Oppsummering fra EUGMS 2017

- Nice 20. – 22. september
- 1350 deltakarar frå 47 land
- 38 (?) frå Norge
- Neste møte: Oktober 10-12, 2018 i Berlin,

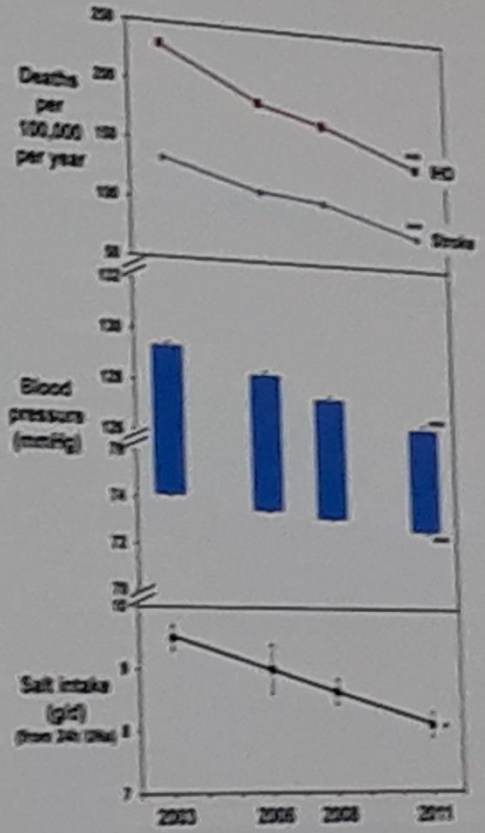
Dagens plan

- Yngve Müller Seljeseth: ernæring, forebygging av kognitiv svikt, pro et contra HT og antikoagulasjon
- Ingrid Wiig: D-vitamin. Pro et contra statiner
- Leiv Otto Watne: How to prevent delirium in post-intervention ?

Yngve Müller Seljeseth

Ålesund

Salt intake reductions, blood pressure and deaths from Coronary Heart Disease England 2003 to 2011



Feng J He et al. BMJ Open 2014;4:e004549

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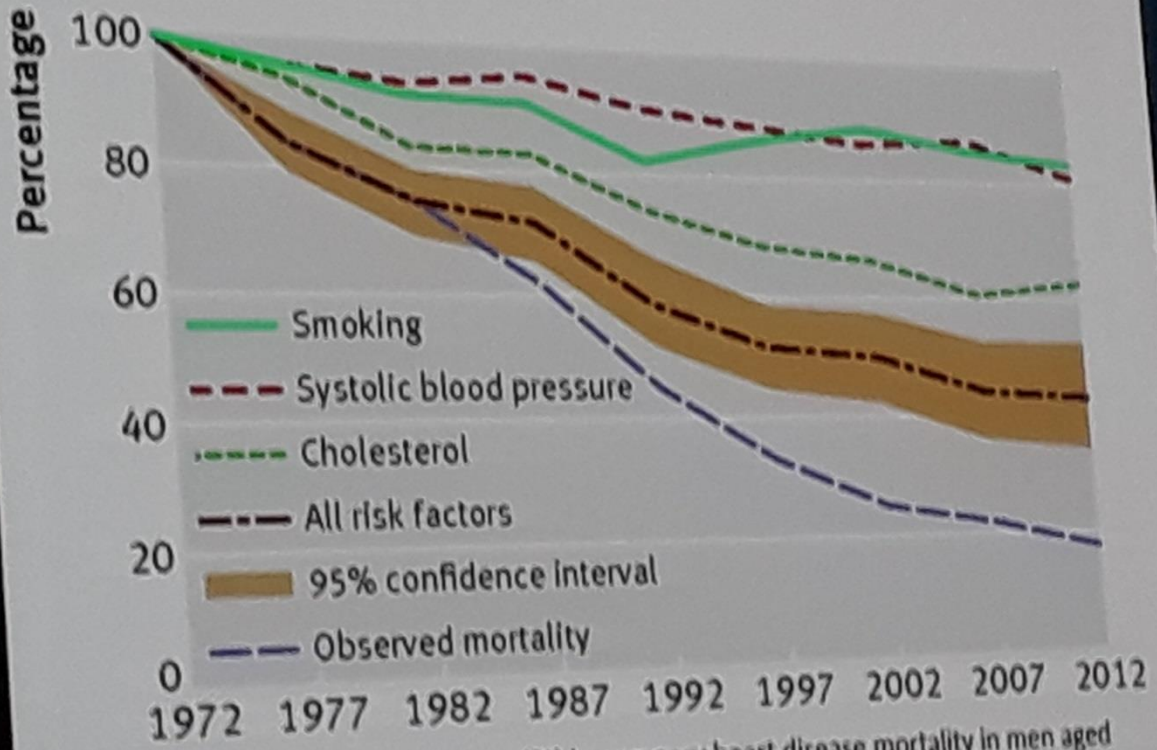
...and men



Predicted and observed reduction (%) in coronary heart disease mortality in men aged 35-64 years, 1972-2012 Jousilahti et al BMJ 2016

Forhindre underernæring, protein wasting

- Tilby næringsdrikker i påvente av behandling og under behandling der det går
- Servere fristende måltid under dialyse
- Tilsette proteinpulver på maten ved dårlig matlyst
- Ernærings shot, orale ernæringsdrikker med ekstra protein

- Lausannemeny!

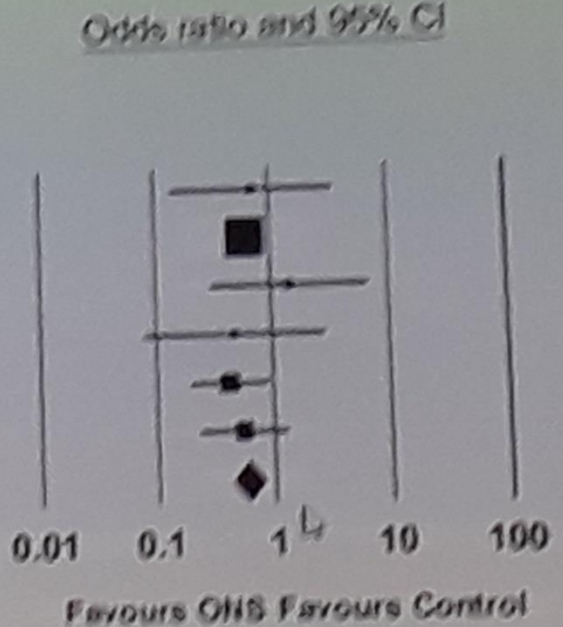
07:42

Prevention of muscle loss in older CKD patients

- Maintain energy requirements: 26-35 kcal/kg/day according to physical activity/clinial condition : individualization !
- Dialysis: High protein requirements : 1.2 - 1.5 g/kg/day
- Enriched-protein meals during dialysis
- If PEW established: ONS and/or IDPN are efficient
- Supplementation of micronutrients necessary
- Individualized prescription of electrolytes/calcium
- Correction of metabolic acidosis
- Non dialysis CKD: low protein diets (with enough calories)
- Other interventions (vitamine D – n-3 fatty acids) - low evidence

Meta analysis: Supplementation of ONS and readmission rate

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Chapman et al 2009	0.711	0.140	3.606	0.681
Garibaldi et al 2006	0.615	0.414	0.912	0.016
Gazzotti et al 2003	1.448	0.302	6.929	0.643
Miller et al 2006	0.478	0.079	2.879	0.421
Norman et al 2011	0.426	0.196	0.924	0.031
Price et al 2005	0.557	0.234	1.324	0.185
	0.591	0.434	0.804	0.001



Stratton et al. Ageing Research Reviews, Volume 12, Issue 4, 2013

Vitamin		Functions	Deficiency Disease
A	Retinol, β-carotene	Visual pigments in the retina; regulation of gene expression and cell differentiation; β-carotene is an antioxidant	Night blindness, xerophthalmia, keratinization of skin
D	Calciferol	Maintenance of calcium balance; enhances intestinal absorption of Ca^{2+} and mobilizes bone mineral	Rickets = poor mineralization of bone; osteomalacia = bone demineralization
E	Tocopherols, tocotrienols	Antioxidant, especially in cell membranes	Extremely rare—serious neurologic dysfunction
K	Phylloquinone, menaquinones	Coenzyme in formation of γ-carboxyglutamate in enzymes of blood clotting and bone matrix	Impaired blood clotting, hemorrhagic disease
B_1	Thiamin	Coenzyme in pyruvate and α–ketoglutarate, dehydrogenases, and transketolase; poorly defined function in nerve conduction	Peripheral nerve damage (beriberi) or central nervous system lesions (Wernicke-Korsakoff syndrome)
B_2	Riboflavin	Coenzyme in oxidation and reduction reactions; prosthetic group of flavoproteins	Lesions of corner of mouth, lips, and tongue; seborrheic dermatitis
Niacin	Nicotinic acid, nicotinamide	Coenzyme in oxidation and reduction reactions, functional part of NAD and NADP	Pellagra—photosensitive dermatitis, depressive psychosis
B_6	Pyridoxine, pyridoxal, pyridoxamine	Coenzyme in transamination and decarboxylation of amino acids and glycogen phosphorylase; role in steroid hormone action	Disorders of amino acid metabolism, convulsions
	Folic acid	Coenzyme in transfer of one-carbon fragments	Megaloblastic anemia
B_{12}	Cobalamin	Coenzyme in transfer of one-carbon fragments and metabolism of folic acid	Pernicious anemia = megaloblastic anemia with degeneration of the spinal cord
	Pantothenic acid	Functional part of CoA and acyl carrier protein; fatty acid synthesis and metabolism	
H	Biotin	Coenzyme in carboxylation reactions in gluconeogenesis and fatty acid synthesis	Impaired fat and carbohydrate metabolism, dermatitis
C	Ascorbic acid	Coenzyme in hydroxylation of proline and lysine in collagen synthesis; antioxidant; enhances absorption of iron	Scurvy—impaired wound healing, loss of dental cement, subcutaneous hemorrhage

