High Potency Vitamins in CKD "To B or not to B"

Piera Calissi BSc(Pharm) PharmD FCSHP
Interior Health Authority Renal Program
Kelowna, BC
October 2010

Conflicts

I have not conflicts of interest to declare.

Objectives

- After attending this session, the participant will be able to:
  - recognize where vitamin therapy may be indicated in CKD patients
  - critically evaluate the current evidence based literature describing the use of high potency vitamin therapy in CKD patients
  - safely and effectively use high potency vitamin therapy in a typical CKD patient

Vitamin B Complex

- Vitamin B1-thiamine
- Vitamin B2-riboflavin
- Vitamin B3-niacin/niacinamide
- Vitamin B5-Pantothenic acid
- Vitamin B6-pyridoxine
- Vitamin B7-biotin
- Folic Acid (aka Vitamin B9)
- Vitamin B12-Cyanocobalamin

Why supplement B vitamins in CKD?

- Deficiency
  - Typical diet of CKD patients low in B-vitamins
  - Uremia in stage 5 CKD can affect activity of pyridoxine (B6) and folic acid
  - B-vitamin loss during dialysis
- Suppression of hyperhomocysteinemia and prevention of cardiovascular disease (CVD)

Deficiency

B-Vitamin Deficiency and CKD

- The typical renal failure diet is low in B-vitamins
- Uremic toxins present in Stage 5 CKD interfere with active moiety of vitamin B6 and membrane transport of folate
- Dialysis removes small, water soluble vitamins (B-vitamins and vitamin C)
  - High-flux HD>conventional HD
  - HD=PD

Semin Dial 1997; 10: 272-277

Consequences of unaddressed B-Vitamin Deficiency

- Virtually all unsupplemented "pre-dialysis" and dialysis patients develop pyridoxine (B6) deficiency
  - exacerbated by high-flux HD
- Cyanocobalamin (B12) deficiency, is protein bound- deficiency not common in dialysis
- Folic acid deficiency can occur in unsupplemented CKD patients
- Anemia related to deficiencies of folic acid, pyridoxine (B6) and cyanocobalamin (B12)

Seminars Dial 1997; 10: 272-277

Prevention of B-Vitamin Deficiency in CKD

- Dialysis patients should receive minimum daily supplementation with to prevent deficiency:
  - Folic acid 0.8-1 mg
  - Pyridoxine (B6) 10 mg
  - Cyanocobalamin (B12) 6 mcg

Seminar Dial 1997; 10: 272-277

CKD and B-Vitamin Deficiency

- Recommendation: Supplementation with a renal vitamin preparation, such as Renavite®1 tablet PO DAILY (Post-HD, applicable):
  - 1.5mg thiamine (B1)
  - 1.7mg riboflavin (B2)
  - 6ug cyanocobalamin (B12)
  - 10mg pyridoxine (B6)
  - 10mg pantothenic acid (B5)
  - 20mg niacinamide (B3)
  - 100mg vitamin C
  - 300 ug biotin (B7)
  - 1mg folic acid

Stage 3 and 4 CKD-Draft

- Draft Renal Dietitian's Position Statement:
  - Renavite® would be indicated in Stage 3 and 4 CKD patients with inadequate nutritional intake:
    - Eating less than 50% of meals and/or consuming less than 1500 kcal/day
    - Chronically poor or erratic eating habits
    - Reduced appetite, nausea, vomiting, taste changes or food aversions
    - Undesirable weight loss
    - Food insecurity

Treatment of Overt B-vitamin Deficiency

B-Vitamin	Deficiency	Sign / Symptoms	Treatment
Thiamine (B1)	Beri-Beri	CHF; peripheral neuritis (Wet) Peripheral neuropathy (dry)	100 mg/d IM/IV x7, then 5-30 mg/d PO x 1 month
Thiamine (B1)	Wernicke's Encephalopathy Wernicke-Korsakoff Syndrome	Nystagmus, eye MM weakness, ataxia, confabulatory psychosis	100 mg IV, then 50-100 mg/d IM/IV- until eating balance diet
Niacin (B3)	Pellegra	Dermatitis, diarrhea, dementia, leading to death (4Ds) Red beefy tongue	50-100 mg PO tid-qid

Harrison's Practice 2010; Lexi-Drugs 2010

Treatment of Overt B-vitamin Deficiency

B-Vitamin	Deficiency	Signs/ Symptoms	Treatment
Pyridoxine (B6)	Drug-Induced Deficiency	Neuritis	100-200 mg/day PO
Folic Acid	-	Megaloblastic Anemia	0.4 mg/day IV/IM/SC/PO
Cyanocobalamin (B12)	Perinicious anemia – malabsorption Low intake	Megaloblastic anemia; infection; Peripheral neuropathy, disequilibrium, optic atrophy, irritability, forgetfulness; ↓positional, vibrational sense, reflexes; +ve Romberg/Babinski; dementia, psychosis	1000 mcg/d x 5 days, then 500-1000 mcg/month; 250 mcg/d PO (if intrinsic factor present)

Harrison's Practice 2010; Lexi-Drugs 2010

High-Potency B-Vitamin Supplementation

Background

- CVD and CKD
  - CKD patients are at high risk for development of and mortality from CVD
  - Hyperhomocysteinemia is a non-traditional risk factor for CVD
  - Hyperhomocysteinemia is found in >90% of ESRD on dialysis
  - From NHANES, homocysteine levels were 9-11X higher in patients with Clcr<60 mL/min/1.73 m2

Homocysteine (Hcy)

- Inherited hyper-Hcy treated with folic acid, cyanocobalamin and pyridoxine have ↓Hcy levels and CV events-"homocysteine hypothesis"
- General population studies show a strong relationship between Hcy and CV events
- However, RCTs in patients with CVD have found neither a reduction in CV events nor mortality with txt with B-vitamins

Am J Kidney Dis 2009; 54: 478-489

B Vitamins and Homocysteine-Endothelial Dysfunction

- Folic acid ↓Hcy by ~25% and cyanocobalmin by an additional 7%
- pyridoxine is also effective to lower homocysteine
- Although folic acid reduces homocysteine levels in CKD patient, it does not improve endothelial dysfunction markers

Am J Kidney Dis 2009; 54: 478-489

B-Vitamin Supplementation and CKD Outcome Studies

Dialysis

Wrone 2004

Design	Multicentre, Randomized, Placebo Controlled
Population	578 Adult patients undergoing HD or PD; Excluded patients receiving IDPN, anticipating LR Kidney Tx, receiving anti-seizure medication, residing in an institution or terminally ill. Median follow-up was 24 months. (N. California, USA)
Intervention	renal vitamin containing folic acid 5 mg or renal vitamin containing folic acid 15 mg daily (identical looking capsules)(R&D Laboratories)
Comparator	Standard therapy with a renal vitamin containing folic acid 1 mg daily
Outcomes	Main outcomes: CV events and mortality (coronary artery intervention, MI, stroke, TIA, CEA, limb amputation, or death) Secondary outcomes: vascular access thrombosis (in AVFs),

