CORATA Belgique
5ème Congrès de Biologie Clinique

Oxidative stress workup :

Scam or future?

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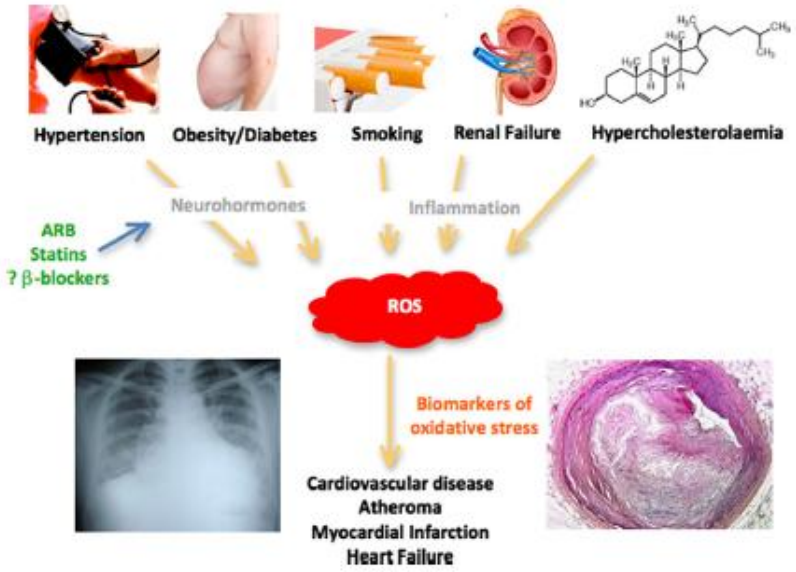
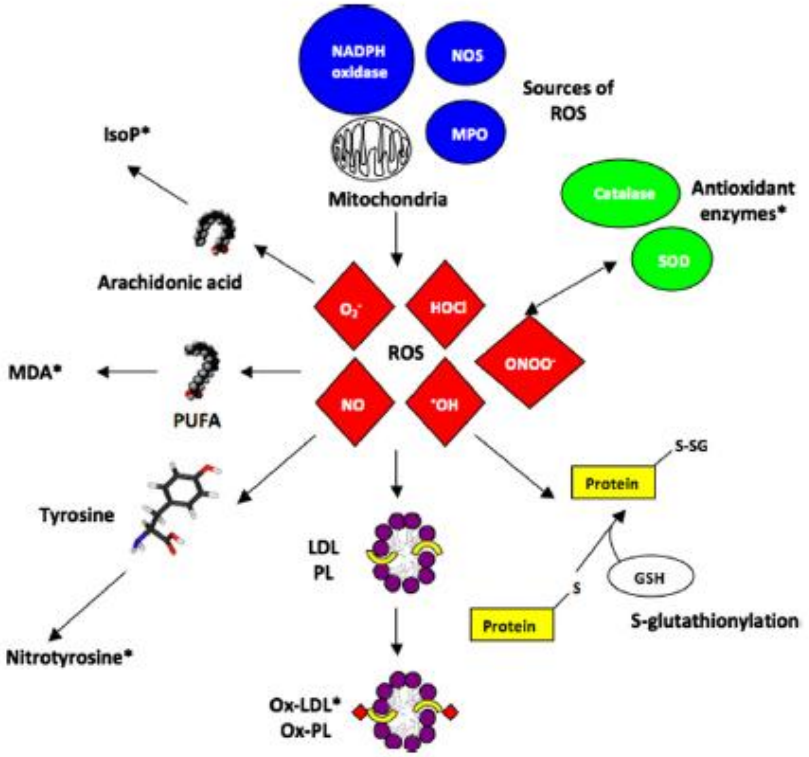
Conflict of Interest Declaration

✓ The body's trillion or so cells face formidable threats, from lack of food to infection with a virus.

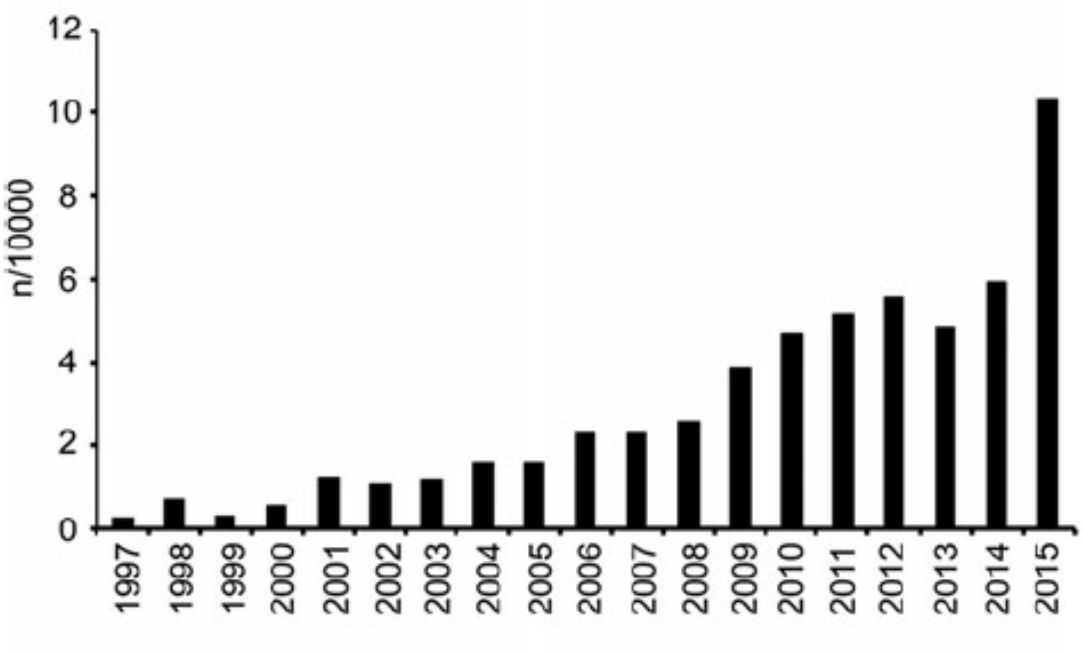
✓ Free radicals represents another constant threat and came to public attention in the 1990s:

- ➢ Capable of damaging cells and genetic material
- ➢ Can change the instructions coded in a strand of DNA
- ➢ Make a circulating low-density lipoprotein molecule more likely to get trapped in an artery wall





Frijhoff et al.; 2015
T.H. Chan, 2014
Ho et al.; 2013



Hundreds, probably thousands, of different substances that can act as antioxidants.

Most familiar:

Vitamin C, vitamin E, beta-carotene, and other related carotenoids, along with the minerals selenium and manganese.

Joined by glutathione, coenzyme Q10, lipoic acid, flavonoids, phenols, polyphenols, phytoestrogens,

Frijhoff et al.; 2015
T.H. Chan, 2014

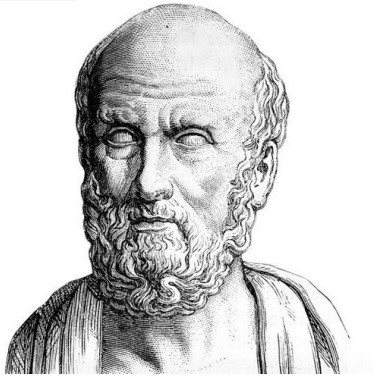
Web-shopping

- Cholestérol
- Vitamin A
- Vitamin E
- Vitamin C
- Coenzyme Q10

- SOD
- GPX

- LDLox
- LpPLA2
- GPX
- Acide urique
- Ferritine

Scam ?



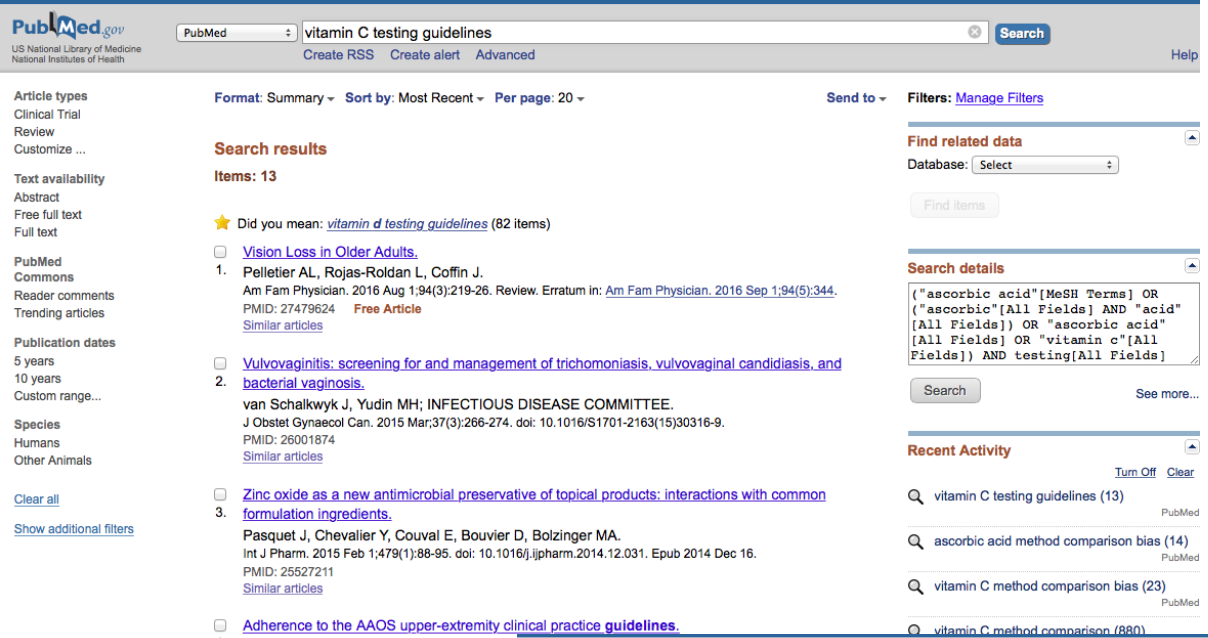
Antioxidant supplements represent a >> $500 million dollar industry

Future ?


