New Medicine Assessment

Renal Vitamins (Renavit®)

for use in patients undergoing dialysis

Recommendation: Renavit® is recommended as routine supplementation in patients undergoing haemodialysis. **Amber 0**

Summary of supporting evidence:

- Water soluble vitamins were studied in a two to four year prospective observational study of 16,345 adult haemodialysis patients.[1] Patients administered water-soluble vitamins had a significantly lower mortality risk (RR 0.84; 95%CI 0.76-0.94, p=0.001) than those who did not receive vitamins. Based on this study the European Best Practice Guidelines (EBPG) and Renal Association Clinical Practice Guidelines for Nutrition in CKD recommend dialysis patients are prescribed water soluble vitamin supplements
- Folic acid, pyridoxine hydrochloride (vitamin B_6) and cyanocobalamin (vitamin B_{12}) once daily was compared to placebo in a 3.2-year double-blind randomised controlled trial in 2,056 patients with high homocysteine levels and advanced chronic kidney disease.[2] Vitamin treatment had no effect on all-cause mortality, myocardial infarction, stroke, amputation or a composite of these 3 plus all-cause mortality.
- A series of smaller open label and blinded studies of 12 – 43 months duration also failed to consistently show a mortality or cardiovascular risk benefit of folic acid when given with or without other B vitamins.[3-8]
- Three meta-analyses which have considered the evidence in support renal vitamins in patients with renal disease have published conflicting results. The first included 10,863 patients with end stage kidney disease or chronic kidney disease.[9] This found that homocysteine lowering with folic acid (with or without other B vitamins) had no overall effect on cardiovascular events, cardiovascular mortality or all-cause mortality. The impact on cardiovascular events did not differ significantly according to kidney disease classification.
- The second meta-analysis included 4,836 patients with end stage kidney disease or chronic kidney disease. The meta-analysis found that folic acid (with or without other B vitamins) had no overall effect on the total number of cardiovascular events, the total number of strokes or the total all-cause mortality.
- The third meta-analysis included 3,886 patients with end stage renal disease or advanced kidney disease. The meta-analysis found that folic acid therapy (with or without other B vitamins) significantly reduced the risk of the occurrence of all fatal and nonfatal cardiovascular events while the risk of nonfatal MI / nonfatal stroke / death from cardiovascular causes was not significant.
- The conclusions of the first two meta-analyses are felt to be more reliable as they included higher patient numbers (10,863 and 4,836 v 3,886), additionally the third meta-analysis summated the separate reports for various cardiovascular outcomes to derive a figure for a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular cause resulting in the potential for some participants to contribute to the

outcome more than once.

- There are no trials considering the mortality or cardiovascular risk impact of the Renavit® preparation. The constituents within Renavit® correlate closely with the amounts of water-soluble vitamins recommended within guidance; however these recommendations reflect expert opinion due to a lack of evidence from clinical trials.
- Homocysteine lowering had no effect on adverse event rates. However, the rates of reported adverse events varied noticeably between studies, ranging from 1.8% (adverse events leading to withdrawal from study treatment) to 89.1% (adverse events including "many transient minor complaints, such as dizziness, nausea or headache")
- Based on population estimates it is anticipated that the annual costs of treating all newly initiated patients would range from £4,791 to £7,300 annually. The application estimated 500 patients initially and then 120 annually. This equates to £22,815 annually for an initial cohort of 500 patients then an additional £5,475.60 annually.

Details of Review

Name of medicine (generic & brand name)**:** Renavit® (contains range of water soluble vitamins)
Strength(s) and form(s): 1 tablet contains – vitamin B_1 3 mg, vitamin B_2 1.7 mg, vitamin B_6 10 mg, vitamin B_{12} 0.006 mg, vitamin C 120 mg, Biotin 0.3 mg, Folic acid 1 mg, Nicotinamide 20 mg, Pantothenic acid 10 mg.
Dose and administration: 1 tablet daily, swallowed not chewed. Unless otherwise indicated by prescriber
BNF therapeutic class / mode of action: Appendix 2: Borderline substances A2.4 Feed supplements[10]
Licensed indication(s): ACBS dietary management of water-soluble vitamin deficiency in adults with renal failure on dialysis.[10]
Proposed use (if different from, or in addition to, licensed indication above): To be initiated by renal consultant/SpR. All current haemodialysis patients to be reviewed and initiated on treatment as appropriate. Subsequently, all patients commenced on regular haemodialysis to be initiated on treatment.
Course and cost: £12.50 for 100 tablets at 1 daily this equates to an annual cost of £45.63[11]
Current standard of care/comparator therapies: There are no licensed products for this indication. Patients may receive a combination or Vitamin B Co Strong, ascorbic acid and folic acid or Ketovite® has been used, however its license is for the prevention of vitamin deficiency in conditions such as galactosaemia, disaccharide intolerance, phenylketonuria and other disorders of carbohydrate or amino acid metabolism, as well as in patients who are on restricted, specialised or synthetic diets.
Relevant NICE guidance: There is currently no relevant NICE guidance.

