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ABSTRACT BOOK

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**Results:** 1077 consecutive STEMI patients aged >75 years were included. Of those, 798 received PPCI, 59.4% were men, 34.5% diabetic, 74.5% hypertensive, 10.9% smoked, 14.1% had previous history of chronic kidney disease, 9.7% of stroke and 15% of myocardial infarction. On admission 15.1% had a Killip III-IV. PS matching yielded a sample size of 169 patients with and without PPCI, and 173 with and without PPCI/EPCI. Receiving PPCI was associated with a reduced endpoint risk during hospitalization [odds ratio (OR) = 0.55 (95% Confidence interval (CI) = 0.34–0.89)]. In addition, receiving PPCI/EPCI also reduced endpoint risk although to a lesser extent (OR = 0.61 (95% CI = 0.39–0.95).

**Conclusions:** Both PPCI and EPCI improved in-hospital prognosis in elderly patients with STEMI. If this benefit is confirmed, clinical guidelines should take it into account.

## W3-O8 | Platelets from diabetic patients show a distinct signature in chaperone proteins: implications in platelet aggregation and thrombosis

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**Background:** Diabetic patients show increased risk of atherothrombosis. Chronic hyperglycemia and/or insulin resistance leads to increased oxidative stress affecting cellular function. The molecular understanding of the platelet pathophysiological changes in diabetes may help in elucidating its prothrombotic effects.

**Purpose:** To investigate the differential proteomic profile of platelets from diabetic patients and non-diabetic controls in order to identify novel protein signatures in diabetes.

**Methods:** The cytosolic proteome of platelets from 10 diabetic patients and 10 matched controls were analyzed by 2-DE followed by MALDI-TOF/TOF identification, and validated by western blot. Platelet aggregation and thrombus formation analyses were used to test the effect of identified proteins.

**Results:** Platelet proteomic analysis revealed significant differences between diabetics and controls in 15 proteins related to platelet aggregation, cell migration, and homeostasis. In the cytosol of platelets, diabetic patients showed higher levels of Heat shock cognate 71 kDa (HSPA8) and stress-induced protein 1 (STIP-1), and lower levels of Heat shock protein 90 (Hsp90), a complex of chaperones associated with platelet function and aggregation. Functional analyses in normal platelets revealed that neither HSP8 nor STIP-1 modulates platelet aggregation induced by ADP, but they decrease collagen-induced platelet aggregation. HSPA8 decreases clotting time by promoting blood coagulability through the extrinsic pathway, and inhibiting HSPA8 with apoptozole resulted in reduced platelet aggregation induced by both ADP and collagen. The Hsp90 inhibitor onalespib induced a decrease in platelet aggregation induced by ADP and collagen, and had no effects on blood coagulability. STIP1 tended to decrease clotting time by promoting blood coagulability through the intrinsic pathway, although in a non-significant manner.

**Conclusion:** Diabetic patients show increased HSPA8 and STIP-1, and decreased Hsp90 cytosolic levels in platelets. This alteration in the HSPA8/Hsp90/STIP1 complex seems to induce a haemostatic dysfunction and alterations in platelet aggregation associated with diabetes and its thrombotic complications.

## W3-O9 | A missense mutation in the Tbx5 transcription factor causes long QT syndrome

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**Background:** Tbx5 is a transcription factor that enhances the expression of the SCN5A gene which encodes the Nav1.5 channels responsible for the cardiac sodium current (INa). The Long QT syndrome type 3 (LQT3) is associated with gain-of-function SCN5A mutations that increase the sustained component of the INa (INaL). We identified a missense Tbx5 mutation (p.D111Y) in a LQT3 patient in whom no mutations in SCN5A were found. We tested whether p.D111Y Tbx5 could underlie the LQT3 of the patient by analyzing its functional consequences.

**Material and methods:** INa and INaL were recorded using the whole-cell patch-clamp in HL-1 cells transfected with human native (WT) and mutated Tbx5 as well as in ventricular myocytes from cardiac–specific transgenic-like mice created on the basis of adeno-associated virus gene transfer.

