

PRACTICAL POINTERS
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Beneficial In Preventing Recurrence Of VTE And Major Vascular Events

11-1 LOW DOSE ASPIRIN FOR PREVENTING RECURRENT VENOUS THROMBOEMBOLISM: The ASPIRE Study

Patients who have had a first episode of unprovoked venous thromboembolism (VTE) are at high risk of recurrence after anticoagulant therapy is discontinued.

VTE was considered to be unprovoked if it occurred in the absence of these transient risk factors during the preceding 2 months:

Confinement to bed for more than 1 week.

Major surgery.

Trauma requiring a cast.

Pregnancy or the puerperium.

Use of oral contraceptive pills or hormone replacement therapy.

Because anticoagulants are inconvenient to take and increase risk of bleeding, many patients discontinue them after 3 to 6 months despite recommendations to prolong therapy.

This double-blind randomized placebo-controlled trial evaluated the efficacy of low-dose aspirin (vs placebo) in preventing recurrence of VTE.

Subjects had completed initial anticoagulation with heparin and warfarin (recommended for 6 to 12 months) after a first episode of unprovoked VTE.

STUDY

1. VTE (in the lower extremity) and pulmonary embolism were symptomatic and objectively diagnosed.
2. All patients underwent venous ultrasound at baseline to determine whether there was residual VTE in order to distinguish between residual thrombosis and recurrence of VTE in subsequent assessments.
3. After completion of initial anticoagulation therapy (26 weeks or more) with heparin followed by warfarin, patients were randomized to:
 - 1) Enteric coated aspirin 100 mg daily, or
 - 2) Placebo.
4. Patients were asked to take aspirin for a minimum of 2 years—to a maximum of 4 years.
5. The primary outcome was a recurrence of VTE, defined as a composite of

symptomatic, objectively confirmed deep-vein thrombosis, nonfatal pulmonary embolism (PE), or fatal pulmonary embolism. The diagnosis of recurrence of VTE required the presence of new symptoms and objective evidence on a new thrombosis by imaging.

6. The study began in 2003 and ended in 2012.

RESULTS

1. Randomized 822 patients (mean age 54) at 56 sites in 5 countries; 73% had received anticoagulation for at least 6 months before randomization. The median time between cessation of anticoagulation and randomization was 7 days; median follow-up = 37 months.

2. The index event: proximal deep-vein thrombosis alone in 57%; PE alone in 28%; both in 14%.

3. Primary outcome:

	Placebo (N = 411)	Aspirin (N = 411)	Hazard ratio (HR)
Recurrent VTE	18%	14%	
Rate per year	6.5%	4.8%	0.74 (not significant)

4. Of 100 patients, 58 in the placebo group, and 42 in the aspirin group, VTE recurred while the patients were receiving the study drug. The analysis of data from patients while they were receiving the study drug showed a significant benefit with aspirin; 7.6% per year for placebo; 4.8 for aspirin (HR = 0.651 statistically significant).

5. The risk of recurrence of VTE was greater in the first year.

6. Secondary outcome:

Composite of VTE, myocardial infarction, stroke, and cardiovascular death occurred in 88 patients assigned to placebo, and 62 assigned to aspirin--8.09% vs 5.2% per year; HR = 0.66. (Statistically significant)

7. Clinically relevant bleeding:

Occurred in 8 patients assigned to placebo (6 major) and 14 in those assigned to aspirin (8 major). There was no statistically significant difference.

8. Net clinical benefit:

Defined as a reduction in the rate of a composite of VTE, MI, stroke, major bleeding, and death from any cause, aspirin was associated with a 33% reduction in the outcome, with an event rate of 9% per year in the placebo groups vs 6% per year in the aspirin group. (HR = 0.67)

9. Adverse events and discontinuation of study drug:

Gastrointestinal adverse effects leading to discontinuation occurred in 14 aspirin patients vs 2 placebo. Adverse events leading to hospitalization occurred in 28% of placebo group and 25% in the aspirin group.

During follow-up, 132 placebo patients discontinued, and 117 aspirin patients discontinued the study drug.