Background and context

Good nutrition is hugely important to general health and wellbeing; whilst the focus is usually on the number of calories consumed or protein intake etc. the micronutrients, which include vitamins and minerals, also have an important role to play. Vitamins are classified as either water or fat soluble i.e. those that the body can store excess amounts of and those where excess quantities are eliminated in urine. The body uses vitamins and minerals, in conjunction with other compounds, for a large number of functions. The water soluble B vitamins have a wide variety of uses, including to aid the release of energy from food eaten, to maintain a healthy nervous system, for skin and eye health, and to produce and maintain healthy red blood cells amongst others.[12] Another water soluble vitamin, vitamin C, is necessary for the maintenance of healthy connective tissue, to help wound healing and to protect cells and keep them healthy.[13]

Patients with renal failure on haemodialysis generally have poorer nutrition than the general population with insufficient dietary protein and energy intake in approximately 23% of patients and reductions in body fat and muscle stores in up to 40% of patients.[14] They are also at risk of lower serum levels of water soluble vitamins, caused by abnormal renal metabolism, dietary restriction, poor gastrointestinal absorption and dialysate losses, with greater losses with high-flux and high efficiency dialysis.[15]

The European Best Practice Guidelines (EBPG)[15] and Renal Association Clinical Practice Guidelines for Nutrition in CKD[16] recommend dialysis patients are prescribed water soluble vitamin supplements; however the EBPG guidance notes that due to insufficient evidence from clinical trials for recommending administration of vitamins, the recommendation only reflects expert opinion and cannot be considered as a clinical guideline.

A standard over the counter multivitamin cannot be used as these also contain fat soluble vitamins which are not eliminated renally; dangerously high levels could be reached if these were administered. However, there is not a specific medication containing only water soluble vitamins which is licensed for use in dialysis patients. Renavit® has been produced for this condition; though it is a food supplement rather than a medication, it is prescribable on the NHS under the ACBS list.[10] Alternative water soluble vitamin products include Ketovite® which is a licensed medication for the prevention of vitamin deficiency in conditions such as galactosaemia, disaccharide intolerance, phenylketonuria and other disorders of carbohydrate or amino acid metabolism, as well as in patients who are on restricted, specialised or synthetic diets.[17]

A request was received to use Renavit® in all haemodialysis patients; this review considers the evidence for that use. Renavit® is a food for medical purpose rather than a medicine, for this reason trial evidence is limited. To adequately consider the request, the evidence in support of water soluble vitamins in dialysis has been reviewed, including a comparison of the available products (Renavit® and Ketovite®) to the daily amounts recommended in guidance.

Summary of evidence

Summary of efficacy data in proposed use:

Evidence in support of renal vitamins in patients on dialysis is limited to one large and a number of small Randomised Controlled Trials (RCTs) and one large observation study. Based on data from the observational study[1] the EBPG guidelines[15] and Renal Association Clinical Practice Guidelines for Nutrition in CKD[16] recommend patients with CKD are prescribed water soluble vitamin supplements. The RCTs are summarised in three meta-analyses which have published conflicting results.

The 'International Variation in Vitamin Prescription and Association with Mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS)'[1] was a prospective observational study using the patient cohort from the DOPPS I study. 16,345 adult haemodialysis patients were followed; they were randomly selected from 308 representative dialysis facilities in seven countries including the United States, Japan and five European countries. Data was gathered at 4-month intervals from 1997 in the US facilities, 1998 in European ones and 1999 in the Japanese facilities until spring 2001.

The mean age of the patients was 59.9 years, men made up 56.5% of the study population. The information relating to vitamin use was taken from patient charts by a study coordinator in each facility, lists of all medications both prescription and over-the-counter (OTC) were collected. If an item was stated as 'multivitamin' it was assumed to contain water-soluble vitamins; the use of fat-soluble vitamins was not included in the analysis. There was wide variation in rates of water soluble vitamin use, from 3.7% of the cohort in the UK to 71.9% in the US. The highest rate in Europe was in Spain at 37.9%, whilst the rate of use in Japan was 5.6%. The purpose of the study was to evaluate whether the use of water soluble vitamins in haemodialysis patients had an impact on the rate of hospitalisation or mortality.

