la dieta in corso di terapia con AVK: dati recenti

Il modello della Fibrillazione Atriale

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SAPIENZA
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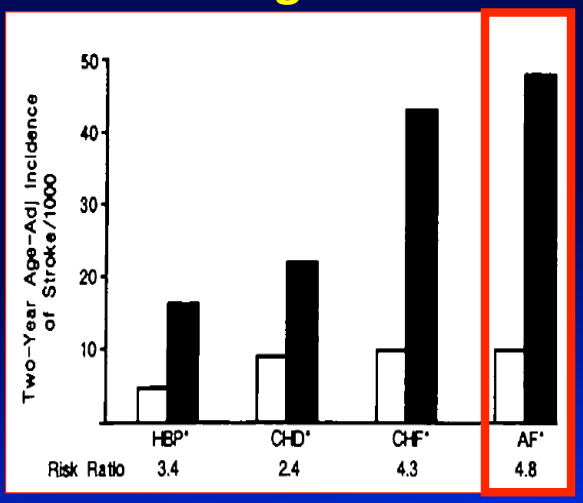
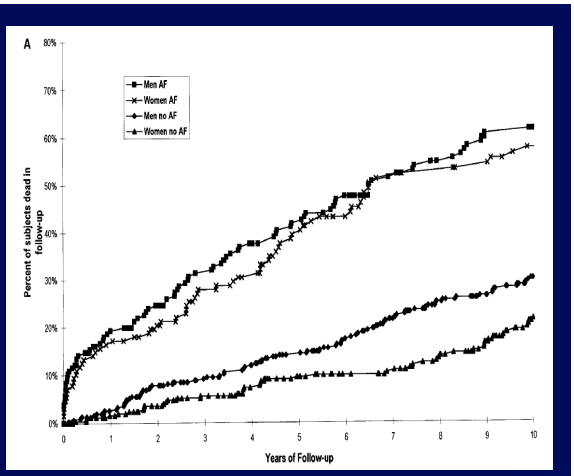
- FA Ictus ed eventi cardiovascolari
- TTR ed eventi cardiovascolari
- Dieta e TTR
- Conclusioni

Fibrillazione Atriale (FA) e rischio di ictus ischemico

Lo studio Framingham



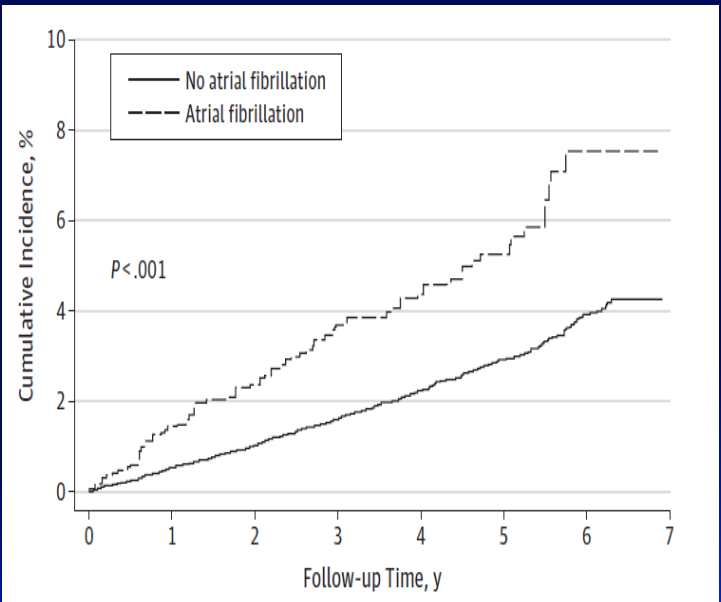


Ictus
RR 4,8

Mortalità
OR 1,5 men
OR 1,9 women

Stroke. 1991;22:983-988

FA e rischio di Infarto del Miocardio



Studio prospettico di coorte con 23 928 partecipanti dal Reasons for Geographic and Racial Differences in Stroke (REGARDS). Follow-up mediano di 4.5 anni, 648 IMA registrati.
La FA era associato ad un rischio doppio di avere IMA (HR 1.96 [95%CI, 1.52-2.52]).

*Soliman et al. JAMA Intern Med.*2013

TABLE 1] Baseline Characteristics of Whole Cohort and According to the Occurrence of the Primary Outcome

Characteristics	Overall (N = 1,019)	CVEs		*P* Value
		No (n = 908)	Yes (n = 111)	
Anthropometric and metabolic data				
Age, y	73.2 ± 8.7	72.8 ± 8.8	76.6 ± 7.1	<.001
Female sex	43.8	44.2	40.5	.480
BMI, kg/m²	27.4 ± 4.8	27.4 ± 4.9	27.3 ± 4.2	.904
Waist circumference, cm	103.3 ± 13.8	103.3 ± 14.0	102.7 ± 12.4	.708
Cardiovascular risk factors				
Arterial hypertension	87.6	87.1	91.9	.170
Metabolic syndrome	52.1	50.6	64.9	.005
History of MI/cardiac revascularization	25.1	22.8	44.1	<.001
Diabetes mellitus	20.6	19.8	27.0	.082
Heart failure	16.3	14.9	27.9	.001
History of stroke/TIA	16.1	14.5	28.8	<.001
Current smoking	9.7	9.4	12.4	.299
Concomitant therapies				
Antiplatelets	18.5	18.0	23.4	.195
ACE inhibitors/ARBs	70.1	70.4	67.6	.582
β-Blockers	40.7	42.4	27.9	.004
Statins	42.3	42.7	38.7	.476
Oral antidiabetic drugs	14.9	14.7	16.2	.863
Amiodarone	23.9	23.9	24.3	.907

Data are presented as mean ± SD or %. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CVE = cardiovascular event; MI = myocardial infarction; TIA = transient ischemic attack.