Tilskudd

- Observasjonsstudier på sammenheng
- Ikke samme effekt ved tilførsel, men som regel ikke konstatert mangel!
- Vitamin D – angitt best effekt av jevnt inntak og ikke pulser med høye doser – sistnevnte øker fallfare
- Vitamin C og andre antioksidanter – måle mangel før tilskudd
- Obs vitamin B12 og cancerutvikling

Forebygging av kognitiv svikt, MCI og progresjon av demens

- Presentert en rekke studier av varierende størrelse og kvalitet
- Leve sunt mtp kardiovaskulær sykdom
  - Usikker effekt av flerumettede fettsyrer
- Bevege seg
- Ta utdanning – diskusjon om kompensasjon ved symptomer eller reelle nevronale endringer
- Ikke diskutert monoklonale antistoffer som potensiell mulighet!
- Acetylcholinesterasehemmere/memantin diskutert i seponeringsstudie. Men uklart om inkluderte var vurdert på vedvarende effekt av medikamentet og personlig mistenker jeg det bare er en forventet effekt av medikamentet og ikke argument for vedvarende bruk!

Pro et contra hypertensjon og antikoagulasjon

Ingrid Wiig

St Olav

Vitamin D og dets effekt på eldre mennesker.
Heike Bischoff-Ferrari

Dual action of Vitamin D

Muscle → Direct effect on muscle mass and function → Falls Fragility Fractures

Bone → Calcium Absorption Anti-resortive benefit on bone → Falls Fragility Fractures

Primer of Metabolic Bone Diseases 2015. Bischoff-Ferrari et al.: Chapter Falls

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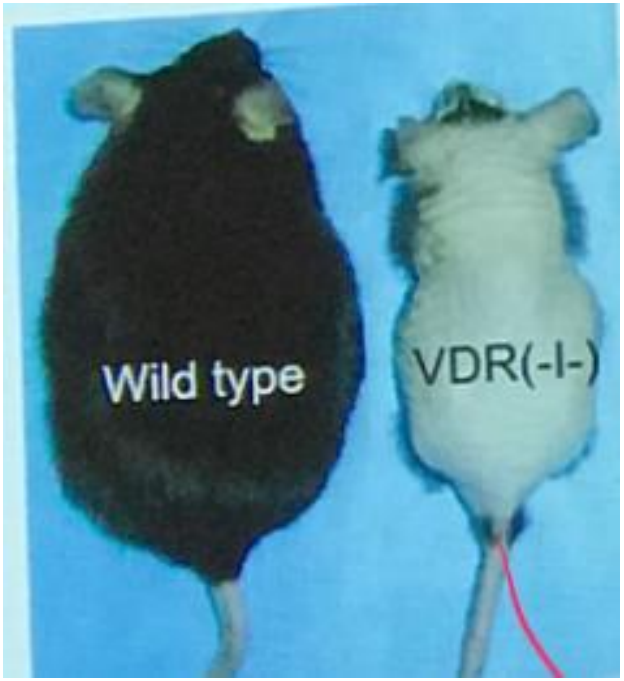
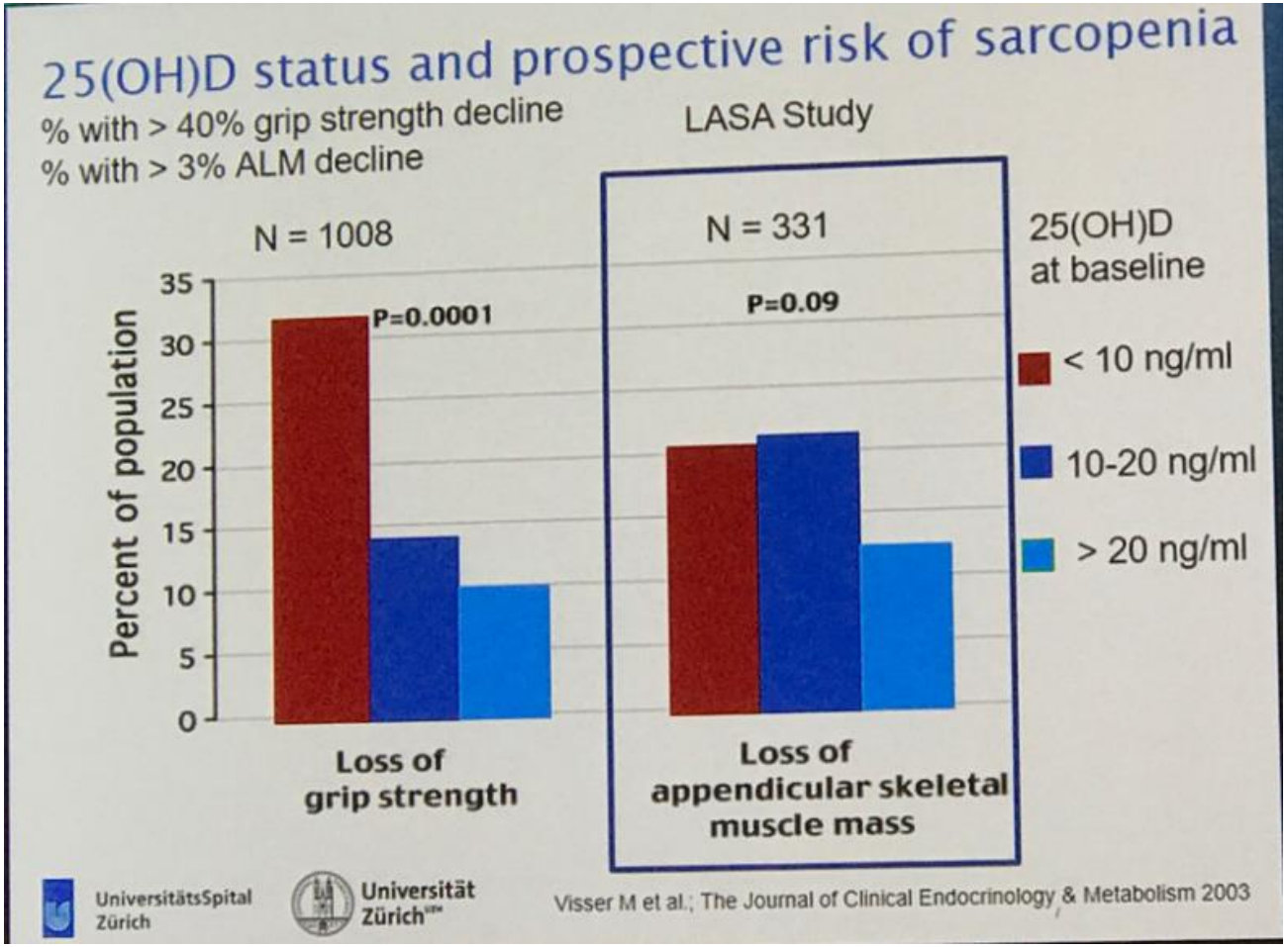
Universität Zürich

Dyreforsøk med mus har vist at mus som mangler vitamin d reseptorer (VDR (-I-)) har små muskelfibre.
I tillegg får de

- Hypertensjon
- Venstre ventrikkelhypertrofi og svikt
- Mineraliseringsdefekt i benmarg
- Redusert insulinsekresjon



Lavt nivå av vit-D fører til muskelsvinn



Muskelfunksjon
Metaanalyse av studier på vitamin D's effekt på muskelfunksjon i voksne 60+

Signifikant effekt på
-postural sway
Timed up and go
Muskelstyrke i underekstremitetene

- Alle studiene viste at daglige doser på 800 IU eller mer ga positiv effekt på balanse og/eller muskelstyrke.

