

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS
MAY 2008

ARE PLACEBOS EFFECTIVE? IF SO, WHY AND HOW? [5-1]

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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 MAY 2008

Non-Specific Effects Can Produce Clinically Significant Outcomes.

5-1 COMPONENTS OF PLACEBO EFFECT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Aside from the provision of a specific therapeutic regimen, a medical encounter might elicit non-specific benefits—what are most often called placebo effects.

Such non-specific effects in a clinical setting can be separated into 3 components: 1) a patient’s response to observation and assessment only (Hawthorne effect), 2) patient’s response to the administration of a therapeutic ritual (placebo treatment alone), and 3) the patient’s response to the patient-practitioner interaction added to the placebo.

This randomized, controlled trial of the effect of placebo therapy entered 262 participants with IBS (ROME II criteria). The placebo was sham acupuncture. Patients were completely unaware of the study’s primary aim to examine non-specific effects.

Subjects were randomized to:

- 1) “Waiting list” controlled for effects of assessment and observation (Hawthorne effect), and the natural course of the disease. Subjects received neither placebo nor interaction with the health care provider.
- 2) “Limited interaction” provided placebo treatment. At the first visit, participants received limited interaction with the investigator (< 5 minutes). Practitioners explained this was a “scientific study” for which they had been instructed not to converse with the patient. The sham needles were placed, and the patient left alone for 20 minutes after which the practitioner returned to “remove the needles”.
- 3) “Augmented interaction” provided 6 sessions of placebo (sham acupuncture) using the same procedures as with group 2. In addition, each week they received an augmented patient-practitioner relationship that began with the first visit (45 minutes) and continued weekly for 6 weeks. Content included questions concerning symptoms, relationships and lifestyles, non-gastrointestinal symptoms, and how the patient understood the “cause” and “meaning” of the condition. The interviewer incorporated a warm, friendly manner; active listening, empathy, and communication of confidence and a positive expectation.

Outcome assessment at week 3:

	Waiting list (n=87)	Limited (n = 88)	Augmented (n = 87)
Global improvement scale (1-7)	3.8	4.3	5.0
% with adequate relief of symptoms	28	44	62
Improved symptom severity score (0-100)	30	42	82
Improved quality of life score (0-12)	3.6	4.1	9.3

Placebo treatment with only limited interaction with practitioners was slightly superior to staying on a waiting list. A therapeutic ritual alone (limited placebo treatment) has a modest benefit, in some persons, beyond no treatment.

“These results indicate that such factors as warmth, empathy, duration of time spent with the patient, and the communication of positive expectations might significantly affect clinical outcome.”

Conclusion: Factors contributing to the placebo effect can be progressively combined in a manner resembling a graded dose escalation of component parts. Non-specific effects can produce statistically and clinically significant outcomes. The patient-practitioner relationship is the most robust component.

How long did the improvement last?

“Augmented” interaction takes time. This is the problem of its use in primary care.

It would have been interesting if the investigators had added a 4th group—“augmented interaction” without the placebo. Would this be just as effective? Also to compare the alleged “placebo” drug with a substance known to be inactive (eg, lactose).

I do not doubt that many interventional procedures given by practitioners of “alternative medicine” do indeed comfort the patient. (Witch doctors have practiced throughout history.) But, I doubt they have altered the outcome of any underlying physical disease. A response to a placebo does not prove that a serious underlying disease does not exist. Nevertheless, there must be some change in the patient’s brain associated with the response. We just do not know what it is.,

Patient compliance is also important in determining outcome. Those who are strictly compliant with the treatment, be it placebo or scientifically established as beneficial, will lead to better outcomes than non-compliant patients.

Many people use placebos with no physician input. They purchase “herbal and alternative” remedies which they have read about or which have been recommended by friends.

If a “placebo” is indeed proved to be effective, it should be entered into the practice of scientific medicine, and no longer termed a “placebo”. Every effort should be made to determine the pharmacological basis of its benefit.

Primary care clinicians may not object to their patient using a placebo if it is proven not to be harmful. But they should also add their time in active listening, empathy, communication, and emotional support.

When a scientifically proven therapy is available, physicians should strongly advise against use of placebo treatment. There is, however, a placebo component of all the effective drugs we prescribe. This can be a helpful adjunct to our standard therapy. If a patient is receiving maximum therapy from a standard proven therapy, I would not discourage addition of a placebo if the patient believes it helpful and I am absolutely certain that it is harmless.

“We Should Take Advantage Of Time And Intervene Early”

5-2 AGE AS A MODIFIABLE RISK FACTOR FOR CARDIOVASCULAR DISEASE.

Age is not considered a modifiable risk factor, but it outranks all those that are—lipids, BP, and smoking—as a predictor of cardiovascular events.

An analysis of the Framingham Study showed that age alone produced a receiving operator characteristic curve (ROC curve) of 0.731 for angina, myocardial infarction and coronary disease death. Addition of LDL-cholesterol increased it to only 0.746. Age + systolic BP + smoking produced a value of 0.791, which is marginally different from age alone.

Thus, apart from age and sex, the classical modifiable causative factors for cardiovascular disease seem to affect the individual risk of clinical disease to only a small extent. Yet the evidence of substantial benefit from interventional studies is incontrovertible, To suggest that hypertension and hyperlipidemia are unimportant is unreasonable.

The effect of factors such as dyslipidemia on the development of cardiovascular disease (CVD) is established both by the magnitude of the deviation of that factor from normal, and by the duration of exposure. This point is key. Conventional analyses do not distinguish between the biological changes of aging within the arteries—the non-modifiable effects of disintegration of tissues over time—and those produced by exposure over time to risk factors such as atherogenic dyslipidemia. Since arteries are damaged over time, we should take advantage of time and intervene early.

By calculating risk in the short term, and treating age as an independent risk factor, major guidelines discourage drug treatment until clinical events are common.

Early intervention will produce early benefits, but the larger issue is the effect of early intervention on the long-term clinical expression of disease. Cholesterol lowering will produce much greater total benefit if achieved earlier rather than later in life. In the absence of major risk factors by age 50, serious clinical cardiovascular disease by any age is unlikely.

“If age is as important as conventional analyses show, and if its effects are not modifiable, as conventional wisdom declares, the potential for prevention is limited. We believe this distressing conclusion is incorrect. Age can be deconstructed into the time-related effects of disintegration that affect all of us versus the time-related effects of exposure to the modifiable causal factors that affect some of us more than others.”

The Framingham Heart Study Prediction Score I have on file (now 10 years old) excludes persons with known heart disease and diabetes. It is designed to predict 10-year risk of CHD.

It includes 1) age; 2) total cholesterol, 3) smoking, 4) HDL-c level, and 5) systolic BP.

It does not include BMI, waist circumference, and physical fitness.

