Pediatric hyperlipidemias in Serbia "State of the art"

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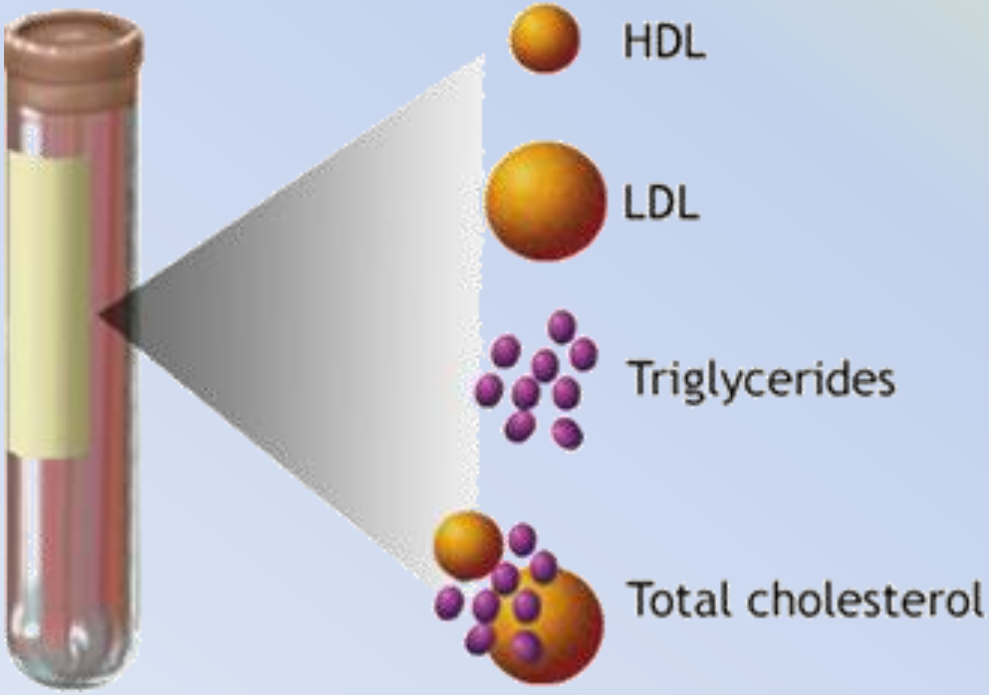
Serbia has the largest number of Roman emperors born outside of Italy – 17 altogether.

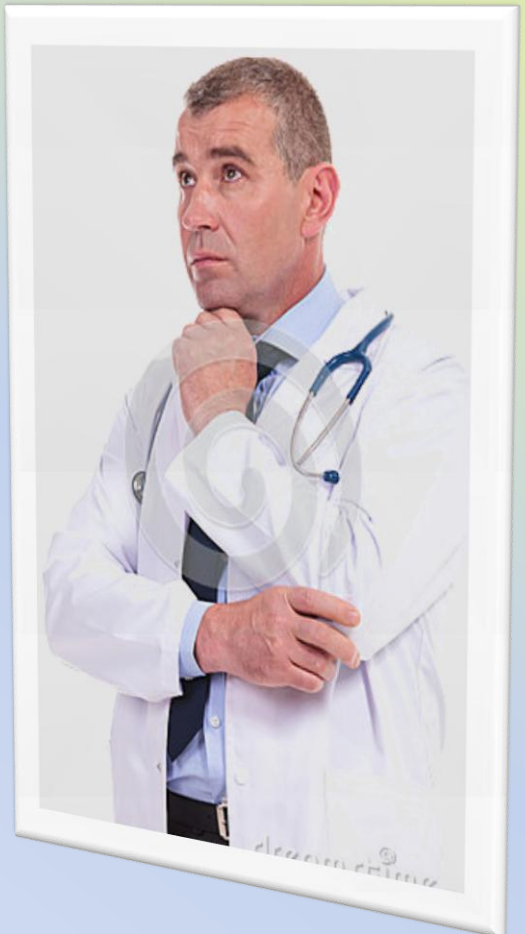
Constantine I


FORUM SHOPPING CENTER

CARDIOVASCULAR RISK PREDICTION IN
OBESE CHIDREN

It is reality that the majority pediatricians in Serbia are not in comfort zone managing children with dyslipidemias (DS). Generally they are unaware about potential short and long term health risks of DS and have significant concerns about "harms" that could be associated with potential treatment of children with DS.