10. The median time patients received the study drug was 27 months; median follow-up time was 37 months.

DISCUSSION

1. Although the results of this trial did not show a statistically significant reduction in the primary outcome of recurrent VTE with aspirin (compared with placebo), it did show that aspirin reduced the secondary composite outcome of major vascular events by 34% without increasing risk of bleeding.
2. This is a significant net clinical benefit.
3. With fewer patients recruited than originally planned, the ASPIRE trial by itself was not powered to show a statically significant reduction in the primary outcome. But when combined with the WARFASA¹ study, which entered patients with baseline characteristics similar to the present study, a clear benefit was evident. The combined results of the 2 studies show a highly significant 32% reduction in recurrence of VTE and a reduction of 34% in the rate of major vascular events with no excess of bleeding.
4. There was a high rate of discontinuation in the ASPIRE Trial. This likely led to underestimation of the potential benefit of aspirin.
5. When patients discontinue initial anticoagulation with heparin-warfarin, the rate of recurrence of VTE is about 10% in the first year, and 30% within 10 years. Recurrent VTE is associated with a case fatality rate of 5 to 10%, and a risk of post-thrombotic syndrome.
6. Vitamin K antagonists prevent recurrence, but many patients are not willing to accept extended therapy because of risk of bleeding and the inconvenience.
7. Aspirin, although substantially less effective than warfarin, provides an attractive alternative because it is simple and inexpensive.
8. Patients who have had a first unprovoked VTE appear to have greater risk of arterial thrombosis and CVD death. Aspirin is associated with an overall reduction in the risk of major thrombotic events (arterial as well as venous) and CVD death.
9. In absolute terms, this trial suggests that, for every 1000 patients treated with

aspirin for 1 year, there would be:

17 fewer episodes of VTE

28 fewer major thrombotic events

5 non-fatal bleeding episodes.

CONCLUSION

Low-dose aspirin is beneficial in preventing recurrence of VTE and major vascular events in patients who had a first episode of unprovoked VTE once they have completed the initial course of anticoagulation therapy.

NEJM November 22, 2012; 367: 1974-87 Original investigation by the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) Investigators, first author Timothy A Brighton, University of Sydney Australia

1 The Warfarin and Aspirin (WARFASA) trial: “Aspirin for preventing the recurrence of venous thromboembolism” NEJM 2012; 33366: 1959-67

(See the following abstract. Ed.)

It may be that the study did not find any statistically significant increase in bleeding associated with aspirin. This is a stretch, The power of the study was not great enough to reveal a significant increase. Overwhelming evidence shows that even low doses of aspirin increase risk of bleeding.

Aspirin is much less effective in preventing recurrence of VTE than warfarin.

The risks of arterial thrombosis and cardiovascular death are increased in patients with unprovoked VTE

Whether to switch to aspirin or continue warfarin or another anticoagulant is a personal preference of the patient

Aspirin Reduces Major Vascular Events As Well As Recurrence Of VTE

11-2 ASPIRIN FOR DUAL PREVENTION OF VENOUS AND ARTERIAL THROMBOSIS

Aspirin is conventionally regarded as an agent that prevents arterial thrombosis. This effect is mediated through inhibition of platelet cyclo-oxygenase, resulting in decreased synthesis of thromboxane, a platelet activator.

In high-risk patients, aspirin reduces the frequency of arterial thrombosis by one quarter.

In 1977, aspirin was shown to reduce the risk of VTE after hip surgery. Now, guidelines include aspirin for preventing VTE after orthopedic surgery.

However, many experts regard aspirin as inferior for this indication, preferring treatment with conventional anticoagulants (heparin, fondaparivux, warfarin, or the newer agents dabigatran and rivaroxaban).

Anticoagulants are especially active in the low-flow, low-shear, venous vasculature where fibrin-rich clots form—in contrast to the high-flow, high-shear arterial circulation where platelet adhesion and aggregation are more important.

For patients with unprovoked VTE, the risk of a recurrence after 3- to 12- month treatment with warfarin, dabigatran, or rivaroxaban rises transiently to as high as 20 in 100 patient-years, before settling at a long-term rate of about 5 per 100 patient-years

Could aspirin represent a reasonable option between the extremes of indefinite anticoagulation and no ongoing anticoagulation, particularly from the additional perspective of concomitant prevention of arterial thrombosis?

A dual benefit of aspirin in both arterial and venous circulations might be expected.

Atherosclerosis is a risk factor for unprovoked VTE.