**Results:** Overexpression of WT and p.D111Y Tbx5 in HL-1 cells significantly increased the peak INa density from $-52.6 \pm 5.5$ to $-78.7 \pm 11.3$ and $-71.0 \pm 11.0$ pA/pF, respectively ($n \geq 15$), leaving unaffected the time- and voltage-dependent properties of the current. p.D111Y

Tbx5, but not Tbx5 WT, significantly increased the INaL density from $-2.9 \pm 0.5$ to $-4.6 \pm 0.8$ pA/pF ($n \geq 15$). These results were completely reproduced in cardiomyocytes from mice overexpressing WT or p.D111Y Tbx5. Nav1.5 channels phosphorylation by βIV-spectrin–targeted calcium/calmodulin-dependent kinase II (CaMKII) increased the INaL and the QT duration. In luciferase-reporter assays we demonstrated that Tbx5 WT enhanced the expression of Nav1.5, while reduced that of CaMKII and βIV-spectrin, by binding to the promoters of the respective human encoding genes. Conversely, p.D111Y Tbx5 enhanced the expression of Nav1.5, CaMKII, and βIV-spectrin leading to an increased Nav1.5 phosphorylation.

**Conclusions:** These results demonstrate that p.D111Y Tbx5 fails to repress the expression of the genes encoding CaMKII and βIV-spectrin, effects that increase the INaL and can account for the QT prolongation. Thus, TBX5 could be a novel gene associated with the LQT3.

## W3-O10 | Increased vascular LDL permeability and retention as a triggering factor for accelerated atherosclerosis in a mouse model of progeria

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**Background:** Hutchinson-Gilford progeria syndrome (HGPS) is a very rare genetic disease triggered by progerin, a mutant form of an important nuclear protein called lamin A. The affected children undergo accelerated ageing with premature atherosclerotic disease and death from myocardial infarction or stroke in their teens. Since most HGPS patients have normal serum LDL, HDL and total cholesterol levels, it remains intriguing how progerin accelerates atherosclerosis.

**Material and methods:** In this study, we used two atherosclerosis-prone mouse models of HGPS: Apoe-/-LmnaG609G/G609G with ubiquitous progerin expression (like HGPS patients), and Apoe-/-LmnaLCS/LCSSM22αCre with vascular smooth muscle cell (VSMC)-specific progerin expression. For atherosclerosis burden evaluation, aortas were stained with Oil Red O. For histology studies, OCT-embedded aortic arch sections were stained with Masson's Trichrome. To assess changes in gene expression, RNA sequencing was performed in medial aortas. For LDL permeability and retention experiments, LDLs isolated from human blood were fluorescently labelled with Atto565 and injected intravenously to 16-week-old mice fed normal chow. Aorta was extracted 1 or 20 hours post-injection and fluorescent images of the whole mount tissue were acquired using a confocal microscope.

**Results:** Apoe-/-LmnaG609G/G609G and Apoe-/-LmnaLCS/LCSSM22αCre mice fed normal chow showed increased atherosclerosis burden in the thoracic aorta at 16 weeks of age. Aortas of both mutant models contained regions with VSMC loss and increased collagen content. Consistent with the histopathological studies, VSMC-containing medial aortas from Apoe-/-LmnaG609G/G609G and Apoe-/-LmnaLCS/LCSSM22αCre mice presented altered expression of numerous genes related to extracellular matrix. Remarkably, aortas of both progeria models showed increased endothelial permeability for LDL as well as augmented LDL retention in the aortic wall.

**Conclusions:** Progerin alters gene expression in VSMCs and causes their loss in the media, which results in changes in the extracellular matrix amount and composition. These alterations trigger increased vascular LDL permeability and retention leading to exaggerated atherosclerosis.

## W3-O11 | Canonical Wnt pathway activation is protective in the myocardium after infarction

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**Background:** LDL receptor-related protein 5 (LRP5) triggers the canonical Wnt pathway which participates in cell function regulation, including lipoprotein metabolism, macrophage mobility and phagocytosis. We have recently shown its protective function in the heart after MI. The aim of this study was to investigate whether canonical Wnt signaling pathway activators can induce myocardial repair after acute-myocardial infarction (MI).

**Materials and methods:** MI was induced in normocholesterolemic and hypercholesterolemic Wt and Lrp5-/- mice by coronary ligation in the presence and absence of Wnt pathway activators. Infarct size, LRP5 and Wnt signaling proteins were measured. LRP5 and the different metabolic pathways involved in myocardial damage post-MI were analyzed in isolated cardiomyocytes, myofibroblasts and endothelial cells.