Patients administered, compared with those not administered, water-soluble vitamins had a significantly lower mortality risk (RR 0.84; 95% CI 0.76-0.94, p=0.001) adjusted for age, sex, race and comorbid conditions among others. When only the 83.3% of patients who did not switch water-soluble vitamin status throughout the study were included, the results were similar (RR 0.88; p=0.003). The risk of hospitalisation for patients taking water-soluble vitamins was lower, but unlike for mortality, the result was not significant (RR 0.94; 95% CI 0.85-1.04, p=0.24). The study also looked at mortality by facility; when grouping facilities use by 10% increments they found facility-level mortality was lower for units where patients had greater water-soluble vitamin use (RR, 0.98 95% CI 0.95-1.00 p=0.05 e.g. for 40% versus 30% use).

The authors suggested that the lower mortality risk may be due to water-soluble vitamin use decreasing serum homocysteine levels and thus decreasing cardiac mortality, a leading cause of mortality in haemodialysis patients.[1] They also speculated that the use of water-soluble vitamins could be accompanied by greater protein intake, as suggested by the greater nPCR (normalised protein catabolic rate, an indicator of nutrition) seen among water-soluble vitamin users in this study; they went on to state that better nutrition has been shown to correlate with improved survival. The study concluded that whilst it had provided evidence of an association between haemodialysis patients' use of water-soluble vitamins and reduced mortality, only a randomised trial could prove that the use of such vitamins improves outcomes. It went on to suggest that as

initiation of the prescribing of these vitamins is easy and low risk, practitioners may wish to consider their use whilst awaiting definitive data from interventional studies.[1]

Three meta-analyses have been published in 2011[18] and 2012[9, 21]. The first considered folic acid therapy and cardiovascular disease in ESRD or advanced kidney disease[18] while the second and third considered the effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease.[9]

In total, 7 studies that investigated the mortality benefit of renal vitamins in patients with end stage kidney disease requiring dialysis were identified and were included within the three meta-analyses and are summarised below.

The first trial was a 3.2 year double-blind RCT of 2,056 veterans with homocysteine levels (≥ 15 µmol/L) and advanced chronic kidney disease (estimated creatinine clearance ≤30 mL/min) (n=1,305) or end stage renal disease (n=751). [2]

Participants received either 40 mg folic acid, 100 mg of pyridoxine hydrochloride (vitamin B_6) and 2 mg of cyanocobalamin (vitamin B_{12}) once daily or placebo. The primary outcome was time to death from any cause; vitamin treatment had no effect on all-cause mortality (hazard ratio 1.04; 95% CI 0.91-1.18 p=0.60) with 448 (43.4%) deaths in the treatment group and 436 (42.6%) in the placebo group over the 3.2 years of the study. The lack of effect of vitamin treatment on all-cause mortality was also present in the subgroup of patients with end stage renal disease.

No significant effects were demonstrated for the secondary outcomes of myocardial infarction, stroke, amputation, a composite of these 3 plus all-cause mortality, time to initiation of dialysis, and time to thrombosis of arteriovenous access in haemodialysis patients.

The second double blind RCT randomised 650 end-stage renal disease patients undergoing haemodialysis to active treatment (folic acid 5 mg, cobalamin 50 µg, vitamin B_6 20 mg) or to placebo (folic acid 0.2 mg, cobalamin 4 µg, vitamin B_6 1 mg) three times a week for two years, patients in both groups also received 6 other water-soluble vitamins. The primary outcome was mortality of any cause; 31% of patients in the active treatment group and 28% of patients in the placebo group died during the study period, therefore treatment had no effect on total mortality HR 1.13; 95% CI 0.85 to 1.50, P=0.51. [3]

The third double-blind RCT of 510 patients on dialysis (468 on haemodialysis, 42 patients on peritoneal dialysis) investigated the treatment effect of 1, 5 or 15 mg of folic acid given concomitantly with renal multivitamins with a median follow up of 24 months. The findings failed to support any effect of doses above 1 mg/day on cardiovascular disease or other outcomes.[4]

The additional evidence in support of renal vitamins in patients on haemodialysis, relates to 4 papers of 315[5], 186[6], 114[7], and 81[8] patients respectively (Table 1). Zongas et al.[5] found that a median of 3.6 years of folic acid 15 mg per day produced a non-significant decrease in first MI, stroke or death from cardiovascular causes (6.7 per 100 patient years in the folic acid group versus 8.2 events per 100 patient years in the placebo group, HR 0.93 (0.58-1.48 p=0.75). Despite homocysteine levels reducing by 19% in the folic acid group, high dose folic acid did not slow atheroma progression or improve cardiovascular morbidity or mortality in patients with CRF.