EVIDENCE


ABUS DE
CONFIANCE

Analytical reliability?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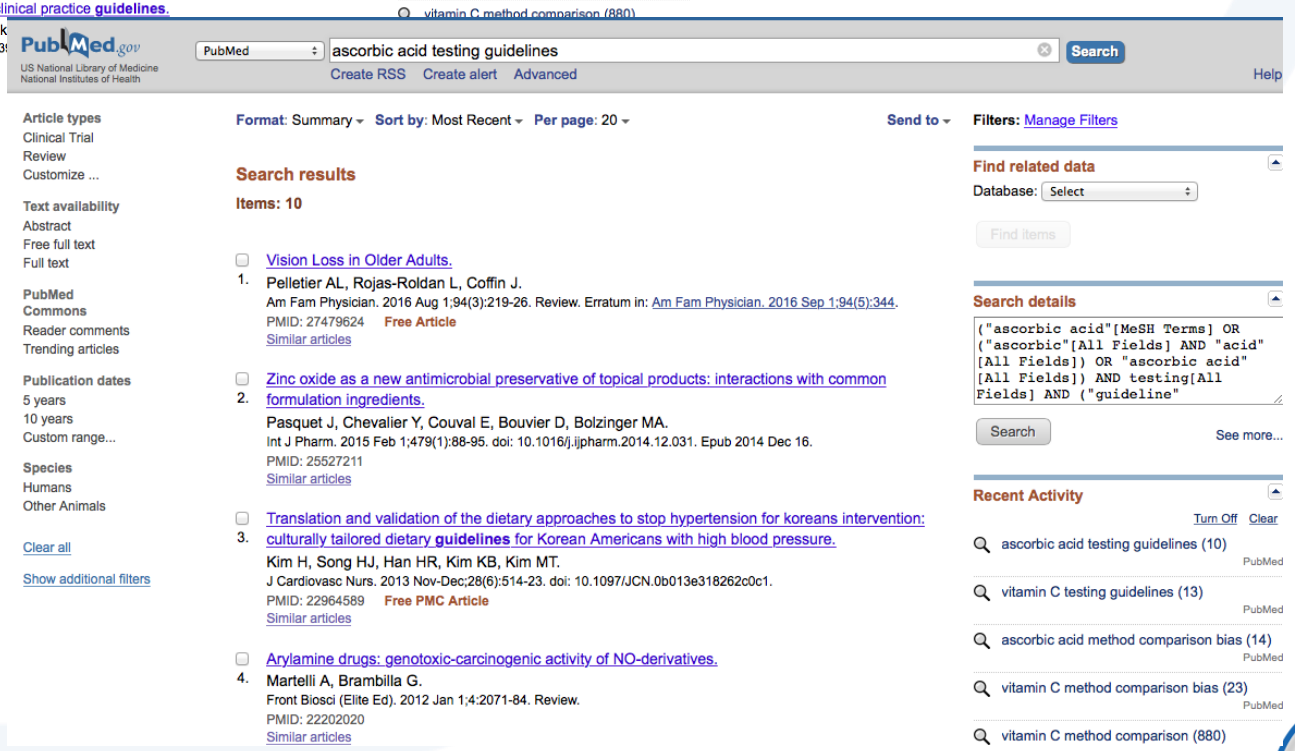
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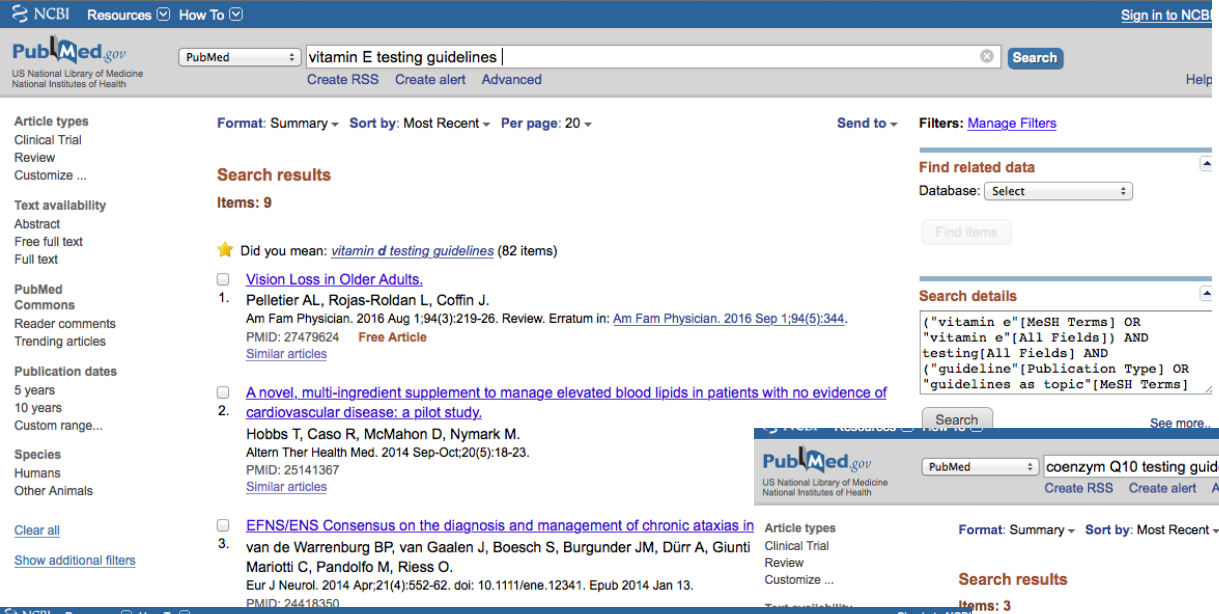
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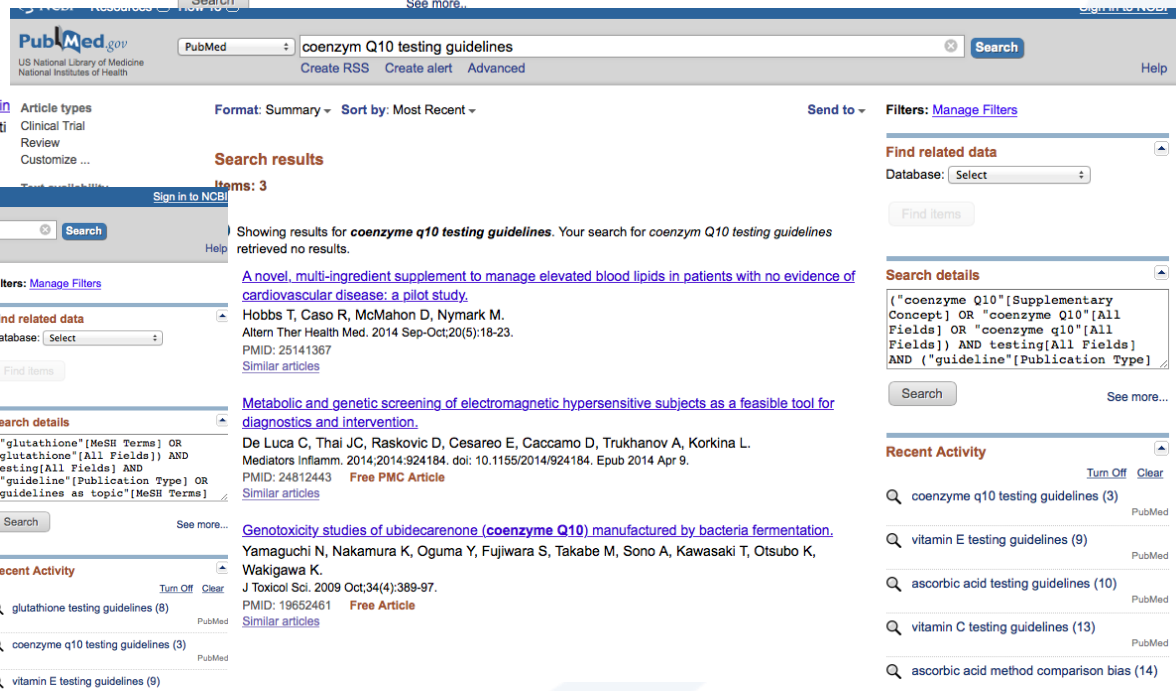
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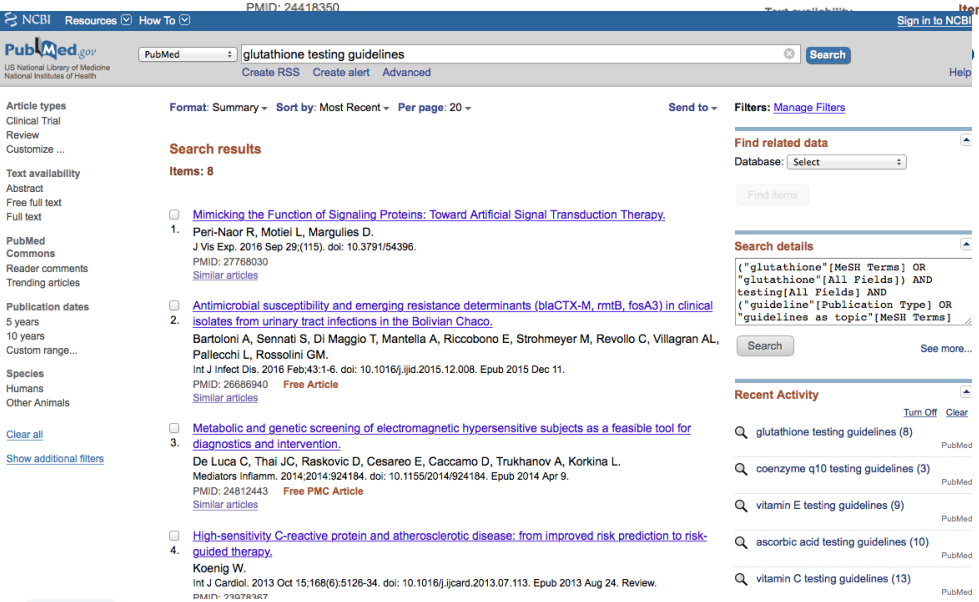
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Testing for biomarkers of oxidative stress

Large variety of testing methods have been proposed and applied

- Methods based on inhibited autoxidation studies (kinetics of oxygen consumption)
- Analytical determination of secondary oxidation products (e.g. carbonyl compounds)
- The majority of testing methods, however, do not involve substrate autoxidation.
  - ELISA
  - GC-MS/MS, LC-MS/MS
  - competitive bleaching of a probe (e.g. ORAC assay, β-carotene, crocin bleaching assays, and luminol assay)
  - reaction with a different probe (e.g. spin-trapping and TOSC assay)
  - indirect methods based on the reduction of persistent radicals (e.g. galvinoxyl, DPPH and TEAC assays), or of inorganic oxidizing species (e.g. FRAP, CUPRAC and Folin-Ciocalteu assays).

Testing for biomarkers of oxidative stress

Nothing but the Truth Manual
$120.00

Six Sigma Risk Analysis
$90.00

PHOTO GALLERY

- a-amylase: articles with values from non-healthy subjects have been eliminated, thus resulting in lower within and between-subject biological variation estimates: CV_I from 9.5% to 8.7% and CV_G from 29.8% to 28.3%.
- a-carotene: analyte included in this edition because the first paper appeared in 2005
- a-Tocopherol: analyte included in this edition because data were found recently
- Amyloid A: a paper describing values for within and between-subject biological variation for this analyte was just found and results are incorporated in this fourth edition for the first time.
- Ascorbic acid (Vitamin C): a paper from 1994 was just found and results have been added
- ?-carotene: analyte included in this edition because the first paper appeared in 2005
- C reactive protein: one paper published in 2005 has been added, thus lowering the median value compared with that published in the third edition.
- Endothelial growth factor: a paper describing values for within and between-subject biological variation for this analyte was published in 2005 and has been incorporated in this fourth edition.
- d-aminolevulinic acid: analyte included in this edition because the first paper appeared in 2005
- Endothelial growth factor: analyte included in this edition because the first paper appeared in 2005
- Free carnitine: a paper describing values for within and between-subject biological variation for this analyte was found and the analyte has been incorporated in the fourth edition.
- Lutein: analyte included in this edition because the first paper appeared in 2005
- Lycopene: analyte included in this edition because the first paper appeared in 2005
- Lymphocyte CD4: analyte included in this edition because the first paper appeared in 2005
- Porphobilinogen: analyte included in this edition because the first paper appeared in 2005
- Porphyrins: analyte included in this edition because the first paper appeared in 2005
- Prostate-specific antigen (PSA): a new paper from 2005 has been added. Also, data from prostate cancer patients have been eliminated. This amendment caused higher CVI values compared with the 2003 edition CVI from 14.0% to 18.1%
- Retinol: analyte included in this edition because the first paper appeared in 2005
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- Dr David Burnett's new book on ISO 15189
- Empower IVD Globe Meeting Report
- European Approaches to Analytical Goal-

Testing for biomarkers of oxidative stress

Table 1. Components of biological variation, II, and RCV for vitamins in plasma, whole blood, or erythrocytes.

Vitamin	Units	Mean	Median	Range	CV_I, %	CV_G, %	II	RCV, %
A (retinol)	μmol/L	2.19	2.20	1.30–3.80	6.2	21	0.36	21.3
E (α-tocopherol)	μmol/L	32.4	31.0	19.2–56.0	7.6	21	0.37	21.9
E/Cholesterol	μmol/mmol	6.39	6.29	4.23–10.9	7.0	15	0.54	22.4
Lutein	μg/L	192	178	92.4–367	13	31	0.42	36.0
Lycopene	μg/L	199	196	42.0–435	22	33	0.69	63.4
α-Carotene	μg/L	47.2	39.7	10.3–191	24	65	0.38	69.2
β-Carotene	μg/L	276	259	67.2–748	18	48	0.38	49.3
K (phylloquinone)	nmol/L	1.59	1.45	0.21–6.50	38	44	0.88	108
K/Triglycerides	nmol/mmol	1.45	1.32	0.23–4.14	30	46	0.72	90.7
B_1 (TDP)	ng/g Hb	501	486	361–775	4.8	12	0.47	15.8
Whole blood B_2 (FAD)	nmol/L	384	377	252–554	5.8	10	0.59	17.1
Erythrocyte B_2 (FAD)	nmol/g Hb	2.33	2.15	1.13–4.61	6.4	11	0.75	25.5
Plasma B_6 (PLP)	nmol/L	52.9	51.1	23.1–155	20	34	0.61	58.0
Erythrocyte B_6 (PLP)	nmol/g Hb	354	349	191–740	14	24	0.60	41.4
Plasma C (ascorbic acid)	μmol/L	47.8	47.0	6.33–95.2	20	21	0.95	56.2

Table 2. Laboratory method imprecision (CV_A) and desirable specifications for imprecision, bias, and total error derived from biological variation data.

