

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS
OCTOBER 2001

ANTIHYPERTENSION DRUGS — ANY BENEFIT BEYOND BP-LOWERING?

EXTRACRANIAL CAROTID STENOSIS — SUGGESTIONS FOR TREATMENT

TRANSIENT MONOCULAR BLINDNESS — ANY BENEFIT FROM CAROTID ENDATERECTOMY?

VALUE OF CALCIUM SUPPLEMENTATION IN YOUNG GIRLS

ACE INHIBITOR REDUCES RISK OF TYPE 2 DIABETES.

FAMILIAL BREAST CANCER — HOW IMPORTANT THE RISK IN FIRST DEGREE RELATIVES?

NARRATIVE MEDICINE — WHAT IS IT?

RESPONSE TO LOSS, FUTILITY, AND UNREALISTIC HOPES

BENEFIT OF PATIENT CENTEREDNESS AND POSITIVE APPROACH

PROGNOSTIC VALUE OF A NORMAL OR NONSPECIFIC ELECTROCARDIOGRAM IN ACUTE MI

FAST DIAGNOSIS OF MYOCARDIAL INFARCTION

CONTRIBUTION OF RESPIRATORY SYNCYTIAL VIRUS TO COMMUNITY "FLU"

ELEVATED MIDLIFE BLOOD PRESSURE INCREASES RISK IN OLDER AGE

THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE

ACUTE CORONARY SYNDROMES — TWO NEW MARKERS FOR RISK

NEW TREATMENT FOR CONGESTIVE HEART FAILURE

EPIDEMIOLOGY AND DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION.

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HIGHLIGHTS OCTOBER 2001

10-1 CARDIOVASCULAR PROTECTION AND BLOOD PRESSURE REDUCTION: A Meta-Analysis

On average, all antihypertensive drugs have similar long-term efficacy and safety in providing cardiovascular protection.

Compared with diuretics and beta-blockers, calcium channel blockers might protect more against stroke and less against myocardial infarction. This results in an overall cardiovascular benefit similar to that of old classes of antihypertension drugs.

10-2 EXTRACRANIAL CAROTID STENOSIS

Symptomatic CS

All should receive antiplatelet medication: aspirin, clopidogrel (*Plavex*), or the combination of aspirin and dipyridamole. Anticoagulant therapy is not routinely recommended.

Endarterectomy: Indicated for patients with 70% to 99% stenosis who are good candidates for surgery and have had symptoms within the past 2 years. For those with 50% to 69% stenosis decision for surgery should be made on the clinical features that influence risk of stroke vs the risks of surgery.

Asymptomatic CS:

Surgery should be individualized and considered for those under age 80 with stenosis > 60% if an experienced surgeon is available. Presence or absence of coexisting conditions, life expectancy, and patient preferences should be considered.

10-3 TRANSIENT MONOCULAR BLINDNESS ASSOCIATED WITH CAROTID ARTERY STENOSIS.

As compared with hemispheric TIA, TMB associated with internal carotid stenosis carries a better prognosis with respect to subsequent stroke. Endarterectomy may improve prognosis in the group with other risk factors for stroke.

Practical point: This does have some clinical application to primary care. Patients with TMB may be informed more accurately about prognosis. Clinician and patient may more easily reach agreement about treatment.

10-4 GAIN IN BONE MINERAL MASS IN PREPUBERTAL GIRLS 3-5 YEARS AFTER DISCONTINUATION OF CALCIUM SUPPLEMENTATION.

Calcium supplementation during childhood and adolescence increases bone mass. Peak bone mass at the end of the prepubertal period is a major determinant of risk of osteoporotic fractures in later life.

Practical point: Primary care clinicians should make sure their adolescent girl patients receive adequate intake of calcium and vitamin D. Supplementation is often needed.

10-5 RAMIPRIL AND THE DEVELOPMENT OF DIABETES

Ramipril, an ACE inhibitor, reduced risk of developing diabetes in high risk individuals. The number need to treat to benefit one patient is high

10-7 NARRATIVE MEDICINE

Narrative competence is the competence that human beings use to absorb, interpret, and respond to stories others tell. Everyone has a story to tell. Along with scientific ability, physicians need the ability to listen to the narratives of the patient, grasp and honor their meaning, and be moved to act on the patient's behalf.

10-8 "I WISH THINGS WERE DIFFERENT": EXPRESSING WISHES IN RESPONSE TO LOSS, FUTILITY, AND UNREALISTIC HOPES

"When the emotion is unrealistic hope, loss, futility, or grief that seems overwhelming or otherwise is very difficult to address, physicians should consider joining with the patient and family in the expression of a wish that their circumstances were different."

In these challenging situations physicians may attempt to respond empathetically by stating "I'm sorry". This well intentioned response, although frequently appropriate, may be misinterpreted and misdirected.

Practical point: Primary care clinicians will develop their own individual approaches when encountering difficult emotional situations. This suggestion is a worth-while approach.

10-9 OBSERVATIONAL STUDY OF EFFECT OF PATIENT CENTEREDNESS AND POSITIVE APPROACH ON OUTCOMES OF GENERAL PRACTICE CONSULTATIONS.

Patient-centered approach includes five components.

- 1) Communication and partnership with the doctor.
- 2) Personal relationship with the doctor.
- 3) Health promotion.
- 4) Positive approach to diagnosis and prognosis.
- 5) Interest in the effect of the illness on the patient's life.

If the doctor provides a positive patient-centered approach, patients will be more satisfied, more enabled, and may have less symptom burden and fewer rates of referral.

10-10 PROGNOSTIC VALUE OF A NORMAL OR NONSPECIFIC ELECTROCARDIOGRAM IN ACUTE MYOCARDIAL INFARCTION

In a large cohort of hospitalized patients with eventually established acute MI, those presenting with an initially normal or non-specific ECG had lower in-hospital mortality than those with initially diagnostic ECGs. However, absolute rates of mortality and complications were unexpectedly high.

Practical point: Among patients presenting with suspected acute MI, some will be discharged home without a proper diagnosis. Although they are relatively few, the consequences may be disastrous. These patients should be rechecked the next day even though the clinician feels the risk of MI is small. It would be reasonable to routinely give these patients prophylactic aspirin and even low-dose beta-blockers before discharge home.

10-11 FAST DIAGNOSIS OF MYOCARDIAL INFARCTION

A new test procedure now approved by the FDA simultaneously measures 3 cardiac markers: troponin I, creatine kinase-MB, and myoglobin. All are released by the damaged myocardium.

It can be performed quickly at the bedside. It is very predictive in ruling out acute MI.

