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Abbreviated Class Review: Multivitamins and Antioxidants

Month/Year of Review: March 2014 **End date of literature search:** February 2014
Current PDL Class: None

Research Questions:

- Is there evidence to support and cover the use of specific products with good value, including multivitamins, iron products, and mono-vitamin supplements?
- Are certain reformulations of vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?

Conclusions:

- Based on a high quality systematic review of patients with cardiovascular disease (CVD), there is insufficient evidence for commonly used supplements (vitamin E, coenzyme Q10, magnesium) used by patients with CVD in terms of efficacy and harms on long term clinical outcomes (mortality, thrombotic events, and serious adverse events). Low-strength evidence suggests benefits of vitamin K (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes.[1]
- Based on a high quality systematic review in the general population, there is moderate quality evidence of no benefit on all-cause mortality (RR 0.95; 95% CI 0.81-1.11) or CVD with a multivitamin in nutrient-sufficient adults and evidence that beta-carotene, vitamins A, C, D, and E; selenium, folic acid, and calcium have no benefit on CVD, cancer or all-cause mortality. There is insufficient evidence to evaluate the B vitamins (1, 2, 6 and 12) on CVD, cancer, or all-cause mortality outcomes. [2] Another systematic review demonstrated no difference in mortality with antioxidants in adults (RR 1.02; 95% CI 0.98-1.05) and a significantly higher mortality with beta-carotene (RR 1.05; 95% CI 1.01-1.09) and vitamin E (RR 1.03; 95% CI 1.00-1.05).[3]
- There is insufficient and conflicting evidence that multivitamin supplementation in men may lower cancer incidence (RR 0.93; 95% CI 0.87-0.99; NNT 98 over 11.2-12.5 years) but no effect in women. This suggests a small reduction in overall cancer incidence in men with a multivitamin after 11.2 to 12.5 years of follow-up (HR 0.92; 95% CI 0.86-0.998; NNT 82-131). [2]
- In another fixed effects meta-analysis, vitamin or antioxidant supplements were not associated with a reduced risk of major CV events (RR 1.00; 95% CI 0.98-1.02) for primary or secondary prevention.[4]

- There is high quality evidence of no beneficial effect on CVD, cancer, or all-cause mortality with vitamin E supplementation in the general population.
- There is high quality evidence that supplementation with beta-carotene increases the risk of lung cancer in those at high risk.
- Oral iron therapy remains first line treatment for iron deficiency anemia. These include the ferrous salts, such as ferrous fumarate, ferrous sulfate, and ferrous gluconate. Due to no evidence of a difference in efficacy, evaluate comparative costs in executive session for preferred products.
- There is moderate quality evidence, based on 2 systematic reviews, that homocysteine-lowering B vitamins do not reduce the risk for overall mortality or myocardial infarction.[5,6] Evidence is more conflicting for its effects on risk of stroke.
- The evidence is insufficient and conflicting to support the use of vitamin E for treatment of Alzheimer's disease (AD). A recent fair quality RCT demonstrated that participants with mild to moderate AD receiving vitamin E had significantly slower decline than those receiving placebo as measured by the ADCS-ADL Inventory (LS mean change from baseline was 3.15 units less than the decline in the placebo group; p=0.03). This translates into a delay in progression in the vitamin E group of 6.2 months (95% CI 5.4-7.4) compared with the placebo group.[7]

Recommendations:

- Based on evidence of no benefit on mortality, CVD, or cancer outcomes with multivitamins or antioxidant multivitamin supplements, prior authorize agents and approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency (Appendix 1).
- For mono vitamin supplements with evidence to support their use or insufficient evidence to make strong conclusions, evaluate comparative costs in executive session due to no evidence of superiority of individual products over another to list specific agents as preferred and non-preferred. This includes calcium, vitamin D, folic acid, vitamin B, and the ferrous salt formulations.
- After comparative cost consideration in executive session, the Committee recommended making products without an AAC and no utilization non-preferred. The Committee also recommended making Nascobal, Ferrous Sulfate Oral Susp and Drops, Pyridoxine Lozenge and Lozenge HD, Vitamin D3 Wafers, and Vitamin D2 & D3 Drops non-preferred on the PMPDP and to not grandfather current patients. The Committee recommended making all other products preferred on the PMPDP.
- Bring back a review of other minerals and electrolytes for further decision-making.

Background:

Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.[1] This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements [8] Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.[9] While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies, particularly vitamin A and iron deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.[10]

There has been contradictory evidence for potential role of vitamin D and omega-3 fatty acids in the prevention of cancer and cardiovascular disease (CVD) and large gaps remain in the current evidence. The large Women's Health Initiative trial randomized 36,282 postmenopausal women to a daily combination of calcium and low-dose vitamin D3 or to placebo for a mean of 7 years. Results showed that the vitamin combination did not reduce the risk for cancer, CHD, or stroke, and its effect on 25(OH)D levels was small.[11,12] However, there are no RCT's evaluating vitamin D doses large enough to produce substantial changes in 25(OH)D levels. The ongoing VITamin D and OmegA-3 Trial (VITAL) is a large 5 year RCT designed to assess the role of vitamin D and omega-2 fatty acids in the primary prevention of cancer and CVD.[12]

Iron deficiency is the most common nutritional disorder worldwide and oral iron therapy can be used first line as supplemental iron, including in pregnant women and children.[13] Adherence to oral iron therapy can be a barrier to treatment because of gastrointestinal adverse effects. Many preparations are available, varying widely in dosage, formulation (quick or prolonged release), and chemical state (ferrous or ferric form). The World Health Organization recommends the use of ferrous salts, which are considered the most effective and cost-effective treatment and preferred to ferric supplements, which show poorer absorption.[14] Delayed release formulations have been developed to attempt to alleviate some of the gastrointestinal intolerances. The incidence of gastrointestinal side effects has been shown to be lower with controlled-release iron formulations, however; none have showed a difference in the discontinuation rates between them.

