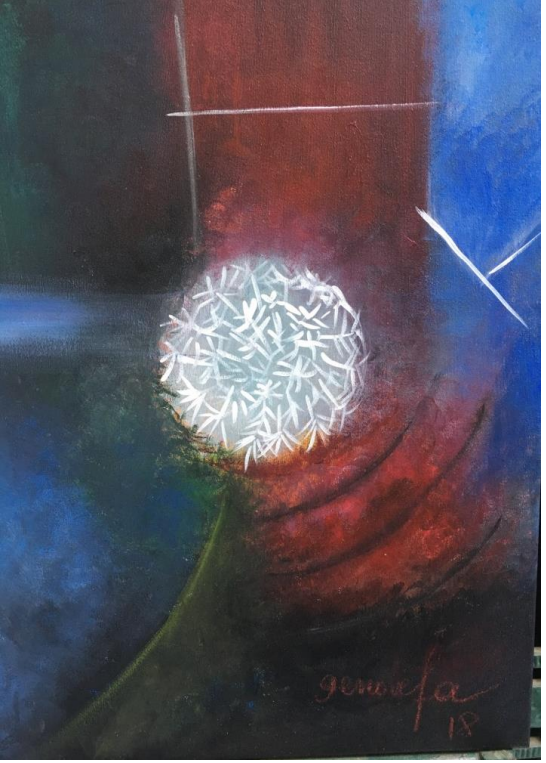


Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

Γενοβέφα Κολοβού, Διευθύντρια Καρδιολογικού Τομέα, Υπεύθυνη Μονάδας LDL Αφαίρεσης, Υπεύθυνη Εξωτερικών Ιατρείων και Προληπτικής Καρδιολογίας, Ωνάσειο Καρδιοχειρουργικό Κέντρο

Disclosures

- Attended conferences, advisory boards and gave talks sponsored by MSD, Vianex, Amgen, Sanofi, Lilly

- Chairperson: Expert Panel on:
    1. Postprandial lipaemia, 2010, 2016
    2. Longevity syndrome

Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

- Δυσλιπιδαιμίες στους νεφροπαθείς
- Σωματόπαυση
- Θεραπεία
- Οδηγίες
- Συμπεράσματα