Areuza et al.[6] found that 2 years of folic acid 10 mg three times per week had no effect on cardiovascular events (HR 1.24, 95% CI:0.74-2.10). Righetti et al (2006)[7] investigated the mortality benefit of folic acid 5 mg daily (or alternate days depending on folate levels) for a median of 871 days. Composite cardiovascular end-points events occurred in 51% of patients overall, in 26 of 63 (41%) treated patients and in 32 of 51 (63%) of untreated patients (p=0.05). Righetti et al (2003)[8] assessed the efficacy of folic acid 5 mg or 15 mg daily versus placebo for 1 year. New cardiovascular events were observed in 36% of untreated patients and 25% of treated patients (p=0.08).

In its assessment of the effect of homocysteine lowering on cardiovascular events the first meta-analysis published in 2012[9] included ten studies reporting 3,045 cardiovascular events among 10,863 participants. This included five of the seven papers above and an additional 5 papers which were undertaken in patients with chronic kidney disease. Righetti et al[7] was excluded as it did not report a composite cardiovascular indicator, while Righetti[8] et al was excluded as it did not include more than 100 patient years of data. The meta-analysis found that homocysteine lowering had no overall effect on cardiovascular events (RR 0.97, 95%CI 0.92 to 1.03, P=0.326), cardiovascular mortality (RR 0.97, 95% CI 0.82 to 1.16) or all-cause mortality (RR 1.02, 95% CI 0.95 to 1.10). The impact on cardiovascular events did not differ significantly according to kidney disease classification.

The second meta-analysis published in 2012[21] considered the effect of homocysteine lowering on cardiovascular outcomes in chronic kidney disease patients. The meta-analysis included ten studies reporting 1,023 cardiovascular events among 4,836 participants. This included all of the seven papers above and three papers which were undertaken in patients with chronic kidney disease. The meta-analysis found that folic acid (with or without other B vitamins) had no overall effect on the total number of cardiovascular events (RR 0.94, 95% CI 0.84 to 1.05, P=0.30), the total number of strokes (RR 0.83, 95% CI 0.57 to 1.19, P=0.31) or the total all-cause mortality (RR 1.00, 95% CI 0.92 to 1.09, P=0.98)

The meta-analysis published in 2011; folic acid therapy and cardiovascular disease in ESRD or advanced kidney disease,[18] included 3886 patients from the 7 RCTs summarised above. The meta-analysis found that folic acid therapy (with or without other B vitamins) significantly reduced the risk of the occurrence of all fatal and nonfatal cardiovascular events by 15% (RR 0.85; 95%CI 0.76 to 0.96, P=0.009), in an additional analysis the risk of nonfatal MI / nonfatal stroke / death from cardiovascular causes was reduced by a non-significant 13 to 14% (RR 0.87; 95%CI 0.75 to 1.00, P=0.06).

There were significant methodological differences between the two meta-analyses published in 2012 versus the 2011 meta-analysis; the 2011 meta-analysis summated the separate reports for various cardiovascular outcomes to derive a figure for a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular cause resulting in the potential for some participants to contribute to the outcome more than once. Conversely the 2012 meta-analyses used the trial definition where the studies composite was not reported. Due to the potential of participants being able to contribute to the outcome more than once in the 2011 analysis it is felt that the conclusions of the two meta-analyses published in 2012 are more reliable.

Renavit® composition:

The composition of Renavit® tablets in comparison to alternative water-soluble vitamin product Ketovite® and the daily amount recommended in the guidelines is in the table below:

Component	Renavit® 1 tablet daily[19]	Ketovite®* 3 tablets daily[17]	Recommended daily amount[15]
Thiamine (Vitamin B1)	**3 mg**	**3 mg**	**1.1-1.2 mg**
Riboflavin (Vitamin B2)	**1.7 mg**	**3 mg**	**1.1-1.3 mg**
Nicotinamide (Vitamin B3)	**20 mg**	**9.9 mg**	**14-16 mg**
Calcium pantothenate (Vitamin B5)	**10 mg**	**3.48 mg**	**5 mg**
Pyridoxine (Vitamin B6)	**10 mg**	**0.99 mg**	**10 mg**
Cobalamin (Vitamin B12)	**0.006 mg**	**0**	**0.0024 mg**
Vitamin C (Ascorbic Acid)	**120 mg**	**49.8 mg**	**75-90 mg**
Biotin	**0.3 mg**	**0.51 mg**	**0.003 mg**
Folic acid	**1 mg**	**0.75 mg**	**1 mg**

* three tablets of Ketovite also contains fat soluble vitamins, 1.5mg vitamin K and 15mg vitamin E

Neither Renavit® nor Ketovite® has a composition that exactly matches the daily amount recommended in the European guidelines[15]

Summary of safety data:

The DOPPS study did not consider the safety of the vitamin supplements used; additionally it did not provide information on the quantities of individual water soluble vitamins taken.