Patients with unprovoked VTE are at increased risk for arterial cardiovascular events.

The two clinical trials (WARFAS and ASPIORE) had very similar enrollment criteria and outcome measures, making them available for misanalysis. Together, the two indicate that aspirin reduces recurrence of VTE as well as the rate of major vascular events. Moreover, these benefits were achieved with a low risk of bleeding.

When the two trials were combined, there was a 32% reduction in the rate of recurrence of VTE, and a 34% reduction in the rate of major vascular events (composite of VTE, MI, stroke, and cardiovascular death).

How should primary care clinicians respond in treating patients with unprovoked VTE? Before considering prescribing aspirin, it is important to treat these patients for at least 3 months of effective anticoagulation to avoid early recurrence. For patients who then wish to stop anticoagulation, aspirin 100 mg daily will reduce risk of VTE as well as arterial cardiovascular events.

Aspirin is inexpensive, does not require monitoring, and does not accumulate in patients with renal insufficiency (in contrast to dabigatran and rivaroxaban). If bleeding occurs, and surgery is required, the antiplatelet effects of aspirin can be reversed with platelet transfusion.

Among patients with unprovoked VTE who have completed initial anticoagulation, aspirin would seem to be a reasonable option of long-term dual prevention of recurrent VTE and arterial cardiovascular events.

NEJM November 2012, 367: 2039-41 Editorial by Theodore E Warkentin, McMaster University, Hamilton, Ontario, Canada

1 Aspirin to Prevent Recurrent Venous thromboembolism (ASPIRE) Investigators, first author Timothy A Brighton, University of Sydney Australia

2 The Warfarin and Aspirin (WARFASA) trial: “Aspirin for preventing the recurrence of venous thromboembolism” NEJM 2012; 33366: 1959-67

Enhanced platelet activity is shared by VTE and arterial thrombosis. Both should benefit from aspirin.

Aspirin must be started immediately after initial anticoagulation is stopped because the risk of recurrence rises abruptly.

The long-term risk of recurrence of VTE is then about 5% per year. Aspirin reduces this risk by about 1/3. The risk of a composite of major vascular events is also increased after unprovoked VTE. Aspirin also reduces this risk by about 1/3.

“Breast Cancer Screening Saves Lives.”

11-3 BENEFITS AND HARMS OF BREAST CANCER SCREENING:

An Independent Review

Whether breast cancer (BC) screening does more harm than good has been debated extensively. The main questions are how large the benefit is in terms of reduced BC mortality, and how substantial the harm is in terms of overdiagnosis.

The National Cancer Director, England requested formation of an independent unbiased Panel to review the evidence of benefits and harms of BC screening by mammography in the UK.

The Panel reviewed the extensive published work, including randomized, controlled trials. These, however, were dated from the 1980s or earlier. Since then, treatment and management of BC has changed and improved.

The Cochrane Review provided 13 years of follow-up from the randomized trials.

Estimates of the absolute benefits of screening in reducing BC deaths varied widely.

The Panel concludes:

“Breast cancer screening saves lives.”

The evidence suggests a 20% reduction in BC mortality in women invited to participate (vs controls) in a 20-year screening program.

(Invited women ages 50-70; every 3 years).

The reduction corresponds to one BC death prevented for every 235 women invited to screening, and one death averted for every 180 women who attended screening.

This likely prevents about 1300 BC deaths per year.

There is a cost to women’s wellbeing. Screening detects cancers that would not have come to clinical attention in the woman’s lifetime were it not for screening (overdiagnosis). The Panel estimated that, in women invited to screening, about 19% were over diagnosed (expressed as a proportion of cancers diagnosed in the invited group).

The Panel emphasizes that these figures are best estimates based on inadequate data. But considers any excess mortality that arises from investigation and treatment of BC to be minimal, and substantially outweighed by the benefits of treatment.

The Panel estimates that for every 10 000 UK women invited to screening, about 681 BCs will be discovered and 43 deaths from BC will be prevented.

Of the 681, 129 will represent overdiagnosis.