Point scores for a 65 year old man:

Age 11

Total cholesterol > 200 1

<i>Smoking</i>	<i>1</i>
<i>HDL-c < 40</i>	<i>2</i>
<i>Systolic BP > 160</i>	<i>3</i>

Thus, the total points for age far outweigh the sum of all other risk factors.

A score of 11 for age alone predicts an 8% incidence of CHD over the following 10 years.

Adding all the other risk factors (total = 18) increases risk to over 30%

I believe the authors have a good point. They suggest that the risk score is weighted by age, likely calculated on a basis of average risk for the age.

But not all men age 65 are at the same risk.

We cannot modify age. We can modify the other risk factors. They should be modified at younger ages.

I understand the American College of Pediatricians now advises checking of risk factors in some children.

No Benefit In Control Of Hba1c, BMI, Hypoglycemia, Or Use Of Oral Drugs

5-3 EFFICACY OF SELF-MONITORING OF BLOOD GLUCOSE IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Self-monitoring of blood glucose is widely advocated for patients with type-2 diabetes (**DM-2**) who do not require insulin. There is conflicting evidence as to its value.

This prospective randomized, controlled trial of self-monitoring of blood glucose vs no monitoring, entered 184 outpatients. All patients were under age 70, and had newly diagnosed DM-2. None were taking insulin. None had previously self-monitored glucose levels. All underwent a structured core education program. The self-monitoring group received additional education on monitoring. Follow-up for one year at intervals of 3 months.

A treatment algorithm was given to all patients for use of oral antidiabetes drugs.

If HbA1c >7.5% add metformin and titrate to a maximum of 2 g daily.

HbA1c still > 7.5%—add gliclazide 80 mg daily (a sulfonylurea not marketed in the US) and titrate to a maximum of 320 mg daily.

HbA1c still > 7.5% consider addition of a thiazolidinedione or transfer to insulin.

Outcome measures at one year:

At baseline HbA1c averaged 8.7%. HbA1c fell in both groups, there was no difference between groups—6.9% vs 6.9%.

Participants in the monitoring group were more depressed—6% higher on the depression subscale. There was also a trend toward increased anxiety in this group.

No differences in treatment satisfaction.

No differences in reported hypoglycemia. No difference in use of oral drugs.

No difference in BMI.

Evidence suggests that some patients consider monitoring uncomfortable, intrusive, and unpleasant.

Conclusion: In these patients with newly diagnosed type-2 diabetes, in comparison with a control group, self-monitoring of blood glucose concentration had no benefit in control of HbA1c, BMI, hypoglycemia, or use of oral drugs.

I believe self monitoring will be more efficacious in patients taking insulin.

Note that the uptake of regular monitoring in the monitoring group was not very high. Of 96 participants, only 63 carried out over 80% of the instructed number of determinations.

In the US, many patients with DM-2 are self-monitoring.. I believe many would not be willing to give it up.

Both Are Effective. Prednisolone Is Safer.

5-4 USE OF ORAL PREDNISOLONE OR NAPROXIN FOR THE TREATMENT OF GOUTY ARTHRITIS

NSAIDs are now first choice for treatment of acute gouty arthritis despite their gastrointestinal and cardiovascular risks. About 40% of upper g.i. bleeding events are attributable to NSAIDs. Risk is highest during the first week of use. The American Heart Association has recommended restricted use because of cardiovascular risks, which include loss of renal function, fluid retention, and interaction with anticoagulants.

Systemic corticosteroids do not have important drawbacks in the short term.

This randomized, double-blind equivalence trial entered 120 patients (mean age 58) with monoarticular arthritis. All had gout confirmed by identification of monosodium urate crystals in synovial fluid.

A quarter of the eligible patients had to be excluded because of direct safety risks if they had been treated with naproxin.

Randomized to: 1) Prednisolone 35 mg once daily, or 2) naproxin 500 mg twice daily for 5 days.

Primary outcome = pain measured on a 100 mm visual analogue scale. Disability related to the affected joint was also scored on a scale of 0 to 100.

Scores on 100 mm visual analogue scale at baseline and after 90 hours:

	Pain		General disability		Walking disability	
	Prednisolone	Naproxin	Prednisolone	Naproxin	Prednisolone	Naproxin
Baseline	62	59	59	55	71	67
After 90 h	17	13	17	13	17	13
Reduction	45	46	42	42	54	54

Outcomes at 90 hours were within the predefined 10% margin of equivalence. “We conclude that prednisolone was clinically equivalent to naproxin in treatment of gout.”

At 3 weeks, all patients reported complete relief of symptoms.

Adverse effects were similar between groups.

Conclusion: Although prednisolone and naproxin were equally effective in the initial treatment of gouty arthritis over 4 days, the present study provides a strong argument to consider prednisolone as first treatment option.

In the USA, prednisone would be used, often at a dose of 40 mg daily.

Treatment should begin as soon as possible.

I believe the choice would depend on which drug is immediately available. Prednisone requires a prescription. It could be kept on hand with the doctor's permission.

“It Is Not Too Late To Start Antihypertension Therapy”

5-5 TREATMENT OF HYPERTENSION IN PATIENT 80 YEARS OF AGE OR OLDER

Evidence of benefit in treating hypertensive patients 80 years of age and older is inconclusive. It has been suggested that antihypertension therapy may reduce risk of stroke while increasing the risk of death.

This trial aimed to clarify risk and benefits of treatment in the very elderly.

If the mean systolic BP was between 160 and 199, subjects were randomized to: 1) Indapamide (*Lozol*; Servier; a diuretic) sustained release 1.5 mg or 2) placebo.

If needed to reach target BP (less than 150/80), perindopril (*Aceon*; an ACE-inhibitor) 2 mg or 4 mg was added.

Main fatal and non-fatal endpoints in the intention to treat population:

	Rate per 1000 person-years		Absolute difference
	Active	Placebo	
All Stroke	12	18	6
Death from stroke	7	11	4
Death			
From any cause	47	60	13
From cardiovascular causes	24	31	7
From cardiac causes	6	8	2
From heart failure	2	3	1
Fatal or non-fatal			
Any myocardial infarction	2	3	1
Any heart failure	5	15	10
Any cardiovascular event	34	51	17

Adverse events: Only 3 in the placebo group and 2 in the treatment group were classified as possibly having been due to the trial medication.

There have been concerns related to the inverse association of death from any cause and BP in the very old, and about the efficacy and safety of antihypertension therapy in this age group. There was speculation that

impaired cardiac and renal function, orthostatic hypotension, cognitive impairment, subjective adverse effects, and polypharmacy would detract from the clinical benefit in the very old.

This study puts the question of usefulness of treating hypertension in the very old to rest, and provides important guidance to physicians.

Conclusion: Antihypertension treatment with indapamide, with or without perindopril in persons 80 years or older, is beneficial.

This is an important clinical observation in primary care.

If an elderly patient is diagnosed as hypertensive for the first time, I believe drug therapy should be begun at lower doses than for younger persons. And very gradually increased.