J Am Soc Nephrol 2004; 15: 420-26

Results-Primary Outcome

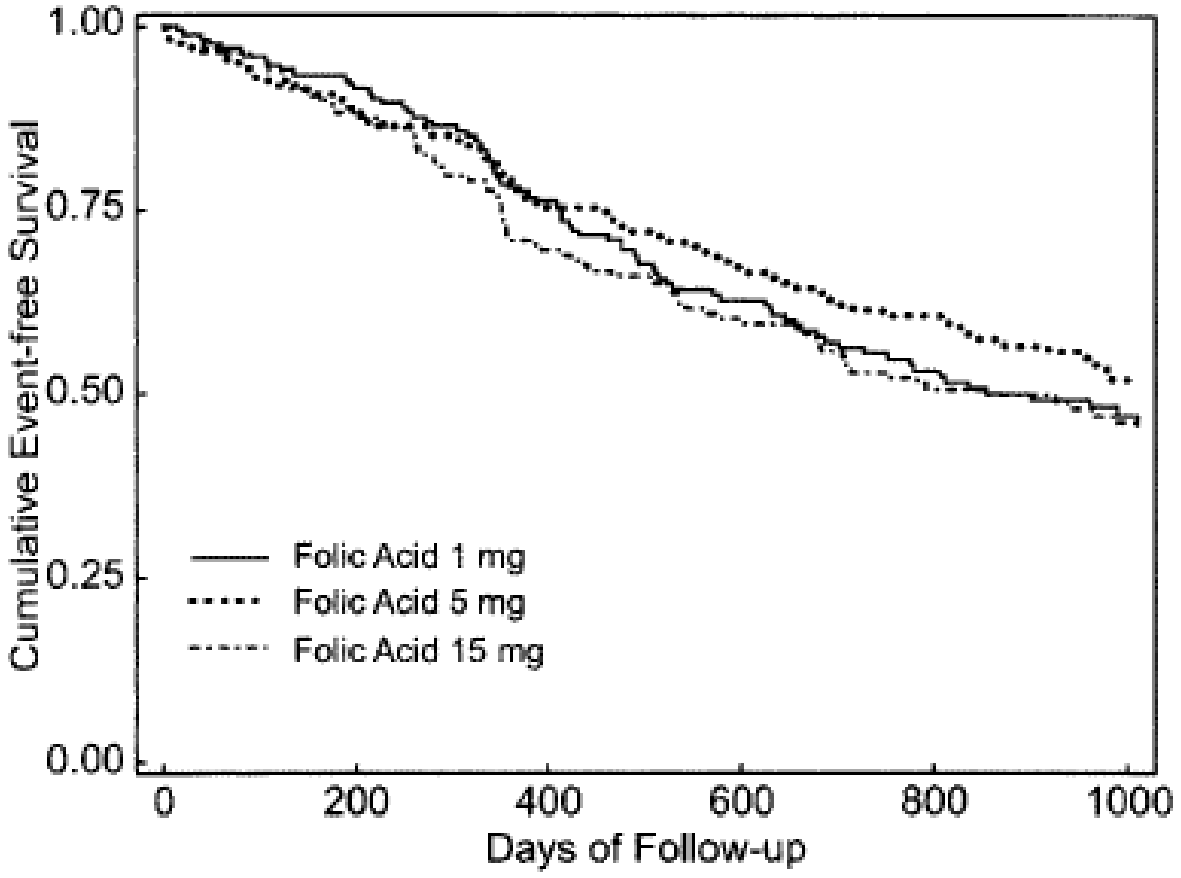


Figure 2. Event-free survival by folic acid group.

P=0.47

Results

Table 2. Number of events at 24 mo by folic acid group and baseline total homocysteine quartile (low to high)

	Treatment Arm		
	1 mg (n = 168)	5 mg (n = 176)	15 mg (n = 166)
Myocardial infarction	4	5	4
Cerebrovascular accident	8	10	9
Transient ischemic attack	1	3	3
Revascularization procedure[a]	4	8	6
Death	56	44	61
Vascular access event[b]	70	68	66

Baseline Hcy lowest to highest

	Homocysteine Quartile			
	Q1 (n = 128)	Q2 (n = 130)	Q3 (n = 125)	Q4 (n = 127)
Myocardial infarction	4	2	2	5
Cerebrovascular accident	9	7	5	6
Transient ischemic attack	4	1	1	1
Revascularization procedure[a]	6	7	3	2
Death	51	39	40	31
Vascular access event[b]	49	53	57	45
Serum albumin, mean, g/L	38.4	39.4	40.4	40.8

[a] Includes cardiac surgery, percutaneous coronary intervention, and carotid endarterectomy.
[b] Includes vascular access thrombosis and new permanent vascular access.

CV Event Rate +death:

P=-0.033

Conclusion

- "For patients with ESRD treated with dialysis, these results do not support administration of folic acid beyond the generally recommended 1 mg/d."

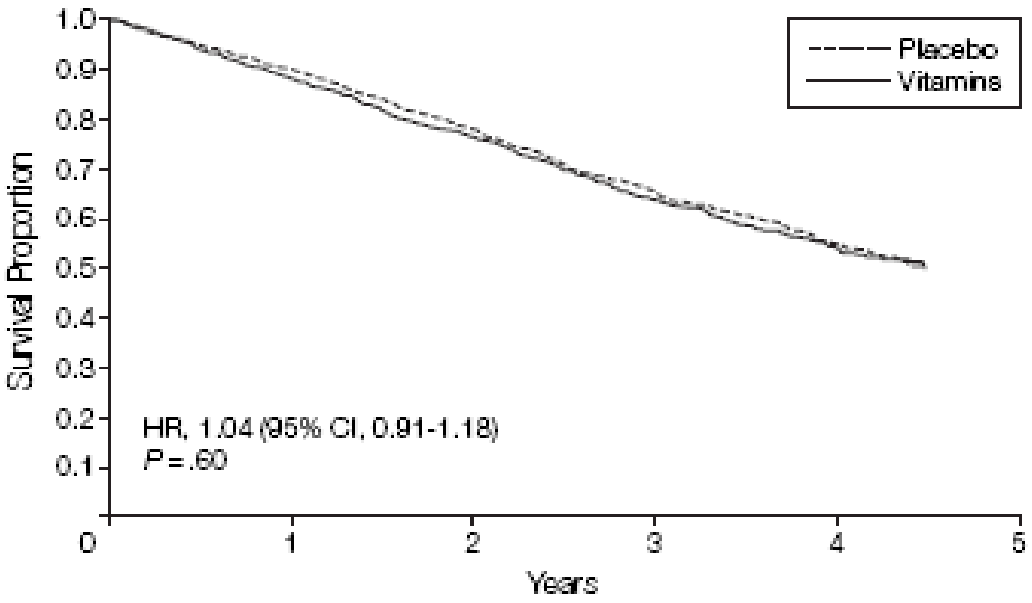
HOST

Design	Multicentre, Randomized, Placebo Controlled
Population	2056 Adult (>21 years), ESRD, receiving maintenance HD or PD or with a Clcr<30 mL/min.; Plasma Homocysteine ≥15 mmol/L; Mean followup 3.2 years
Intervention	**Folic acid 40 mg/pyridoxine 100 mg/cyanocobalamin 2 mg/d** (Also allowed to take MV containing folic acid≤1 mg)
Comparator	Placebo (identical looking capsule)
Outcomes	Primary- death from any cause Secondary- time to MI, stroke or amputation of any extremity and a composite of these 3 plus all-cause mortality. Time to AV access thrombosis (HD Patients only).