Δυσλιπιδαιμίες στους νεφροπαθείς

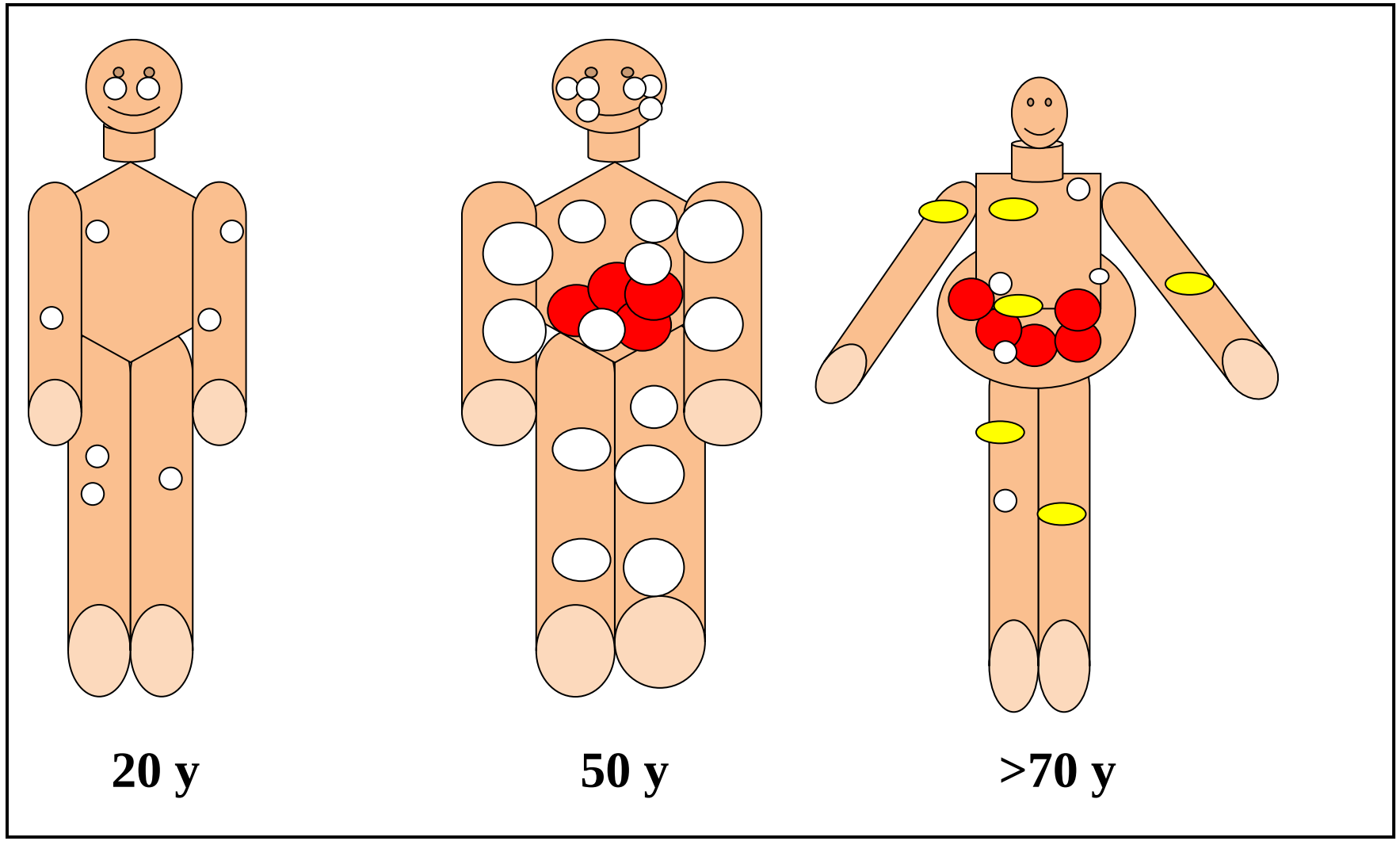
- Πρωτοπαθείς: τύπου III δυσλιπιδαιμία, FCH, σύνδρομο χυλομικροναιμίας
- Δευτεροπαθείς : μικτές δυσλιπιδαιμίες

Μικτές δυσλιπιδαιμίες

↑ ΟΧ + ↑ ΤΓΛ

↓ HDL
↑ μικρές πυκνές LDL
↓ δραστηριότητα της LpL
↑ PPL

Αθηρογόνο λιπιδαιμικό προφίλ



Aging leads to ↓ subcutaneous fat (white circles, peripherally first, then centrally), ↑ abdominal fat (red circles) and deposit of fat in muscles, bone marrow and others (yellow circles)

Κολοβού Γ. Ανδρόπαυση, Εμμηνόπαυση, Σωματόπαυση και Καρδιαγγειακό Σύστημα. 2010 εκ. Info Health

Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

- Δυσλιπιδαιμίες στους νεφροπαθείς
- Σωματόπαυση
- Θεραπεία
- Οδηγίες
- Συμπεράσματα

Σωματόπαυση

- Η αύξηση της διάρκειας της ζωής του ανθρώπου, έχει σαν συνέπεια, την παράταση της χρονικής περιόδου, στη διάρκεια της οποίας ♂ και ♀ διαβιούν υπό συνθήκες ένδειας των ορμονών του φύλου τους **(εμμηνόπαυση, ανδρόπαυση).**
- Οι μεγαλύτερες μεταβολές, που αφορούν και τα δύο φύλα, παρατηρούνται μετά τα 65 (**σωματόπαυση**).

