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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 20-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 6 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2008

Sustained Beneficial Effects On Vascular Complications And Death Over 13 Years

2-1 EFFECT OF A MULTIFACTORIAL INTERVENTION ON MORTALITY IN TYPE 2 DIABETES

A previously reported 8-year prospective randomized trial (Steno-2 study) of intensified multitarget interventions aimed at several risk factors concomitantly vs conventional treatment, reported a reduction in vascular complications of DM-2 by about 50%.

This article reports an observation only follow-up of an additional 5 years to determine death rate, and effects in intensive vs conventional therapy on microvascular and macrovascular diseases over a total of 13 years.

During the first 8 years:

1. Risk factor reductions were much greater in the intervention group: glycated hemoglobin, systolic BP, diastolic BP, triglycerides, LDL-cholesterol and total cholesterol levels remained considerably lower than in the conventional group.
2. Risk of complications: hazard ratios of cardiovascular disease, stroke, myocardial infarction, revascularization procedures, nephropathy, retinopathy, neuropathy and amputations were much lower in the intervention group.

During the last 5 years:

1. Differences in risk factor reductions gradually decreased in the conventional group, so that at the end of 13 years, there were little differences between groups in glycated hemoglobin, BP, triglycerides, LDL-cholesterol, and total cholesterol. This was mainly because the control group received better interventions in the last 5 years.
2. Risk of complications, however remained considerably in favor of the intervention group: hazard ratios of risk of overall death, death from cardiovascular disease, cardiovascular events, and requirement for retinal photocoagulation remained between 0.4 and 0.5.

Conclusion: In patients with DM-2, intensive intervention with multiple drug combinations and behavioral modification had sustained beneficial effects with respect to vascular complications and rates of death from any cause and death from cardiovascular causes.

As compared with conventional care, the benefits of 8 years of intensive risk-factor reduction persisted for5 years after the trial ended. This is not surprising. The earlier and the longer risk-reduction interventions are applied, the greater the benefit in reducing complications.

I believe that if intensive therapy had begun at a much earlier age (eg 30 instead of 55), risk reductions of complications of DM-2 would have been much greater.

The article states that the study did not determine which of the interventions contributed most to the benefits. I believe BP and lipid control would contribute more to reduction in complications than control of HbA1c.

Ask first—"Are you taking your medication properly"

2-2 IMPORTANCE OF THERAPY INTENSIFICATION AND MEDICATION NON-ADHERENCE FOR BLOOD PRESSURE CONTROL IN PATIENT WITH CORONARY DISEASE

This retrospective study over 10 000 patients with CAD in a large integrated managed care organization evaluated the impact of medication non-adherence and therapy intensification on reaching BP goals.

BP control was based on serial BP measurements over time. Median follow-up = 5years. The median number on BP measurements per patient was 20.

Determined adherence to 5 different anti-hypertension drugs based on pharmacy records.

Identified 3 groups based on determinations of systolic BP over time:

1) Normal-normal: mean systolic = 126 mm Hg which remained stable over time. (87%)

2) High-normal: mean systolic started at 146 and decreased to 128. (8%)

3) High-high: mean systolic started with systolic at 154 and ended with systolic of 152. (5%)

Compared with the high-normal group, those in the high-high group had:

1) Non-adherence odds ratio = 1.7

2) Therapy intensification odds ratio = 1.3

Compared with the normal-normal group, those in the high-high group had:

1) Non-adherence odds ratio = 1.5

2) Therapy intensification odds ratio = 2.7

Patients with uncontrolled hypertension (high-high group) were more likely to be non-adherent to treatment and to receive intensification of anti-hypertension therapy.

Medication non-adherence may be an explanation for the continuously elevated BP levels despite upward titration of drug dose and addition of another drug.

Conclusion: Medication non-adherence can help explain why BP levels remain high despite intensification of anti-hypertension medications. Successful BP control is seen with a combination of

intensification of therapy and adherence. Interventions to enhance medication adherence must be coupled with therapy intensification

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This is a practical clinical application in primary care practice. It applies, not only to patients with CAD, but to all patients with hypertension.

As a knee-jerk reaction for patients who are not achieving target BP levels, we often increase dose or add a second or third drug.

The correct first response is to ask the patients if they are taking their present medication properly. We may even check with the local pharmacy asking about frequency of prescriptions filled.

Empirical Antimicrobial Therapy Is The Cornerstone of C-AP Treatment.

2-3 COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (**C-AP**) is common in elderly patients—annually about 2 per 100 in persons over age 65.

Most are treated as outpatients. In patients suitable for outpatient treatment, mortality is less than 1%. The remaining patients require in-hospital treatment. In those admitted to intensive care units mortality is up to 36%.

Streptococcus pneumoniae is the most common pathogen implicated in C-AP. In hospitalized patients with C-AP, it accounts for about 2/3 of all deaths.

Other bacterial causes include: *Haemophilus influenzae* and *Morxaella catarrhalis* in patients with underlying lung disease; and the so-called atypical pathogens, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp, which are present in about ¼ of C-AP episodes.

Viral pathogens are increasingly recognized as causes of C-AP. Influenza is the leading pathogen.

The editorialist addresses 4 important new additions or changes in management suggested in the most recent guidelines:

1) New diagnostic techniques to make an etiological diagnosis. Tests for antigens of *S pneumoniae* and *Legionella* in urine are easily collected. Results are obtained rapidly and are not affected by prior antibiotic use.
2) A simple predication rule to gauge severity of the C-AP and risk of death
3) Time to antibiotic administration. Suggested to begin in the emergency department.
4) Duration of antibiotic therapy.

I enjoyed this commentary. It packed a lot of information in a few pages. Consult the full abstract for details.

The Johns Hopkins antibiotic guide (www.hopkins-abxguide.org) as of June 2007 suggests 6 antibiotics for empiric outpatient treatment of uncomplicated C-AP. Primary care clinicians must choose. Which one? Amoxicillin is often considered the drug of choice for oral treatment of S pneumoniae, even in the era of escalating penicillin resistance. Since S pneumoniae is the most common cause, would it not be a suitable first choice?

Strongly Associated With Increased Risk Of Gout

2-4 SOFT DRINKS, FRUCTOSE CONSUMPTION, AND THE RISK OF GOUT IN MEN

Fructose is the only carbohydrate known to increase uric acid levels. Fructose accentuates degradation of purine nucleotides, and increases purine synthesis. The urate-raising effect is exaggerated in people with hyperuricemia.

This study examined relation between intake of fructose and sugar-sweetened soft drinks on incident gout in men. Fructose is a mono-saccharide. Half of the disaccharide, sucrose, is fructose. The total fructose intake is therefore equal to the intake of free fructose plus half of the intake of sucrose.