10-12 CONTRIBUTION OF INFLUENZA AND RESPIRATORY SYNCYTIAL VIRUS TO COMMUNITY CASES OF INFLUENZA-LIKE ILLNESS

In individuals with influenza-like illness, there is a substantial potential for confusion between illness caused by RSV and IV. In this study about 20% of adults with flu-like symptoms were positive for respiratory syncytial virus. RSV is an important pathogen contributing to the burden of illness in the entire community in winter.

Practical point: Watch for development of RSV vaccine for adults.

10-13 ELEVATED MIDLIFE BLOOD PRESSURE INCREASES RISK IN ELDERLY PERSONS: The Framingham Study

Elevated BP during the midlife decades contributes to the risk of stroke in older age. Optimal prevention of late-life stroke will likely require control of midlife BP.

Practical point: Hypertension should be controlled throughout life.

10-14 THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES.

A single measurement of BNP obtained within a few days of onset of ischemic symptoms provided powerful risk-stratification information across the entire spectrum of acute coronary syndromes.

It predicted long term risk of death and non-fatal coronary events. The prognostic usefulness persisted after adjustment for the presence of HF and other important predictors of mortality.

The authors suggest — B-type natriuretic peptide should be measured after an acute coronary syndrome in order to identify the risk of adverse outcomes. Treatment should be adjusted accordingly.

Practical point: Primary care clinicians should keep this marker in mind. It has not yet reached frequent clinical application, but probably will in the near future.

10-15 ACUTE CORONARY SYNDROMES — BEYOND MYOCYTE NECROSIS

Tests for neurohumoral activation (elevated brain natriuretic peptide) and inflammation (C reactive protein) may augment our ability to identify patients at risk of adverse events, and potentially help to reserve the most expensive and aggressive therapies to individuals at highest risk.

Practical point: These two proteins will be increasingly used as risk markers.

10-16 CONGESTIVE HEART FAILURE TREATMENT

The FDA has approved nesiritide (*Natrecor*), a preparation of human B-type natriuretic peptide, for intravenous treatment of acutely decompensated congestive heart failure (ADCHF).

10-17 EPIDEMIOLOGY AND DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION.

A brief explanation of the pathophysiology of *H pylori* gastritis. Why do some develop duodenal ulcers and some develop gastric ulcers and cancer?

No cardiovascular protection beyond BP-lowering effect

10-1 CARDIOVASCULAR PROTECTION AND BLOOD PRESSURE REDUCTION: A Meta-Analysis

Do antihypertensive drugs offer cardiovascular protection beyond their BP lowering effect? This has been debated. Studies differ. Several report more favorable protection against cardiovascular complications when one type of antihypertensive drug is compared with another. Two quantitative reviews reached opposite conclusions with respect to calcium-channel blockers compared with diuretics or beta-blockers.

This sophisticated statistical study assessed whether antihypertension drugs offer cardiovascular protection beyond their BP-lowering effect.

Conclusion: All antihypertension drugs had similar long-term efficacy and safety which depended only on their BP-lowering effect.

STUDY

1. Searched for outcome trials that tested drugs to lower BP in normotensive and hypertensive patients.

None had overt heart failure.

2. The quantitative review included nine trials -- over 62 000 patients.
3. All trials were randomized and controlled and published in peer reviewed journals. All assessed BP and cardiovascular events. All had a follow-up of over 2 years.

RESULTS

1. Compared with old drugs (diuretics and beta-blockers), calcium-channel blockers (**CCBs**) and ACE inhibitors (**ACE**) offered similar overall cardiovascular protection.
2. CCBs provided more reduction in risk of stroke, and less protection in risk of myocardial infarction.

DISCUSSION

1. "Results of outcome trials for antihypertensive drugs can be explained by blood pressure differences between groups."
2. All antihypertension drugs had similar long-term efficacy and safety.
3. "Our results show the desirability of lowering blood pressure as much as possible to achieve the greatest reduction in cardiovascular complications."
4. In older persons with isolated systolic hypertension, lowering systolic by 10 mm Hg reduced the risk of stroke by 38% and myocardial infarction 23%.
5. In patients with predominantly diastolic hypertension, corresponding benefits produced by a 5-6 mm Hg reduction in diastolic pressure were 38% and 16%.
6. "Blood pressure at entry explained little additional variance."
7. CCBs and ACE reduced fatal and non-fatal outcomes as effectively as diuretics or beta-blockers. Compared with the older drugs, they gave the same overall protection against cardiovascular complications. But, CCBs provided more reduction in risk of stroke and less reduction in risk of myocardial infarction.
8. "Our analysis does not indicate to what extent blood pressure should be lowered. This issue remains unsettled."
9. The BP gradients (fall in BP when treated) largely accounted for most differences in outcome. "These findings emphasize the desirability of blood pressure control."
10. "The hypothesis that ACE inhibitors might affect outcome beyond their blood pressure lowering effects remains unproved."

CONCLUSION

On average, all antihypertensive drugs have similar long-term efficacy and safety in providing cardiovascular protection.

Compared with diuretics and beta-blockers, CCBs might protect more against stroke and less against myocardial infarction. This results in an overall cardiovascular benefit similar to that of old classes of antihypertension drugs.

Lancet October 20, 2001; 358: 1305-15 Original investigation, first author Jan A Staessen, Katholieke Universiteit Leuven, Belgium. www.thelancet.com

Comment:

This is a long and detailed statistical analysis. Clinicians having expertise and interest in statistical applications will be able to analyze the study in more detail than I could. The study did appear to me to be authoritative. I focused on their conclusions.

The primary goal of therapy of hypertension is to reduce the BP gradually, with care to avoid adverse effects. And to lower the BP as much as possible consistent with individual patient's response.

Since most patients with hypertension will require dual or triple therapy, the decision about choice of individual drugs becomes less demanding. I believe many primary care clinicians will stick to the "golden oldies" ó diuretics and beta-blockers. They are much less costly over the years of therapy needed to treat hypertension. In low dose they are safe and well tolerated. This study will reassure primary care clinicians who begin therapy with these two drugs.

A most interesting point: BP-lowering benefits depended mainly on the mm of Hg the pressure was reduced, independent of the initial BP. RTJ

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Surgery of medical treatment? Still a dilemma

10-2 EXTRACRANIAL CAROTID STENOSIS

("Clinical Practice" is a feature of NEJM which reviews common clinical problems. The reviewer cites evidence for various strategies, reviews formal guidelines, and concludes with clinical recommendations.