Pastori, Pignatelli e al Chest 2014

Predittori dell' IMA: nostra esperienza

MACE (3,4%/anno)	HR	CI 95%		p
Età ≥75	2.65	1.69	4.17	<0.001
Sindrome Metabolica	1.96	1.22	3.13	0.005
Pregresso stroke/TIA	1.82	1.13	2.93	0.013
Scompenso Cardiaco	1.79	1.10	2.91	0.018
Pregresso IMA/ rivascolarizzazione	1.75	1.11	2.74	0.015

Pastori, Pignatelli et al. Chest 2014

- FA Ictus ed eventi cardiovascolari
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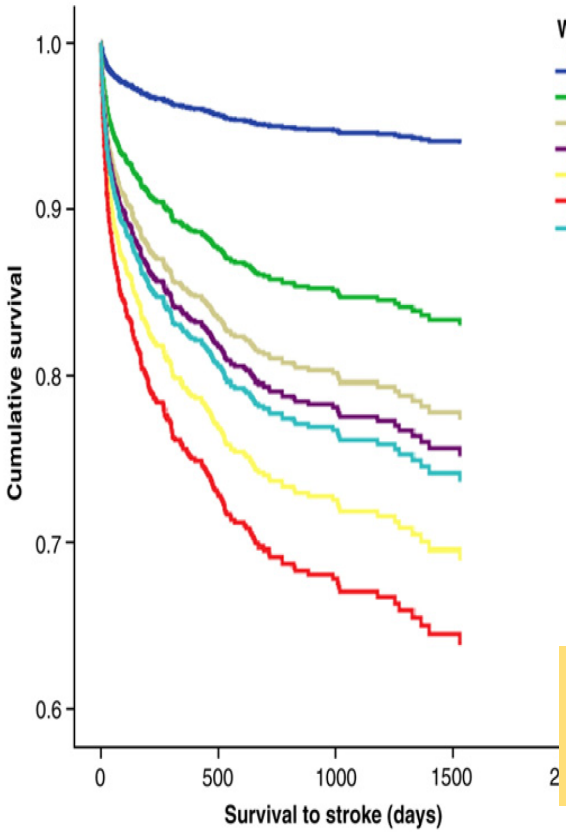
TTR e rischio di stroke

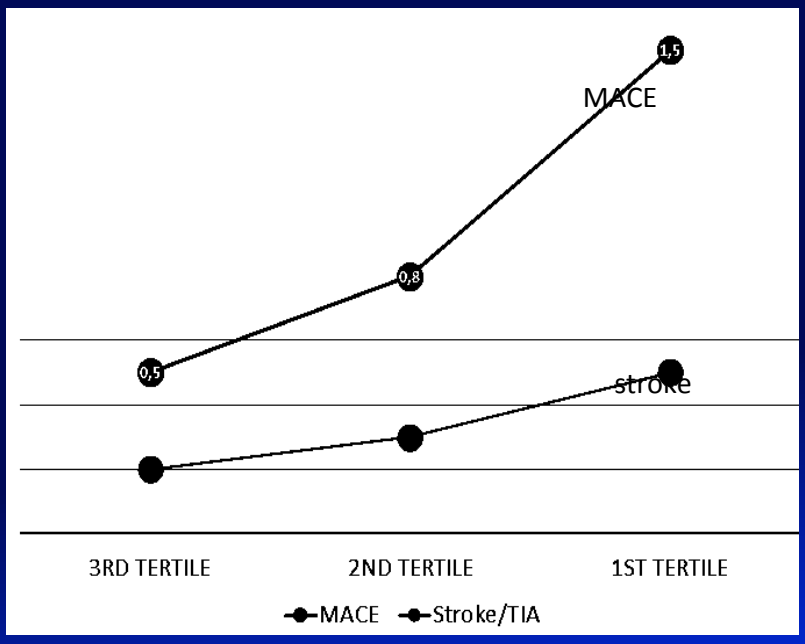


Warfarin control	$CHADS_2$ score ≥2		
Stroke	Exp(B)	95% CI	p
0 – 30%	1.468	(0.844-2.551)	0.174
31 – 40%	1.215	(0.767-1.926)	0.407
41 – 50%	0.933	(0.628-1.385)	0.729
51 – 60%	0.837	(0.554-1.265)	0.399
61 – 70%	0.608	(0.335-1.105)	0.103
71 – 100%	0.203	(0.050-0.820)	0.025

2,235 NVAF PATIENTS FROM A retrospective cohort design using linked inpatient, haematology and mortality data from Cardiff and the Vale of Glamorgan, UK

Morgan 2009 Thrombosis Research

IMA e qualità della TAO



% di MACE e Stroke nei terzili di TTR

Pastori, Pignatelli et al. Int J Cardiol 2015

Fattori legati al rischio cardiovascolare residuo

QUALITA' DELLA TAO (TTR)

STRESS OSSIDATIVO (Nox2, F2-IsoP)

RISCHIO CV RESIDUO

ATTIVAZIONE PIASTRINICA (TxB_2)