Evidences

Autopsy studies

Non-invasive subclinical C-V imaging studies

Mendelian randomization studies

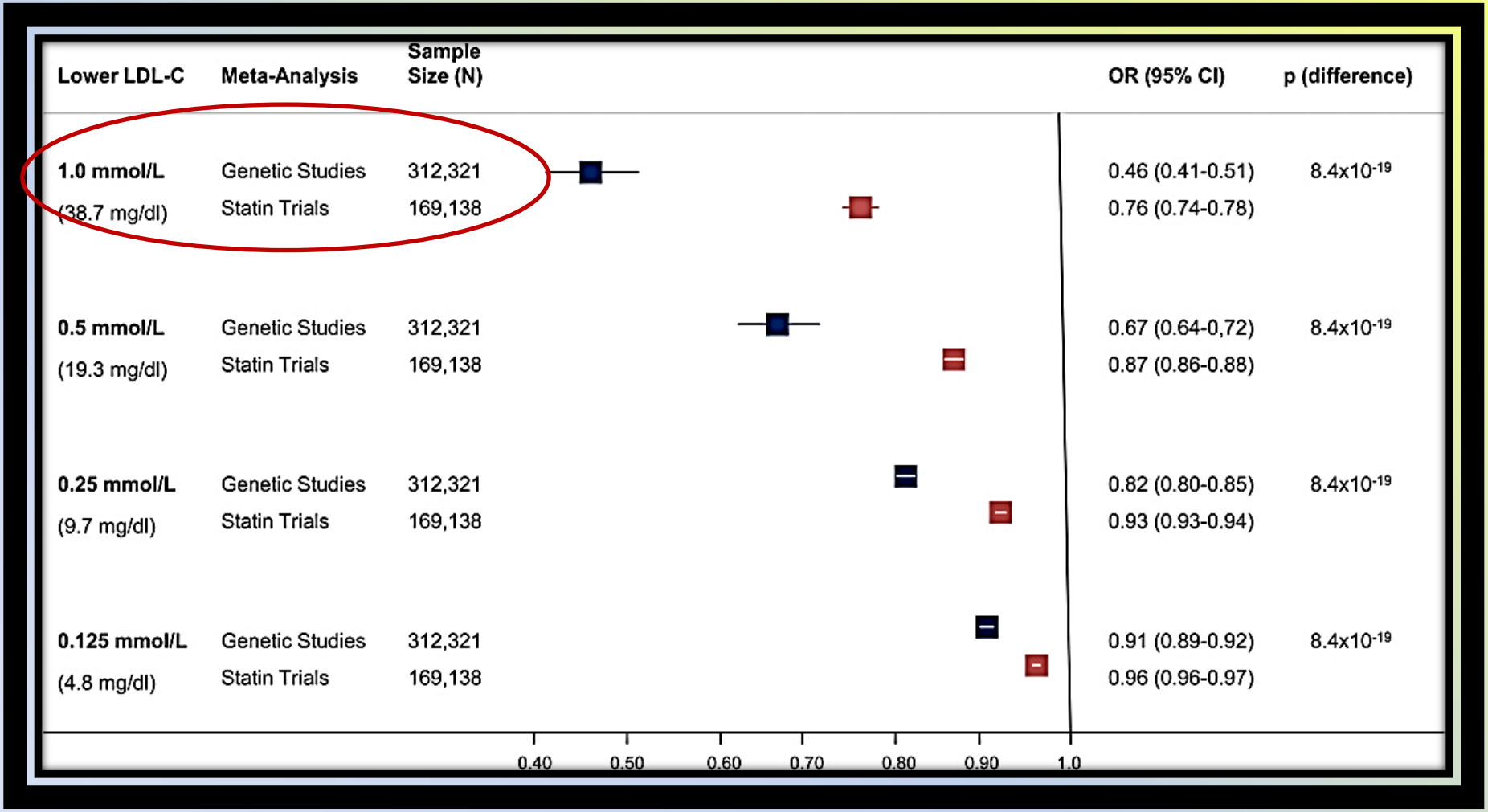
Evidences

- The Bogalusa Heart Study showed that an increasing number of childhood CV risk factors exponentially increased the atherosclerotic burden noted at autopsy after accidental death.

- The Pathobiological Determinants of Atherosclerosis in Youth Study of individuals aged 15 to 30 years who had died traumatically showed that a 30 mg/dL incremental increase in non-HDL-C was the equivalent of 2 years of vascular aging.

Evidences

- **Cardiovascular Risk in Young Finns Study - higher low-density lipoprotein cholesterol (LDL-C) at ages 12 to 18 years was independently associated with greater carotid intima media thickness (IMT) in adulthood.**



Meta-analysis 312,321 paratcipants with different SNPs
LDL-C reduction of 1 mmol/l (38.7 mg/dl)
= 54.5% lower CVS risk (OR: 0.46, 95% CI: 0.41 to 0.51; p 2.15 1045)

Ference BA et al Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012 Dec 25;60(25):2631-9.

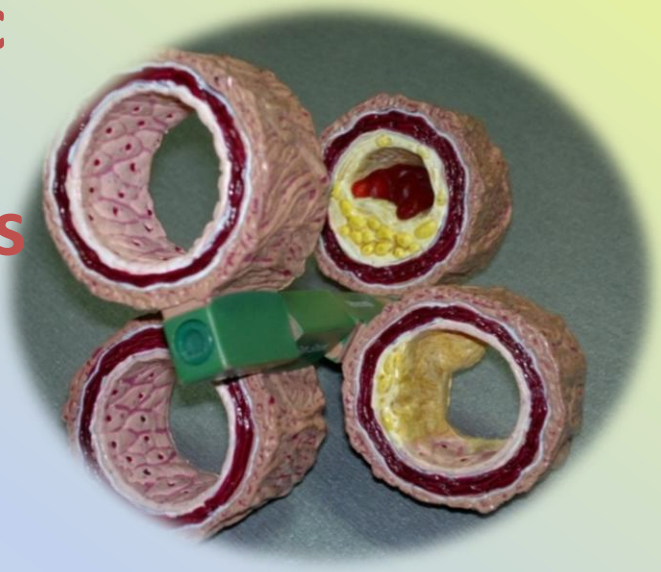
Mendelian randomization studies

- **Loss-of-function PCSK9 mutations** → The number of LDL receptors is high → The circulating level of LDL cholesterol (LDL-C) is low.