Practical Pointers has abstracted many articles concerning carotid stenosis. RTJ)

Carotid stenosis (**CS**) is an important cause of transient ischemic attacks (**TIA**) and stroke. Carotid atherosclerosis accounts for up to 20% of cases of brain infarction. In a patient with sudden transient monocular blindness (**TMB**) who has a history of diabetes, hypercholesterolemia, or cigarette smoking, carotid stenosis should be first on the differential diagnosis list.

There are two main strategies for treatment of CS:

1) Stabilize or halt progression of the carotid plaque through risk modification and medication: control of hypertension, diabetes, lipids (including statins); abstinence from smoking; elimination of excessive use of alcohol (*light to moderate use has been associated with a reduction in risk of stroke*) ; and increase in physical activity. Antithrombotic agents should be used. (Benefit of oral anticoagulants has not been shown.)

2) Surgery: endarterectomy or angioplasty with stenting.

Carotid endarterectomy for *symptomatic* CS:

For patients with symptomatic CS of 70% or more, the value of endarterectomy has been established. An absolute reduction of 17% in risk of subsequent stroke has been reported. [NNT(prevent one stroke over 5 years) = 6] Carotid endarterectomy is the best option in this group.

For patients with symptomatic stenosis of 50% or less, no benefit of surgery has been reported.

Benefit of endarterectomy in those with symptomatic CS of 50%-69% stenosis is clearly less than those with more severe stenosis. In the latter group, benefits are greatest in those with greater stenosis, males over age 75, and patients with recent history of stroke (not TIA). Benefits of surgery are greater in those with other risk factors.

Carotid endarterectomy for *asymptomatic* carotid stenosis:

Asymptomatic CS is a clear risk factor for stroke. The risk is lower than that associated with symptomatic CS. (Ipsilateral stroke up to 3% per year in those with > 50% stenosis.) Risk is somewhat higher for those with increasing stenosis. The value of surgical treatment is debatable. Some trials have reported benefits from surgery are greater than that of medical therapy. One trial reported an absolute reduction in risk of stroke of about 6% over 5 years. [NNT = 17], But, asymptomatic patients undergoing surgery have complications from angiography as well as risk of perioperative stroke and death. "On the basis of absolute risk of stroke, it was clear that a rate of perioperative complications (stroke and death) of more than 3% would eliminate the potential benefit. Such low complication rates are unusual in community-hospital settings."

Conclusions and recommendations:

Symptomatic CS

All should receive antiplatelet medication ó aspirin, clopidogrel (*Plavex*), or the combination of aspirin and dipyridamole. Anticoagulant therapy is not routinely recommended.

Endarterectomy: Indicated for patients with 70% to 99% stenosis who are good candidates for surgery and have had symptoms within the past 2 years. For those with 50% to 69% stenosis, decision for surgery should be made on the clinical features that influence risk of stroke vs the risks of surgery.

Asymptomatic CS:

Surgery should be individualized and considered for those under age 80 with stenosis > 60% if an experienced surgeon is available. Presence or absence of coexisting conditions, life expectancy, and patient preferences should be considered.

The author prescribes statins even if lipids are normal, ACE inhibitors for those with hypertension, and antiplatelets for all, along with appropriate lifestyle changes. (*See algorithm figure 1 p 1117*)

NEJM October 11, 2001; 345: 1113-1118 "Clinical Practice" commentary by Ralph L Sacco, Columbia University College of Physicians and Surgeons, New York. www.nejm.org

Surgery is beneficial in select patients

10-3 PROGNOSIS AFTER TRANSIENT MONOCULAR BLINDNESS ASSOCIATED WITH CAROTID ARTERY STENOSIS.

Transient monocular blindness (**TMB**; amaurosis fugax) accounts for about 25% of transient ischemic attacks (**TIAs**) involving the anterior cerebral circulation. (About 50 000 cases per year in the US.) TMB is evidence of disease of the internal carotid artery. It is a risk factor for ischemic stroke.

Previously, two large clinical trials reported that endarterectomy is effective in reducing risk of stroke in patients with symptomatic internal carotid artery stenosis.

This study asks: What is the natural history of TMB treated medically? Does carotid endarterectomy benefit patients with TMB?

Conclusion: Endarterectomy may be beneficial in patients with TMB who also have other risk factors for stroke.

STUDY

1. The North American Symptomatic Carotid Endarterectomy Trial entered over 2800 patients. All had a history of TIA of non-disabling stroke associated with carotid stenosis.
2. Randomized to optimal medical treatment or optimal medical treatment plus endarterectomy.
3. The present study compared the risk of stroke in the subset of patients with TMB vs risk of stroke among patients presenting with hemispheric TIA.
4. Assessed the effect of endarterectomy vs medical treatment in patients with TMB and hemispheric TIA.

RESULTS

1. Medical treatment: 198 patients with TMB vs 417 with hemispheric TIA. Over 3 years, those with TMB had about half the risk of ischemic stroke as those with hemispheric TIA. (Relative risk = 0.53).
2. In the TMB patients, six factors were associated with increased risk: Age > 75; male sex; history of hemispheric TIA or stroke; history of intermittent claudication; carotid stenosis 80% to 94%; and absence of collateral circulation.

3. Outcomes TMB	3-year risk of ipsilateral stroke		Absolute risk reduction	NNT
	Medical	Surgical		
No of risk factors				
0 or 1 (low risk)	2%	4%	2% (harm)	50 (harm)
2 (moderate risk)	12%	7%	5% (benefit)	20
3 (high risk)	24%	10%	14% (benefit)	7

(All patients had stenosis > 50%)

DISCUSSION

1. TMB is a common manifestation of internal carotid stenosis. It is a warning of impending stroke.
2. In this large series, the 3-year risk of ipsilateral stroke was less in those with TMB as compared with those with hemispheric TIA. The strokes which did occur were less disabling in patients with TMB than in those presenting with hemispheric TIA. (Perhaps because of better collateral circulation.)
3. Each small group of cells in the retina is more sensitive than a group of cells of similar size in the brain. Thus, a small platelet-fibrin embolus will more readily become clinically manifest in the retina. TMB may frequently result from small emboli that would be less likely to cause brain infarction.
4. In patients with TMB, the subset having high risk and stenosis of 80% to 94%, endarterectomy would be effective in preventing stroke over 3 years in one of every 7 patients undergoing surgery.

CONCLUSION

As compared with hemispheric TIA, TMB associated with internal carotid stenosis carries a better prognosis with respect to subsequent stroke. Endarterectomy may improve prognosis in the group with other risk factors for stroke.