17 RCTs

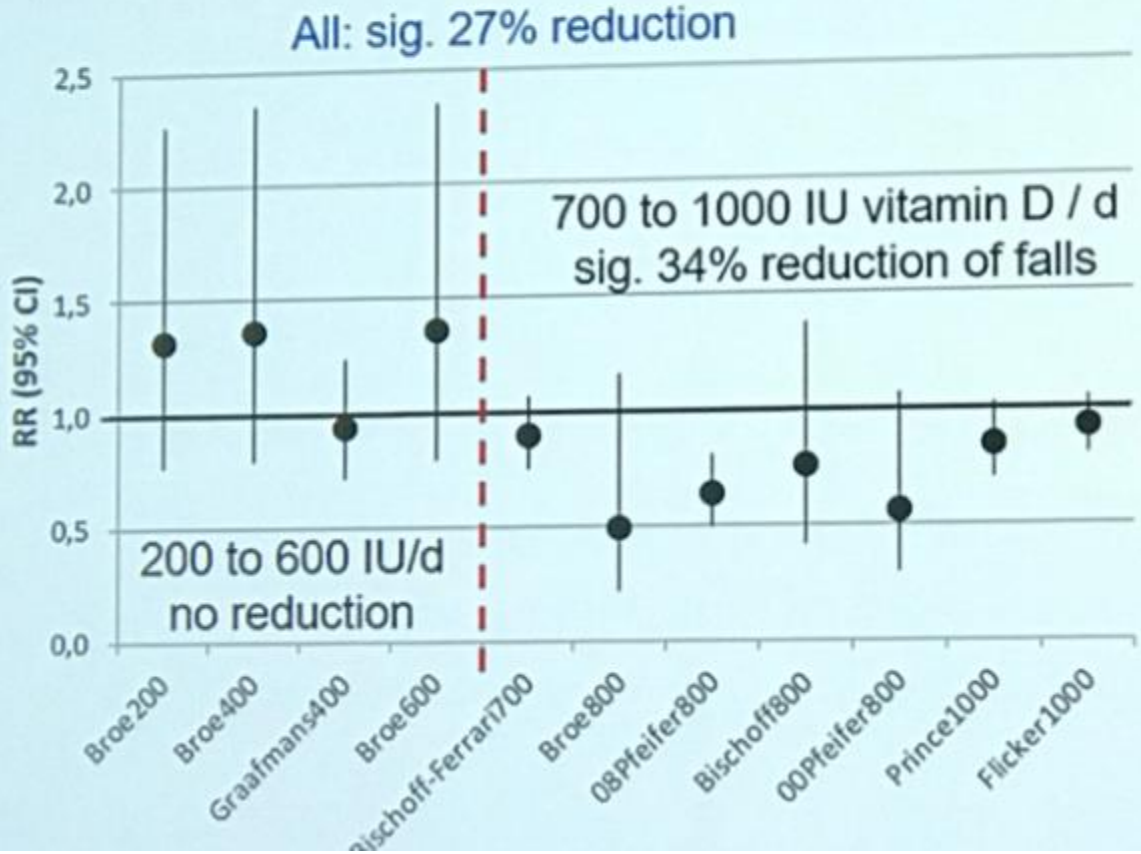
- **no significant effect** of vitamin D supplementation in adults with **25(OH)D levels > 25 nmol/l**.

- **large effect of vitamin D supplementation** on hip muscle strength among those with **25(OH)D levels < 25 nmol/l** (SMD 3.52, 95%CI 2.18, 4.85).

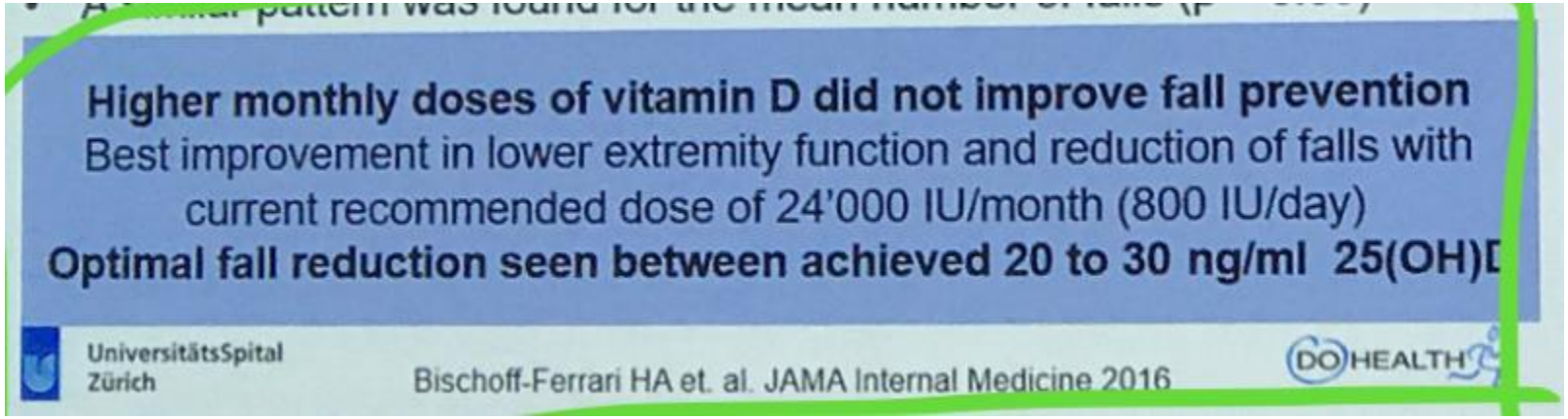
Stockton KA et al.; OP Int 2011

Vitamin D Dose and Fall Reduction

8 RCTs (n = 2426) sorted by dose given

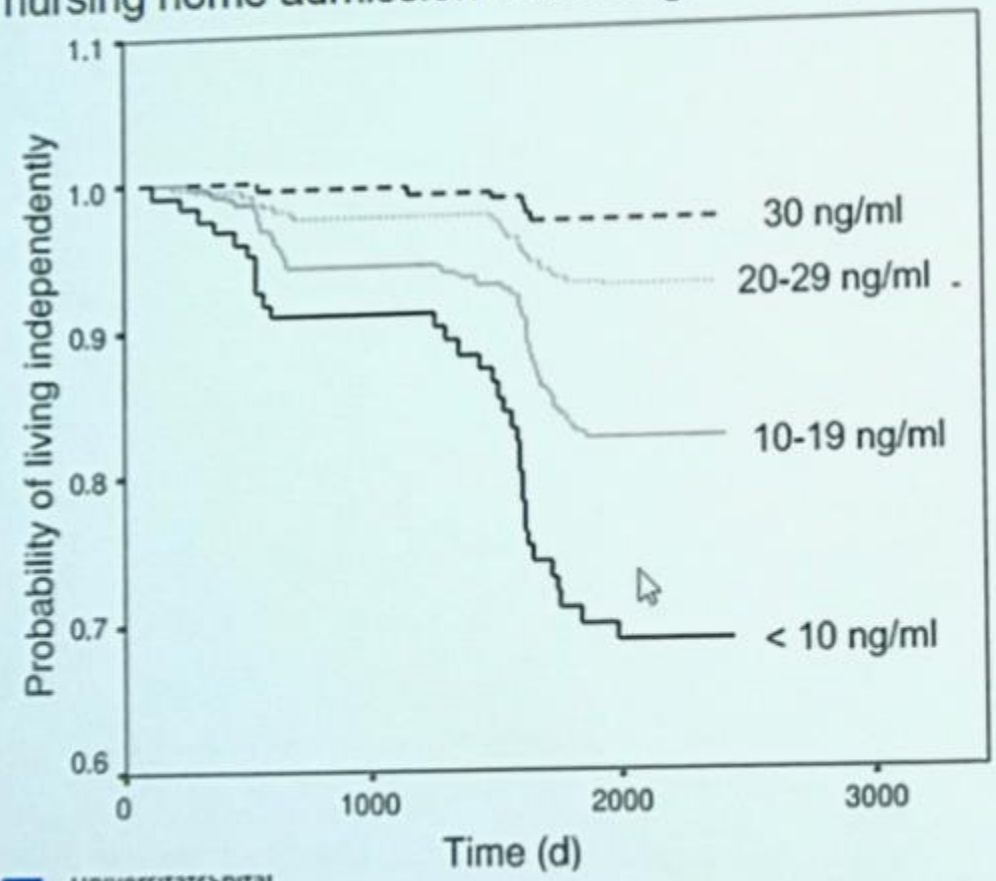


Bischoff-Ferrari, et al. BMJ 2009 and 2011


Higher monthly doses of vitamin D did not improve fall prevention
Best improvement in lower extremity function and reduction of falls with current recommended dose of 24'000 IU/month (800 IU/day)
Optimal fall reduction seen between achieved 20 to 30 ng/ml 25(OH)D
UniversitätsSpital Zürich
Bischoff-Ferrari HA et. al. JAMA Internal Medicine 2016
DO HEALTH

