Tatu Miettinen 80 years Symposium: 
Cholesterol: From Metabolic Mechanisms to Clinical and Population Strategy
Helsinki, October 21, 2010

Program Description:
Y. Antero Kesäniemi, M.D., Ph.D., Petri Kovanen, M.D., Ph.D., Timo Strandberg, M.D., Ph.D, Matti Jauhiainen, Ph.D., Organizers

Tatu Miettinen 80 years symposium: Cholesterol: From Metabolic Mechanisms to Clinical and Population Strategy organized by his long-time friends and the Finnish Atherosclerosis Society took place in Helsinki, Finland October 21, 2010. This symposium honoured professor Tatu Miettinen’s magnificent life-long research achievements and celebrated his 80 year birthday. The program included DVD greeting from Tatu Miettinen’s friend professor Scott M. Grundy and a number of presentations on atherosclerosis, cholesterol metabolism and clinical and population strategies, by the Finnish investigators on the field. Sessions were devoted to public health, regulation of cholesterol metabolism, development of atherosclerotic plaque, cholesterol as a risk factor in childhood, adulthood and late age, ectopic fat, female cardiovascular risk and genetic studies on sudden cardiac death. The meeting went very well presenting the development of our understanding in cholesterol metabolism that laid the basis for the treatment of our patients and whole populations. Exciting new research was also presented. The results of ongoing clinical trials are eagerly waited to further understand the value of lowering LDL to very low levels and raising HDL for the prevention of cardiovascular diseases. The full program of oral presentations can be seen at slide page 1.

Speakers summaries:

Summaries of presentations and/or slides are included below where these were provided by the speakers.

Speaker: Jussi Huttunen M.D., Former Director General of the National Public Health Institute of Finland
Title of the presentation: Science, mentoring and public health

Abstract: A successful health policy always begins always with identification the problem. The next step is making the public, the decision-makers and the actors aware of the problem. This is followed by formulation and implementation the policy and the programmes contained in the policy. Finally, the success of policy is evaluated using a combination of process and outcome indicators and, based on the results of the evaluation, the necessary changes made in further implementation of the policy.
In the late 1950's the life expectancy of Finnish men was slightly over 60 years and that of Finnish women ca.70 years. International comparisons showed that the cardiovascular mortality was the highest in the world. After 50 years of active work the situation has drastically changed. Mortality from coronary heart disease has decreased about 80% both in men and in women aged 30-59 years.
The rapid decline of the coronary heart disease is due to several factors. Smoking has rapidly declined and a radical change has taken place in the dietary habits of the nation. Butter has been replaced with soft margarine, high-fat milk with low fat milk and the consumption vegetables has continually increased. All these changes are reflected in serum cholesterol levels. In the early 1970's, Finland had the highest population level in
the world, close to 7.0 mmol/l. Today we are at or below the EU average and gradually approaching the goal of 5.0 mmol/l, a value considered totally unrealistic for 50 years ago. The Finnish success is based on a clearly defined and evidence-based policy and wide consensus among different actors: academia, clinicians, government, municipalities, non-governmental organizations and, in the end, food industry. Professor Tatu Miettinen and his pupils have played a key role in producing the evidence and in building consensus for the formulation and implementation of the policy. (slide pages 2-3)

Speaker: Antero Kesäniemi, Oulu University Hospital
Title of the presentation: From cholesterol metabolism to clinical trials