The Health Professionals Follow-up study followed a prospective cohort of over 46 000 men beginning in 1986. No subject had a history of gout. All participants completed a questionnaire on diet, medical history and dugs. All were asked how often during the previous year they had consumed sugar sweetened soft drinks, diet soft drinks, and different types of fruits and fruit juices. The questionnaire was updated every 4 years.

Ascertained the incident cases of gout by biennial questionnaire.

Increasing intake of sugar-sweetened soft drinks was associated with increasing risk of gout. Compared with the reference consumption of less than one serving monthly, the risk of gout for 5-6 servings weekly = 1.3; for one serving daily = 1.5; and for two or more servings daily = 1.9.

Relative risk of gout according to fifths of fructose intake were: 1.00; 1.3; 1.4; 1.8; and 2.0

Diet soft drinks were not associated with risk of gout.

Low purine diets are often high in carbohydrates, including fructose. “These data provide prospective evidence that the risk posed by free fructose intake could be at least as large as that by purine rich foods such as meat. “

Conclusion: Consumption of sugar sweetened soft drinks and fructose is strongly associated with increased risk of gout among men .

Compromised The Diagnostic Accuracy Of Both Mammograms And Biopsy.

2-5 ESTROGEN PLUS PROGESTIN AND BREAST CANCER DETECTION BY MEANS OF MAMMOGRAPHY AND BREAST BIOPSY

This study examined the effects of combined hormone therapy vs placebo on BC detection by mammography and biopsy.

Randomized over 16 000 postmenopausal women (ages 50 to 79; median = 63) to: 1) Combined 0.625 mg/d (**CEE**) + 2.5 mg/d (**MPA**) *Prempro* Wyeth Ayerst), or 2) Placebo

Followed subjects periodically for over 5 years. Required mammograms and breast examinations every year.

Determined incidence of BC, and recommendations for further breast imaging studies and biopsy.

CEE + MPA group vs the placebo group:

A. Invasive BCs 199 vs 150

B. BC was diagnosed at a more advanced stage

C. More mammograms with abnormalities (35% vs 25%).

D. The cumulative percentage with clinically indicated breast biopsies was higher (10% vs 6%).

Conclusion: Use of combined hormone therapy for 5 years resulted in more than 1 in 10 women having otherwise avoidable mammograms, and 1 in 25 having an otherwise avoidable breast biopsy, Combined hormone therapy compromised the diagnostic accuracy of both mammograms and biopsy.

A study from the WHI in JAMA April 12, 2006; 295 (See Practical Punters April 2006) reported that CEE alone vs placebo, in over 10 500 women who had undergone a hysterectomy, there was no increase in incidence of BC over 7 years. Indeed, CEE-alone was associated with a small decrease in invasive BC and ductal carcinoma.

Progesterone is the risk factor for BC, not estrogen.

Some investigators have proposed the benefit of progesterone in reducing endometrial cancer when dual hormone is prescribed is offset by the increase in breast cancer.

A similar study from the WHI reported in Archives Intern Med February 13, 2006; 166 (See Practical Pointers February 2006) reported that CEE-alone vs placebo in over 10 000 women over 7 years did not increase the incidence of coronary heart disease. Neither did it protect against CHD.

The USPSTF (Annals Internal Medicine May 17, 2005) recommends against routine use of combined hormone therapy for prevention of chronic conditions in postmenopausal women. There may be an increased risk of coronary heart disease, breast cancer, venous thromboembolism, stroke, and dementia. Harms are likely to outweigh benefits.

Also recommends against routine use of estrogen-alone for prevention of chronic conditions. Harms include: increased risk of venous thromboembolism, stroke, dementia. There is insufficient evidence regarding effects on incidence of breast cancer, and ovarian cancer. Harms are likely to outweigh benefits.

Use of hormonal therapy for menopausal symptoms should be limited to the lowest dose for the shortest period.

Surgery Showed Significantly More Improvement In Pain, Function, and Satisfaction,

2-6 SURGICAL VERSUS NON-SURGICAL THERAPY FOR LUMBAR SPINAL STENOSIS

This study assessed the 2-year outcomes of patients with spinal stenosis (without degenerative spodylolisthesis) between patients undergoing surgery vs those treated non-surgically.

The original design of the study included: 1) a group (n = 289) randomized to surgery (posterior decompression) vs no-surgery, and 2) a group (n = 365) enrolled in an observational cohort. There was a large cross-over to surgery. At 2 years, 43% of those originally assigned to receive no-surgery underwent surgery. Because of this high cross-over to surgery by individuals in the no-surgery groups, the as-treated analysis was the main outcome measure.

Both cohorts combined (as treated):

Roughly, 400 patients in the two cohorts combined received surgery at some point;
and 250 received no-surgery.

At 2 years, on the SF-35 0 to 100 scale, the mean improvement in bodily pain and physical function in the surgery cohort vs the no-surgery group was modest (about 10-12 points)

The final SF-36 score for the surgery group was considerably below the present normal scores adjusted for age and sex.

Conclusion: In the as-treated analysis, when the randomized and observational cohorts were combined, patients who underwent surgery showed significantly more improvement in pain, function, satisfaction, and self-rated progress than did patients who were treated non-surgically.

The large cross-over to surgery would indicate that these subjects were very uncomfortable, and would be willing to undergo major surgery to obtain relief. Relief was modest. Certainly no panacea.

Associated With Increased Risks Of Some Malignancies.

2-7 BODY-MASS INDEX AND INCIDENCE OF CANCER

This systematic review and meta-analysis assessed the strengths of associations between BMI and different cancers.

Literature search identified prospective studies of 20 types of cancer. Analyzed 221 datasets (over 282 000 incident cases of cancer).

Quantified risks of different types of cancer associated with a 5 kg/m^2 (~ 15 kg in men and 13 kg in women) increase in BMI over an average BMI of 23 kg/m^2

In men, a 5 kg/m^2 increase in BMI was strongly associated with: esophageal adenocarcinoma, thyroid , renal, and colon cancers. (Relative risks varied from 1.24 to 1.52.)

In women, a 5 kg/m^2 increase in BMI was strongly associated with: endometrial, gall bladder, Esophageal, and renal cancers. (RR varied from 1.34 to 1.59)

Considering that the majority of men and women in the USA are overweight or obese, and that the prevalence of obesity is expected to increase, excess body weight could contribute to a substantially larger burden of cancer.

Conclusion: Increased BMI is associated with increased risk of common and less common malignancies.

I hesitated to abstract this article. I could not think of a practical application.

It is likely an important clinical point, however, that primary care clinicians should know about.

"No Better Than Placebo"

2-8 EFFECT OF GLUCOSAMINE ON HIP OSTEOARTHRITIS

This 2-year randomized, placebo-controlled trial compared GS with placebo to evaluate effect on symptomatic and radiographic progression of osteoarthritis (**OA**) of the hip.