- FA Ictus ed eventi cardiovascolari
- TTR ed eventi cardiovascolari
- Dieta e TTR
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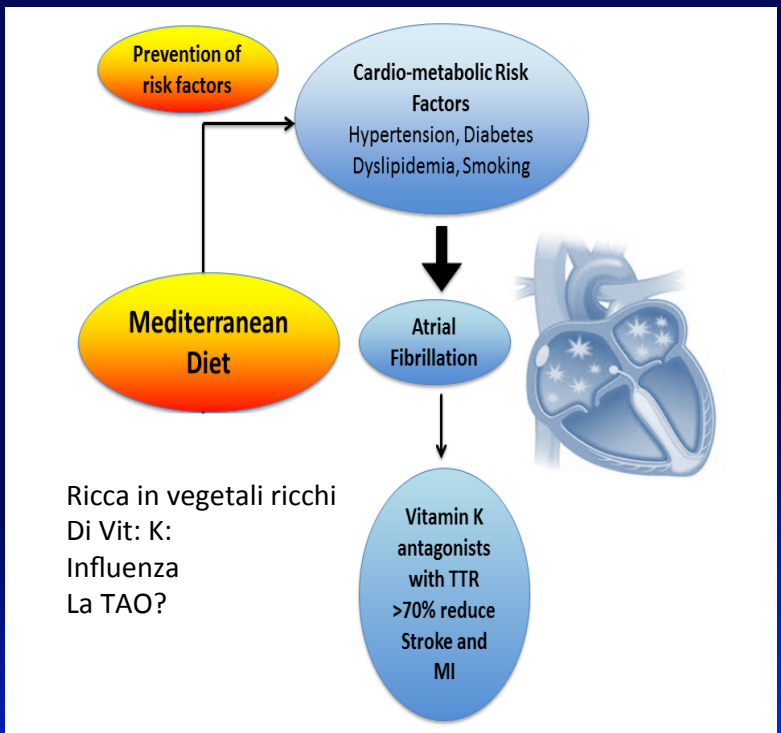
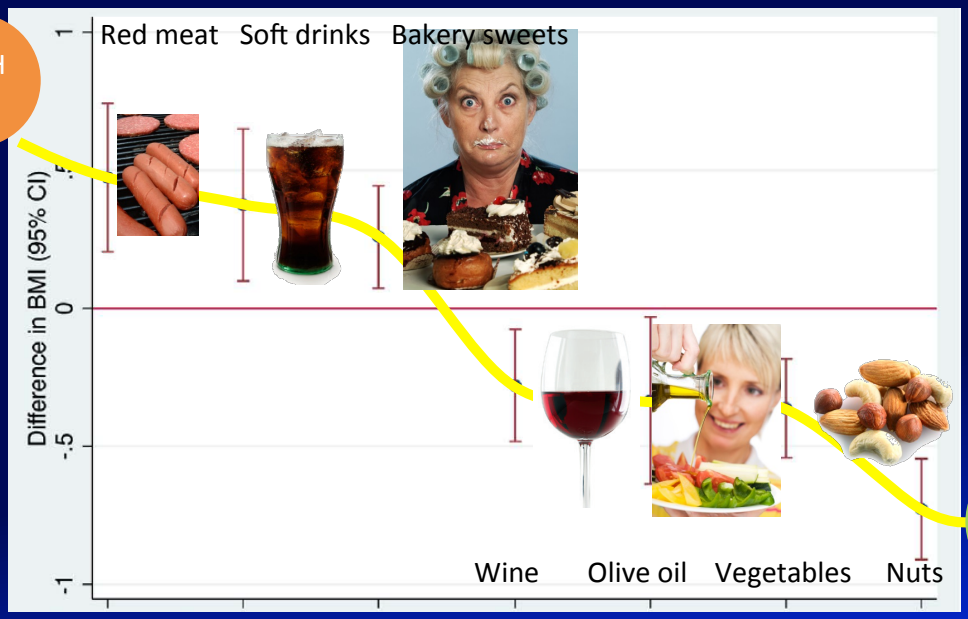
Approcci terapeutici: la dieta



Ricca in vegetali ricchi
Di Vit: K:
Influenza
La TAO?

Pignatelli Europace 2015

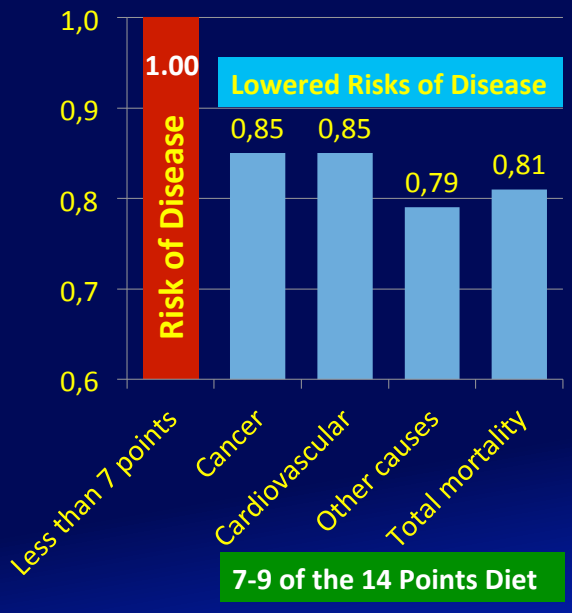
Individual Foods and BMI Differences



Mediterranean diet study

PLoS. Vol. 7. Issue 8. e43134.

MediterraneaN dIET sCORE AND MORTALITY



- Getting 7 to 9 points of the Predimed diet means lowered risk of disease.
- Compare those with 7-9 points to those with fewer than 7 points. More points means decreased risk of these diseases:
  - 15% ↓ risk of cancer
  - 15% ↓ risk of cardiovascular disease
  - 21% ↓ risk of death from other causes
  - 19% ↓ risk of death from all causes

Harvard Study: 6-7 years of follow-up: 6,137 men; 11,278 women
American Journal Clinical Nutrition. 2014;99:172-180.

SUDDEN CARDIAC DEATH risk lowered in Women

- The Women's Health Initiative study included 93,122 women and 10.5 years of follow-up.
- Women with a high score (7 to 9 points) had a 33% decrease in sudden cardiac death, compared to women with a low score (less than 7 points).

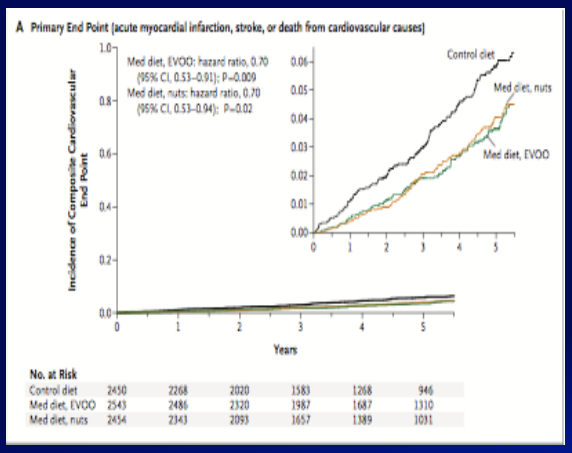
Women's Health Initiative Study.
American Journal of Clinical Nutrition. 2014;99:344-51.