The world somatopause is coming from the Hellenic words
soma = body and pauses = stop

Σωματόπαυση

- Η σωματόπαυση ευθύνεται για τις:

  σωματικές δυσλειτουργίες

  -σαρκοπενία,

  -δυναμοπενία,

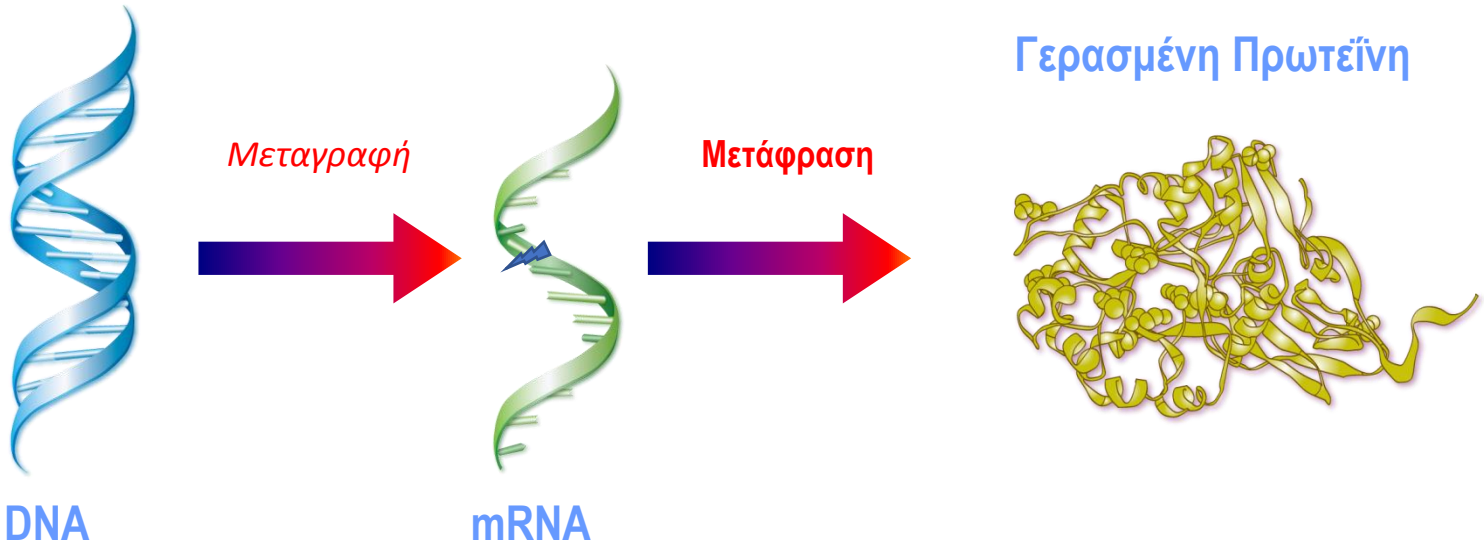
  -σύνδρομο ευπάθειας

  πνευματικές δυσλειτουργίες

- Σχετίζεται με αυξημένη συχνότητα εμφάνισης διαφόρων νοσημάτων.