	Desirable specification			
Vitamin	I,[a] %	B, %	TE, %	CV_A, %
A	3.2	5.4	10.7	4.1
E	3.8	5.6	11.9	3.1
E/Cholesterol	3.5	4.1	9.9	3.8
Lutein	6.5	8.5	19.2	2.4
Lycopene	11.2	9.9	28.1	5.4
α-Carotene	12.0	17.4	36.8	6.5
β-Carotene	9.1	12.9	27.9	3.4
K	19.3	14.6	45.9	9.0
K/Triglycerides	15.2	13.8	38.6	10
B_1	2.4	3.1	7.1	3.0
B_2 (whole blood)	2.9	3.0	7.8	2.1
B_2 (erythrocytes)	3.2	4.3	9.6	6.5
B_6 (plasma)	10.1	9.8	26.3	3.6
B_6 (erythrocytes)	6.8	6.8	18.0	6.1
C	10.0	7.2	23.7	3.4

[a] I, imprecision; B, bias; TE, total error.

Talwar et al.; 2005

Testing for biomarkers of oxidative stress

Guideline

Laboratory Medicine Best Practice Guideline: Vitamins A, E and the Carotenoids in Blood

***Ronda F Greaves,[1,2,3] Gerald A Woollard,[1,4] Kirsten E Hoad,[1,5] Trevor A Walmsley,[1,6] Lambro A Johnson,[1,7] Scott Briscoe,[1,7] Sabrina Koetsier,[1,8] Tamantha Harrower,[1,9] Janice P Gill[1,8]**

Table 5. Biological variation and desirable specification for performance.[30,86]

		Biological Variation		Desirable specification		
Matrix	**Measurand**	**CVw**	**CVg**	**Imprecision (%)**	**Bias (%)**	**Total Error (%)**
P-	Retinol	6.2	21	3.1	5.5	10.6
S-	Retinol	13.6	19	6.8	5.8	17.1
S-	β-Carotene	36	39.7	18	13.4	43.1
S-	α-Tocopherol	13.8	15	6.9	5.1	16.5
(B)Eryth-	Vitamin E (α-Tocopherol)	7.6	21	3.8	5.6	11.9

P, plasma; S, serum; B, blood; CVw, intra-individual biological variation; CVg, inter-individual biological variation.

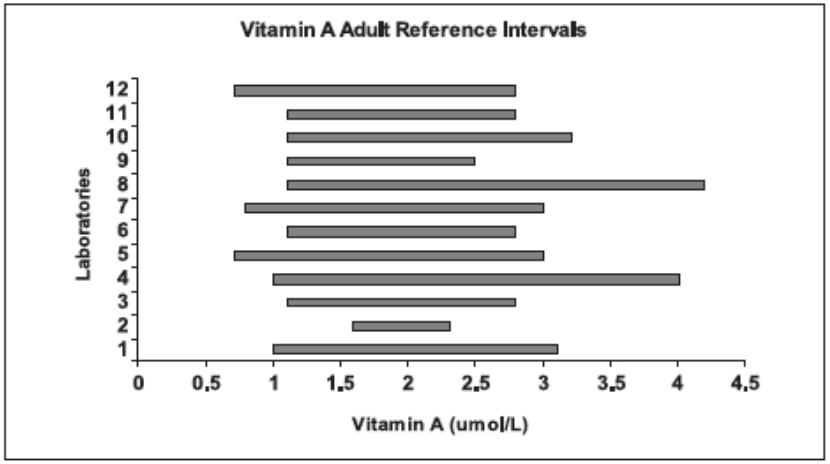
Testing for biomarkers of oxidative stress

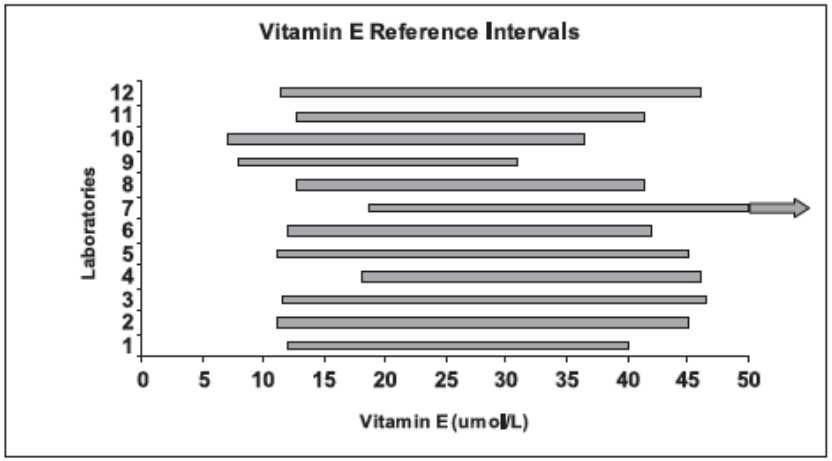
Table 1. CoQ10 Levels in Healthy Populations

Study	Reference, Mean±SD (µmol/L)	Indexed to LDL (µmol/mmol)	Index to Total Cholesterol (µmol/mmol)
Niklowitz et al[23] (n=10)	1.11±0.24	N/A	N/A
Sohmiya et al[24] (n=29)	0.75±0.22*	N/A	0.16±0.05
Miles et al[25] (n=106)	1.04±0.33	0.33±0.1	0.20±0.05
Duncan et al[26] (n= 24)	0.675±0.315	N/A	N/A
Niklowitz et al[27] (n=14)	1.02±0.3	N/A	0.24±0.07

CoQ10 indicates Coenzyme Q10; and LDL, low-density lipoprotein.
*units in µmol.

Sharma et al.; 2016





Greaves et al.; 2016

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15.4K Tweets

#Germany
7,841 Tweets

#StreetArt
4,105 Tweets

#Iran
24.8K Tweets

Van Overtveldt

All Mentions Settings

Dr Patrick Twomey @DrTwomey · Sep 20
Replying to @DAMGRU
Useless and non-specific

catherine.margot77 and 3 others followed you · Sep 20

Noel Larsen liked a Tweet you were mentioned in · Sep 18

Lefevre @Lefevra2
Hi @DAMGRU.

Romeu @patyy5550 · Sep 16
Replying to @DAMGRU
Les cobbayes ça été les français pas ds les laboratoires
Translate from French

Who to follow · Refresh · View all

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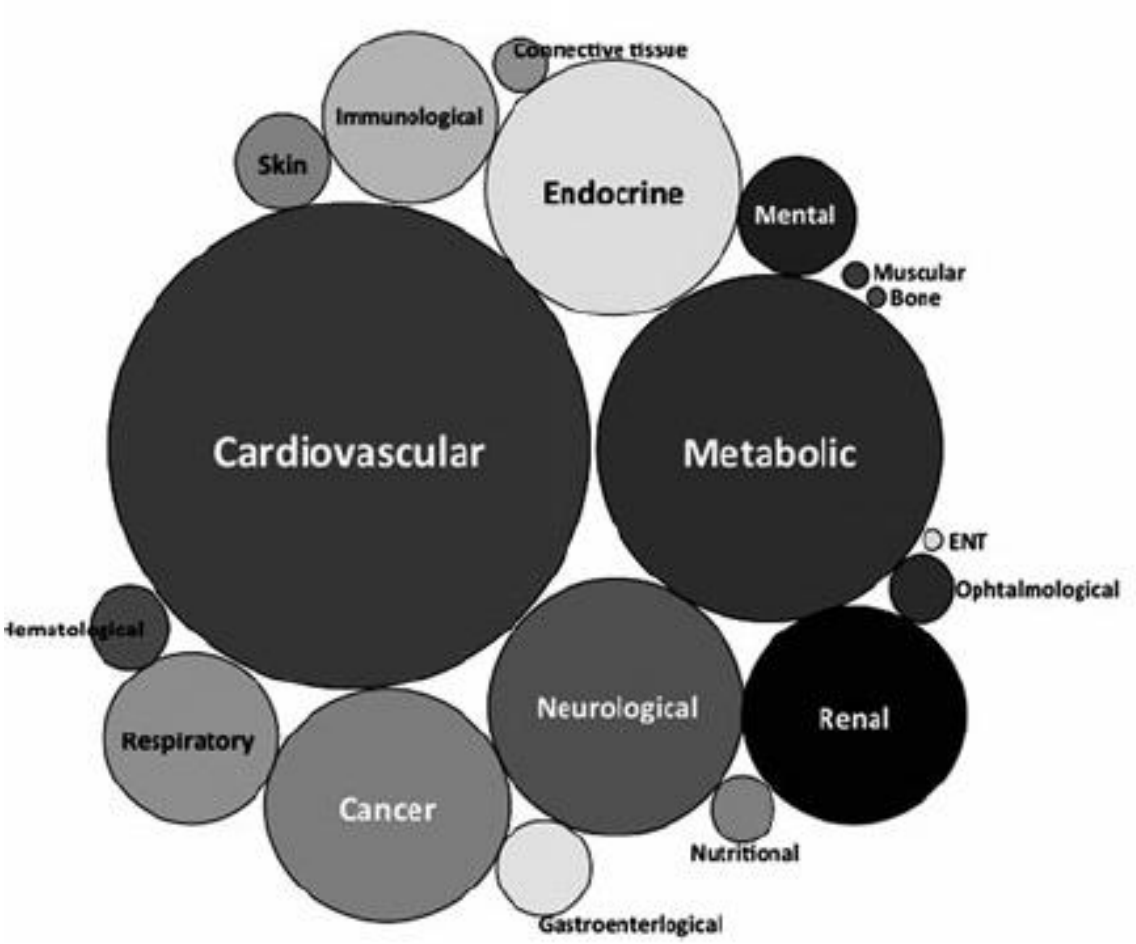
Clinical Evidence?

Evidence ?



Frijhoff et al.; 2015

Evidence ?

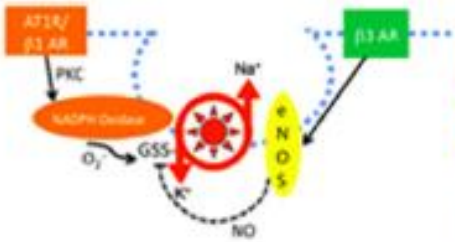
UNIVERSITY OF OXFORD

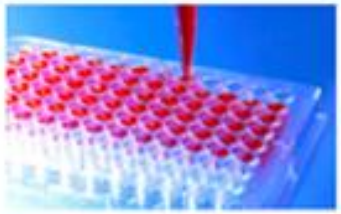
Level	Type of evidence
1a	Systematic review with homogeneity of randomized control trials
1b	Individual randomized control trial with a narrow confidence interval
1c	All or none related outcome
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low-quality randomized control trials, e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	Systematic review with homogeneity of case–control studies
3b	Individual case–control study
4	Case-series (and poor-quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Cardiovascular diseases ?

Table 1
Advantages and disadvantages of various biomarkers of oxidative stress.