NEJM October 11, 2001 345: 1084-90 Original investigation by the North American Symptomatic Endarterectomy Trial Collaborators, first author Oscar Benavente, University of Texas at San Antonio

www.nejm.org

Comment:

Primary care clinicians who deal with this risk must have a close relationship with the vascular surgeons. The risk of stroke complicating endarterectomy must be less than 3%.

Stroke which complicates an endarterectomy done for TMB or TIA will be devastating to patient, clinician, and surgeon. RTJ

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A reminder to the young to gain as much bone mass as possible

10-4 GAIN IN BONE MINERAL MASS IN PREPUBERTAL GIRLS 3-5 YEARS AFTER DISCONTINUATION OF CALCIUM SUPPLEMENTATION.

Calcium supplementation during childhood and adolescence increases bone mass. Peak bone mass at the end of the prepubertal period is a major determinant of risk of osteoporotic fractures in later life.

Does benefit persist after discontinuation of supplementation in young females?

This follow-up study assessed possible residual benefits after 3 years.

Conclusion: Calcium phosphate taken during the prepubertal period caused an increase in bone mass which persisted beyond the end of supplementation.

STUDY

1. In an original controlled study, girls age 8 received Ca over 1 year. Their bone mass increased

significantly more than those receiving placebo.

2. The present study measured bone variables in 116 girls who, at age 8, had received supplementation with milk-derived calcium phosphate 850 mg daily for 48 weeks, or placebo.
3. Remeasured bone density 4 years after discontinuation of calcium when subjects were age 12.

RESULTS

1. At 4 year follow-up the bone mineral mass was higher in 6 sites in the originally treated group vs the placebo group. The difference seemed to be due mainly to a greater gain in the size of bone without a significant change in bone mineral density.
2. Girls in the treated group gained more height as compared with the placebo group (+ 2 cm). The gain was mainly due to increase in height of the lumbar spine.

DISCUSSION

1. Increases in bone mineral mass resulting from calcium supplementation in young girls during 1 year were maintained for more than 3 years after discontinuation.
2. The observed increase was due to a greater increase in the size of bone.

CONCLUSION

Calcium supplementation provided to prepubertal girls for 1 year might result in a greater peak bone mass and thereby a reduction in the risk of fragility fractures in later life.

Lancet October 13, 2001; 358: 1208-12 Original investigation, first author J P Bonjour, University Hospital, Geneva, Switzerland. www.thelancet.com

Comment:

I abstracted this article as a reminder that adequate calcium and vitamin D intake in young girls is needed to increase bone mass. Supplementation is often required. A greater achieved bone mass at age 18 will protect against later osteoporosis.

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ACE inhibitor confers a small protective effect.

10-5 RAMIPRIL AND THE DEVELOPMENT OF DIABETES

Complications of diabetes can be reduced or prevented by improving glucose control, lowering blood pressure, controlling lipids, smoking cessation, and taking ACE inhibitors. Lifestyle modifications are basically important in both prevention and treatment.

These investigators recently reported that the ACE-inhibitor ramipril (*Altace*) reduces rates of myocardial infarction, stroke, diabetic nephropathy, and death among high-risk people with diabetes.

This study investigated the effectiveness of ramipril in preventing diabetes among high risk persons.

Conclusion: Ramipril was associated with lower rates of development of diabetes.

STUDY

1. Considered a subset of patients in the HOPE study¹ (n > 5500). All had evidence of vascular disease.
None had known diabetes. All were considered at high risk for development of diabetes.
2. All were over age 55 (mean = 66)
3. Randomized to: 1) ramipril up to 10 mg daily, or 2) placebo.
4. Follow-up = 4.5 years. Main outcome measure = self-reported diagnosis of diabetes.

RESULTS

1. Over 250 subjects developed diabetes during follow-up of 4.5 years
2. Of those taking ramipril 3.6% developed diabetes; vs 5.4% of those taking placebo.
(Absolute difference = 1.8% NNT(4.5 years to benefit 1 person) = 55)

DISCUSSION

1. Ramipril reduced risk of a new diagnosis of diabetes among persons considered at high risk of diabetes.
2. Previous studies reported that patients treated with ramipril had lower fasting glucose and lower HbA1c levels than those taking placebo, or diuretics and beta-blockers.
3. Hypokalemia substantially impairs insulin secretory response. ACE inhibitors raise serum K by reducing aldosterone secretion, thereby lowering renal K excretion. (Aldosterone is the sodium retaining - potassium excreting hormone.)

CONCLUSION

Ramipril, an ACE inhibitor, reduced risk of developing diabetes in high risk individuals.

JAMA October 17, 2001; 286: 1882-85 Original investigation by the HOPE study investigators, first author Salem Yusef, McMaster University Hamilton, Ontario, Canada. www.jama.com

1 "Heart Outcomes Prevention Evaluation (HOPE) Trial" NEJM 2000; 342: 145-53. The HOPE trial entered over 9000 subjects, all considered at high risk. All had evidence of cardiovascular disease or diabetes plus one or more additional cardiovascular risk factors. (Ie, a secondary prevention trial.) Over 4.5 years, those randomized to ramipril experienced lower rates of vascular outcomes (death, stroke, myocardial infarction, heart failure). Only a small part of the benefit was attributed to lowering BP. The NNT for 4.5 years was high for each outcome (40 to 200).

Comment:

Ten mg of Altace costs over \$1.30 wholesale -- out \$500 yearly. Primary care clinicians and their patients must agree on the acceptable benefit/harm-cost ratio of this therapy. Ramipril for 4.5 years would cost over \$2500 to gain a one in 55 chance of reducing incidence of diabetes. Although ramipril is generally well tolerated, many

patients will withdraw because of cost, lack of interest, or adverse effects. On the other hand, patients may consider the benefit high (prevention of diabetes). The benefit/harm-cost ratio of life-style measures to prevent diabetes is much greater. RTJ

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Most women with affected first-degree relatives will never develop BC themselves.

10-6 FAMILIAL BREAST CANCER: Collaborative Reanalysis of Individual Data From 52 Epidemiological Studies Including 58 201 Women with Breast Cancer and 101 986 Women Without the Disease.

Women with a family history of breast cancer (BC) are at increased risk of the disease. This study asks: How is risk of BC in an individual influenced by familial patterns of the disease?

Conclusion: The majority of women who develop BC have *no* associated family history of the disease. Women who have first degree relatives with BC are at increased risk, but the majority will never develop BC.

STUDY

1. Acquired individual data from 52 studies of first-degree relatives (mother, sister, daughter) of over 58 000 women who had BC. Compared data with over 101 000 matched controls without the disease.

