. Prof. Rothwell talked about the aspirin effects in low and major acute ischaemic stroke patients and highlighted that aspirin is very effective in stroke prevention. In the second part of his lecture, the speaker presented very interesting data on the main harms linked to the aspirin use like the haemorrhagic stroke and the GI bleeding and highlighted that in the first case the optimum BP control may minimize the excess strokes caused by aspirin. In conclusion, Prof. Rothwell pointed out that the main effect of aspirin on bleeding is characterized by the increase of severity than the incidence of bleeding per se and that probably aspirin present a neuroprotective effect possibly due to prostaglandin-mediated effects on the microvasculature that can explain its effect in the reduction of the disabling stroke.





- Why does aspirin stop working, based on the data presented by the speaker?
- What are the major harms of the aspirin use, based on the data presented by the speaker?
- What is the effect of aspirin in major acute ischaemic stroke, based on the data presented by the speaker?
- What is the effect of aspirin after TIA or minor ischaemic stroke, based on the data presented by the speaker?
- What are the main results of the EXPRESS study presented by the speaker?

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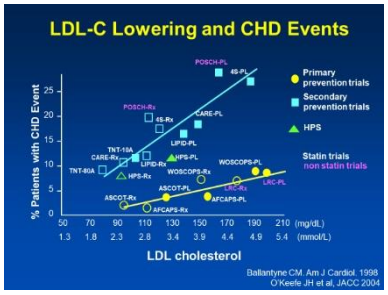
Clinical trials with novel lipid targets in coronary heart disease

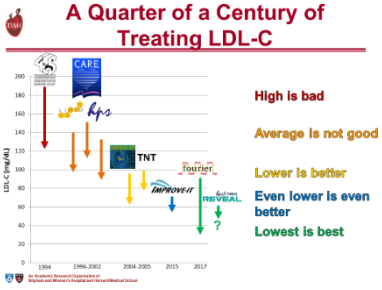


The main topic of Prof. Giugliano presentation was Clinical trials with novel lipid targets in coronary heart disease. The speaker, coming from Boston (USA), presented very interesting data on the novel lipid targets reached in recent clinical outcome trials. Going deeper in his lecture, Prof. Giugliano talked about the IMPROVE-IT study and presented very interesting data starting from the study rationale and methods, by highlighting that the association between ezetimibe and simvastatin reduced the LDL-C of about 69.5 to 53.7 mg/dl compared to simvastatin alone and MI, stroke and ischaemic stroke better than simvastatin alone. Talking about PCSK9 inhibitors, Prof. Giuliano presented very interesting data, starting from their typical mutations leading to the gain or the loss of function. More in particular the speaker presented the main data given by the clinical studies running on hypercolesterolemic patients on the effects of these monoclonal agents and highlighted that in stable patients affected by CHD, the gain in reduction of major events was highly significative. In the second part of his lecture, Prof. Giugliano presented very interesting data given by clinical studies running in patients treated with PCSK9 inhibitors on the spatial working memory, by highlighting that the drugs and the very high LDL-C reduction did not interfere with the patients' cognitive assessment. The speaker talked also about new durable molecules aiming to inhibit the PCSK9 synthesis. By highlighting that these new drugs are already tested in phase I studies. Finally, Prof. Giugliano presented very interesting data on the CEPT inhibitors studies running in patients already affected by CVD. In conclusion, the speaker pointed out that the optimum LDL level for human can be about 25 mg/dl, sufficient for nourishing body cells with cholesterol.

Types of CV Outcomes — fourier

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	12.6	14.6	0.85 (0.79-0.92)
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88)
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
MI	4.4	6.3	0.73 (0.65-0.82)
Stroke	2.2	2.6	0.79 (0.66-0.95)
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86)
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	4.8	4.3	1.04 (0.91-1.19)

Sabatine MS et al. *NEJM* 2017; 376:1713-1722



- What are the main results of the IMPROVE-IT study, based on the data presented by the speaker?
- What's about the mechanism of action of the monoclonal antibodies able to inhibit the mutated PCSK9, based on the data presented by the speaker?
- What's about the effect of Evolocumab on the coronary artery plaque volume, based on the data presented by the speaker?
- What's about the spatial working memory strategy index after 20 months of evolocumab treatment?
- What is the main mechanism of action of the CEPT inhibitors, based on the data presented by the speaker?