Biomarker	Advantages	Disadvantages	Comments	References
IsoPs	Can be detected in various samples (serum, urine) and has been shown to be elevated in the presence of a range of CV risk factors.	Current methods of quantification are impractical for large-scale screening (GC/MS) or requires further validation (immunoassay kits).	No evidence linking this biomarker to clinical outcomes yet.	[22,24,25]
MDA	Technically easy to quantify spectrophotometrically using the TBARS assay. ELISA kits to detect MDA also have good performance. Studies show MDA can predict progression of CAD and carotid atherosclerosis at 3 years.	TBARS assay is non-specific (can detect aldehydes other than MDA) and sample preparation can influence results	Shows promise as a clinical biomarker, however does not have a functional impact on the pathophysiology of CVD.	[33,34,39,40]
Nitrotyrosine	Human studies have demonstrated association with CAD independent of traditional risk factors	Circulating levels are not equivalent to tissue levels. Current detection methods are expensive and impractical for scaling up.	Nitrotyrosine formation on particular cardiovascular proteins have direct effect on function.	[43,55]
S-glutathionylation	S-glutathionylation of SERCA, eNOS and Na^+–K^+ pump demonstrated as biomarkers as well as role in pathogenesis.	Detection of S-glutationylation prone to methodological artefact. Access to tissue (myocardium, vasculature) where modification occurs presents a clinical obstacle.	Modified Hb currently being investigated as biomarker.	[10,13,58,65]
MPO	Commercial assays available. Strong evidence that MPO correlates with CVD risk.	Influenced by sample storage and time to analysis.	MPO is a promising biomarker for CVD risk prediction.	[1,69,74–76,97–99]
OxLDL	Elevated in CAD, increasing OxLDL correlates with increasing clinical severity. Also is predictive of future CAD in healthy population. Good reproducibility from frozen samples.	Reduction in OxLDL by antioxidant pharmacotherapy has not been matched by reduction in CVD severity.	ELISAs for OxLDL detection readily available.	[80–83]
ROS-induced changes to gene expression	The expression of several genes may be measured simultaneously using microarray technology, potentially increasing the power of this biomarker.	Microarray technology can be manually and computationally expensive.	It is unclear if expression profiles of cells in biological samples reflect that in cardiovascular tissues.	[87,88]
Serum antioxidant capacity	GPX-1 demonstrated to be inversely proportional to CAD. Commercial kits available to measure antioxidant capacity. Reproducibly quantified despite frozen sample storage.	Antioxidant activity in serum may not reflect that of cellular microdomains that are important to the pathogenesis of CVD.	Clinical relevance of antioxidant quantification to CVD risk need further investigation	[90]





Biomarker discovery → **Validation and Assay Development** → **Clinical Validation** → **Clinical Application**

Genomics
Transcriptomics
Proteomics
Metabolomics

Assessment of sample preparation and high-throughput biomarker assays suitable for clinical use

Large-scale clinical studies to establish the role of biomarker in diagnosis, prognosis and treatment of CVD

ROS-induced changes in gene expression

S-glutathionylation

Isoprostanes

OxLDL

MPO

Net antioxidant capacity of serum

Nitrotyrosine

MDA

Ho et al.; 2013

Review

Vitamin C and Heart Health: A Review Based on Findings from Epidemiologic Studies

Melissa A. Moser and Ock K. Chun *

Department of Nutritional Sciences, University of Connecticut, Storrs, CT 06269, USA;
melissa.a.moser@uconn.edu

The current literature provides little support for the use of vitamin C supplementation to reduce heart disease risk.

Many cohort studies and randomized trials have shown no relationship between vitamin C intake and heart disease risk, while few have suggested moderate benefits, and some have even suggested slight increases in risk.

Importantly, multiple studies have documented increases in cardiovascular risk associated with the use of supplemental vitamin C, even when taken in doses of about 1000 mg per day, which is half of the established Tolerable Upper Intake Level (UL) of 2000 mg

The lack of consistency within the body of research on this topic has called into question the roles of antioxidants in the human body, and has even cast doubt on the LDL oxidative hypothesis

Vitamin C supplementation for the primary prevention of cardiovascular disease (Review)

Al-Khudairy L, Flowers N, Wheelhouse R, Ghannam O, Hartley L, Stranges S, Rees K

Eight trials with 15,445 participants randomised.

The largest trial with 14,641 participants provided data on our primary outcomes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vitamin C supplementation				
Major cardiovascular event Physicians Follow-up: mean 8 years	**86 per 1000**	**85 per 1000** (77 to 94)	**HR 0.99** (0.89 to 1.10)	14,641 (1 study)	⊕⊕◯◯ **low** [1,2]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome. Grey literature search is unlikely to introduce publication bias. See Appendix 2 for major cardiovascular event checklist
Cardiovascular mortality Physicians Follow-up: mean 8 years	**35 per 1000**	**35 per 1000** (29 to 42)	**HR 1.02** (0.85 to 1.22)	14,641 (1 study)	⊕◯◯◯ **very low** [1,2,3]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome. Grey literature search is unlikely to introduce publication bias. See Appendix 2 for major cardiovascular event checklist

All-cause mortality Physicians Follow-up: mean 8 years	**110 per 1000**	**117 per 1000** (107 to 128)	**HR 1.07** (0.97 to 1.18)	14,641 (1 study)	⊕◯◯◯ **very low** [1,2,3]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome. Grey literature search is unlikely to introduce publication bias. See Appendix 2 for major cardiovascular event checklist
Total myocardial infarction (fatal and non-fatal) Physicians Follow-up: mean 8 years	**34 per 1000**	**36 per 1000** (30 to 42)	**HR 1.04** (0.87 to 1.24)	14,641 (1 study)	⊕⊕◯◯ **low** [1,2]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome. Grey literature search is unlikely to introduce publication bias. See Appendix 2 for major cardiovascular event checklist
Total stroke (fatal and non-fatal) Physicians Follow-up: mean 8 years	**34 per 1000**	**30 per 1000** (25 to 36)	**HR 0.89** (0.74 to 1.07)	14,641 (1 study)	⊕⊕◯◯ **low** [1,2]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome. Grey literature search is unlikely to introduce publication bias. See Appendix 2 for major cardiovascular event checklist
Self-reported CABG/ PTCA Participant self-reports Follow-up: mean 8 years	**97 per 1000**	**93 per 1000** (84 to 103)	**HR 0.96** (0.86 to 1.07)	14,641 (1 study)	⊕⊕◯◯ **low** [1,2]	Inconsistency was difficult to evaluate given that one trial assessed the primary outcome.

There is limited low- and very low-quality evidence currently on the effect of vitamin C supplementation and risk of CVD risk factors.

A Randomized Factorial Trial of Vitamins C and E and Beta Carotene in the Secondary Prevention of Cardiovascular Events in Women

Results From the Women's Antioxidant Cardiovascular Study

Nancy R. Cook, ScD; Christine M. Albert, MD; J. Michael Gaziano, MD; Elaine Zaharris, BA; Jean MacFadyen, BA; Eleanor Danielson, MIA; Julie E. Buring, ScD; JoAnn E. Manson, MD, DrPH

Effects of ascorbic acid (500 mg/d), vitamin E (600 IU every other day), and beta carotene (50 mg every other day) on the combined outcome of myocardial infarction, stroke, coronary revascularization, or CVD death among 8171 female health professionals at increased risk.

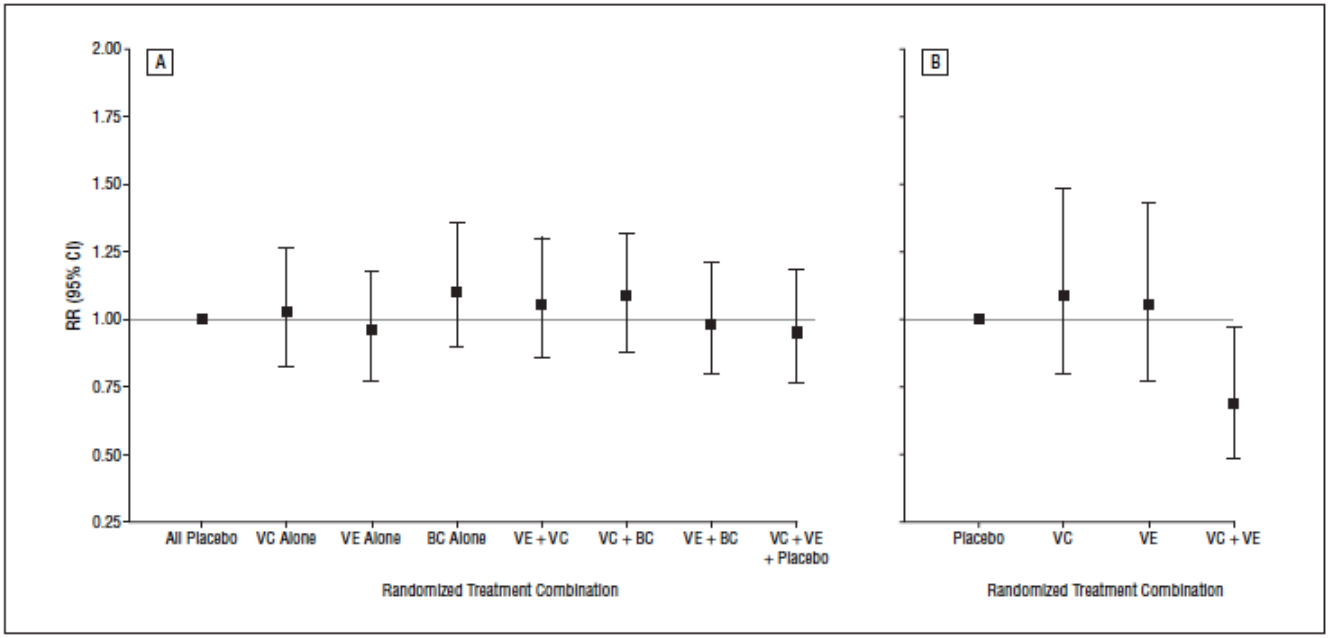


Figure 3. Relative risks (RRs) and 95% confidence intervals (CIs) of major cardiovascular disease (CVD) by 8 combinations of all 3 active antioxidant assignments relative to the all placebo group (A) or of stroke by combinations of active vitamin C (ascorbic acid) (VC) and vitamin E (VE) assignments relative to the groups with placebo VC and VE (B). BC indicates beta carotene.

There were no overall effects of ascorbic acid, vitamin E, or beta carotene on cardiovascular events among women at high risk for CVD.

A Randomized Factorial Trial of Vitamins C and E and Beta Carotene in the Secondary Prevention of Cardiovascular Events in Women

Women's Antioxidant Cardiovascular Study

ascorbic acid (500 mg/d), vitamin E (600 IU every other day), and beta carotene (50 mg every other day)

Table 2. Relative Risk (RR) of Cardiovascular Outcomes by Randomized Antioxidant Intervention Group in the Women's Antioxidant Cardiovascular Study

	Vitamin C (Ascorbic Acid)				Vitamin E				Beta Carotene			
Outcome	Active, No.	Placebo, No.	RR (95% CI)	*P* Value	Active, No.	Placebo, No.	RR (95% CI)	*P* Value	Active, No.	Placebo, No.	RR (95% CI)	*P* Value
Major CVD[a]	731	719	1.02 (0.92-1.13)	.71	708	742	0.94 (0.85-1.04)	.23	731	719	1.02 (0.92-1.13)	.71
MI, stroke, CVD death	419	415	1.01 (0.88-1.16)	.87	399	435	0.90 (0.78-1.03)	.12	435	399	1.09 (0.95-1.25)	.21
MI[b]	140	134	1.05 (0.83-1.33)	.70	131	143	0.91 (0.72-1.15)	.44	135	139	0.97 (0.77-1.23)	.82
Fatal	15	19	0.79 (0.40-1.55)	.49	18	16	1.11 (0.57-2.18)	.76	10	24	0.42 (0.20-0.87)	.02
Nonfatal	125	115	1.09 (0.85-1.41)	.50	113	127	0.88 (0.69-1.14)	.34	125	115	1.09 (0.85-1.40)	.51
Revascularization[b]	446	443	1.01 (0.89-1.15)	.88	438	451	0.96 (0.85-1.10)	.59	438	451	0.98 (0.86-1.11)	.71
Total CHD	510	489	1.05 (0.93-1.19)	.46	491	508	0.96 (0.85-1.09)	.52	500	499	1.01 (0.89-1.14)	.92
Stroke[b]	138	160	0.86 (0.69-1.08)	.21	137	161	0.84 (0.67-1.05)	.12	161	137	1.17 (0.93-1.47)	.17
Ischemic	123	148	0.83 (0.66-1.06)	.13	121	150	0.79 (0.62-1.01)	.06	143	128	1.12 (0.88-1.42)	.37
Hemorrhagic	13	12	1.09 (0.50-2.39)	.83	15	10	1.47 (0.66-3.27)	.35	17	8	2.13 (0.92-4.93)	.08
Fatal	15	18	0.84 (0.42-1.67)	.63	18	15	1.15 (0.58-2.28)	.69	22	11	1.98 (0.96-4.07)	.07
Nonfatal	123	142	0.87 (0.68-1.10)	.25	119	146	0.80 (0.63-1.02)	.08	139	126	1.10 (0.87-1.40)	.42
TIA	203	218	0.93 (0.77-1.13)	.49	205	216	0.94 (0.78-1.14)	.54	201	220	0.91 (0.75-1.10)	.35
CVD death[b]	206	189	1.10 (0.90-1.33)	.37	193	202	0.94 (0.77-1.15)	.56	211	184	1.14 (0.94-1.39)	.18
Total mortality	504	491	1.03 (0.91-1.17)	.62	502	493	1.00 (0.89-1.14)	.95	505	490	1.03 (0.91-1.17)	.65