J Am Med Assoc 2007; 298: 1163-1170

Results-Primary Outcome

Figure 2. Kaplan-Meier Estimates of Survival



Placebo, No.						
At risk	1024	922	800	672	603	588
Deaths	0	102	224	352	421	436
Vitamins, No.						
At risk	1032	910	790	660	596	584
Deaths	0	122	242	372	436	448

There were at total of 884 deaths.

Primary and Secondary Outcomes

Table 4. Primary and Secondary Outcomes

End Point	No. (%) of Patients With an Event		Hazard Ratio (95% CI)[a]	*P* Value[b]
	Vitamin Group (n = 1082)	Placebo Group (n = 1024)		
Primary outcome				
All-cause mortality	446 (43)	435 (43)	1.04 (0.91-1.18)	.60
Secondary outcomes				
MI (fatal and nonfatal)	139 (13)	150 (15)	0.86 (0.67-1.08)	.18
Stroke (fatal and nonfatal)	37 (4)	41 (4)	0.90 (0.58-1.40)	.64
Amputation	60 (6)	53 (5)	1.14 (0.79-1.64)	.50
Composite of all-cause mortality, MI, stroke, or amputation	523 (51)	525 (51)	0.99 (0.88-1.12)	.85
Dialysis in advanced chronic kidney disease patients only (n = 1305)	365 (55)	340 (53)	1.07 (0.92-1.24)	.39
Thrombosis in hemodialysis patients (n = 1397)	166 (24)	163 (23)	1.01 (0.81-1.25)	.97

Abbreviations: CI, confidence interval; MI, myocardial infarction.
[a] Hazard ratios were adjusted for kidney disease strata.
[b] *P* values were based on the unadjusted log-rank test.

Conclusion

- “Treatment with high dose folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced CKD or ESRD”

Heinz 2009-Meta-analysis

Design	Separate meta-analyses of retrospective (11) prospective (12) and interventional (5) studies
Population	ESRD treated at least 1 month with HD or CAPD
Intervention	Retrospective and Prospective: influence of B vitamins (folic acid, vitamin B-6 and vitamin B-12) on homocysteine levels Interventional: effect of B vitamins (folic acid, vitamin B-6 and vitamin B-12) on risk of mortality and CV morbidity
Comparator	Not applicable
Outcomes	Primary outcome: total mortality Secondary Outcomes: occurrence of 1st fatal or non-fatal CV event (MI, USA, coronary vascularization procedures, sudden cardiac death, stroke, PAD, Pulmonary embolism, thrombosis). Shunt thrombosis NOT considered an outcome.

Am J Kidney Dis 2009; 54: 478-489

Retrospective Studies

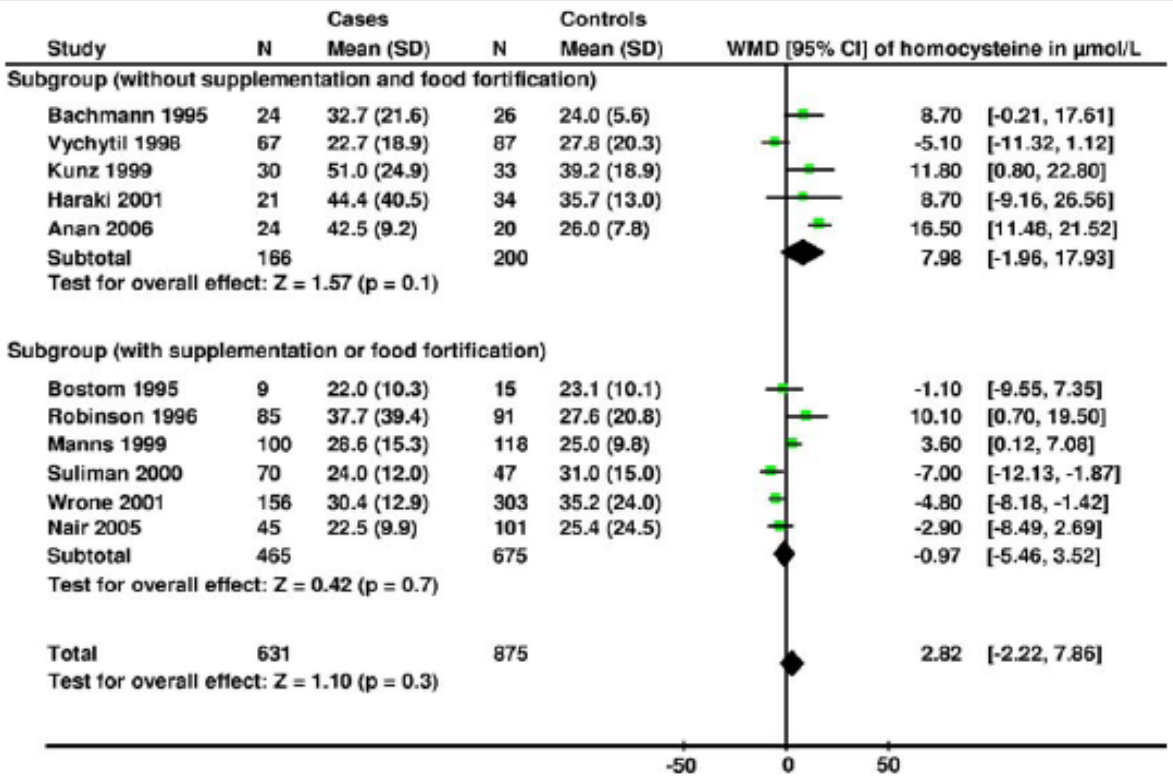


Figure 2. Retrospective studies: pooled means of total homocysteine concentrations of patients with (cases) or without (controls) cardiovascular disease. Data expressed as weighted mean differences (WMDs) for all studies and for subgroups with vitamin supplementation or food fortification as characteristics (subgroup with supplementation/fortification: studies with > 50% of patients using water-soluble vitamin supplements or mandatory folic acid food fortification during study period; analysis of the supplementation in individual patients was not possible). Abbreviation: CI, confidence interval.

