model, in T2D with ischemic stroke in comparison to T2D patients without stroke. The lower insulin sensitivity, i.e. the increased IR, in the T2D patients was accompanied with increases in traditional risk factors, especially LDL-cholesterol levels, and the decreases in glutathion-dependent antioxidant enzyme activity. Those differences in metabolic risk factors could not be demonstrated among the subtypes of ischemic stroke in the T2D patients.

Although IR has been shown to play an important role in a range of neurodegenerative disorders (Huntington and Alzheimere disease, spinocerebelar ataxia), the accompanying pattern of metabolic changes is reported to be different. The differences are most prominent in the changes in lipid metabolism and in addition the IR in neurodegenerative diseases is shown to be accompanied with the decrease in insulin secretion even in nondiabetic subjects, which could not be demonstrated in cerebrovascular disorders in nonidiabetics.

Due to the fact that both neurogenic and cerebrovascular components might contribute to cognitive dysfunction, which is reported to be frequent in diabetic patients, and with respect to the recent findings that insulin administration might improve cognitive function, the importance of the previously reported metabolic determinants for the development of cognitive dysfunction in T2D still remains to be clarified.

ISP23: Aspirin efficacy in diabetes

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Diabetes is a major risk factor of cardiovascular morbidity and mortality. In such a pathology associated with a high incidence of cardiovascular events it should be easy to show the efficacy of an efficient therapy. But at the opposite every individual prospective and retrospective study (older studies as well as the most recent ones) evaluating the efficacy of aspirin failed to report a benefit in diabetic patients in cardiovascular disease. Several recent meta-analyses confirm and amplify the observation that diabetic patients don’t significantly benefit of an aspirin treatment in primary as well as in secondary prevention. The « AntiPlatelet Triallist’ Collaboration meta-analysis » showed in secondary prevention a limited relative benefit of an antiplatelet treatment (lower that what is observed in non diabetic patients) which is non significant when selecting the trials studying only aspirin as antiplatelet therapy. As a consequence diabetic patients can be considered resistant to the anti-thrombo-ischemic effects of aspirin. We were one of the first to demonstrate that among the causes of resistance to aspirin diabetic patients are characterized by a higher platelet turn over which explains the progressive loss of antiplatelet effect of aspirin after a delay dosing with a recovery of subnormal platelet functions before the next dosing in 20 to 30 % of diabetic patients. Several major groups have achieved consistent observations. The accelerated turn over of platelets in diabetic patients has several explanations. The possibilities to counteract this resistance are the improvement of the metabolic equilibrium of diabetics, the twice a day administration of aspirin or the switch to another antiplatelet agent. Among the other antiplatelet agents tested the first one was clopidogrel : even if the diabetics get a better clinical benefit with clopidogrel compared to aspirin (tested only in secondary prevention) the reduction of cardiovascular events is much less in diabetic patients than in non diabetic. This relative resistance of diabetic patients to clopidogrel is only partially explained by the accelerated platelet turn over but mostly explained differences in the metabolism of clopidogrel (a prodrug) in diabetic patients. Better understanding of the antiplatelet agents in diabetic patients should help to launch studies specifically designed for diabetic patients.

ISP24: New oral anticoagulants

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For more than 50 years vitamin K antagonists (VKAs) were the only orally available drugs for the prevention of thromboembolism in patients with atrial fibrillation (AF). Recently, a direct thrombin inhibitor (dabigatran) and two factor Xa inhibitors (apixaban and rivaroxaban) were approved for the same indication. New drugs have unique safety and efficacy profiles and they are expected to completely alter AF management. The new oral anticoagulants (OACs) differ significantly offering the clinician the chance to tailor anticoagulation to individual patient’s needs. Diabetic patients are a population of particular concern. Diabetic patients with AF are by definition at moderate-high risk for thromboembolism and should be treated with OAC. Patients with diabetes were adequately represented in landmark clinical trials that assessed safety and efficacy of new OACs. In the subgroup analyses, new OACs seemed to be at least as safe and effective as warfarin in diabetic patients.