RESULTS

1. Of the 58 000 women with BC, 7500 (13%) had a first degree relative who also had BC (12% had one affected relative; 1% had two or more).
2. Of the controls (no BC), 7% had first degree relatives with BC.
3. Risk of BC increased with the increasing numbers of affected family members. Compared with women with BC who had no affected relatives, risk ratio was 1.8 for those with one affected relative; 2.9 for those with 2, and 3.9 for those with three.
4. For women of any given age, the younger the relative was at diagnosis, the greater the risk.
5. For women up to age 50 with 0, 1, or 2 or more affected first degree relatives, risk was 1.7%; 3.7%, and 8.0% respectively.
6. For women up to age 80 with 1, or 2 affected first degree relatives risks were 7.8%; 13.3%; and 12.1%. Estimates of death from BC up to age 80 were 2.3%; 4.2%; and 7.6%.

DISCUSSION

1. The study confirms the well-established increased risk of BC among women with a family history of BC. "It also shows that most women with one or more affected first-degree relatives will never develop BC themselves."
2. "Most women who develop BC do not have an affected first-degree relative with the disease."
3. The study also confirmed that the risk of BC was greater in women having a first degree relative

who developed BC at an early age (eg, < 35 vs >60); those who had more than one affected relative; those who had fewer children; those whose children were born at a later age (eg, > 30 vs < 20); those who had an early menopause; and those who used oral contraceptives within 10 years (vs those whose last use was 10 or more years ago).

4. Implications for counseling women:

In more developed countries, lifetime probability of developing BC between ages 20 and 80 = 8% (one in 13) vs 13% (one in 8) among those with one affected relative; and 21% (one in 5) with two affected relatives.

Corresponding estimates of death from BC are 2.3%; 4.2% and 7.6%

Most women with one or more relatives with BC are unlikely themselves to develop BC, and even less likely to die of it. In developed countries, of women with 2 or more affected first degree relatives, about 4 out of five would never acquire BC, and 12 of 13 would not die from the disease.

For women with a first degree relative who develop BC, the onset of BC is likely to be after age 50.

The majority of women who develop BC have no mother, sister, or daughter with the disease. Eight of nine women who develop BC have no first degree relatives with the disease.

5. Screening only women with family members with the disease would miss the large majority of BCs.

CONCLUSION

Eight out of 9 women who develop BC do not have any first degree relative with BC. Although women who have a first degree relative with BC are at increased risk, most will never develop BC.

The lifetime *excess* incidence of BC is 6% for women with one affected first degree relative, and 13% for women with two.

Lancet October 27, 2001; 1389-99 Original investigation from the collaborative Group on Hormonal Factors in Breast Cancer, ICRF Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford, UK.

Comment: Good news and bad news. Women with family members who have BC may not be at as high risk of developing BC as they feared. Women without family history as well as those with a family history still remain at high risk over the decades. RTJ www.thelancet.com

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Recommended Reading: Every patient has a story to tell. Listen carefully!

10-7 NARRATIVE MEDICINE

(This article is a good example of the many messages in the recent literature which relate to the doctor-patient relationship, especially the primary care clinician-patient relationship. An adequate abstract would be almost as long as the original article. Read the original! RTJ)

Narrative competence is required to practice primary care medicine effectively. That is, the ability to acknowledge, absorb, interpret, and act on the stories and plights of others. Medicine practiced with narrative competence (narrative medicine) is proposed as a model for humane and effective practice.

There are 4 central narrative situations: Physician and patient; Physician and self; Physician and colleagues; Physicians and society.

With narrative competence, physicians can reach and join their patients through illness, recognize their own personal journeys through medicine, acknowledge kinship with and duties toward other health care professionals, and inaugurate consequential discourse with the public about health care.

By bridging the divides that separate physicians from patients, themselves, colleagues, and society, narrative medicine offers fresh opportunities for respectful, empathic, and nourishing medical care.

Despite dazzling technological progress in diagnosis and treatment, physicians sometimes lack the capacity to recognize the plights of their patients, to extend empathy towards those who suffer, and to join honestly and courageously with patients in their illnesses. A scientific competent medicine alone cannot help a patient grapple with the loss of health or find meaning in suffering. Along with scientific ability, physicians need the ability to listen to the narratives of the patient, grasp and honor their meaning, and be moved to act on the patient's behalf.

Narrative competence is the competence that human beings use to absorb, interpret, and respond to stories.

JAMA October 17, 2001; 286: 1897-1902 "The Patient-Physician Relationship" Commentary by Rita Charon, College of Physicians and Surgeons of Columbia University, New York. www.jama.com

Comment:

I believe primary care clinicians would understand the term better if it were changed from "narrative medicine" to narrative-based medicine". "Evidence-based" medicine is the scientific basis of medicine. "Narrative-based" medicine is the art.

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RECOMMENDED READING "Words That Make a Difference"

10-8 "I WISH THINGS WERE DIFFERENT": EXPRESSING WISHES IN RESPONSE TO LOSS, FUTILITY, AND UNREALISTIC HOPES

Physicians encounter many powerful and painful emotions, including anger, sadness, fear, grief, loss, hopelessness, and blame. Many studies suggest that physicians should express empathy in response to emotion-laden statements to ensure that patients feel listened to and understood. These physician responses usually consist of efforts to comprehend how things feel to the patient and to express that understanding back to the patient.

Situations of loss, guilt, or hopelessness are particularly hard for physicians to respond to empathetically. They may avoid the subject entirely. When a patient expresses overwhelming anger or disappointment with limitations in medicine, physicians may be afraid that any explicit response to the patient's emotion may be construed as evidence of physician's failure, mistake, or inadequacy.

In these challenging situations physicians may attempt to respond empathetically by stating "I'm sorry". This well intentioned response, although frequently appropriate, may be misinterpreted and misdirected.

"We have found that saying 'I wish . . . (*things were different*)' to a patient and family is a more effective initial response."

Saying "I'm sorry" is potentially problematic for several reasons. And that saying "I wish. . ." would carry more significance when delivering bad news, when responding to unrealistic hopes, expressions of loss, grief, or hopelessness, and responding to disappointment in the physician or in the limits of medicine.

(A table on p 544 presents representative clinical scenarios in which expressions of wishes might be appropriate.)

"Expressing wishes has the power to humanize the medical encounter in some of its most challenging moments. Such statements can help clinicians and patients to share emotional stance to the patient's condition, and yet at the same time, tacitly acknowledge the difficult realities of the patient's prognosis."

"When the emotion is unrealistic hope, loss, futility, or grief that seems overwhelming or otherwise is very difficult to address, physicians should consider joining with the patient and family in the expression of a wish that their circumstances were different."