If antihypertension drugs have already been prescribed, first make sure the patient is actually taking the medication as prescribed. If so, the dose may be very gradually increased, or a second drug added at low dose.

Other risk factors should not be ignored.

Carotid Bruit Significantly Associated With Increased Likelihood Of Cardiovascular Death

5-6 CAROTID BRUITS AS A PROGNOSTIC INDICATOR OF CARDIOVASCULAR DEATH AND MYOCARDIAL INFARCTION

Clinical trials have shown benefit from carotid endarterectomy for *symptomatic* patients with severe (70-99%) carotid stenosis. However, a carotid bruit is a weak predictor of cerebrovascular events in patients who are otherwise asymptomatic for cerebrovascular conditions.

The uncertainty about prognostic implications has led the USPSTF to recommend against routine auscultation for carotid bruits.

This meta-analysis was based on a literature search which included over 17 000 patients followed up to 4 years. All studies (mostly prospective cohort studies) reported incidence of MI and cardiovascular death in adults. Median range = age 65.

All studies had extractable data for cardiovascular outcomes in individuals with carotid bruits.

Eight studies assessed MI in patients with bruits. The pooled estimate of myocardial infarction was 3.7 per 100 patient-years. In 16 studies assessing cardiovascular death, the pooled estimate of yearly deaths was 2.9 per 100 patient-years. In patients without bruits the rate was 1.1 per 100 patient-years.

“Our study has shown that the presence of a carotid bruit significantly increased the likelihood of cardiovascular death or myocardial infarction.” Cardiovascular death or MI were twice as likely in patients with bruits compared to those without.

The presence of a carotid bruit per se is not an independent risk factor of coronary disease, rather, its presence identifies a subgroup that is at high risk of having similar pathological changes in the coronary arteries. Carotid bruit is only a marker of risk to add to many other risk factors. The incremental value of a bruit is not known.

Conclusion: Auscultation for carotid bruit in patients at risk for heart disease could help select those who might benefit the most from aggressive modification strategy for cardiovascular risk.

I believe many primary care clinicians do listen for carotid bruits in elderly patients and in other patients at high risk.

If the patient has no cerebrovascular symptoms, I would not alarm the patient by mentioning the possibility of TIA and stroke unless other risk factors were present. If symptoms are present, urgent consultation is required.

The presence of a carotid bruit may be associated with increased risk. But, it is not known how much, or whether it is an independent risk factor.

If present in the absence of any other risk factors, I doubt if it indicates increased risk of coronary disease. If other risk factors are present, advice for reduction of all risk factors may be intensified.

Contrary To Past Observational Studies, This Randomized Trial Reported No Benefit

5-7 EFFECT OF FOLIC ACID AND B VITAMINS ON RISK OF CARDIOVASCULAR EVENTS AND TOTAL MORTALITY AMONG WOMEN AT HIGH RISK FOR CARDIOVASCULAR DISEASE.

Elevated homocysteine levels have been directly associated with cardiovascular risk in observational studies. Daily supplements with folic acid, vitamin B6 and vitamin B12, or a combination, reduce homocysteine levels.

In the most recent meta-analysis of observational studies, a 25% lower homocysteine level was associated with a 32% lower risk of CHD in women and a 15% lower risk in men.

This double-blind placebo-controlled trial entered over 5400 professional women (age 42 and older; mean age = 63) All had either a history of CVD, or 3 or more risk factors for CVD.

Randomized to:

- 1) Combination pill containing folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg)
2. Matching placebo.

Main outcome = composite outcome of myocardial infarction, stroke, coronary revascularization, and CVD mortality. Duration of therapy = 7 years.

In the placebo group there was no apparent reduction in homocysteine. In the folate group, levels were significantly reduced

There was no difference at any time in the cumulative incidence of the primary combined end point (combined myocardial infarction, stroke, coronary revascularization, and CVD mortality) between groups. [Active group – 14.9%; placebo – 14.3%.]

The risk of death from any causes was also similar between groups—9.2% vs 9.4%.

“Until further data become available, it is essential to remain firmly grounded on the available evidence, and to admit that, once again, experimental and observational data do not always transfer into therapeutic benefits.”

There is no role at present for routine screening for elevated homocysteine levels. And no role for homocysteine lowering by B vitamins.

Conclusion: In this trial, a combination of high doses of folic acid, B6, and B12 over 7 years had no beneficial effect (or adverse effects) on a combined outcome of total major cardiovascular events in population of high-risk of women.

This is another good example of how observational-epidemiological studies may mislead us. Many physicians (including the editor of Practical Pointers) were convinced of the benefits of folic acid in reducing risk.

Fortunately, this intervention caused no harm.

Fashions in medicine, even though seemingly firmly established, do change.

“The Finer Points Of Patient Care Should Be Built On A Basis Of Good Manners.”

5-8 ETIQUETTE-BASED MEDICINE

The editorialist comments, that during his recent hospitalization, he found the Old World manners of his European-born surgeon, and his reaction to them, revealing.

“Whatever he might have been feeling, his behavior—dress, manners, body language, eye contact—was impeccable. I wasn’t thinking ‘what compassion’, instead. I found myself thinking ‘what a professional—‘what a gentleman’.” The impression he made was remarkably calming. “It helped to confirm my suspicion that patients may care less about whether their doctors are reflective and empathetic than they are respectful and attentive.”

There have been many attempts to foster empathy and compassion in clinicians, but none to systematically teach good manners. “The very notion of good manners may seem quaint and anachronistic, but it is at the heart of the mission of other service-related professions.” Doctors can behave in certain specified ways that will result in the patient’s feeling well treated.

How could we implement an etiquette-based approach to patient care? The author proposed that we develop a checklist of physician etiquette for the clinical encounter. This would include:

Ask permission to enter the room. Wait for an answer

Introduce yourself, showing your ID badge

Shake hands (wear gloves if needed)

Sit down. Smile appropriately

Briefly explain your role on the team

Ask the patient how he or she is feeling about being in the hospital

This does not address the way the doctor feels, only how he or she behaves. It complements, rather than replaces, efforts to train physicians to be more humane.

I believe all of us could benefit from these suggestions.

However, reading about them or hearing about them in lectures will not have the impact that observing them from a role model will have.

ABSTRACTS MAY 2008

Non-Specific Effects Can Produce Clinically Significant Outcomes.

5-1 COMPONENTS OF PLACEBO EFFECT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Aside from the provision of a specific therapeutic regimen, a medical encounter might elicit non-specific benefits—what are most often called placebo effects.

Such non-specific effects in a clinical setting can be separated into 3 components: 1) a patient's response to observation and assessment only (Hawthorne effect), 2) patient's response to the administration of a therapeutic ritual (placebo treatment alone), and 3) the patient's response to the patient-practitioner interaction added to the placebo.