Abstract: The detailed method of quantitative determination of bile acids and neutral sterols by Scott M. Grundy, Tatu Miettinen and E.H. Ahrens, Jr. in early 60’s was a key advantage in our understanding of overall cholesterol metabolism. Further work helped to understand the role of synthesis and excretion of cholesterol in the regulation of plasma LDL levels. Detailed studies in the randomly recruited population sample showed that cholesterol absorption efficiency is an important regulator of plasma LDL levels and the clearance of LDL from plasma can be envisioned to be regulated by the absorption, synthesis and excretion of cholesterol as shown in the figure. The specific agent that inhibits intestinal absorption of cholesterol, ezetimibe, lowers LDL by some 20 %. A recent study by Lakoski et al. surprisingly suggested that the change in plasma cholesterol by ezetimibe and by simvastatin treatment was positively correlated indicating that those individuals who respond to statin for example by a 30 % reduction in the plasma LDL levels also respond to ezetimibe by the similar kind of reduction. The model of cholesterol malabsorption can be observed in patients with celiac disease and gluten free diet normalizes cholesterol absorption rate and also normalizes plasma LDL and the receptor mediated clearance of LDL from plasma. Recent work has elucidated the alterations in the metabolism of LDL in patients with renal failure. The clearance of LDL seems to be related to the severity of renal impairment the remarkable reduction in LDL catabolism (even to the same level as observed in patients with familial hypercholesterolemia) being observed only in patients with advanced renal failure (estimated glomerular filtration rate under 30 ml/min/1.73 m²). Barker’s hypothesis (fetal undernutrition) seemingly predisposes to atherosclerotic diseases at later life. Preliminary results in our animal studies interestingly showed that the pups of the mothers with caloric restriction at the age of one month have higher cholesterol and lower adiponectin levels than those of the mothers with normal caloric supply. Scandinavian Simvastatin Survival Study (4S) was the landmark study showing that lowering LDL results in lowering of total and cardiovascular death and no effect on cancer death or other noncardiac death. Several studies thereafter have confirmed these results. However, some recent studies have shown that the progression of degenerative aortic stenosis cannot be affected by effective lipid lowering (Simvastatin and Ezetimibe in Aortic Stenosis; SEAS) and patients with heart failure (Controlled Rosuvastatin Multinational Trial in Heart Failure; CORONA) and renal failure (An Assessment of Survival and Cardiovascular Events; AURORA) under statin treatment have equal incidence of cardiovascular endpoints as those under placebo therapy. Interestingly new ongoing studies hypothesize that lowering plasma LDL beyond that achieved in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial might help our patients. IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) has recruited 18 000 patients with the acute coronary syndrome testing this hypothesis. Another area under current investigation is HDL-cholesterol and Heart Protection Study-2 (HPS2-THRIVE; Treatment of HDL to Reduce
the Incidence of Vascular Events) is testing the question whether raising HDL by extended release niacin with laropiprant, that will prevent the flushing, compared to placebo in 25 000 patients with cardiovascular disease might give additional help to our patients. Another interesting approach is the CETP inhibition where by first agent torcetrapib was not successful. However, studies using new agents like dalcetrapib and anacetrapib will show whether the remarkable increase in HDL cholesterol might result in further reduction of cardiovascular endpoints. (slide pages 4-10

Speaker: Timo Strandberg, University of Oulu, Finland
Title of the presentation: Cholesterol in a life course study (the Helsinki Businessmen Study)

Abstract: One of the old age paradoxes is that the risk related to cholesterol may appear differently when measured in middle age and old age. We have assessed this paradox in the Helsinki Businessmen Study, a life course study of men born in 1919-1934 (n=3490) with baseline evaluations during the 1960s. Total follow-up time extends now to January 2010 - up to 47 years. During this time 54 % of the men have died. We have earlier published follow-up data up to 2002 (1). When total mortality was related to baseline cholesterol, there was a graded and highly significant increase of mortality by every mmol/L increase of cholesterol. Unpublished analyses with mortality data up to 2010 show that lowest mortality and most years gained are observed among those with baseline cholesterol below 4 mmol/L (Figure 1). It should be noted that that during follow-up the cholesterol difference between baseline cholesterol groups has grown smaller, due to secular changes and medications (one third of survivors using statins in the year 2003). Lower cholesterol in midlife was also related to better health related physical quality of life (assessed with RAND-36/SF-36) in old age (1). Psychological quality of life in old age was not associated with midlife cholesterol level, contrasting fears that low cholesterol would adversely affect mental health. However, the relation between cholesterol measured in old age (a random sample in the year 2003) and subsequent follow-up mortality is essentially flat (Fig. 2). This probably reflects the fact that endogenously lowered cholesterol in old age often associates with frailty and consequently worse prognosis, and therefore the favorable effect of low cholesterol is diluted. After adjusting for age, comorbidity and physical function statin treatment actually associated with better prognosis (hazard ratio 0.75) also in older men. Cholesterol has a bidirectional association with prognosis, which easily causes confusion, and the mechanisms can only be elucidated with a life course study. Measured in midlife, cholesterol has a strong association with mortality, and statin studies have demonstrated a clear and favorable effect of cholesterol reduction on vascular events and mortality (2). However, in old age endogenously low cholesterol may be a sign of reduced reserves and frailty, and therefore associate with mortality risk. But it is these background factors - not low cholesterol - that cause the worse prognosis. (slide pages 11-12)

