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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
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HIGHLIGHTS AND *EDITORIAL COMMENTS* DECEMBER 2010

"Show Great Promise"

12-1 THERAPEUTIC POTENTIAL OF ORAL FACTOR Xa INHIBITORS

Two studies in this issue of NEJM affirm the efficacy and safety of the new oral factor Xa inhibitors, rivaroxaban and apixaban in the management of thromboembolic disease.

One study compared enoxaparin (a low molecular weight heparin) followed by warfarin, with rivaroxaban. Treatment was continued for 3 to 6 months in patients with acute symptomatic deep vein thrombosis (DVT). Rivaroxaban had non-inferior efficacy with respect to recurrent DVT, with similar rates of hemorrhage. A continuing part of the study compared rivaroxaban with placebo for up to 12 months. This confirms the continuing risk of DVT after initial treatment, and lends support to extending the duration of anticoagulation therapy, particularly given the low rates of major bleeding with rivaroxaban (less than 1 in 100).

The second study concerned patients undergoing total hip replacement. Participants were randomized to apixaban orally twice daily, or enoxaparin (a low molecular weight heparin) subcutaneously once daily. Treatment was continued for 35 days after surgery. Apixaban was associated with lower rates of venous thrombosis without any increase in bleeding.

The oral factor Xa inhibitors represent a major advance in prevention and treatment of thromboembolic disease. Faction Xa is situated at the junction of the intrinsic and extrinsic coagulation pathways proximal to thrombin. As compared with warfarin, these new compounds will prove safer in clinical practice. They are highly specific, administered in fixed doses, do not interact with diet,, and have fewer interactions with other drugs. Their rapid onset of action obviates the need for heparin at the beginning of treatment. The shorter half-life may improve their overall safety profile, but also may result in increased risks of recurrent VTE if doses are missed.

Subjects in clinical trials are usually younger, have less comorbidity, are likely to be more adherent to taking the drug, and are specifically selected to have less risk of bleeding than real-life patients. Both the risk of hemorrhage and thrombosis increase substantially with age. This may limit generalizability.

The factor Xa inhibitors show great promise.

Big Pharma is hot on the trail after these drugs. It will be interesting to find out which one (or ones) will win. They will have to compete with the direct thrombin *inhibitors dabigatran. (See Practical*

Pointers September 2009 [9-4]). Factor Xa inhibitors are a long-awaited advance. They have many advantages over heparin-warfarin, but the risk of bleeding persists.

VT Is Chronic Disease. How Do We Prevent Recurrence?

12-2 RISK ASSESSMENT FOR RECURRENT VENOUS THROMBOSIS

Venous thrombosis (**VT**) is common, with an incidence of about one case in 1000 person-years. In one third of patients deep VT is complicated by pulmonary embolism **(PE**). Short term mortality from PE is high, and depends on age and presence of underlying co-morbidities such as cancer and cardio-pulmonary disease.

VT is a chronic disease. It often recurs. Risk of recurrence is about 20-25% within 5 years, and is higher in patients with unprovoked VT. Risk of recurrence depends mainly on presence or absence of acquired and congenital risk factors, and may vary substantially between patients. A systematic review reported the case fatality rate of recurrent venous thromboembolism (**VTE**) was 3.6%

VTE risk assessment is of practical importance. Patients at highest risk of recurrence will benefit from long-term anticoagulation, whereas patients at low risk will be exposed unnecessarily to bleeding.

This review discusses different approaches to assessment of recurrence of VTE in patients with VT of the lower extremity or PE after completion of anticoagulant treatment. It is based on an extensive search of the literature. (97 citations)

A. Clinical features associated with high risk of recurrence of VT:

Unprovoked VT: Risk of recurrence is especially high when the initial VT is unprovoked (ie, the event occurred in the absence of temporary risk factors such as surgery, trauma, pregnancy, or use of female hormones.) Risk of recurrence over 5 years has been as high as 25% in patients with unprovoked VT or PE. Risk of recurrence declines when the temporary cause (eg, estrogen) is removed.

Estrogen use: Women who continue hormone therapy after VT are at high risk of recurrence. Risk of recurrence is less when this temporary cause of VT is removed.

Deep VT: One study reported that all patients with a recurrence had initial proximal deep VT. None with distal (calf) VT had a recurrence. The low rate of recurrence in patients with isolated calf VT has been confirmed by several other observational studies.

Pulmonary embolism. Data from one study showed that the risk of recurrence is more than two-fold higher in patients with symptomatic PE than in patients with asymptomatic PE.

Sex: Risk of recurrent VT is higher in males-- a nearly 4 -fold increase compared with females.

Cancer: Risk of recurrence in patients with cancer is regarded as high.

Residual VT: Recurrence has been reported higher in those with residual VT than in those without.

Weight: The effect of bodyweight on recurrence is nearly linear, so even modest weight loss may reduce risk.

Recurrent VT: Repeated episodes (more than 2 episodes) of VT predisposes to recurrence. It increases the risk of development of post-thrombotic syndrome.

Family history: Investigators who assessed the association between a positive family history of VT and risk of recurrence reported that the family history did not predict recurrence.

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B. Laboratory markers associated with increased risk of recurrent VT:

Includes high concentrations of fibrinogen, factor VIII , and factor IX; factor V Leiden; hyperhomocysteinemia; and prothrombin mutations; increased generation of thrombin; partial deficiency of antithrombin, protein C and protein S, and phospholipid antibodies.

C. Relevance of laboratory screening:

"Abnormalities that are associated with an increased risk of venous thrombosis, and that are detectable with laboratory techniques, can be established in more than 50% of patients with a first unprovoked venous thrombosis." Identification of thrombophilic defects to improve patient care can be a tempting prospect. Screening has been advocated repeatedly, and is now done on a routine basis in many institutions. However-- " Our review shows that these tests have, at most, a small effect on the risk of recurrence." Screening is indicated only when individuals with increased risk can be identified and there is an effective treatment with a positive benefit-risk balance.

"There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event nor the prevention of recurrence."

D. D-dimer[1]

The D-dimer test has a high negative predictive value.[2] It has become an integral part of many diagnostic algorithms to exclude acute VT and PE. The test can be used to separate patients into groups of high or low risk of recurrent VT.

D-dimer concentrations measured one month after discontinuation of oral anticoagulants have a high negative predictive value for recurrence irrespective of the presence or absence of hereditary thrombophilia.