The 2012 meta-analysis reported on the tolerability of homocysteine lowering therapies as reported in seven trials and stated that: Homocysteine lowering had no effect on adverse event rates (relative risk 1.00, 95% confidence interval 0.92 to 1.08, P=0.93). The rates of reported adverse events varied noticeably between studies, ranging from 1.8% (adverse events leading to withdrawal from study treatment) to 89.1% (adverse events including “many transient minor complaints, such as dizziness, nausea or headache”)[9]

Conducting searches for vitamin supplements and safety yielded no recent results relevant to either Renavit® or Ketovite®.

The SPC for Ketovite®, which contains water-soluble vitamins, had no stated undesirable effects.[17]

Strengths and limitations of the evidence:

Strengths: DOPPS:

- A very large cohort of patients from multiple centres around the world.
- An appropriate cohort of patients, all receiving haemodialysis.
- Data gathered at regular intervals over 2 to 4 years dependent on country.
- An appropriate patient orientated outcome of mortality
- Included all the water soluble vitamins

Weaknesses: DOPPS:

- A prospective observational study rather than a randomised controlled trial
- Information about vitamin use was taken from patient charts by a study co-ordinator. Patients and co-ordinators filling out survey forms may have reported prescription medications well but not over the counter purchases of nutritional supplements
- No information on which water soluble vitamins were taken or the quantities, just that a patient did or did not take vitamin supplements. If only stated as multivitamin these were assumed rather than confirmed, to contain water soluble vitamins.
- Not specifically covering the use of the product reviewed, Renavit®

Strengths: meta-analyses of smaller trials

- Several smaller studies drawn together, providing an overview of use in a larger cohort of patients.
- Comprehensive search and selection process to determine only appropriate trials included
- Trials included specifically covered use of the water soluble B vitamins included in Renavit®, though not always in the same proportions.

Weaknesses: meta-analyses of smaller trials

- The conclusions drawn by the three meta-analyses were contradictory; the 2011 meta-analysis having used summated individual results to provide composite endpoints with the danger of outcomes being counted more than once.
- The 2012 meta-analyses included studies in a wider patient cohort than just end-stage kidney disease or haemodialysis patients where Renavit® would be used.

Summary of evidence on cost effectiveness:

There is no published evidence on the cost effectiveness of Renavit® as a vitamin supplement for dialysis patients in the UK.

Prescribing and risk management issues:

Renavit® is a food supplement rather than a medicine but is prescribable under ACBS.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Renavit®	1 tablet daily	100 for £12.50	£45.63
Ketovite®	1 tablet three times daily	100 for £9.21	£100.85
Costs based on MIMS list prices April 2015. [11]			

This table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

No available discounts known

Productivity, service delivery, implementation:

Not anticipated to have any impact on productivity/service delivery.

Anticipated patient numbers and net budget impact:

According to the UK Renal Registry report for 2014, in the UK 109 per million population new patients starting renal replacement therapy.[20] This reflects initiation for 7006 new patients a year nationally. By 90 days 66.1% of patients are on haemodialysis, 19% on peritoneal dialysis, 9.5% have a functioning transplant and 5.3% have died or stopped treatment.

Assuming a Lancashire population of approximately 1.47 million,[20] it would be anticipated that around 160 patients annually would be initiated on renal replacement therapy. Using the proportions above, it would be expected that around 105 would be on haemodialysis, 30 on peritoneal dialysis, 15 would have a functioning transplant and 9 would have died or stopped treatment. If just the 105 patients on haemodialysis were initiated on Renavit®, that would equate to an annual cost of £4,791. Also including those patients on peritoneal dialysis would increase that figure to £6,160. If all 160 anticipated patients were to receive Renavit®, this would equate to an additional £7,300 annually.

The application estimated 500 patients initially and then 120 annually. This equates to £22,815 initially then £5,475 annually.

Innovation, need, equity:

Renavit® is not an innovative medicine; however there are no licensed water soluble vitamin preparations for use in renal dialysis patients. Renavit® is a food supplement but prescribable under ACBS.