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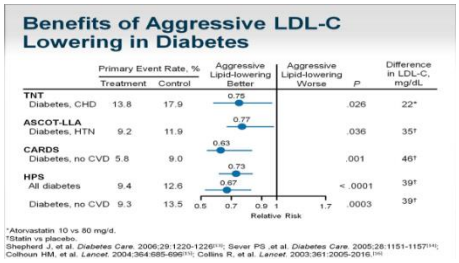
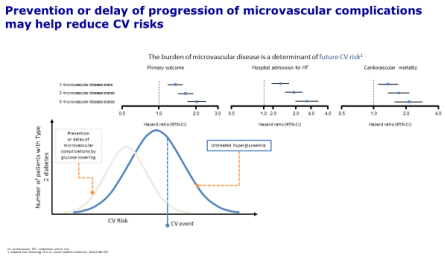
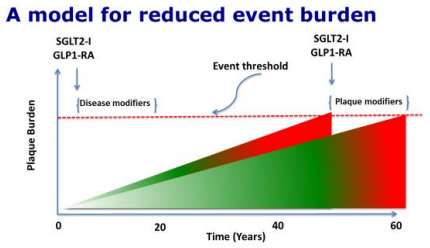
Is glucose still a valuable target in diabetic vascular disease?



Prof. Avogaro from Padua (IT), spoke about "Is glucose still a valuable target in diabetic vascular disease?" and presented very interesting data on the rate of death and hospitalization for CVD in diabetic patients. Going deeper in his lecture, Prof. Avogaro talked about the main lipid trials running in diabetics and highlighted that lowering cholesterol and decreasing BP have a more beneficial effects on outcomes in these patients than those obtained with the Hb!Ac reduction. In the main part of his lecture, the speaker presented very interesting data on the CVD and on the microangiopathy prevalence in diabetic patients, by highlighting that the presence of microangiopathy is one of the worse symptoms leading to major vascular complications. Prof. Avogaro presented also other very interesting data on the DPP-4 inhibitors given by the major CV outcome studies running in patients treated with these drugs and on the GLP-1 RA CV outcome trials. Finally, Prof. Avogaro presented other very interesting data given by clinical studies running in diabetic patients treated with SGLT2 inhibitors, by highlighting that these drugs induce a quite consistent in body weight, a reduction in BP and more in particular they dramatically reduce the CVD incidence. In conclusion, Prof. Avogaro pointed out that the new antidiabetic drugs are able to increase the time free of events for the diabetic patients.





- Why normalization of glucose should be a priority in the clinical practice, based on the data presented by the speaker?
- What are the main results of the Look-AHEAD study, based on the data presented by the speaker?
- What's about the major DPP4-inhibitors CV outcome studies, based on the data presented by the speaker?
- What are the main results of the GLP-1 RA CV outcome trials presented by the speaker?

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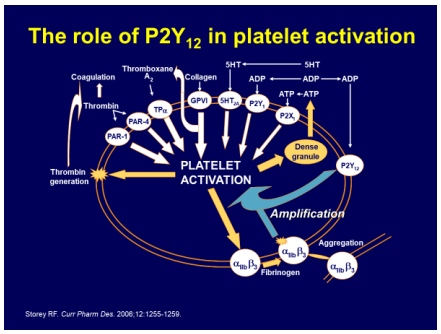
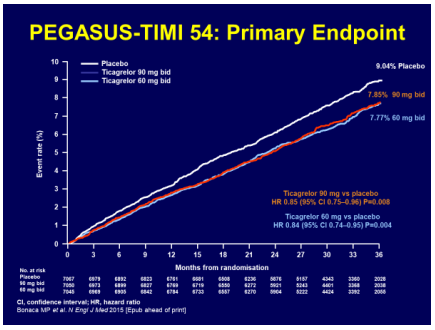
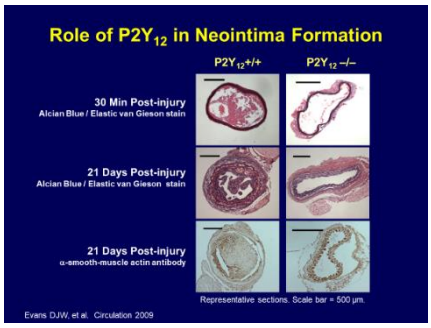
Antiplatelet therapy targeting the platelet P2Y12 receptor