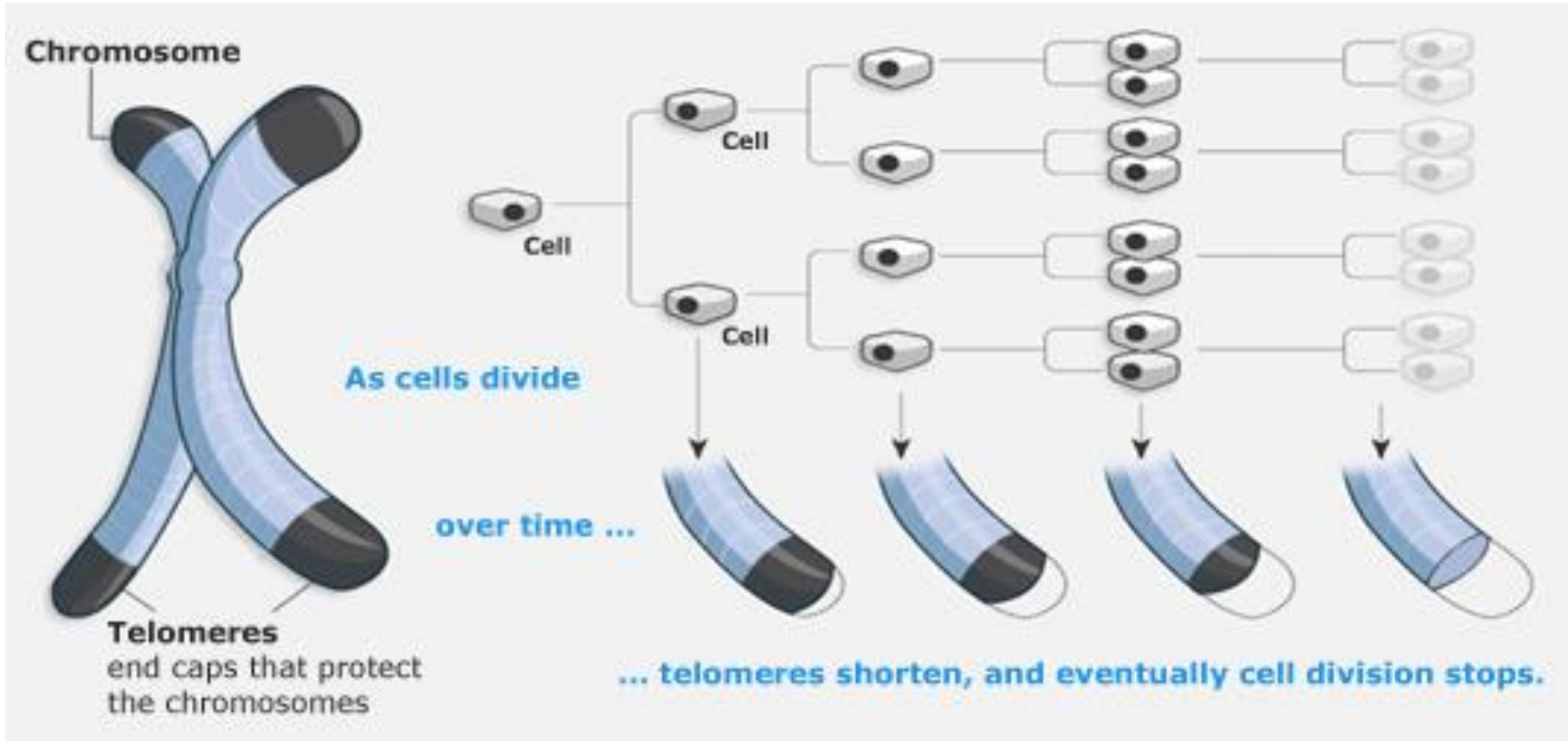
Σωματόπαυση

- **Μοριακή εξήγηση** (αλλαγές της γονιδιακής έκφρασης) η μετάφραση της γενετικής πληροφορίας δεν γίνεται με ακρίβεια, με αποτέλεσμα τη σύνθεση παθολογικών πρωτεϊνών



Σωματόπαυση

- **Κυτταρική εξήγηση** (αύξηση των γερασμένων κυττάρων) σε κάθε κυτταρικό πολλαπλασιασμό χάνεται ένα κομμάτι τελομερών (επαναλαμβανόμενες αλληλουχίες στο τέλος κάθε χρωμοσώματος).


Chromosome
Telomeres
end caps that protect
the chromosomes
Cell
Cell
Cell
As cells divide
over time ...
... telomeres shorten, and eventually cell division stops.