This trial, in patients with irritable bowel syndrome (**IBS**), tested whether these 3 distinct potential contributions can be separated and then combined to produce progressive improvement in clinical outcomes.

Conclusion: Factors contributing to the placebo effect can be progressively combined in a manner resembling a graded dose escalation of component parts. Non-specific effects can produce clinically significant outcomes.

STUDY

1. Randomized, controlled trial of the effect of placebo therapy entered 262 participants with IBS (ROME II criteria).
2. The placebo was sham acupuncture. Patients were completely unaware of the study's primary aim to examine non-specific effects.
3. Randomized to:
 - 1) "Waiting list" controlled for effects of assessment and observation (Hawthorne effect), and the natural course of the disease. Subjects received neither placebo nor interaction with the health care provider.
 - 2) "Limited interaction" provided placebo treatment. At the first visit, participants received limited interaction with the investigator (< 5 minutes). Practitioners explained this was a "scientific study" for which they had been instructed not to converse with the patient. The sham needles were placed, and the patient left alone for 20 minutes after which the practitioner returned to "remove the needles".
 - 3) "Augmented interaction" provided 6 sessions of placebo (sham acupuncture) using the same procedures as with group 2. In addition, each week they received an augmented patient-practitioner relationship that began with the first visit (45 minutes) and continued weekly for 6 weeks. Content included questions concerning symptoms, relationships and lifestyles, non-gastrointestinal symptoms, and how the patient understood the "cause" and "meaning" of the condition. The interviewer incorporated a warm, friendly manner; active listening, empathy, and communication of confidence and a positive expectation.
4. Patients were allowed to continue medications for IBS which were taken before the trial.

5. Evaluated at 3 and 6 weeks. Results at 3 weeks provided data for the primary end point. Those who remained on placebo for an additional 3 weeks serve to provide observations on non-specific effects over time.

6. Outcome assessment at week 3:

	Waiting list (n=87)	Limited (n = 88)	Augmented (n = 87)
Global improvement scale (1-7)	3.8	4.3	5.0
% with adequate relief of symptoms	28	44	62
Improved symptom severity score (0-100)	30	42	82
Improved quality of life score (0-12)	3.6	4.1	9.3

7. Outcomes at 6 weeks: The observed values for all outcome measures rose and were consistent with the author's predictions of order of improvement. Improvements in mean symptom severity and quality of life in the limited group were only slightly higher than the waiting list group. Actually, an improvement in the quality of life was slightly lower in some subjects in the limited group vs the waiting list group. But was much higher in the augmented group

8. More than 80% reported no side effects. The most common adverse effect was pain during sham needle placement, and redness and pain after "needle removal". (Between 5% and 10%). Other adverse effects were reported rarely and were not serious.

DISCUSSION

1. "In this large prospective study of placebo effects we found that such effects can be disentangled into three components that can be recombined to produce incremental improvement in symptoms."
2. An enhanced relationship with a practitioner, together with the placebo treatment provided the most robust effect.
3. Placebo treatment with only limited interaction with practitioners was slightly superior to staying on a waiting list. A therapeutic ritual alone (limited placebo treatment) has a modest benefit, in some persons, beyond no treatment.
4. The magnitude of non-specific effects in the augmented group was clinically significant. Over half of the patients with IBS in the augmented group achieved improvement in symptoms.
5. The magnitude of improvement is comparable with the responder rate in clinical trials using drugs to treat IBS.
6. "These results indicate that such factors as warmth, empathy, duration of time spent with the patient, and the communication of positive expectations might significantly affect clinical outcome."
7. The authors chose IBS for study because they suspected that non-specific effects are most likely to be demonstrable in disorders defined by subjective symptoms rather than more objective measures of disease.
9. Non-specific effects may have a considerable clinical impact.

CONCLUSION

Factors contributing to the placebo effect can be progressively combined in a manner resembling a graded dose escalation of component parts. Non-specific effects can produce statistically and clinically significant outcomes. The patient-practitioner relationship is the most robust component.

BMJ May 3, 2008; 336: 999-1003 Original investigation, first author Ted J Kaptchuk, Harvard Medical School, Boston Mass.

An editorial in this issue of BMJ, first author David Spiegel, Stanford University, School of Medicine, Stanford CA, comments, asking “What is the Placebo Worth?”

A recent study testing pain relief from analgesics showed that merely telling patients they were receiving a novel form of codeine (actually a placebo) that was worth \$2.50 rather than 10 cents, increased the proportion of patients reporting pain relief from 61% to 85%. When the price of the placebo was reduced, so was the pain relief.

What is the best practice with regard to placebo? What do placebos mean for patient care? The article reported that, in patients with IBS in the observation-only group, the global improvement scale was 3%; in the procedure-alone group 20%, and 37% in the placebo + treatment with augmented-quality contact each week. The contact involved questions about symptoms and beliefs about them, and a “warm friendly manner”, empathy, and communication of confidence and positive expectations.

In contrast, the doctor-patient relationship in the sham acupuncture-only group sounds like a caricature of procedure-based medicine practiced under strict time limitations.

Perhaps the ratcheting down of the time that doctors spend with patients and our modern emphasis on drugs and procedures is “penny wise and pound foolish”.

It is widely assumed by skeptics that most, if not all, of the benefit of “alternative” or “integrative” medicine comes from the placebo effect. But, is it possible that the alternative medical community has tended historically to understand something important about the experience of illness and the ritual of the doctor-patients interactions that the rest of medicine might do well to hear? Patients with IBS have a chronic condition that can deeply affect their quality of life. They usually have a story to tell about their suffering and want it to be heard. An empathetic ear may be just what they need.

Many people may be drawn to alternative practitioners because of the holistic concern for their wellbeing they are likely to experience. Many also may experience appreciable placebo responses.

Why shouldn't we try to understand what alternative practitioners know and do? This may help explain why so many patients are prepared to be treated by them, even when many of the treatments are unproven.

Whatever the specifics, the take home message is clear. Primary care clinicians treat patients in a context that can either improve or worsen outcome. The meanings and expectations created by the interactions of doctors and patients matter physically, not just socially. A good doctor-patient relationship can tangibly improve patients' responses to treatment, placebo or otherwise.

An editorial in this issue of BMJ by Fiorna Godlee, editor of BMJ comments:

The biggest scope for added value in the clinical encounter is making the right diagnosis, and giving the right treatments, certainly. But how much of that added value is or could be achieved by what we tend to dismiss as the placebo effect? For some conditions, the placebo effect may be one of the most powerful tools in the medical bag—but only if you know how to use it. It is more than just a neutral comparator against which active treatments are evaluated in randomized, controlled trials. It is more than just a sugar pill.

A constructive doctor-patient relationship can tangibly improve responsiveness to treatment, be it placebo or otherwise. Good doctors know this and don't let alternative practitioners monopolize this crucial aspect of medical care.