Methods:

A Medline literature search ending June 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for the following dietary and vitamin groups was conducted: vitamins A, B, C, D and E, multivitamin preparations, antioxidant vitamins, vitamin B12, folic acid, and iron replacement therapy. Omega-3 fatty acids were excluded, as these were evaluated in a separate P&T review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Efficacy Summary:

Systematic Reviews:

1. A systematic review by Marik, et. Al evaluated the benefits and risks of dietary supplements in Westernized societies.[10] They included RCTs in nonpregnant adults that evaluated clinical endpoints and were at least a year long. Sixty three studies were included that evaluated B-carotene, vitamins A, B6, B12, C, D, and E; folic acid, calcium, selenium, omega-3 fatty acids, glucosamine, saw palmetto, and milk thistle. Results of no benefit were shown in 45 studies, with 10 of these showing a trend toward harm and 2 showing a trend toward benefit. Beneficial results were reported in 12 studies; 6 studied vitamin D in

elderly patients and 3 studied omega-3 fatty acids in patients with cardiovascular disease. The authors concluded that with the potential exceptions of vitamin D supplementation in the elderly and omega-3 fatty acid use in those with cardiovascular disease, there is no data to support the widespread use of dietary supplements in Westernized populations. In addition, certain commonly used supplements (B-carotene, vitamin A, and vitamin E) may be harmful. [10]

2. A comparative effectiveness review by AHRQ evaluated the evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings.[1] A total of 69 studies contributed to the meta-analysis; no systematic reviews were identified. Most of the evidence was graded as insufficient and most had low statistical power due to short-term efficacy design. Strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events, limiting the generalizability of the results. The authors concluded that the many limitations of the evidence made it difficult to make meaningful conclusions for most supplement-drug combinations. Low-strength evidence suggests benefits of omega-3 fatty acids (incremental improvement of triglyceridemia), vitamin K, (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes. Evidence on harms was inconclusive. No evidence on clinical effectiveness outcomes was found for Echinacea, garlic, ginseng, niacin, red yeast, vitamin A, or vitamin D supplementation coadministered with a CV drug. No evidence on intermediate outcomes was identified for effects of vitamin A or vitamin D supplementation in combination with CV drugs. No study analyzed statistical interactions between a supplement and a CV drug in terms of clinical outcomes. Additional specific conclusions based on supplement type are as followed:

   Coenzyme Q10: There is insufficient evidence to determine the effectiveness of the combination of a CV drug (ACE inhibitors) and coenzyme Q10 compared to placebo on all-cause mortality and quality of life. When evaluating intermediate cardiovascular outcomes, there was insufficient to low quality of evidence, based on 4 RCTs with unclear CHD risk, mixed CHD risk, and high CHD risk. Overall, no significant differences were demonstrated between coenzyme Q10 in combination with a cardiovascular drug versus drug alone in levels of the following: C-reactive protein, high-density lipoprotein (HDL) cholesterol, non-HDL-C, total cholesterol, triglycerides, ejection fraction, or systolic blood pressure. Low grade evidence from one trial concluded no significant differences in HDL-C with coenzyme Q10 in combination with fenofibrates versus fenofibrates alone.

   Vitamin E: There was insufficient evidence evaluating Vitamin E in combination with cardiovascular drugs on clinical outcomes such as CV mortality. There were 10 RCTs that measured intermediate outcomes and examined its use with antiplatelet agents or statins. Also, evidence from a well-powered pragmatic trial in women showed no benefit of adding vitamin E to daily aspirin on the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death. There was insufficient evidence based on one small trial of no difference in total cholesterol and triglyceride levels between vitamin E in combination with an antiplatelet agent versus antiplatelet alone. There was low quality evidence that the combination of vitamin E and nifedipine significantly lowered total cholesterol (MD -35.96 mg/dl, 95% CI -46.96 to -24.96), LDL, and triglycerides, but not HDL or systolic blood pressure in 30 elderly patients at high risk of CHD. There was no significant difference in lipid profile in trials with vitamin E and gemfibrozil or vitamin E-statin combinations (insufficient evidence). There was also no significant difference in blood pressure, C reactive protein, prothrombin time, and platelet count for vitamin E-statin combinations versus cardiovascular drugs alone.

   Vitamin K: There was insufficient evidence to evaluate mortality and stroke when vitamin K was coadministered with warfarin. There is low quality evidence that supplementation with vitamin K may improve the stability of warfarin therapy. One trial showed that the percentage of time INR was in therapeutic range was improved in the group receiving vitamin K in combination with warfarin compared to warfarin alone (RR 9.0, 95% CI 1.42 to 16.57). The number of patients achieving stable INR was also higher in the combination group (RR 2.56, 95% CI 1.24 to 5.38).