Prospective Observational Studies-Mortality

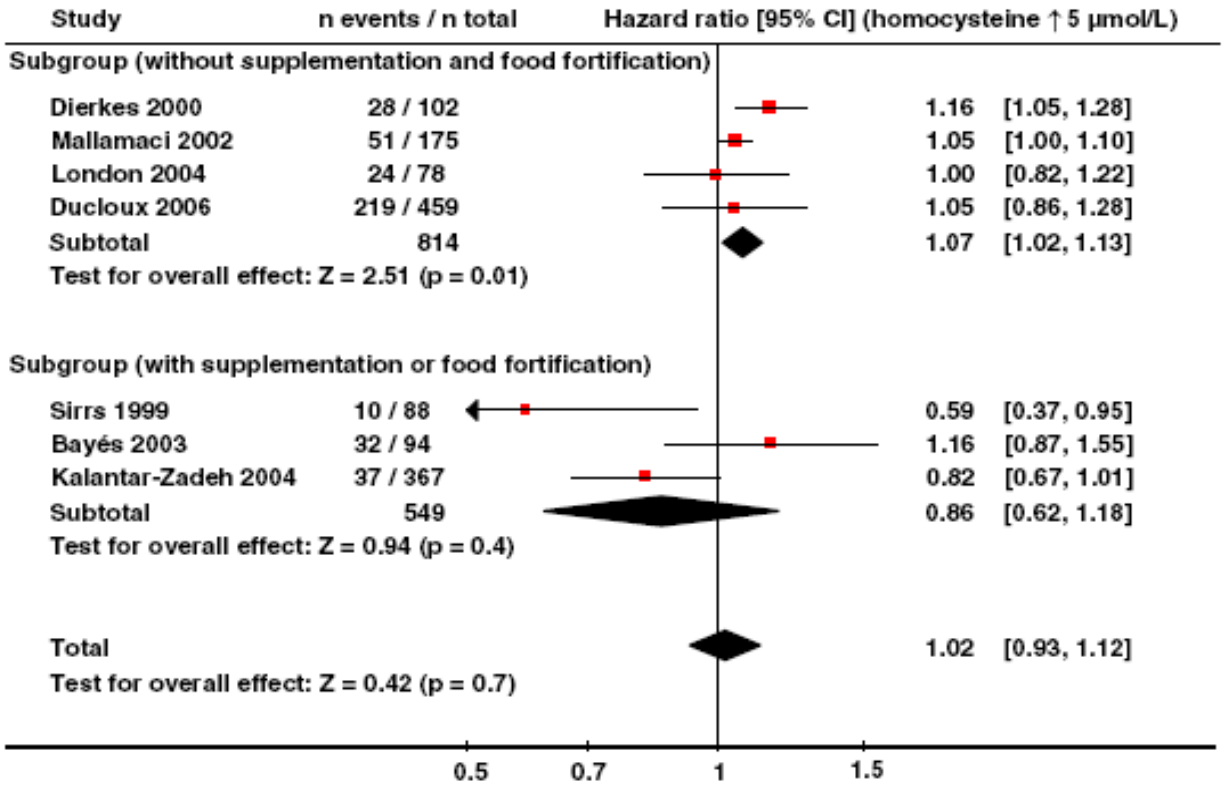


Figure 3. Prospective observational studies: pooled logarithms of the hazard ratio (HR) for mortality associated with a 5-µmol/L increase in total homocysteine level. Data are given as pooled HRs for all studies and for subgroups with vitamin supplementation or food fortification as characteristics (subgroup with supplementation/fortification: studies with > 50% of patients using water-soluble vitamin supplements or mandatory folic acid food fortification during study period; analysis of the supplementation in individual patients was not possible). Abbreviation: CI, confidence interval.

Prospective Observational Studies- CV events

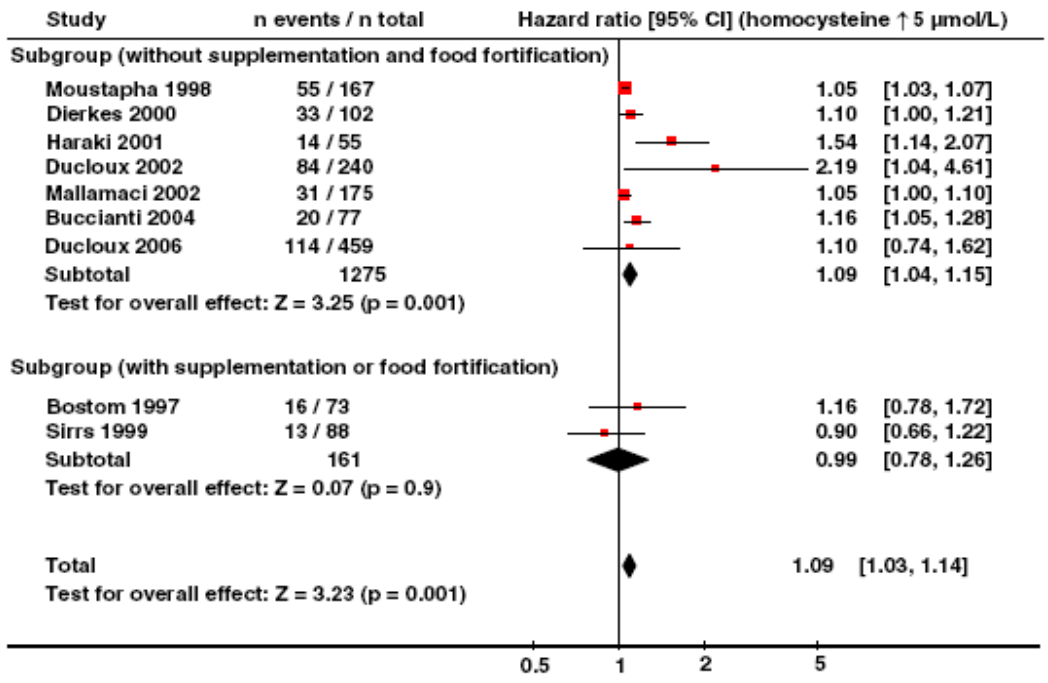


Figure 4. Prospective observational studies: pooled logarithms of risk estimates of cardiovascular events associated with a 5-µmol/L increase in total homocysteine level. Data are given as pooled hazard ratios for all studies and for subgroups with vitamin supplementation or food fortification as characteristics (subgroup with supplementation/fortification: studies with > 50% of patients using water-soluble vitamin supplements or mandatory folic acid food fortification during study period; analysis of the supplementation in individual patients was not possible). Abbreviation: CI, confidence interval.