If a sham treatment plus a good doctor-patient interaction can be so powerful, doesn't this become a useful treatment in its own right? If so, can we get over the ethical problem that giving a placebo traditionally involves deceiving the patient?

Placebo now has its own evidence base, with benefit shown in a range of conditions and an excellent safety profile. (*But not if the diagnosis is missed, . RTJ*)

The author concludes that where an effective placebo treatment exists, not offering it may be unethical.

“We Should Take Advantage Of Time And Intervene Early”

5-2 AGE AS A MODIFIABLE RISK FACTOR FOR CARDIOVASCULAR DISEASE.

Age is not considered a modifiable risk factor, but it outranks all those that are—lipids, BP, and smoking—as a predictor of cardiovascular events.

Is conventional wisdom correct? Are all the effects of aging immutable?

How do we deal with the dilemma that atherosclerosis is often well underway before middle age, whereas clinical complications are common only after middle age?

Should pharmacological prevention be delayed until just before risk of death and myocardial infarction accelerate—a position that major guidelines have taken— or should we intervene earlier?

These authors believe that we can accomplish more through prevention than is presently believed, if we reframe our understanding of the relation between age, the classic risk factors, and vascular disease.

An analysis of the Framingham Study showed that age alone produced a receiving operator characteristic curve (ROC curve) of 0.731 for angina, myocardial infarction and coronary disease death. Addition of LDL-cholesterol increased it to only 0.746. Age + systolic BP + smoking produced a value of 0.791, which is marginally different from age alone.

Thus, apart from age and sex, the classical modifiable causative factors for cardiovascular disease seem to affect the individual risk of clinical disease to only a small extent. Yet the evidence of substantial benefit from

interventional studies is incontrovertible, To suggest that hypertension and hyperlipidemia are unimportant is unreasonable.

The effect of factors such as dyslipidemia on the development of cardiovascular disease (CVD) is established both by the magnitude of the deviation of that factor from normal, and by the duration of exposure. This point is key. Conventional analyses do not distinguish between the biological changes of aging within the arteries—the non-modifiable effects of disintegration of tissues over time—and those produced by exposure over time to risk factors such as atherogenic dyslipidemia. Since arteries are damaged over time, we should take advantage of time and intervene early.

Another reason why guidelines undervalue the contribution of causal factors such as dyslipidemia is that they generally limit the period of risk that they predict. Only after 60 years of age does the frequency of CVD accelerate so dramatically that it eventually accounts for at least 40% of deaths. The short observation period restricts our appreciation of the true importance of the modifiable factors for CVD. Moderate, but extended exposure to risk factors will be sufficient to cause myocardial infarction and death.

By calculating risk in the short term, and treating age as an independent risk factor, major guidelines discourage drug treatment until clinical events are common.

Coronary artery disease can be substantial even in the 3rd decade of life. For now, we have to rely on recognition of factors such as dyslipidemia and hypertension, which have been linked to early onset of disease.

Early intervention will produce early benefits, but the larger issue is the effect of early intervention on the long-term clinical expression of disease. Cholesterol lowering will produce much greater total benefit if achieved earlier rather than later in life. In the absence of major risk factors by age 50, serious clinical cardiovascular disease by any age is unlikely.

Lifestyle factors are important to advocate, but unlikely to be adequate, especially in those with pronounced abnormalities of BP or lipids. Pharmacological treatment is more potent, but risk factors and costs must be taken into account.

Those with the most abnormal LDL-c values will have the most to gain from treatment since the absolute benefit per unit of reduction in LDL-c is directly related to the starting value.

“If age is as important as conventional analyses show, and if its effects are not modifiable, as conventional wisdom declares, the potential for prevention is limited. We believe this distressing conclusion is incorrect. Age can be deconstructed into the time-related effects of disintegration that affect all of us versus the time-related effects of exposure to the modifiable causal factors that affect some of us more than others.”

Lancet May 3, 2008; 371: 1547-49 “Viewpoint”, first author Allen D Snideman, Royal Victoria Hospital, Montreal, Quebec, Canada

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No Benefit In Control Of Hba1c, BMI, Hypoglycemia, Or Use Of Oral Drugs

5-3 EFFICACY OF SELF-MONITORING OF BLOOD GLUCOSE IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Self-monitoring of blood glucose is widely advocated for patients with type-2 diabetes (**DM-2**) who do not require insulin. There is conflicting evidence as to its value.

This trial investigated the effect of self-monitoring on glucose control, and attitudes and satisfaction with treatment in patients with newly diagnosed DM-2,

Conclusion: Self-monitoring had no effect on glycemic control. It was associated with a decrease in well-being.

STUDY

1. Prospective randomized, controlled trial of self-monitoring of blood glucose vs no monitoring, entered 184 outpatients. All patients were under age 70, and had newly diagnosed DM-2. None were taking insulin. None had previously self-monitored glucose levels. All underwent a structured core education program. The self-monitoring group received additional education on monitoring.
3. Those in the self-monitoring group were provided with a glucose monitor, and asked to monitor four fasting and four postprandial capillary blood glucose measurements each week. They were advised on appropriate responses to high or low readings (eg, diet, and exercise).
4. A treatment algorithm was given to all patients for use of oral antidiabetes drugs.
If HbA1c >7.5% add metformin and titrate to a maximum of 2 g daily.
HbA1c still > 7.5%—add gliclazide 80 mg daily (a sulfonylurea not marketed in the US¹) and titrate to a maximum of 320 mg daily.
HbA1c still > 7.5% consider addition of a thiazolidinedione or transfer to insulin.
5. Main outcome = between group differences in HbA1c, psychological indices, use of oral hypoglycemic drugs, BMI, and reported hypoglycemic rates. Follow-up for one year at intervals of 3 months.

RESULTS

1. Of the 96 participants in the self-monitoring group, 63 carried out over 80% of requested blood glucose monitoring .
2. Outcome measures at one year:
 - 1) At baseline, HbA1c averaged 8.7%. HbA1c fell in both groups, there was no difference between groups—6.9% vs 6.9%
 - 2) Participants in the monitoring group were more depressed—6% higher on the depression subscale. There was also a trend toward increased anxiety in this group.
 - 3) No differences in treatment satisfaction.

- 4) No differences in reported hypoglycemia. No difference in use of oral drugs.
- 5) No difference in BMI.

DISCUSSION

1. This trial included a rigorous treatment algorithm, which was successful in reducing HbA1c in both groups equally at 12 months. This was an important difference between this and other trials.
2. Evidence suggests that some patients consider monitoring uncomfortable, intrusive, and unpleasant.

CONCLUSION

In these patients with newly diagnosed type-2 diabetes, in comparison with a control group, self-monitoring of blood glucose concentration had no benefit in control of HbA1c, BMI, hypoglycemia, or use of oral drugs.

BMJ May 24 2008; 336; 1174-77 Original investigation, first author Maurice J O'Kane, Altnagelvin Hospital, Western Health and Social Care Trust, Northern Ireland.