Magnesium: There was insufficient evidence of no difference in myocardial infarction between oral magnesium + beta-blockers compared to beta-blockers alone. Three RCTs evaluated intermediate outcomes with magnesium in combination with hydrochlorothiazide or beta-blockers in participants with hypertension. In two trials, systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ significantly between the magnesium hydrochlorothiazide combinations versus hydrochlorothiazide-alone groups (insufficient evidence). There was also no significant difference with the combination of magnesium plus beta-blockers versus beta-blockers alone (insufficient evidence).

Multivitamins and Antioxidant Multivitamins:

3. A 2013 AHRQ systematic evidence review for the U.S. Preventive Services Task Force (USPSTF) evaluated the evidence for the use of multivitamins or single nutrients and functionally related nutrient pairs for the primary prevention of CVD and cancer in the general population with a generally adequate diet.[2] A total of 26 studies were ultimately included in the analysis, with 4 good-quality RCTs and one good-quality cohort study that evaluated the effects of a multivitamin supplement. No impact on all-cause mortality was found in any of the multivitamin RCTs reporting this outcome (RR 0.95; 95% CI 0.81-1.11). Two RCTS reported on CVD and cancer outcomes, and showed no impact on most types of fatal and nonfatal CVD events with the use of a multivitamin, with one trial reporting a small benefit for fatal MI. Both trials suggested a small reduction in overall cancer incidence in men after 11.2 to 12.5 years of follow-up (HR 0.92; 95% CI 0.86-0.998). Another trial showed no impact on overall cancer from a 5-component multivitamin. A subgroup analysis showed a protective effect on any cancer among men (RR 0.69; 95% CI 0.53 to 0.91), but not women. From the two trials, one cancer case would be prevented if 98 men used a daily multivitamin for 11.2 years (NNT 83) to 12.5 years (NNT 131). No consistent evidence of harms from multivitamins was observed from the four RCTs.

   No trials reported incidence of CVD, cancer, or all-cause mortality for 4 B vitamins (1, 2, 6, and 12), iron, zinc, magnesium, niacin, calcium/magnesium, folic acid/vitamin B12, or folic acid/vitamin B6).[2] Overall, the evidence for beta-carotene, vitamins A, C, D, and E; selenium; folic acid; calcium; and some combinations found no evidence for a benefit of the supplement on CVD, cancer, or all-cause mortality. Two studies of beta-carotene for those at high risk for lung cancer found that those in the supplement groups were at a significantly higher risk of developing or dying from lung cancer. For most supplements, there were a limited number of studies, with the exception of vitamin E, which included 6 fair- to good-quality trials that all produced no effects on the measured endpoints.

4. Another systematic review assessed the efficacy of vitamin and antioxidant supplements in the prevention of CV diseases through a meta-analysis of RCTs.[4] Trials with at least 6 months of follow-up were included. Trials were assessed for quality using the Jada scale. A total of 50 trials were included in the final analysis (294,478 participants). Thirty were primary prevention trials and 20 were secondary prevention trials. In the fixed effects meta-analysis of all 50 trials, use of vitamin or antioxidant supplements was not associated with reduced risk of major CV events (RR 1.00; 95% CI 0.98-1.02). The effect sizes of the smaller trials tended to be less than 1.0, while the larger ones tended to be null. Subgroup analysis, showed that low dose vitamin B_6 supplementation slightly decreased the risk of major CV events (RR 0.92; 95% CI 0.85-0.99) in the fixed effects meta-analysis. No significant association was found by type of outcome, type of prevention, type of study design, methodological quality, duration of treatment, funding source, and provider of the supplements. Vitamin E supplementation was associated with a decreased risk of myocardial infarction; however these beneficial effects were shown only in trials with supplements provided by the pharmaceutical industry.

5. Another systematic review evaluated only antioxidant vitamins (vitamin E, beta-carotene, and vitamin C) and their effect on CV outcomes.[15] Published and unpublished randomized trials were included from the literature search. The 5-point Jadad score was used to evaluate the quality of the inclusive trials. A total of 29 articles were included in the meta-analysis. Trials with both participants with high CV risk factors or previous CV disease and individuals without CV risk factors. The overall meta-analysis demonstrated no effect on major CV events with antioxidant vitamin supplementation (RR 1.00; 95% CI 0.96-1.03; p=0.79) without evidence of heterogeneity of effect. Supplementation was shown to reduce the risk of myocardial infarction by 2%, but this different was not clinically or statistically significant (RR 0.98; 95% CI 0.92-1.04; p=0.54), with little heterogeneity. There was also no significant effect seen on stroke risk (RR 0.99; 95% CI 0.93-1.05; p=0.65) or total death (RR 1.03; 95% CI 0.98-1.07; p=0.22).

6. Authors recently looked to determine whether multivitamin-multimineral supplementation, used for primary or secondary prevention, increased the risk of mortality[16] Only RCTs were included and the primary outcome was all-cause mortality. Trials were assessed for internal validity using the Cochrane guidelines. After review, 21 studies met inclusion criteria and were included in the review (n=91,074). Four studies had either an unclear or high risk of bias. Across all pooled studies, no significant effect of supplementation on all-cause mortality was observed (RR 0.98; 95% CI 0.94-1.02) and there was little evidence of heterogeneity (I^2=15.72%; p=0.25). Removal of the 4 studies with a high risk of bias did not significantly change the risk estimate. A trend towards a reduction in the risk of all-cause mortality was seen in the 13 primary prevention trials, and no significant effect was found in the secondary prevention trials (RR 1.04; 95% CI 0.98-1.11). Multivitamin supplementation had no effect on mortality due to vascular causes or cancer.