Interventional Studies: Fatal and Non Fatal CV Events, total Mortality

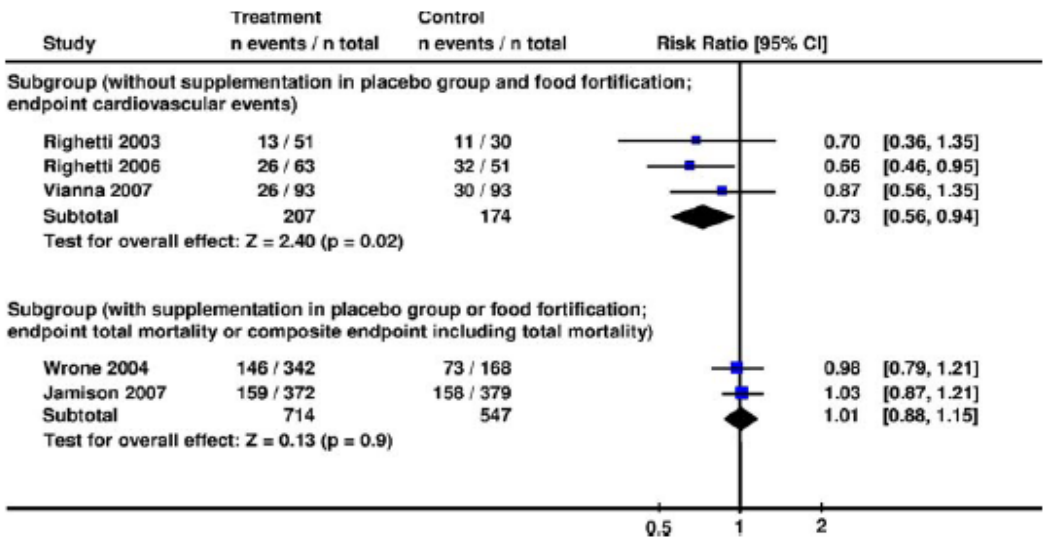


Figure 5. Intervention studies: pooled risk estimates for fatal and nonfatal cardiovascular events and total mortality associated with homocysteine-lowering treatment with B vitamins. Data are given as pooled risk ratios for all studies and for subgroups with vitamin supplementation or folic acid food fortification in the placebo group as characteristics (subgroup with supplementation/fortification: studies with > 50% of patients using vitamin supplements or mandatory folic acid food fortification during study period; analysis of the supplementation in individual patients was not possible). Abbreviation: CI, confidence interval.

Conclusion

- "Total homocysteine may be a risk factor for CV events and total mortality in patients with ESRD not receiving vitamin supplementation or folic acid food fortification. There may be potential for reducing CV disease in this population by folic acid supplementation."

Heinz 2010

Design	Multicentre, Randomized, double-blind, placebo controlled
Population	650 Adults (20-80 years), with ESRD treated at least 1 month with HD, regardless of homocysteine levels. Median follow-up 2.1 years
Intervention	Folic acid 2.5 mg, cyanocobalamin 25 mcg, pyridoxine 10 mg tablets; 2 tablets post-HD; Tablets also contained 6 other water-soluble vitamins similar to daily allowances.
Comparator	Folic acid 0.1 mg/cobalamin 2 mcg/pyridoxine 0.5 mg (Placebo); 2 tablets post-HD. Tablets also contained 6 other water-soluble vitamins similar to daily allowances
Outcomes	Primary outcome: total mortality Secondary Outcomes: occurrence of 1st fatal or non-fatal CV event (MI, USA, coronary vascularization procedures, sudden cardiac death, stroke, PAD, Pulmonary embolism, thrombosis). Shunt thrombosis NOT considered an outcome.

Circulation 2010; 121: 1432-1438

Results

Table 2. Plasma Levels of Total Homocysteine, Serum Levels of Folate, Serum Levels of Cobalamin, and Plasma Levels of PLP at Baseline and After 6 Months in a Subgroup of 97 Patients

	Baseline	At 6 mo	*P*, Baseline vs 6 mo*	Changes During 6 mo
Total homocysteine, μmol/L				
Placebo (n=37)	28.8 (14.1–68.2)	22.3 (9.8–54.1)	0.07	−1.8 (−42.3–15.05)
Active treatment (n=59)	28.7 (16.5–69.4)	18.8 (7.2–33.6)	<0.001	−10.4 (−35.8–2.5)
P (placebo vs treatment)†	0.49	0.03		0.001
Folate, nmol/L				
Placebo (n=37)	11.8 (5.7–61.4)	15.0 (8.2–83.6)	0.05	3.0 (−22.9–16.4)
Active treatment (n=54)	12.7 (5.7–118.5)	81.8 (34.0–117.4)	<0.001	66.4 (−2.0–105.8)
P (placebo vs treatment)†	0.35	<0.001		<0.001
Cobalamin, pmol/L				
Placebo (n=38)	288 (140–690)	399 (227–731)	<0.001	125 (−158–372)
Active treatment (n=58)	279 (72–999)	407 (163–1058)	<0.001	100 (−225–459)
P (placebo vs treatment)†	0.45	0.87		0.36
PLP, nmol/L				
Placebo (n=38)	20.6 (9.9–135.5)	22.1 (8.0–284.0)	0.53	0.4 (−58.0–218.7)
Active treatment (n=57)	26.0 (8.8–333.6)	80.5 (14.1–305.7)	<0.001	58.4 (−238.9–259.3)
P (placebo vs treatment)†	0.35	<0.001		<0.001

Data are given as medians (5th to 95th percentiles).
*Wilcoxon matched-pairs rank test for repeated measurements.
†Mann-Whitney *U* test.

Primary and Secondary Outcomes

Table 3. Primary and Secondary Outcomes in the Treatment Groups, Respective Causes of Mortality, Individual Cardiovascular End Points, and the Corresponding HRs With 95% CIs

	Active Treatment (n=327), n (%)	Placebo (n=323), n (%)	Crude HR (95% CI)	*P*	Adjusted* HR (95% CI)	*P*
Primary outcome						
Total mortality	102 (31)	92 (28)	1.13 (0.85–1.50)	0.51	1.14 (0.85–1.52)	0.37
Secondary outcome						
Cardiovascular events	83 (25)	98 (30)	0.80 (0.60–1.07)	0.13	0.79 (0.59–1.07)	0.13
Category of causes of mortality						
Cardiac causes	37 (11)	32 (10)	1.18 (0.73–1.89)	0.50	1.26 (0.77–2.06)	0.36
Vascular causes	6 (2)	10 (3)	0.61 (0.22–1.68)	0.34	0.51 (0.18–1.42)	0.20
Sepsis and infections	28 (9)	22 (7)	1.30 (0.74–2.27)	0.36	1.19 (0.67–2.10)	0.55
Tumors	8 (2)	7 (2)	1.17 (0.43–3.23)	0.76	1.44 (0.50–4.17)	0.50
Other causes	14 (4)	15 (5)	0.95 (0.46–1.97)	0.89	1.00 (0.48–2.11)	0.99
Unknown	9 (3)	6 (2)	1.56 (0.56–4.39)	0.40	1.74 (0.61–4.98)	0.31
Individual cardiovascular events						
Myocardial infarction (nonfatal and fatal)	20 (6)	19 (6)	1.06 (0.57–1.99)	0.86	1.00 (0.53–1.88)	0.99
Coronary vascularization procedures	8 (2)	18 (6)	0.44 (0.19–1.02)	0.06	0.44 (0.19–1.03)	0.06
Unstable angina pectoris	5 (2)	15 (5)	0.32 (0.12–0.89)	0.03	0.32 (0.12–0.89)	0.03
Sudden cardiac death	22 (7)	24 (7)	0.93 (0.52–1.66)	0.81	1.04 (0.57–1.91)	0.89
Stroke (nonfatal and fatal)	11 (3)	15 (5)	0.74 (0.34–1.62)	0.45	0.73 (0.33–1.60)	0.43
Peripheral artery disease	26 (8)	34 (11)	0.74 (0.45–1.24)	0.26	0.77 (0.46–1.31)	0.34
Pulmonary embolism and thromboses	7 (2)	6 (2)	1.16 (0.39–3.44)	0.79	1.14 (0.37–3.48)	0.82

*Cox regression analysis adjusted for age, sex, diabetes mellitus, hypertension, time on dialysis, C-reactive protein, and albumin.