Cook et al.; 2007

Coenzyme Q10 and Inflammation

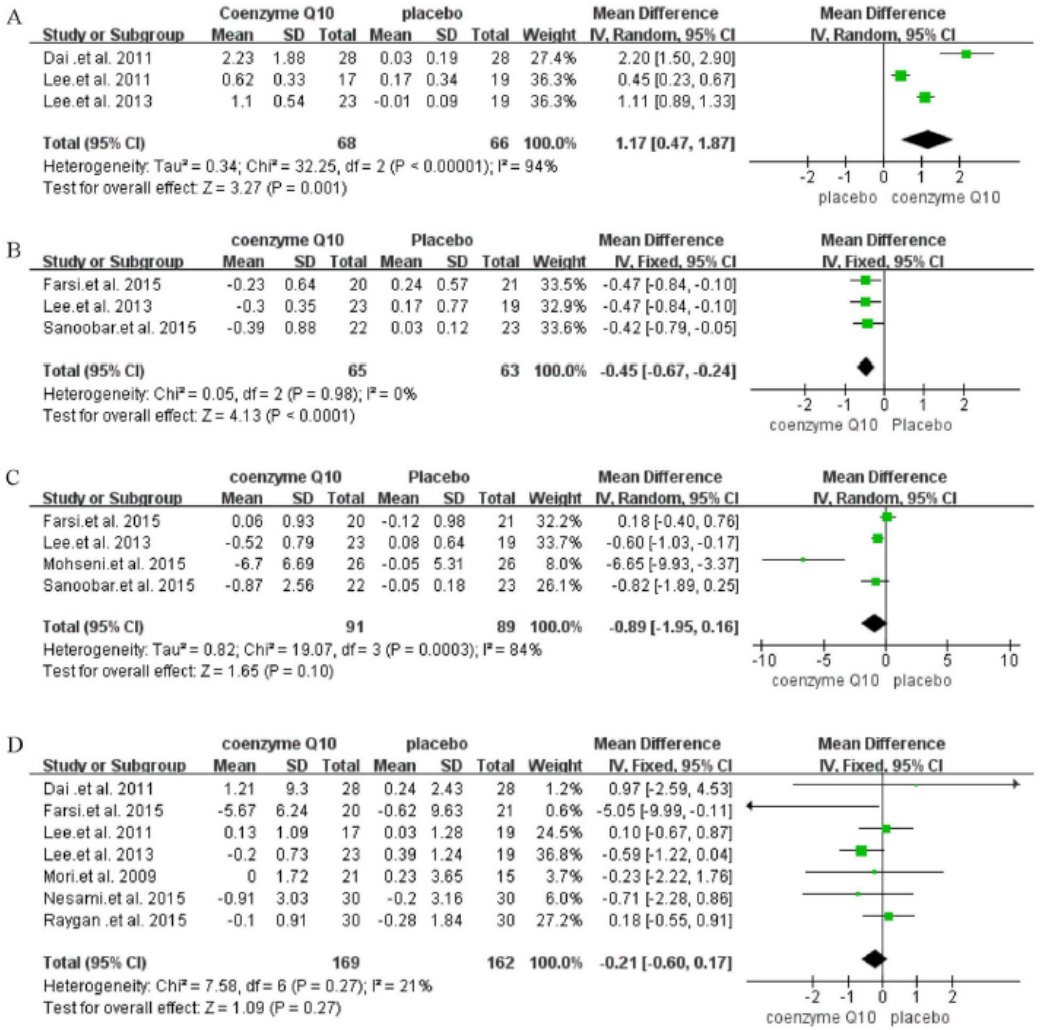


Fig 3. Forest plot of comparisons of Coenzyme Q10 supplementation versus placebo (outcomes: A: serum Coenzyme Q10, B: tumor necrosis factor-alpha, C: interleukin-6, D: C reactive protein).

doi:10.1371/journal.pone.0170172.g003

CoQ10 supplementation may partly improve the process of inflammatory state.

The effects of CoQ10 on inflammation should be further investigated by conducting larger sample size and well-defined trials of long enough duration.

Zhai et al.; 2016

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

European Heart Journal (2017) **38**, 1553–1560
doi:10.1093/eurheartj/ehx033

REVIEW

Frontiers in Cardiovascular Medicine

Lipoprotein(a): the revenant

Baris Gencer[1], Florian Kronenberg[2], Erik S. Stroes[3], and François Mach[1]*

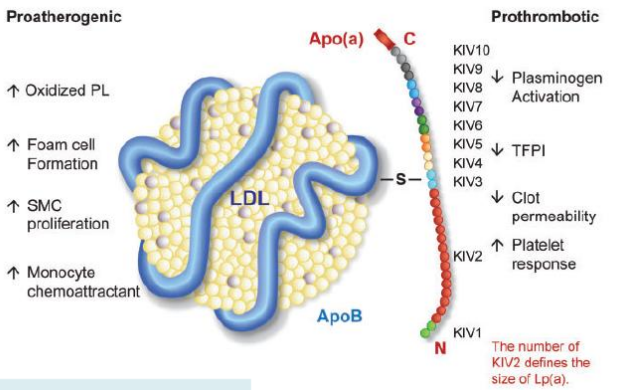


Table 1 Association between Lp(a) concentrations and clinical CVD outcomes

1. Association between Lp(a) levels and CHD events in large major prospective cohorts	
The emerging risk factors collaboration[12]	Pooled individual participant data analysis from 126 634 subjects in 36 cohorts showed a 16% higher risk of CHD events for each 1 SD increase of Lp(a).
The Copenhagen city heart study (N = 8637) The Copenhagen general population study (N = 29'388) The Copenhagen ischaemic heart disease study (N = 2461).[3] The Bruneck study.[20]	HR for CHD events was 2.6 (95% CI 1.6–4.1) for the 95th vs. 22th percentile of Lp(a), HR 1.22 (95% CI 1.09–1.37) per doubling of Lp(a), and HR 1.08 (95% CI 1.03–1.12) for continuous Lp(a). HR for incident CVD was 1.37 per 1-SD higher Lp(a) level (SD = 32 mg/dL) and 2.37 when comparing the top fifth quintile with other quintiles.
2. Association between Lp(a) levels and heart failure events	
The Copenhagen general population study.[14]	HR for heart failure events was 1.79 (95% CI 1.18–2.73) for the 99th vs. 34 percentiles.
3. Association between Lp(a) levels and recurrent MACE in secondary prevention	
Meta-analysis of 18 978 subjects with CHD from 11 studies.[27]	OR for MACE was 1.40 (95% CI 1.15–1.71) for the highest vs. lowest quantile of Lp(a).
Cohort of patients treated with percutaneous coronary intervention for acute coronary syndromes.[24]	In 569 patients and well controlled LDL-C, higher vs. lower median Lp(a) value was associated with mortality and recurrent acute coronary syndromes (HR 1.69, 95% CI 1.03–2.70).
4. Association between Lp(a) levels and aortic valve disease	
Cohorts for Heart and Aging Research in Genomic Epidemiology consortium.[28]	Lp(a) genetic variation was associated with incident aortic stenosis (HR per allele, 1.68; 95% CI, 1.32–2.15) and aortic-valve replacement (HR 1.54; 95% CI, 1.05–2.27) in a large Swedish cohort; the association with incident aortic stenosis was also replicated in an independent Danish cohort.
The Copenhagen City Heart Study and the Copenhagen General Population Study.[29]	Elevated Lp(a) levels were associated with aortic valve stenosis of 1.2 (95% CI 0.8 to 1.7) for 22nd to 66th percentile levels (5 to 19 mg/dL), 1.6 (95% CI 1.1 to 2.4) for 67th to 89th percentile levels (20 to 64 mg/dL), 2.0 (95% CI 1.2 to 3.4) for 90th to 95th percentile levels (65 to 90 mg/dL), and 2.9 (95% CI 1.8 to 4.9) for levels greater than 95th percentile (>90 mg/dL), vs. levels less than the 22nd percentile (<5 mg/dL; trend, P < 0.001).
Cohort of patients with aortic valve stenosis.[30]	The progression rate from mild-to-moderate aortic stenosis and aortic valve replacement was higher in top tertiles of Lp(a).

CHD, coronary heart disease; CI, confidence intervals; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odd ratio.

Table 2 Summary of recommendations from the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) regarding the screening for lipoprotein(a)

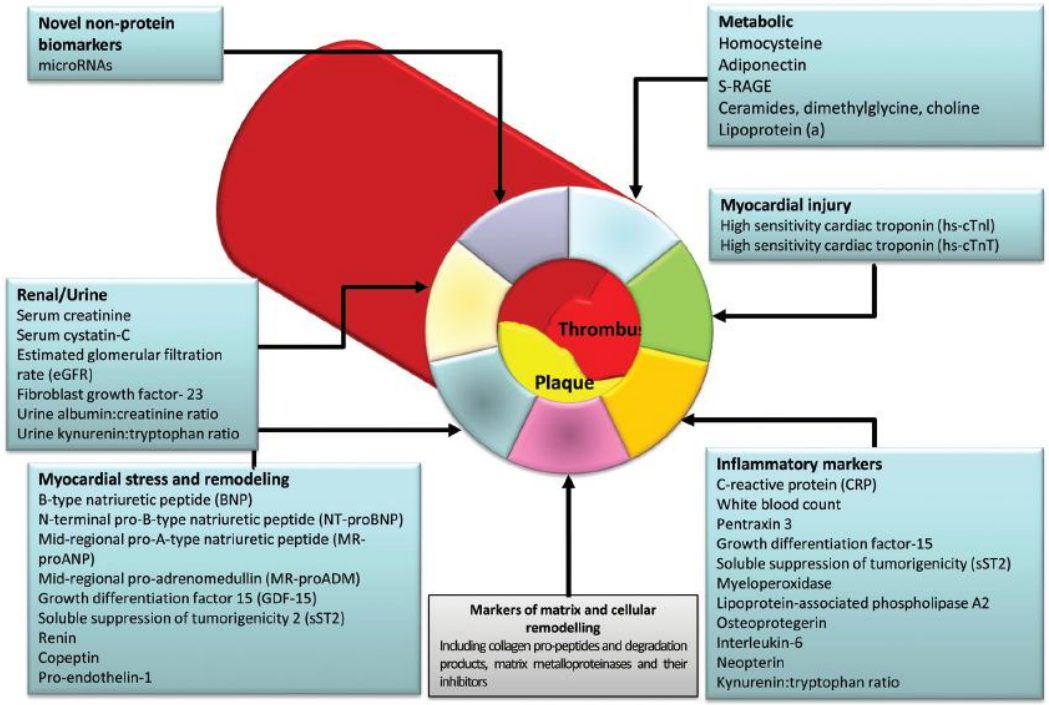
2010 EAS Consensus Panel[2]	Lp(a) should be measured once in all subjects at intermediate or high risk of CVD who present with: • Premature CVD. • Familial hypercholesterolemia. • A familial history pf premature CVD and/or elevated Lp(a). • Recurrent CVD despite statin treatment. • ≥3% 10-year risk of fatal CVD according to the European guidelines and • ≥10% 10-year risk of fatal and/or non-fatal CHD according to AHA guidelines.
2016 ESC Guidelines for the management of dyslipidaemias.[4]	Lp(a) should be recommended in selected cases at high risk, in patients with family history of premature CVD, and for reclassification in subjects with borderline risk. Lp(a) screening should be considered in individuals with: • Premature CVD (< 55 years in men and < 65 years women). • Familial hypercholesterolemia. • A family history of premature CVD and/or elevated Lp(a). • Recurrent CVD despite optimal statin treatment. • ≥5% 10-year risk of fatal CVD according to SCORE. Treatment with a PCSK9 antibody may be considered in FH patients with CVD or with other factors putting them at very high risk for CHD, such as other CV risk factors, family history and high Lp(a).