7. To assess the beneficial and harmful effects of antioxidant supplements for prevention of mortality in adults, a Cochrane systematic review and meta-analysis was done.[3] The systematic review included 78 RCTs that evaluated antioxidants in adult participants from the general population (primary prevention), or were patients with stable, chronic diseases (Secondary prevention). Fifty six trials (82%) were considered to have a low risk of bias. A random effects meta-analysis showed neither a higher or lower mortality with antioxidant supplements (RR 1.02; 95% CI 0.98-1.05), but a fixed-effects meta-analysis showed a statistically significant higher mortality (RR 1.03; 95% CI 1.01-1.05). Heterogeneity between studies was low, with an I^2 of 12%. In the 56 trials with a low risk of bias, both the fixed-effect model and random-effects model meta-analyses showed that the antioxidants were associated with higher mortality (12.9% vs. 10.6%; RR 1.04; 95% CI 1.01 – 1.07). Beta-carotene (RR 1.05; 95% CI 1.01-1.09) and vitamin E (RR 1.00-1.05) were associated with significantly higher mortality, whereas vitamin A, vitamin C, and selenium were not associated with higher or lower mortality.

8. Another review also evaluated, multivitamin-multimineral use and CV disease and cancer incidence[17] Only prospective studies were included, however; this review did include observational trials in addition to interventional trials and only looked at supplementation in primary prevention among health adults. Studies included in the Macpherson systematic review[16] were often excluded because they were conducted among nutritionally deficient populations. A total of 15 studies were included in the review. Twelve were prospective observational studies and only 3 were RCTs. A meta-analysis was not conducted by the authors. The author found that supplementation with multivitamin-multiminerals does not appear to increase all-cause mortality, cancer incidence or mortality, or CVD incidence or mortality. However, this is based mostly on observational data which is not as strong as data from RCTs.

9. The Department of Veterans Affairs Health Services Research and Development conducted a systematic review evaluating nutritional supplements for age related macular degeneration (AMD).[18] A thorough literature search was conducted, internal validity of each study was assessed using the Cochrane Risk of Bias tool, and the overall quality of the body of evidence was evaluated using the GRADE method. A total of 38 articles met inclusion criteria for review. A total of 7 RCTs evaluated nutritional supplements in AMD patients. A significant effect in preventing functional loss was found only in the two largest trials (good evidence). The largest study included 3640 subjects and followed them for 7 years. In this study, a beneficial effect was observed with a combination of antioxidants (vitamin C, vitamin E, and beta carotene) plus zinc (OR 0.63; 99%CI 0.44-0.92), but only in subjects with Categories 3 and 4 AMD. No significant change was reported in mild AMD subjects. The evidence also showed that certain nutritional supplements have significant potential harms,

including increased mortality and congestive heart failure in high risk patients with vitamin E, increased risk of prostate cancer with vitamin E, and increased risk of lung cancer among smokers with beta-carotene.

Vitamin D and Calcium:

According to DynaMed, calcium supplements are generally recommended for hypocalcemia, hypoparathroidism, and for the treatment and prevention of osteoporosis.[19] There is level 2 evidence of reduced fracture risk with calcium supplementation and calcium plus vitamin D in older adults and level 3 evidence that calcium supplementation in postmenopausal women appears to improve bone density but effects on fracture remain uncertain.

10. A meta-analysis was done evaluating vitamin D supplementation and its effects on overall mortality.[20] A literature search was conducted through January 2013, to identify RCTs, and trials were assessed for quality using the Cochrane Collaboration's tool. A total of 42 RCTs that met inclusion criteria were included in the final analysis (n=85,466). Calcium supplementation was also used in 26 trials and the majority of participants were women. In the 29 trials with follow-up less than 3 years, vitamin D did not significantly decrease all-cause mortality in the vitamin D group compared to placebo (13.3% vs. 12.2%; RR 1.03; 95% CI 0.97-1.12; p=0.28; I^2=12%). In the 13 trials with follow-up of 3 years or longer, data demonstrated a decrease in all-cause mortality in the vitamin D group compared to placebo (10.9% vs. 11.5%; RR 0.94; 95% CI 0.90-0.98; p=0.001; I^2=0%). Results were similar when excluding the trials that had a high risk of bias. There is insufficient evidence to draw conclusions of the effect of vitamin D on specific mortality. The authors concluded that long term supplementation of vitamin D may have a beneficial effect on overall mortality (with a modest effect size), especially in patients with vitamin D insufficiency and younger than 80 years. Vitamin D in a dose of 800 IU daily or less was round to be more favorable than a dose greater than 800 IU and treatment with cholecalciferol was more favorable than ergocalciferol. Future studies are needed to evaluate the efficacy on specific mortality, such as cancer and CV disease.