For every BC death prevented, about 3 overdiagnosed cases will be identified and treated. Of the approximately 307 000 women age 50-52 who are invited to screening every year, just over 1% would have an overdiagnosed cancer during the next 20 years,

The major harm of screening considered by the Panel was overdiagnosis. Because BCs are detected earlier with screening, the cancer incidence is expected to be higher in screened women during the screening period. The period between detecting of a cancer by screening and when it would have presented clinically is the lead time. In theory, when screening stops, the diagnosed cancer incidence should fall, so by the end of the screening period plus lead time, the cumulative incidence in the screened and control populations should be the same. Some screen –detected cancers, however, might never progress to become symptomatic in the absence of screening, and some women would die from other causes before the BC becomes evident. These cancers are nonetheless treated. This adverse consequence of screening is called overdiagnosis, and is defined as the detection of cancers that would never have been found were it not for screening. It refers to all cancers, invasive of in situ, because both are actively treated.

The Panel concluded that a vast range of estimates of overdiagnosis could be obtained from observational studies. Uncertainty surrounds this evidence.

The Panel believes that overdiagnosis occurs. Women consequently have the cancers treated by surgery, and in many cases by radiotherapy and chemotherapy. But neither the woman nor her doctor can know whether this particular cancer would be one that would have become apparent without screening and could possibly lead to death, or one that would have remained undetected during the rest of the woman's lifetime.

The Panel thinks the best answer to the question "If I am invited to enter into the screening program and am given a cancer diagnosis during the screening period, what is the likelihood of overdiagnosis". The Panel believes the evidence suggests one in 77 women age 50 invited to screening for 20 years will have an overdiagnosed cancer—a rate of 129 per 10 000 women invited to screening.

Ductal carcinoma in situ:

DCIS is a malignant tumor that arises from the epithelial tissues of the breast. However, the malignant cells do not infiltrate beyond the limiting basement membrane, and remain within the ducts where they arise. So DCIS is not, by itself a life-threatening disease.

DCIS is more frequently screen-detected than symptomatic.

DCIS can be associated with invasive cancer and can be a marker of malignancy.

DCIS can also relapse into cancer. After wide excising of screen-detected DCIS, without any further treatment, relapse can occur in 19% of cases, and was invasive in half of these cases.

It is wrong, however, to assume that all DCIS represents overdiagnosis.

The relevant question is therefore not whether DCIS progresses to invasive cancer (which it can), but whether it might progress to invasive cancer that causes symptoms within the woman's lifetime.

In the diagnosis of DCIS with a screening program, a balance has to be struck between the potential benefits for some women of detection and treatment of a pre-cancer and the treatment of something that would never have affected the woman in her lifetime.

Other harms:

Pain from the mammogram is enough to deter about 4% women from a repeat study.

About 4% are recalled for repeat screening mammography and possible biopsy. Of these women, nearly one in 5 will have cancer. Of the remainder, 70% will need only further imaging, and 30% a biopsy.

All will suffer psychological distress.

Information should be made available in a transparent and objective way to women invited to screening so they can make informed decisions.

Lancet, November 17, 2012; 380: 1778-86 Original investigation by the Independent UK Panel of Breast Cancer Screening. Correspondence to: Prof. Sir Michael Marmot, UCL, London UK
Lancet, November 17, 2012; 380: 1714 Editorial by the Lancet Staff.

This is a good example of how difficult the “science” of medicine can be. After years of investigation by many authorities, doubt remains. The best the clinician can do then, is to clearly present the benefit / harm-cost ratio of an interventions, and guide the individual to the best personal decision.

No matter what choice the patient makes, anxiety, bother, and expense will remain.

The UK Panel did not discuss monetary costs. Costs of the mammography program in the USA must reach billions of dollars over the years.

I believe, compared with the UK, more patients in the US would be recalled for a second mammogram; more will undergo biopsy and unnecessary surgery. I believe this is a more important consideration in the US than overdiagnosis is in the UK. Few women in the US, after being told they have a BC that will likely not be fatal, would choose a long period of observation. They would choose immediate surgery.

In addition, women now live longer and would be more likely to experience clinical expression of a BC during their lifetime.

A Modest But Statistically Significant Reduction In Total Cancer

11-4 MULTIVITAMINS IN THE PREVENTION OF CANCER IN MEN: Randomized Controlled Trial The Physicians’ Health Study II

Multivitamins are regularly taken by at least one third of the US population.