- Very low lifetime risk of coronary heart disease.

Kent ST, Rosenson RS, Avery CL, et al. PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: data from the REGARDS Study and CHARGE Consortium. Circulation 2015;132:A9793.

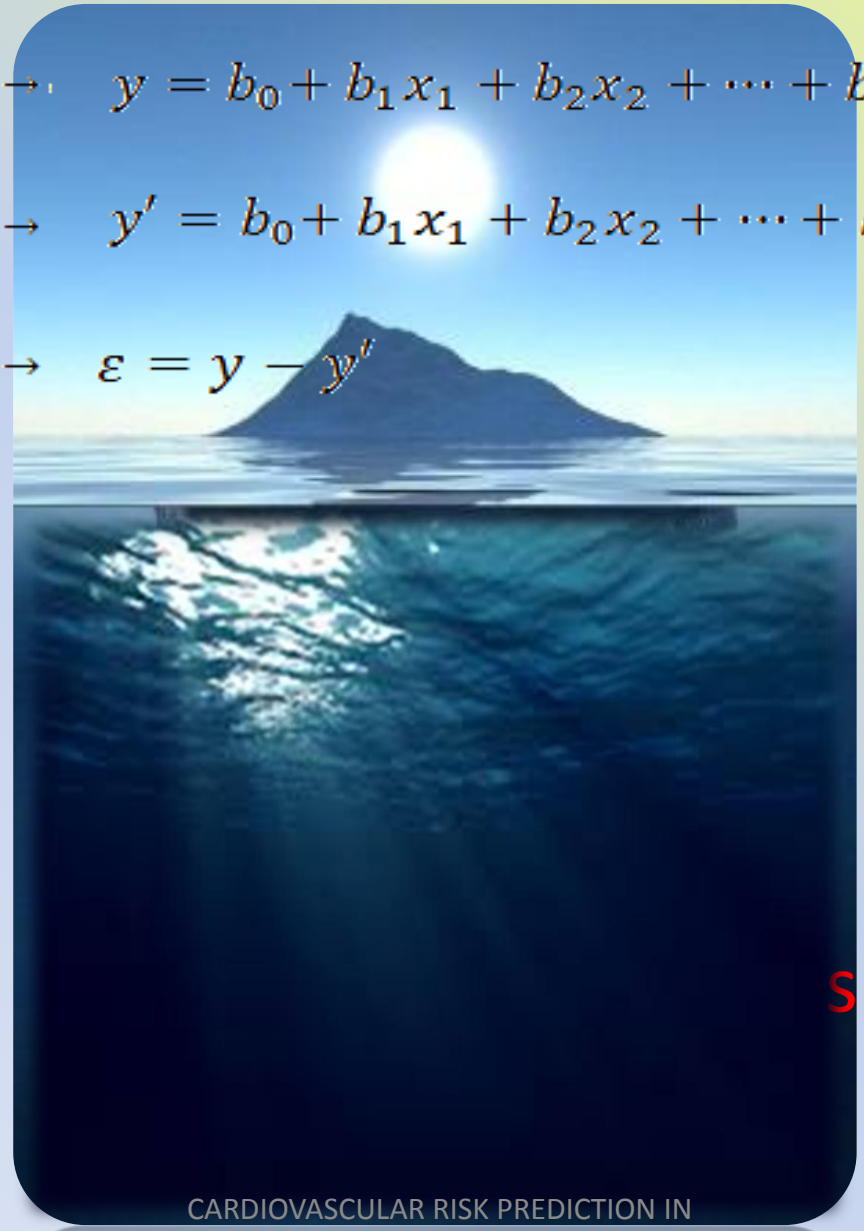
The problem is that by relying on so-called risk factors for symptomatic cardiovascular disease the epidemiologists and clinical trialists are focusing on markers that are statistically associated with the disease process but are not the biological disease process itself