11. A systematic review evaluated the evidence of RCTs to assess the efficacy of oral vitamin D supplementation in depression compared to placebo.[21] The review as done in accordance to the Cochrane Handbook. After a literature search and review, 6 studies met the inclusion criteria and were included in the final meta-analysis. Results showed no significant effect of vitamin D supplementation on depression, with the standardized mean difference (SMD) of -0.14 (95% CI -0.41 to 0.13; p=0.32) and substantial heterogeneity (I2=77%; p<0.001). Two trials used a dichotomous outcome for response and these trials showed no overall effect of vitamin D supplementation on depression (OR 0.93; 95% CI 0.54 to 1.59; p=0.79). None of the subgroup analysis showed any significant effect of vitamin D supplementation on depression. A sensitivity analysis also showed no significant effect when excluding studies with a high risk of bias or short duration of intervention. No significant difference in adverse events was found between placebo and vitamin D groups.

12. A systematic review and meta-analysis evaluated whether vitamin D supplementation affects bone mineral density (BMD) due to recent data showing no effect of vitamin D supplementation on fracture prevention.[22] Authors used the PRISMA guidelines to conduct the meta-analysis and only included RCTs. Studies of individuals with other disorders likely to affect bone and calcium metabolism (chronic kidney disease, pregnancy, glucocorticoid use) were not eligible. The primary endpoint was the percentage change in bone mineral density from baseline. There was a significant difference in the weighted mean difference (WMD) in femoral neck BMD (0.8; 95% CI 0.2-1.4; p=0.005), but with evidence of heterogeneity. There was no statistically significant effect on lumbar spine BMD (WMD 0.0; 95% CI -0.2 to 0.3; p=0.8), hip BMD (WMD 0.2; 95% CI -0.1 to 0.4; p=0.17), and total body BMD (WMD -0.3; 95% CI -0.7 to 0.1;

p=0.2) with vitamin D supplementation. Meta-regression analysis showed no significant interactions between age, vitamin D concentration, sex, study duration, vitamin D dose, baseline BMD, or number of participants and BMD. The authors concluded that continuing widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seems to be inappropriate.

13. A 2013 draft systematic review was released by AHRQ on Vitamin D and Calcium and clinical outcomes.[23] Based on the evidence, it was difficult to make any strong conclusions on the association of vitamin D supplementation, calcium intake, or the combination of both nutrients with the various health outcomes because most of the findings were inconsistent. Due to the large degree of clinical and methodological heterogeneity across studies, it was not possible to perform an updated meta-analysis.

Iron therapy:

14. A systematic review was conducted to analyze the tolerability of several oral iron supplements.[14] Clinical or observational studies were including from a literature search through 2009. This review has many inherent limitations and therefore results need to be interpreted with caution. Individual trials were not assessed for quality and there were no restrictions on the type of clinical studies included. In total, 111 studies were included in the analysis. This analysis showed that extended-release ferrous sulfate had the lowest incidence of adverse events, and all other formulations were compared to it. Ferrous fumarate and ferrous sulfate were shown to have the highest rate of gastrointestinal adverse events. The heterogeneity of the studies was not evaluated or mentioned and it appears that the studies differed in terms of doses used, severity of iron deficiency, and study design.

Vitamin B:

15. A recent meta-analysis looked at the effect of Vitamin B supplementation and the risk of cerebrovascular disease.[5] Only RCTs through August 2012 were included that compared B vitamins with placebo, very low-dose B vitamins, or usual care with a minimum follow-up time of 6 months. Fourteen articles (n=54,913) were included in the meta-analysis and were assessed for quality by two investigators. Results demonstrated a trend toward benefit of B vitamin intake to lower homocysteine levels and reduce stroke events (RR 0.93; 95% CI 0.86-1.00; p=0.05), but no benefit on specific subtypes such as transient ischemic attacks or myocardial infarction (RR 1.00; 95% CI 0.94-1.07; p=0.98) outcomes. Analyses specific to vitamin B_{12} did not show a significant benefit for reduction of stroke events. There was also no change in rates of morbidity and mortality of tumors in B vitamin groups (RR 1.05; 95% CI 0.98-1.11; p=0.17)

16. A recent meta-analysis evaluated the effect of vitamin B supplementation on stroke.[24] From a comprehensive literature search, 18 RCTs met inclusion criteria. The studies compared B-vitamin supplementation to a placebo for reduction of incident stroke in patients with chronic kidney disease (7 trials), CV or stroke (8 trials) or healthy individuals (1 trial). Pooling the trials demonstrated that there was no evidence that B-vitamin supplementation protected against stroke risk (RR 0.91, 95% CI 0.82-1.01; p=0.075). No statistically significant heterogeneity was observed between trials for incident stroke (I^2=22.8%). After excluding the trial that included patients with a glomerular filtration rate less than 50, vitamin-B supplementation was associated with a nonsignificant reduction in the risk of stroke (RR 0.91; 95% CI 0.83-1.00; p=0.06). Subgroup analysis suggested that B-vitamin supplementation might reduce the risk of stroke if included trials had a man/woman ratio of more than 2 or subjects received doses of folic acid less than 1 mg.

17. A Cochrane systematic review was conducted to assess the clinical effectiveness of homocysteine-lowering interventions in people with or without pre-existing cardiovascular disease.[6] This review showed that homocysteine-lowering B vitamins (folic acid, B6, and/or B12) in patients at risk of CV disease do not reduce the risk for myocardial infarction or overall mortality and may not reduce the risk for stroke. Twelve RCTs were found of homocysteine-lowering vitamins in adults with risk of or established CV disease. Compared to placebo or standard care, there was no difference seen in myocardial infarction (RR 1.02; 95% CI 0.95-1.01), all-cause mortality (RR 1.01; 95% CI 0.96-1.07), or stroke (RR 0.91; 95% CI 0.82-1.01).