Vitamin D Status and Loss of Autonomy: admission to nursing home

nursing home admission according to categories of 25(OH)D at BL



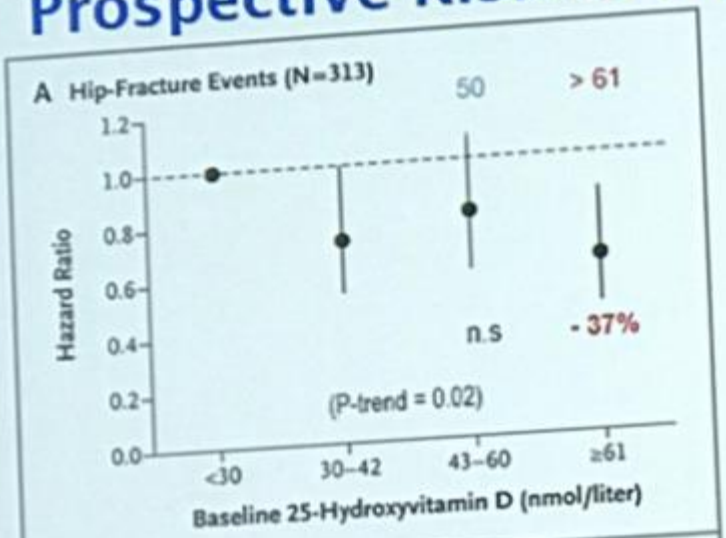
Higher BL 25(OH)D was associated with a lower risk of nursing home admission.

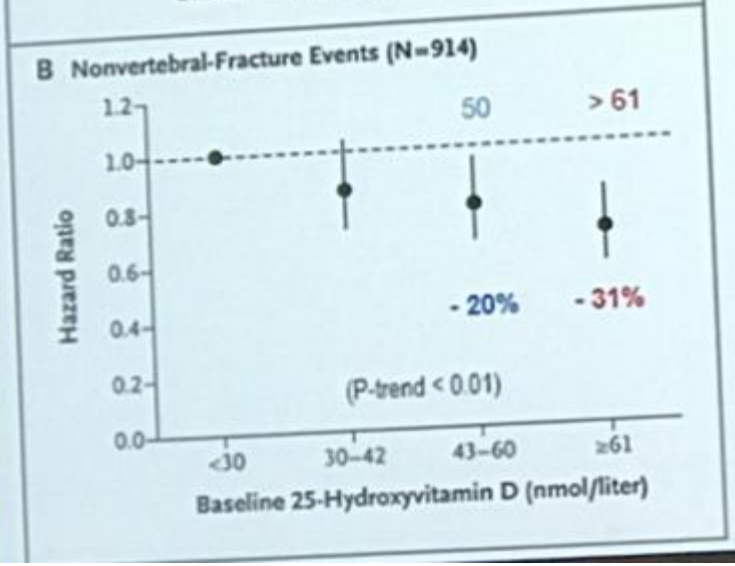
LASA
Age 65+
N = 1260
FU = 6 yrs

Universitätsspital Zürich

Visser M et al.; *Am J Clin Nutr* 2006

25(OH)D status and **Prospective Risk of hip fracture**





In 4383 persons 65 years of age or older:

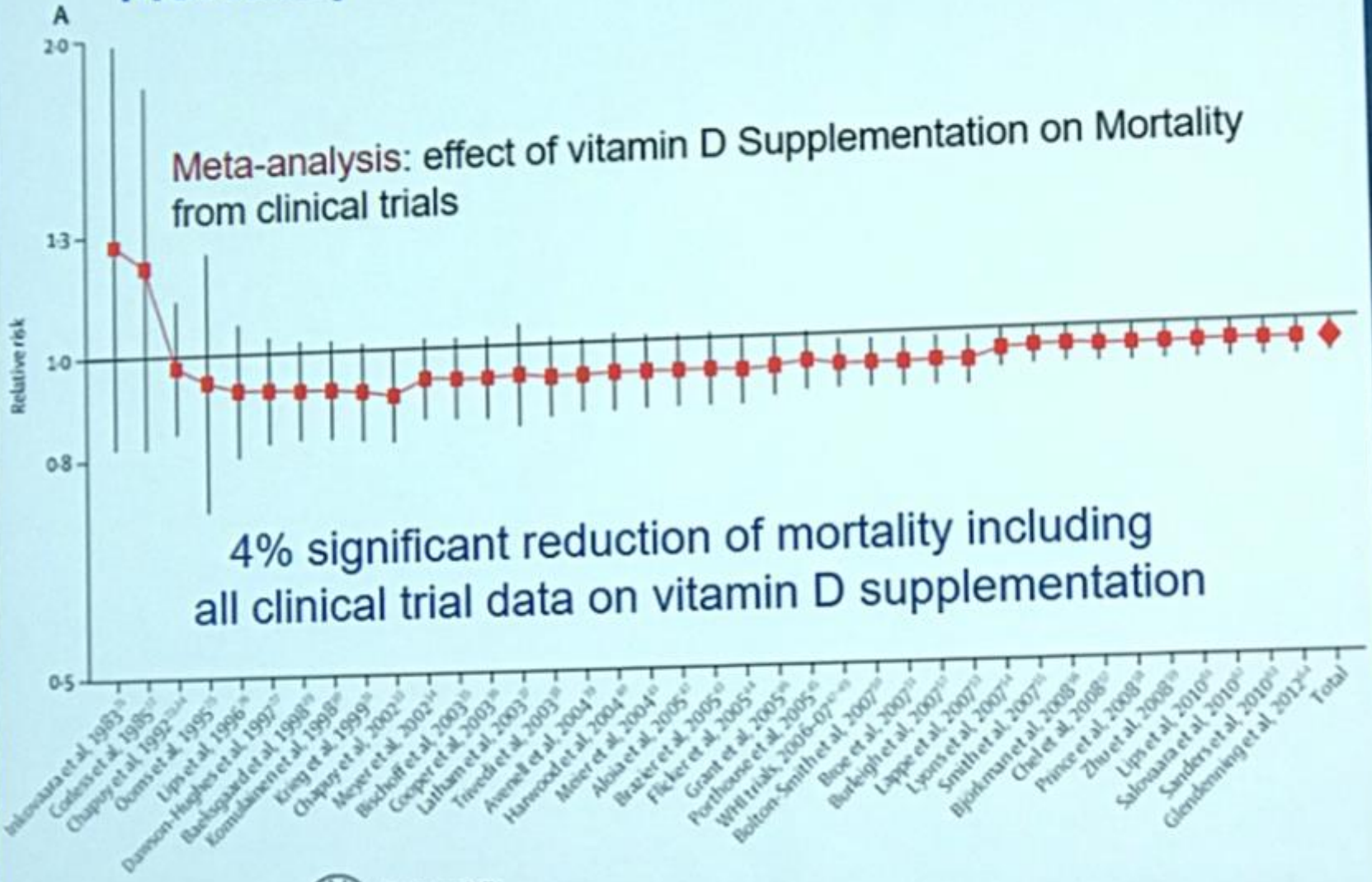
- Seniors with 25(OH)D levels > 24 ng/ml achieved **37%** hip fracture reduction as compared with persons with baseline levels of less than 30 nmol per liter

- Seniors with 25(OH)D levels > 24 ng/ml achieved **31%** non-vertebral fracture reduction

Adjusting for assignment (treatment or control), age group, sex, and type of dwelling

Bischoff-Ferrari HA et al. N Engl J Med 2012;367:40-49.

Mortality and Vitamin D Supplementation



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Bolland et al. Lancet Endocrinology 2014

Summary
-- What does Vitamin D prevent in older People?