Annals Int Med October 2, 2001; 135: 551-555 "Medical Writings", commentary, first author

Timothy E Quill, University of Rochester School of Medicine, Rochester NY. www.annals.org

Comment: Primary care clinicians will develop their own individual approaches when encountering difficult emotional situations. This suggestion is a worth-while approach.

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How to improve patient-centered approach in primary care

10-9 OBSERVATIONAL STUDY OF EFFECT OF PATIENT CENTEREDNESS AND POSITIVE APPROACH ON OUTCOMES OF GENERAL PRACTICE CONSULTATIONS.

The patient-centered model of the doctor consultation is widely advocated. In practice its use is probably limited.

This study measured patient's perceptions of patient-centeredness and the relation of these perceptions to outcomes.

Conclusion: Components of patient's perceptions can be measured reliably. If the doctor provides a positive patient-centered approach, patients will be more satisfied, more enabled, and may have less symptom burden and fewer rates of referral.

STUDY

1. Observational study of over 850 consecutive patients used questionnaires to measure patient's perceptions of patient-centeredness. Identified components of patient's perceptions.
2. Assessed how these components related to outcomes.
3. Main outcome measures: patient's satisfaction, enablement, and burden of symptoms.

RESULTS

1. Analysis identified 5 distinct components of patient's perceptions that can be measured reliably:
 - 1) Communication and partnership with the doctor:

The doctor was interested in my worries and what I thought the problem was; encouraged me to ask questions; was sympathetic; and carefully explained plan of treatment. We discussed and agreed together what the problem was and the plan of treatment.
 - 2) Personal relationship with the doctor:

Knows me and my history and understands me and my emotional needs.
 - 3) Health promotion:

Advised me about how to prevent and lower risk of future illness.
 - 4) Positive approach to diagnosis and prognosis:

Was definite and explained clearly what the problem was; was positive about when the problem would settle.
 - 5) Interest in the effect of the illness on the patient's life:

Was interested in the effect of the problem on my family and my personal life and on my everyday activities.
2. *Satisfaction* was related to communication, partnership, and a positive approach.

Enablement was greater when the doctor had greater interest on the effect of the disorder on the patient's life, stressed health promotion, and adopted a positive approach.

Symptom burden was reduced when the doctor's approach was positive.

Referrals were fewer if the patients felt they had a personal relationship with the doctor.
3. Patients who felt the doctor approached the illness using these criteria were more satisfied with their care.

CONCLUSION

If the doctor provides a positive patient-centered approach, patients will be more satisfied, more enabled, and may have less symptom burden and fewer rates of referral.

BMJ October 20, 2001; 323: 908-11 "Primary Care" Original investigation, first author Paul Little, Southampton University, Southampton, UK www.bmj.com/cgi/content/full/323/7323/908

Comment:

The study addressed the patient's side of the doctor-patient relationship. I turned it around in my mind to assess the doctor's side. Primary care clinicians may use the components of the study as a check list to define how well they are

practicing patient-centeredness. Patient-centeredness combines the best of narrative-based medicine and evidence-based medicine. RTJ

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Patients with suspected myocardial infarction & a normal ECG must be followed closely

10-10 PROGNOSTIC VALUE OF A NORMAL OR NONSPECIFIC ELECTROCARDIOGRAM IN ACUTE MYOCARDIAL INFARCTION

Finding a normal or nonspecific ECG in patients presenting with chest pain is usually considered to portend a low rate of mortality and life-threatening complications. Deferred outpatient testing (within 72 hours) is frequently recommended for these low-risk patients.

However, the mortality rate of patients with proven myocardial infarction (**MI**) and a normal initial ECG has been well described and may be quite high. A recent analysis reported that 2% of patients with acute MI were inadvertently discharged from the emergency department. A normal ECG finding was the main reason these patients were sent home.

This study compared in-hospital mortality among patients with an MI who had an initially normal or non-specific ECG with those who had an MI with an initially diagnostic ECG.

Conclusion: Patients admitted to hospital with chest pain who had a normal or non-specific ECG had lower in-hospital mortality. Yet absolute rates of death were still unexpectedly high.

STUDY

1. The National Registry of Myocardial Infarction compared risks of in-hospital death and life-threatening complications among patients with normal vs diagnostic initial ECGs.
2. Multicenter observational study enrolled over 390 000 patients (mean age = 68). All presented with a clinical history suggestive of acute MI, were hospitalized, and subsequently were considered to have had an acute MI on basis of the clinical presentation, CK-MB or other cardiac enzymes, an ECG compatible with acute MI, positive scintigraphic or autopsy evidence, or a discharge diagnosis of MI.
3. Determined numbers of patients with an ECG that was initially normal with those with an initial ECG with non-specific ST or T wave changes, and with those with a diagnostic ECG (ST elevation or depression and/or left bundle branch block).
4. Main outcome measure = in-hospital mortality; secondary outcome = composite of mortality + adverse in-hospital cardiac events.

RESULTS

1. Of 390 000 patients in whom MI was established, 8% had a normal initial ECG; 35% had a non-specific ECG; 57% had diagnostic ECGs.
2. In-hospital mortality was 6%; 9%; and 12% respectively. (Note that those with an initially normal ECG had about half the mortality as those with diagnostic ECGs.)
3. For the composite outcome measure, rates were 19%; 27%; and 35%.
4. There were clinical hints of differences:

The normal ECG group tended to be younger, male, to have a lower rate of prior MI, and a lower rate of history of congestive failure. Fewer arrived at the hospital within 6 hours of onset of symptoms. Symptoms were more likely to be atypical. More were admitted to the monitoring unit than to intensive care. More developed non-Q-wave MI. Fewer were treated with aspirin.
5. Among those with an initially normal or non-specific ECG, about 1/5 went on to develop frank ST elevation or left bundle branch block on subsequent ECGs.
6. Mortality was higher in subgroups of patients within the 3 ECG groups. Those presenting at age greater than 75, with tachycardia, and evidence of congestive failure (rales and jugular venous distention), as well as those presenting without chest pain had a higher risk of death. Mortality was lower in men younger than 65 who had an ejection fraction of 40% or greater.

DISCUSSION

1. Patients presenting with symptoms compatible with acute MI who had initially normal or non-specific ECGs had lower, but clinically significant, short-term mortality rates compared with those with initially diagnostic ECGs.
2. "The unexpected finding of this study was that patients with an initially normal ECG had a substantial mortality rate, one that approximates the 30-day risk for patients with ST-segment elevation treated in recent trials of reperfusion therapies."
3. In patients with an acute MI, a normal or non-specific initial ECG does *not* indicate that the patient will have a favorable hospital course.

CONCLUSION

In a large cohort of hospitalized patients with eventually established acute MI, those presenting with an initially normal or non-specific ECG had lower in-hospital mortality than those with initially diagnostic ECGs. However, absolute rates of mortality and complications were unexpectedly high.

JAMA October 24/31, 2001; 286: 1977-84 Original investigation from the National Registry of Myocardial Infarction, first author Robert D Welch, Wayne State University School of Medicine, Detroit, Mich.

www.jama.com

Comment:

Among patients presenting with suspected acute MI, some will be discharged home without a proper diagnosis. Although they are relatively few, the consequences may be disastrous. These patients should be rechecked the next day even though the clinician feels the risk of MI is small. It would be reasonable to routinely give these patients prophylactic aspirin and even low-dose beta-blockers before discharge home. RTJ

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An aid to quick diagnosis

10-11 FAST DIAGNOSIS OF MYOCARDIAL INFARCTION

A recent study demonstrated that simultaneous measurement of 3 markers of myocyte necrosis (troponin I, creatine kinase MB, and myoglobin) significantly increased detection of acute coronary syndromes as compared with use of each marker alone.

This fast, simple, inexpensive protocol for diagnosing myocardial infarction (**MI**) is reported to rule out MI within 90 minutes and to lower the number of hospital admissions. The test, now approved by the FDA, takes 15 minutes at the bedside. It is repeated 3 or 4 times. It simultaneously measures 3 cardiac markers: troponin I, creatine kinase-MB, and myoglobin. All are released by the damaged myocardium.

When combined with the ECG and clinical history it is highly accurate in ruling out an acute MI. Only one of 500 patients sent home from the ED after negative tests returned with an MI within a month.

JAMA October 24/31; 286: 1961 "Quick Uptakes" commentary by JAMA staff. See also circulation 2001; 103: 1832-37 www.jama.com

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Respiratory syncytial virus is a frequent cause of "flu" in adults

10-12 CONTRIBUTION OF INFLUENZA AND RESPIRATORY SYNCYTIAL VIRUS TO COMMUNITY CASES OF INFLUENZA-LIKE ILLNESS

Respiratory syncytial virus (**RSV**) is an important cause of lower respiratory tract infections in adults as well as in children.

RSV is best known for its tendency to cause bronchiolitis in infants. But, it can affect all age groups, causing both upper and lower respiratory infections which range in severity from subclinical to pneumonia and death.

One study reported that RSV in adults was among the 4 most frequent pathogens: *S pneumoniae*, influenza virus (**IV**), *Mycoplasma pneumoniae*, and RSV.

Acute respiratory illness from any cause affects about 1/3 of all elderly persons each winter.

RSV can be confused clinically with influenza. The need to improve understanding of the burden of illness, transmission, and detection of RSV in adults in community settings has become more evident with the development of interventions for treatment of IV and the development of vaccines for RSV.

This study compared the prevalence of infections with RSV and IV over 3 winter seasons.

Conclusion: In patients with influenza-like illness, there was a substantial potential for confusion between illnesses caused by RSV and those caused by IV.

STUDY

1. Community-based study of over 3 successive winters obtained nasopharyngeal swabs from patients with influenza-like illness. Examined them for RSV and IV by polymerase chain reaction.
2. Related findings to the clinical incidence of influenza-like illness and acute bronchitis.

RESULTS

1. Of a total of over 2200 swabs, 480 were positive for RSV and 709 positive for IV. Both types were identified in all age groups for between 12 and 20 weeks each winter.
2. Age distribution over 3 winters:

Age	Influenza positive	RSV positive
15-44	31%	20%
45-64	29%	19%

DISCUSSION

1. In each of 3 winter seasons, RSV was identified in community-dwelling individuals of all age groups diagnosed as having influenza-like illness. "RSV is therefore an important pathogen contributing to the burden of illness in the entire community in winter."
2. The relative proportions of the two viruses changed over the seasons. More were positive for IV during the peak of the influenza-like illness.
3. In most cases the pathogen isolated can be assumed to have caused the illness. Nevertheless, there was a minority of patients who had both viruses present at the same time.
5. The frequency of acute bronchitis in winter is always substantially higher than that ascribed to influenza. The authors believe that at least some of these cases are due to RSV.
6. In the UK, the excess mortality of RSV infections is estimated at about 22 000 per year. Hospital admissions reflect this.
7. This study reaffirms the need for continuous surveillance of RSV as an important public-health issue. It raises the question of a rational vaccination policy for both IV and RSV.
8. In addition, when the two illnesses occur simultaneously in the community, there is a need to distinguish between the two if specific antiviral treatment is to be prescribed.

CONCLUSION

In individuals with influenza-like illness, there is a substantial potential for confusion between illness caused by RSV and IV. RSV is an important pathogen contributing to the burden of illness in the entire community in winter.

Lancet October 27, 2001; 358: 1410-16 Original investigation, first author M C Zambon, PHLS Central Public Health Laboratory, London. www.thelancet.com

Comment:

This could account for some of the patients who get "flu" despite receiving vaccine. It would also explain some failures to respond to neuraminidase inhibitors. The public health implications are considerable. A RSV vaccine for adults could result in great benefits.

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Another reason to treat elevated BP in middle-age

10-13 ELEVATED MIDLIFE BLOOD PRESSURE INCREASES RISK IN ELDERLY PERSONS: The Framingham Study

The most important modifiable risk factor for stroke is an elevated blood pressure (BP). Risk prediction models consider the BP at the time of risk prediction (current BP). They do not adjust for the potential impact of BP in the past (antecedent BP).

This study asks: Does antecedent BP (BP 10 to 20 years prior) have any value in assessing risk of stroke at age 60, 70, or 80?

Conclusion: Yes it does.

STUDY

1. The community-based Framingham study has gathered long term information about cardiovascular risks.

Over 5000 stroke-free subjects were enrolled from 1948 to 1953. All were followed to the end of 1998.

2. Determined 10-year risk of initial ischemic stroke for decades beginning with age 60, 70, and 80. (Eg, for a 40 year old subject enrolled in 1950 and reaching age 60 alive and without stroke, the study provided information on the occurrence of stroke in the decade 60 to 70.) If the same individual reached the age of 70 free of stroke, he or she provided an additional 10 years of follow-up from age 70 to 80.

3. Considered 3 aspects of BP:

Current BP (time of risk prediction at baseline ó age 60, age 70, or age 80)

Recent BP ó average of determinations of BP in the decade preceding. (Ie, for an individual age 60, the average BP during age 50 to 60.)