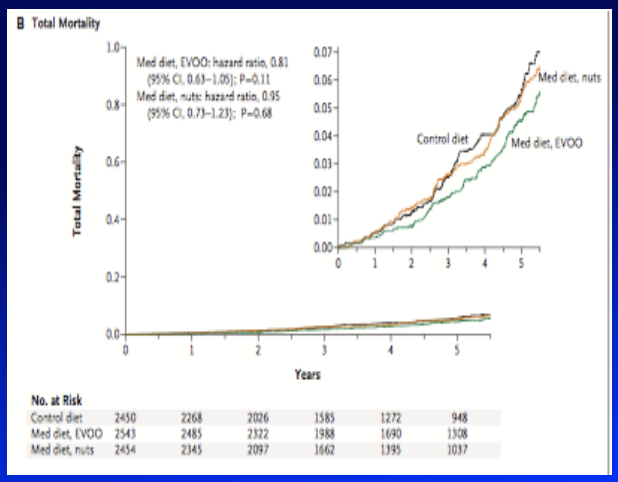
PREDIMED STUDY

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†‡			
Mean	29.9±3.7	29.7±3.8	30.2±4.0
<25 — no. (%)	195 (7.7)	204 (8.3)	164 (6.7)
25–30 — no. (%)	1153 (45.3)	1163 (47.4)	1085 (44.3)
>30 — no. (%)	1195 (47.0)	1087 (44.3)	1201 (49.0)
Waist circumference — cm	100±10	100±11	101±11
Waist-to-height ratio†§	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)¶	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†‖	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)**	1821 (71.6)	1799 (73.3)	1763 (72.0)
Family history of premature CHD — no. (%)††	576 (22.7)	532 (21.7)	560 (22.9)

NEJM, 2013

PREDIMED STUDY





NEJM, 2013

La dieta mediterranea si può usare nei pazienti in TAO? Alimenti ricchi di Vit K influiscono con la qualità della terapia?

Observational studies

Author/Year	Typ						
Lubetsky 1999 [1]	Obse	Custo´dio das Do˜res 2007 [5]	Cross-sectional	PT and INR (single value)	Vitamin K1 intake and amounts of foods rich in phylloquinone consumed as estimated using 24 h recall and FFQ of 97 items of foods.	115 patients receiving warfarin. The main indication for anticoagulant therapy was arterial disease (58%) and DVT (38%).	The median intake of phylloquinone was in average 76 -120 µg/day. Phylloquinone intake was inversely correlated with PT and INR.
Cushman 2001 [2]	Obse	Kim 2010 [6]	Observational	CV of INR and of warfarin dosage	Average daily vitamin K intake based on a three-day food diary with the Food Composition Table of Korea.	66 patients taking warfarin (AF, valves, dilated cardiomyopathy, systemic embolism).	Median daily vitamin K intake was 161.3 (31.3-616.6) µg/day. CVs of both INR and warfarin doses were negatively and independently correlated with dietary vitamin K intake.
Penning-van Beest 2002 [3]	Nest cont	Rombouts 2010 [7]	Nested case–control study	Sub-therapeutic INR (<2.0 for low intensity <2.5 for high intensity).	Usual vitamin K intake assessed by a FFQ. Fifty-seven questions were asked about 42 food items, 31 of which were vegetables or fruits.	1157 patients: AF (606), DVT (262), valves (37), arterial disease (151), prophylaxis (101). Stable anticoagulation defined as 4 consecutive INRs in the range.	Average intake was 200 µg in controls and 208 µg in cases. A 20% decrease was found in the risk of a sub-therapeutic INR in patients with a high vitamin K intake and a 33% increase in patients with a low dietary vitamin K intake.
Franco 2004 [4]	Obse	Rasmussen 2012 [8]	Cross-sectional	Warfarin dose. VKORC1 and CYP2C9 polymorphism	Dietary vitamin K intake with FFQ. Each food was assigned a unit value by dividing the vitamin K content in µg per 100 g	244 patients: AF (140), DVT (67), Mechanical heart valve (29).	Median Vitamin K was approximately 217 µg/day . Vitamin K intake positively correlated with warfarin dose.

Under review

Interventional studies investigating the relationship between dietary Vitamin K/foods and anticoagulation

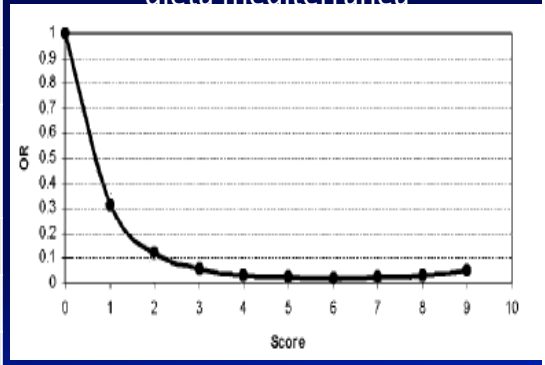
Author (year)	Year	Type of study	Measure of anticoagulation	Nutrient analysed	Population	Results / Conclusions
Pedersen [1]	1991	Interventional	Range INR 2.0-3.6	Vitamin-K-rich vegetables or equivalent amounts of oral phytomenadione and consumption of vitamin-K-poor vegetables.	37 patients on stable anticoagulation: divided in: 1 (n=5), 2 (n=7) or 7 (n=13) days with high intake of vitamin-K-rich vegetables, high intake of vitamin-K-poor vegetables for 6 days (n=7), or habitual diet supplemented with 1000 µg of phytomenadione daily (n=5).	Five patients who consumed vitamin-K-rich vegetables exceeded the upper therapeutic limit. No changes in the vitamin-K-poor group were observed.
Schurgers [2]	2004	Interventional Cross-Over	PT, INR, FII and FVII	Phase I: dietary vitamin K 50 µg–500 µg) supplementation. Phase II: effect of vitamin K–rich foods	12 healthy volunteers.	The threshold K1 dose causing a statistically significant lowering of the INR was 150 µg/day in women and 200 µg/day in men.
Franco [3]	2004	Interventional	INR (3 values in the interventional	4-day in-hospital dietary intervention; 2 groups: vitamin K-	12 patients with stable anticoagulation (two	The mean baseline vitamin K intake was 118±51 µg/day (range 18-211). INR increased progressively in