Antiplatelet therapy targeting the platelet $P2Y_{12}$ receptor, was the topic discussed by Prof. Storey from Sheffield (UK). More in particular the speaker presented very interesting data starting from the explanation of the role played by the $P2Y_{12}$ receptors in amplifying the platelet activation. Going deeper in his lecture, Prof. Storey talked about very interesting experiments running in $P2Y_{12}$ positive and negative mice on the mean thrombus area and highlighted that in the $P2Y_{12}$ negative mice the mean thrombus area was significantly lower than the one of the $P2Y_{12}$ positive mice. In the main part of his lecture, the speaker presented very interesting data on the main mechanisms of platelet activation and inhibition given by the major clinical trials like the CURE study running in patients undergoing PCI and treated with clopidogrel. Prof. Storey discussed also the results of the PLATO study running in patients undergoing PCI and aimed to compare ticagrelor vs clopidogrel both in association with aspirin. In the second part of his lecture, Prof. Storey spoke about the GLOBAL LEADERS study aimed to compare the effectiveness of 1 month of ticagrelor plus aspirin followed by ticagrelor alone vs a current-day intensive dual antiplatelet therapy (DAPT) in 16000 patients undergoing PCI and presented very interesting data on the Sheffield observational study running on more than 10.000 consecutive invasively-managed ACS patients. The speaker talked also about cangrelor and presented very interesting data on its pharmacodynamics and clinical effects. Finally, Prof. Storey presented very interesting data on the PEGASUS-TIMI 54 study running in stable patients with prior MI in the last three years and spoke about the correlation between platelets and inflammation and about the effects of the $P2Y_{12}$ inhibitors on the fibrin colt density that has been increased by inflammation.





- What is the main PLATO primary end-point, based on the data presented by the speaker?
- What's about the PEGASUS-TIMI trial design, based on the data presented by the speaker?
- What are the main results of the PEGASUS-TIMI study, based on the data presented by the speaker?
- What is the relationship between platelets and inflammation, based on the data presented by the speaker?
- Do the P2Y12 inhibitors have any effect on an early atherogenesis muse model, based on the data presented by the speaker?

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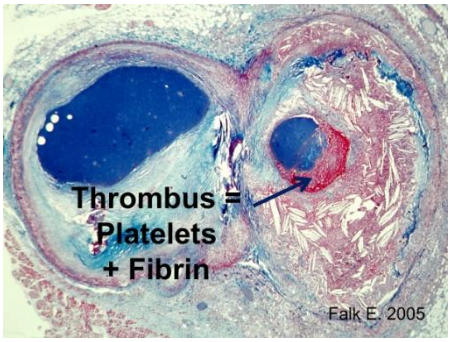
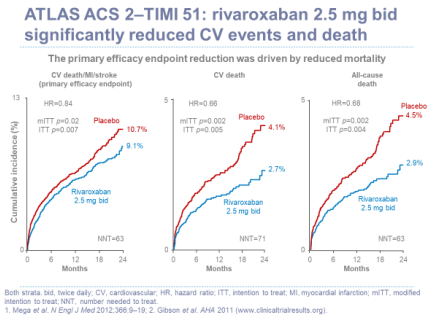
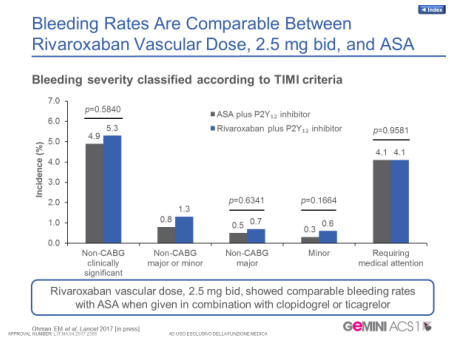
Anticoagulants in atherothrombosis



Prof. De Caterina from Chieti (IT), spoke about Anticoagulants in atherothrombosis. More in particular, the speaker talked about anticoagulants in patients at high risk of atherothrombosis secondary to atrial fibrillation or venous thromboembolism and in atherothrombosis per se. Going deeper in his lecture, Prof. De Caterina presented very interesting data on the anticoagulants rationale and implementation in atherothrombosis. More in particular the speaker talked about two examples of the thrombus formation characterized by the concomitant presence of platelets and fibrin and about the need for tackling both platelets and coagulation with the aim to prevent the thrombus formation. In the main part of his lecture, Prof. De Caterina presented very interesting data on the use of anticoagulants in the acute phase and in the long-term setting, given by the main clinical studies running in patients under anticoagulant therapy, like the WARIS-II trial, where the use of Vit. K antagonists was affected by a huge amount of bleeding. In the second part of his lecture, Prof. De Caterina presented very interesting data on the possibility to reintroduce anticoagulants in this scenario and highlighted the new role played by rivaroxaban. Speaking about the studies running in patients treated with rivaroxaban, Prof. De Caterina highlighted that despite the very interesting results on CV mortality reduction, there was a significantly increase in fatal bleeding and fatal ICH. More in particular the speaker presented very interesting data given by the ATLAS ACS 2-TIMI 51 study, the GEMINI ACS 1 study and by the COMPASS study. In conclusion, Prof. De Caterina pointed out that a NOAC, in small doses, may either replace aspirin or be added on top of aspirin for providing important long-term beneficial effects in atherothrombosis, striking the best balance between efficacy and safety.