Patients with an especially low risk of recurrence can be identified with lower cutoff concentrations of D-dimer. Patients with a first unprovoked VT or PE and concentrations less than 250 pg/mL have a 60% lower risk of recurrence rate than those with concentrations more than 250.

In one study, which measured D-dimer anticoagulation, rather than after discontinuation, a 250 ng/mL cutoff was predictive of a low risk of recurrence in women.

Two systematic reviews of D-dimer have assessed risk stratification. D-dimer is the only laboratory criterion for thrombophilia that has been used to establish the duration of anticoagulation treatment in a large randomized setting. Patients with low concentrations after withdrawal of anticoagulation had a low risk of recurrence (4 per 100 person-years). Persons with high levels who stopped anticoagulation after 6 months had an increased risk of recurrence (10 per 100 person-years) compared with those who received anticoagulation for more than 6 months.

Repeated testing of D-dimer after withdrawal of anticoagulation following a first unprovoked VT could help establish the optimum duration of treatment.

E. Clinical characteristics of patients and laboratory markers:

A prospective cohort study of over 900 subjects with unprovoked VT or PE were followed for a median of 43 months after discontinuation of anticoagulation. Many possible causes of recurrence were included. Only the patient's sex, thrombosis location, and D-dimer were related to increased risk of recurrence.

I believe this is a reasonable assessment of the state of the art regarding VTE. Many points are still not clear. Deciding duration of anticoagulant therapy still requires clinical judgment. D-dimer is a big help.

The reviewer's comment on screening tests is apt. There is no reason to screen for a disease if nothing can be done to treat or change risk. However, some patients may wish to know if they carry a heritable defect in the clotting mechanism.

I wondered why males are more prone to recurrence. Females carry the estrogen.

The new anticoagulants (factor Xa inhibitors and thrombin inhibitors) will, hopefully, bring major improvements.

Strongly Associated With Incident HF And CV Death Independent Of Standard Risk Variables

12-3 ASSOCIATION OF SERIAL MEASURES OF CARDIAC TROPONIN T USING A SENSITIVE ASSAY WITH INCIDENT HEART FAILURE AND CARDIOVASCULAR MORTALITY IN OLDER ADULTS.

These investigators hypothesized that, in community-dwelling older patients without a prior diagnosis of heart failure (**HF**), measurable high sensitivity cardiac troponin T **(hscTnT)** would be common, and higher concentrations would be associated with greater risk of new onset HF and cardiovascular death (**CV death)** independent of traditional risk factors. Serial measurements over time could reflect a change in risk.

A nation-wide prospective cohort study included 4221 community-dwelling persons age 65 and older. None had prior HF. Main outcome measure = new onset HF and CV death through 2008 with respect to hscTnT concentrations. Measured hscTnT at baseline (1989-1990) and again after 2 to 3 years. The analytical measurement of hscTnT ranges from 3.0 to 10 000 pg/mL

The value at the 99th percentile cutoff in a healthy reference population is 13.5 pg/mL.

Divided participants into 5 equal size categories according to baseline:

Less than 3.0 pg/mL (undetectable); 3.0 to 5.44; 5.45 to 8.16; 8.17 to 12.94; > 12.94

Determined cumulative incidence of HF and CV death for each category over 18 years.

At baseline, higher hscTnT was related to multiple traditional risk factors: age, known CHD, depressed kidney function, ECG abnormalities, abnormal ejection fraction, and increased ventricular mass.

If hscTnT remained undetectable 2 to 3 years after baseline, risk was lower than if it became detectable.

If hscTnT was *detectable* at baseline and *increased* over time, risks *increased*. If hscTnT *decreased* over time, risks *decreased*.

Lower concentrations of hscTnT were associated with a gradient of risk for new-onset HF and CV death in ambulatory persons over age 65, independent of clinical variables. Low hscTnT concentrations frequently change over time. The changes in risk of HF and CV death are concordant with the direction of change.

Concentrations of hscTnT were detectable and of prognostic value in nearly 2/3 of a large geographically and ethnically diverse, stable, but at-risk population of ambulatory older adults without a prior diagnosis of HF.

Baseline levels of hscTnT, below the levels that would be expected to be detected with conventional assays, strongly associate with incident HF and CV death, independent of standard risk prediction variables. Changes in hscTnT determined during 2 to 3 years in subjects who remained free of HF, even when occurring in concentrations well under the 99th percentile of healthy young blood donors, are prognostically significant.

The markedly increased range of measures of hscTnT enables estimation of a gradient of risk across the majority of older individuals, including those with absence of clinical risk factors (other than age), and also permits examination of the significance of changing hscTnT.

Conclusion: Detectable hscTnT levels were present in the majority of community-dwelling older persons without known heart failure. Higher concentrations--within normal range established for younger persons -- reflect a great burden of cardiovascular risk. Changes in hscTnT levels over time were common and corresponded with a change in HF and CV death.

I hesitated to include this article because it is not yet a practical point for primary care. It is provocative, and, I believe, carries promise for the future.

The hscTnT test may lead to increasing sensitivity in detecting risk. It is a more sensitive marker than any risk factor now in use. It is more specific to the heart than C-reactive protein. It may turn out to be relatively simple and inexpensive.

What should the primary care clinician do when the test shows increased risk?
When patients are informed about increased risk, some (perhaps a few) may increase compliance with a more healthy lifestyle. Some may benefit from added medication. I doubt, however, if many would benefit beyond the advice given to patients on the basis of standard risk factors. Poor compliance remains a roadblock. Do we need another risk factor?

The statement that exercise increases the hscTnT levels in patients with ischemic heart disease raises the point: Can hscTnT be used as an inexpensive marker of exercise-induced ischemia?

Extending The Validity of BMI as A Prediction Tool

12-4 BODY MASS INDEX AND MORTALITY AMONG 1.4 MILLION WHITE ADULTS

Studies vary in estimating the strength of the relationship between high BMI and all-cause mortality. Inconsistencies could be due to confounding by tobacco use and disease-related weight loss. Differences in age and length of follow-up vary.

Pooled analyses provide the opportunity to examine these issues in a large diverse population with use of standard analytic approaches across studies.

This study examined the relationship between BMI and all-cause mortality in a pooled analysis of 19 prospective studies of predominantly white (non-Hispanic) adults (n = 1.46 million). The study

included 160 087 deaths. It examined the extent to which the relationship between BMI and all-cause mortality varied with smoking and prevalent disease.

The principal objectives were to assess the optimal BMI range and to provide stable estimates of the risks associated with being overweight, (BMI 25.0 to 29.9), obese (BMI 30.0 to 39.9), and morbidly obese (BMI > 40) with minimal confounding due to smoking and prevalent disease.

Predefined BMI levels; 15.0 to 18.4; 18.5 to 19.9; 20.0 to 22.4; 22.5 to 24.9; 25.0 to 27.4; 27.5 to 29.9; 30.0 to 34.9; 35.0 to 39.9; and 40.0 to 49.9.

Defined BMI of 22.5 to 24.9 as the reference category. (Hazard ratio [**HR**] = 1.00)

The age-standardized rate of death from any cause was generally lowest among participants with a BMI 22.5 to 24.9 (the reference group). The HR increased with progressively higher and lower BMI.

There was a contrast in the pattern between healthy subjects who had never smoked and the pattern observed when all subjects were included in the analysis. The nadir of the curve flattened and expanded to the BMI range of 20.0 to 24.5 when the analysis was restricted to healthy participants who never smoked.

Adjustments for alcohol, physical activity, education, and marital status slightly reduced the HR estimates for those with a BMI 25.0 and higher.

When men and women were combined to increase statistical power, the nadir of the HRs remained at 1.00 for BMI 20.0 to 25.5.

The increased HRs for those with BMIs under 20.0, as compared with 22.5 to 24.9, were reduced in those reporting higher-level of physical activity. (Being lean and fit.)

Both overweight (and possibly underweight) were associated with increased all-cause mortality in participant who never smoked and did not have cancer or heart disease at baseline.

These associations were strongest among those whose BMI was ascertained before age 50.

Among healthy persons who had never smoked, the estimated HR for all-cause mortality per 5-unit increase in BMI rose by 1.32

Smoking and preexisting conditions cause weight loss. They are powerful confounders. Analyses that include them lack validity.

The association between underweight and increased mortality was probably, at least in part, due to preexisting disease.

Conclusion: For non-Hispanic white persons, both overweight and obesity are associated with increased all-cause mortality, and underweight may be as well. All-cause mortality is generally lowest within the BMIs range of 20.0 to 24.9. These results are most relevant to white persons living in affluent societies.

BMI is calculated by dividing the weight in kilograms by the height in meters squares.

Several years ago, people were exhorted to: "Know your cholesterol". A good update would be: "Know your BMI". Obviously, overweight and obesity are major public health problems, and knowing that the patient's BMI is high is a major application of primary care.

This information is not new. The study does advance the validity of BMI as a prediction tool, especially since the authors tried to eliminate confounding due to smoking and preexisting disease.

BMI is a valid predictor only for those who, at baseline, are healthy and do not smoke. Smoking and preexisting disease are major confounders.

BMI is a more meaningful predictor for younger persons.

Younger healthy persons who do not smoke can be told that, if their BMI reaches 30, their risk of death is about a third higher than those who are not overweight. If it reaches 35, the risk is increased to two thirds.

The goal should be to maintain BMI between 20 and 25.

Being underweight (BMI under 20) is not necessarily a disadvantage, especially if the individual does not smoke, maintains fitness, and has no underlying disease. The risk of underweight is not as high as the risk of overweight and obesity.

12-5 ANALGESIC USE IN THE ELDERLY

Pain is widespread among the general public. It is difficult to treat to the satisfaction of many patients. A recent study from Sweden found the overall presence of pain was 46%, with prevalence increasing to 55% in those over age 70.

About half of patients with chronic pain had not received a formal diagnosis or known the reason for the pain.

In response to perceived inadequacies of pain management, there are efforts to focus more on the treatment of pain and less on the cause. Many clinics now routinely ascertain pain scores along with other vital signs, regardless of the nature of a patient's visit.

The California legislature had enacted several laws stating in patient's bill of rights: "A patient who suffers from severe chronic pain has the option to choose opioid medications, and the patient's physician may refuse to prescribe opioids. However, that physicians shall inform the patient that there are physicians who specialize in the treatment of pain with methods that include use of opioids."

There are few novel treatments to offer for treatment of pain. Most new analgesics are derivatives or reformations of opioids or aspirin. The development of coxibs marked attempts to develop a somewhat novel class of analgesics. They were met with intense scrutiny and some were removed from the market following an increase in cardiovascular mortality.

Prescribing habits of US physicians for chronic pain has changed in recent years. There has been an increase in prescriptions for opioids for non-cancer pain, especially for women over age 65 with chronic pain. A 2005 study reported that 9% of females over 65 with chronic pain used opioids for more than 90 days, a 35% increase from 2000. Use of opioids in this population is problematic given that users are prone to falls, cognitive impairment, and respiratory depression.

A study in this issue of Archives[1] was based on a large administrative claim database. The cohort consisted of patients diagnosed with osteoarthritis or rheumatic pain who received new prescriptions for an analgesic. Patients were divided into 3 groups according to the analgesic class--NSAIDS, coxibs, and opioids. Those with cancer and in Hospice care were excluded. They were well matched for most baseline characteristics.

The authors found substantial increases in morbidity and mortality in patients who used opioids. Fractures of the hip and pelvis occurred three times as frequently in this group. Humerus fractures were 9 times more frequent. Total fractures were 5 times more frequent than in patients using NSAIDs. There was also an increase in myocardial infarction, a risk that surpassed the risk of MI in users of coxibs.

There was also a statistically significant increase in all-cause mortality, compared with NSAIDs. (Hazard ratio = 1.87) There was no significant difference in mortality between users of coxibs and other NSAIDs.

The investigators did not distinguish between types of opioid used (eg, methadone vs codeine), its dose, or its duration.

Some physicians may prescribe opioids because they perceive them to be less toxic to the gi tract and kidney than NSAIDs and less toxic to the cardiovascular system than coxibs. These assumptions may no longer hold up.

Patients with rheumatoid arthritis make up about 10% of patients with chronic musculo-skeletal pain. Much can be done to relieve pain by use of conventional disease -modifying anti-rheumatic drugs. The chronic pain or knee osteoarthritis can be relieved by non-pharmacological treatment: exercise, weight loss, and physical therapy as well as arthroplasty.

Despite increased awareness of the dangers posed by opioids and other analgesics, the FDA recognizes that the extensive prescribing of these medications will continue, and warrants increased

government regulation that we hope balances risk management with the need for adequate access to pain management.

The clinician (*and patient)* will remain responsible for balancing the risks and benefits when choosing the dose and class of analgesic.

Archives Internal Medicine December 13/27 2010; 170: 1976-78 Editorial by Jonathan Graf, University of California, San Francisco.

1 "The Comparative Safety of Analgesics in Older Adults with Arthritis" Annals Internal Medicine December 13/27, 2010:170: 1979-86. Original investigation, first author Daniel H Solomon, Brigham and Women's Hospital, Boston, Mass

This study examined the comparative safety of non-selective NSAIDs (nsNAIDs), selective cyclo-oxygenase 2 inhibitors, and opioids. It was based on Medicare records 1999 to 2005.

After propensity score matching at baseline, the 3 analgesic cohorts were well balanced of baseline covariates. Mean age was 80; 85% female;

Incident rates per 1000 person-years:

	NSAIDs	HR*	Coxibs	HR	Opioids	HR
Myocardial infarction	14	1.00	20	1.63	29	2.25
Heart failure	30	1.00	34	1.26	45	1.63
GI bleeding	21	1.00	12	0.60	21	1.07
Fracture	28	1.00	19	0.96	101	4.47
Al-cause mortality	48	1.oo	47	1.16	75	1.87
Falls	26	1.oo	18	0.78	41	1.64

(* Referent Hazard Ratio)

Conclusion : The safety of analgesics varies, depending on the safety event studied. Opioid use exhibits an increased risk of many safety events compared with NSAIDs.

Editors and investigators continue to stress hazard ratios when comparing safety of one drug with another. The introductory abstract often cite hazard rations (HR) along with confidence intervals, and, sometimes, P values. This jumbles the abstract and, in my view, often makes it unreadable.

HRs may give the patients an indication that one drug is safer than another in some respects. But this information does not allow patients (or clinicians) to make a judgment about accepting or rejecting the risk. Acceptance of risk depends on how great the benefit.

In this study, fractures occurred in 28 of 1000 patients each year vs 101 per 1000 each year for opioids--an increase of about 7 in 100 each year for those taking opioids vs NSAIDs.

I feel sure that some patients would be willing to accept this degree of risk to obtain greater relief from pain.

As usual, patients should be informed so they may make personal decisions.

ABSTRACTS DECEMBER 2010

"Show Great Promise"

12-1 THERAPEUTIC POTENTIAL OF ORAL FACTOR Xa INHIBITORS

Venous thromboembolism (**VTE**) is the third leading cause of cardiovascular death, after myocardial infarction and stroke.

Total hip and knee arthroplasty are procedures with the highest risk of VTE.

Two studies in this issue of NEJM [1,2] affirm the efficacy and safety of new oral factor Xa inhibitors, rivaroxaban and apixaban in the management of VTE.

The first study concerned acute symptomatic deep venous thrombosis. Rivaroxaban was compared with enoxaparin (a low-molecular weight heparin) followed by warfarin. Treatment was continued for 3 to 6 months. Rivaroxaban had non-inferior efficacy in prevention of recurrent VTE, with similar rates of hemorrhage. This study confirms the continuing risk of VTE after initial treatment, and lends support to extending the duration of anticoagulant therapy for venous thrombosis, particularly given the low rates of major bleeding with rivaroxaban (less than 1 in 100).

The second study concerned patients undergoing total hip replacement. Participants were randomized to apixaban orally twice daily or enoxaparin subcutaneously once daily. Treatment continued for 35 days after surgery. Apizaban was associated with lower risk of VTE without any increase in bleeding.

Subjects in clinical trials are usually younger, have less comorbidity, are likely to be more adherent to taking the drugs, and are specifically selected as having less risk for bleeding than real-life patients. Both the risk of hemorrhage and thrombosis increase substantially with age. This may limit generalizability

Currently, millions of people receive no therapy for VTE, or receive therapy that has not been proven to be effective. Many lack access to monitoring of warfarin.

The oral factor Xa inhibitors represent a major advance in prevention and treatment of thromboembolic disease. Factor Xa is strategically positioned at the junction of the intrinsic and extrinsic coagulation pathways, proximal to thrombin. As compared with warfarin, these new compounds will prove safer in clinical practice. They are highly specific, administered in a fixed dose, do not interact with diet, and have fewer interactions with other drugs. Half-life is shorter than warfarin (9 to 12 hours vs 20 and above). Their rapid onset of action obviates need for heparin at the beginning of

treatment. The shorter half-life may increase their overall safety profile, but may result in increasing risks of VTE if doses are missed.

There are 3 other factor Xa inhibitors in development. They have multiple pathways of elimination from the body, including variation in excretion by the kidney. They are metabolized differently by the liver. All are undergoing phase 3 trials in prevention of embolism due to atrial fibrillation.

Concomitant antiplatelet therapy is discontinued and considered contraindicated.

Factor Xa inhibitors show great promise.

NEJM December 23, 2010; 363: 2559-61 Editorial by Elaine M Hylek, Boston University School of Medicine, Editorial by Elaine M Hylek, Boston University School of Medicine

1 "Oral Rivaroxaban for Symptomatic Venous Thromboembolism" NEJM December 20, 2010; 363: 2499-2510 Original investigation by the EINSTEIN investigators, Academic Medical Center, Amsterdam, Netherlands. Funded by Bayer Schering Pharma and Ortho-McNeil.

This open-label randomized non-inferiority study in patients with acute symptomatic deep venous thrombosis (DVT) consisted of 2 parts:

A. Acute DVT study:

Entered 3442 patients with acute symptomatic deep vein thrombosis. Compared oral rivaroxaban 15 mg twice daily with subcutaneous enoxaparin given for 3 weeks. This was followed by rivaroxaban 20 mg once daily for up to 12 months, compared with oral vitamin K anticoagulants (eg, warfarin).

Results:	Rivaroxaban	Vitamin K antagonist
Recurrent DVT	2.1%	3.9%
(Absolute difference = 0.9%; about one in 100 favoring rivaroxaban,)		
Major bleeding	0.8%	1.2%
Death from bleeding	1.2%	0.3%
(About 1 in 100 due to rivaroxaban.)		