Vitamin E:

18. A systematic review from Cochrane Collaboration assessed the efficacy of Vitamin E for Alzheimer's dementia (AD) and mild cognitive impairment (MCI).[25] All RCTs comparing vitamin E to placebo for patients with either AD or MCI were included. Only three trials met the inclusion criteria. Two were trials of vitamin E for the treatment of AD and one was a trial of vitamin E to delay progression from amnestic MCI to dementia. All three had a low risk of bias. The two trials evaluating AD patients were not able to be pooled based on different outcome measures. One trial found no significant difference in survival time to one of the four end points between the vitamin E and placebo groups (RR 0.70; p=0.08) in patients with AD. The study in MCI patients found no significant difference in the probability of progression from MCI to AD over the 3 years between the vitamin E group and placebo group (HR 1.02; 95% CI 0.74-1.41; p=0.91). The authors concluded that there was no strong evidence that vitamin E when compared to placebo was efficacious in improving outcomes of AD or MCI.

Clinical Guidelines

The Endocrine Society

Clinical Practice guidelines were updated in 2011 focusing those who are at risk for vitamin D deficiency.[26] These guidelines were guided by systematic reviews of the evidence and consensus decisions. The task force used the GRADE approach to make evidence based recommendations. Strong recommendations include the phrase "we recommend" and weak recommendations use the phrase "we suggest". Main recommendations are as follows:

- Recommend screening is only recommended in individuals at risk for vitamin D deficiency (high quality evidence). There is no evidence demonstrating benefits of screening for vitamin D deficiency at a population level.
- Measurement of 25(OH)D is reasonable in the following at risk groups:
    - Rickets, osteomalacia, osteoporosis, chronic kidney disease, hepatic failure, malabsorption syndromes, hyperparathyroidism, certain medications, African-American and Hispanic children and adults, pregnant and lactating women, older adults with a history of falls, older adults with a history of nontraumatic fractures, obese children and adults, granuloma-forming disorders, lymphomas

Recommended dietary intakes of vitamin D for patients at risk for vitamin D deficiency

- Infants and children aged 0-1 require at least 400 IU/d of vitamin D and children 1 year and older require at least 600 IU/d to maximize bone health; however, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1000 IU/d of vitamin D (weak recommendation; high quality evidence).
- Adults 19-50 years require at least 600 IU/d of vitamin D to maximize bone health and muscle function; however, to raise the blood level of 25(OHD) above 30 ng/ml may require at least 1500-2000 IU/d of vitamin D (weak recommendation, high quality evidence).
- All adults aged 50-70 and 70+ require at least 600 and 800 IU/d, respectively, of vitamin D to maximize bone health and muscle function. However, to raise the blood level above 30 ng/ml may require at least 1500-2000 IU/d of supplemental vitamin D (weak recommendation; high quality evidence)
- Pregnant and lactating women require at least 600 IU/d of vitamin D and at least 1500-2000 IU/d may be needed to maintain a blood level of 25 (OH)D above 20 ng/ml (weak recommendations, moderate quality evidence).

Treatment and Prevention Strategies

- Either vitamin D2 or vitamin D3 should be used for the treatment and prevention of vitamin D deficiency (weak recommendation; high quality evidence).
- For children 1-18 years who are vitamin D deficient, the suggested treatment is 2000 IU/d of vitamin D for at least 6 weeks or with 50,000 IU of vitamin D2 once a week for at least 6 weeks followed by maintenance therapy of 600-1000 IU/d (weak recommendation; high quality evidence).
- All adults who are deficient should be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 week or its equivalent of 6000 IU/d, followed by maintenance therapy of 1500-2000 IU/d (weak recommendation; high quality evidence).
- Recommend prescribing vitamin D supplementation for fall prevention, but do not recommend prescribing supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (high quality evidence).

National Osteoporosis Foundation:

In 2013, the National Osteoporosis Foundation released a reference on the prevention, diagnosis and treatment of osteoporosis in the US.[27] This guide addressed postmenopausal women and men age 50 and older using evidence mainly from RCTs. It is recommended that adequate daily calcium and vitamin D is ensured to help reduce fracture risk. If adequate dietary calcium cannot be obtained, dietary supplementation is indicated up to the recommended daily intake. They recommend with the IOM recommendations of 1000mg per day of calcium for men age 50-70 and 1200mg per day of calcium for women age 51 and older. Intakes in excess of 1200 to 15000 mg per day have limited potential for benefit and may increase the risk of developing kidney stones, CV disease, and stroke. They also recommend an intake of 800 to 1000 IU of vitamin D per day for adults age 50 and older. Adults who are vitamin D deficient may be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week or the equivalent daily dose for 8-12 weeks to achieve a 25(OH)D blood level of approximately 30 ng/ml.