Entered 222 patients with OA of the hip recruited from general practices in the Netherlands.

Patients were representative of those using O-T-C glucosamine.

Randomized to: 1) GS 1500 mg (2-750 mg pills given once daily), or 2) placebo.

Primary outcomes (intention-to-treat):

A. Western Ontario and McMaster Universities (WOMAC) pain and function subscales over 2 years. Scores on these subscales range from 0 to 100. 0 = no symptoms.

B. Joint space narrowing by X-ray after 2 years.

Change from baseline on WOMAC scale (0 to 100) at 2years:

	Placebo	GS	Difference favoring GS
Pain overall	-0.30	-1.90	1.60
Function overall	+0.38	-1.69	2.07
Stiffness	-2.19	-3.43	1.24

(Slightly favoring GS. Neither statistically nor clinically significant.)

Joint space narrowing did not differ between groups at 2 years.

Conclusion: “Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis.”

Does the fact that glucosamine has remained a popular O-T-C- preparation for years mean that it is effective? I do not think so.

Does the lack of studies reporting definitive outcomes mean that glucosamine is not effective? I do not think so.

I believe we may conclude that benefits of GS, if any, are small. And that there is a large placebo effect.

How should we respond when patients ask about glucosamine? I would not prescribe it. I would not advise patients to avoid it. If the patient experiences relief, fine—even though it may be a placebo effect. I would not deny a patient the benefit of a placebo.

It would have been meaningful if the investigation had included a no-treatment group (GS vs placebo vs no-treatment).

A Clustering Of Adverse Events During The 90 Days After Cessation Of Clopidogrel

2-9 INCIDENCE OF DEATH AND ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH STOPPING CLOPIDOGREL AFTER ACUTE CORONARY SYNDROME.

It has been hypothesized that withdrawal of clopidogrel (*Plavix*) may be associated with a “rebound effect”—

an increase in adverse events after cessation of the drug. This may be due to a transient hyperthrombotic state.

This study assessed the incidence of death and acute myocardial infarction (**AMI**) after stopping treatment.

Retrospective cohort study of over 3000 patients (mean age 67) with ACS who were treated with

post-hospital clopidogrel therapy. About half had received medical therapy; half PCI

Relative risk (RR) of death or AMI within 90 days of discontinuation was higher than risk within 91 to 180 days.

A. Medically treated patients (n= 1568) who stopped clopidogrel during follow-up:

Death or AMI = 17% (n = 263)

Death or AMI during 0 to 90 days after stopping clopidogrel = 61%

Death or AMI during 91 to 180 days = 21%

Death or AMI during 181 to 220 days = 10%

B. PCI treated patients with stents (n = 1569) who stopped clopidogrel during follow-up:

Death or AMI = 8% (n = 119)

Death or AMI during 0 to 90 days after stopping clopidogrel = 59%

Death or AMI during 91 to 180 days = 24%

Death or AMI during 181 to 270 days = 7%

These findings support the hypothesis of a rebound hyper-thrombotic period after stopping the drug.

The magnitude of risk in the initial 90 days was consistent regardless of whether the patients took clopidogrel for 3, 6, 9, or more than 9 months. The association is likely independent of treatment duration.

Even though absolute event rates were low, the relative increase in adverse events in the early period after cessation was nearly 2-fold higher than later periods. Considering the number of patients using clopidogrel, risks are significant when extrapolated to the population of users.

Conclusion: There was s clustering of death and acute myocardial infarctions in the 90 days after withdrawal of clopidogrel therapy.

I wondered if this study would be of interest to primary care.

Some primary care clinicians do follow ACS patients after being discharged by the cardiologist.

Although benefit is not confirmed, it would seem reasonable to taper clopidogrel for a longer period, perhaps up to one year.

T4 Adequately Replaces Serum T3 Levels In Most Patients

2-10 THYROXINE MONOTHERAPY AFTER THYROIDECTOMY

Given the complex regulation of T4 conversion to T3,. it is theoretically possible that replacement therapy with pure T4 may not precisely reduplicate a thyroid hormone milieu that involves two

hormones, not one. There had been lingering doubt about whether the serum T3 levels that are attained with T4 therapy are truly normal for the individual patient.

The controversy surrounding thyroid hormone therapy stems, in part, from important aspects of normal thyroid physiology. It is T3, rather than T4 that mediates thyroid hormone action by binding to nuclear thyroid hormone receptors in virtually all tissues. Serum T3 has 2 sources: 1) About 20% comes directly from the thyroid, 2) the other 80% is derived from the mono-deiodination of T4 in peripheral tissues which activates T3. Thus, T4 acts as a pro-hormone for T3. T4 has essentially no intrinsic biological activity of its own.

In a study in the February 20, 2008 issue of JAMA, of patients who underwent total thyroidectomy, replacement T4 given to maintain normal TSH levels, resulted in normal T3 levels in almost all subjects. But, in a few patients, T3 levels, for whatever reason, were lower postoperatively than preoperatively despite normal TSH levels.

The data presented by the study “seems to lay to rest, once and for all, the notion that T4 therapy alone is inadequate to replace serum T3 levels back to normal in the overwhelming majority of patients”.

There may be an occasional patient who does not achieve normal T3 levels when T4 supplementation is adequate. It would be simple to substitute T4 + T3 therapy in these patients as an n = 1 trial in patients with hypothyroidism who do not attain normal T3 levels despite normalization of TSH, and to those who do not achieve adequate symptoms control.

ABSTRACTS FEBRUARY 2008

Sustained Beneficial Effects On Vascular Complications And Death Over 13 Years

2-1 EFFECT OF A MULTIFACTORIAL INTERVENTION ON MORTALITY IN TYPE 2 DIABETES

The rate of death among patients with type 2 diabetes (**DM-2**) is approximately twice as high as that among persons without the disorder.

A previously reported 8-year prospective randomized trial (Steno-2 study) of intensified multitarget interventions aimed at several risk factors concomitantly vs conventional treatment, reported a reduction in vascular complications of DM-2 by about 50%.

This article reports an *observation only* follow-up of an additional 5 years to determine death rate and effects in intensive vs conventional therapy on microvascular and macrovascular diseases over a total of 13 years.

Conclusion: Intensified interventions for a total of 13 years had sustained beneficial effects on vascular complications and death.