1 Many other sulfonylureas are available for \$4 for a months supply. Go to Goggle \$4 prescriptions.

A second article in this issue of BMJ reports that self-monitoring in *not* cost effective.

Favors Prednisolone. Both Are Effective. Prednisolone Is Safer.

5-4 USE OF ORAL PREDNISOLONE OR NAPROXIN FOR THE TREATMENT OF GOUTY ARTHRITIS

Gout has a substantial effect on the population. An estimated 1% to 2% of adults have gout. This creates a substantial burden on work-related and medical costs.

Colchicine is now rarely used. It has a narrow therapeutic window. NSAIDs are now first choice for treatment of acute gouty arthritis despite their gastrointestinal and cardiovascular risks. About 40% of upper g.i. bleeding events are attributable to NSAIDs. Risk is highest during the first week of use. The American Heart Association has recommended restricted use because of cardiovascular risks, which include loss of renal function, fluid retention, and interaction with anticoagulants.

Patients with gout are usually at an age when g.i. effects may be more common., Many have comorbid renal and cardiovascular disease.

Systemic corticosteroids do not have important drawbacks in the short term. However, studies of the benefits of corticosteroids on gout are limited.

This study investigated equivalence of naproxin and prednisolone in primary care.

Conclusion: The drugs were equivalent in reducing pain of gouty arthritis. Prednisone is safer.

STUDY

1. Randomized, double-blind equivalence trial entered 120 patients (mean age 58) with monoarticular arthritis. All had gout confirmed by identification of monosodium urate crystals in synovial fluid.
2. Randomized to: 1) Prednisolone 35 mg once daily, or 2) naproxin 500 mg twice daily for 5 days.
3. Primary outcome = pain measured on a 100 mm visual analogue scale. Disability related to the affected joint was also scored on a scale of 0 to 100.
4. Determined responses to pain, general disability and walking disability 8 times for up to 90 hours, and after 90 hours.

RESULTS

1. Scores on 100 mm visual analogue scale at baseline and after 90 hours:

	Pain		General disability		Walking disability	
	Prednisolone	Naproxin	Prednisolone	Naproxin	Prednisolone	Naproxin
Baseline	62	59	59	55	71	67
After 90 h	17	13	17	13	17	13
Reduction	45	46	42	42	54	54

2. On day 4, 80% of the prednisolone group and 87% of the naproxin group had clinically significant improvement.
3. Mean reduction in pain for each 12-hour interval on the 100 mm visual analogue scale was prednisolone -5.6; naproxin -5.8.
4. Adverse effects were similar between groups: gastric or abdominal pain 15%; itch or dizziness 7%; dyspnea or palpitation 5%; miscellaneous 21%. None was considered important.
5. At 3 weeks, all patients reported complete relief of symptoms.

DISCUSSION

1. Outcomes at 90 hours were within the predefined 10% margin of equivalence. "We conclude that prednisolone was clinically equivalent to naproxin in treatment of gout."
2. In the subjects (mean age 58) many patients had risk factors which may be aggravated by NSAIDs: hypertension 53%; cardiovascular morbidity 18%.
3. No patients were excluded because of the risks from prednisolone. A quarter of the eligible patients had to be excluded because of direct safety risks if they had been treated with naproxin: serious renal disease, serious other comorbidity; a history of upper g.i. ulcer or bleeding; and the current use of an anticoagulant drug. "For them a 5-day course of prednisolone would have been no problem."
4. The additional costs of gastroprotective drugs added to NSAIDs should be taken into account.

CONCLUSION

Although prednisolone and naproxin were equally effective in the initial treatment of gouty arthritis over 4 days, the present study provides a strong argument to consider prednisolone as first treatment option.

Lancet May 31, 2008; 371; Original investigation, first author Hein J E M Janssens, Radboud University, Nijmegen, Netherlands.

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“It Is Not Too Late To Start Antihypertension Therapy”

5-5 TREATMENT OF HYPERTENSION IN PATIENT 80 YEARS OF AGE OR OLDER

Evidence of benefit in treating hypertensive patients 80 years of age and older is inconclusive. It has been suggested that antihypertension therapy may reduce the risk of stroke while increasing the risk of death.

This trial aimed to clarify risk and benefits of treatment in the very elderly.

Conclusion: Treatment with indapamide with and without perindopril was beneficial.

STUDY

1. Multicountry, randomized, double-blind, placebo-controlled trial entered over 3800 patients.
All were age 80 and over (mean = 84; 22% age 85-89; 5% 90 or over) and had persistent hypertension (sustained systolic BP 160 and over). Mean BP while sitting was 173/91. None had a serum creatinine level over 1.7 mg/dL or elevated potassium. 12% had a history of cardiovascular disease; 7% diabetes.
2. Subjects were instructed to stop all antihypertension medications for 2 months during which several BP readings were obtained.¹ Subjects with isolated systolic hypertension were included.
3. If the mean systolic BP was between 160 and 199 subjects were randomized to:
 - 1) Indapamide (*Lozol*; Servier; a diuretic) sustained release 1.5 mg or 2) placebo.
4. If needed to reach target BP (less than 150/80), perindopril (*Aceon*; an ACE-inhibitor) 2 mg or 4 mg was added.
5. No other antihypertension medications were used.
6. Primary end point was any stroke (fatal or non-fatal). Median follow up = 2 years. Analysis by intention-to-treat.

RESULTS

1. During the 2-month run-in period, 30 patients died. (No comment on cause. Some must have died of cardiovascular disease.)
2. At 2-years:
About 1/4 of the subjects were taking indapamide alone, 1/4 indapamide + perindopril 2 mg, and half were taking indapamide + perindopril 4 mg.

BP had fallen by a mean of 15/7 in the placebo group, and 30/13 in the active-treatment group—a difference of 15/7 between groups.

Target BP was reached in 20% of the placebo group and 48% of the active-treatment group.

3. Main fatal and non-fatal endpoints in the intention to treat population:

	Rate per 1000 person-years		Absolute difference
	Active	Placebo	
All Stroke	12	18	6
Death from stroke	7	11	4
Death			
From any cause	47	60	13
From cardiovascular causes	24	31	7
From cardiac causes	6	8	2
From heart failure	2	3	1
Fatal or non-fatal			
Any myocardial infarction	2	3	1
Any heart failure	5	15	10
Any cardiovascular event	34	51	17

4. For stroke, 51 events occurred in the active treatment group vs 69 in the placebo group (not quite statistically significant)—11 strokes prevented per 1000 patients treated for 2 years. Fatal stroke was reduced by 39%.

There was a 21% reduction in the overall rate of death from any cause in the active group.

The rate of death from cardiovascular causes was reduced by 23%; fatal and non-fatal heart failure by 64%.

Rate of any cardiovascular event was reduced by 34%.