Σωματόπαυση

- Το **οξειδωτικό stress,** έχει συσχετιστεί ισχυρά με τον κυτταρικό θάνατο.
- Το **μέγεθος του οξειδωτικού stress** οριοθετεί την επιβίωση του κυττάρου

  -χαμηλής έντασης stress – επιβίωση του κυττάρου

  -μέτριας έντασης – θάνατος με απόπτωση

  -υψηλής έντασης – κυτταρικός θάνατος

>50 ετών, παρατηρείται:

↓ ηπατικής μάζας κατά 25%-50%,
↓ ηπατικής ροής αίματος κατά 10% -15%
↓ νεφρική μάζας κατά 25%-30%
↓ νεφρικής ροής αίματος κατά 1%/έτος

Σωματόπαυση

Απώλεια των κυττάρων είναι γραμμική

~38 εκατομμύρια το χρόνο

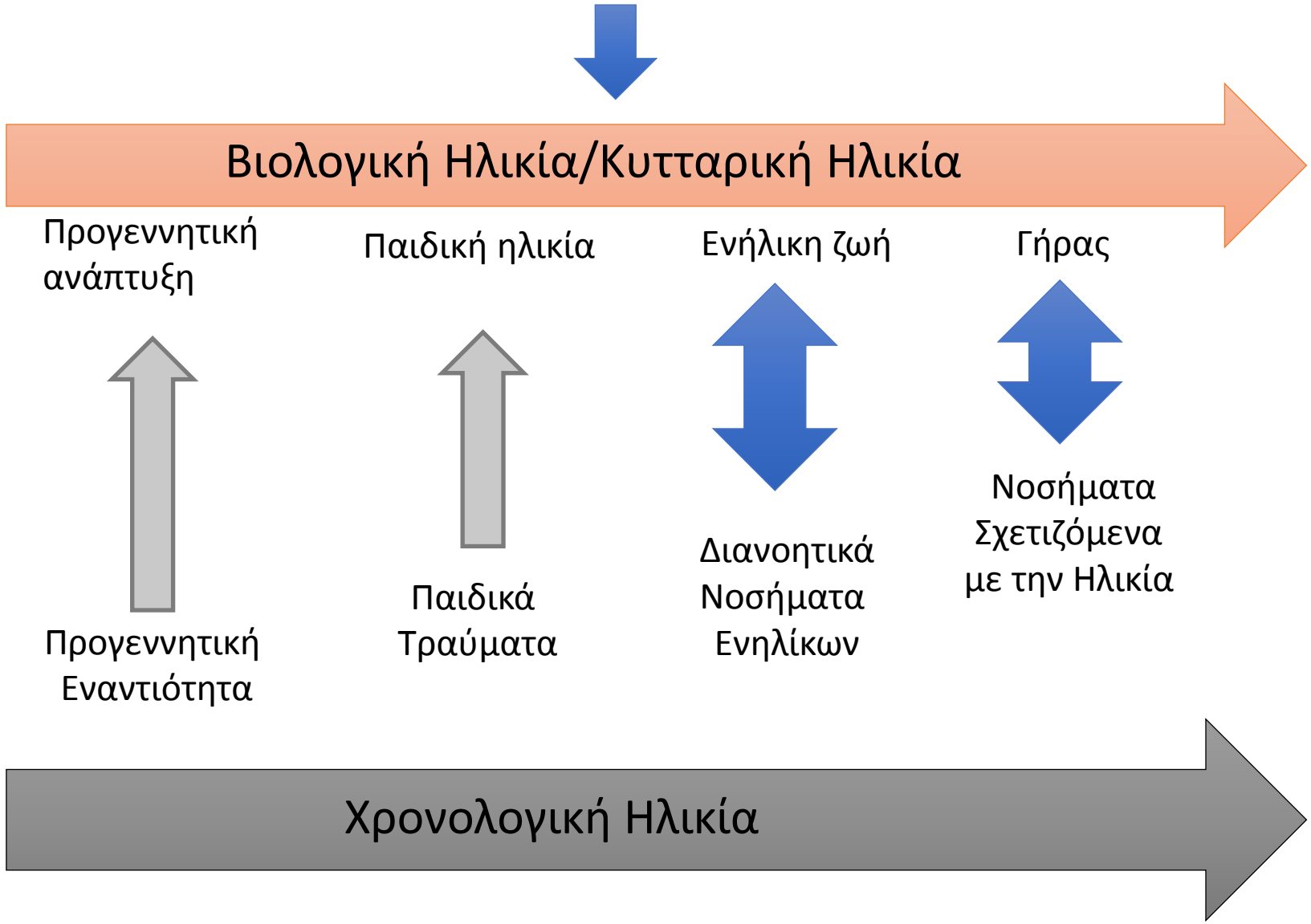
Ageing

- **Primary ageing** is the steady and currently expected sum of changes, physiological, genetic, molecular, that occur with the passage of time from fertilization to death (slow movements, fading vision, impaired hearing, reduced ability to adapt to stress, decreased resistance to infections, and others).

- **Secondary ageing** processes result from degenerative diseases and poor health practices (no exercise, smoking, excess fat and other forms of self-damage).

Kolovou G, Bartzilai, Bentos A, Caruso C, Franceschi C, Sikora E, Capri M, Avery P, Bilianou H, Panotopoulos G, Katsiki N, Mikhailidis D. Ageing, Longevity, Exceptional Longevity and Related Genetic Markers, Positional Paper. Curr Vasc Pharmacol, 2012

Υγιής Τρόπος Ζωής



Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

- Δυσλιπιδαιμίες στους νεφροπαθείς
- Σωματόπαυση
- Θεραπεία
- Οδηγίες
- Συμπεράσματα

Elderly with dyslipidemia and CKD

Questions to answer

- Is statin therapy efficacious and safe in older patients (>75 years of age)?
- What is a net benefit of statin therapy in this age group?

LL drugs in patients with CKD