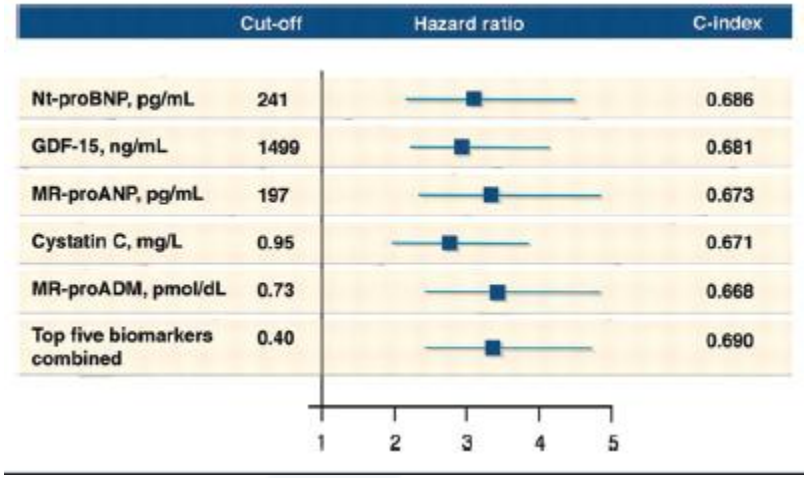
AHA, American Heart Association; CV, cardiovascular; CVD, cardiovascular disease; Lp(a), lipoprotein(a); PCSK9, proprotein convertase kexin 9.

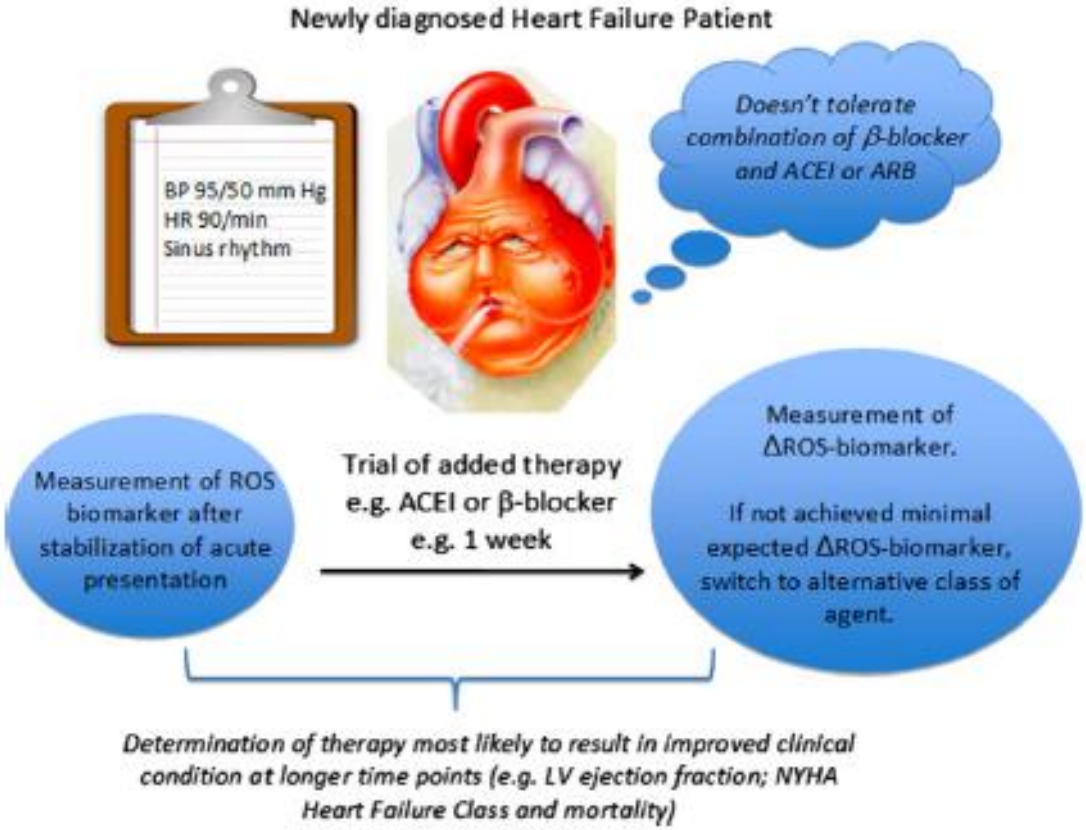
Clinical Chemistry 63:1
165–176 (2017)

State of the Art: Blood Biomarkers for Risk Stratification in Patients with Stable Ischemic Heart Disease

Torbjørn Omland[1*] and Harvey D. White[2]



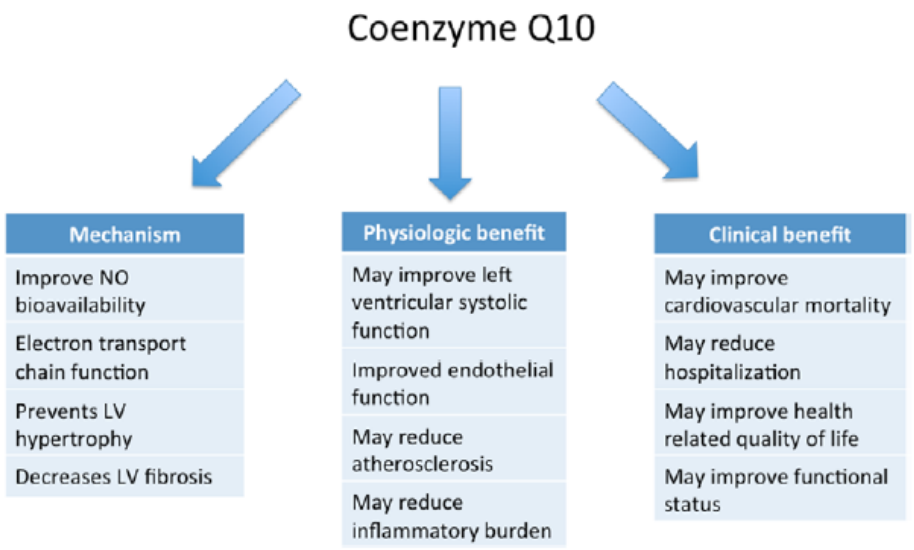



Newly diagnosed Heart Failure Patient
BP 95/50 mm Hg
HR 90/min
Sinus rhythm
Doesn't tolerate combination of β-blocker and ACEI or ARB
Measurement of ROS biomarker after stabilization of acute presentation
Trial of added therapy
e.g. ACEI or β-blocker
e.g. 1 week
Measurement of ΔROS-biomarker.
If not achieved minimal expected ΔROS-biomarker, switch to alternative class of agent.
Determination of therapy most likely to result in improved clinical condition at longer time points (e.g. LV ejection fraction; NYHA Heart Failure Class and mortality)

Ho et al.; 2013

Coenzyme Q10 and Heart Failure
A State-of-the-Art Review

Q-SYMBIO randomized controlled trial demonstrated a reduction in major adverse cardiovascular events with CoQ10 supplementation in a contemporary HF population



Clinical Question	Recommendation
Should clinicians initiate CoQ10 in patients with HF?	ACC/AHA guidelines currently do not recommend initiation of nutritional supplementation as treatment (including CoQ10) in patients with current or previous symptoms of HFrEF (level of evidence B, class III recommendation). Although the results of Q-SYMBIO[29] have suggested an improvement in the primary MACE end point at 2 y, the small event numbers, difficulties in patient recruitment, and an unexpectedly large treatment effect with wide confidence intervals limits the interpretability of the results. At this time point, CoQ10 initiation cannot be recommended to patients with HF
Are there certain subgroups of patients with HF that may have significant benefit from CoQ10?	RCTs' evaluating CoQ10 in patients with HF have focused on HFrEF. The Q-SYMBIO trial did not suggest an interaction between CoQ10 therapy and subgroups. Currently, we do not recommendation for the use of CoQ10 in specific subgroups of patients with HF
If patients are already taking CoQ10, what should clinicians' recommend with regard to future use?	Given the absence of a signal to harm in Q-SYMBIO, a detailed discussion of the risks and benefits of CoQ10 should occur between the patient and the clinician. Given the similar molecular structure of CoQ10 to vitamin K, patients who are taking warfarin should have international normalized ratios carefully and potentially more frequently checked

Sharma et al.; 2016

Cancer ?

Vitamin E in the Primary Prevention of Cardiovascular Disease and Cancer

The Women's Health Study: A Randomized Controlled Trial

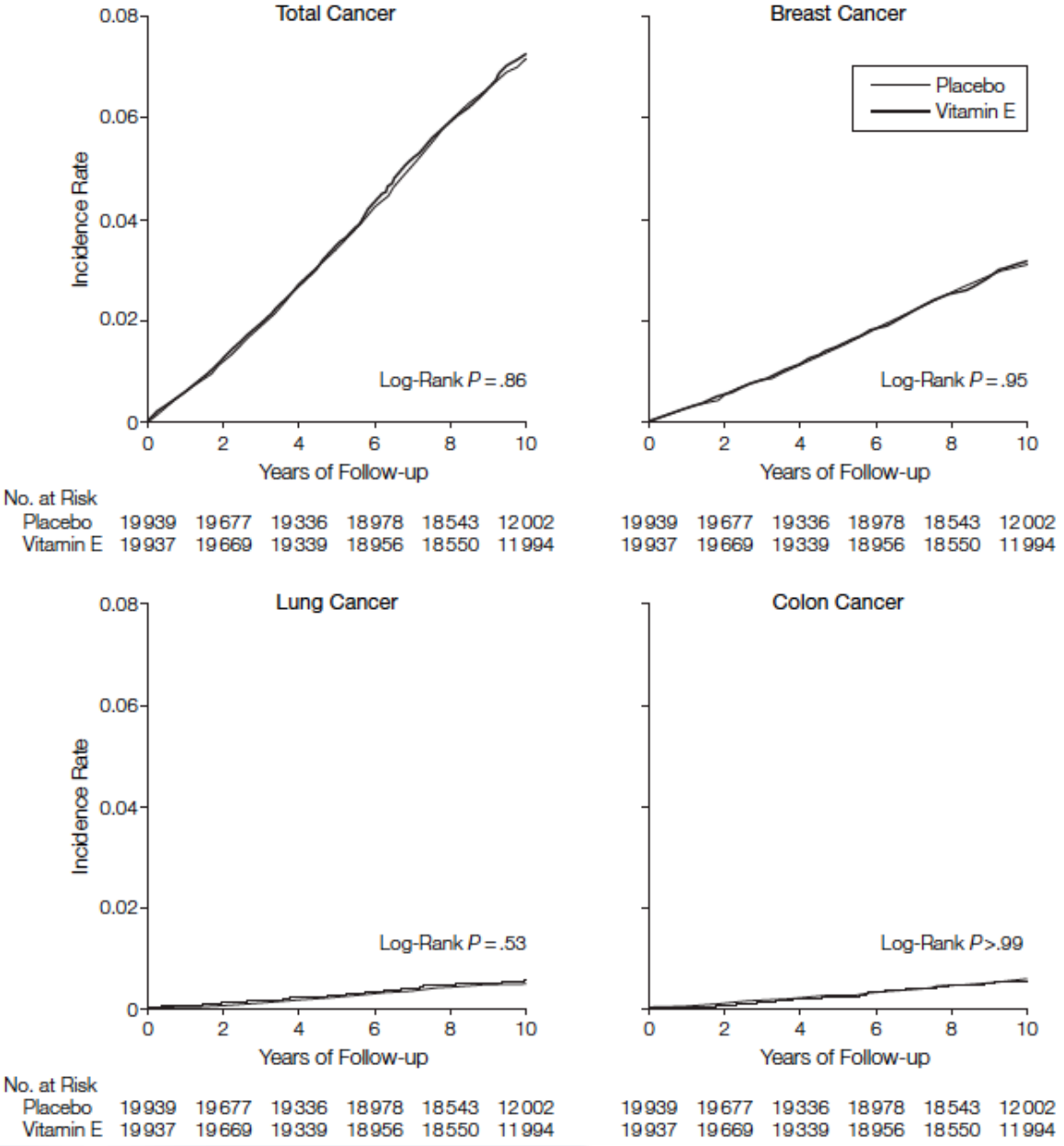
600 IU of natural-source vitamin E on alternate days

Table 2. Relative Risks of Cardiovascular Disease, Cancer, and Total Mortality by Group, Women's Health Study

Outcome	No. of Events: Vitamin E (n = 19 937)	No. of Events: Placebo (n = 19 939)	Relative Risk (95% CI)	*P* Value
Major cardiovascular event*	482	517	0.93 (0.82-1.05)	.26
Myocardial infarction	196	195	1.01 (0.82-1.23)	.96
Nonfatal	184	181	1.02 (0.83-1.25)	.87
Fatal	12	14	0.86 (0.40-1.85)	.70
Stroke	241	246	0.98 (0.82-1.17)	.82
Nonfatal	220	222	0.99 (0.82-1.19)	.93
Fatal	21	24	0.88 (0.49-1.57)	.66
Ischemic†	194	197	0.99 (0.81-1.20)	.88
Hemorrhagic†	44	48	0.92 (0.61-1.38)	.68
Cardiovascular death	106	140	0.76 (0.59-0.98)	.03
Total invasive cancer	1437	1428	1.01 (0.94-1.08)	.87
Breast	616	614	1.00 (0.90-1.12)	.95
Lung	107	98	1.09 (0.83-1.44)	.52
Colon	107	107	1.00 (0.77-1.31)	.99
Cancer death	308	275	1.12 (0.95-1.32)	.17
Total mortality	636	615	1.04 (0.93-1.16)	.53