STUDY

1. The first part to the study (1993-2001) entered 160 patients (mean age at baseline = 55) with DM-2. All subjects had persistent microalbuminuria and were considered to be at increased risk of complications All received a blocker of the renin-angiotensin system (because of the albuminuria), and low dose aspirin.
2. Subjects were randomized to:
    1) Intensive therapy target-driven therapy involving a combination of medications and behavioral modifications. Targets included: HbA1c less than 6.5%; total cholesterol under 175 mg/dL; fasting triglyceride level less than 150 mg/dL; systolic BP less than 130, and diastolic less than 80. Subjects were offered periodic individual consultations during the 8 years.
    2) Conventional therapy was provided by patients' general practitioners. The treatment goals for reductions in risk factors for micro- and macro-vascular disease were much less strict than in the Intensive therapy group.
3. The second 5-year part of the study was observational only, with no continuing oversight of compliance with the interventions.
4. Primary outcome = death from any cause.

RESULTS

1. At the end of the first 8 years of the study, 67 of the intensive group remained, and 63 of the conventional group remained—a total of 130 of the original 160 subjects.
2. Intensive therapy was superior to conventional therapy.
    A. During the first 8 years:
        1. Risk factor reductions were much greater in the intervention group: glycated hemoglobin, systolic BP, diastolic BP, triglycerides, LDL-cholesterol and total cholesterol levels remained considerably lower than in the conventional group.
        2. Risk of complications: hazard ratios of cardiovascular disease, stroke, myocardial infarction, revascularization procedures, nephropathy, retinopathy, neuropathy and amputations were much lower in the intervention group.
    B. During the last 5 years:
        1. Differences in risk factor reductions gradually decreased in the conventional group, so that at the end of 13 years, there were little differences between groups in glycated hemoglobin, BP, triglycerides, LDL-cholesterol, and total cholesterol. This was mainly because the control group received better interventions in the last 5 years.
        2. Risk of complications, however, remained considerably in favor of the intervention group: hazard ratios of risk of overall death, death from cardiovascular disease, cardiovascular events, and requirement for retinal photocoagulation remained between 0.4 and 0.5.

DISCUSSION

1. After a mean of 13 years, there was an absolute risk reduction of death from any cause among patients receiving intensive care vs those receiving conventional care. Risk of death in the conventional group was about 50%; in the intensive care group about 30%.
2. The difference in cumulative risk of death and cardiovascular events continued to increase as time increased from 8 to 13 years.
3. The study was not designed to determine which of the interventions contributed most to the benefits.
4. The effect of BP reduction on cardiovascular end points usually occurs within months; the effect on lipid lowering within 2 years, and the effects of glucose lowering occurs even later.
5. Since intensive multifactorial care of patients with DM-2 leads to reduced rates of death and cardiovascular disorders, the early and meticulous implementation of current treatment guidelines remains a major challenge.

CONCLUSION

In patients with DM-2, intensive intervention with multiple drug combinations and behavioral modification had sustained beneficial effects with respect to vascular compilations and rates of death from any cause and death from cardiovascular causes.

NEJM February 7, 2008; 358: 580-91 Original investigation (The Steno-2 study), first author Peter Gaede, Steno Diabetes Center, Copenhagen, Denmark.

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Ask first—"Are you taking your medication properly"

2-2 IMPORTANCE OF THERAPY INTENSIFICATION AND MEDICATION NON-ADHERENCE FOR BLOOD PRESSURE CONTROL IN PATIENT WITH CORONARY DISEASE

Despite the importance of BP control in secondary prevention, fewer than 50% of patients with CHD in clinical practice reached BP levels recommended by national guidelines.

The currently recommended treatment goal is less than 140/80. Lower targets may be more beneficial.

This study of patients with CAD evaluated the impact of medication non-adherence and therapy intensification on reaching BP target goals.

Conclusion: Medication non-adherence can help explain why BP levels remain elevated despite intensification of anti-hypertension drugs.

STUDY

1. Retrospective study over 10 000 patients with CAD in a large integrated managed care organization evaluated the impact of medication non-adherence and therapy intensification on reaching BP goals.
2. BP control was based on serial BP measurements over time. Median follow-up = 5years. The median number on BP measurements per patient was 20.
3. Determined adherence to 5 different anti-hypertension drugs based on pharmacy records.
4. Medication adherence was calculated as the proportion of days covered for filled prescriptions of anti-hypertension drugs. Therapy intensification included dosage increase or increase in number of anti-hypertension drugs prescribed.
5. Primary outcome = uncontrolled hypertension (systolic BP) over time.
6. Defined 3 clinically relevant groups according to systolic BP over time:

1) Normal-normal had systolic less than 140 at baseline and maintained under 140 over time.

2) High-normal started with a high systolic BP which decreased to normal over time.

3) High-high started with a high systolic and remained high over time.

RESULTS

1. Identified 3 groups based on determinations of systolic BP over time:
   1) Normal-normal: mean systolic = 126 mm Hg which remained stable over time. (87%)
   2) High-normal: mean started at 146 and decreased to 128. (8%)
   3) High-high: mean started with systolic at 154 and ended with systolic of 152. (5%)
2. Some individuals in all three groups received therapy dose-intensification and increase in number of medications prescribed. Some individuals in all 3 groups were also classified as non-adherers.
3. Those in the high-high group were more likely to receive therapy intensification—increase in dose and increase in number of drugs prescribed.
4. Compared with the high-normal group, those in the high-high group had:
   1) Non-adherence odds ratio = 1.7
   2) Therapy intensification odds ratio = 1.3
5. Compared with the normal-normal group, those in the high-high group had:
   1) Non-adherence odds ratio = 1.5
   2) Therapy intensification odds ratio = 2.7

COMMENT

1. In this large cohort of patients with CAD, about 13 % had uncontrolled hypertension. Over a 5-year period, the number decreased to 5%
2. Patients with uncontrolled hypertension (high-high group) were more likely to have intensification of anti-hypertension therapy and to be non-adherent to treatment. Medication non-adherence may be an explanation for the continuously elevated BP levels despite upward titration of drug dose and addition of another drug.
3. Efforts to improve medication adherence must be coupled with therapy intensification to achieve desired BP levels.
4. Both therapy intensification and medication adherence are important components for achieving BP goals. They need to be evaluated concurrently to identify gaps in hypertension care.
5. Adherence to treatment with placebo is associated with improved patient outcomes (the *healthy user*

effect). Patients who are adherent to treatment with medications may be more likely to follow lifestyle recommendations and to practice other healthy behaviors.

CONCLUSION

Medication non-adherence can help explain why BP levels remain high despite intensification of anti-hypertension medications. Successful BP control is seen with a combination of intensification of therapy and adherence. Interventions to enhance medication adherence must be coupled with therapy intensification

Archives Intern Med February 11,2008; 168: 271-76 Original investigation, first author P Michael Ho, Denver Veterans Administration Medical Center. Based on data from the Kaiser Permanente of Colorado, Aurora.

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Empirical Antimicrobial Therapy Is The Cornerstone of C-AP Treatment.

2-3 COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (**C-AP**) is common in elderly patients—annually about 2 per 100 in persons over age 65.