- United States Renal Data System Dialysis Morbidity and Mortality Study: Wave 2, statin use in the dialysis population ➡ 32% risk ↓ in CVD mortality.
- A post hoc analysis ALLIANCE Study (579 pts with CKD, CHD, and dyslipidemia): atorvastatin ↓ primary outcome by 28%

- The Assessment of Lescol in Renal Transplant (ALERT) Study (fluvastatin vs PL in post–renal transplant pts) CVD reduction was not lower.
- PREVENT-IT: no CVD morbidity/mortality benefit of pravastatin over PL
- Deutsche Diabetes Dialyse Studie (4D study, 1255 pts): atorvastatin vs PL, no effect on the primary CHD. Fatal stroke higher in pts receiving atorvastatin
- Cardiovascular Events in Patients Undergoing Hemodialysis (AURORA) Study: 2776 pts with and without DM (rosuvastatin vs PL), no effect on primary endpoint, incidence of nonfatal stroke was higher in the statin group.

LL drugs in patients with CKD

- Study of Heart and Renal Protection (SHARP, 6247 CKD pts not on dialysis and 3023 on dialysis)

  ↓ CVD events 2.5% ➡ 1.5% at GFR 30–60 mL/min/1.73 m^2 in dialysis pts

  ↑ 7.9%, 10.2%, 10.9%, and 15% as GFR declined to 30-60, 15-30.

- Meta-analyses: statins ↓ all-cause mortality in CKD but not in pts receiving dialysis.

- CTT (183,000 pts)

  statin-based treatment became smaller as GFR declined

  no benefit in pts on dialysis + risk of stroke was higher with LDL-C lowering

LL drugs in patients with CKD

- The value of lowering cholesterol in ESKD patients has been called into question because of the U-shaped association with mortality in ESKD.
- Moreover, hypocholesterolemia has been shown to be a negative acute phase reactant that portends high mortality in ESKD and a predictor of mortality in acute kidney injury.

Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

- Δυσλιπιδαιμίες στους νεφροπαθείς
- Σωματόπαυση
- Θεραπεία
- Οδηγίες
- Συμπεράσματα

Patient Management Groups, Secondary ASCVD Prevention

IIa	B-R	7. In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences (S4.1-23–S4.1-31).
IIa	C-LD	8. In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences (S4.1-3, S4.1-10, S4.1-23, S4.1-26, S4.1-31–S4.1-36).

Clinical ASCVD: ACS, MI, stable or unstable angina, arterial revascularization, stroke, TIA or PAD, aortic aneurysm

Primary recommendation, Elderly >75 years

High-intensity statin therapy is indicated

if this cannot be used

Moderate-intensity statin therapy can be initiated

Cholesterol Treatment Trialists' (CTT) meta-analysis of statin

Clinical ASCVD: ACS, MI, stable or unstable angina, arterial revascularization, stroke, TIA or PAD, aortic aneurysm

Primary recommendation, Elderly >75 years, **LDL-C goals**

↓ ≥50%

if

LDL-C ≥70 mg/dL on maximally tolerated statin therapy

+

Ezetimibe

Consider before initiation of statin: benefits vs adverse effects

Cholesterol Treatment Trialists' (CTT) meta-analysis of statin

Specific Supportive Text, among pts ≥75 years with ASCVD

- RCTs, **moderate-intensity statin therapy:** ↓ major CV events in >75 years.
- **Upper age cutoff for moderate-intensity statin therapy was not identified** in pts with ASCVD.
- High- vs moderate-intensity statins in >75 years with ASCVD

  No heterogeneity among age groups >75, >65 to ≤75, and ≤65 years

Specific Supportive Text, among pts ≥75 years with ASCVD

- RCTs: moderate intensity vs PL
  ↓ major vascular events

- Older adults have: ↑ adverse events
  ↓ statin adherence
  ↑ discontinuation rates with high-intensity statins

Decision to initiate moderate- or high-intensity statin should be based on expected benefit vs competing comorbidities

Recommendations for Patients With DM and >75 years

COR	LOE	Recommendations
I	A	1. In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated (S4.3-1–S4.3-9).
IIa	B-NR	2. In adults 40 to 75 years of age with diabetes mellitus and an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it is reasonable to assess the 10-year risk of a first ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk (S4.3-10, S4.3-11).
IIa	B-R	3. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more (S4.3-12, S4.3-13).
IIa	B-NR	4. In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy (S4.3-5, S4.3-8, S4.3-13).
IIb	C-LD	5. In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more (S4.3-14, S4.3-15).
IIb	C-LD	6. In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician–patient discussion of potential benefits and risks (S4.3-5, S4.3-8, S4.3-13).

Specific Supportive Text

- ASCVD risk ↑ with age in DM.
- Studies with DM2t without ASCVD, incident rates of MI: 26 /1000 person-years in those >75 ys
- DM1t: 10-year fatal CVD risk in those >75 ys: 70% in men and 40% in women
- Meta-analysis of the JUPITER and HOPE-3 demonstrated benefits in ASCVD ↓ >70 vs <70 years of age
- Higher 10-year ASCVD risk, the greater is the benefit from increased LDL-C reduction.

Specific Supportive Text

- ASCVD is ↑ in >75 ys with DM who are not receiving statins, particularly those with additional RFs.

- The benefit of initiating statin therapy is limited by their ↓ **life span** or ↑ **adverse effects.**

- Reasonable to have a discussion about initiating moderate-intensity statin therapy with pts who have had **DM2t for ≥10 years or DM1t for ≥20 ys** and with pts with ≥ **1 RFs or complications, such as diabetic retinopathy, neuropathy, nephropathy.**

Primary Prevention in Elderly

Recommendations for Older Adults Referenced studies that support recommendations are summarized in Online Data Supplements 18 and 19.		
COR	**LOE**	**Recommendations**
IIb	B-R	1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (S4.4.4.1-1–S4.4.4.1-8)
IIb	B-R	2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy (S4.4.4.1-9).
IIb	B-R	3. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy (S4.4.4.1-10, S4.4.4.1-11).