References
2. CTT Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010; epub November 9, 2010
Abstract: Atherosclerosis is an inflammatory disease. This was noticed already 150 years ago by the famous pathologist Rudolph Virchow in Berlin. The notion still exists, and actually it is the foundation of our current research efforts aimed at understanding the pathogenesis of atherosclerosis. Learning about the initiating agent leading to an inflammatory response in the arterial intima has been the main goal in such research. Both exogenous and endogenous antigens have been proposed as initiators of atherogenesis. Among the exogenous antigens, various micro-organisms have been studied. No single micro-organism has been unequivocally been identified as a major cause of the disease. Rather, the life-long bacterial burden is considered to exert a continuous effect at the atherosclerosis-susceptible sites, and so accelerating the development of atherosclerosis. Among the endogenous antigens, or auto-antigens, oxidized LDL has been the most studied object. Its role as an activator of both innate and adaptive immunity has gained considerable support from experimental studies. Currently, vaccination programs against proatherogenic antigens of both exogenous (Chlamydia pneumoniae) and endogenous (oxidized LDL) origin are being developed. Most recently, cholesterol crystals were found to elicit strong proinflammatory action on macrophages. This action is mediated by the NLRP3 inflammasome and results in the secretion of IL-1beta, a cytokine with a strong proinflammatory and proatherogenic activity. Finally, we need to acknowledge that there is no atherosclerosis without initial retention and ensuing intracellular and extracellular accumulation of cholesterol (and other lipids) derived from circulating atherogenic, i.e. apoB-containing lipoprotein particles. A continuous inflammatory response to such retention is the key element necessary for the evolution of an atherosclerotic plaque, and, ultimately, for the atherothrombotic clinical sequelae caused by erosion or rupture of a vulnerable plaque. (slide pages 13-14)

Abstract: LQTS (Long QT syndrome)
- Four founder mutations account for 70% of the known LQTS mutation spectrum in Finland
- At least one in 250 Finns carry a mutant gene
- Increased susceptibility to arrhythmias (and SCD?)

CPVT (Catecholaminergic polymorphic ventricular tachycardia)
- A rare disease increasing risk of SCD
- Mutations vary from family to family

ARVC (Arrhythmogenic right ventricular cardiomyopathy)
- One in 200 Finns carry a desmosomal gene mutation associated with ARVC
- Reduced penetrance: What else is needed for the phenotype to develop?

F: Noncholesterol sterols, Helena Gylling, Department of Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
Serum contains other sterols than cholesterol called non-cholesterol sterols, which can be quantitated with gas-liquid chromatography. Tatu Miettinen took an interest in these
compounds from the beginning of the eighties. He showed that especially the serum levels of cholesterol precursors squalene, cholestenol, desmosterol, and lathosterol could be used as markers of whole-body cholesterol synthesis (1). In addition, serum plant sterols campesterol and sitosterol, and cholestanol, a metabolite of cholesterol, reflected cholesterol absorption efficiency (1,2). Since the absolute analyses of cholesterol metabolism are expensive and laborious, serum non-cholesterol sterols offered a convenient method as surrogate markers of cholesterol metabolism to be used even in large populations. This method was well adopted in clinical lipidology worldwide. However, some caveats should be taken into consideration when the non-cholesterol sterols are used as surrogate markers of cholesterol metabolism. The validity of the method was tested by Miettinen et al. in several populations extending from healthy subjects to type 2 diabetics. However, the validity should be tested in ‘new’ patient groups and during interventions. There obviously is no quality control between the nowadays numerous laboratories performing non-cholesterol sterol analyses, which might partly explain the large variations in serum non-cholesterol sterol levels between different studies. When using the surrogate markers, the whole delicate entity of cholesterol metabolism and the numerous factors affecting it have to be taken into consideration.