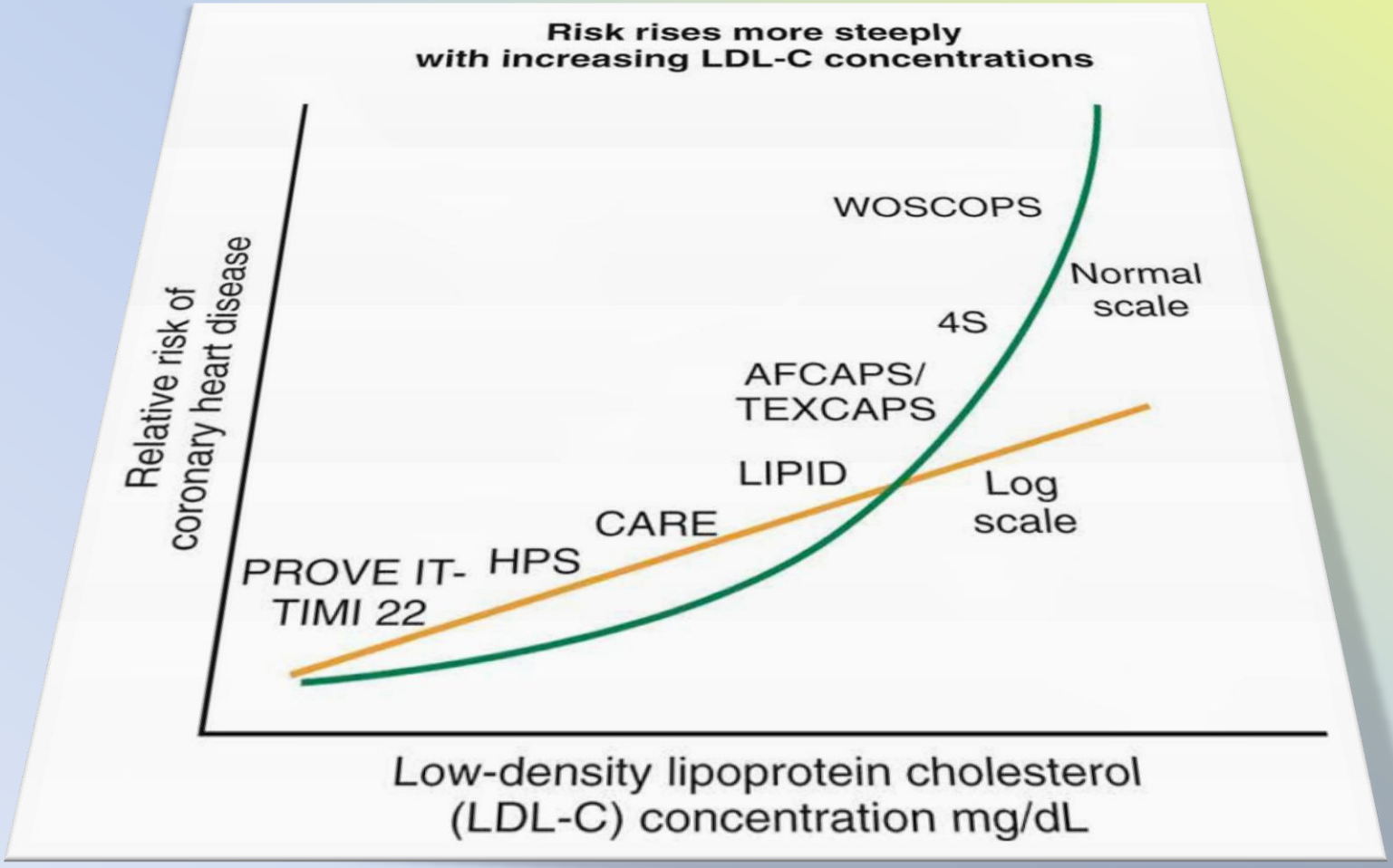


observed data → $y = b_0 + b_1 x_1 + b_2 x_2 + \cdots + b_p x_p + \varepsilon$

predicted data → $y' = b_0 + b_1 x_1 + b_2 x_2 + \cdots + b_p x_p$

error → $\varepsilon = y - y'$




Risk rises more steeply
with increasing LDL-C concentrations
Relative risk of coronary heart disease
WOSCOPS
Normal scale
4S
AFCAPS/
TEXCAPS
LIPID
Log scale
CARE
HPS
PROVE IT-
TIMI 22
Low-density lipoprotein cholesterol
(LDL-C) concentration mg/dL