Lee et al.; 2005

Figure 3. Cumulative Incidence Rates of Cancer



Lee et al.; 2005

Effects of Long-term Vitamin E Supplementation on Cardiovascular Events and Cancer

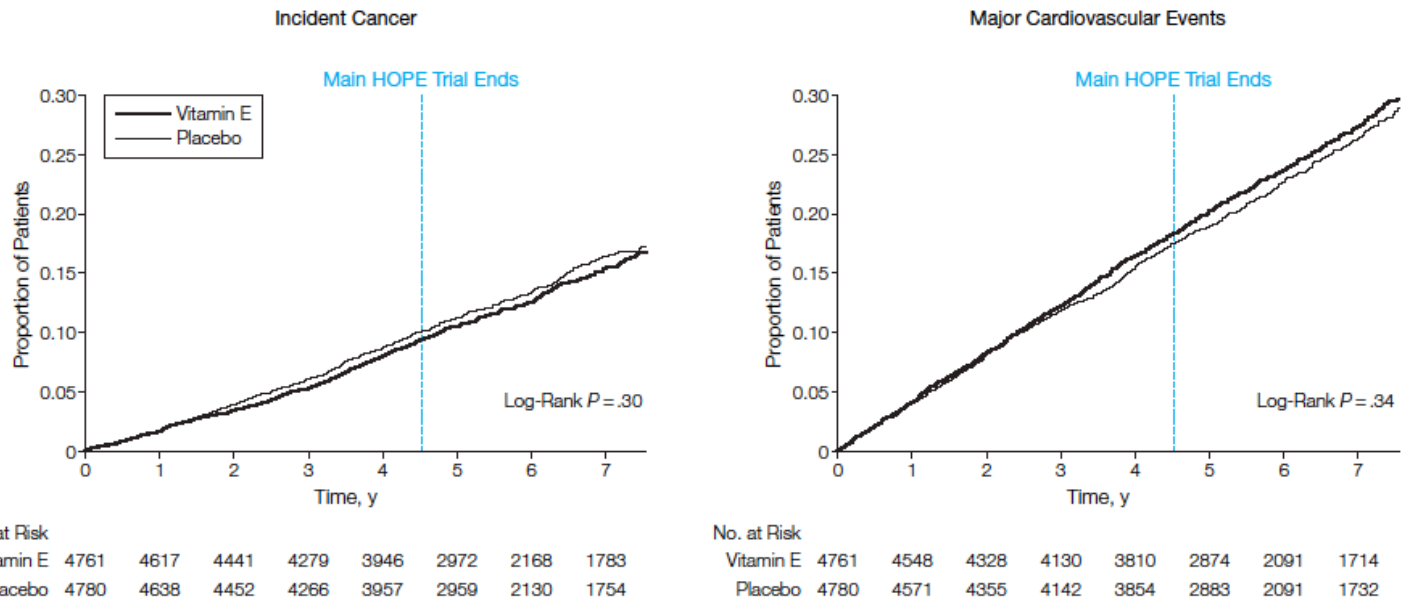
A Randomized Controlled Trial

The HOPE and HOPE-TOO Trial

Patients at least 55 years old with vascular disease or diabetes mellitus was extended

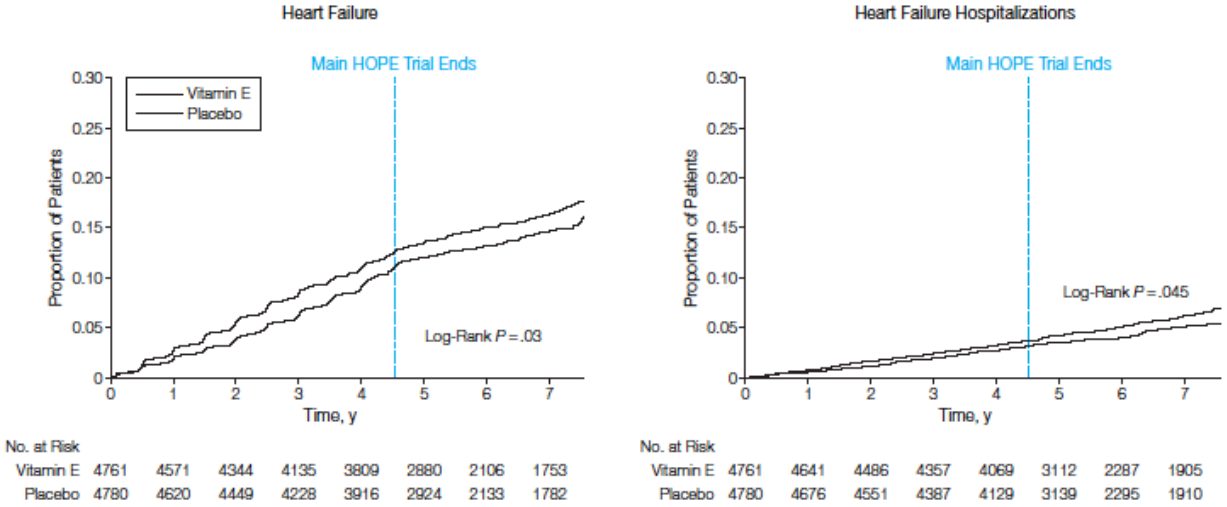
Daily dose of natural source vitamin E (400 IU) or matching placebo.

Figure 2. Kaplan-Meier Analysis of the Effects of Vitamin E on Incident Cancer and Major Cardiovascular Events for All 9541 Study Patients

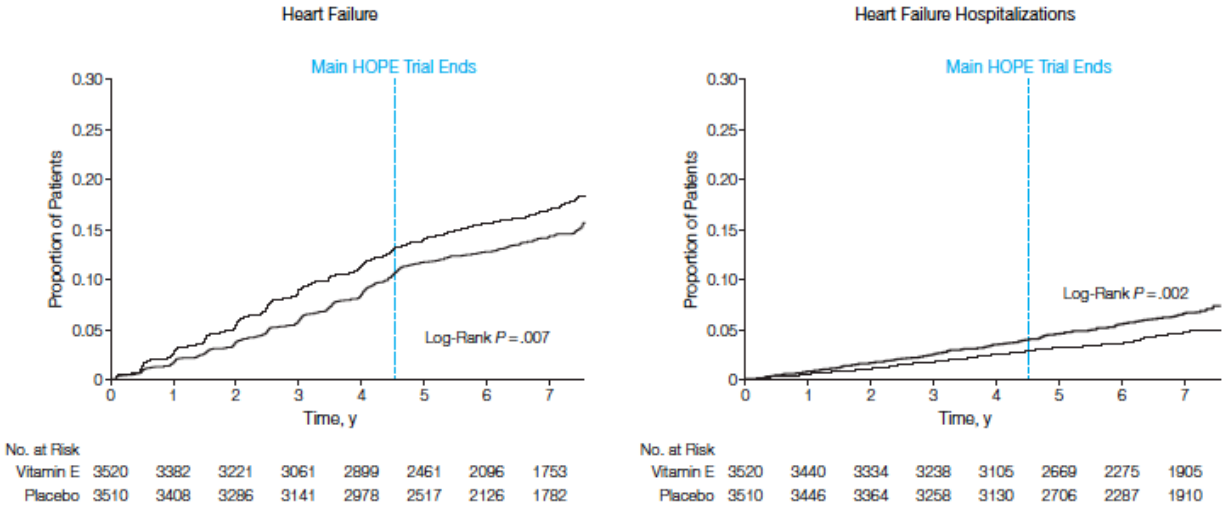


Lonn et al.; 2005

All HOPE Study Patients



Patients at Centers Continuing in the HOPE-TOO Trial Extension



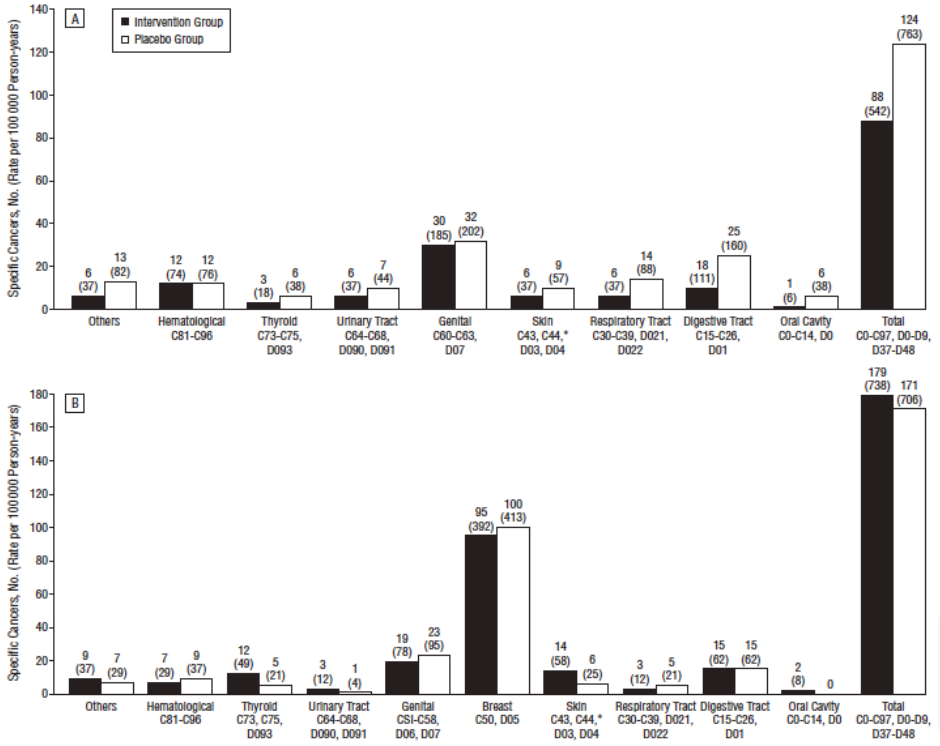
In patients with vascular disease or diabetes mellitus, long-term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase the risk for heart failure.

Lonn et al.; 2005

The SU.VI.MAX Study

A Randomized, Placebo-Controlled Trial of the Health Effects of Antioxidant Vitamins and Minerals

13 017 French adults (7876 women aged 35-60 years and 5141 men aged 45-60 years)
All participants took a single daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc, or a placebo



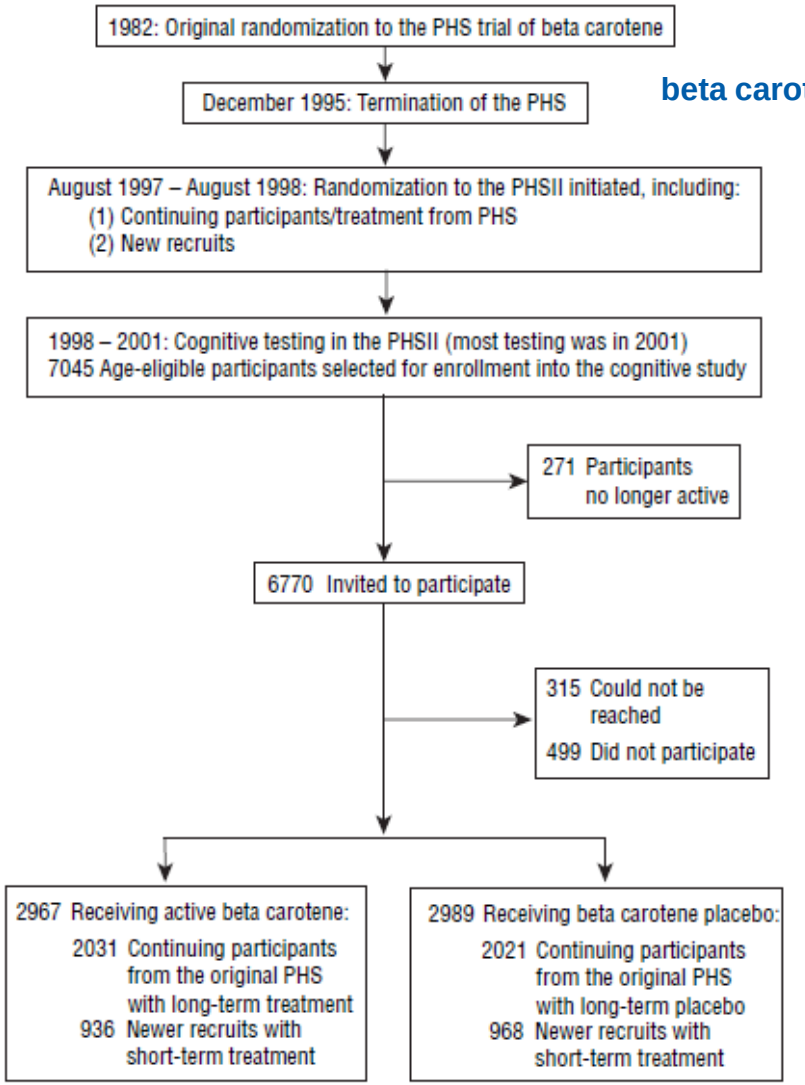
After 7.5 years, low-dose antioxidant supplementation lowered total cancer incidence and allcause mortality in men but not in women.