There are several lines of evidence that link **vitamin D to several components of the instrument library of sarcopenia**

- including muscle mass, muscle strength, function and muscle quality

and **key consequences of sarcopenia**

- including falls, hip fractures, loss of autonomy and mortality

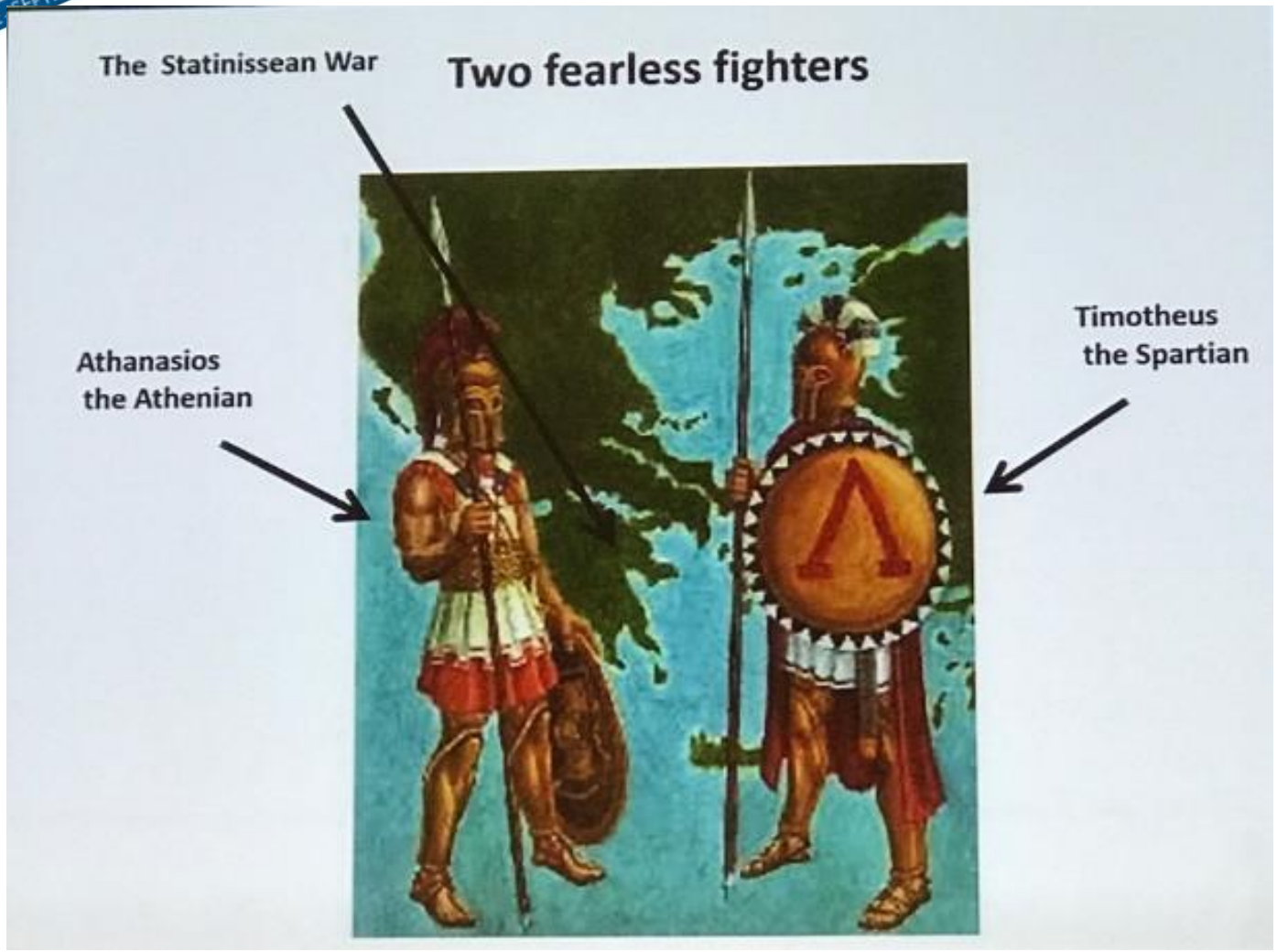
- Based on the current literature these components may improve most among seniors with vitamin D deficiency
- The vitamin D dose with best evidence for fall and fracture prevention is 800 IU per day (24'000 IU/month)

- Evidence from large RCTs that tests the benefit of vitamin D in the prevention of sarcopenia and frailty is missing to date

Lese mer om emnet?

- http://www.rheumatologynetwork.com/news/interview-dr-bischoff-ferrari-addresses-vitamin-d-intake

Statiner etter 80 år pro-con



Pro – Timo Sandberg

(professor i geriatri, universitetene i Helsinki og Oulu)

- Resultater indikerer at en genetisk predisposisjon for høye LDL-nivå bidrar til dødelighet hele livet, også hos de eldste eldre
- En gunstig LDL genetisk risikoprofil er assosiert med familiær lang levetid

Median life expectancy in average health in old age

- Age 85: men 4.7, women 5.9 years
- Age 90: men 3.2, women 3.9 years

- **Statins have proven efficacy for secondary prevention starting within 2 years**

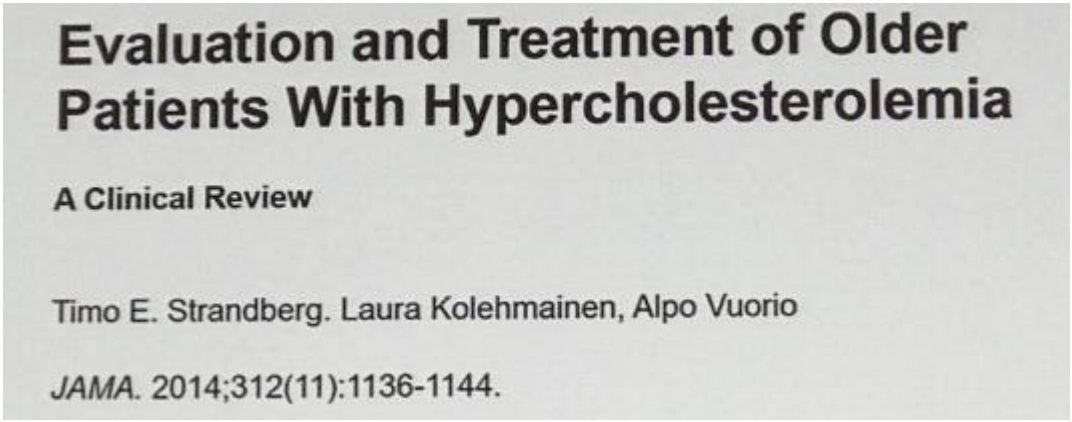
Pro,- er statiner skadelige i høy alder?

- Muskel-effekter
  - Velkjent, men sjelden (1-5%)
  - Ofte nocebo effekt
  - Finnes ikke sikker evidens på at det påvirker mobilitet/fysisk funksjon
- Diabetes
  - Hos de som ville få diabetes uansett
  - Med hvilken klinisk signifikans, spesielt hos de eldste?
- Frailty
  - Statiner fører ikke til frailty/skrøpelighet, men kan til og med forebygge??
  - Fordeler uavhengig av multi prognostisk indeks (MPI)

    (Pilotto et al: PlosOne 2015, Am J Cardiol 2016)

Pro: «eldre» er heterogene

- Til og med 80+ vil kunne ha fordeler av statiner
- Seponer aldri statiner grunnet høy alder alene
- Oppstart av statin hjelper ikke en pasient i terminal fase
  - Og ingen guideline råder deg til det!



Con: Athanase Benetos

(Prof. Indremedisin og geriatri, Universitetet i Nancy, Fr.)

- Kolsterol-relatert risiko
- Statiners fordeler
  - Pimærprevensjon
  - Sekundærprevensjon
- Stainrelaterte bivirkninger

- …. I folk over 80??

No positive association between total cholesterol and mortality after the age of 65

- Krumholz HM, et al. Lack of association between [illegible] and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA. 1994
- Weverling Rijnsburger AW et al, The Rotterdam Study: Lancet, 1997
- Scats IJ et al; Honolulu Heart Program. Lancet 2001
- Brescianin S et al; Italian Longitudinal Study on Aging. J Am Geriatr Soc. 2003
- Schupf N et al; Northern Manhattan Study J Am Geriatr Soc. 2005
- Melton PE et al; Mennonite community J Hum Biol. 2006
- Spada RS et al ; Sicilian study Arch Gerontol Geriatr. 2007

JUPITER
in the "older group"
>70; mean 74 years

- Rosuvastatin therapy had significant:
- - **beneficial effects for CVD morbidity and mortality** (HR: 0.61 [95% CI, 0.46–0.82]),
- **…but rates of all-cause death did not differ significantly between the statin group and the placebo** group.