U.S. Preventive Services Task Force (USPSTF): Multivitamins for primary prevention

In February 2014, the USPSTF released updated recommendations on multivitamins for the primary prevention of CV disease and cancer in healthy adults.[28] The previous recommendations were from 2003 and concluded that the evidence at the time was insufficient to assess the balance of benefits and harms of the use of supplements of vitamins A, C or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer of CVD in asymptomatic adults. The new evidence was based on the AHRQ systematic review described above. [2] The following is a summary of recommendations and evidence:

- The current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of CV disease or cancer (I statement).
- The current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (with the exception of beta-carotene and vitamin E) for the prevention of CV disease or cancer (I statement.)
    - Across all of the supplements studied (Vitamin A, vitamin C, vitamin D with or without Calcium, Vitamin E, Selenium, Folic acid), there was no evidence of beneficial effect on CV disease, cancer, or all-cause mortality. However, there were a limited number of studies for most nutrients and differences made pooling difficult. Therefore, they concluded that they were not able to conclude with certainty that there is no effect.
    - The USPSTF did conclude with moderate certainty that the net benefit of Beta carotene is negative, due to an increased risk for lung cancer and that the net benefit of vitamin E supplementation is zero due to no effect on CV disease, cancer, or all-cause mortality.
- The USPSTF recommends against the use of beta-carotene of vitamin E supplements for the prevention of CV disease or cancer (D recommendation). This is based on adequate evidence that supplementation with beta-carotene or vitamin E in healthy populations without nutritional deficiencies does not reduce the risk of CV disease or cancer.
- There is inadequate evidence on the harms of supplementation with multivitamins and most single vitamins, minerals, or functional pairs.
- There is adequate evidence that supplementation with vitamin E has little or no significant harms and that supplementation with beta-carotene increases the risk of lung cancer in persons who are at increased risk of lung cancer.

U.S. Preventive Services Task Force (USPSTF): Vitamin D and calcium supplementation

In 2013, the USPSTF released guidelines for Vitamin D and calcium supplementation to prevent fractures in adults.[29] The USPSTF commissioned 2 systematic evidence reviews and a meta-analysis on supplementation to assess the effects on bone health outcomes in community-dwelling adults, the association of vitamin D and calcium levels with bone health outcomes, and the adverse effects of supplementation. They concluded that:

- The current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men (I statement).
- The evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D3 and greater than 1000 mg of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women (I statement).
- The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D3 and 1000 mg or less of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women (D recommendation).
- Vitamin D supplementation is effective in preventing falls in community-dwelling adults aged 65 years or older who are at increased risk for falls (B recommendation).

These recommendations are based on an AHRQ systematic review that examined the benefits and harms of vitamin D with or without calcium supplementation on clinical outcomes of cancer and fractures.[30] Sixteen RCTs examined the effects of vitamin D with or without calcium supplements on fracture outcomes. Four of these were poor quality. A random effects meta-analysis with 5 RCTs showed no significant difference in total fracture between vitamin D supplementation and placebo (RR 1.03; 95% CI 0.84-1.26), with high heterogeneity across studies (I2=60%). Eleven RCTs compared the combination of vitamin D and calcium supplementation with placebo in mostly postmenopausal women and demonstrated a reduced risk for total fracture as compared with placebo (RR 0.88; 95% CI 0.78-0.99), with moderate heterogeneity (I2=36%). Subgroup analysis showed that the pooled effect estimated differed according to setting; the risk reduction was smaller in community-dwelling elderly persons or postmenopausal women than institutionalized elderly persons. There was no risk reduction among community-dwelling women with history of fracture (RR 1.02; 95% CI 0.89-1.16). Meta-regression analysis did not show differential effects depending on the daily dose of vitamin D or the baseline 25-(OH)D concentration. The evidence was not robust event to draw conclusions about the benefits or harms of vitamin D supplementation for cancer prevention.

Randomized Controlled Trials

1. A 2014 fair quality double-blind, placebo-controlled, RCT (n=561) compared either 2000 IU/d of alpha tocopherol (Vitamin E), 20 mg/d of memantine, the combination, or placebo in 613 patients with mild to moderate Alzheimer's disease (AD) at 14 Veterans Affairs medical centers.[7] The objective was to determine if they slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor. The primary outcome for the study was the Alzheimer's disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory, designed to assess functional abilities to perform activities of daily living. There is no definitive minimally clinically important difference for the ADCS-ADL, which makes it hard to interpret the clinical significance. Results demonstrated that, over the mean follow-up time of 2.27 years, participants receiving alpha tocopherol had significantly slower decline than those receiving placebo as measured by the ADCS-ADL Inventory (LS mean change from baseline was 3.15 units less than the decline in the placebo group; p=0.03). This translates into a delay in progression in the alpha tocopherol group of 6.2 months (95% CI 5.4-7.4) compared with the placebo group. There was no statistically significant difference in change from baseline between the placebo group and the memantine and alpha tocopherol combination group or between placebo and memantine. The treatment effect was larger in the more severe group of participants. There were no significant differences between treatment groups on total adverse events or serious adverse events. There was no significant difference in mortality between alpha tocopherol (7.3%; HR

0.87; 95% CI 0.67-1.13), memantine (11.3%; HR 1.06; 95% CI 0.91-1.24), alpha tocopherol plus memantine (9.0%; HR 0.94; 95% CI 0.57-1.54) and placebo (9.4%), respectively. Overall attrition rates were high, although similar between groups.