B. Continued treatment study:

Followed completion of the acute DVT study. Randomized 1198 patients to rivaroxaban 20 mg daily vs placebo for an additional 12 months.

Results:	Rivaroxaban	Vitamin K antagonist
Recurrent DVT	1.3%	7.1%
(Absolute difference favoring rivaroxaban by 5.8%; one in 20)		
Major bleeding	0.7%	0

Clinically relevant bleeding	5,4%	1.2%
(Absolute difference favoring placebo; one in 25)		

Conclusion: Rivaroxaban offers a simple single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-risk profile of anticoagulation.

2. "Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement" NEJM December 23, 2010; 363:2487-98 first author Michael Rud Lassen, University of Copenhagen , Denmark. Funded by Bristol-Myers Squibb and Pfizer.

This double-blind multicenter trial randomized 5407 patients (mean age 60) undergoing hip replacement to: 1) oral apixaban of 2) subcutaneous enoxaparin for 35 days after hip replacement. After exclusions, 3860 were included in the primary efficacy analysis. Performed bilateral venographic studies at the end of the period.

The primary efficacy outcome was a composite of deep vein thrombosis, non-fatal pulmonary embolism, and death from any cause during the treatment. period

Results	Apixaban	Enoxaparin
Primary efficacy	1.4%	3.9%
(Absolute difference = 2.5%; one in 40 favoring apixaban)		
Major and clinically significant		
bleeding events	4.8%	5.0%
(Absolute difference = 0.2%; one in 500 favoring placebo)		

Thirteen of 22 major bleeding events in the apixaban group occurred before the first dose had been given, and were likely due to surgery. Likewise, 7 of 18 major bleeding events in the enoxaparin group occurred before the first postoperative dose.

Conclusion: Apixaban, after hip replacement, compared with enoxaparin, was associated with lower rates of VTE without increased bleeding.

VT Is Chronic Disease. How Do We Prevent Recurrence?

12-2 RISK ASSESSMENT FOR RECURRENT VENOUS THROMBOSIS

Venous thrombosis (**VT**) is common, with an incidence of about one case in 1000 person-years. In one third of patients deep VT is complicated by pulmonary embolism (**PE**). Short term mortality from PE is high, and depends on age and presence of underlying co-morbidities such as cancer and cardio-pulmonary disease.

VT is a chronic disease. It often recurs. Risk of recurrence is about 20-25% within 5 years, and is higher in patients with unprovoked VT. Risk of recurrence depends mainly on presence or absence of acquired and congenital risk factors, and may vary substantially between patients. A systematic review reported the case fatality rate of recurrent venous thromboembolism (**VTE**) was 3.6%

Standard therapy has been heparin followed by vitamin K antagonists (eg, warfarin) for several months, a regimen which almost always prevents recurrence as long as continued, albeit at the risk of bleeding. Major bleeding occurs in about 3% per year in clinical trials, and is higher in routine practice.

VTE risk assessment is of practical importance. Patients at highest risk of recurrence will benefit from long-term anticoagulation, whereas patients at low risk will be exposed unnecessarily to bleeding.

This review discusses different approaches to assessment of recurrence of VTE in patients with VT of the lower extremity or PE after completion of anticoagulant treatment. It is based on an extensive search of the literature. (97 citations)

Risk factors for recurrent VTE:

Until the late 1980s risk of recurrence of VT was estimated on the basis of only a few patient characteristics such as presence or absence of triggering factors: concurrent PE, or previous VT, and with a few laboratory tests such as measurement of protein C and protein S. The natural history of VTE was poorly understood, and many risk factors were yet to be discovered. Appropriate clinical studies were absent.

From then on, high quality studies and advances in laboratory techniques led to discovery of many risk factors of both a first and recurrent VT and to the perception that VT is a chronic disease with a high recurrence rate.

Clinical features associated with high risk of recurrence of VT:

Unprovoked VT: Risk of recurrence is especially high when the initial VT is unprovoked (ie, the event occurred in the absence of temporary risk factors such as surgery, trauma, pregnancy, or use of female hormones). Risk of recurrence over 5 years has been as high as 25% in patients with unprovoked VT or PE. Risk of recurrence declines when the temporary cause (eg, estrogen) is removed.

Estrogen use: Women who continue hormone therapy after VT are at high risk of recurrence. Risk of recurrence is less when this temporary cause of VT is removed.

Deep VT: One study reported that all patients with a recurrence had initial proximal (thigh) deep VT. None with distal (calf) VT had a recurrence. The low rate of recurrence in patients with isolated calf VT has been confirmed by several other observational studies. Recurrent ipsilateral deep VT increases

the likelihood of development of post- thrombotic syndrome, which is associated with increased risk of recurrence of VT.

Pulmonary embolism. Data from one study showed that the risk of recurrence is more than two-fold higher in patients with symptomatic PE than in patients with asymptomatic PE.

Sex: Risk of recurrent VT is higher in males-- a nearly 4 -fold increase compared with females.

Cancer: Risk of recurrence in patients with cancer is regarded as high.

Residual VT: Recurrence has been reported higher in those with residual VT than in those without.

Weight: The effect of bodyweight on recurrence is nearly linear, so even modest weight loss may reduce risk.

Antiphospholipid syndrome: Risk of recurrence of VT in patients with antiphospholipid syndrome seems to be higher after venous thrombosis than after arterial thrombosis.

Vena cava filter: Presence of a vena cava filter raises risk of recurrence up to 1.5-fold after 8 years. Thrombosis at the site has been reported in 10% of patients.

Recurrent VT: Repeated episodes (more than 2 episodes) of VT predisposes to recurrence. It increases the risk of development of post-thrombotic syndrome.

Family history: Investigators who assessed the association between a positive family history of VT and risk of recurrence reported that the family history did <u>not</u> predict recurrence.

All of these factors are of high clinical relevance.

Laboratory markers associated with increased risk of recurrent VT:

There is a strong evidence for increased risk of recurrence for:

- High concentration of fibrinogen, factor VIII , and factor IX
- Hyperhomocysteinemia
- Factor V Leiden
- Prothrombin mutation
- Increased generation of thrombin

Weaker evidence for:

- Partial deficiency of antithrombin, protein C, protein S
- Phospholipid antibodies

Relevance of laboratory screening:

"Abnormalities that are associated with an increased risk of venous thrombosis, and that are detectable with laboratory techniques, can be established in more than 50% of patients with a first

unprovoked venous thrombosis." Identification of thrombophilic defects to improve patient care can be a tempting prospect. Screening has been advocated repeatedly, and is now done on a routine basis in many institutions. However-- " Our review shows that these tests have, at most, a small effect on the risk of recurrence. Screening is indicated only when individuals with increased risk can be identified and there is an effective treatment with a positive benefit-risk balance.