Plant sterols are an interesting group of sterols derived from plants. In man they are present not only in serum but also in tissues. In the vascular wall including atheromatous plaques and stenotic aortic valves (3) their concentration correlate with the serum values suggesting that the higher the serum plant sterol levels, the higher the plant sterols in vascular wall (4; Fig 1). Their serum levels increase up to two-fold during statin treatment or during consumption of plant sterol products (3). Plant stanol consumption decreases the plant sterols in serum and in tissues (3). During parenteral nutrition, serum plant sterol levels can increase even 100-fold.

Regarding the future perspectives of non-cholesterol sterols, is there anything left to be studied? Yes, there is. Today, serum non-cholesterol sterol analysis can be used clinically to diagnose cholestasis, malabsorption, phytosterolemia, or Smith-Lemli-Opitz syndrome, but there may be even more indications to clinical use. The individual metabolism of non-cholesterol sterols is not characterized in detail in man, and the clinical relevance especially of the plant stanols and sterols is not clear. (slides page 19)

References
1 Miettinen TA, Tilvis RS, Kesäniemi YA. Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. Am J Epidemiol 1990;131:20-31
3 Gylling H, Miettinen TA. The effects of plant stanol ester in different subject groups. European Cardiology 2010;6:18-21

Speaker: Jorma Viikari, University of Turku, Turku, Finland
Title of the presentation: Cholesterol: from childhood to adulthood

Abstract: Serum cholesterol level is typically < 2 mmol/l at birth globally. The level increases rapidly during the first days and the maximum childhood level is reached before puberty. During puberty total cholesterol and its main fractions LDL-cholesterol and HDL-cholesterol decrease. After puberty the levels start to increase, but HDL-cholesterol of men
remains at clearly lower level than that of women, which is thought to explain at least partly, why women are better protected against atherosclerosis than men. Serum cholesterol levels have decreased in western countries from 1970’s, also in Finland, and the present level in childhood is typically below 4.5 mmol/l and in middle-aged adults below 5.5 mmol/l. The main reason for that has been the change in quality of dietary fat. In studies dealing with synthesis and absorption of cholesterol in 12-18 years old Finnish boys Miettinen showed that logical maintenance of cholesterol homeostasis was generally present in teen-agers (Miettinen et al, Atherosclerosis 2008;200:177-83.). Serum cholesterol is known to track already in childhood almost similar to that in adulthood. Therefore it was of interest whether also indicators of cholesterol synthesis and absorption track in teen-agers. Both synthesis markers and absorption markers tracked at approximately same level as serum cholesterol itself (Miettinen et al Nutr Metab Cardiovasc Dis 2009;19:525-31.). Although much has been achieved as to serum cholesterol levels in children and adults, the obesity development starting in childhood forms now the biggest threat for new increase in cardiovascular morbidity and in fact it is possible that children of today may live less healthy lives than their parents (Olshansky et al N Engl J Med 2005;352:1138-45.).

Speaker: Marja-Riitta Taskinen, Department of Medicine, Division of Cardiology, Helsinki University Hospital and Biomedicum, Helsinki, Finland
Title of the presentation: *Ectopic fat and lipid metabolism*
(Slide pages 22-34)

Abstract: Estrogens, lipids and female cardiovascular risk, Matti Tikkanen, Department of Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland
Women have the same risk factors for atherosclerotic cardiovascular disease (CVD) as men. Although this is true also for the lipid risk factors, the majority of studies indicate that elevated triglyceride (Tg) levels in combination with decreased HDL-cholesterol have a greater impact on CVD risk in women than in men. In addition, adverse changes in these two risk factors are more pronounced in type 2 diabetic women than in diabetic men, possibly contributing to the relatively greater loss of CVD protection in women. Despite the difference in lipid risk factor impact, statin therapy is recommended for both women and men. Statins are useful also in lowering the small,dense LDL-levels which often accompany high Tg concentrations. (Slide pages 35-38)

Speaker: Reijo Tilvis, Department of Medicine, Geriatric Clinic, University of Helsinki, Helsinki, Finland
Title of the presentation: *Changing pattern of risk factors in old age*