4. Benefits of treatment began to appear within the first year.

5. There were no significant differences between groups with regard to changes in potassium, glucose, or creatinine.

6. Adverse events: Only 3 in the placebo group and 2 in the treatment group were classified as possibly having been due to the trial medication.

DISCUSSION

1. “Antihypertensive treatment based on indapamide (1.5 mg sustained release), with and without 2 or 4 mg of perindopril, reduces risk of death from stroke, and death from any cause in very elderly patients.”

2. The risk of heart failure was especially impressive in the active vs the placebo subgroup treated for 4 years (2% vs 7%).

3. An unexpected finding of the trial was the reduction in death from any cause with active treatment.
4. Given the known changes in serum potassium level that can occur with thiazide diuretics and an ACE-inhibitor, in combination, they are likely to have a neutral effect. Potassium levels were similar in both groups in this study.
5. Indapamide has also been shown to have a neutral effect on blood glucose and lipids.
6. The results support a target BP of 150/80. The target was reached in about 50% of treated patients after 2 years.

CONCLUSION

Antihypertension treatment with indapamide, with or without perindopril in persons 80 years or older, is beneficial.

NEJM May 1, 2008; 358: 1887-98 by the Hypertension in the Very Elderly Trial (HYVET), first author Nigel S Beckett, Imperial College, London

The study was stopped prematurely for ethical reasons because of the significant (unexpected) benefit with regard to death from any cause.

An editorial in this issue of NEJM by John B Kostis, University of Medicine and Dentistry of New Jersey, New Brunswick comments and expands on this article

There is a continuous, approximately linear increase in systolic BP with increasing age for values beginning as low as 115/75.

In one very large trial, the risk of fatal stroke for those with systolic over 180 was about 15 times as high, and the risk of fatal ischemic heart disease 7 times as high as the rates among those with optimal BP.

The risk has been found in all age groups, but the strength of the association declines with increasing age as demonstrated by a meta-analysis of 1 million participants. Among persons age 50-59, the rate of death from stroke increases by a factor of 16 for those with systolic BP 180 and only by a factor of 3 among persons age 80 to 89.

In the HYVET study, active treatment as compared with placebo, was associated with a 21% reduction in the relative risk of death from any cause, a 64% reduction in relative risk of heart failure, and a 30% reduction in relative risk of stroke.

There have been concerns about the efficacy and safety of antihypertension therapy in this age group. There was speculation that impaired cardiac and renal function, orthostatic hypotension, cognitive impairment, subjective adverse effects, and polypharmacy would detract from the clinical benefit in the very old.

HYVET puts to rest the question of usefulness of treating hypertension in the very old. It provides important guidance to physicians.

Like all clinical trials, those involving old persons with hypertension, must also involve individualized treatment that takes into account the factors that are associated with aging as well as individual preference.

The results of HYVET prove that it is not too late to start antihypertension therapy in older people and expands the upper limit of the age spectrum for which there is evidence of a treatment benefit.

Bruit Significantly Associated With Increased Likelihood Of Cardiovascular Death

5-6 CAROTID BRUITS AS A PROGNOSTIC INDICATOR OF CARDIOVASCULAR DEATH AND MYOCARDIAL INFARCTION

Clinical trials have shown benefit from carotid endarterectomy for *symptomatic* patients with severe (70-99%) carotid stenosis. However, a carotid bruit is a weak predictor of cerebrovascular events in patients who are otherwise asymptomatic for cerebrovascular conditions.

The uncertainty about prognostic implications has led the USPSTF to recommend against routine auscultation for carotid bruits.

Carotid bruits are probably a better indicator of generalized atherosclerosis than for risk of stroke. Several studies have reported that patients with carotid disease are more likely to die from cardiovascular than from cerebrovascular disease.

This study investigated whether carotid bruits could be used as a prognostic factor to determine subsequent rates of cardiovascular death and myocardial infarction. **(MI)**

Conclusion: Auscultation for carotid bruits could help select those who might benefit from an aggressive strategy to lessen cardiovascular risk.

STUDY

1. A meta-analysis based on a literature search included over 17 000 patients followed up to 4 years. All studies (mostly prospective cohort studies) reported incidence of MI and cardiovascular death in adults. Median range = age 65.
2. All studies had to have extractable data for cardiovascular outcomes in individuals with carotid bruits.

RESULTS

1. Eight studies assessed MI in patients with bruits. The pooled estimate of myocardial infarction was 3.7 per 100 patient –years.
2. Four studies provided a direct comparison of risk of MI in patients with and without bruit. The pooled odds ratio (bruit vs no bruit) was 2.15.
3. In 16 studies assessing cardiovascular death, the pooled estimate of yearly deaths was 2.9 per 100 patient-years. In patients without bruits the rate was 1.1 per 100 patient-years.

DISCUSSION

1. “Our study has shown that the presence of a carotid bruit significantly increased the likelihood of

cardiovascular death or myocardial infarction .” Cardiovascular death or MI were twice as likely in patients with bruits compared to those without.

2. These atherosclerotic changes, which cause turbulent flow in the artery, might indicate a system-wide vascular pathological change, including the coronary arteries.
3. “Since auscultation is a swift and inexpensive test, it could be used in every patient who might be at risk of coronary disease to aid the clinician in assessment of risk.”
4. The presence of a carotid bruit per se is not an independent risk factor of coronary disease, rather, its presence identifies a subgroup that is at high risk of having similar pathological changes in the coronary arteries.
5. “Our analysis shows that the presence of a carotid bruit meets the definition of a coronary risk equivalent to a 37% increase over 10 years.”
6. This should lead to aggressive modification of risk factors that are recommended for diabetes or peripheral artery disease.
7. The investigators admit a number of limitations to their study.

CONCLUSION

Auscultation for carotid bruit in patients at risk for heart disease could help select those who might benefit the most from an aggressive modification strategy for cardiovascular risk.

Lancet May 10, 2008; 371: 1587-94 Original investigation, first author Christopher A Pickett, Walter Reed Army Medical Center, Washington DC.

An editorial in this issue of Lancet, first author Victor Aboyans, Dupuytren University Hospital, Limoges, France, comments and expands on the article;

This article does not deal with risks for TIA and stroke in association with bruit.

A bruit will not be audible in a large number of patients with significant carotid disease. In addition, sensitivity of hearing bruit is low. Ie, many physicians who auscult the artery will not hear a bruit in patients who do indeed have a bruit.

Carotid bruit is only a marker of risk to add to many other risk factors. The incremental value of a bruit is not known.

In the study, almost a third of the subjects already had atherosclerotic disease, hyperlipidemia, diabetes, and were smokers.

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Contrary To Past Observational Studies, This Randomized Trial Reported No Benefit

5-7 EFFECT OF FOLIC ACID AND B VITAMINS ON RISK OF CARDIOVASCULAR EVENTS AND TOTAL MORTALITY AMONG WOMEN AT HIGH RISK FOR CARDIOVASCULAR DISEASE.