"There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event, nor the prevention of recurrence. Results from a prospective cohort study of patients after a first episode of venous thrombosis, showed that tests for heritable thrombophilia are unable to predict recurrences in the first 2 years after stopping anticoagulation treatment.

"Data from another study showed that, in patients with a first deep venous thrombosis, the risk of recurrence was much the same in patients with and those without a thrombophilic defect. The same investigators also showed (in a case-control study) that testing for inherited thrombophilia was not associated with a reduced rate of recurrence of venous thrombosis.

"Routine screening for single laboratory markers should not be done in patients with a first venous thrombosis for various reasons:

> "Venous thrombosis has many causes, and many patients have more than one abnormality, and the effect of combined defects on risk of recurrence is not known.
>
> "Determination of laboratory risk factors can be costly, not standardized, and too elaborate for routine use.
>
> "Routine testing of patients might lead to overtreatment, or cause unnecessary concern because there are no clinical consequences of a positive result."

D-dimer[1]

The D-dimer test has a high negative predictive value[2] It has become an integral part of many diagnostic algorithms to exclude acute VT and PE. The test can be used to separate patients into groups of high or low risk of recurrent VT.

D-dimer concentrations measured one month after discontinuation of oral anticoagulants have a high negative predictive value for recurrence irrespective of the presence or absence of hereditary thrombophilia.

Patients with an especially low risk of recurrence can be identified with lower cutoff concentrations of D-dimer. Patients with a first unprovoked VT or PE and concentrations less than 250 pg/mL have a 60% lower risk of recurrence rate than those with concentrations more than 250.

In one study, which measured D-dimer during anticoagulation, rather than after discontinuation, a

a 250 ng/mL cutoff was predictive of a low risk of recurrence in women.

Two systematic reviews of D-dimer have assessed risk stratification. D-dimer is the only laboratory criterion for thrombophilia that has been used to establish the duration of anticoagulation treatment in a large randomized setting. Patients with low concentrations after withdrawal of anticoagulation had a low risk of recurrence (4 per 100 person-years). Persons with high levels who stopped anticoagulation after 6 months had an increased risk of recurrence (10 per 100 person-years) compared with those who received anticoagulation for more than 6 months.

Repeated testing of D-dimer after withdrawal of anticoagulation following a first unprovoked VT could help establish the optimum duration of treatment.

Clinical characteristics of patients and laboratory markers:

The combination of clinical characteristics (location of the thrombus, sex, age) with laboratory testing is an approach to assessment of risk of recurrence.

In a 4-year study, which included over 600 patients with a first unprovoked VT, combinations of 4 risk factors (absence of symptoms suggesting post-thrombotic syndrome, D-dimer concentrations less than 250 ng/mL during anticoagulation therapy, body mass index less that 30, and age under 65) identified a cohort of women at low risk of recurrence. This does not apply to men.

Followed a prospective cohort study of over 900 subjects with unprovoked VT or PE for a median of 43 months after discontinuation of anticoagulation. Many possible causes of recurrence were included. Only the patient's sex, thrombosis location, and D-dimer were related to increased risk of recurrence.

An online risk calculator has been developed to estimate the risk of recurrence. It needs validation.

In the past few decades, assessment of the risk of recurrence after an episode of VT has substantially improved through understanding the natural course of the disease and characteristics of factors that establish risk of recurrence. "However, we are not able to predict recurrence on the basis of laboratory abnormalities (*except D-dimer*) with enough precision to recommend implementation to clinical practice."

New anticoagulants (antithrombin and anti Factor Xa) have predictable dose-response associations. They have the potential to replace conventional anticoagulants. Risk of bleeding remains a concern.

Lancet December 11, 2010; 376:2032-39 Review article, first author Paul Alexander Kyrle, Medical University of Vienna, Austria.

1 D-dimer is a small protein fragment, a product of fibrin degradation (by plasmin). It is so named

because it contains two cross linked D fragments, which are linked with one molecule of fibrinogen Absence of D-dimer essentially rules out thrombosis. A positive test does not firmly establish thrombosis It main use is to exclude thrombotic disease when the probability of thrombosis is low. (Source: Wikipedia)

2. Negative predictive value tests the likelihood that a negative test will rule-out the disease.
   If the predictive value of a negative test (eg, a negative D-dimer) for a disease (eg VT) is very low, then a patient with a negative D-dimer is unlikely to have VT.

Strongly Associated With Incident HF And CV Death, Independent Of Standard Risk Predication Variables

12- 3 ASSOCIATION OF SERIAL MEASURES OF CARDIAC TROPONIN T USING A SENSITIVE ASSAY WITH INCIDENT HEART FAILURE AND CARDIOVASCULAR DEATH

Elderly individuals comprise the largest group of patients hospitalized for heart failure (**HF**) Almost a million are admitted to hospitals each year. Once HF is diagnosed, older patients respond less well to guideline-based therapy. They are also more likely to require readmission and are at higher risk of death.

Blood-based biomarkers, including C-reactive protein, natriuretic peptides, and troponins have been advocated as adjuncts to clinical risk factors to identify older patients at high risk for adverse cardiovascular outcomes. But studies have reported inconsistent results.

A highly sensitive cardiac troponin T (**hscTnT**) assay has been developed. The assay has detected circulating hscTnT in almost all patients with ischemic heart disease and chronic HF. It provides independent prognostic information with respect to HF admissions and cardiovascular death (**CV death**).

These investigators hypothesized that, in community-dwelling older persons without a prior history of HF, measurable hscTnT would be common, and higher concentrations would be associated with a greater risk of new-onset HF and CV death, independent of traditional risk factors. Serial measurements over time could reflect a change in risk.

