

depressed in both atherosclerotic and aneurysmal lesions. Patients with dilated aorta and patients undergoing aneurysmal repair also have markedly decreased serum levels of cathepsin C. The role of cathepsin S in elastin degradation and atheroma formation was studied more directly using targeted disruption of the cathepsin S gene on the atherosclerosis-prone LDLr<sup>-/-</sup> background. Lack of cathepsin S markedly decreased atherosclerosis, as indicated by the plaque size. Cathepsin S-deficient mice showed better-preserved elastin in the tunica media after 12 (p<0.001) and 26 (p<0.02) weeks on a western diet. Because SMC migration from the tunica media to the intima requires proteolytic degradation of elastin, and cathepsin S-deficient SMC express much less elastolytic activity (p<0.0001), the compound mutant mice had fewer SMC and less collagen in the intimal lesions, probably due to the reduced SMC, the major source of collagen in arteries. We recently established endothelial cells as a novel source of cathepsins and showed that cathepsin S-deficiency impairs microvessel development in a wound-healing model. These findings may have implications for cancer therapy and atherosclerotic plaque progression and complication. Our findings *in situ*, *in vitro* and *in vivo* establish an important role for cathepsins in vascular remodeling.

**3WS18-6 Metalloproteinases (MMPs) can stabilise or destabilise atherosclerotic plaques**

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At least 14 MMPs, including collagenases (MMP-1,-8,-13,-14), gelatinases (MMP-2,-9), stromelysins (MMP-3,-7,-10,-11), metalloelastase (MMP-12) and membrane-type MMPs (MMP-14 to -17) have been described in vascular cells. Their expression is not co-ordinate but occurs in stages. Gelatinases are more readily induced and activated than other MMPs e.g. by stretch, cell-matrix contact, injury and oxidant stress. Gelatinases degrade smooth muscle cell (SMC) basement membranes and promote cell migration. Although involved in early proliferation other proteases are present in proliferating VSMC. Additional matrix-independent actions contribute.

Inflammatory mediators and CD40 ligation coordinately induce gelatinase, collagenases and stromelysins in SMC but selectively induce collagenases in macrophages. Induction is via several transcription factors, including AP-1 and NF- $\kappa$ B. There is also post-transcriptional regulation by a pathway sensitive to inhibition by statins. Conversion of macrophages to foam cells increases both collagenases and stromelysins in part by producing an autocrine foam-cell activator of collagenase expression (FACE). The basis of stromelysin expression is still unknown.

Hence, gelatinases participate in vascular repair, neointima formation and atherosclerotic plaque formation. The progressive activation of other MMPs by more extreme stimuli and may provoke matrix destruction and plaque rupture. Our results suggest that selective targeting of specific MMPs may be necessary to reduce plaque instability.

**3WS19 HEALTH ECONOMICS AND POLICY**

**3WS19-1 Lessons from international comparisons in the treatment, costs and outcomes of ageing related diseases related to atherosclerosis**

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Aggregate medical spending varies widely across countries. Large cross-national variations also exist in the frequency and mix of medical services provided, especially the type of technology applied. These differences should have an effect on health outcomes. However, studies to date have demonstrated less variation in outcomes than expected. This study has compared treatments, expenditures and outcomes for ischaemic disease and stroke, examining these differences in relation to the varying organisational structures and economic incentives. Experts from twenty industrialised countries have participated in the study. The population studied refers to the relevant patient groups for the population aged 40 and over. The study used large nationally representative administrative datasets of patients.

Striking differences exist in terms of the diffusion of technologies, which cannot be explained by the diffusion of medical knowledge. Economic factors play a significant role, including provider-payment incentives, and supply side regulations. Levels of resources employed in health care systems vary more according to supply incentives than to pure "demand" patterns. Epidemiological trends are shaped by economic factors, as some countries achieve lower mortality and improved outcomes mainly by using upstream population-based

approaches, whereas others experience an intensive use of curative high technologies.

Understanding cross-country variations in outcomes and performance is a complex issue. Outcomes of medical interventions, as measured in terms of case fatality or survival rates, are sensitive to treatment patterns, themselves influenced by medical and non-medical economic factors. The potential roles for other confounding factors (socio-economic status, residual case-mix) also need to be considered. Differences in expenditure per treatment were significant, and related to length of stay for some countries.

**3WS19-2 Control and prevention of CVD in Thailand: Current responses and future challenges**

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**Objective:** To analyze the CVD's situation in Thailand with respect to health policy and to develop suitable control intervention

**Method:** Literature review, researches conference and focus group discussion on progress of problem, effectiveness of existing intervention launched and synthesis of appropriate disease control programs

**Result:** Evidence indicates trend of increasing risks for atherosclerotic diseases notably diabetic, hypertension, hyperlipidemia and obesity. Only tobacco consumption had a decreasing trend. 12% of primary school children were overweight. Adult population diabetic and hypertension prevalence was 8% and 20.5%, but poor awareness and inadequate control. As a result, stroke and ischemic heart diseases rank 3 and 9 for men, and 2 and 10 for women of total Disable Adjusted Life Year (DALY) loss in 1998. Interventions for primary reduction of risks require a comprehensive strategy for population and at risk individuals to create awareness, early case detection and quality services to control risk factors through drug and non-drug interventions. Primary prevention should be focused, as effective secondary prevention requires massive resources. Program assessment indicates needs for intensive efforts on advocacy, inter-sectoral coordination and society empowerment. The government should ensure adequate resources, and create healthy environments. Social security scheme is seen as an entry point for programs among private employee. Primary care units could play a major role for effective clinical and community based interventions.

**Conclusion:** Suitable cost-effectiveness and integrated preventive interventions that based on dynamic information are required to handle the increasing complexity of CVD problems.

**3WS19-3 Treatment of cardiac patients in Canada: The effect of Canada's single-payer health care system on access to care and patient outcomes**

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**Objective:** Canada's single-payer universal health care system attempts to provide equitable access to all "medically necessary" services, according to medical need and not ability to pay.

**Methods:** We review published studies conducted to determine the extent to which Canada's health care system has achieved these goals.

**Results:** A number of studies show survival rates after an acute myocardial infarction (AMI) are similar in Canada and the US despite the fact that US patients receive 2 to 5-fold higher rates and quicker access to interventional procedures like cardiac catheterization, percutaneous coronary interventions (PCIs) and coronary artery bypass graft (CABG) surgery. On the other hand, there is evidence of underuse of CABG surgery in left main patients, inequitable access based on socioeconomic access, and underuse of secondary prevention medications.

**Conclusions:** Canadians have timely access to invasive cardiac procedures although evidence of underutilization exists. Opportunities for improving quality of cardiac care exist in Canada.

**3WS19-5 Macro and micro costing of atherosclerosis-related diseases in the Japanese health care system**

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**Objective:** To examine the structures of costs of health care at macro- and micro-levels in Japan, regarding atherosclerosis-related diseases.

WEDNESDAY