Abstract: It is generally accepted that tobacco smoking, diabetes, hypertension and hypercholesterolemia (= major risk factors) and surrogates of metabolic syndrome including obesity, hypertriglyceridemia, and inadequate exercise are invariably associated with arteriosclerotic cardiovascular disease and poor survival. Numerous long-term prospective population-based aging studies aimed at indentifying predictors of successful aging have re-tested the validity of this Framingham paradigm that seems to be less valid in older populations than in the original study. The long-term prospective population studies have revealed a huge number of connections between early events and health indicators in old age. Most of them are not causal- rather parallel phenomena.
The major messages of large-scale population studies could be concentrated in five sentences:
- Almost all deviations from the norm (if not too rare or not too frequent) can be risk and prognostic indicators.
- Conventional risk factor levels are age-dependent.
- The impact of each risk indicator depends on the point in time: both calendar age and life expectancy.
- The predictors of successful aging (free of disability) are essentially similar than those of longevity.
- Mild symptoms and mild disturbances often predict rapid progression of decline.

As an example of age-associated changes of a major risk factor, the association of serum total cholesterol with coronary heart disease and total mortality has been less consistent in older people. In fact, both U- and J- shaped as well as inverse relationships have been reported between serum total cholesterol levels and mortality in unselected older populations.

The predictive role of serum cholesterol was also tested in the Helsinki Aging study, in which three birth cohorts (at entry 75, 80 and 85 years) were examined in 1990 and followed for 17 years. In this study total cholesterol declined in old age (0.2 mmol/L), and low cholesterol was associated with poor health and multimorbidity and mortality risk (Fig.1. Panel A). Indicators of cholesterol synthesis and absorption also decreased with age and deteriorating health, and low values predicted increased mortality (Fig. 1). Adjusted for age and gender lower cholesterol (< 5 mmol/L) (HR = 1.39, 95 %, CI 1.29-177, P = 0.009), lower lathosterol/cholesterol (= an indicator of cholesterol synthesis, HR = 1.42, 95% CI 1.20-1.69, P<0.001), and lower sitosterol/cholesterol (= an indicator of cholesterol absorption, HR  1.24, 95% CI 1.04-1.48, P 0.014). When cholesterol, lathosterol and sitosterol to cholesterol ratios were tested simultaneously as survival covariates, all three parameters (both as continuous and categorized variables) were significant and independent predictors of all-cause mortality. Furthermore, the effects of low cholesterol synthesis, absorption and serum levels on survival were additive (Fig.2). In fact, the median survival times were 10.9 and 3.6 years when the serum levels of TC, lathosterol, and sitosterol were all high and low, respectively.

That endogenously lowered cholesterol - due to ageing, frailty and diseases - is a mortality predictor fits to the concept of senile devitalization rather than to that of reverse epidemiology (Fig.3). It does not mean that cholesterol lowering treatment would be harmful in old age. On the contrary, various analyses have demonstrated that the statin treatment is associated with improved survival in older people, too. Thus, the active and passive cholesterol lowering may have different clinical consequences. (Slide pages 39-43)
Program of the meeting:
Cholesterol: From Metabolic Mechanisms to Clinical and Population Strategy
Tatu Miettinen 80 years Symposium
21st October, 2010
Biomedicum Helsinki, luentosali 1, Haartmaninkatu 8, FI-00290 Helsinki, Finland

9.15 – 9.30 Opening: Antero Kesäniemi, Department of Internal Medicine, Oulu University Hospital, Oulu, Finland
Chairpersons Antero Kesäniemi and Jorma Viikari

9.30 - 10.00 Scott M. Grundy, University of Texas Southwestern Medical Center, Dallas, Texas, USA: Video presentation

10.00 – 10.35 Jussi Huttunen, Finnish Medical Society Duodecim, Helsinki, Finland: “Science, mentoring and public health”

10.35 - 11.00 Break
Chairpersons Petri Kovanen and Helena Gylling

11.00 - 11.35 Antero Kesäniemi, Department of Internal Medicine, Oulu University Hospital, Oulu, Finland: “From cholesterol metabolism to clinical trials”

11.35 - 12.10 Timo Strandberg, Department of Public Health Science and General Practice, University of Oulu, Unit of General Practice, Oulu University Hospital, Oulu, Finland: “Life-course in the long prospective follow-up studies”