HeFH

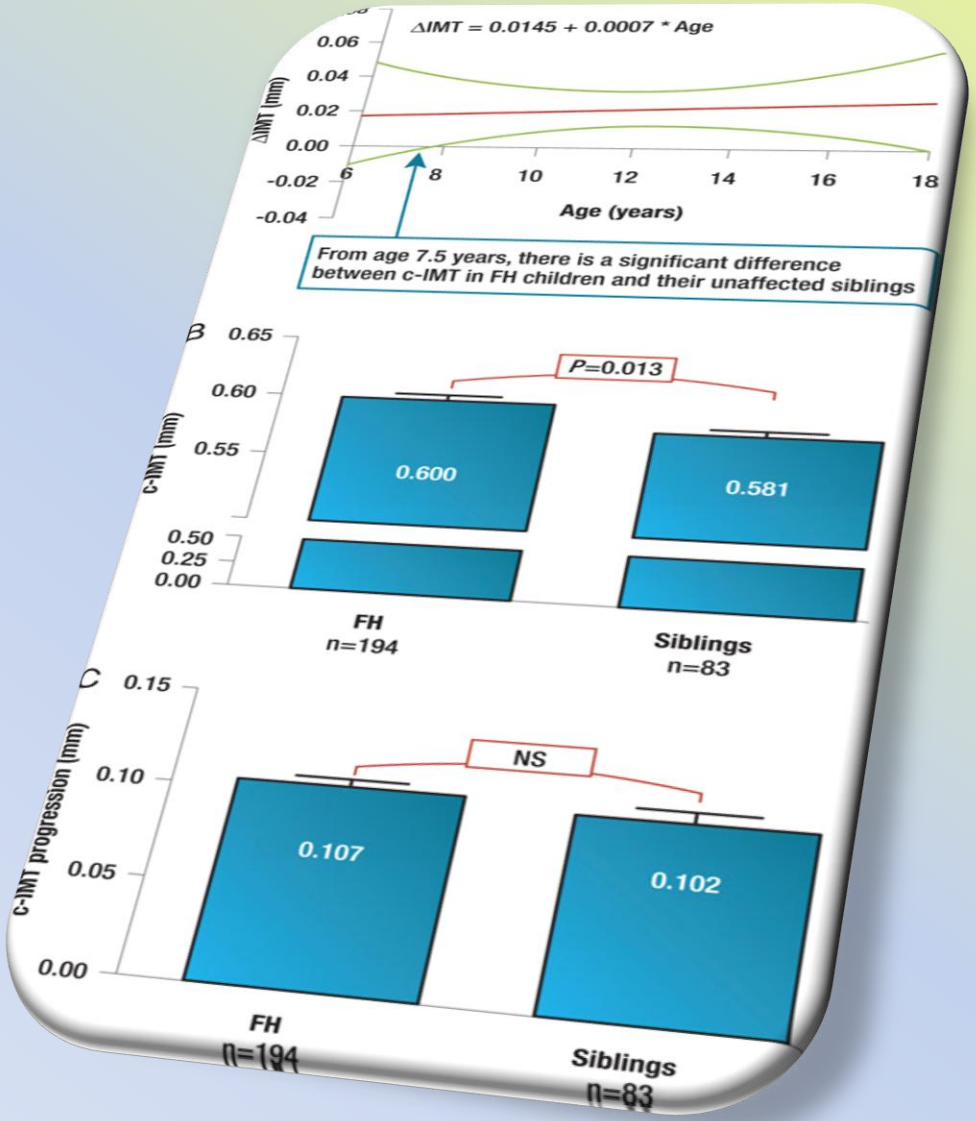
Familial hypercholesterolemia (FH) is an excellent biologic model demonstrating the link between childhood lipid levels and CV disease events because high levels of LDL-C are present from birth.

“Simone Broom registry data“

51% of untreated affected men developed clinical CV disease by age 50 years

- **Mortality was 100 fold increased in age group of 20-40 years and 4 fold in the 40-59 year age group.**

Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet. 1969;2(7635):1380–1382



Kusters DM, WiegmanA, Kastelein JJ, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. Circ Res 2014;114:307–310

Coronary calcification is present in 25% of 11–23 year olds with phenotypic HeFH

Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. Circulation 1998;98:2580–2583.

Must do’s for all pediatricians to be aware of this problem and to know what to do in this clinical setting.

Table 3 Screening for familial hypercholesterolaemia in children and adolescents

- If DNA testing is available, cascade screening of families is recommended using both a phenotypic and genotypic strategy. If DNA testing is not available, a phenotypic strategy based on country, age- and gender-specific LDL-C levels should be used.
- Children with suspected HeFH should be screened from the age of 5 years; screening for HoFH should be undertaken when clinically suspected (both parents affected or xanthoma present) and as early as possible.
- Age at screening should be similar for boys and girls.
- Universal screening in childhood may also be considered.

Wiegman A, Gidding SS, Watts GF et al. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015 Sep 21;36(36):2425-37. for the

Unfortunately, what has been lost in years of debate about lipid screening is the most important reason to do this in the first place, which is to identify children with familial hypercholesterolemia (FH)