To date, large scale randomized controlled trials (RCT) testing single or small numbers of higher-dose individual vitamins and minerals for cancer prevention have generally found a lack of effect.

The 2010 Dietary Guideline for Americans stated “For the general healthy population, there is no evidence to support use of multivitamin/mineral supplements in the primary prevention of chronic disease.”

Nevertheless, many persons take them precisely for this reason.

The Physicians' Health Study represents the only large-scale randomized, double-blind, placebo-controlled trial testing the long-term effects of a common multivitamin in the prevention of chronic disease.

STUDY

- 1 PHS II is a RCT evaluating the balance of risks and benefits of a daily multivitamin/mineral supplement (*Centrum Silver*) vs a placebo.
2. The original study also determined efficacy of beta carotene, vitamin E, and vitamin C vs placebos. All were discontinued for lack of efficacy.
3. PHS II, begun in 1999, entered 14 641 male physicians age 50 and over (mean age at baseline 64). All were well nourished.
4. Participants took the multivitamin or a placebo daily through June 2011. (Median follow-up = 11 years.)
5. Primary endpoints were total cancer (excluding non-melanoma skin cancer) and major cardiovascular events.

RESULTS

1. At baseline, the 2 groups were comparable in BMI and smoking, (40% former smokers; 4% current smokers). Current aspirin use was 77%, reflecting the results of the PHS I trial, which reported benefits on primary prevention of cardiovascular disease. Nine % had a history of cancer; 5% had history of CVD.
2. During the follow-up, 2669 men in the multivitamin group had confirmed cancer: 1373 prostate; 210 colorectal cancer.
3. A total of 2757 men died during follow-up; 859 due to cancer.
4. Multivitamin use and total cancer incidence during follow-up:
 - A. Overall (first cancer only):

Multivitamin	17.0 per 1000 person-years
Placebo	18.3 per 1000 person years.
 - B. Men taking multivitamins (vs placebo) had a modest reduction in total cancer incidence (hazard ratio [HR] = 0.92)
 - C. Approximately half of all incident cancers were prostate cancer, many of which were at an early stage. But, the multivitamin had no effect on incidence of prostate cancer (9.1 and 9.2 per 1000 person years).

- D. Excluding prostate cancer, the multivitamin was associated with a statistically significantly reduced risk of total cancer. (HR = 0.88)
 - E. There were no statistically significant reductions in individual site-specific cancers: colorectal, lung, and bladder.
 - F. There was no statistically significant difference in risk of cancer mortality (4.9 vs 5.6 events per 1000 per year; HR = 0.88), or total mortality (HR = 0.94 multivitamin vs placebo)
5. Effect of adherence: At the end of the trial, 33% had stopped taking the multivitamin. There was no difference in incidence of total cancer between those that continued and those that discontinued.
6. Adverse effects of multivitamins:
No significant adverse effects on gastrointestinal tract, fatigue, drowsiness, skin discoloration, or migraine.

DISCUSSION

1. In this large-scale trial among middle-aged and older men, long-term daily multivitamin use was associated with a modest, but statistically significant, reduction in the primary endpoint of total cancer after more than a decade of treatment.
2. There was no evidence that this effect was driven by any individual site-specific cancers.
3. Total cancer rates were likely influenced at the time of the trial by the increased surveillance for prostate-specific antigen and subsequent diagnosis of prostate cancer.
4. Other studies:
 - A. In the Cancer Preventing Study II, which followed more than 1 million US adults beginning in the early 1980s, multivitamin use was not associated with cancer mortality.
 - B. The Women's Health Initiative found that multivitamins had little or no relationship with risk of breast cancer or other cancers in over 160 000 women followed for a mean of 8 years.
 - C. Among 35 000 Swedish women, multivitamin use was associated with a 19% increase in risk of breast cancer during a 10-year period.
 - D. Other observational studies suggest protective relationships of multivitamins, no association, or possible harm. Studies showing an association between multivitamins and specific cancers are typically of long duration, allowing for an increased statistical power. For example, increasing duration of multivitamin use was strongly associated with a reduced risk of colon cancer in the Nurses' Health Study followed for up to 15 years. A long latency period was also noted in the Cancer Prevention Study II, with an inverse association between multivitamin use with both colon cancer incidence and mortality after more than a decade of use.