Under review

Questionario di valutazione di aderenza alla dieta mediterranea

	Componenti della dieta	Punti
1.	Olio d'oliva (1 o più cucchiai/die)	+1
2.	Frutta (1 o più porzioni/die)	+1
3.	Vegetali o insalata (1 o più porzioni/die)	+1
4.	Frutta (1 o più porzioni/die) e vegetali (1 o più porzioni/die)	+1
5.	Legumi (2 o più porzioni/settimana)	+1
6.	Pesce (3 o più porzioni/settimana)	+1
7.	Vino (1 o più bicchieri/die)	+1
8.	Carne (< 1 porzione/die)	+1
9.	Pane bianco (<di 1/die) e riso (<di 1/settimana) o Pane di cereali integrali (più di 5/settimana)	+1
	Punteggio Totale	0-9

Riduzione eventi cardiovascolari per ogni punto di aderenza alla dieta mediterranea



Curva di validazione del questionario alimentare

Martinez-Gonzalez et al. European J of ClinNutr (2004)

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Table I Baseline characteristics of the study cohort

	Overall (n = 553)	First tertile of Med-Diet 0–4 points (n = 165)	Second tertile of Med-Diet 5 points (n = 144)	Third tertile of Med-Diet 6–9 points (n = 244)	P*
Age (years)	72.9 ± 8.3	72.5 ± 9.0	72.7 ± 9.3	73.3 ± 7.0	0.590
Gender (females) (%)	40.0	42.4	44.4	35.7	0.173
Body mass index (kg/m^2)	27.3 ± 4.3	27.3 ± 4.8	27.8 ± 4.2	26.9 ± 4.0	0.121
CHA_2DS_2-VASc score	3.4 ± 1.5	3.5 ± 1.6	3.3 ± 1.4	3.4 ± 1.5	0.405
Time in therapeutic range (%)	65.5 ± 17.8	63.6 ± 16.5	67.4 ± 18.6	65.7 ± 18.2	0.172
Mean week dosage of warfarin (mg)	26.0 ± 11.7	26.7 ± 10.6	26.0 ± 13.5	25.7 ± 11.0	0.812
Mean week dosage of acenocumarol (mg)	14.7 ± 6.5	13.0 ± 5.4	16.6 ± 6.4	15.0 ± 7.0	0.022**
Number of INR analysis, n	63.0 (35.0–98.0)	74.0 (44.5–104.0)	55.5 (32.2–92.5)	64.0 (35.0–98.7)	0.037***
Mean days between two controls (days)	18.9 ± 7.1	19.1 ± 8.0	19.0 ± 6.3	18.6 ± 7.0	0.716
Past medical history					
Arterial hypertension (%)	87.5	87.3	89.5	86.5	0.680
Diabetes (%)	19.2	20.6	18.2	18.9	0.850
History of stroke/TIA (%)	14.5	18.8	13.3	12.3	0.167
Heart failure (%)	14.3	17.6	9.1	15.2	0.092
History of MI/CHD (%)	20.3	21.2	16.8	21.7	0.476
Number of drugs, n	5.8 ± 2.4	5.7 ± 2.4	5.7 ± 2.5	5.9 ± 2.3	0.824
Anti-platelet therapy (%)	10.8	7.9	11.8	12.3	0.349
ACE inhibitors/ARBs (%)	73.6	70.7	74.3	75.3	0.582
β-Blockers (%)	42.1	42.7	39.7	43.0	0.812
Ca-antagonists (%)	33.8	36.6	30.9	33.6	0.580
Amiodarone (%)	30.7	30.1	33.1	29.8	0.784

Med-Diet, Mediterranean diet; TIA, transient ischaemic attack; MI, myocardial infarction; CHD, coronary heart disease; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.
*ANOVA.
**First tertile vs. second and third, $P = 0.016$.
***First tertile vs. second and third, $P = 0.029$.

Pignatelli et al. EUROPACE 2015

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Table 2 Food frequencies and mean TTRs according to the consumption different food components of the Med-Diet

	Consumptions (%)	Mean TTR (%)		P
		Yes	No	
1. Olive oil (≥1 spoon/day)	90.1	65.6 ± 18.0	64.4 ± 15.9	0.618
2. Fruit (>1 serving/day)	88.4	66.0 ± 18.0	62.2 ± 16.5	0.115
3. Vegetables or salad (≥1 serving/day)	69.3	65.5 ± 18.4	65.6 ± 16.5	0.942
4. Fruits (≥1 serving/day) and vegetables (≥1 serving/day)	67.1	65.6 ± 18.5	65.3 ± 16.4	0.875
5. Legumes (≥2 servings/week)	40.7	66.2 ± 17.6	65.0 ± 18.0	0.451
6. Fish (≥3 servings/week)	17.9	66.1 ± 18.5	65.4 ± 17.7	0.708
7. Wine (≥1 glass/day)	36.0	65.6 ± 17.2	65.5 ± 18.2	0.913
8. Meat (<1 serving/day)	71.2	66.3 ± 17.9	63.7 ± 17.6	0.124
9. [White bread (<1/day) and rice (<1/week)] or whole-grain bread (>5/week)	38.0	66.8 ± 17.6	64.7 ± 18.0	0.181