2. A large, fair-quality, randomized, double-blind, placebo-controlled trial evaluated whether long-term MVI supplementation decreases the risk of total and site-specific cancer events among male physicians.[31] Men were randomized and stratified by age, prior cancer, prior CV disease, and original beta carotene treatment assignment. The primary end points were total cancer and major CV events, which were measured using the intention-to-treat principle (n=14,641). Overall, 9.0% had a baseline history of cancer and 5.1% with a baseline history of CV disease. Participants were followed up for a mean of 11.2 years. Adherence at 4 years was 76.8% for the MVI group and 77.1% for placebo (p=0.71); at 8 years, adherence was 72.3% and 70.7%, respectively (p=0.15); and at the end of follow-up, adherence was 67.5% and 67.1%, respectively (p=0.70). Overall, the rates of total cancer were 17.0 and 18.3 per 1000 person-years in the MVI and placebo groups, respectively. Men taking MVIs had a modest reduction in total cancer incidence (HR 0.92; 95% CI 0.86-0.998; p=0.04). There was no effect of a MVI on prostate cancer (HR 0.98; 95% CI 0.88-1.09; p=0.76). Total mortality was not significantly reduced (HR 0.94; 95% CI 0.88-1.02; p=0.13) and neither was cancer mortality. Based on prespecified hypothesis, daily MVI use was associated with a reduction in total cancer among the 1312 men with a baseline history of cancer (HR 0.73; 95% CI 0.56-0.96; p=0.02), but this result did not significantly differ from that observed among 13,329 men initially without cancer.

3. A very recent fair-quality double-blind, placebo-controlled RCT evaluated whether high-dose multivitamins are effective for the secondary prevention of CV events (n=17.8).[32] Patients at least 50 years of age who had a sustained myocardial infarction at least 6 weeks before were randomly assigned to receive oral vitamins and IV chelation infusions, oral placebo and IV chelation infusions, oral vitamins and placebo IV infusions, and oral placebo and placebo IV infusions. The primary end point was a composite of time to death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. Only 18% of the subjects were women and baseline characteristics were similar between groups. Overall treatment adherence was poor; a total of 46% of patients discontinued their regimen during the study (46% in the placebo group and 46% in the vitamin groups). The most common reason for discontinuation was declining to continue taking the vitamins or placebo. Patients received treatment for a median of 31 months. A total of 76% of subjects completed at least 1 year of oral therapy and 48% completed 3 years. Women were more likely to discontinue than men. There was no difference in the primary outcome between the vitamin group and placebo group (27% vs. 30%; HR 0.89; 95% CI 0.75-1.07; p=0.21). There were no significant differences in any of the individual outcomes (death, MI, stroke, hospitalization for angina) and no significant difference in CV death. However, the results for the individual outcomes were very imprecise due to few events for each component. Serious adverse events were similar between groups (15% in the vitamin group vs. 12% in placebo).

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Appendix 1: Prior Authorization Criteria

Multi-Vitamins and Antioxidant Multivitamin Combinations

Goal(s):

- Approve only for documented nutritional deficiency or diagnosis associated with nutritional deficiency (i.e. Cystic Fibrosis)

Length of Authorization: 12 months

Requires PA: All multi-vitamins in HIC3 = C6Z, C6I and C6G

Covered Alternatives: Upon PA approval, only vitamins generically equivalent to those listed below will be covered:

GSN	Generic Name	Example Brand
002532	MULTIVITAMIN	DAILY VITE or TAB-A-VITE
039744	MULTIVITS,TH W-FE,OTHER MIN	THEREMS-M
002523	MULTIVITAMINS,THERAPEUTIC	THEREMS
064732	MULTIVITAMIN/IRON/FOLIC ACID	CEROVITE ADVANCED FORMULA
048094	MULTIVITAMIN W-MINERALS/LUTEIN	CEROVITE SENIOR
002064	VITAMIN B COMPLEX	VITAMIN B COMPLEX
058801	MULTIVITS-MIN/FA/LYCOPENE/LUT	CERTAVITE SENIOR-ANTIOXIDANT
047608	FOLIC ACID/VITAMIN B COMP W-C	NEPHRO-VITE
022707	BETA-CAROTENE(A) W-C & E/MIN	PROSIGHT
061112	VIT A,C & E/LUTEIN/MINERALS	OCUVITE WITH LUTEIN
066980	MULTIVITAMIN/FA/ZINC ASCORBATE	SOURCECF
067025	PEDIATRIC MULTIVIT #22/FA/ZINC	SOURCECF
058068	MULTIVITAMIN/ZINC GLUCONATE	SOURCECF
068128	PEDIATRIC MULTIVIT #32/FA/ZINC	AKEDAMINS
061991	PEDI MULTIVIT #40/PHYTONADIONE	AQUADEKS
066852	MULTIVITS&MINS/FA/COENZYME Q10	AQUADEKS
068035	MULTIVITS&MINS/FA/COENZYME Q10	AQUADEKS

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny, (Not covered by the OHP)

Approval Criteria		
2. Does the patient have a documented nutrient deficiency **OR** 3. Does the patient have an increased nutritional need resulting from severe trauma (e.g. severe burn, major bone fracture, etc.) **OR** 4. Does the patient have a diagnosis resulting in malabsorption difficulties (e.g. Crohns disease, Cystic Fibrosis, bowel resection or removal, short gut syndrome, gastric bypass, renal dialysis, dysphagia, achalasia, etc.) **OR** 5. Does the patient have a diagnosis that requires increased vitamin or mineral intake?	**Yes:** Approve up to 1 year	**No:** Pass to RPh; Deny for Medical Appropriateness.

P&T / DUR Action: 3/27/2014 (MH/KK)
Revision(s):
Initiated: