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This index-synopsis is a reference document based on articles abstracted from 6 flagship journals. July – December 2012. It provides a means of reviewing and recalling to memory, in an evening or two, practical clinical points of importance to primary care published during that time.

The numbers in the brackets refer to the month and sequence the article appeared. For example, [8-3] refers to the 3rd article abstracted in August 2012.

The index lists, in alphabetical order, terms mentioned in the synopsis during the 6 months

Monthly issues containing the full abstracts for the past 10 years may be found on the website (www.practicalpointers.org).

I hope you find Practical Pointers for Primary Care Medicine useful and interesting.

Richard T. James Jr. M.D. Editor/Publisher

PRACTICAL CLINICAL POINTS JULY-DECEMBER 2012

[7-1] TEACHING PHYSICIANS TO THINK ABOUT COSTS; Editorial

Efforts To Teach Costs-Consciousness And Stewardship Of Resources

Primary care clinicians should be constantly aware of medical costs and choose tests and interventions that produce the highest benefit / harm-cost ratio.

Our profession has traditionally rewarded the broadest differential diagnosis that uses resources as if they were unlimited. Now, financial implications have become part of the national conversation. Terms like "value-based purchasing", "choosing wisely", and "pay for performance" have entered the healthcare system.

We can no longer ignore the financial implications of our decisions.

The real goal is not cost containment per se, but better use of evidence-based medicine and Bayesian principles.

Protecting our patients from financial ruin is fundamental to doing no harm.

[7-2] RETHINKING OUR APPROACH TO PHYSICAL ACTIVITY: Editorial

A Behavior That Should Be Part Of Everyday Life

Physical activity (PA) is about using the body in ways it was designed, which is to walk often, run sometimes, and move in ways where we physically exert ourselves regardless of whether it is work, at home, in transport, or during leisure time.

Physical inactivity is a major contributor to death and disability from non-communicable disease. (NCD). We have been slow to recognize its importance.

One problem is that PA is often perceived only in the context of controlling obesity, and therefore inactivity is considered minor or secondary risk factor for NCD.

Physical inactivity is a significant predictor of CVD, type-2 diabetes, obesity, some cancers, poor skeletal health, some aspects of mental health, and mortality, as well as poor quality of life.

Being active is a major contributor to overall physical and mental health.

Clearly, PA has vast potential to improve health throughout the world.

[7-3] POOR HEALTH DOES NOT ALWAYS MEAN AN UNHAPPY LIFE: Observational study

Many Patients In Poor Health Are Still Satisfied With Life

A program to measure wellness in the UK showed that 40% of people who rate their own health as bad or very bad nevertheless report medium to high levels of satisfaction with life.

Respondents were asked:

1) How satisfied are you with your life?
2) To what extent do you feel that things you are doing are worthwhile?
3) How happy did you feel yesterday?
4) How anxious did you feel this morning?

Three quarters rated their life satisfaction at 7 or more out of 10; 80% gave the same rating for the worthwhile question. Just 1 of 10 was unhappy yesterday; 22% rated their anxiety as high.

[7-4] REFINING PHYSICIAN'S ROLE IN ASSISTED DYING: Editorial

Is There Is A Compelling Case For Legalized Assisted Dying?

Terminally ill patients spend their final months making decisions about medical care and disposition of assets. Many are completing advanced directives to withhold life-sustaining treatment.

A controversial aspect of this trend toward a more self-directed dying process is the question of assisted dying—whether patients should have the option to acquire a lethal dose of a drug with the explicit intention to end their lives.

Generally, this process is illegal. But it has been approved and used in the Netherlands and in Oregon and several other states. The law outlines a careful rigorous process for determining eligibility for assisted dying.

Critics have voiced objections.

This editorialist believes that momentum is building for assisted death.

[7-5] A POOLED ANALYSIS OF VITAMIN D DOSE REQUIREMENTS FOR FRACTURE PREVENTION: Meta-analysis of randomized trials

Supporting The Recommendations Of The IOM

Most fractures occur in persons over age 65.

This study identified 11 double-blind randomized trials on persons over age 65 that evaluated D supplementation, alone or in combination with calcium, as compared with controls.

Divided the group into 5 categories according to the actual prescribed dose of D—from 0-360 IU to 790-2000 IU. The actual intake was between 100 and 840 IU.

On the basis of the actual dose taken, there was a 30% reduction in hip fractures at the highest intake— >790 IU. There was no reduction in fracture in those whose actual intake was less than 790 IU.

This suggests that D supplements in elderly patients should be 800 IU /day.

[7-6] VITAMIN D—BASELINE STATUS AND EFFECTIVE DOSE: Editorial

Nutrients Are Not Like Drugs

There has been more ink spilled over the efficacy of D than that of most nutrients.

If D is actually efficacious, why these inconsistencies? In patients whose baseline level of D is within normal range, adding more will not produce a meaningful response. Most trials of D have paid little attention to baseline status.

If the patient is deficient, the dose will raise blood levels

If the patient is not deficient, the dose may increase blood levels slightly, but will not benefit.

In this regard, nutrients and supplements are not like drugs. More is not necessarily better.

7-7 CDC PILOT PROGRAM WILL OFFER FREE RAPID HIV TESTS THROUGH PHARMACIES: Medical news and perspective

A New Public Health Initiative. Free And Discreet Testing Will Overcome Barriers

This program is designed to test the feasibility of routinely offering free HIV testing. During a 2-year program, pharmacists from 12 urban and 12 rural areas with high prevalence of HIV will be trained to administer the tests, counsel patients, and refer those with positive results.

The CDC recommends that all adults and adolescents be tested at least once for HIV.

The test consists of collecting an oral fluid sample by swabbing. It is placed in a developer vial and sent off for testing for antibodies to HIV.

Sensitivity of the test is 92% (8% false negatives); specificity is 99.9% (0.1% false positives).

This initiative can make testing routine and help identify the hundreds of thousands of Americans who are unaware that they are infected.

[8-1] EFFECTS OF LOWERING LDL-CHOLESTEROL WITH STATIN THERAPY IN PEOPLE WITH LOW RISK OF VASCULAR DISEASE Meta-analysis

Treating Everyone With A Statin Drug, Age Being The Only Indication

Uncertainty remains about whether statin therapy is of overall net benefit in primary prevention of CVD (in patients with no history of CVD). This meta-analysis assessed the benefit /harm-cost ratio of lowering LDL-cholesterol in low risk patients.

At baseline, participants were separated into 5 categories based on risk of a major vascular event over 5 years.: < 5%. 5% to 9%; 10% to 19%; 20% to 29%; and 30% and over.

Risk of major cardiovascular events per 40 mg/dL reduction in LDL-cholesterol (1 mmol) in those with <5% risk over 5 years was reduced by 38%, and in those with 5%-9% risk was reduced by 31%. The proportional reduction in risk was similar to the reduction in those considered at much higher risk.

In absolute terms, major vascular events per 1000 individuals treated over 5 years were avoided in 6 persons and vascular deaths avoided in 1.2.

The benefit / harm-cost ratio of statins in patients at low risk greatly exceeds any known hazard of statin therapy.

[8-2] STATINS FOR EVERYONE BY AGE 50 YEARS? Editorial

Whether Populations Will Be Well Served By Substituting the Present Pharmacologically Dominated Research Findings For Lifestyle-Related Diseases Is Debatable

The preceding study extends the lower level of risk for major vascular events beyond that recommended by current guidelines.

Adopting a lower threshold of 10% would classify 83% of men and 50% of women older than 60 as needing statins.

Because people over age 50 are likely to be at greater risk, it world be pragmatic to use age as the only indication for statin treatment.

But, whether populations will be well served by substituting the present pharmacologically dominated research findings for lifestyle-related disease is debatable.

[8-3] CARDIOVASCULAR RISK ASSESSMENT IN THE 21ST CENTURY: Editorial

Is Screening With Coronary Artery Calcium Score Appropriate In Primary Care?

An editorial states the best way to predict CVD risk over the ensuing 10 years is still the Framingham risk score. (FRS)

The FRS predicts likelihood of a cardiovascular event in the next 10 years using several simple risk factors that are easy to obtain and inexpensive. Adding some other conventional risk factors does not materially add predictability because of a high correlation with factors already in the FRS.

Patients with diabetes, known CVD, or a family history of early CVD are automatically at higher risk. They need no further risk assessment.

Recently the coronary artery calcium score (CACS) has been used to screen for CVD. The CACS may reclassify some patients as being at higher risk, but it involves radiation exposure and is expensive.

The editorialist is no fan of the CACS for screening in primary care.

[8-4] IMPROVING PATIENTS QUALITY OF LIFE AT THE END OF LIFE: Editorial

Set Appropriate Treatment Goals And Focus On QOL, Not Solely On Survival At Any Costs.

Key predictors of quality of life (QOL) just before death:

Associated with worse QOL: Intensive care stay in the final week;
hospital death; patient worry; feeding tube; chemotherapy in the final week.

Associated with better QOL: Religious prayer or meditation; pastoral care;
patient-physician therapeutic alliance.

There is a significant role for physicians when cure is unavailable by cultivating a therapeutic alliance with the patient, promoting pastoral services, reducing worry, and avoiding unnecessary hospitalization.

It seems to be a paradox in assessing QOL when the expected death is only hours away. Nevertheless, the concept persists. It speaks to the absence of unnecessary pain and discomfort, and acceptance of the inevitability of the short time left.

Physicians must convey the emotionally difficult message of prognosis, the true efficacy and futility of treatments, and when palliation is the best treatment.

One introduction to a conversation about terminal care is to ask the patient "Are you at peace?"

[8-5] LIFELONG MANAGEMENT OF AMYLOID-BETA METABOLISM TO PREVENT ALZHEIMER'S DISEASE: Editorial

It Takes Decades For Alzheimer's Disease To Develop

Alzheimer disease (AD) is characterized by accumulation of amyloid beta (AB) protein in the CNS. An amyloid precursor protein is involved in the process.

Thus far, experimental therapeutic efforts to lower AB and slow progression of dementia have failed.

AB deposition in the CNS can be detected as long as 25 years before AD symptoms begin. This implies that primary prevention of AD must begin years before presentation of AD symptoms. The 20 billion dollar question: How early must we intervene to delay onset of AD? Should we begin to think of lifetime control of AB metabolism the same way we think of cholesterol metabolism?

[9-1] ASSOCIATION OF BP LEVEL AND ALL-CAUSE MORTALITY IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES: Cohort Study

"Lower The Better Is Not Better"

Guidelines recommend maintaining BP at 140/90 in people with hypertension in the general population. And below 130/80 in high-risk patients (diabetes, cardiovascular disease, cerebrovascular disease, kidney disease).

Aggressive lowering of BP has been questioned. To date there is little evidence indicating a cardio-protective effect of BP below 130/80. In this large observational study, BP below 130/80 was not associated with decreased risk of all-cause mortality in patients with newly-diagnosed diabetes. It may be advisable to maintain BP between 130-139/80-85,

[9-2] USE OF A SINGLE TARGET BLOOD PRESSURE LEVEL IN TYPE-2 DIABETES MELLITUS FOR ALL CARDIOVASCULAR RISK REDUCTION: Editorial

Newer Guidelines Are Likely To Suggest A Goal For Patients With Diabetes Of Less Than 140

For years, all major guidelines have recommended a target BP of less than 130/80 for patients with diabetes—based almost exclusively on retrospective analysis of primary outcome trials. But the issue of optimum BP goal for patients with diabetes remains unresolved. A recent meta-analysis did not support lower, more aggressive target BP for overall cardiovascular risk reduction.

[9-3] MIDLIFE FITNESS AND THE DEVELOPMENT OF CHRONIC CONDITIONS

Fitness May Be Associated With Compression Of Mortality In Older Age

In a cohort of over 18 000 healthy participants, midlife fitness was associated with a lower risk of chronic health conditions in men and women over age 65: Congestive heart failure, ischemic heart disease, stroke, diabetes, COPD, chronic kidney disease, and Alzheimer's.

As midlife fitness increased from treadmill time of 11 minutes to 23 minutes, the number of chronic conditions in older age declined from 4700 to 1800.

Higher fitness may be associated with compression of morbidity in older age.

[9-4] ARE ORGANIC FOODS SAFER OR HEALTHIER THAN CONVENTIONAL FOODS?

The Evidence Does Not Suggest Marked Health Benefits From Consuming Organic Foods

This study synthesized the literature on health, nutrition, and safety of organic foods

The study did not find robust evidence to support the claim that organic foods are more nutritious. Of all nutrients evaluated, only one (phosphorous) was higher in conventional foods. Conventional foods had a 30% higher risk of pesticide contamination. Conventional chicken and pork had a higher risk for contamination with antibiotic resistant bacteria. The evidence does not suggest marked health benefits from consuming organic foods.

[9-5] ASSOCIATION BETWEEN OMEGA-3 FATTY ACIDS SUPPLEMENTS AND RISK OF MAJOR CARDIOVASCULAR DISEASE EVENTS.

No Significant Association With Major Vascular Outcomes Across Various Patient Populations

A meta-analysis of 20 randomized trials evaluated the effect of omega-3 polyunsaturated fatty acids supplements on all-cause death, cardiac death, sudden death, myocardial infarction, and stroke. There was no significant association between O-3 and major vascular outcomes across various patient populations. The finding does not support use of O-3 as an intervention in everyday practice.

[9-6] PHYSICIANS WARNINGS FOR UNSAFE DRIVERS AND THE RISK OF TRAUMA FROM ROAD CRASHES

Decreases Subsequent Road Crashes

The Ontario government has encouraged physicians to directly warn patients who are considered a danger to drive. Over 100 000 drivers received a warning for alcoholism, epilepsy, dementia, sleep disorders, stroke, and diabetes. Many younger drivers were warned. In the year following implementation of the warnings, there was a 46% reduction in road crashes as determined by visits to the Emergency Departments. But the warnings also increased prevalence of mood disorders and compromised the doctor-patient relationship.

[10-1] PHYSICAL ACTIVITY AND MORTALITY IN INDIVIDUALS WITH DIABETES MELLITUS: Prospective Cohort Study(EPIC)

Inverse Association With Total Mortality And CVD Mortality. But Not Many Patients With DM Adhere To The Advice

The EPIC study is an ongoing prospective study of 519 978 men and women age 35-70 from 10 European countries.

Within EPIC, a cohort of patients with diabetes (DM; 12%) was established at baseline between 1992 and 2000. The cohort was divided into 4 groups according to physical activity (PA): inactive; moderately inactive; moderately active, and active.

After a median follow-up of 9 years, 13% of DM participants died (Death due to CVD accounted for 28% of all deaths (n = 212). In these patients, PA was inversely associated with total and CVD mortality. The lowest hazard ratios (HR; active vs inactive) was observed in persons categorized as moderately active or active.

Leisure time PA and walking time were also inversely associated with a lower risk of CVD and total mortality.

Participants who walked 5 to 9 hours per week had lower CVD mortality compared with those in the inactive group.

In this prospective analysis of individuals with diabetes, higher levels of total PA, leisure time PA, and walking were associated with lower risk of total and CVD mortality.

Evidence from the present study and from previous studies supports the widely held view that PA is beneficially associated with lower mortality in people with DM.

Because not many patients with DM adhere to this advice, future research should elucidate the determinants of physical inactivity and design successful strategies to promote active lifestyles.

[10-2] MULTI-MORBIDITY: WHEN AND HOW TO TAKE A PALLIATIVE APPROACH TO CARE: Editorial

Using good judgment and communications with the patient and family

For patients with multi-morbidities, there has been a call for a paradigm shift from the disease-based model to a focus on palliative care. As patients with multi-morbidity age, and healthcare providers face increasing problems with delivering complex care, doctors must consider when it is appropriate to broach the subject of scaling back or stopping treatment. They then must decide in what particular order to taper or eliminate treatments. This includes minimizing unnecessary and ineffective medication (polypharmacy).

For patients who have borne a large burden of multiple drugs, frequent diagnostic tests, and numerous health appointments, making this transition is often a relief.

A palliative approach should be made much earlier in some patients**.**

[10-3] TALKING TO PATIENTS ABOUT DEATH: Editorial

Patients Need Truthful Information

People have an optimistic bias. This helps us to deny the inevitability of death.

A recent study of 1200 people with metastatic cancer reported that many felt their treatments world cure them. If patients have unrealistic expectations, we have a serious problem that we need to address.

Were the patients in the study not actually told their disease was incurable? Did they not choose to believe? Did they not fully understand?

Observational studies report that only 1/3 of doctors actually state the prognosis of an incurable disease at any time. Many patients facing death have not heard the word “hospice”.

Patients may not choose to believe. Many do not believe their treatments will not cure them.

It is possible to tell patients more effectively that they have a terminal illness. And to share information that would enable them to better plan the rest of their lives. This may take a series of conversations over time.

The prognosis should be stated early, advanced directives made, hospitalization avoided, and pain controlled.

Patients need truthful information in order to make good decisions.

[10-4] THE OVERUSE OF DIAGNOSTIC IMAGING AND THE CHOOSING WISELY INITIATIVE: Editorial

Twenty % To 50% of High-Tech Imaging Provides No Useful Information And May Be Unnecessary.

"Health in America costs too much."

One reason is overuse of diagnostic tests.

Imaging studies have grown faster than any other physician services in the Medicare population.

The authors of this article prepared a list of imaging tests that are overused. Duplication of tests is common, especially when there is a change in physicians or when the report of a prior test is not readily available.

Why is imaging overused?

Fear of malpractice suits leads to ordering tests for fear of overlooking something

Advanced imaging equipment installed in physician's offices. (Self referral)

Patient demand.

Radiologists themselves must acknowledge their potential conflict of interest.

The article cites 8 specific imaging tests the "Choosing Wisely" campaign lists may be overused.

[10-5] NO PROVEN BENEFIT IN DRUG TREATMENT FOR PATIENTS WITH MILD HYPERTENSION: Cochrane Review

Iconoclastic: For Continuing Debate. Will Physicians change treatment goals?

A Cochrane Review found that treating patients with stage 1 (mild) hypertension (140-159/90-100) had no benefit in patients who had no preexisting cardiovascular disease.

Data from 4 randomized controlled trials (drug treatment vs placebo) of patients with mild hypertension treated for 4 to 5 years did nor reduce total mortality, coronary heart disease, or stroke.

Until now, it had been assumed that treating mild hypertension is beneficial. Guidelines have been based on opinion and a combination of assumptions.

Some have criticized the study because of the relatively few subjects and for the short follow-up.

The JNC-7 National Committee still recommends lifestyle modification and drug treatment to achieve a BP below 140/90.

[11-1] LOW DOSE ASPIRIN FOR PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM: Randomized Controlled Trial The ASPIRIN Study

Beneficial in preventing recurrence of VTE and Major Vascular Events.

Patients who have had a first episode of VTE are at risk for recurrence when anticoagulants are stopped.

This RCT evaluated the efficacy of low-dose aspirin (vs placebo) in preventing recurrent VTE. Subjects had completed initial anticoagulation with heparin and warfarin (recommended for 6 to 12 months) after a first episode of unprovoked VTE.

They were then randomized to 1) enteric coated aspirin 100 mg daily, or 2) placebo. Patients were asked to take aspirin for a minimum of 2 years to a maximum of 4 years.

Recurrent VTE: 1)aspirin 14% of 411 vs 2) placebo 18% of 41 Hazard ratio = 0.74 (not significant).

However, a composite of VTE, myocardial infarction, stroke, and cardiovascular death occurred in 88 of the placebo group vs 62 in the aspirin group. (8.0% vs 5.2%) per year; Hazard ratio = 0.66—statistically significant.

Defined as this composite outcome, the net clinical benefit of aspirin was a 33% reduction. (9% per year in the placebo group vs 6% per year in the aspirin group.)

Clinically relevant bleeding (6 major) occurred in 8 placebo patients vs 14 in those assigned to aspirin (8 major). No statistically significant difference.

[11-2] ASPIRIN FOR DUAL PREVENTION OF VENOUS AND ARTERIAL THROMBOSIS: Editorial Commenting On the Preceding Article

Aspirin Reduces Major Vascular Events As Well As Recurrence Of VTE

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).

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

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.

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.

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.

[11-3] BENEFITS AND HARMS OF BREAST CANCER SCREENING: An Independent Review by an Expert Panel

Breast Cancer Screening Saves Lives. Overdiagnosis is common.

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 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.

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.

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.

Some screen –detected cancers 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.

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.

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.

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

A Modest But Statistically Significant Reduction In Total Cancer

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."

PHS II is a RCT evaluating the balance of risks and benefits of a daily multivitamin/mineral supplement (Centrum Silver) vs a placebo. The original study also examined efficacy of beta carotene, vitamin E, and vitamin C vs placebos. All were discontinued for lack of efficacy.

PHS II, begun in 1999, entered 14 641 male physicians age 50 and over (mean age at baseline 64). All were well nourished.

Participants took the multivitamin or a placebo daily through June 2011. (Median follow-up = 11 years.)

Multivitamin use and total cancer incidence during follow-up:

Overall (first cancer only):

Multivitamin 17.0 per 1000 person-years

Placebo 18.3 per 1000 person-years.

Men taking multivitamins (vs placebo) had a modest reduction in total cancer incidence (hazard ratio [HR] = 0.92)

There were no statistically significant reductions in individual site-specific cancers: colorectal, lung, and bladder.

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)

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.

11-5 MULTIVITAMINS IN THE PREVENTION OF CARDIOVASCULAR DISEASE IN MEN: The Physicians' Health Study II

No Beneficial Effect

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

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.

11-6 EFFECTIVENESS OF SULFONYLUREA AND METFORMIN MONOTHERAPY ON CARDIOVASCULAR EVENTS IN TYPE-2 DIABETES: Retrospective Cohort Study

Metformin Wins Again

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.

Composite outcome = hospitalization for MI, stroke, or death

Crude rates/ 1000 person-years (unadjusted):

	Metformin	Sulfonylurea
Composite outcome	10.4	18.2
CVD events (AMI and stroke)	8.2	13.5

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

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.

[11-7] TOPICAL IVERMECTIN LOTION FOR TREATMENT OF HEAD LICE: Randomized, double-blind Trial

Remarkably effective

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 1) ivermectin lotion or 2) vehicle control. The application was left on for at least 10 minutes before rinsing the head with water.

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%

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

P[11-8] CDC's UPDATE ON TREATMENT OF GONORRHEA: MMWR Report

To Keep One Step Ahead Of Resistance

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 2006-20011. And updates the CDC's recommendations for treatment.

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

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.)

12-1 PREVALENCE OF, AND RISK FACTORS FOR, AUTOPSY-DETERMINED ATHEROSCLEROSIS AMONG US SERVICE MEMBERS 2001-2011: Observational study

Begins At An Early Age. Progresses. Start Prevention Early

An early breakthrough in understanding the natural history of atherosclerotic heart disease was achieved in 1963, when the Armed Forces Institute of Pathology reported a 77% prevalence of coronary atherosclerosis (CAS) among US soldiers killed in the Korean war

This cross-sectional study determined the prevalence of atherosclerosis among US service members who died in Iraq and Afghanistan in support of combat operations or of unintentional injuries.

Included 3832 service members age 18 to 59, mean age 25, 98% white

The prevalence of CAS was 8.5%.

Older age, lower education level, higher BMI, hypertension and prior diagnosis of dyslipidemia were associated with higher prevalence of CAS.

Targets for further improvement remain. Health care systems should continue to help patients reduce CVD risk beginning in childhood and continuing throughout adult life.

About 1 in 50 of the young cohort had severe CAS. Prevalence increased dramatically between ages 20 and 40.

12-2 ASSOCIATION BETWEEN FISH CONSUMPTION, LONG CHAIN OMEGA-3 FATTY ACIDS, AND RISK OF CARDIOVASCULAR DISEASE: Systematic Review and Meta-analysis

Modest Benefit From Fatty Fish. No Benefit Non-fatty Fish or Supplements

Fish consumption is considered one of the key components of a cardio-protective diet. Current guidelines encourage consumption of a variety of fish, preferably oily fish, at least twice a week.

Overall, 38 unique studies met inclusion criteria and were included in the meta-analysis

The relative risk of CVD for fish intake of 2 to 4 savings per week vs 1 or fewer serving, was 0.94. And for 5 or more servings vs 1 or fewer servings a week was 0.88

In a dose-response meta-analysis, an increase of 2 servings per week of any fish was associated with a 4% reduced risk.

In a subset of studies (62 799 participants) the relative risk for white fish was 1.03 and for fatty fish was 0.84.

In twelve randomized trials (N = 62 040) of fish oil (omega-3) supplements, participants in the intervention arm on average consumed 1.8 g of O-3. daily usually as a capsule.

After an average of 3 years, those with prior cardiovascular disease, a total of 800 cerebrovascular events occurred in the intervention group vs 763 in the controls. (Pooled relative risk = 1.03.)

The corresponding pooled relative risk for primary prevention (2 trials) was 0.98 and for secondary prevention trials (10 studies) was 1.17.

There was no evidence of an inverse association from O-3 supplements in primary and secondary prevention.

12-3 USE OF HbA1c IN THE DIAGNOSIS OF DIABETES: Editorial

Avoids Need For Fasting. Lower Biological Variability. Good Predictor Of Future Complications Of Diabetes. Can Be Used To Diagnose Diabetes In Most People. Many Exceptions

In 2011, the WHO and a UK expert advisory group recommended that a HbA1c cut-point of 48 mmol/mol (6.5%) or more should be used for diagnosis.

Unless the diagnosis is clear, a second confirmatory measurement is needed as soon as possible. If this is less than 48, the diagnosis of diabetes should not be made.

Patients with a level of 42-47 should be considered at high risk for diabetes and provided with intensive lifestyle advice and retested annually.

Those with levels less than 42 may still be at high risk and should be treated according to clinical indications, with retesting at least every 3 years.

A major benefit of HbA1c is that it avoids the need for fasting.

The test should not be used to diagnose type 1 diabetes, in persons who are acutely ill, in children and young adults, in pregnant women, and in those who may have gestational diabetes. In these conditions, glucose values can change quickly, and HbA1c values may not accurately reflect glycemic exposure.

The recommendations aims to improve the detection of diabetes by making the process of testing easier.

12-4 COMPARATIVE EFFECTIVENESS OF WARFARIN AND NEW ORAL ANTICOAGULANTS FOR THE MANAGEMENT OF ATRIAL FIBRILLATION AND VENOUS THROMBOEMBOLISM: Systematic review

Patients Already Taking Warfarin And Have Good INR Control Have Little To Gain By Switching

Warfarin (W) has a narrow therapeutic window, and wide variability in anti-coagulant effect. It requires regular monitoring. In practice, 30% to 50% of the time the International Normalized Rations (INR) fall outside the therapeutic range.

Recently, new oral anticoagulants (NOACs) have emerged: 1) inhibitors of activated factor X (FXI; Rivaroxaban: *Xarelto* and Apixaban: *Eliquis*) and 2) direct thrombin inhibitors (DTI; Dabigatran: *Pradaxa*)

They have a more direct anticoagulant effect and eliminate the need for routine monitoring. But they lack specific antidotes to reverse bleeding. This is more worrisome when drug clearance may be prolonged as in the elderly and patients with renal impairment. They are expensive.

Extensive literature search found 6 good-quality randomized studies involving 61 424 patients. Three studies evaluated NOACs for chronic atrial fibrillation (AF); 3 evaluated treatment of venous thrombo-embolism (VTE). All studies compared NOACs vs adjusted-dose warfarin.

AF studies: (n = 50 579; mean age > 70)) compared apixaban, dabigatran, or rivaroxaban vs W for stroke prevention. Estimated absolute risk difference = 8 fewer deaths and 4 fewer hemorrhagic stroke for every 1000 patients treated with NOACs. Other outcomes did not differ significantly.

VTE studies: (n = 10 846) evaluated dabigatran or rivaroxaban vs W. Mean age = 50 t0 55. Mortality did not differ between NOACs and W.

NOACs were superior to W for some clinical outcomes, including mortality, in patients with AF. They were similar to W for primary outcomes in patients with VTE.

The effects on bleeding are complex. Fatal bleeding was significantly lower with FXIs than for W, but not for dabigatran vs W. In contrast, GI bleeding was increased in patients receiving NOACs vs W.

Follow-ups for NOACs are generally short-term. It is possible that additional adverse effects will emerge with more widespread and longer-duration use.

Dabigatran and FXIs have the advantage of more predictable anticoagulation, fewer drug interactions and equal or better mortality and vascular outcomes compared with W.

NOACs are a viable option for patients requiring long-term anticoagulation. Treatment benefits compared with W are small and depend on the control achieved by W.

There are no direct comparisons between individual NOACs.

NOACs should be used with caution in elderly patients and those with renal dysfunction. This would eliminate a host of patients.

Guidelines suggest that patients already taking W and maintaining good INR control have little to gain by switching to dabigatran.

12-5 THE RISK OF HIP FRACTURE AFTER INITIATING ANTIHYPERTENSIVE DRUGS IN THE ELDERLY

In the elderly, should drug treatment begin at half dose?

More than 50% of all adults over age 65 have hypertension. The likelihood of developing hypertensions during an average lifespan is more than 90%. Over 70% of newly diagnosed hypertensive patients over age 60 take anti-hypertension drugs.

Initiating anti-hypertension drugs in elderly patients can potentially cause orthostatic hypotension with associated symptoms such as dizziness, faintness, or syncope. This effect is acute, occurs over a relatively short time, and may lead to falls and hip fractures.

This study examined the association between the initiation of anti-hypertension drugs and immediate risk of hip fracture in a large population of community-dwelling elderly persons.

There were 301 591 newly treated elderly hypertensive patients (mean age 81; 81% female; 6% had previous hip fracture). All were living in the community.

Those who started an anti-hypertension drug had a 43% increased risk of hip fracture in the first 45 days of treatment compared with the control periods.

The incident rate-ratio of hip fractures were generally consistent among 5 different classes of drug. But only ACE and beta-blockers reached statistical significance.

Further subdivision of the post-exposure risk period into 0 to 14 days and 15 to 44 days indicated that elderly people who initiated any anti-hypertension drug for treatment of hypertension had a 54% increase in hip fracture during the 15 to 44 day period. This increased trend was observed for most drug classes. It was statistically significant for ACE and beta-blockers.

In this study, use of any anti-hypertension drug was associated with increased risk of hip fracture during the first 45 days of treatment, especially in days 15 to 44.

The risk of hypo-tension related to ACE inhibitors has been related to venodilation and venues pooling with a fall in cardiac output. Beta-blockers cause bradycardia and decrease cardiac output and also cause confusion, which may result in falls. Thiazides decrease plasma and extra cellular fluid volume.

Anti-hypertension drugs were associated with immediate increased hip fractures during the initiating of treatment for hypertensive community dwelling elderly patients.

Caution is advised when initiating these drugs in the elderly.

12-6 ASSOCIATION OF AN INTENSIVE LIFESTYLE INTERVENTION WITH REMISSION OF TYPE-2 DIABETES: Randomized, Controlled Trial

Can Go Into Remission—Rarely And With Difficulty

Traditionally diabetes has been considered a progressive, incurable disease. This notion is supported by the strong association with genetics and family history, the high prevalence of microvascular complications, and the loss of beta-cell mass and function, frequently present at diagnosis.

Randomized, controlled trial (2001-2004; last follow-up 2008) compared an intensive lifestyle intervention (ILI) with a diabetes support and education (DSE) control. The ILI included weekly group and individual counseling for 6 months followed by 2 sessions per month and regular refresher group follow-up in years 2 to 4.

Entered and followed 4503 US adults with DM-2 and a body mass index of 25 and higher. DM-2 was defined as a fasting plasma glucose of at least 126 mg/dL or HbA1c of at least 6.5%.

Main outcome—partial or complete remission of diabetes. Partial remission of diabetes was defined as a transition from meeting criteria for diabetes to a pre-diabetes level of glycemic (fasting plasma glucose 100-125, and HbA1c 5.7% to 6.4%) with no anti-hyperglycemic medication. Complete remission was a transition to full normalization of glucose (fasting < 100; HbA1c < 5.7%).

The sample was predominantly middle-aged, and of diverse race/ethnicity education level and medication status. None had undergone bariartic surgery.

At year 1, participants in the ILI group lost more weight (-8.6% vs 0.7%) and at year 4 (-4.7% vs -0.8% %). And had greater increases in fitness at year 1 (21% vs 5.3%) and at year 4 (4.9% vs -1.5%).

Absolute prevalence of complete remission:

	Year 1	Year 4
ILI	1.3%	0.7%
DSE	0.1%	0.2%

Among those who had a remission in the ILI group, about 1/3 returned to clinical diabetes status each year.

Any remission during the first year was significantly associated with fewer years since diabetes diagnosis, lower BMI, lower baseline HbA1c, not taking insulin, a greater 1-year weight loss, and strong fitness improvement.

Complete remission was rare. Likelihood of remission was greater in the first year.

Remission was notably higher in those with substantial weight loss, fitness improvement, shorter duration of diabetes, or lower HbA1c at entry.

Bariatric surgery has been associated with substantially greater weight loss and greater rates of remission of diabetes than with this study