Pignatelli et al. EUROPACE 2015

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Table 3 Mean TTR according to the presence of selected variables

	Mean TTR		P
	Presence	Absence	
Gender (female)	65.8 ± 18.2	65.3 ± 17.6	0.739
Arterial hypertension	66.1 ± 17.9	62.0 ± 16.6	0.076
Diabetes	62.1 ± 16.7	66.4 ± 17.9	0.026
History of stroke/TIA	64.3 ± 18.5	65.8 ± 17.7	0.481
HF	62.8 ± 18.7	66.0 ± 17.6	0.138
History of MI/CHD	62.8 ± 16.9	66.3 ± 17.9	0.059
Anti-platelet therapy	65.2 ± 17.9	65.8 ± 17.7	0.807
ACE inhibitors/ARBs	67.2 ± 17.5	61.5 ± 17.4	0.001
β-Blockers	64.3 ± 17.8	66.8 ± 17.6	0.107
Ca-antagonists	66.7 ± 17.8	65.2 ± 17.6	0.371
Amiodarone	65.5 ± 18.3	66.2 ± 16.2	0.676

HF, heart failure; TIA, transient ischaemic attack; MI, myocardial infarction; CHD, coronary heart disease; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Pignatelli et al. EUROPACE 2015

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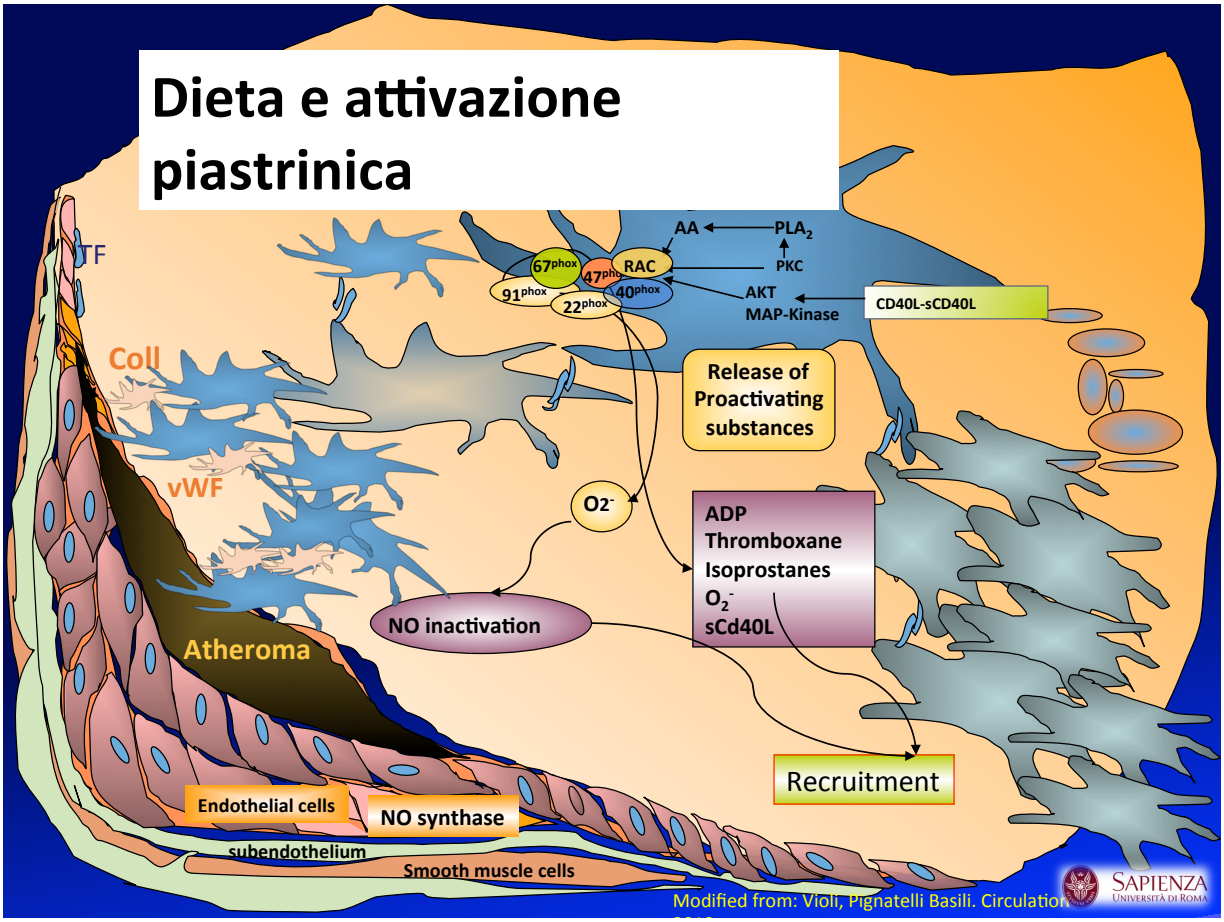
Dieta e attivazione piastrinica