Most are treated as outpatients. In patients suitable for outpatient treatment, mortality is less than 1%. The remaining patients require in-hospital treatment. In those admitted to intensive care units mortality is up to 36%.

Streptococcus pneumoniae is the most common pathogen implicated in C-AP. In hospitalized patients with C-AP, it accounts for about 2/3 of all deaths.

Other bacterial causes include: *Haemophilus influenzae* and *Morxaella catarrhalis* in patients with underlying lung disease; and the so-called atypical pathogens, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp, which are present in about ¼ of C-AP episodes.

Staphylococcus aureus is a rare cause of C-AP. It is most prevalent in influenza outbreaks. As prevalence of methicillin-resistant *S aureus* increases worldwide, physicians should be aware of the potential for the infections to cause life-threatening necrotizing C-AP.

Viral pathogens are increasingly recognized as causes of C-AP. Influenza is the leading pathogen.

*Enterobacteriacea*e. *E coli*, and *Klebsiella pneumoniae* rarely cause C-AP.

Incidence of aspiration pneumonia in the community is poorly defined. It occurs more frequently than reported. It is often unrecognized.

Despite the use of many diagnostic techniques to make an etiological diagnosis, nearly half remain undiagnosed.

Deciding where and how to manage patients with C-AP is a costly issue. Due to the common absence of early etiological diagnoses, empirical antimicrobial therapy is the cornerstone of C-AP treatment. There are few disorders that are so controversial in terms of management.

The editorialist addresses 4 important new additions or changes in management suggested in the most recent guidelines:

1) New diagnostic techniques to make an etiological diagnosis.

Commercially available urinary antigen tests for detection of *S pneumoniae* (detects the C-polysaccharide which is common to all types), and *L pneumophilia.* Urinary tests are obtained rapidly, and are easily collected. Results are obtained rapidly and are not affected by prior antibiotic use. The detection of *L pneumophilia* antigen in urine is an important advance.

2) Recent prediction rules to gauge severity and risk of death.

CURB is a practical assessment. It is now widely used. All but one point are readily available at the bedside.

Confusion

Urea concentration over 7 mmol//L (Over 19 mg/dL of urea)

Respiratory rate of 30 and over

Systolic BP less than 90

Diastolic pressure less than 60

Age 65 and older.

Scores;

0 to 1 have a low risk of death and might be suitable for outpatient care.

2 (mortality 9%) should be considered for hospital-supervised treatment.

3 and above are at higher risk of death (20% and more) and should be treated in the hospital, sometimes with initial intensive care.

3) Time to antibiotic administration:

The Infectious Diseases Society of America guidelines has recommended that antibiotic treatment be started within 4 hours. Intuitively, we associate timeliness with lower mortality. However, there have been misdiagnoses as a result of time constraints leading to inappropriate use of resources. The time target is difficult to achieve. Newer guidelines recommend no specific time window for the first antibiotic dose, and simply suggest giving

the first dose in the emergency department. A correct diagnosis of C-AP seems more important than the time of the first dose.

4) Duration of antibiotic therapy

Current recommendations are for a duration of at least 5 days. Patients should be afebrile for 48-72 hours, and should have no more than one C-AP-associated sign of clinical instability before discontinuation.

A recent meta-analysis of 15 randomized trials did not find any differences in clinical success for short courses (7 days or fewer) vs extended courses of azithromycin, beta-lactams, and fluoroquinolones.

For C-AP due to Legionella, levofloxacin 500 mg for 7-14 days and 750 mg for 5 days were associated with clinical resolution. Azithromycin 500 mg daily for 8 days was also effective.

The final decision on duration of therapy has to take into account many clinical features related to the host, the infectious agent, the severity of the illness, and the initial response to therapy.

Lancet February 9, 2008; 371: 455-58 Comment, first author Javier Garau, University of Barcelona, Spain.

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Strongly Associated With Increased Risk Of Gout

2-4 SOFT DRINKS, FRUCTOSE CONSUMPTION, AND THE RISK OF GOUT IN MEN

Conventional dietary recommendations for gout have focused on restriction of purine and alcohol intake, not on sugar-sweetened soft drinks.

Although such drinks contain low levels of purines, they contain large amounts of fructose.

Fructose is the only carbohydrate known to increase uric acid levels. Fructose accentuates degradation of purines, and increases purine synthesis. The urate-raising effect is exaggerated in people with hyperuricemia.

This study examined relation between intake of fructose and sugar-sweetened soft drinks on incident gout in men.

Conclusion: Consumption of sugar-sweetened soft drinks and fructose was strongly associated with increased risk of gout.

STUDY

1. The Health Professionals Follow-up study followed a prospective cohort of over 46 000 men beginning in 1986. No subject had a history of gout.
2. All participants completed a questionnaire on diet, medical history, and drugs. All were asked how often during the previous year they had consumed sugar sweetened soft drinks, diet soft drinks, and different types of fruits and fruit juices. The questionnaire was updated every 4 years.
3. Fructose is a mono-saccharide. Half of the disaccharide, sucrose, is fructose. The total fructose intake is therefore equal to the intake of free fructose plus half of the intake of sucrose.
4. Ascertained the incident cases of gout by biennial questionnaire.
5. Primary end point = incident cases of gout.

RESULTS

1. During 12 years of follow-up, documented 755 cases of gout.
2. Increasing intake of sugar-sweetened soft drinks was associated with increasing risk of gout. Compared with the reference consumption of less than one serving monthly, the risk of gout for 5-6 servings weekly = 1.3; for one serving daily = 1.5; and for two or more servings daily = 1.9.
4. Relative risk of gout according to fifths of fructose intake were: 1.00; 1.3; 1.4; 1.8; and 2.0
5. Diet soft drinks were not associated with risk of gout.
6. Among other items contributing to fructose, total fruit juice intake was also associated with increased risk of gout. Compared with men who consumed less than one glass of fruit juice a month, the relative risk of gout among those consuming two or more glasses daily was 1.8
7. Increasing intake of apples and oranges was also associated with risk of gout.

DISCUSSION

1. The risk of incident gout increased substantially with increasing intake of sugar sweetened soft drinks.
2. The risk of gout increased with increasing fructose intake. It was about twice as high among men in the highest fifth of fructose consumption than among men in the lowest fifth.
3. These associations were independent of dietary and other risk factors such as body mass index, age, hypertension, diuretic use, alcohol intake, and history of chronic renal failure.
4. The magnitude of the risk of incident gout posed by sugar-sweetened soft drinks was slightly larger that that of spirits. (Fructose shares ethanol's urate-raising mechanism. Glucose and other simple sugars do not have the same effect.)
5. Fructose could also indirectly increase levels of uric acid by increasing insulin resistance and

circulating insulin levels.

6. Low purine diets are often high in carbohydrates, including fructose. "These data provide prospective evidence that the risk posed by free fructose intake could be at least as large as that by purine rich foods such as meat. "
7. The conventional low purine diet approach allowing fructose intake could worsen the overall net risk of gout attacks.

CONCLUSION

Consumption of sugar sweetened soft drinks and fructose is strongly associated with increased risk of gout among men .

BMJ February 9, 2008; 336: 309-12 Original investigation first author Hyon K Choi, University of British Columbia, Canada.

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Compromised The Diagnostic Accuracy Of Both Mammograms And Biopsy.

2-5 ESTROGEN PLUS PROGESTIN AND BREAST CANCER DETECTION BY MEANS OF MAMMOGRAPHY AND BREAST BIOPSY

In the USA, about 25 million prescriptions are written yearly for hormonal therapy. For women with a uterus, progestins are usually prescribed to prevent the effect of estrogen in increasing risk of uterine cancer.

The Women's Health Initiation trial (2003) reported that combined conjugated equine estrogen (**CEE**) plus medroxyprogesterone acetate (**MPA**) vs placebo increased the number of mammograms with abnormalities and breast cancers (**BC**) that were larger and diagnosed at more advanced stages.

The present study (an extension of the WHI trial) examined the effects of combined hormone therapy vs placebo on BC detection by mammography and biopsy.

Conclusion: Combined therapy for about 5 years resulted in more than 1 in 10 women having otherwise avoidable mammography, and a 1 in 25 chance of receiving an otherwise avoidable breast biopsy.

STUDY

1. Randomized over 16 000 postmenopausal women (ages 50 to 79; median = 63)[1] to:

1) Combined 0.625 mg/d (**CEE**) + 2.5 mg/d (**MPA**) *Prempro* Wyeth Ayerst), or

2) Placebo

2. Followed subjects periodically for 6 years. Required mammograms and breast examinations every year.
3. Determined incidence of BC, and recommendations for further breast imaging studies and biopsy.
4. Breast cancer included invasive BC and ductal carcinoma in situ.
5. The study was stopped early, before 6 years, because more risks than benefits were associated with the combined drugs.

RESULTS

1. CEE + MPA group vs the placebo group:
   A. Invasive BCs 199 vs 150
   B. BC was diagnosed at an a more advanced stage
   C. More mammograms with abnormalities (35% vs 25%).
   D. The cumulative percentage with clinically indicated breast biopsies was higher (10% vs 6%).

DISCUSSION

1. Combined hormone therapy was associated with an increased number of invasive BCs.
2. The BCs diagnosed in the hormone group were at a more advanced stage.
3. Hormone therapy also increased the frequency of clinically indicated breast biopsies.
4. The sensitivity of mammograms for detecting BC in the hormone group was substantially lower than in the placebo group.
5. More mammograms with abnormalities in the hormone group continued to be seen for one year after discontinuation of therapy. The practice of discontinuing hormone therapy for a short interval before a mammogram is done is not likely to have an effect on either mammogram findings or BC diagnoses.
6. There are economic and emotional costs associated with abnormal mammograms and breast biopsy.

CONCLUSION

Use of combined hormone therapy for 5 years resulted in more than 1 in 10 women having otherwise avoidable mammograms, and 1 in 25 having an otherwise avoidable breast biopsy,

Combined hormone therapy compromised the diagnostic accuracy of both mammograms and biopsy.

Archives Intern Med February 25 2008; 168: 370-377 Original investigation from the Women's Health Study, first author Rowan T Chlebowski, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA

1 Age 50-59 33%

Age 60-69 45%

Age 70-79 21%

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Surgery Showed Significantly More Improvement In Pain, Function, and Satisfaction,

2-6 SURGICAL VERSUS NON-SURGICAL THERAPY FOR LUMBAR SPINAL STENOSIS

Patients with spinal stenosis (**SS**) typically present with radicular leg pain, or with neurogenic claudication (pain in the buttocks or legs on walking or standing that resolves when sitting down, or on lumbar flexion).

It is the most common reason for lumbar-spine surgery in persons over age 65.

Indications for surgery vary widely across geographic areas. Persons with radiographic evidence of stenosis are frequently asymptomatic. Careful clinical correlation between symptoms and imaging is critical.

This study assessed the 2-year outcomes of patients with SS (without degenerative spodylolisthesis) between patients undergoing surgery vs those treated non-surgically.

Conclusion: In the as treated analysis, patients who underwent surgery showed greater improvement at 2 years.

STUDY

1. The original design of the study included: 1) a group (n = 289) randomized to surgery (posterior decompression) vs no-surgery, and 2) a group (n = 365) enrolled in an observational cohort.
2. Subjects had a mean age of 65. and had symptoms defined as severe for at least 12 weeks. None had spodylolisthesis. 80% had classical neurogenic claudication. 79% had associated dermatonal pain radiation.
3. There was a large cross-over to surgery. At 2 years, 43% of those originally assigned to receive no-surgery underwent surgery. Because of this high cross-over to surgery by individuals in the no-surgery groups, the as-treated analysis was the main outcome measure.

4. Primary outcome at 2 years = measures of pain and physical function.

RESULTS

1. Both cohorts combined (as treated):

   Roughly, 400 patients in the two cohorts combined received surgery at some point; and 250 received no-surgery.

   At 2 years, on the SF-35 0 to 100 scale, the mean improvement in bodily pain and physical function in the surgery cohort vs the no-surgery group was modest (about 10-12 points)

   The final SF-36 score for the surgery group was considerably below the present normal values adjusted for age and sex. **1**

2. Modest improvements also occurred in the no-surgery group at 2 years.

DISCUSSION

1. In patients with image-confirmed spinal stenosis without spodylolisthesis, surgery was superior to no-surgery in relieving symptoms and improving function.
2. In the as-treated analysis, the treatment effect for surgery was seen as early as 6 weeks, and appeared to reach a maximum at 6 months.

CONCLUSION

In the as-treated analysis, when the randomized and observational cohorts were combined, patients who underwent surgery showed significantly more improvement in pain, function, satisfaction, and self-rated progress than did patients who were treated non-surgically.

NEJM February 21,2008; 358: 794-810 Original investigation by the Spine Patient Outcome Research Trial (SPORT) investigators, first author James N Weinstein, Dartmouth Medical School, Hanover, New Hampshire.

1 My calculations from figure 2 page 805 RTJ

This report is complex, and difficult to abstract. It presents pages of data.

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Associated With Increased Risks Of Some Malignancies.

2-7 BODY-MASS INDEX AND INCIDENCE OF CANCER

"Excess body weight, whether in people who are overweight (BMI 25-29.9) or obese (BMI 30 or greater) is increasingly recognized as an important risk factor for some common types of cancer."

This systematic review and meta-analysis assessed the strengths of associations between BMI and different cancers.