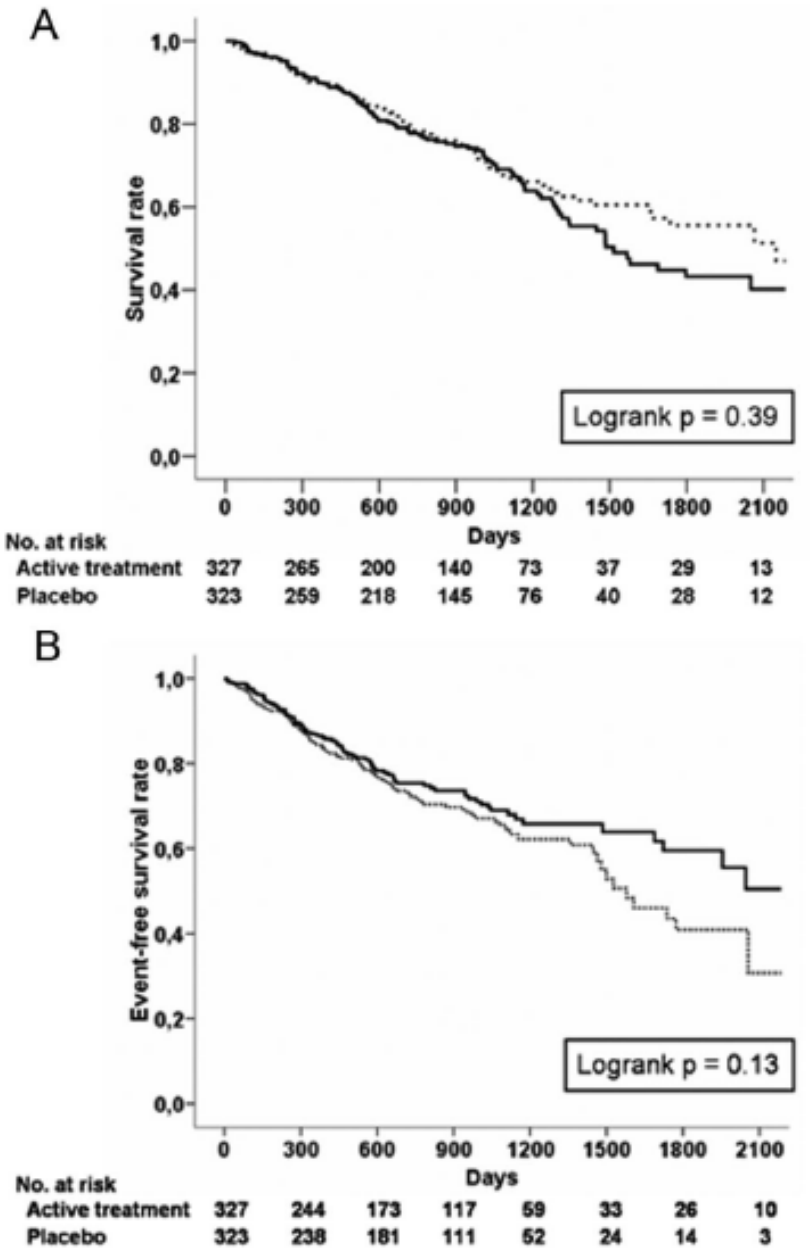


Figure 2. Primary end point of total mortality (A) and secondary end point of fatal and nonfatal cardiovascular events (B). Kaplan-Meier estimates of survival in the active treatment group vs placebo group. Solid line indicates active treatment; dashed line, placebo.

Conclusions

- "Increased intake of folic acid and vitamin B6 did not reduce total mortality or had significant effect on the risk of CV events in patients with ESRD."

Non-dialysis CKD

Renal HOPE-2

Design	Multicentre, Randomized, Placebo Controlled
Population	Adults ≥55 years with a history of CVD (coronary, cerbrovascular or peripherial vascular) or diabetes with additional risk factors for atherosclerosis, irrespective of homocysteine levels. Patients taking ≥0.2 mg folic acid excluded. **Post-Hoc analysis** of 619 participants with a Clcr<60 mL/min. Median follow-up 5 years.
Intervention	Folic acid 2.5 mg/pyridoxine 50 mg/vitamin B-12 1 mg/d
Comparator	Placebo
Outcomes	Primary- death from CV causes, MI and stroke. Secondary-total ischemic event (including death from CV causes, MI, stroke, hospitalization for USA and revascularization), total mortality, hospitalization for USA, hospitalization for CHF, revascularization, cancer incidence and cancer death. Other outcomes included TIAs, VTEs and fractures.

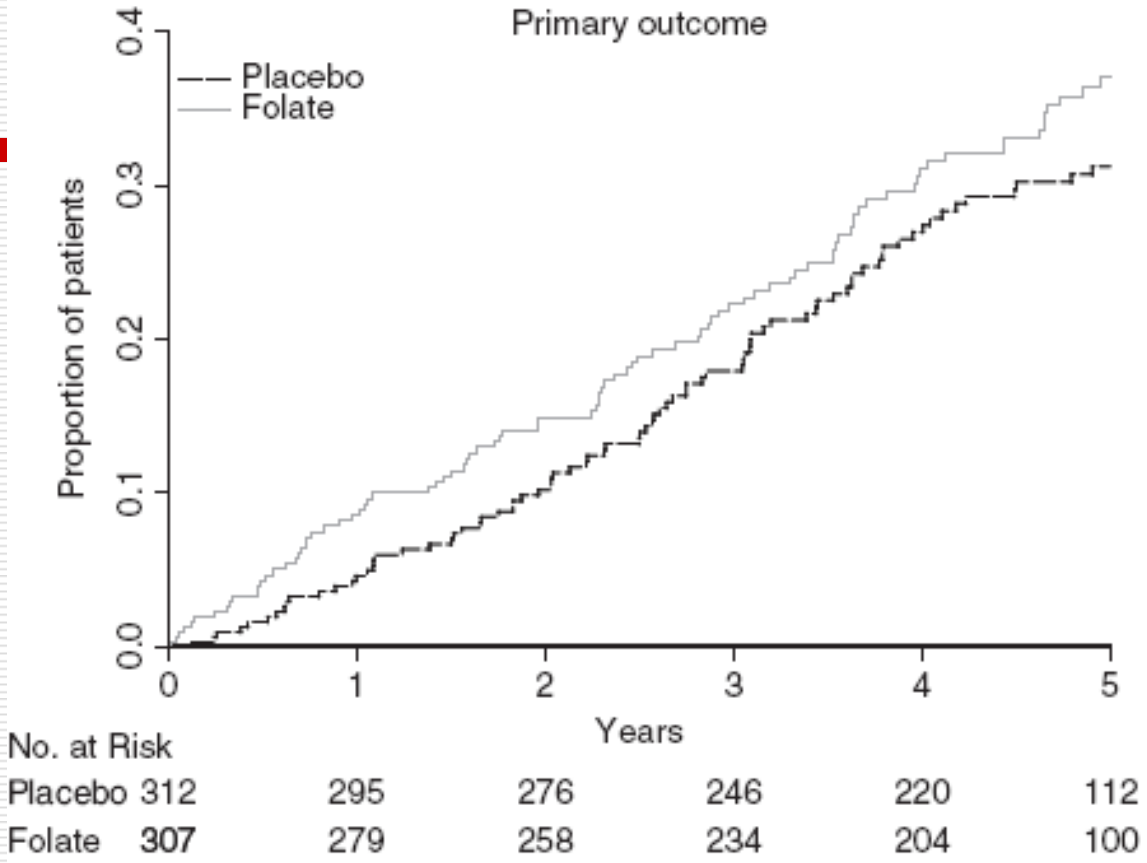


Fig. 1. Composite primary endpoint: Kaplan–Meier estimates of the proportion of participants with renal insufficiency with the composite primary outcome in the active vitamin treatment group and the placebo group. The relative risk of the composite primary outcome in the active vitamin treatment group as compared with the placebo group was 1.19 (95% confidence interval, 0.88–1.61).