Nevertheless, new OACs need to be handled with caution. Health care systems should emphasize on the implementations of the directions derived from their clinical trials. Physicians that handle these drugs should be aware of their limitations and contraindications. Moreover, new OACs might not require monitoring of their anticoagulation effects but the patient requires regular follow-up and reassessment of his thromboembolic and haemorrhagic risk. From that perspective new OACs should be ideally handled by specialized physicians preferably in the same organized infrastructures that handled VKAs. Organized anticoagulation clinics would provide guidance on who to treat and how intensively to treat and also provide immediate solutions in cases that anticoagulation should be ceased or even reversed. There are also instances where quantifying the anticoagulant effect may be important. The new drugs will be efficient, safe and cost-effective only if they are appropriately used.

ISP25: Early left ventricular dysfunction in diabetes

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T2DM is cause of CV complications, atherosclerosis, heart failure and death. DYDA is a prospective, multicenter epidemiological study in 960 T2DM patients, aged >45 years and without overt cardiac diseases. Baseline echocardiographic examination revealed a high prevalence of preclinical LV systolic (21%) and diastolic dysfunction (27%) or both (12%) (LVD), measured by midwall shortening (MFS) and transmitral flow pattern, respectively, as previously reported. Patients were followed-up for 2 years. In the present abstract, we report data on echocardiographic re-evaluation and clinical events. Systolic LVD (SLVD) was defined as EF <50% or MFS <15%; diastolic LVD (DLVD) was identified in all conditions different from “normal”, defined as transmitral E/A ratio between 0.75 and 1.5 and E velocity deceleration time >140 msc. The primary outcome was a composite of major events (all-cause death and hospital admissions). Secondary end-point was the incidence of new LVD.

Follow-up data were available on 957 patients. During the follow-up 15 deaths (1.6%, 3 CV death, 11 non CV death, 1 of unknown etiology) and 181 hospital admissions were observed in 139 patients (48 for CV cause, 133 for non CV cause). In multivariate analyse, older age (67 vs 56 yrs OR 1.4195%CI 1.05-1.88), high LDL (134 vs 93 mg/dL OR 1.39, CI 1.08-1.78), low HDL (57 vs 42.5 mg/dL OR 0.76, CI 0.60-0.98), high HbA1c (7.6 vs 6.0% OR 1.3, CI 1.05-1.62), peripheral arterial disease (OR 3.49, CI 1.54-7.9) and treatment with
repaglinide (OR 2.01, CI 1.17-3.46) were independently associated with a major event. LVD was observed at baseline or during follow-up in 88.1% (616/699) of patients; a systolic LVD in 63.9% (338/529), and a diastolic LVD in 66.5% (463/696). In a multivariate analysis, older age (67 vs 56 yrs OR 2.45, 95% CI: 1.86-3.23), high HbA1c (7.6 vs 6.0% OR 1.25, 95% CI:1.01-1.54), high heart rate (80 vs 68 bpm OR 1.23, 95% CI: 1.03-1.47) and high DBP (90 vs 78 mmHg OR 2.29, 95% CI: 1.41-3.72) were independently associated with DLVD; whereas SLVD was associated only with waist circumference (106 vs 92 cm OR 1.39, 95%CI:1.05-1.84). New onset of systolic LVD (either EF <50% or MFS <15%) was observed in 66/388 pts (17.0%) and that of diastolic LVD in 126/572 pts (22.0%).

In is concluded that in patients with DM without overt cardiac disease at baseline, LVD is a frequent finding, and is associated with older age, higher HbA1c, heart rate, diastolic BP and waist. In these patients, all-cause death or hospitalization occurred in nearly 16% of the cases at mid-term follow-up, being the great majority of them of non-CV reason. Independent predictors of such adverse clinical events were older age, pathologic lipid profile, poor control of DM, peripheral arteriopathy and repaglinide therapy.

ISP26: How molecular imaging may guide personalized cardiovascular risk assessment and care?