- E. A meta-analysis of 8 large randomized trials of folic acid and vitamin B supplementation found no effect on total cancer.
 - F. In the Women's' Health Initiative, those randomized to vitamin D (400 IU) + calcium (1000 mg) had a reduction in total cancer similar to that observed in PHS II.
 - G. A Chinese Cancer Prevention Trial targeting 29 584 adults with low baseline nutritional status, a combination of beta-carotene, vitamin E, and selenium for 6 years found significant reductions in total mortality, cancer mortality, and gastric cancer mortality.
 - H. The Heart Protection Study tested high doses of these 3 nutrients among individuals with adequate dietary intake and found no reductions in total or site-specific cancers.
 - I. A randomized placebo-controlled trial in France of antioxidants, vitamins, and minerals in 13 017 participants randomized to low-dose combinations of vitamin C, vitamin E, beta-carotene, selenium and zinc found no overall effect on total cancer, but there was a reduction in risk of total cancer in women only.
5. It is difficult to identify any single mechanism through which individual or multiple components may reduce cancer risk. The reduction in total cancer risk in PHS II argue for a broader combination of low-dose vitamins, rather than an high-dose vitamin and minerals.

CONCLUSION

In this large-scale randomized trial of 14 641 middle-aged men, a daily multivitamin supplement was associated with a (statistically) significant, but modest, reduced risk of total cancer during a follow-up of 11 years.

JAMA November 14, 2012; 308; 1871-80 Original investigation by the Physicians' Health Study II, first author J Michael Gaziano, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.

Sponsored by the National Institute of Health, and the BASF Corporation

The vitamin connection refused to die.

You must be as confused as I am.

I am not convinced.

This group of well nourished physicians must have had normal vitamin and mineral blood levels. The addition of supplements must have raised levels above normal. Vitamins are not like drugs. The blood level of all drugs is zero before administration. Blood levels of vitamins are normal or low in

individual patients at onset of therapy. If the blood level is normal, no benefit would be expected from the supplement.

Centrum Silver contains 31 different minerals and vitamins. Some “daily values” varied above and below normal. The formula changed somewhat over the years. We must ask: Which vitamin(s) produced the benefit, if any? Several individual vitamins have been tested and found to have no benefit on cancer incidence.

I do not recall any other study in which a large group of ingredients were given in one pill. Would a study containing all available antibiotics in one pill, or all anti-hypertension drugs in one pill be considered valid?

As the article suggested, these results were reported in the lay press. The Charlotte Observer October 18 reported that “Those taking a daily vitamin experienced 8 percent fewer cancers than subjects taking dummy pills”.

I would not prescribe multivitamins for cancer prevention. This may lead to a false sense of security in some patients, and reduce their compliance with interventions which may reduce cancer risk

I cannot resist mentioning PHS I. This study was started in 1981 to determine if aspirin would prevent myocardial infarctions and other cardiovascular events. The (primary preventions) trial compared aspirin (Bufferin; 325 mg every other day) vs placebo. Over 22 000 male physicians were randomized. The Data and Safety Monitoring Board stopped the trial ahead of schedule because it was clear that aspirin had a significant effect (44% reduction) on the risk of myocardial infarction. The trial was published in NEJM July 20, 1989.

Millions of healthy men subsequently began to take daily aspirin for primary prevention. It became quite a fad. Over the years, the bloom came off because of the increased risk of bleeding caused by aspirin. Now, aspirin is used mainly for secondary prevention and for primary prevention in those at high risk.

No Beneficial Effect

11-5 MULTIVITAMINS IN THE PREVENTION OF CARDIOVASCULAR DISEASE IN MEN

This part of PHS II determined whether long-term multivitamin (MVT) supplementation decreases risk of major CVD events among men.

Randomized, double-blind placebo-controlled trial of a daily MVT (*Centrum Silver*) began in 1997 with continued treatment and follow-up through 2011. Entered a total of 14 641 male physicians initially age 50 and older (mean = 64). Randomized to daily MVT of placebo.

Included 754 men with a history of CVD at randomization.

Main outcome = composite endpoint of major CVD events—non-fatal myocardial infarction, non-fatal stroke, and CVD mortality.

During a median follow-up of 11 years, there were 1732 confirmed major CVD events. MVT had no effect on major CVD events—11 events per 1000 person-years vs 10.8 events.