Primary and Secondary Outcomes

Table 4. Outcomes in participants with renal insufficiency

Outcome	Active group ($N=307$)	Placebo group ($N=312$)	Relative risk (95% CI)*	P value*
	Number of participants (%)			
Primary outcome and its components				
Composite of death from cardiovascular causes, myocardial infarction or stroke	90 (29.3)	80 (25.6)	1.19 (0.88–1.61)	0.250
Death from cardiovascular causes[a]	56 (18.2)	47 (15.1)	1.24 (0.84–1.83)	0.272
Myocardial infarction[a]	55 (17.9)	52 (16.7)	1.10 (0.76–1.61)	0.607
Stroke[a]	20 (6.5)	21 (6.7)	1.00 (0.54–1.85)	0.997
Secondary outcomes				
Total ischaemic events	126 (41.0)	128 (41.0)	1.04 (0.82–1.33)	0.738
Death from cardiovascular causes, myocardial infarction, stroke, hospitalization for unstable angina or revascularization				
Death from any cause	86 (28.0)	75 (24.0)	1.20 (0.88–1.63)	0.256
Hospitalization for unstable angina	38 (12.4)	24 (7.7)	1.70 (1.02–2.83)	0.043
Hospitalization for heart failure	44 (14.3)	24 (7.7)	1.98 (1.21–3.26)	0.007
Revascularization	44 (14.3)	57 (18.3)	0.79 (0.54–1.18)	0.249
Incident cancer	44 (14.3)	43 (13.8)	1.07 (0.70–1.63)	0.757
Death due to cancer	13 (4.2)	16 (5.1)	0.85 (0.41–1.77)	0.664
Other outcomes				
Transient ischaemic attack	12 (3.9)	20 (6.4)	0.62 (0.31–1.28)	0.198
Venous thromboembolism	3 (1.0)	1 (0.3)	3.17 (0.33–30.4)	0.318
Pulmonary embolism and deep vein thrombosis				
Fractures	27 (8.8)	35 (11.2)	0.79 (0.48–1.31)	0.365

CI, denotes confidence interval.
[a]All participants with this outcome are included.
*P-values were calculated with the use of the log-rank test.

Hospitalization for HF

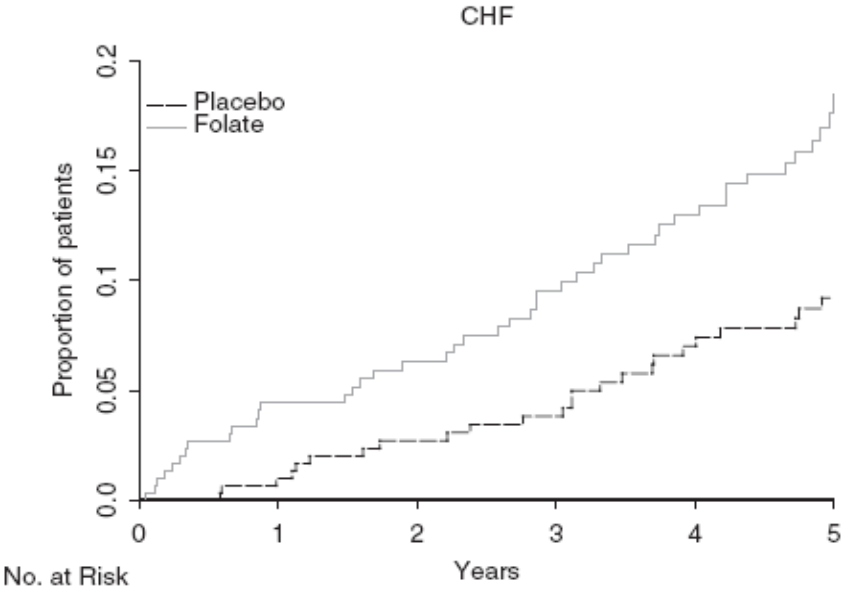


Fig. 2. Hospitalization for heart failure. Kaplan–Meier estimates of the proportion of participants with renal insufficiency with heart failure in the active vitamin treatment group and the placebo group. The relative risk of hospitalization for heart failure in the active vitamin treatment group as compared with the placebo group was 1.98 (95% confidence interval, 1.21–3.26).

Primary and Secondary Outcomes

Table 5. Number of outcomes and event rates (in brackets) in participants with and without renal insufficiency

Outcome	Renal insufficiency $N=619$	No renal insufficiency $N=2691$	RR (95% CI)	P
Primary	170 (6.30)	419 (3.29)	1.96 (1.64–2.34)	<0.0001
Myocardial infarction	107 (3.96)	288 (2.26)	1.78 (1.42–2.22)	<0.0001
Fatal myocardial infarction	50 (1.85)	93 (0.73)	2.53 (1.79–3.57)	<0.0001
CV death	103 (3.81)	177 (1.39)	2.76 (2.17–3.52)	<0.0001
Stroke	41 (1.52)	99 (0.78)	1.98 (1.37–2.84)	0.00025
Death	161 (5.96)	319 (2.50)	2.41 (1.99–2.91)	<0.0001
Hospitalization for unstable angina	62 (2.30)	252 (1.98)	1.15 (0.87–1.52)	0.332
Hospitalization for heart failure	68 (2.52)	137 (1.08)	2.40 (1.80–3.21)	<0.0001
Revascularization	101 (3.74)	496 (3.89)	0.96 (0.77–1.18)	0.676
Transitory ischaemic attack	32 (1.18)	112 (0.88)	1.37 (0.92–2.03)	0.117
Venous thromboembolism	4 (0.15)	41 (0.32)	0.48 (0.17–1.33)	0.159
Fracture	62 (2.30)	222 (1.74)	1.34 (1.01–1.77)	0.043

Number of participants with event (events/100 patient-years) are given.
CI, confidence interval; RR, relative risk; CV, cardiovascular.

Conclusion

- "Active treatment with B vitamins lowered homocysteine levels in participants with CKD but did not reduce CV risk."