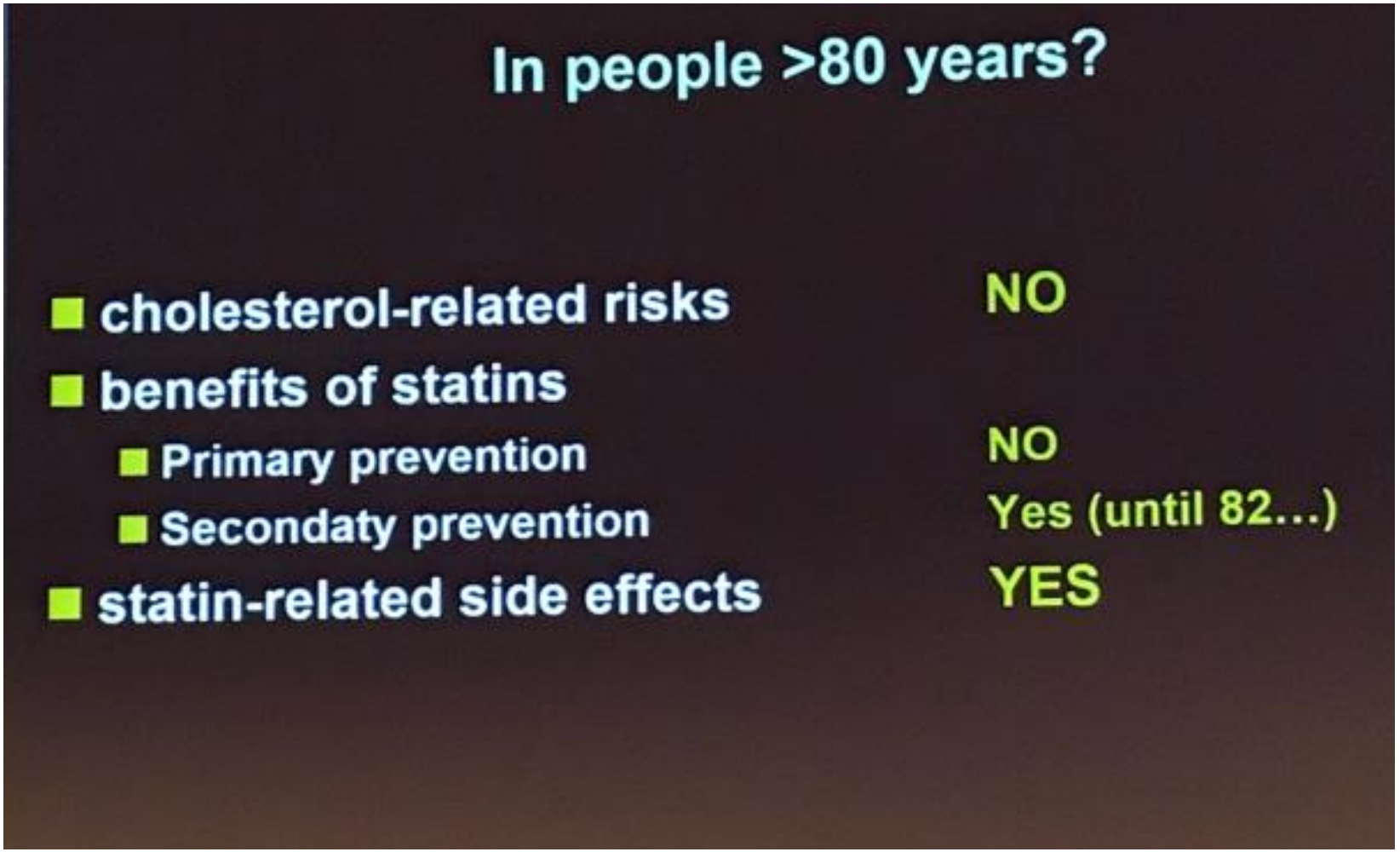
Glynn RJ, et al. Rosuvastatin for primary prevention in older …
Ann Intern Med. 2010; 152(8):488–496.

PROSPER Study
aged 70-82 years (mean 75 years)

- Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals.
- No effect on total mortality
- No effect on strokes
- Slight though statistically significant increase in cancers

Shepherd J et al Lancet. 2002 Nov 23;360(9346):1623-30.

Con: statiner hos de >80?



Leiv Otto Watne

OUS

How to prevent delirium in post-intervention ?

Leiv Otto Watne
Oslo Delirium Research Group
University of Oslo

Outline

- Non-pharmacological prevention
- Pharmacological prevention
- Take home messages

Non-pharmacological prevention

Age and Ageing 2015; 44: 196–204
doi: 10.1093/ageing/afu173
Published electronically 25 No
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SYSTEMATIC REV
Preventing
multicomp
A systemat
literature
Research
JAMA Internal Medicine
on | HEALTH CARE REFORM
ness of Multicomponent Nonpharmacological
nterventions
alysis
rong Yue, MD; Esther Oh, MD; Margaret Puelle; Sarah Dowal, MSW, MPH;
haron K. Inouye, MD, MPH
Nonpharmacological Interventions to Prevent Delirium: An Evidence-Based Systematic Review
RYAN M. RIVOSECCHI, PharmD
PAMELA L. SMITHBURGER, PharmD, MS, BCPS
SUSAN SVEC, RN, BSN, CCRN
SHAUNA CAMPBELL, RN, BSN
SANDRA L. KANE-GILL, PharmD, MS
Postoperative Delirium in Older Adults: Best Practice Statement from the American Geriatrics Society
The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults
Cochrane Library
Cochrane Database of Systematic Reviews
Interventions for preventing delirium in hospitalised non-ICU patients (Review)
Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA
irium
w. The
SENATOR project ONTOP Series
Iosief Abraha[1]*, Fabiana Trotta[1], Joseph M. Rimland[2], Alfonso Cruz-Jentoft[3], Isabel Lozano-Montoya[3], Roy L. Soiza[4], Valentina Pierini[5], Paolo Dessì Fulgheri[5], Fabrizia Lattanzio[2], Denis O'Mahony[6], Antonio Cherubini[1]

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for preventing delirium in hospitalised non-ICU patients (Review)

Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA

«There is strong evidence supporting multi-component interventions to prevent delirium in hospitalized patients»
«Effect sizes were similar in medical (RR 0.69, four studies, n=1365) and surgical settings (RR 0.71, three studies, n=585)

Siddiqi, Cochrane Database Syst Rev. 2016

Multicomponent non-pharmacological prevention works – but how to implement it?

Dissecting Delirium

Phenotypes, Consequences, Screening, Diagnosis, Prevention, Treatment, and Program Implementation

Joseph H. Flaherty, MD[a,*], Jirong Yue, MD[b], James L. Rudolph, MD, SM[c,d]

«Delirium program implementation checklist»

1. Take the pulse on the organization
2. Identify allicances
3. Identify champions
4. Identify the process steps
5. Plan –do – study - act
6. Expand beyond intial area