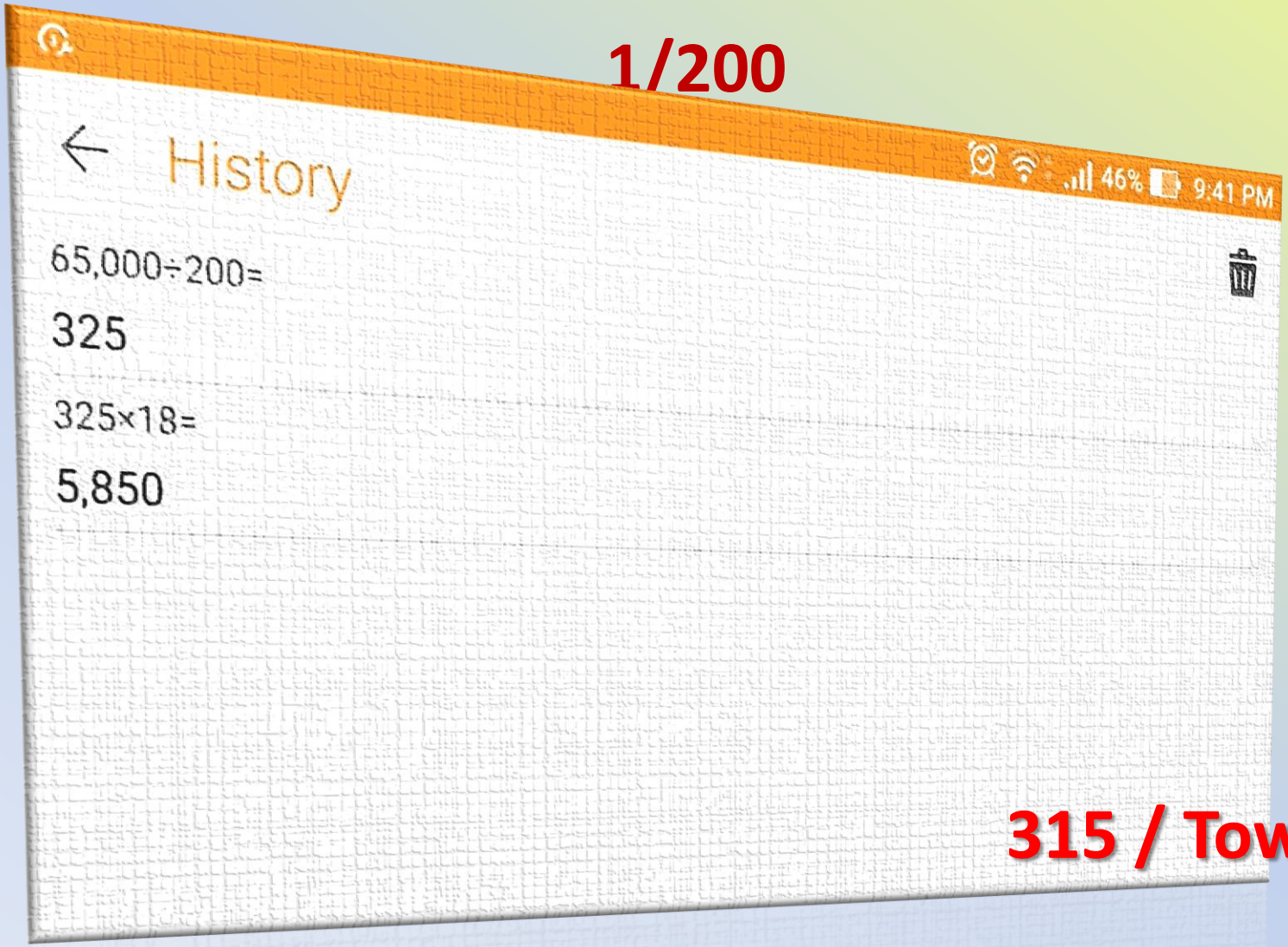
OUR EXPERIENCES

- September 2016 – onwards
- A “Top-down” approach. To affected parents to pass on information directly to their children
- “Bottom-up “ approach - Cascade screening (children with high TC and parents with CVD)

- Primary health center – Pediatric cardiologist (universal screening)
- Coronary unit – Director (Sreening in children from parents < 45 years with acute coronary events)
- Blood samples were obtained fasting , with lipids measured by standard enzymatic methods
- LDL > 3,5 mmol/l + family history

HeFH

1/200



315 / Town Niš

RESULTS

- 15 different families are screened
- 6 - “Top-down” approach
- 9 - “Bottom-up “ approach.

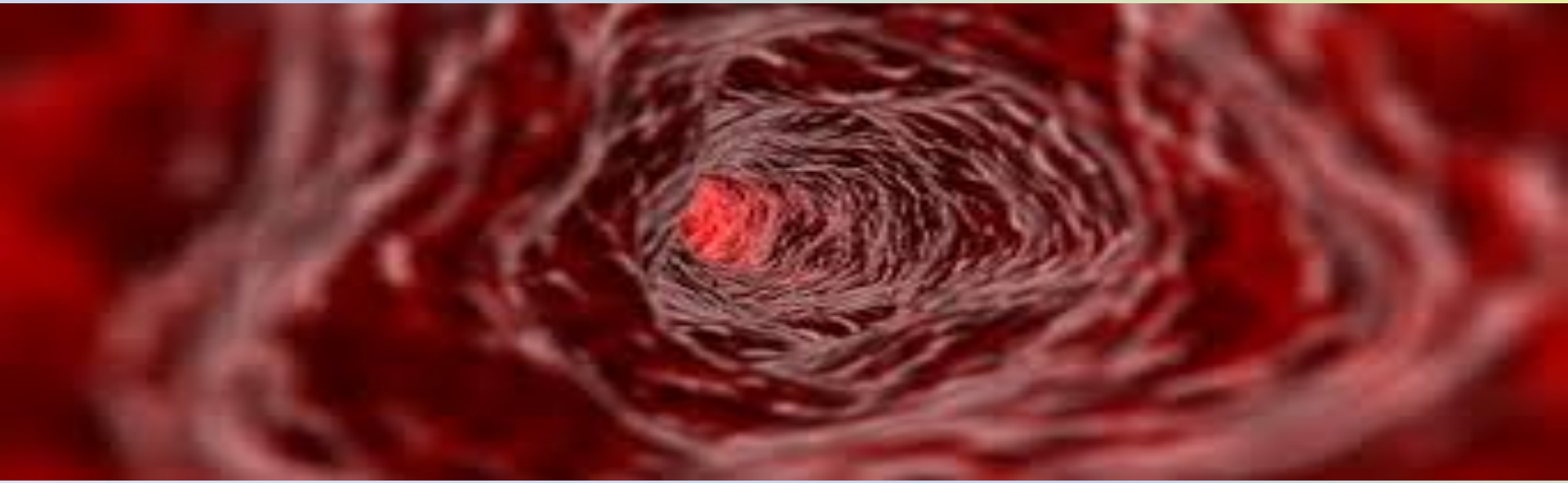
- 11 children (suspected of He FH)
- 2 Parents (suspected of HeFH)
- Genetic analyses - ongoing