Conclusion: Increased BMI is associated with increased risks of some malignancies.

STUDY

1. Literature search identified prospective studies of 20 types of cancer. Analyzed 221 datasets (over 282 000 incident cases of cancer).
2. Quantified risks of different types of cancer associated with a 5 kg/m^2 (~ 15 kg in men and 13 kg in women) increase in BMI over an average BMI of 23 kg/m^2
3. In men, a 5 kg/m^2 increase in BMI was strongly associated with: esophageal adenocarcinoma, thyroid, renal, and colon cancers. (Relative risks varied from 1.24 to 1.52.)
4. In women, a 5 kg/m^2 increase in BMI was strongly associated with: endometrial, gall bladder, esophageal, and renal cancers. (RR varied from 1.59 to 1.34)
5. There were weaker associations with other types of cancer
6. Associations were stronger for men than for women for colon cancer.
7. Associations were stronger for breast cancer in Asia-Pacific women.

DISCUSSION

1. Increased BMI is associated with an increased risk of several cancers in adults.
2. At some sites, risks differed between men and women.
3. Mechanisms for the relationship are not fully understood. Hormonal changes related to obesity may be causal. Candidate-causes are the insulin and insulin-like growth factor axis, sex steroids, and adipokines.
4. Considering that the majority of men and women in the USA are overweight or obese, and that the prevalence of obesity is expected to increase, excess body weight could contribute to a substantially larger burden of cancer.
5. It is not known if weight loss will reduce risk.

CONCLUSION

Increased BMI is associated with increased risk of common and less common malignancies.

Lancet February 16, 2008; 391: 569-78 Original investigation, first author Andrew G Renehan, University of Manchester, UK

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"No Better Than Placebo"

2-8 EFFECT OF GLUCOSAMINE ON HIP OSTEOARTHRITIS

Effectiveness of glucosamine sulfate (**GS**) for treating osteoarthritis (**OA**) is controversial.

In 15 trials (most on knee arthritis) comparing glucosamine with placebo, the overall effect on pain favored glucosamine. However, 8 of the trials reported no effect on pain.

In the Netherlands, GS is available over-the-counter. It is used by many patients, often on advice from their physicians.

This 2-year randomized, placebo-controlled trial compared GS with placebo to evaluate effect on symptomatic and radiographic progression of hip OA. .

Conclusion: GS was no better than placebo.

STUDY

1. Entered 222 patients with OA of the hip recruited from general practices in the Netherlands.
   Patients were representative of those using O-T-C glucosamine.
2. Randomized to: 1) GS 1500 mg (2-750 mg pills given once daily), or 2) placebo.
3. Primary outcomes (intention-to-treat):
   A. Western Ontario and McMaster Universities (WOMAC) pain and function subscales over 2 years. Scores on these subscales range from 0 to 100. 0 = no symptoms.
   B. Joint space narrowing by X-ray after 2 years.

RESULTS

1. Change from baseline on WOMAC scale (0 to 100) at 2 years:

	Placebo	GS	Difference favoring GS
Pain overall	-0.30	-1.90	1.60
Function overall	+0.38	-1.69	2.07
Stiffness	-2.19	-3.43	1.24

(Slightly favoring GS. Neither statistically nor clinically significant.)

2. Joint space narrowing did not differ between groups at 2 years.

3. There were difficulties with protocol adherence. Over 2 years, 18 patients had hip replacement: 6 in the placebo group.; 12 in the GS group.

DISCUSSION

1. Glucosamine sulfate was "no more effective than placebo in modifying the symptoms and radiographic progression of hip osteoarthritis over 24 months."

2. "However, because the mechanism of glucosamine is still not known, we cannot eliminate the possibility that effectiveness of glucosamine is different in the knee than in the hip."

CONCLUSION

"Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis."

Annals Int Med February 19, 2008; 148: 268-277 Original investigation, first author Rianne M Rozendaal, Erasmus Medical Center, Rotterdam, Netherlands.

An editorial in this issue of Annals, "Glucosamine Sulfate in Osteoarthritis: The Jury is Still Out", first author Johannes W J Bijlsma, University Medical Center, Utrecht, Netherlands comments and expands on the study.

Despite more than 4 decades of use and many controlled trials, the effects of glucosamine on pain, function, and delay in joint damage of OA are unproven One explanation may be the lack of a standardized preparation.

The US FDA classifies glucosamine a dietary supplement, and does not require standardization of its content.

The Cochrane Collaboration recently updated its review of glucosamine therapy in osteoarthritis (20 studies; over 2500 patients). The great majority of studies dealt exclusively with knee arthritis. The Cochrane authors separately analyzed trials of glucosamine manufactured by Rottapharm in Italy (a standardized preparation). This preparation decreased pain and increased function more than placebo. Non-Rottapharm preparations did not.

Glucosamine might marginally affect OA of joints other than the hip.

Many studies showed a large placebo effect.

OA is a heterogeneous disease. Signs and symptoms vary over a wide spectrum. Radiologic findings do not correlate well with symptoms. There are differences between hip and knee OA. Synovitis may be more common in the knee. Glucosamine may target synovitis. .

We need better biomarkers and imaging tests for OA.

The debate about glucosamine is far from over.

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A Clustering Of Adverse Events During The 90 Days After Cessation Of Clopidogrel

2-9 INCIDENCE OF DEATH AND ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH STOPPING CLOPIDOGREL AFTER ACUTE CORONARY SYNDROME.

Randomized controlled trials have established the efficacy of clopidogrel (*Plavix*: Bristol-Myers Squibb) following hospitalization for acute coronary syndrome (**ACS**) for patients treated either medically or with percutaneous coronary intervention (**PCI).**

Current guidelines recommend clopidogrel for at least one month, and ideally up to 1 year.

It has been hypothesized that withdrawal of clopidogrel may be associated with a "rebound effect"—an increase in adverse events after cessation of the drug. This may be due to a transient hyperthrombotic state after stopping therapy.

This study assessed the incidence of death and acute myocardial infarction (**AMI**) after stopping treatment.

Conclusion: During the 90 days after cessation of clopidogrel, there was a clustering of adverse events indicating a possible rebound effect.