FA e Attivazione piastrinica

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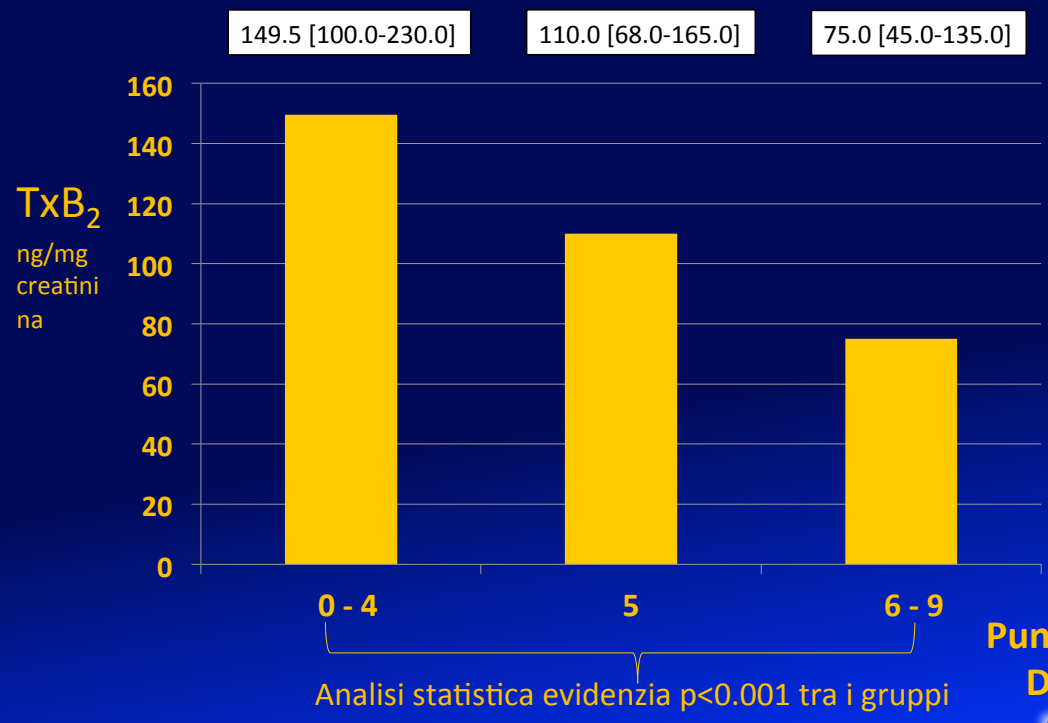
Table I. Baseline characteristics of the study cohort and according to the occurrence of CVEs

	Whole cohort (N = 837)	CVEs		P
		No (n = 738)	Yes (n = 99)	
Age (y)	73.2 ± 8.5	72.9 ± 8.6	75.5 ± 7.4	.001
Women (%)	43.6	44.0	40.4	.52
Body mass index (kg/m^2)	27.2 ± 4.7	27.2 ± 4.7	27.3 ± 4.2	.88
Smokers (%)	9.9	9.8	11.1	.72
CHA_2DS_2-VASc score*	3 (2-4)	3 (2-4)	4 (3-5)	<.001
TTR (%)	63.8 ± 17.2	64.2 ± 17.2	59.3 ± 16.5	.09
Urinary 11-dehydro-TxB_2*	100.0 (56.5-181.0)	98.0 (51.0-170.0)	185.0 (109.0-400.0)	<.001
HAS-BLED score*	2 (1-2)	1 (1-2)	2 (1-2)	.60
Arterial hypertension (treated) (%)	92.8	92.5	94.9	.53
Diabetes mellitus (%)	19.8	18.4	30.3	.007
Heart failure (%)	17.7	15.7	32.3	<.001
History of stroke/TIA (%)	16.7	15.0	29.3	.001
History of MI/cardiac revascularization (%)	24.0	22.4	36.4	.004
Antiplatelets (%)	7.0	7.3	5.1	.53
Statins (%)	37.4	37.4	37.4	.99

*Data expressed as median and IQR.

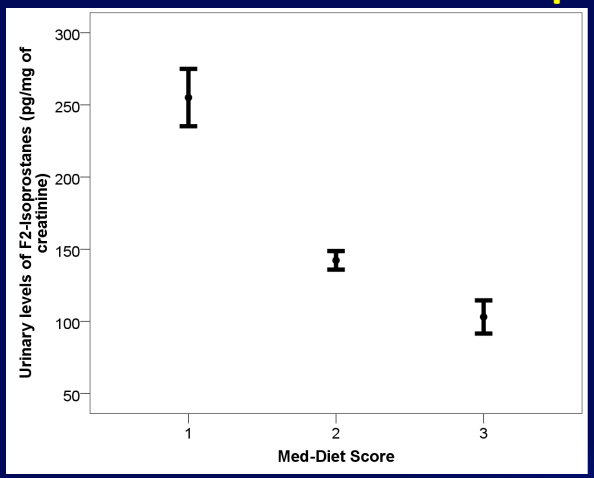
Pastori, Pignatelli et al. Am Heart J 2015

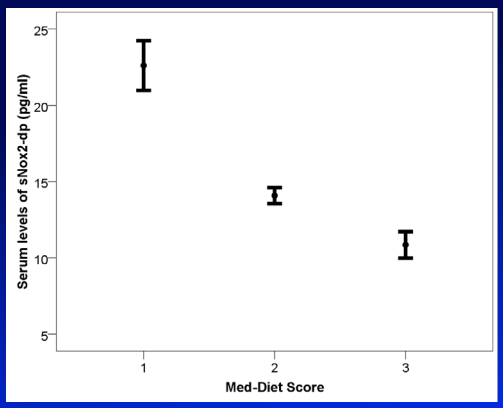
Associazione livelli di TXB_2 e terzili di aderenza alla dieta