- **Have created “Database“ of children with HeFH**
- **Identify 2 parents higly suspected of HeFH (both had also CIMT > 1,5 mm)**

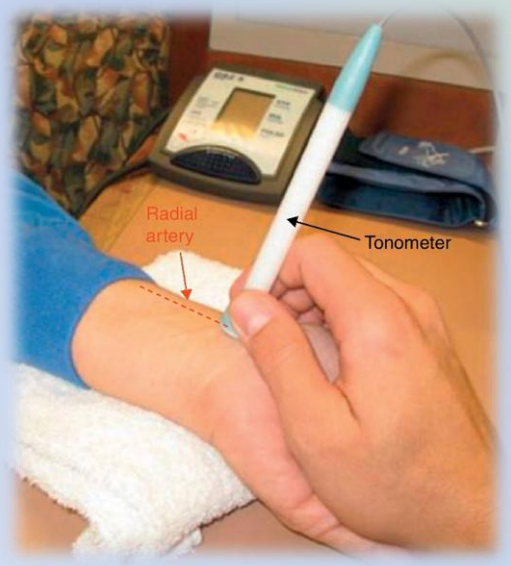
Perspectives

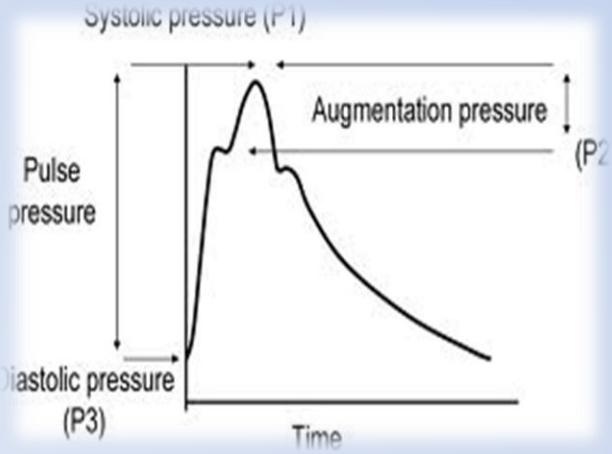
Target organ damages

(ENDOTHELIAL FUNCTION MEASUREMENTS ?)



PERSPECTIVES





Reproducibility
Validity
Normative values

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2	PulsePen wireless device (1000 Hz/16 bit) with winXP/7/8 software, one Ecg module, two Tonometric probes, Usb receiver, Ecg cable and Case	WPP001-ETT	1	8920,00	8920,00
3	Shipment and Insurance		1	350,00	350,00

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Waiting to hear of you soon. With Best Regards.

DiaTecne s.r.l.
Giuseppe Lio

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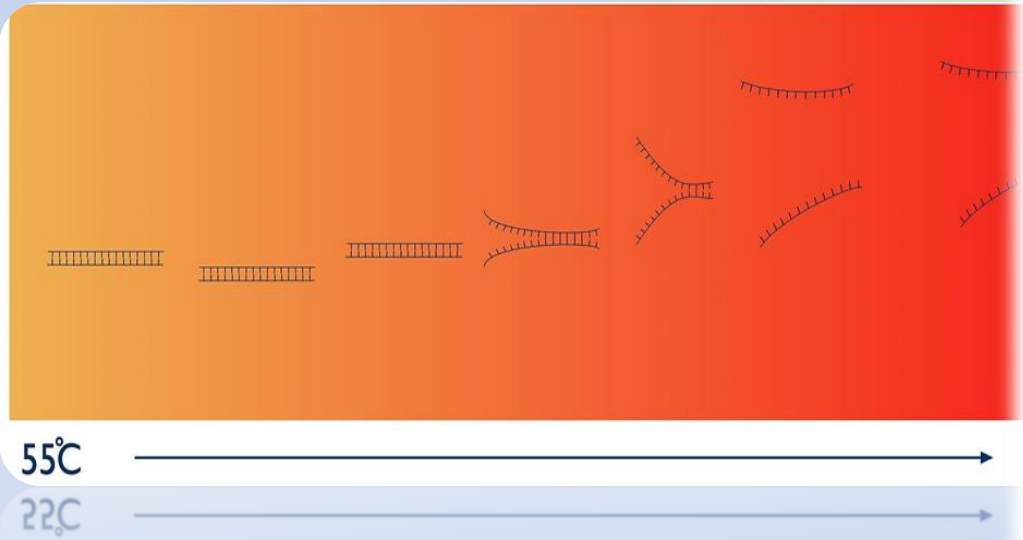
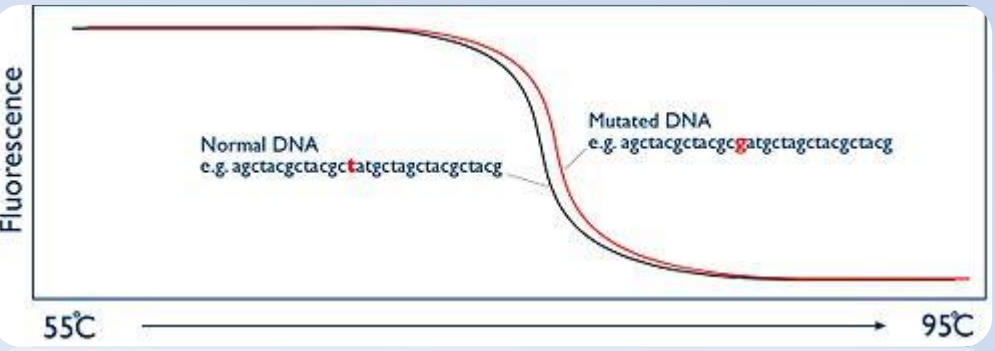
Pg 1 of 1