12.10 - 13.05 Lunch
Chairpersons Timo Strandberg and Marja-Riitta Taskinen

13.05 - 13.40 Petri Kovanen, Wihuri Research Institute, Helsinki, Finland: “Evolution of the atherosclerotic plaque”

13.40 - 14.15 Kimmo Kontula, Department of Medicine, University of Helsinki, Helsinki, Finland: “Finnish founder genes underlying sudden cardiac death”

14.15 - 14.50 Helena Gylling, Department of Clinical Nutrition, University of Kuopio, Kuopio, Finland: “Noncholesterol sterols”

14.50 - 15.15 Break
Chairpersons Kimmo Kontula and Matti Jauhiainen

15.15 - 15.50 Jorma Viikari, Department of Medicine, Turku University Hospital, Turku, Finland: “Cholesterol: from childhood to adulthood”

15.50 - 16.25 Marja-Riitta Taskinen, Department of Medicine, Division of Cardiology, Helsinki University Hospital and Biomedicum, Helsinki, Finland: ”Ectopic fat and lipid metabolism”

16.25 – 17.00 Matti Tikkanen, Department of Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland: ”Estrogens, lipids and female cardiovascular risk”

17.00 - 17.35 Reijo Tilvis, Department of Medicine, Geriatric Clinic, University of Helsinki, Helsinki, Finland: “Changing pattern of risk factors during the life span”

17.35 Closing words: Petri Kovanen, Wihuri Research Institute, Helsinki, Finland
CORONARY HEART DISEASE MORTALITY IN FINLAND 1951 – 2007
/ 100,000 35-64-year old males and females

Miehet / Males
Naiset / Females
SERUM CHOLESTEROL IN 30–59-YEAR OLD MEN
1972–2007

Source: National Institute for Health and Welfare
CHOLESTEROL ABSORPTION CORRELATES WITH LDL-C

Change in Plasma LDL-C (%)  

n=205  

R=0.46  
P<0.001  

BARKER’S HYPOTHESIS
OUR STUDY DESIGN

3 groups of pregnant rats:
1. Control group (ad libitum)
2. 75% of normal food intake
3. 50% of normal food intake

Day 13 and 17
-Gene expression and protein levels (microarrays, RT-PCR, ELISA, Western blotting)
-adiponectin, resistin, ghrelin, leptin

1 day & 1 month old pups
-Growth
-Gene expression and protein levels
-Cholesterol levels
EFFECT OF UNDERNUTRITION IN UTERO ON SERUM CHOLESTEROL AND ADIPONECTIN AT ONE MONTH

Causes of Death

Coronary

Other cardiovascular

Cancer

Other

Placebo 11.5 %

Simvastatin 8.2 %

Scandinavian Simvastatin Survival Group, Lancet 344, 1994
The Statin Decade:
For LDL: “Lower is Better”

Life years gained or lost during life course according to midlife cholesterol level and compared with the mean of the whole cohort.

Years
-3 -2 -1 0 1 2 3

<=4.0 4.1-5.0
5.1-6.0 6.1-7.0
7.1-8.0 8.1-9.0
>9.0
Total mortality in 2003-2010 according to serum cholesterol groups in 2003

P=0.3

Whole cohort

2003 cholesterol group

Total mortality, %

<=4 4.1-5.0 5.1 - 6.0 6.1 - 7.0 7.1 - 8.0
Evolution of an atherosclerosis plaque

Petri Kovanen MD PhD
Wihuri Research Institute
Helsinki, Finland

Tatu Miettinen 80 years Symposium
Biomedicum, Helsinki

October 21, 2010
Atheroma: formation of the lipid core

Modified LDL → Foam cell

Cell death

Lipid core
Finnish Founder Genes
Underlying
Sudden Cardiac Death

Kimmo Kontula
Professor of Medicine
University of Helsinki

Tatu Miettinen 80 Years Symposium
Four founder mutations account for 70% of the known LQTS mutation spectrum in Finland

- Diagnostics and screening
- Also permitting:
  - Population studies (Health 2000)
  - Modifier genes in LQTS
  - Role in sudden death and drug-induced LQTS
MOLECULAR PATHOGENESIS IN CPVT