Supplementation may be effective in men only because of their lower baseline status of certain antioxidants, especially of beta carotene.

Hercberg et al.; 2004

Neurology ?

Physicians' Health Study II (PHSII)



beta carotene arm (50 mg, alternate days)

Grodstein et al.; 2007

Physicians' Health Study II (PHSII)

Table 3. Mean Cognitive Performance With Short-term Treatment Assignment[a]: the Physicians' Health Study II

Cognitive Measure	Placebo Group (n = 968)	Beta Carotene Group (n = 936)	*P* Value
Global score[b]			
Mean *z* score (SD)[c]	0.007 (0.67)	–0.007 (0.67)	
Mean difference (95% CI)	0 [Reference]	–0.014 (–0.07 to 0.05)	.65
Verbal memory[b]			
Mean *z* score (SD)[c]	0.008 (0.72)	–0.008 (0.72)	
Mean difference (95% CI)	0 [Reference]	–0.015 (–0.08 to 0.05)	.64
TICS[b]			
Mean points (SD)[c]	34.29 (2.64)	34.15 (2.57)	
Mean difference (95% CI)	0 [Reference]	–0.13 (–0.37 to 0.10)	.26
Category fluency[b]			
Mean points (SD)[c]	20.09 (6.15)	20.02 (6.14)	
Mean difference (95% CI)	0 [Reference]	–0.06 (–0.62 to 0.49)	.82

Among 4052 continuing participants from the PHS (mean treatment duration, 18 years), the mean global score was significantly higher in the beta carotene group than in the placebo group (mean difference in z scores, 0.047 standard units; P=.03).

On verbal memory, men receiving long-term beta carotene supplementation also performed significantly better than the placebo group (mean difference in z scores, 0.063; P=.007).

We did not find an impact of short-term beta carotene supplementation on cognitive performance

but long term supplementation may provide cognitive benefits.

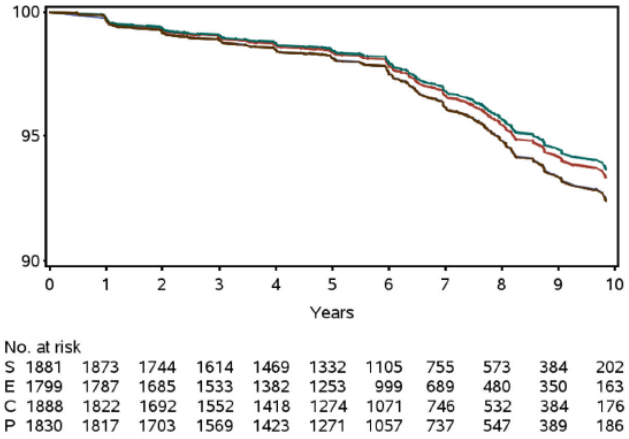
Grodstein et al.; 2007

Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)

JAMA Neurology

Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)

Four-arm randomized controlled trial (RCT) and initiated enrollment in 200117.
SELECT's primary aim was to determine the effectiveness of the antioxidant supplements vitamin E (400 IU/day) and selenium (200 µg/day) alone or in combination in preventing prostate cancer.



	ITT		Weighted**	
Treatment	HR (95% CI)	P value	HR (95% CI)	P value
Vitamin E	0.88 (0.64–1.20)	0.41	0.84 (0.61–1.15)	0.27
Selenium	0.83 (0.61–1.13)	0.23	0.80 (0.59–1.09)	0.16
Combined	1.00 (0.74–1.35)	0.98	0.99 (0.74–1.32)	0.93

Neither supplement prevented dementia. This is the first study to investigate the long term effect of anti-oxidant supplement use on dementia incidence among asymptomatic men.

Kryscio et al.; 2017

Neurol Sci (2017) 38:215–224
DOI 10.1007/s10072-016-2757-9

REVIEW ARTICLE

The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials

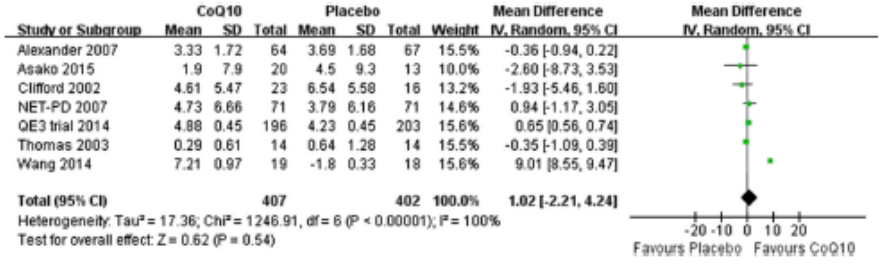


Fig. 2 Forest Plot of effect sizes for UPDRS part 3; *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure

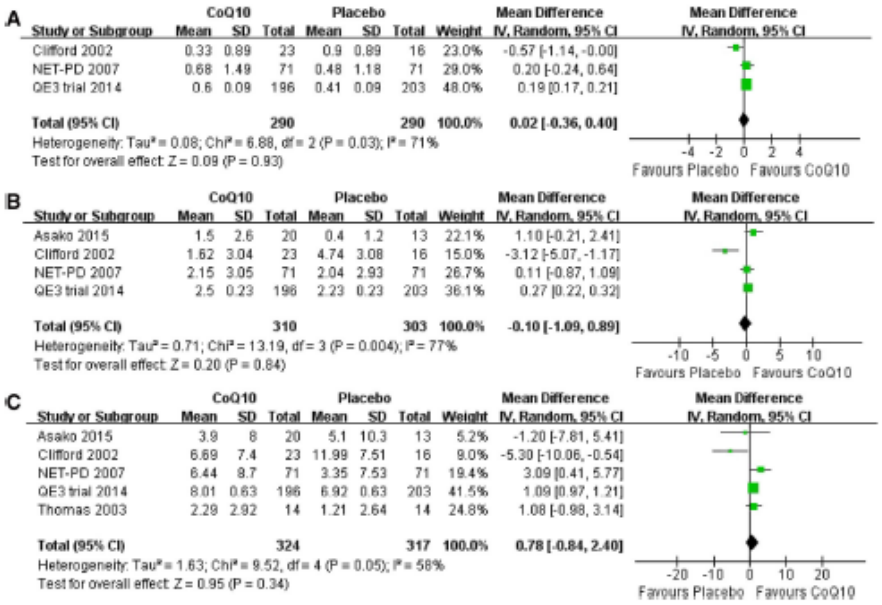


Fig. 3 Forest Plot of effect sizes for UPDRS part 1 (a), UPDRS part 2 (b) and total UPDRS (c)

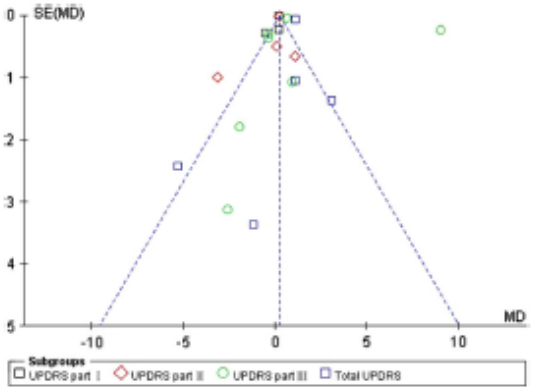


Fig. 4 Bias assessment plot for the effect of CoQ10 supplementation on UPDRS score

The current meta-analysis provided evidence that CoQ10 was safe and well tolerated in participants with PD and no superior to placebo in terms of motor symptoms.

According to these results, we cannot recommend CoQ10 for the routine treatment of PD right now.

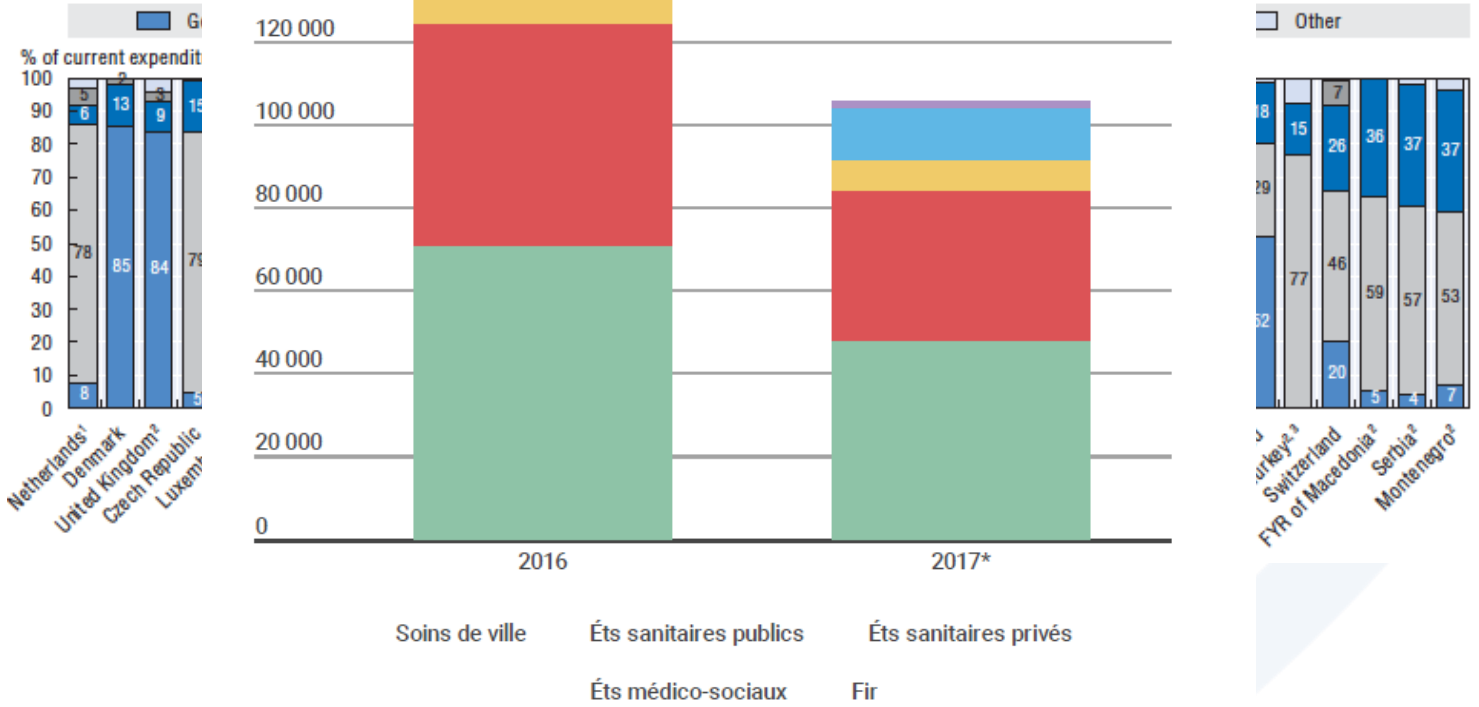
Zhu et al.

What Else?

One target: Value

Clinical

Economic



Zoom sur les remboursements de produits de santé

Concluding Remarks


ERARD
SOUPE de POISSONS
VISSOEP
label Rouge

Thank you very much….

…for your attention !

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