Acceptable diagnostics

Point of Care (PoC) analyzers

High Resolution Melt





THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Kevin Fitzgerald, Ph.D., Suellen White, B.S.N., Anna Borodovsky, Ph.D., Brian R. Bettencourt, Ph.D., Andrew Strahs, Ph.D., Valerie Clausen, Ph.D., Peter Wijngaard, Ph.D., Jay D. Horton, M.D., Jorg Taubel, M.D., Ashley Brooks, M.B., Ch.B., Chamikara Fernando, M.B., B.S., Robert S. Kauffman, M.D., Ph.D., David Kallend, M.D., Akshay Vaishnaw, M.D., and Amy Simon, M.D.

ABSTRACT

BACKGROUND

Inclisiran (ALN-PCSsc) is a long-acting RNA interference (RNAi) therapeutic agent that inhibits the synthesis of proprotein convertase subtilisin–kexin type 9 (PCSK9), a target for the lowering of low-density lipoprotein (LDL) cholesterol.

METHODS

In this phase 1 trial, we randomly assigned healthy volunteers with an LDL cholesterol level of at least 100 mg per deciliter in a 3:1 ratio to receive a subcutaneous injection of inclisiran or placebo in either a single-ascending-dose phase (at a dose of 25, 100, 300, 500, or 800 mg) or a multiple-dose phase (125 mg weekly for four doses, 250 mg every other week for two doses, or 300 or 500 mg monthly for two doses, with or without concurrent statin therapy); each dose cohort included four to eight participants. Safety, the side-effect profile, and pharmacodynamic measures (PCSK9 level, LDL cholesterol level, and exploratory lipid variables) were evaluated.

RESULTS

The most common adverse events were cough, musculoskeletal pain, nasopharyngitis, headache, back pain, and diarrhea. All the adverse events were mild or moderate in severity. There were no serious adverse events or discontinuations due to adverse events. There was one grade 3 elevation in the γ-glutamyltransferase level, which was considered by the investigator to be related to statin therapy. In the single-dose phase, inclisiran doses of 300 mg or more reduced the PCSK9 level (up to a least-squares mean reduction of 74.5% from baseline to day 84), and doses of 100 mg or more reduced the LDL cholesterol level (up to a least-squares mean reduction of 50.6% from baseline). Reductions in the levels of PCSK9 and LDL cholesterol were maintained at day 180 for doses of 300 mg or more. All multiple-dose regimens reduced the levels of PCSK9 (up to a least-squares mean reduction of 83.8% from baseline to day 84) and LDL cholesterol (up to a least-squares mean reduction of 59.7% from baseline to day 84).

CONCLUSIONS

In this phase 1 trial, no serious adverse events were observed with inclisiran. Doses of 300 mg or more (in single or multiple doses) significantly reduced levels of PCSK9 and LDL cholesterol for at least 6 months. (Funded by Alnylam Pharmaceuticals and the Medicines Company; ClinicalTrials.gov number, NCT02314442.)

From Alnylam Pharmaceuticals, Cambridge, MA (K.F., S.W., A. Borodovsky, B.R.B., A. Strahs, V.C., R.S.K., A.V., A. Simon); the Medicines Company, Parsippany, NJ (P.W., D.K.); University of Texas Southwestern Medical Center, Dallas (J.D.H.); Richmond Pharmacology, St. George's University of London, London (J.T.); and Covance Clinical Research Unit, Leeds, United Kingdom (A. Brooks, C.F.). Address reprint requests to Dr. Fitzgerald at Alnylam Pharmaceuticals, 300 Third St., Cambridge, MA 02142, or at kfitzgerald@alnylam.com.

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