STUDY

1. This nation-wide prospective cohort study included 4221 community-dwelling persons age 65 and older at baseline (1989-90.). None had prior HF. Main outcome measure = new-onset HF and CV death through 2008 with respect to hscTnT concentrations.
2. Measured hscTnT at baseline and again after 2 to 3 years. The analytical measurement

for hscTnT ranges from 3.0 to 10 000 pg/mL

3. The value at the 99th percentile cutoff in a healthy reference population is 13.5 pg/mL.

4. Divided patients into 5 equal size categories according the baseline hscTnT: < 3 pg/mL (undetectable) 3.0 to 5.44; 5.45 to 8.16; 8.17 to 12.94; and > 12.94.

5. Determined cumulative incidence of HF and CV death for each category. .

RESULTS

1 Baseline

hscTnT	<3.0 pg/mL (n = 1327)	> 12.9 pg/mL (n = 700)
Age	70	78
Systolic BP	144	143
Estimated GFR < 60)%)????	13	40
Major ECG abnormalities (%)	17	50
Abnormal left ventricular ejection fraction (%)	4	16
Left ventricular mass by ECHO (grams; men)	170	178

(At baseline, increasing levels of hscTnT were related to multiple traditional risk factors: Age, known CHD, depressed kidney function, ECG abnormalities, abnormal ejection fraction, and increased left ventricular mass.)

2. Association of change in hscTnT with subsequent HF and CV death

(Expressed as number per 100 person-years.)

A. All persons with baseline hscTnT	HF		CV death	
Undetectable at follow-up	1.5	1.00	1.1	1.00 (Reference)
Detectable at follow-up	3.7	1.55*	2.8	1.30**

* Hazard ratio (**HR**) for HF (adjusted0

** HR for CV death (adjusted)

(If hscTnT remained undetected after baseline, risk was lower than if it became detectable.)

B. Patients with detectable hscTnT at baseline and at follow-up

	HF		CV death	
50% or greater increase in hscTnT	5.3	1.40*	4.1	1.33**
Change less than 50%	3.3	1.00	2.6	1.00 (Reference)
50% of greater decrease in hscTnT	2.0	0.74	1.6	0.75

* HR) for HF (adjusted0

** HR for CV death (adjusted)

(If hscTnT was detectable at baseline and increased over time, risk increased. If hscTnT decreased over tine, risks decreased.)

DISCUSSION

1. Low concentrations of hscTnT were associated with a gradient of risk for new-onset HF and CV death in ambulatory persons over age 65, independent of clinically variables.
2. Low baseline concentrations frequently change over time. These changes are associated with changes in risk of HF and CV death concordant with the direction of change.
3. Concentrations of hscTnT were detectable and of prognostic value in nearly 2/3 of a large geographically and clinically diverse stable, but at-risk population of ambulatory older individuals without a prior diagnosis of HF.
4. Baseline levels of hscTnT below the levels that we expect to be detected with conventional assays, are strongly associated with incident HF and CV death independent of standard prediction variables.
5. Changes in hscTnT determined during 2 to 3 years in subjects who remained free of HF, even when occurring at concentrations well below the 99^{th} percentile of healthy young blood donors, are prognostically significant.
6. The markedly increased range of measurements of hscTnT enables estimation of a gradient of risk across the majority of older individuals, including those with absence of clinical risk factors (other than age) and also permits examination of the significance of change in hscTnT.
7. The study could not determine the pathophysiology of these results. Previous evidence has shown that exercise-induced cardiac ischemia can lead to transient low-level increases in hscTnT.
8. The study is unique in finding that changes in very low levels of hscTnT are common in older patients and are independently associated with changes in risk of both HF and CV death. Changes are associated with significant absolute change in risk regardless of baseline levels. This suggests a dynamic change in disease progression.
9. The clinical importance of monitoring the change in hscTnT levels for risks of progression to symptomatic HF has yet to be determined. Further studies are needed to assess whether low levels of hscTnT may provide opportunity to motivate specific changes in lifestyle and prompt medical interventions before patients progress to symptoms or cardiac structural changes.

CONCLUSION

Detectable hscTnT levels were present in the majority of older community-dwelling persons without known heart failure. Higher concentrations--within normal range established for younger persons--reflect a greater burden of cardiac risk.

Changes in hscTnT levels over time were common and corresponded with change in risk of heart failure and cardiovascular death.

JAMA December 8, 2010:304: 2494-2502 Original investigation, first author Christopher B deFilippi, University of Maryland School of Medicine, Baltimore Funded by the National Heart, Lung and Blood Institute

A second article appearing in this issue of JAMA extended hscTnT to the general middle-aged population "Association of Troponin T Detected with a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population" JAMA December 8, 2010;304: 2503-12 Original investigation, first author James A deLemos, University of Texas Southwestern Medical Center, Dallas

This multicenter population-based cohort study determined the prevalence of hscTnT in the general population and assessed whether the test is associated with cardiac disease and subsequent mortality.

Measured hscTnT in 3546 individuals age 30 to 65 from 2002 to-2003. Followed participants through 2007 to determine mortality associated with 5 categories of hscTnT.

Also used magnetic resonance imaging of cardiac function and structure through a median of 4 years of follow-up.

Results: hscTnT (> 3.0) pg/mL) was detectable in 25% of the cohort; 37% of men and 13% of women. And in 14% of participants under age 40 and in 53% of those over age 60.

Prevalence of left ventricular hypertrophy increased from 7.5% in those in the lowest category of hscTnT (3.9 to 5.44 pg/mL) to 49%.in those in the highest category (14.0 pg/mL)

During follow-up, there were 151 deaths, including CV deaths. All-cause mortality rose from 1.9% in the lowest category to 28% in the highest level.

Conclusion: hscTnT was associated with structural heart disease and subsequent mortality.

Extending The Validity of BMI as A Prediction Tool

12-4 BODY MASS INDEX AND MORTALITY AMONG 1.4 MILLION WHITE ADULTS

Two thirds of the adult population in the US is currently overweight or obese.

It is well-established that obese persons (body mass index [**BMI**] of 30 or more) have increased death rates from heart disease, stroke and many cancers.

Studies vary in estimating the strength of the relationship between high BMI and all-cause mortality. Inconsistencies could be due to confounding by tobacco use and disease-related weight loss. Differences in age and length of follow-up vary.

Pooled analyses provide the opportunity to examine these issues in a large diverse population with use of standard analytic approaches across studies.