DIVINe

Design	Multicentre, randomized, placebo-controlled trial
Population	238 adult patients (≥18 years) type 1 or 2 diabetics with diabetic nephropathy (UAR 300 mg/day or ≥500 mg protein/day); Excluded: Stage 4 or 5 CKD patients (Clcr<30 mL/min), those awaiting dialysis, or women who were pregnant or unwilling to practice effective contraception
Intervention	B vitamins that contained folic acid 2.5 mg/pyridoxine 25 mg/vitamin B-12 1 mg daily
Comparator	Placebo
Outcomes	Primary: progression of nephropathy assessed by change in GFR (99-Tc radionucleotide) and MDRD (4 variable) Secondary/tertiary: occurrence of vascular events (MI, stroke, revascularization, such as peripherial, cardiac angioplasty or cardiac bypass) and all-cause mortality, cognitive decline (MMSE), and amputation (for peripherial artery disease)

J Am Med Assoc 2010; 303:1603-1609

Results

Table 2. Least Squares Mean Change From Baseline at Prespecified Follow-up Visits by Treatment Group From Mixed Linear Models[a]

	Overall Baseline Mean (SE) Score (n = 238)	LS Mean (SE) Change				*P* Value			Difference in LS Mean Change at 36 mo	
		12 mo (n = 111) (n = 107)	18 mo (n = 104) (n = 101)	24 mo (n = 88) (n = 83)	36 mo (n = 61) (n = 57)	Between Treatment Groups	Among Visits	Treatment × Visit Interaction	Between Groups (95% CI)	*P* Value
Radionuclide GFR										
Placebo	54.7 (1.9)		–8.1 (1.4)		–10.7 (1.7)	.045	<.001	.09	–5.8 (–10.6 to –1.1)	.02
B vitamins			–10.2 (1.4)		–16.5 (1.7)					
MDRD GFR										
Placebo	54.0 (1.8)	–5.4 (1.0)	–8.5 (1.0)	–8.7 (1.1)	–9.1 (1.2)	.26	<.001	.02	–4.4 (–7.8 to –1.0)	.01
B vitamins		–5.5 (1.0)	–8.7 (1.0)	–9.9 (1.1)	–13.5 (1.2)					
Plasma total homocysteine										
Placebo	15.5 (0.3)	1.1 (0.4)		2.1 (0.4)	2.6 (0.4)	<.001	<.001	.16	–4.8 (–6.1 to –3.7)	<.001
B vitamins		–2.7 (0.4)		–2.1 (0.4)	–2.2 (0.4)					
Proteinuria										
Placebo	1.47 (0.11)	0.25 (0.13)	0.33 (0.13)	0.21 (0.14)	0.17 (0.16)	.46	.88	.66	0.05 (–0.39 to 0.50)	.82
B vitamins		0.08 (0.13)	0.11 (0.13)	0.08 (0.14)	0.22 (0.16)					
MMSE score[b]										
Placebo	28.7 (0.12)	–0.08 (0.11)		–0.49 (0.12)	–0.12 (0.14)	.82	.38	<.001	–0.28 (–0.67 to 0.11)	.15
B vitamins		–0.20 (0.11)		0.01 (0.12)	–0.40 (0.14)					

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; LS, least squares; MDRD, Modification of Diet in Renal Disease; MMSE, Mini-Mental State Examination.

[a] Units for radionuclide GFR and MDRD GFR are mL/min/1.73 m^2; for plasma total homocysteine, μmol/L; and for proteinuria, g/24 hours. Stacked numbers of participants for LS mean (SE) change at 12 through 36 months indicate numbers of participants receiving placebo or B vitamins, respectively, for each outcome.

[b] Percentage of patients with score of less than 25 (dementia) at 36 months (3.3% for placebo and 0% for B vitamins).

Secondary and Tertiary Outcomes

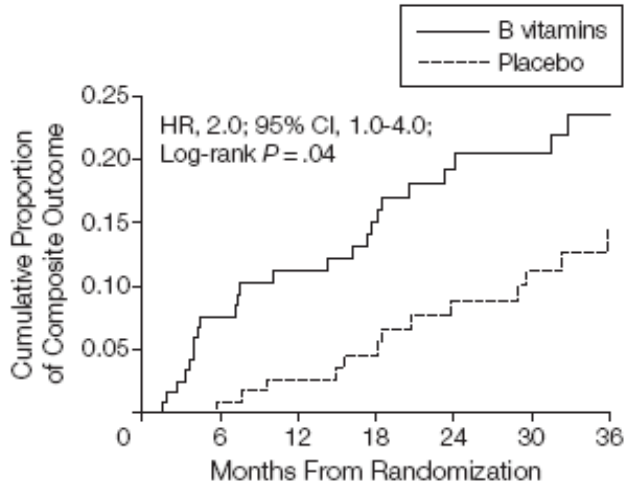
Table 3. Kaplan-Meier 36-Month Risk of Outcomes and Hazard Ratios From Cox Proportional Hazards Regression Model[a]

Outcomes	Outcomes, No. (%)		Hazard Ratio (95% CI)	*P* Value
	Placebo Group (n = 119)	B-Vitamin Group (n = 119)		
Secondary outcomes				
Dialysis	10 (11.7)	10 (12.3)	1.1 (0.4-2.6)	.88
MI	4 (4.6)	8 (7.8)	2.1 (0.6-6.9)	.23
Stroke	1 (1.3)	6 (7.2)	6.6 (0.8-54.4)	.08
Revascularization	5 (6.1)	7 (6.3)	1.5 (0.5-4.6)	.51
All-cause mortality	6 (6.6)	7 (6.7)	1.2 (0.4-3.6)	.72
MI, stroke, revascularization, all-cause mortality	13 (14.4)	24 (23.5)	2.0 (1.0-4.0)	.04
Tertiary outcomes				
MI, stroke, all-cause mortality	10 (10.8)	20 (20.1)	2.2 (1.0-4.6)	.046
Amputation	1 (1.6)	2 (2.1)	2.1 (0.2-23.2)	.54

Abbreviations: CI, confidence interval; MI, myocardial infarction.
[a] Revascularization indicates peripheral and cardiac angioplasty and cardiac bypass procedures. Amputation indicates amputation for peripheral vascular disease.

Primary and Secondary Outcome

Figure 2. Cumulative Proportion of Myocardial Infarction, Stroke, Revascularization, and All-Cause Mortality



No. at risk

B vitamins	119	107	96	87	70	59	45
Placebo	119	117	105	93	81	72	53

HR indicates hazard ratio; CI, confidence interval. The 36-month risk of the composite outcome was 23.5% in the B-vitamin group and 14.4% in the placebo group (log-rank $P = .04$).

Conclusions

"Participants with Stage 1 to 3 CKD, the use of high dose B vitamins (containing 2.5 mg folic acid, 25 mg vitamin B-6, vitamin B12 1 mg) compared to placebo resulted in greater decrease in GFR and an increase in MI and stroke.

Given the recent large-scale clinical trials showing no benefit, and our trial demonstrating harm, it would be prudent to discourage the use of high-dose vitamin B as a homocysteine-lowering strategy outside the framework of properly conducted clinical research."

Food for thought….

- B-vitamin supplementation indicated to:
  - Prevent deficiency in non-dialysis and dialysis CKD patients (e.g. Replavite 1 PO daily)
  - Treat B-vitamin deficiency
- High-potency B-vitamin supplementation is NOT indicated to reduce hyperhomocysteinemia and possible associated CVD risk AND may cause harm