- What are the main difficulties in accepting the triple therapy, based on the data presented by the speaker?
- Can we use rivaroxaban dropping aspirin in ACS patients, based on the data presented by the speaker?
- What are the main results of the GEMINI ACS results presented by the speaker?
- What's about the COMPASS study design, based on the data presented by the speaker?

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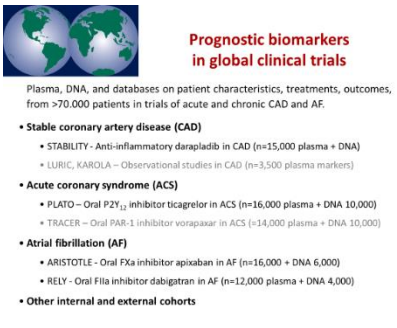
Biomarker analyses of large randomized clinical trials: what have they taught us



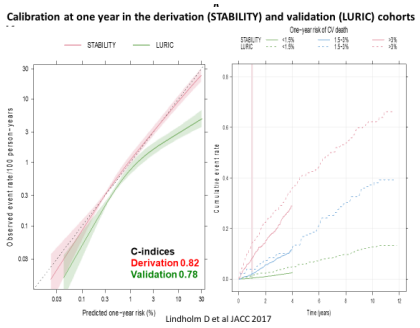
Biomarker analyses of large randomized clinical trials: what have they taught us, was the topic discussed by Prof. Wallentin from Uppsala (SWE), more in particular the speaker talked about the prognostic biomarkers in global clinical trials and about the prognostication risk stratification decision support in CAD and AF patients. Going deeper in his lecture, Prof. Wallentin presented very interesting data given by the stability trial running in patients affected by CHD and treated with darapladib or placebo and aimed to detect the incidence of CV death, MI and stroke after a median follow-up of 3.7 years. The speaker talked about the data of the main established biomarkers tested in this study and about their association with the events developed during the study follow-up. In the main part of his lecture, Prof. Wallentin talked about the development of a biomarker based risk score and presented very interesting data on the importance of some variables included for the CV death prediction, like NT-proBNP, Troponin T, Prev PAD. LDL, GDF-15, age and diabetes. The speaker discussed also the methods applied for the calibration at one year and for the validation. In the second part of his lecture, Prof. Wallentin presented a huge amount of data given by a statistical study on the biomarker based risk score applied for the detection of the risk for ischaemic events, bleeding and mortality in patients treated with different treatment strategies. In conclusion, the speaker pointed out that the most important biomarkers for the identification of increased risk of coronary events in stable CAD patients, were those ones associated with cardiovascular dysfunction and inflammation.

Objectives

To investigate which or which combinations of established biomarkers are associated with specific outcomes in patients with stable coronary heart disease.

Established biomarkers:

- Troponin-T (cTnT-hs), NT-proBNP (Roche)
- GDF-15 and cystatin-C ELISA (Roche)
- IL-6 by ELISA (R&D Systems)
- CRP-hs by immunonephelometry (*CardioPhase*© Siemens)
- Lp-PLA_2 activity (PLAC® Test diaDexus).