References

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Table 1: Summary of key water soluble vitamin studies relevant to use in supplementation of renal dialysis patients

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
1	Prospective observational study	16,345 adult Haemodialysis patients from the DOPPS I study. Mean and median ages were 59.9 years and 62 years. 56.5% were men.	US facilities from 1997, European from 1998 and Japanese from 1999, data gathered at 4-month intervals until spring 2001. Information about vitamin use abstracted from patient charts by a study coordinator in each facility, lists of all mediations OTC and prescription collected. If stated as multivitamin assumed to contain water-soluble vitamins. In the US 72.2% of patients received folate, and 100% of patients received vitamins B_6, B_{12} and ascorbic acid. Use of fat-soluble vitamins was not included in the analysis. Use of water soluble vitamins ranged from 3.7% in UK to 71.9% in US	Mortality. Patients administered water soluble vitamins compared with those who were not had a significantly lower mortality risk (RR 0.84, p=0.001) Hospitalisation Not significant, but risk for hospitalisation was lower among patients receiving water-soluble vitamins than those who weren't (RR 0.94 p=0.24)		Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?:No Intention to treat analysis?: No Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 2 evidence based on Patient orientated outcome, but not a high quality RCT. Risk of bias: High based on no blinding, reliant upon patients accurately completing a survey and a study co-ordinator at each facility collecting the correct information from patients' charts.
2	Double-blind randomised controlled trial	Veterans age over 21 years. Advanced CKD (estimated creatinine clearance ≤30	Daily capsule containing 40 mg folic acid, 100 mg pyridoxine hydrochloride (vitamin B_6) and 2 mg of cyanocobalamin (vitamin	Primary outcome all-cause mortality. No significant effect on	Secondary outcomes included myocardial infarction, stroke, amputation of all or part of a lower extremity, a composite	Patient-oriented outcome measure?: Yes Allocation concealment?:

		mL/min) n=1305 or end-stage renal disease n=751 and high homocysteine levels (≥15 µmol/L) Median duration of follow up was 3.2 years.	B_{12}) or a placebo.	all-cause mortality (448 vitamin group deaths vs 436 placebo group deaths) (hazard ratio HR 1.04; 95%CI 0.91-1.18 Mean baseline homocysteine level was 24.0 µmol/L in the vitamin group and 24.2µmol/L in the placebo group. It was lowered by 6.3µmol/L (25.8%, p<0.01) in the vitamin group and 0.4µmol/L (1.7% p=0.14) in the placebo group at 3 months,	of these 3 plus all-cause mortality, time to initiation of dialysis, and time to thrombosis of arteriovenous access in haemodialysis patients. No significant effects demonstrated for secondary outcomes or adverse events. 129 MIs in vitamin group vs 150 for placebo (HR 0.86 95% CI 0.67-1.08), 37 strokes in the vitamin group vs 41 for placebo (HR 0.90 95%CI 0.58-1.40) and 60 amputations in the vitamin group vs 53 for placebo (HR 1.14 95% CI 0.79-1.64) The composite for MI, stroke, amputations plus mortality (p=0.85) time to dialysis (p=0.97) and time to thrombosis in haemodialysis patients (p=0.97) did not differ between the vitamin and placebo groups.	Yes Blinded if possible?: Yes Intention to treat analysis?: Yes Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 1 evidence based on Patient-orientated evidence from high quality individual RCT Risk of bias: low based on an independent review committee, blinded to treatment assignment, adjudicated all secondary outcome events. An independent data and safety monitoring board monitored the study for safety and scientific integrity.
3	Randomised, double-blind, multicentre, controlled trial	n=650 adults aged 20-80 years from 33 dialysis centres in Germany with end-stage renal disease treated for at least 1 month by hemodialysis. Exclusion criteria included acute	Patients randomised to two treatment groups. Either 2.5 mg folic acid, 25 µg cobalamin and 10 mg vitamin B_6 (treatment group) or 0.1 mg folic acid, 2µg cobalamin and 0.5 mg vitamin B_6 (placebo group) The placebo contained vitamins to prevent vitamin deficiencies in patients assigned to the placebo group and to avoid an influence	Primary outcome was total mortality. 194 of the 650 patients died during the study, 102 (31%) in the active treatment group and 92 (28%) in the placebo group. The treatment therefore had no effect on total mortality (HR	Secondary outcome was the first fatal or non-fatal cardiovascular event (myocardial infarction, unstable angina pectoris, coronary vascularisation procedures, sudden cardiac death. Secondary outcome occurred in 181 of the 650 patients. 83	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?:Yes Intention to treat analysis?: Yes