Flaherty, Clin Geriatr Med 2017

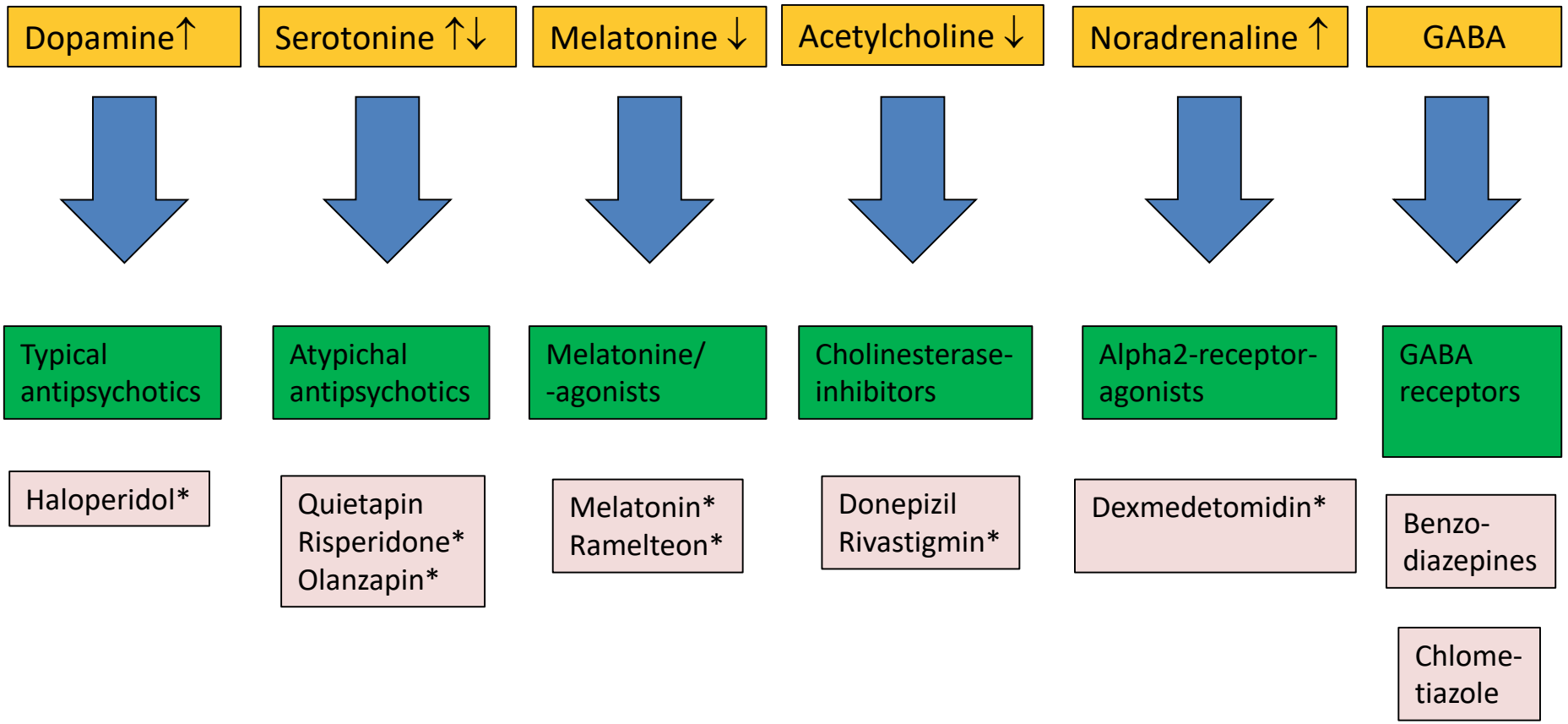
Pharmacological prevention

Randomised trials for prevention of delirium until 2015

Study	Drug	N	Population
Kalisvaart (2005)	Haloperidole vs placebo	430	Hip fracture
Liptzin (2005)	Donepezil vs placebo	80	Elective orthopedic surgery
Prakanrattana (2007)	Risperidone vs placebo	126	Elective cardiac surgery
Sampson (2007)	Donepezil vs placebo	33	Elective orthopedic surgery
Gamberini (2009)	Rivastigmin vs placebo	113	Elective cardiac surgery
Larsen (2010)	Olanzapine vs placebo	400	Elective orthopedic surgery
Sultan (2010)	Melatonin vs midazolam vs clonidine vs placebo	203	Elective orthopedic surgery
Rubino (2010)	Clonidine vs placebo	30	ICU
Marcantonio (2010)	Donepezil vs placebo	16	Hip fracture
Al-Aama (2011)	Melatonin vs placebo	145	Medical patients
De Jonghe (2011)	Melatonin vs placebo	444	Hip fracture
Wang (2012)	Haloperidole vs placebo	457	Non cardiac surgery
Zaslavsky (2012)	Rivastigmine vs placebo	28	Elective surgery
Hakim (2012)	Risperidone vs placebo	101	Cardiac surgery
Hatta (2014)	Ramelteon vs placebo	67	ICU and medical wards

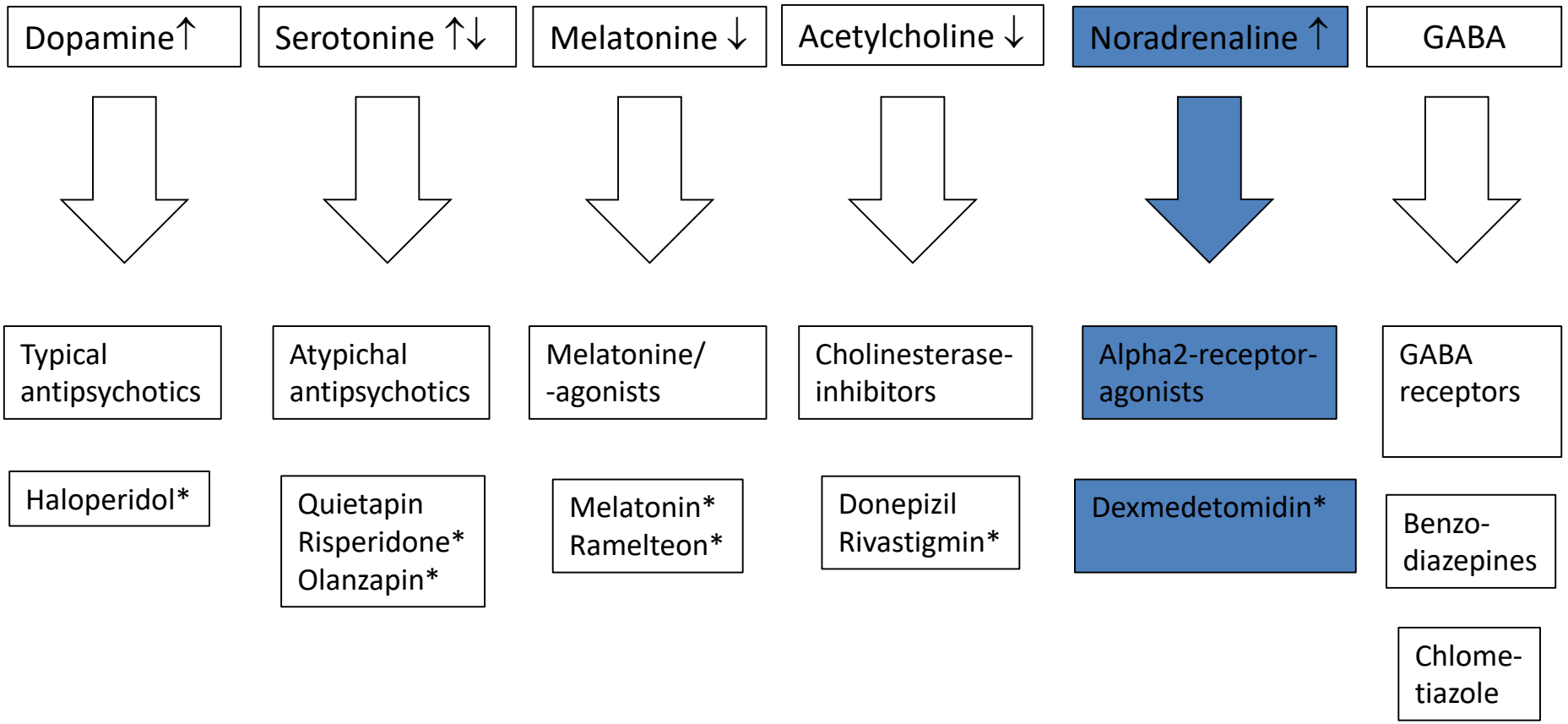
Randomised trials for prevention of delirium 2016 -

Study	Drug	N	Population
Youn (2016)	Rivastigmine vs no patch	62	Hip fracture
Needham (2016)	Rosuvastatin vs placebo	272	ICU
Su (2016)	Dexmedetomidine vs placebo	700	ICU
Liu (2016)	Dexmedetomidine vs placebo	200	Elective orthopedic surgery
Djaiani (2016)	Dexmedetomidine vs propofol	185	Cardiac surgery
Li (2016)	Dexmedetomidine vs midazolam/propofol	126	ICU multitrauma
Royse (2017)	Methylprednisolone vs placebo	498	Cardiac surgery (bypass)
Li (2017)	Dexmedetomidine vs placebo	285	Cardiac surgery
Li (2017)	Nimodipine vs placebo	60	Elective spinal surgery
Tanaka (2017)	Desflurane vs. Propofol	96	Elective orthopedic surgery
Mu (2017)	Parecoxib vs placebo	620	Elective orthopedic surgery
Page (2017)	Simvastatin vs placebo	142	ICU
Avidan (2017)	Ketamine vs placebo	673	Major surgery
Hatta (2017)	Suvorexant vs placebo	72	ICU and regular wards
Leung (2017)	Gabapentin vs placebo	697	Non-cardiac surgery
Deiner (2017)	Dexmedetomidine vs placebo	404	Elective surgery
Sugano (2017)	Yokukansan TJ-54 vs placebo	186	Elective surgery (cancer)



*) some evidence for delirium prevention in RCTs

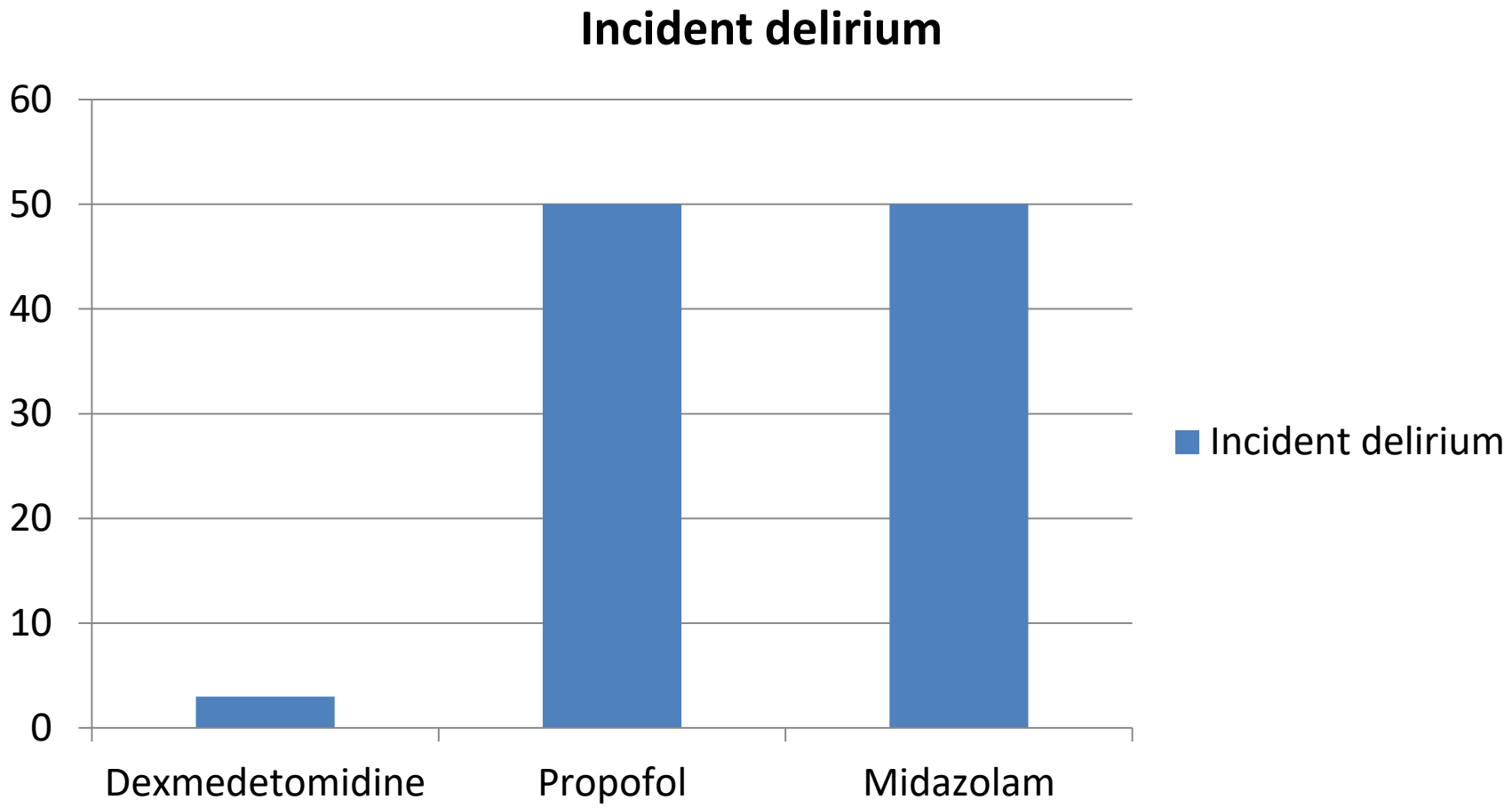
Steiner, Eur J Anaesthesiol 2011
Maldonado, Am J Geriatr Psychiatry 2013