MVT had no effect on participants with a baseline history of CVD.

Conclusion: Among this population, MVT did not reduce major CVD events.

JAMA November 7, 2012; 308: 1751-60 by The Physicians' Health Study II. First author Howard D Sesso, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. .

An Editorial in this issue of JAMA (pp 1802-03) by Eva M Lonn, McMaster University, Hamilton, Ontario, Canada comments and expands on this article.

Despite remarkable scientific advances, CVD accounts for about 1 in 3 deaths in the US.

The major risk factors are well known, but remain ubiquitous in the population—hypertension, obesity, smoking, dyslipidemia, and diabetes. In the NHANES survey 2000-2010, 46% in the US had at least 1 major risk factor.

Strategies to prevent the development of these risk factors are largely related to lifestyles. Effective therapies to lower risk factors are available and can substantially reduce the burden of CVD. Yet the apparently simple task of implementing this knowledge remains extremely challenging and seems at times to be insurmountable. Rates of obesity, diabetes and physical inactivity remain high.

Many individuals resort to use of vitamins and other dietary supplements as a simple and miraculous escape from the difficult and complex task of implementing effective preventive strategies.

More than half of US adults take at least one dietary supplement. About 10% take over 5. The promise of an easy fix for multiple health problems combined with lenient regulations fuels the growth of the dietary supplement industry.

MVT and supplement use distracts from effective CVD prevention. This is the major hazard of using supplements.

CVD is largely preventable, and can be achieved by eating healthy foods, exercising regularly, avoiding tobacco, and, for those with high risk, taking proven, safe, and effective medications.

We all know the interventions which lower risk of CVD. I am not reluctant to repeat them. Failing to convince the public to act on the known lifestyle interventions is a major failure of primary care medicine.

The universal use of supplements must be a triumph of marketing by companies that produce them. And an indicator of the gullibility of the US public.

There must be comfort in taking something.

Unfortunately, Federal law facilitates their use.

Metformin Wins Again

11-6 EFFECTIVENESS OF SULFONYLUREA AD METFORMIN MONOTHERAPY ON CARDIOVASCULAR EVENTS IN TYPE-2 DIABETES

These are the 2 most commonly used drugs for type-2 diabetes (**DM-2**).

This retrospective cohort study compared the hazard of CVD outcomes (acute myocardial infarction [**AMI**] and stroke), and all-cause mortality in patients who initiated metformin or sulfonylurea therapy

Defined a cohort of patients initiating oral therapy for DM-2 (2001-2008). Excluded patients with chronic kidney disease and serious medical illnesses.

STUDY

1. The study entered veterans over age 18: (7% male; 75% white; median age 62) who received regular VA care. Patients were eligible when they filled a first prescription for a sulfonylurea (glyburide and glipizide) or metformin.
2. Primary outcomes = hospitalization for AMI, stroke or death.
3. Composite outcomes of hospitalization for MI, stroke, or death were adjusted for baseline demographic characteristics: medications, cholesterol, HbA1c, serum creatinine, BP, body mass index, health care utilization, and comorbid conditions.

RESULTS

1. Incident prescriptions: metformin (n = 155 025; sulfonylurea (n = 155025)
2. Crude rates/ 1000 person-years (unadjusted):

	Metformin	Sulfonylurea
Composite outcome	10.4	18.2

CVD events (A and stroke) 8.2 13.5

3. Adjusted incidence rate difference = 2.2 more CVD events per 1000 person-years with sulfonylurea. Results were consistent for both glyburide and glipizide.

DISCUSSION

1. This national cohort study of veterans initiating oral treatment for DM-2 found that sulfonylureas were associated with increased hazards of AMI, stroke, and death.
2. The finding of increased hazard for the composite outcome among sulfonylurea users could have resulted from unmeasured confounders that had a greater prevalence among sulfonylurea users. The authors calculated, however, that unmeasured confounders would need to be at least 53% more prevalent among sulfonylurea users than metformin users.
3. The findings do not clarify whether the difference in risk is due to harm from sulfonylureas, benefit from metformin, or both. The reason for the difference remains unknown.
4. The UKPDS (1998) randomized overweight persons with DM-2 to metformin or diet. Those receiving metformin experienced relative risk reductions of 42% for diabetes-associated death and 36% for all-cause mortality.
5. Compared with metformin, sulfonylureas are associated with increases in weight and lipid levels, and greater risk for hypoglycemia, but similar glycemic control.
6. Thus, metformin is recommended as first-line therapy. Sulfonylureas are sometimes preferred because they require little titration and have fewer gastrointestinal adverse effects.
7. The authors estimate that, after 1 year, those taking metformin (vs sulfonylureas) would have a decrease in weight of 3.2 kg, and a slight decrease in LDL-cholesterol and triglycerides and no difference in HbA1c.