		coronary events within the six weeks prior to randomisation, active malignant tumor, pregnancy, lactation, and addiction to drugs or alcohol. Patients who had been taking vitamins before recruitment were included after a washout phase of at least 8 weeks. Median duration of follow up was 2.1 years. Baseline characteristics were well matched between the two groups.	on homocysteine levels	1.13; 95%CI 0.85-1.50; p=0.51)	(25%) in the active treatment group and 98 (30%) in the placebo group. Treatment had no significant effect on fatal and nonfatal cardiovascular events (HR 0.80; 95% CI 0.60 to 1.07; p=0.13)	Adequate power/size?: No Adequate follow-up (>80%)?: No Level 2 evidence based on RCT without adequate power/size – originally intended 350 in each arm and with less than 80% follow up. Risk of bias: low based on blinding of randomization procedure and treatment assignments to all involved in the trial, and the long follow up period (up to 6 years)
4	Randomised, double blind, three-arm study	Adult patients undergoing haemodialysis or peritoneal dialysis Haemodialysis n=468, peritoneal dialysis n=42. Exclusions included patients undergoing intradialytic parenteral nutrition, anticipating a living-related kidney transplant, receiving an anti-seizure medication, residing in an institution, or were	Patients randomly assigned to either group 1) Standard therapy with renal multivitamin containing 1 mg folic acid n=177 2) Renal multivitamin containing 5 mg folic acid n=177 3) Renal multivitamin containing 15 mg folic acid. N=174 All capsules contained 12.5 mg of pyridoxine, 6 µg cobalamin, 60 mg ascorbic acid, 1.5 mg thiamine, 20 mg niacinamide, 10 mg pantothenic acid, 0.3 mg	Primary outcome were cardiovascular events and mortality. These included coronary artery intervention, myocardial infarction, stroke, transient ischemic attack, carotid endarterectomy, limb amputation, or death. No difference in the composite end point at 24 months (43.7% in arm 1, 38.6% in arm 2, 47.1% in arm 3; log-rank p=0.47)	Secondary outcome was vascular access thrombosis (among those with arteriovenous fistulae) Analysing time to first vascular access clot for the haemodialysis patients, the Kaplan-Meier curve revealed no difference in event rates at 24 months between the treatment arms. (36.9% arm 1, 31.1% arm 2, 28.1% arm 3; log-rank p=0.82)	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?: Yes Intention to treat analysis?: No – patients randomised but who never took medication weren't included (n=528 became n=510) Adequate power/size?: Yes

		terminally ill.	biotin.			Adequate follow-up (>80%)?: No – one of the treatment groups had lost 22% of patients to follow-up. Level 2 evidence based on clinical trial at moderate to high risk of bias Risk of bias: High based on not using intention to treat analysis, inadequate follow up in one of the groups.
5	Multicentre, double blind, randomised control trial	n=315. Men and women over 18 years with chronic renal failure for any cause, serum creatinine of -.40 mmol/l or greater (creatinine clearance <25 ml/min). Either awaiting dialysis or already treated with continuous ambulatory peritoneal dialysis, intermittent peritoneal dialysis, or haemodialysis were eligible for the study. If already being treated with folic acid or multivitamins containing folic acid patients were required to withdraw treatment. If a patient had folate deficiency requiring	Randomly assigned to either 15 mg folic acid daily (n=156) or to an identical placebo (n=159)	Primary carotid artery intima-media thickness (IMT) endpoint was change in rate of progression of mean maximum carotid artery IMT. No significant difference in the rate of progression of mean maximum IMT between the groups (0.01 mm/year, 95% CI: -0.01 to 0.03; p=0.43) The primary clinical end point was a composite of myocardial infarction, stroke, and death from cardiovascular cause. For first MI, stroke or death from cardiovascular cause there were 33 (6.7 per	Secondary end points included all fatal and nonfatal cardiovascular events, including myocardial infarction, stroke, unstable angina, revascularisation and peripheral vascular disease. 77 (14.9 per 100 patient years) events in the folic acid group and 86 (16.3 per 100 patient years) in the placebo group (HR 0.95, 95% CI: 0.69-1.30 p=0.75)	Patient-oriented outcome measure?: Yes Allocation concealment?: unclear Blinded if possible?: Yes Intention to treat analysis?: yes Adequate power/size?: yes Adequate follow-up (>80%)?: Yes Level 1 evidence based on high quality RCT with patient orientated outcome Risk of bias: low based on blinding of all involved

		supplementation, they were excluded from the study. Groups were closely matched except for a greater proportion of women in the placebo group (37.7% vs 26.9%) and a greater use of antiplatelet agents, again in the placebo group (31.4% vs 21.8%)		100 patient years) events in folic acid group, 40 (8.2 per 100 patient years) in placebo group. (HR 0.93, 95%CI 0.58-1.48, p=0.75). For all MI, stroke or death from cardiovascular cause there were 46 (8.9 per 100 patient years) events in folic acid group and 55 (10.4 per 100 patient years) in placebo (HR 0.98 95%CI 0.66-1.47 p=0.94)		and good follow up period
6 Abstract only	Randomised double-blind, placebo-controlled trial	Patients with end-stage kidney disease due to any cause, over 18, stable on haemodialysis n=186	Patients received either oral folic acid 10 mg or an identical placebo, three times a week (immediately after dialysis session). Study continued for 2 years.	Homocysteine levels were recorded at admission, 6, 12 and 24 months. From a median 25.0 µmol/L (range9.3-104.0µmol/L) at baseline the placebo group levels remained elevated throughout, but oral folate significantly decreased homocysteine to a median value of 10.5 (2.8-20.3)µmol/L, p<0.01.	Cardiovascular events. 38 patients (Folic acid group 17 vs placebo group 21; p=0.47) died from cardiovascular disease during the study. When looking at cardiovascular events, fatal and non-fatal, the folic acid treatment and lowering of homocysteine blood levels had no effect on cardiovascular events (p=0.41. HR 1.24, 95%CI 0.74-2.10) Carotid artery intima-media wall thickness measured in blinded fashion decreased from 1.94±0.59 mm to 1.67±0.38 mm(p<0.01)	Patient-oriented outcome measure?: No, primary was homocysteine level. However further outcome of cardiovascular events is patient orientated. Allocation concealment?: Unclear from abstract Blinded if possible?: unclear from abstract Intention to treat analysis?: unclear from abstract Adequate power/size?: unclear from abstract Adequate follow-up (>80%)?: unclear from abstract

						Level 3 evidence based on disease orientated outcome Risk of bias: unclear based on limited information available from abstract.
7	Single centre, open, prospective trial	Patients on maintenance haemodialysis for at least 4 months, without treatment with theophylline, oestrogens, or anti-epileptic drugs. n=114.	26 patients taking folic acid at recruitment were not randomised and continued on folic acid therapy (group A) The remaining 88 patients who were not taking folic acid at recruitment were randomised to treatment with folic acid 5mg daily or every other day dependent on folate levels and vitamin B complex where vitamin B_{12} were below the normal limit (group B, n=37) or to remain untreated (group C, n=51) Median follow up was 871 days (2.4 years)	Cardiovascular endpoint a composite variable consisting of: angina with abnormal myocardial scintigraphy or coronarography, fatal and non-fatal MI, symptomatic extracranial carotid artery stenosis resulting in carotid endarterectomy, fatal and non-fatal stroke, sudden death by cardiac arrest. Composite cardiovascular endpoints occurred in 58 of 114 patients (51%) in 26 of 63 treated patients (41%) and in 32 of 51 untreated patients (63%) (x^2 = 6.0; p=0.05) Fatal events rate was similar in every group	Homocysteine levels Analysis of variance for repeated measures showed significant lower homocysteine levels in treated patients, both group A (20.9 ± 1.0 µmol/l) and group B (22.6 ± 1.0 µmol/l) as compared with untreated ones (33.2 ± 1.5 µmol/l)	Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?: No Intention to treat analysis?: Yes Adequate power/size?: No Adequate follow-up (>80%)?: unclear Level 2 evidence based on study at high risk of bias Risk of bias: High based on lack of concealment or blinding, small sample size
8	Randomised controlled trial	Caucasian haemodialysis patients. Inclusion criteria: regular	Randomly assigned to three groups. a) Untreated patients (n=30)	Homocysteine levels: Significant homocysteine lowering effect over time in treated patients as	Cardiovascular morbidity. Non-parametric survival methods show a trend towards a significant	Patient-oriented outcome measure?: No Allocation concealment?:

		maintenance on regular haemodialysis treatment for at least 2 months and absence of folic acid treatment for at least 3 months. Exclusion criteria: patients treated with carbamazepine or valproic acid as they increase homocysteine levels. Oestrogen treated patients because these hormones lower homocysteine. 124 patients screened n=81 who were eligible for the study. 45 male v 36 female. Mean age 64±3 years.	b) 5 mg folic acid per day (n=26) c) 15 mg folic acid per day (n=25) All followed for 12 months.	compared to untreated ones (F=17.1 p<0.01) but there were no significant differences between the two treated groups (F=1.9 p=not significant) Only 12% of treated patients reached normal homocysteine levels.	difference in survival rate for cardiovascular morbidity between treated and untreated haemodialysis patients. However it was not significant. (Mantel-Cox: chi-squared=3.1 p=0.08). Cardiovascular events observed in 36% of untreated patients, and 25% of treated patients showed new vascular accidents.	unclear Blinded if possible?: Yes Intention to treat analysis?: Yes Adequate power/size?: unclear Adequate follow-up (>80%)?: Yes Level 3 evidence based on disease orientated outcome Risk of bias: High based on small number of patients, and unclear information on allocation concealment. Also, reporting cardiovascular morbidity as trending towards significance rather than as non-significant.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)

	• systematic reviews or meta-analyses of RCTs with consistent findings	
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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