Diagram showing the molecular pathways involved in cardiac physiology, including calcium ions (Ca^{2+}) regulation, RyR2 (Ryanodine Receptor 2), FKBP12.6, PKA (Protein Kinase A), cAMP (Cyclic Adenosine Monophosphate), Mg^{2+}, CASQ2 (Cardiac Calmodulin Binding Protein 2), SERCA2a (sarcoplasmic reticulum Ca^{2+}-ATPase 2a), mitochondria, and NCX (Na+/Ca^{2+} Exchanger). The diagram highlights the contraction/relaxation processes in cardiac muscle cells.
The impact of Finnish LQTS, CPVT and ARVC mutations as sudden cardiac death (SCD) genes: A population-based study (collaboration: V Salomaa/NIH, C Newton-Cheh)

- Health and disease histories
- Register data
  - Hospital discharge register
  - Natl Pension Institute
  - Causes-of-death register
- DNA samples

- Molecular genetics
  - Sequenom MS analysis

SCD susceptibility genes
Fig 1. Non-cholesterol sterols in serum and vascular wall

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Correlation of 1980 (vertical column) body mass index (BMI), cholesterol and non-cholesterol sterol to cholesterol ratios with those of 2001 (horizontal row) in the whole population (n = 467).</th>
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<tr>
<td><strong>1980</strong></td>
<td><strong>2001</strong></td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>Cholesterol</td>
</tr>
<tr>
<td>0.563*</td>
<td>0.089</td>
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<tr>
<td><strong>Cholesterol</strong></td>
<td>0.060</td>
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<tr>
<td><strong>Synthesis markers</strong></td>
<td></td>
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<tr>
<td>Cholestolenol</td>
<td>0.155*</td>
</tr>
<tr>
<td>Desmosterol</td>
<td>-0.023</td>
</tr>
<tr>
<td>Lathosterol</td>
<td>0.246*</td>
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<tr>
<td><strong>Absorption markers</strong></td>
<td></td>
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<tr>
<td>Campesterol</td>
<td>-0.069</td>
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<tr>
<td>Sitosterol</td>
<td>-0.075</td>
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<tr>
<td>Avenasterol</td>
<td>-0.117*</td>
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<tr>
<td>Cholesterol</td>
<td>-0.191*</td>
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<tr>
<td>Cholesterol = mg/dl; non-cholesterol sterols = x 10³ μg/mg of cholesterol.</td>
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<td>*P &lt; 0.05 or less.</td>
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**Synthesis and absorption markers track**

TATU MIETTINEN
80yrs
SYMPOSIUM

Ectopic fat and lipid metabolism

Professor Marja-Riitta Taskinen
Department of Medicine, Division of Cardiology
What is ectopic fat accumulation?

↑ Caloric Intake  and/or  ↓ Energy Expenditure

Positive Energy Balance

Inflamed adipose tissue → FFA↑

Lipid overflow into liver, pancreas, muscle and heart

Imbalance between loading and export of lipids results in ectopic fat accumulation at organs
Possible mechanisms linking NAFLD to cardiovascular disease

- Expanded and inflamed visceral fat mass
- Inflammatory cytokines↑
- Insulin resistance↑
- FFA↑
- Chronic inflammation
- Hypercoagulation and hypofibrinolysis
- Atherogenic dyslipidemia
- Dysglycemia and (hepatic) insulin resistance

The Atherogenic Lipoprotein Triad

Lifestyle
- Insulin resistance
- Type 2 Diabetes
- FCH subjects
- Low HDL subjects

Genes
- Small dense LDL

Increased CAD Risk

HDL↓

Large VLDL

Increased VLDL
The fatty liver produces most CVD risk factors

The Fatty Liver: Overproduction of Cardiometabolic Risk Factors

- FIVII, PAI-1
- TNF-α, IL-6
- CRP, SAA
- Angiotensinogen
- Fibrinogen
- ALT, AST

Genetic Predisposition
Caloric excess
Fat in the diet?
Fructose
Sucrose
Regulation of lipid metabolism in the liver

FFA flux

Dietary fatty acids, carbohydrates → DNL → Fatty acid oxidation → VLDL assembly → VLDL secretion
Relationship between VLDL1 production rate and plasma VLDL1 TG pools

\[ r = 0.62 \]
\[ p < 0.001 \]

VLDL1 TG production rate is the predictor for VLDL1 TG pool size

Adiees M et al. ATVB 2005;25:1697-703
VLDL1 TG production is linked with detrimental changes of LDL size and HDL cholesterol

LDL size vs VLDL1 TG production

HDL Chol vs VLDL1 TG production

$r=-0.56$

$p<0.005$

$r=-0.64$

$p<0.001$

The relationship between VLDL1 production and liver fat assessed using proton spectroscopy

Liver fat content is the driving force for VLDL TG overproduction

Why do not all people with a big waist have dyslipidemia?
Potential mechanisms linking fat accumulation in liver and heart

Adipose tissue hypertrophy and inflammation

Insulin resistance
Visceral obesity

Overeating Inactivity

NAFLD

Endothelial dysfunction

↑ TG, FFA
↑ glucose, insulin
↑ E-selectin, CRP
↓ leptin
↓ adiponectin

Cardiac lipotoxicity

Bugianesi E. Hepatology 2008;47:2-4
Potential links between dysfunctional adipose tissue, diabetes and vascular health

FAT → Adiponectin
- → AMPK COX-2

HEART
- Leptin
+ Free Fatty Acids
+ Plasma Triglyceride

- Apoptosis
↑ Inflammation
↑ FAO
Activation of PPARs
↑ FAO
↑ TG accumulation
↑ Ceramide

Mediators linking fatty liver and CVD

Glucose  VLDL  HDL  ALT, AST  Fibrinogen  FVII, PAI-1  Angiotensinogen  CRP, SAA  TNF-α, IL-6

Is myocardial fat associated with liver fat and CVD?
**CV risk factors in women**

- Elevated blood pressure (isol. systolic)
- Cholesterol and other lipid risk factors
- Cigarette smoking
- Diabetes mellitus
- Metabolic syndrome etc.

  **Specific for women:**
  - Early (surgical) menopause
  - Oral contraceptives
  - Postmenopausal hormone treatments starting late (?)
  - Blue collar worker husband
“The combination of low levels of HDL-cholesterol and hypertriglyceridemia likely impart greater risk for women than for men”

Nanette Wenger (AJH 1995;8:945-995)
UKPDS: Typical Lipid Profile in Patients with Diabetes Compared with No Diabetes

- **HDL-C (mmol/L [mg/dL])**
  - Men: DM, no DM, p<0.02
  - Women: p<0.001

- **Triglycerides (mmol/L)**
  - Men: DM, no DM, p<0.001
  - Women: p<0.001

UKPDS, Diabetes Care 1997; 20:1683-1697
Conclusions

- CV disease in women should be prevented by reducing all major risk factors (elevated BP, cigarette smoking, elevated cholesterol and others)
- In the postmenopause, serum lipids should be treated by statins (not by estrogen replacement)
- Hormone replacement therapy should be used for treatment of menopausal symptoms
Fig. 1. Age and gender adjusted 17-year cumulative survival by quartiles of serum total cholesterol (Panel A), by median values of lathosterol/cholesterol ratios (Panel B), and sitosterol/cholesterol ratios (Panel C).

Panel A.
Panel B.

![Graph showing survival analysis with two lines indicating 'Low' and 'High' groups, with a significance level of P<0.001.]
Panel C.
Fig. 2. Years lost by the presence of indicators of diminished cholesterologenesis
Fig 3. Low cholesterol in old age is rather a manifestation of senile devitalization than that of reverse epidemiology.

Senile devitalization rather than reverse epidemiology

Aging

Cholesterol
Blood pressure
BMI

Diseases

Risk relationship

Cholesterol
Blood pressure
BMI

CAD
CVD
AD

Reverse causality
Professor Kesäniemi opening the Symposium.
Professor Petri Kovanen, Professor Tatu Miettinen, Professor Antero Kesäniemi and Professor Timo Strandberg
Tatu Miettinen’s daughters Päivi and Helena, both Medical doctors, and Mrs., Dr. Terikki Miettinen