STUDY

1. Retrospective cohort study of over 3000 patients (mean age 67) with ACS who were treated with post-hospital clopidogrel therapy. About half had received medical therapy; half percutaneous coronary intervention (**PCI**) with stenting.
2. Main outcome = all-cause death, and AMI after stopping clopidogrel.
3. Follow-up—up to 450 days

RESULTS

1. Medically treated patients (n= 1568) who stopped clopidogrel during follow-up
   A. Death or AMI = 17% (n = 263)

      Death or AMI during 0 to 90 days after stopping clopidogrel = 61%

Death or AMI during 91 to 180 days = 21%

Death or AMI during 181 to 220 days = 10%

Relative risk (RR) of death or AMI within 90 days of discontinuation was higher than risk within 91 to 180 days. (RR = 1.98)

Incident rates per 1000 patient-days after stopping clopidogrel

0 to 90 days = 1.31

91 to 180 days = 0.69

181 to 270 days = 0.64

3. PCI treated patients with stents (n = 1569) who stopped clopidogrel during follow-up

A. Death or AMI = 8% (n = 119)

Death or AMI during 0 to 90 days after stopping clopidogrel = 59%

Death or AMI during 91 to 180 days = 24%

Death or AMI during 181 to 270 days = 7%

Relative risk (RR) of death or AMI within 90 days of discontinuation was higher than risk within 91 to 180 days. (RR = 1.82)

Incident rates per 1000 patient-days after stopping clopidogrel

0 to 90 days = 0.57

91 to 180 days = 0.33

181 to 270 days = 0.19

DISCUSSION

1. "We found a clustering of significantly higher risk of death or AMI in the initial 90-day period after stopping treatment with clopidogrel."
2. These findings support the hypothesis of a rebound hyper-thrombotic period after stopping the drug.
3. In-vitro and physiological evidence supports a short-term increase in platelet activation immediately after stopping antiplatelet therapy.
4. Prior studies reported that cessation of use of aspirin is associated with an increased risk of cerebo-vascular and cardiac events compared with continuous aspirin use. However, aspirin is generally recommended for indefinite use in cardiac patients whereas clopidogrel is recommended for a specific course of therapy.
5. The magnitude of risk in the initial 90 days was consistent regardless of whether the patients took clopidogrel for 3, 6, 9, or more than 9 months. The association is likely independent of treatment duration.

6. Even though absolute event rates were low, the relative increase in adverse events in the early period after cessation was nearly 2-fold higher than later periods. Considering the number of patients using clopidogrel, risks are significant when extrapolated to the population of users.
7. We can speculate that the risk of withdrawal would be lessened by gradually tapering clopidogrel over a longer time, or using a higher dose of aspirin after withdrawal. This would require further study.

CONCLUSION

There was s clustering of death and acute myocardial infarctions in the 90 days after withdrawal of clopidogrel therapy.

JAMA February 6, 2008; 289: 532-39 Original investigation, first author P Michael Ho, Denver VA Medical Center, Denver, Colorado

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T4 Adequately Replaces Serum T3 Levels In Most Patients

2-10 THYROXINE MONOTHERAPY AFTER THYROIDECTOMY

Replacement therapy with virtually all clinically relevant hormones has been possible since the middle of the 20th century. The challenge is to administer them in deficiency states in a way that precisely replicates the complex manner in which they are endogenously secreted.

In contrast with the difficulties in replacing protein hormones like insulin that have complex secretory patterns, substitution therapy with small molecules like steroid hormones and thyroxine is relatively simple.

"One might think replicating normal thyroid physiology with thyroxine (**T4**) therapy would be simple, because T4 and tri-iodothyronine (**T3**) serum levels do not display pulsatility or have a circadian rhythm. Why then, does the treatment of hypothyroidism continue to be the subject of so much clinical investigation and continue to engender so much contention?"

Given the complex regulation of T4 conversion to T3,. it is theoretically possible that replacement therapy with pure T4 may not precisely reduplicate a thyroid hormone milieu that involves two hormones, not one. There had been lingering doubt about whether the serum T3 levels that are attained with T4 therapy are truly normal for the individual patient. This uncertainty led to studies exploring combination of T4 plus T3.

The controversy surrounding thyroid hormone therapy stems, in part, from important aspects of normal thyroid physiology. It is T3, rather than T4 that mediates thyroid hormone action by binding to nuclear thyroid hormone receptors in virtually all tissues. Serum T3 has 2 sources: 1) About 20% comes directly from the thyroid, 2) the other 80% is derived from the mono-deiodination of T4 in peripheral tissues which activates T3. Thus, T4 acts as a pro-hormone for T3. T4 has essentially no intrinsic biological activity of its own.

Variations in the de-iodination process may determine in part the serum levels of T4, T3, and thyroid stimulating hormone (**TSH**). In adults, serum T3 levels are also regulated by changes in de-iodination process brought about by starvation, overfeeding, acute and chronic illness, and certain drugs.

None of the numerous randomized-controlled trials comparing T4 vs T4 + T3 combinations have shown any benefit in improving hypothyroid symptoms, or sense of well-being.

This issue of JAMA reports a rather simple, but important proof-of-principle study.[1]

> The study investigated whether serum T3 levels could return to the same level in an individual that it had been before development of hypothyroidism following thyroidectomy.
>
> Patients about to undergo total thyroidectomy for goiter or a suspicious or malignant thyroid nodule had thyroid function tests before surgery (TSH, free T4, and total T3).
>
> After surgery, patients received a dose of T4 that either normalized serum TSH, if they had benign disease, or that suppressed TSH if they had thyroid cancer.
>
> Sixteen weeks after surgery, while receiving T4 replacement, thyroid hormone levels were remeasured.
>
> Outcome: Postoperative serum T3 levels were similar to the preoperative levels as long as serum TSH was within or below the normal range.
>
> But, in 6 patients out of 50, T3 levels, for whatever reason, appeared to be lower postoperatively than preoperatively. “One might speculate that some patients, perhaps approximately 10%, might potentially benefit from T3 supplementation after thyroidectomy”

Despite the demonstration that normal T3 levels can be achieved by pure T4 therapy, a number of recent articles report that persons treated with T4 have worse physical and psychological well-being, cognitive function, and lower mood compared with a control population. How is it possible to account for the fact that participants, who were biochemically euthyroid as judged by normal TSH, free T4, and T3 levels continued to have significant morbidity? There are two leading possibilities:

1) Replacement therapy with T4 imperfectly replaces the normal thyroid hormonal milieu.
2) Patients score lower on quality-of-life scales because they perceive themselves to have chronic illness.

A third less likely hypothesis is that patients with Hashimoto thyroiditis, the leading cause of

hypothyroidism, have low mood and other somatic complaints because of an underlying autoimmune diathesis unrelated to their thyroid function. Some patients do not feel well even when their thyroid function is normal.

However, the data presented by the study “seem to lay to rest, once and for all , the notion that T4 therapy alone is inadequate to replace serum T3 levels back to normal in the overwhelming majority of patients”.

JAMA February 20, 2008; 299: 817-19 Editorial by David S Cooper, Johns Hopkins University School of Medicine, Baltimore MD

1 “Tri-iodothyronine Levels in Athyreotic Individuals During Levothyroxine Therapy” JAMA February 20, 2008; 299: 769-77 Original investigation, first author Jacqueline Jonklaas, Georgetown University Medical Center, Washington DC

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