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Molecular imaging (MI) relates to the visualization and noninvasive quantification of biological processes at the molecular and cellular levels in humans and other living systems [Sinusas A. et al., Circ Cardiovasc Imaging 2008]. Initially confined to preclinical research, recent advances and spreading of cardiovascular MI, particularly positron emission tomography (PET), have allowed its utilization in clinical settings. Simultaneously, there has been a progressive emphasis on primary prevention of cardiovascular diseases, which requires early detection and accurate risk stratification. To be achieved, this goal necessitates to combine risk factors derived from large-scale epidemiological studies, aimed at identifying a group of patients at increased risk among the general population, with individualized phenotypes derived from biological alterations, in order to refine risk assessment within a group at increased risk. Consequently, the application of molecular imaging is expected to provide additional unique pathophysiological insight that will allow a more personalized approach to evaluation and management of cardiovascular disease.

It is now well acknowledged that patients with coronary narrowing due to atherosclerosis will not necessarily benefit from revascularization [Shaw LJ. et al., Circulation 2008], because the relationship between the degree of coronary stenosis (particularly when graded intermediate) and downstream myocardial perfusion is weak [Naya M. et al., J Am Coll Cardiol 2011]. To this regard, coronary flow reserve measured noninvasively by cardiac PET is a powerful predictor of cardiac mortality, and allows to refine risk assessment over and independently from major risk factors, probably because it integrates fluid dynamic effects of both epicardial atherosclerosis and microcirculation [Di Carli MF. et al., Circulation 2011]. Assessment of myocardial blood flow at rest and during vasomotor stress provides insight into early and subclinical alterations of microvascular function, and as such may be useful to monitor therapy in low or intermediate-risk patients [Schindler TH. et al., JACC Cardiovasc Imaging 2010].

A similar approach may apply for plaque inflammation. Inflammation is a determinant of atherosclerotic plaque rupture. This related increase of metabolic activity is detectable by 18fluorodeoxyglucose (FDG) PET [Tawakol A. et al., J Am Coll Cardiol 2006], and radiotracer uptake quantification was shown to be reproducible [Rudd JH. et al., J Nucl Med 2008], thus allowing to monitor the response to drug therapy [Tahara N. et al., J Am Coll Cardiol 2006]. Alternatively, FDG PET has been used as imaging biomarker to assess specific adverse effects suspected of being related to a drug interacting with cholesterol metabolism (CETP safety monitoring). [Fayad ZA. et al., Lancet 2011]

Main limitations of using MI in personalized risk assessment or therapy/safety monitoring are cost (relatively to cost savings), availability, and potential adverse effects related to ionizing radiations hazard. The target population most likely to benefit from such an approach remains to be determined by clinical trials that are already under way.

ISP27: Omega 3 PUFA chain length: a key factor of their efficiency on cardiovascular risk factors in experimental metabolic syndrome

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Background and aims: The impact of dietary n-3 polyunsaturated fatty acids (PUFA), on cardiometabolic risk prevention was evaluated according to chain length, in two rat models of non-obese insulin resistance and hypertension.

Materials and Methods: Fructose-fed rat was used as a model of acquired metabolic syndrome (MS) and spontaneously hypertensive rat (SHR) rat as a model of inherited MS. Rats were submitted to a diet containing either no n-3 PUFA (control) or γ-linolenic acid (ALA) as single n-3 PUFA source or a mix of ALA and its two main longer chain metabolites (LC), eicosapentaenoic and docosahexaenoic acids. During the dietary period, glucose and insulin tolerance tests were performed and serum triglycerides concentration was quantified. Arterial blood pressure was evaluated punctually by tail-cuff or continuously by implanted telemetry. After 10 weeks of feeding, the fatty acid (FA) composition of insulin-sensitive tissues was analysed.

Results: The two experimental models developed insulin resistance and hypertension, associated to an alteration of the specific FA pattern in insulin sensitive tissues. Insulin resistance was also associated to a high cardiovascular risk as evaluated by the increase in blood pressure parameters and especially by the increase in pulse pressure in the fructose-fed rats. LC n-3 PUFA significantly affected the development of insulin resistance, impaired glucose tolerance, blood pressure rise and hypertriglyceridemia, in relation with a strong limitation of the FA composition in the insulin sensitive tissue phospholipids. Conversely, ALA alone affected only hypertriglyceridemia.

Conclusion: Whatever the etiology of insulin resistance, the significant beneficial effects of n-3 PUFA on the prevention of cardiometabolic risk factors can be attributed to the long chain n-3 PUFA but not to the precursor.

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