Dopamine↑
Serotonine ↑↓
Melatonine ↓
Acetylcholine ↓
Noradrenaline ↑
GABA
Typical antipsychotics
Atypichal antipsychotics
Melatonine/ -agonists
Cholinesterase-inhibitors
Alpha2-receptor-agonists
GABA receptors
Haloperidol*
Quietapin
Risperidone*
Olanzapin*
Melatonin*
Ramelteon*
Donepizil
Rivastigmin*
Dexmedetomidin*
Benzo-diazepines
Chlome-tiazole

	Prevention	Treatment
Alfa2 receptor agonists		

Study	Drug	N	Population
Pandharipande (2007)	dexmedetomidine vs lorazepam	106	Surgical/Medical ICU.
Riker (2009)	dexmedetomidine vs midazolam	375	Surgical/Medical ICU.
Maldonado (2009)	dexmedetomidine vs propofol vs midazolam	90	Surgical ICU
Shebabi (2009)	dexmedetomidine vs morphine	299	Surgical ICU
Liu (2015)	Dexmedetomidine vs placeboe	200	elective surgery
Su (2016)	Dexmedetomidine vs placeboe	700	non-cardiac surgery
Djaiani 2016	Dexmedetomidine vs propofol	183	cardiac surgery
Li (2016)	Dexmedetomidine vs midazolam/propofol	126	ICU multitrauma
Li (2017)	Dexmedetomidine vs placebo	285	Cardiac surgery
Deiner (2017)	Dexmedetomidine vs placebo	404	Elective surgery

Maldonado, 2009



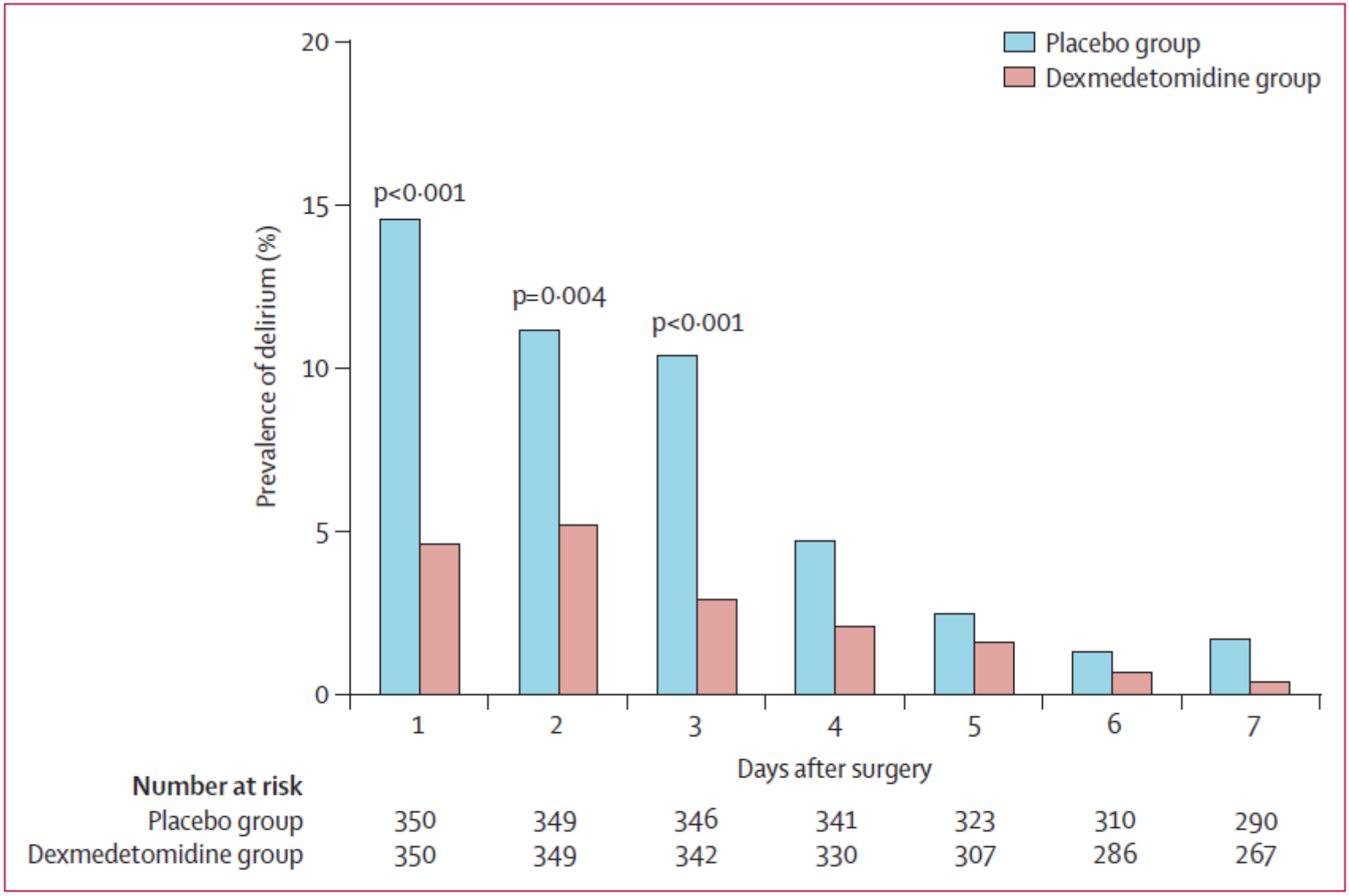


***Figure 2*: Daily prevalence of postoperative delirium**

Sample sizes differ from the first to seventh day because some patients were discharged ~~from hospital or died~~ during this period.

Su, Lancet 2016

JAMA Surgery | Original Investigation

Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery

A Randomized Clinical Trial

Discussion

In this article, we describe intraoperative use of dexmedetomidine in older adults to prevent postoperative delirium. We found that dexmedetomidine did not reduce the incidence of delirium over saline placebo. In total, 12.2% (23 of 189) of

Deiner, JAMA Surg 2017

REVIEWS

Prevention of Post-operative Delirium in the Elderly Using Pharmacological Agents

Patrice Tremblay, MD, CCFP (COE)[1], Susan Gold, MD, FRCPC[2]

- the strongest evidence, still very limited, is for haloperidole, but the appropriate dose and route of distribution remain to be determined»
- «..non-pharmacological measures should be the mainstay of treatment to reduce and prevent post-operative delirium in the elderly»

Tremblay, Can Ger J 2016

Take home messages

- Non-pharmacological prevention works and should be given highest priority. It is harder than it looks.
- Pharmacological prevention shows promise, but more studies are needed. And we are getting them!
- Use your delirium knowlegde to promote geriatrics (and yourself!) at your hospital

EUROPEAN DELIRIUM ASSOCIATION

KEYNOTE SPEAKERS

Henrik Zetterberg: Biomarkers for the Vulnerable Brain

MD, PhD, Professor of Neurochemistry, University of Gothenburg, Sweden and UCL, UK

Karin Neufeld: Delirium Management and Prevention

Associate Professor, Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, USA