Primary Prevention in Elderly

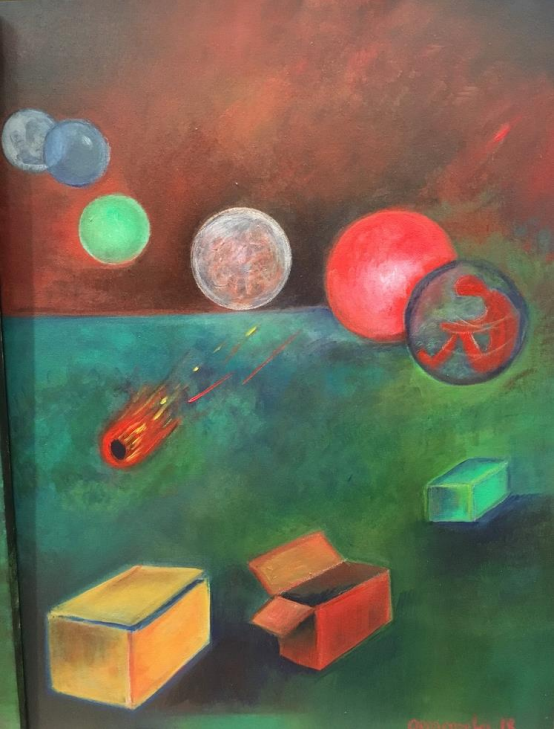
- Aggregate risks associated with statins may exceed their likely benefits.

- Limited life spans may also undercut the minimum time for likely statin benefits, especially the 4-5 ys associated with statins' stroke-reducing benefits.

- Decisions to not initiate statins, or even to deprescribe them, are reasonable in older adults when aggregate risks outweigh potential for meaningful benefit.

Primary Prevention in Elderly

- **No benefit** from pravastatin 40 mg/d vs PL
- **No benefit** from pravastatin 40 mg/d vs usual care
- Meta-analysis (JUPITER and HOPE-3) in those ≥70 ys showed a significant **26%** RRR for nonfatal MI, nonfatal stroke, or CV death.
- Healthy older pts (age ≥70 years) who used statins vs did not: ↓ risk of death but nonsignificant CV event reduction in the statin group.
- **Meta-analyses support primary prevention for adults in their 70s.**



Αντιλιπαιμική αγωγή σε ηλικιωμένους νεφροπαθείς

- Δυσλιπιδαιμίες στους νεφροπαθείς
- Σωματόπαυση
- Θεραπεία
- Οδηγίες
- Συμπεράσματα

- Statins have provide CVD protection in the general population and in early CKD.

- CVD beneficial effect of statins in CKD appears analogous to that seen in the general population, but its benefit in advanced CKD or ESKD remains questionable.

- Relative atherosclerotic burden declines as CKD progresses toward ESKD, while non-atherosclerotic conditions escalate.

- The value of ↓ LDL-C in dialysis patients is less clear and may be associated with higher risk of stroke.

- Mortality in ESKD involves an interplay of multiple factors beyond reduction of LDL-C. The complex interrelationship between inflammation, cholesterol level, and mortality in ESKD warrants further studies.

Primary Prevention in Elderly

- Even a small ↑ in geriatric-specific adverse effects with statins could offset any CV benefit.
- Statins may be indicated if, the potential for benefit is thought to outweigh the risks of adverse effects, drug–drug interactions, and cost.
- Risks associated with statins may be intensified by age and age context (e.g., multimorbidity, polypharmacy, sarcopenia, falls, frailty, and cognitive decline).
-