Elevated homocysteine levels have been directly associated with cardiovascular risk in observational studies. Daily supplements with folic acid, vitamin B6 and vitamin B12, or a combination, reduce homocysteine levels. Some meta-analyses of randomized trials on subjects with preexisting cardiovascular disease (CVD) have shown no benefits. However, in the most recent meta-analysis of observational studies, a 25% lower homocysteine level was associated with a 32% lower risk of CHD in women and a 15% lower risk in men.

Observational trials suggest that benefits of lowering homocysteine levels may be greater in women. And that benefits might be greater if patients were treated for longer periods.

This trial (1996-2005) tested whether a combination of folic acid, B6, and B12 over a mean of 7 years would lower risk of CVD in high-risk women.

Conclusion: There was no benefit.

STUDY

1. Double-blind placebo-controlled trial entered over 5400 professional women (age 42 and older; mean age = 63) All had either a history of CVD, or 3 or more risk factors for CVD.
2. Randomized to:
 - 1) Combination pill containing folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg)
 2. Matching placebo.
3. Main outcome = composite outcome of myocardial infarction, stroke, coronary revascularization, and CVD mortality. Duration of therapy = 7 years.

RESULTS

1. During 7 years, 796 subjects (15%) experienced a CVD event.
2. There was no difference at any time in the cumulative incidence of the primary combined end point between groups. [Active group – 14.9%; placebo – 14.3%.]
3. The risk of death from any causes was also similar between groups—9.2% vs 9.4%.
4. Blood levels were determined in a subset of subjects:
 - 1) Folate: At baseline, folate levels in both groups were 8.9 ng/mL vs 8.8 ng/mL. One third of the study population was considered deficient in folic acid (< 7 ng/mL). At the end of the study the median folate level in the placebo group increased to 15 ng/mL. The increase in the active group was much greater—50% had a level above 40 ng/mL.
 - 2) Homocysteine: In the placebo group there was no apparent reduction. In the folate group, levels were significantly reduced—median = 12 umol/mL, and the number of subjects with baseline elevations of homocysteine (> 15 umol/L) was reduced to 10%.

DISCUSSION

1. “We found no overall effects of a combination of folic acid, vitamin B6, and vitamin B12 on the

primary outcome of total CVD events over 7 years. There was no evidence of a benefit on stroke or any evidence of harm.”

2. These null results are consistent with those previously reported in randomized trials in men.
3. Fortification of grain products mandated in the US in 1996 significantly reduced mean plasma homocysteine, and decreased the prevalence of high homocysteine levels.
4. Initial epidemiological studies were primarily retrospective and suggested that reduction of homocysteine levels would decrease CVD risk by one third.

CONCLUSION

In this trial, a combination of high doses of folic acid, B6, and B12 over 7 years had no beneficial effect (or adverse effects) on a combined outcome of total major cardiovascular events in this population of women at high risk of CVD.

JAMA May 7, 2008; 299: 2027-36. Original investigation , first author Christine M Albert, Brigham and Women’s Hospital, Harvard Medical School, Boston.

Study sponsored by the National Heart, Lung, and Blood Institute and the National Institutes of Health

An editorial in this issue of JAMA by Eva Lonn, McMaster University, Hamilton, Ontario, Canada comments and expands on this article:

In 1969 it was proposed that an amino acid produced during catabolism of methionine causes arterial and venous atherothrombotic disease. Children with extreme elevations of plasma homocysteine (homocysteinuria) due to an inborn error of metabolism, died from premature atherosclerosis. Treatment with high doses of B vitamins, and a low methionine diet improved prognosis.

Epidemiological studies have, in general, demonstrated associations between elevated homocysteine levels and increased risk of CHD, and even stronger risks of stroke. Epidemiological studies also suggested a graded and independent association between CVD risk and homocysteine levels extending from mild and even normal homocysteine levels..

Such retrospective observational studies are inevitably subject to bias and confounding, and may overestimate risks associated with high levels. But subsequent large prospective cohort studies in general supported the earlier findings. A meta-analysis of prospective cohort studies demonstrated that after accounting for known CHD risk factors, a 25% lower homocysteine level was associated with an 11% lower risk of CHD, and a 19% lower risk of stroke.

As recently as 2005, The American Heart Association stated that “The lowering of the population mean level of total homocysteine is estimated to have prevented 17 000 deaths from coronary causes each year.” Folic acid was included by some authorities in the proposed “polypill” to be taken by all adults to reduce population incidence of CVD.

“Until further data become available, it is essential to remain firmly grounded on the available evidence, and to admit that, once again, experimental and observational data do not always transfer into therapeutic benefits.”

There is no role at present for routine screening for elevated homocysteine levels. And no role for homocysteine lowering by B vitamins.

“The Finer Points Of Patient Care Should Be Built On A Basis Of Good Manners.”

5-8 ETIQUETTE-BASED MEDICINE

The editorialist comments, that during his recent hospitalization, he found the Old World manners of his European-born surgeon, and his reaction to them, revealing.

“Whatever he might have been feeling, his behavior—dress, manners, body language, eye contact—was impeccable. I wasn’t thinking ‘what compassion’, instead. I found myself thinking ‘what a professional—‘what a gentleman’.”

The impression he made was remarkably calming. “It helped to confirm my suspicion that patients may care less about whether their doctors are reflective and empathetic than they are respectful and attentive.”

Medical education should place more emphasis on this aspect of the doctor-patient relationship—“etiquette-based medicine”.

There have been many attempts to foster empathy and compassion in clinicians, but none to systematically teach good manners. “The very notion of good manners may seem quaint and anachronistic, but it is at the heart of the mission of other service-related professions.” Doctors can behave in certain specified ways that will result in the patient’s feeling well treated.

How could we implement an etiquette-based approach to patient care? The author proposed that we develop a checklist of physician etiquette for the clinical encounter. This would include:

- Ask permission to enter the room. Wait for an answer.
- Introduce yourself, showing your ID badge
- Shake hands (wear gloves if needed)
- Sit down. Smile appropriately.
- Briefly explain your role on the team
- Ask the patient how he or she is feeling about being in the hospital.

The list can be modified to address a variety of clinical situations, explaining an ongoing workup, delivering bad news, preparing for discharge.

This does not address the way the doctor feels, only how he or she behaves. It complements, rather than replaces, efforts to train physicians to be more humane.

Trainees are likely to learn more from watching colleagues act with compassion than from hearing them discuss it.

We should continue our efforts to develop compassionate physicians, but let's not overlook the possibility of the more immediate benefits of emphasizing good behavior.

“The finer points of patient care should be built on a basis of good manners.”

NEJM May 8, 2008; 358: 1988-89 “Perspective” by Michael W Kahn, Beth Israel Deaconess Medical Center, Boston, Mass.

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