CONCLUSION

The study suggests a modest, but clinically important increased hazard of AMI, stroke, or death associated with initiation of sulfonylurea compared with metformin.

Metformin is supported for first-line treatment of DM-2.

Annals Internal Medicine November 6, 2012; 157: 601-610 Original investigation, first author
Christine L Roumie, Nashville VA Affairs Medical Center, Nashville, TN

11-7 TOPICAL IVERMECTIN LOTION FOR TREATMENT OF HEAD LICE

There is increasing resistance to permethrin and pyrethrins. New therapies are needed. The established second-line treatments, lindane and malathion, have limitations related to safety and other concerns.

Oral ivermectin is used extensively to treat nematode infections and scabies.

This article describes 2 multicenter, randomized double-blind trials of efficacy and safety of a single application of a new 0.5% ivermectin lotion.

Eligible patients were healthy children, 6 months of age or older. All agreed not to comb out nits. All had active infections with 3 or more live lice on scalp or hair.

Subjects received a single 4-ounce tube containing either ivermectin lotion or vehicle control. The application was left on for at least 10 minutes before rinsing the head with water.

The primary efficacy end point was the number of index patients who were free of lice by day 2 and remained free through days 8 and 15.

Significantly more patients in the ivermectin group were free of lice the day after application and through day 15.

Combined insertion-to-treat analysis:

	Ivermectin	Control
Free of lice day 2	131 of 138 (95%)	46 of 147 (31%)
Remained louse free at day 15	104 of 141 (74%)	26 of 148 (18%)
Pruritus free on day 2	67%	43%

This is similar to the reported 92% efficacy 1 day after oral ivermectin.

Safety of ivermectin

Pruritus (the most frequent sign of pediculosis), excoriation, and erythema in less than 1%-- not definitely related to the study drug. Two of 379 had eye irritation.

Conclusion: Ivermectin has a well-established safety profile. A single 10-momite at-home topical application showed high efficacy within 24 hours. Most patients remain louse free.

NEJM November 1, 2012; 367: 1687-93 Original investigation, first author David M Pariser, Eastern Virginia Medical School, Norfolk.

Funded by Topaz Pharmaceuticals (Now Sanofi Pasteur)

I expect the wily lice to develop resistance to ivermectin.

11-8 CDC's UPDATE ON TREATMENT OF GONORRHEA

Treatment of gonorrhea has been complicated by the ability of *Neisseria gonorrhoeae* to develop resistance to anti-microbials. This report, from the CDC's Gonococcal Isolate Surveillance Project describes laboratory evidence of declining cefixime susceptibility among urethral *N gonorrhoeae* isolates collected in the US 2006-2011. And updates the CDC's recommendations for treatment.

Ceftriaxone is a safe, well-tolerated injectable cephalosporin that is known to be highly effective in a single dose for treatment of gonorrhea.

Resistance to ceftriaxone is expected to emerge.

To delay emergence of resistance to ceftriaxone, combination therapy using 2 anti-microbials with different mechanisms of action is recommended.

The use of azithromycin as a second drug is preferred to doxycycline because of the convenience and advantages of a single-dose therapy and the higher prevalence of gonococcal resistance to tetracyclines than to azithromycin.

A test for cure (ideally with culture) should be conducted one week after treatment. Clinicians should ensure that the patient's sex partners from the preceding 60 days be evaluated promptly.

For treatment of uncomplicated urogenital, rectal, and pharyngeal gonorrhea:

- 1) Ceftriaxone 250 mg single intramuscular dose PLUS
- 2) Azithromycin 1 g orally in a single dose.

(Combination therapy will also ensure treatment of co-occurring *Chlamydia trachomatis*.)

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