Pignatelli et al Clin Nutr 2014

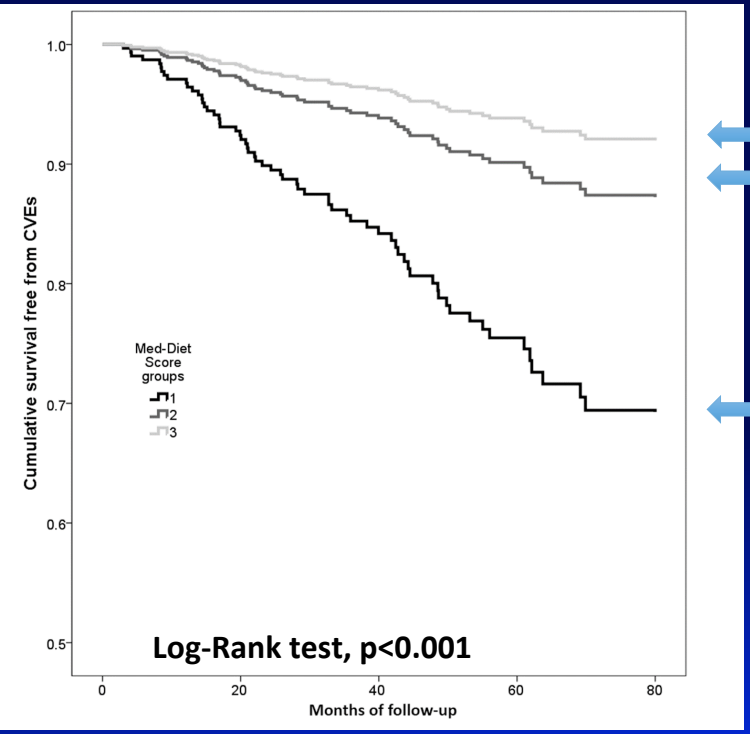
Dieta e stress ossidativo: NADPH ossidase e Isoprostani





Pastori D et al. Antiox Redox Sig 2015

Dieta ed eventi cardiovascolari



Aderenza alla dieta

Alta

Media

Bassa

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Stress ossidativo ed FA

	Overall	Cardiovascular event		P-value
	n=950	No (n=827)	Yes (n=123)	
Age (years)	73.3 ± 8.8	72.9 ± 8.9	76.5 ± 7.5	<0.001
Persistent/permanent AF	58.5	57.3	67.5	0.032
Male gender no. (%)	55.5	55.8	56.1	0.951
CHA_2DS_2-VASc score	3.49 ± 1.64	3.41 ± 1.63	4.34 ± 1.51	<0.001
Total cholesterol (mg/dl)	180.6 ± 45.4	179.8 ± 42.7	185.5 ± 61.4	0.335
Triglycerides (mg/dl)	124.7 ± 64.7	124.5 ± 63.0	126.4 ± 75.7	0.816
Fasting blood glucose (mg/dl)	101.2 ± 29.3	101.2 ± 28.4	101.8 ± 35.1	0.870
TTR (%)	63.9 ± 16.9	64.2 ± 16.9	59.3 ± 16.7	0.095
Urinary 8-iso-$PGF_{2\alpha}$ (pg/mg creat)#	104.5 [60–177]	100 [54–161]	160 [120–320]	<0.001
sNOX2-dp (pg/ml) #	9 [6–19]	9 [6–18]	13 [8–24]	<0.001
Hypertension (%)	84.9	84.7	87	0.515
Diabetes mellitus (%)	18.5	17.5	26.0	0.023
Heart failure (%)	16.1	15.2	27.6	0.001
History of stroke/TIA (%)	16.5	14.7	29.3	<0.001
History of MI (%)	24.8	22.8	40.7	<0.001
Anti-platelet drugs (%)	20.6	19.9	26.0	0.115
ACE inhibitor/ARBs (%)	63.4	63.8	61.8	0.672
β blockers (%)	33.4	32.7	27.7	0.050
Calcium channel blockers (%)	28.9	31.4	29.5	0.675
Statins (%)	36.6	39.4	35.7	0.440
Antiarrhythmic drugs (%)	33.2	33.9	27.6	0.115

Data expressed as medians [interquartile ranges]. AF: atrial fibrillation, TTR: time in therapeutic range, TIA: transient ischaemic attack, MI: myocardial infarction, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers, 8-iso-$PGF_{2\alpha}$: prostaglandin PGF2alpha, sNOX2-dp: soluble NOX2-derived peptide.

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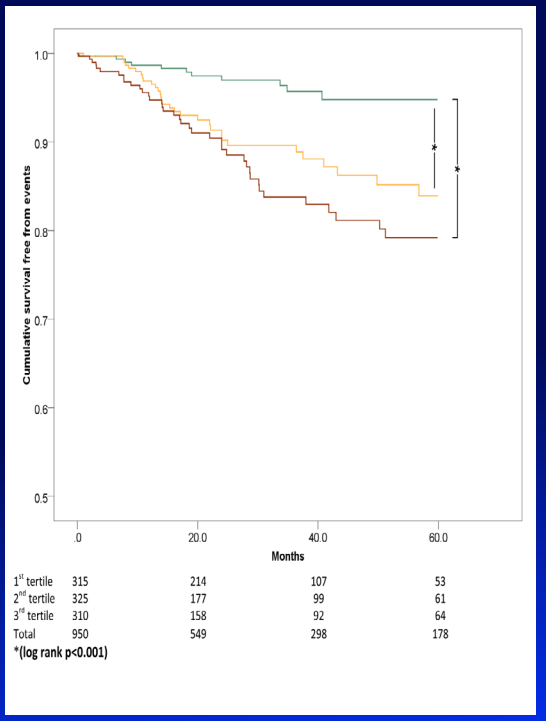
Stress ossidativo ed FA

- **Kaplan-Meier curves estimates of survival free from all-cause mortality according to tertiles of urinary 8-iso-PGF2α.**
- Green line: lower tertile
- yellow line: second tertile
- brown line: third tertile of 8-iso-PGF2α.



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- FA Ictus ed eventi cardiovascolari
- TTR ed eventi cardiovascolari
- Dieta e TTR
- Conclusioni

Adherence Med-Diet is not associated with changes in
TTR in a cohort of AF patients suggesting that food contained in such diet does not interfere with VKAs.

adherence to Med-Diet could be associated with a reduction of CVEs, through an antioxidant effect, as shown by a concomitant down- regulation of Nox2 and decreased excretion of F2-IsoP

Med-Diet adherence is inversely associated to urinary excretion of 11-dehydro-TxB2, suggesting that Med-Diet may favorably affect platelet function in AF patients.