Lindholm D et al JACC 2017

- What are the most important biomarkers for the identification of coronary events in CAD patients, based on the data presented by the speaker?
- What are the main characteristics of the patients included in the study, based on the data presented by the speaker?
- What's about the importance of the variables included for the prediction of CV death, based on the data presented by the speaker?
- What is the methodology applied by the speaker for the development of the biomarker based risk score?
- What are the objectives of the study presented by the speaker based on the data obtained from the STABILITY study, based on the data presented by the speaker

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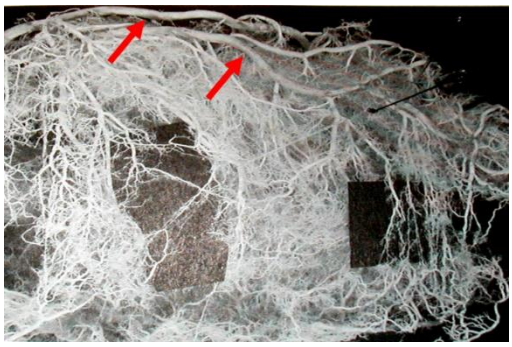
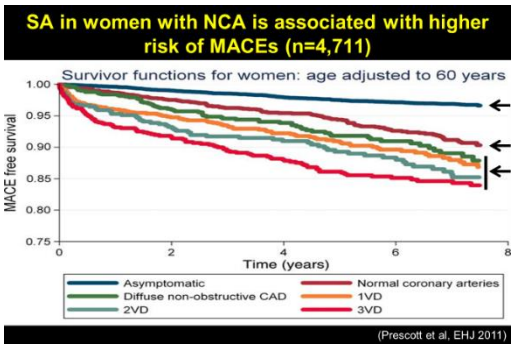
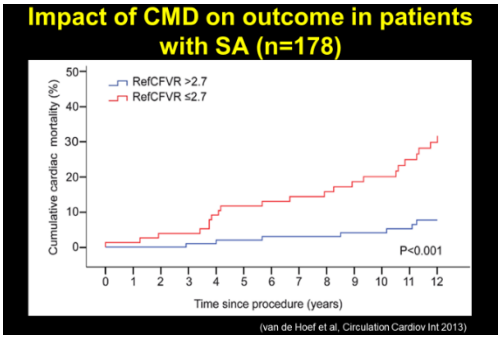
Ischemic heart disease without atherothrombosis



Prof. Crea from Rome (IT), presented very interesting data on Ischemic heart disease without atherothrombosis. Going deeper in his lecture, the speaker talked about the coronary microvascular dysfunction, more in particular about the form characterized by the absence of myocardial disease and obstructive CAD and presented very interesting data on the so called "X Syndrome", that actually is addressed as microvascular angina (MVA), by highlighting the cardiac and ischemic nature of this disease. Prof. Crea presented very interesting data on the incidence of disease, on outcomes and on the pathophysiology and highlighted that this disease is deeply associated with bad outcomes. In the second part of his lecture, Prof. Crea talked about MINOCA, that is the myocardial infarction without obstruction at the coronary artery level. Speaking about patients with coronary microvascular dysfunction linked with myocardial diseases like the HF and presented very interesting data on HF with preserved EF, on the main pathophysiologic mechanisms and on the main risk factors of MVA and HFpEF. Talking about the relationship between microvascular dysfunction and CAD, the speaker highlighted that these two forms are strictly linked one to the other. Finally, the speaker presented very interesting data on the main mechanisms of the cardiac microvascular obstruction and about therapy, by highlighting that till now there is no treatment for these patients. In conclusion, Prof. Crea pointed out that CMD plays a key role in microvascular angina, in HFpEF, in stable CAD and in ACS but without any tailored treatment developed till now.





- Is the X Syndrome a cardiac disease, based on the data presented by the speaker?
- What's about the incidence of microvascular angina, based on the data presented by the speaker?
- What are the outcomes of patients affected by microvascular angina, based on the data presented by the speaker?
- What are the main pathophysiology findings of the MVA, based on the data presented by the speaker?
- What's about the treatment of MVA patients, based on the data presented by the speaker?
- What's about the pathophysiological mechanism of HF with preserved EF, based on the data presented by the speaker?

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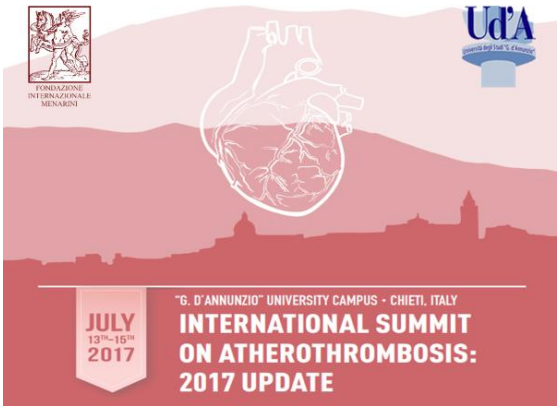

For a deeper knowledge on these topics, please visit the International Menarini Foundation web site where You can find all the speeches in their full version.

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