The Prospective Studies Collaboration assessed the association between BMI and mortality among 900 000 persons in studies that were designed primarily to estimate risk factors for cardiovascular disease. They concluded that both overweight and obesity were associated with increased all-cause mortality, and the optimal BMI was 22.5 to 25.0. However, many conclusions were based on analyses that included smokers and persons with preexisting cancers, possibly underestimating the association between BMI and all-cause mortality and overestimating optimal BMI.

This study examined the relationship between BMI and all-cause mortality in a pooled analysis of 19 prospective studies of predominantly white (non-Hispanic) adults (n = 1.46 million). The study included 160 087 deaths. It examined the extent to which the relationship between BMI and all-cause mortality varied with smoking and prevalent disease.

The very large sample and diverse population enabled the investigators to examine variations accrediting to age, sex, follow-up time and physical activity.

The principal objectives were to assess the optimal BMI range and to provide stable estimates of the risks associated with being overweight, (BMI 25.0 to 29.9), obese (BMI 30.0 to 39.9), and morbidly obese (BMI > 40) with minimal confounding due to smoking and prevalent disease.

STUDY

1. Inclusion criteria:

All included studies had more than 5 years of follow-up, and more than 1000 deaths. The baseline year was 1970 or later. At baseline, all studies ascertained height and weight (self reported)

and smoking status. Most studies had information on prevalent conditions, particularly cancer and heart disease, alcohol consumption, education level, mental status, and level of physical activity.

The study was limited to non-Hispanic whites because the relationship between BMI and mortality may differ across racial and ethnic groups.

Also eliminated persons age 85 and older and those with extreme BMIs (less than 15, and more than 50)

2. Study variables and follow-up:

Variables were formatted into standard categories:

Smoking (never, past, and current). Number of years since stopping smoking (less than 10, 10 to 20, and over 20)

Alcohol consumption (grams per day)

Overall physical activity (low, medium, high).

Education (less than high school, high school, some college, college graduate and postgraduate).

Marital status.

Followed participants from baseline to death, end of follow-up, or loss to follow-up.

Recorded cause of death.

3. Analysis by BMI levels:

Predefined categories; 15.0 to 18.4; 18.5 to 19.9; 20.0 to 22.4; 22.5 to 24.9; 25.0 to 27.4; 27.5 to 29.9; 30.0 to 34.9; 35.0 to 39.9; and 40.0 to 49.9.

Defined BMI of 22.5 to 24.9 as the reference category. (Hazard ratio [HR] = 100 for death as compared to those whose BMIs are over 24.9 and under 22.5)

RESULTS

1. Characteristics of the study cohorts:

Women comprised over half of the cohort. Median age at baseline = 58. Median BMI = 26.2; 53% had smoked; 13% were current smokers.

During a 10-year follow-up, a total of 35 369 deaths were reported among subjects who were healthy at baseline (no history of cancer or heart disease) and who had never smoked.

The prevalence of current smoking decreased with increasing BMI: 25% with BMI 15 to 18.4; vs 8% with BMI 40.0 to 49.9.

The number of former smokers increased from 27% to 44%.

Preexisting cancer and emphysema was slightly more common in the low BMI category.

Preexisting heart disease increased with increasing BMIs.

Physical inactivity and lack of a college degree were associated with a higher BMI.

2. BMI and all-cause mortality:

The age-standardized rate of death from any cause was generally lowest among participants with a BMI 22.5 to 24.9. The HR increased with progressively higher and lower BMI.

The shape of the relationship between BMI and the HR for death changed with the sequential exclusion of current and former smokers, and participants who had reported cancer or heart disease at baseline.

There was a contrast in the pattern between healthy subjects who had never smoked and the pattern observed when all subjects were included in the analysis. The nadir of the curve flattened and expanded to the BMI range of 20.0 to 24.5 when the analysis was restricted to healthy participants who never smoked.

HR for *healthy* women who never smoked rose from 1.00 (reference) to 1.47 as BMI fell to 15.0. And rose from 1.00 to 2.61 as BMI rose to 40.0.

HR for *all* women in the cohort rose from BMI 1.00 (reference) to 2.02 as BMI fell to 15.0. And rose from 1.00 to 1.99 as BMI rose to 40.0 and above. *(Figure 1 page 2214)*

Hazard ratios were broadly similar for men, except for the 2 highest BMIs, for which the HR rose to 2.06 and 2.93 in those who never smoked and did not have cancer or heart disease at baseline.

Adjustments for alcohol, physical activity, education, and marital status slightly reduced the HR estimates for those with a BMI 25.0 and higher,

When men and women were combined to increase statistical power, the nadir of the HRs remained at 1.00 for BMI 20..0 to 25.5.

HRs varied with the age at which BMI was first ascertained. For a BMI of 25.0 or higher as compared with BMI 22.5 to 24.9, the HRS were higher for those entered at age 20 to 49 than for those entered after age 70. Annual excess mortality was higher in older participants because the absolute death rates were higher.

The increased HRs for those with BMIs under 20.0 as compared with 22.5 to 24.9 were reduced in those reporting higher-level of physical activity. (Being lean and fit.)

DISCUSSION

1. Overweight (and possibly underweight) were associated with increased all-cause mortality in participants who never smoked and did not have cancer or heart disease at baseline.
2. These associations were strongest among those whose BMI was ascertained before age 50.

3. The lowest all-cause mortality was generally observed in the BMI range of 20.0 to 24.5.
4. In addition to the present study, all other studies showed the being overweight increases all-cause mortality.
5. Among healthy persons who had never smoked, the estimated HR for all-cause mortality per 5-unit increase in BMI rose by 1.32
6. Smoking and preexisting conditions cause weight loss and are powerful confounders. Analyses that include them lack validity.
7. The association between underweight and increased mortality was probably, at least in part, due to preexisting disease.
8. The associations between all-cause mortality and lower BMIs was weaker in those who were physically active (lean and fit) than among those who were inactive.
9. Being underweight cannot be ruled out as a cause of increased all-cause mortality.

CONCLUSION

For non-Hispanic white persons, both overweight and obesity are associated with increased all-cause mortality, and underweight may be as well.

All-cause mortality is generally lowest within the BMIs range of 20.0 to 24.9.

These results are most relevant to white persons living in affluent societies.

NEJM December 2, 2010; 363: 2211-19 Original investigation, first author Amy Berrington de Gonzalez, National Cancer Institute / National Institutes of Health, Bethesda, MD

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