Remote BP ó average of determinations of BP 10 to 20 years before baseline. (Ie, for an individual age 60 at baseline, his or her average BP during age 40 to 50.)

RESULTS

1. Almost 500 strokes were observed.

A. Recent antecedent BP:

In subjects age 60 at baseline followed for 10 years, the recent antecedent BP (at age 50-59) influenced incidence of stroke between age 60 and 70. Relative risk of stroke per standard deviation increment from the mean BP during ages 50-59 was 1.8.

In subjects age 70 at baseline followed for 10 years, the recent antecedent BP (at age 60-69) influenced incidence of stroke between age 70-79. Relative risk of stroke per standard deviation increment from the mean BP during ages 60-69 was 1.5.

B. Remote antecedent BP:

Similar increases in incidence of stroke were seen in those whose BP was elevated 10 to 20 years prior.

2. The effect was evident for recent and remote antecedent BP in hypertensive and non-hypertensive subjects, and demonstrable for systolic, diastolic and pulse pressures.
3. As expected, higher levels of BP at baseline (eg, age 60) predicted a greater incidence of stroke during the decade 60-69.

DISCUSSION

1. The risk of stroke doubles in each successive decade after age 55. The great majority of strokes occur after age 65.
2. The cumulative effect of long-term exposure to an elevated BP may partly explain this age-associated increase in risk. Antecedent BP levels were associated with increased risk of ischemic stroke even after adjustment for current BP levels. The effect was robust.
3. In the Framingham study, about 1/4 of strokes occurred in individuals whose current BP was in the non-hypertensive range. "While this is not entirely surprising, given the continuum of risk, the importance of past BP elevation as a potentially modifiable risk factor for prevention of stroke in this group should not be overlooked."
4. The study strongly suggests that midlife BP levels continue to affect the future risk of stroke not only over a short span, but over more prolonged periods, up to 30 years.
5. "While the reduction in risk achieved by antihypertensive treatments is impressive at any age, and particularly in elderly persons, treatment of hypertension in older subjects who have been exposed to elevated BP levels for many years leaves their risk well above that of nonhypertensive subjects."
6. To achieve optimal reductions in risk of stroke in elderly persons it may be necessary to prevent, diagnose, and manage BP elevations throughout adulthood.

CONCLUSION

Elevated BP during the midlife decades contributes to the risk of stroke in older age. Optimal prevention of late-life stroke will likely require control of midlife BP.

Comment: This makes sense. Wear and tear on the cerebral arteries over the years would reasonably lead to risk.

A new and valuable prognostic bio-marker

10-14 THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES.

Brain (B-type) natriuretic peptide (BNP)¹ is a 32 amino-acid neurohormone synthesized mainly in the ventricular myocardium. It is released into the circulation in response to ventricular dilation and pressure overload. It promotes sodium excretion, causes vasodilation, and inhibits both the renin-angiotensin-aldosterone axis and sympathetic nervous activity.

Plasma levels are increased in congestive heart failure (HF) in proportion to the degree of left ventricular dysfunction and the severity of symptoms.

After an acute myocardial infarction (MI) levels of BNP rise rapidly during the first 24 hours and then tend to stabilize.

Measurement of BNP between 1 to 4 days after a transmural (ST elevation) MI provides prognostic information that is independent of ventricular ejection fraction and other important baseline variables.

This study evaluated the prognostic implications of cardiac neurohormonal activation as reflected by plasma levels of BNP across the entire spectrum of acute coronary syndromes.

Conclusion: A single measurement of BNP obtained in the first few days provided predictive information.

STUDY

1. Measured BNP in plasma of over 2500 patients obtained a mean of 40 hours after onset of ischemic symptoms.
2. All met one or more of the following entrance criteria: ECG changes (ST depression or elevation of at least 0.5 mm, T wave inversion of at least 3mm in at least 3 leads, or left bundle branch block); elevated levels of cardiac markers; a history of coronary disease; or age > 65 in patients with diabetes or vascular disease.
3. Correlated BNP levels with clinical outcomes.

RESULTS

1. Height of BNP was correlated with the risk of death, heart failure, and MI at 30 days and 10 months.
2. The rate of death increased in a stepwise fashion as levels of BNP increased. Odds ratios of death at

10 months in the second, third and fourth quartiles of BNP were 4, 4, and 6 compared with those in the first quartile. The association remained significant in those with ST elevation MI, those with MI without ST elevation, and in those with unstable angina.

3. A level of BNP more than 80 pg/mL was associated with the risk of new or recurrent MI, and new or worsening heart failure and death.

DISCUSSION

1. A single measurement of BNP obtained within a few days of onset of ischemic symptoms provided powerful risk-stratification information across the entire spectrum of acute coronary syndromes.
2. "Activation of the cardiac neurohormonal system may be a unifying feature among patients at high risk of death after acute coronary syndromes."
3. The association between BNP and long term risk of death was independent of presence or absence of heart failure (HF), troponin I levels, ECG changes, and other known predictors.
4. High level of BNP was associated with an increased risk of non-fatal endpoints of new progressing HF, and MI.
5. A level of 80 pg/mL is an appropriate predictive threshold among patients with acute coronary syndromes.
6. Previous studies have indicated that, after an acute MI, a higher level of BNP is associated with a larger infarct, increased likelihood of ventricular remodeling, a lower ejection fraction, and increased likelihood of HF and death.
7. Unlike traditional cardiac biomarkers used to predict risk among patients with acute coronary syndromes, BNP has a putative role in the counter-regulatory response to ischemia. It may act as an index of the degree of underlying impairment of left ventricular function.
8. Of interest of The level of BNP increases rapidly and transiently after exercise testing in patients with chronic stable angina. The degree of elevation is correlated with the size of the ischemic area.
9. These findings suggest that the prognostic implications of BNP are distinct from those of myocardial necrosis, including patients with unstable angina and those without troponin I elevation.
10. For a biomarker to be clinically useful, it must help clinicians select appropriate therapy. Patients with elevated troponin I after acute coronary syndromes appear to derive benefit from an early aggressive strategy that includes potent antiplatelet and antithrombotic therapy and early revascularization. Patients with a high BNP may therefore benefit from more intensive interventions of antiplatelet, antithrombotic, beta-blockade, ACE inhibition, and early revascularization.
11. Equally importantly, patients who have normal BNP after an acute event appear to have a particularly low long-term risk of death and heart failure. Less intense management may be appropriate in this group.

CONCLUSION

Across the spectrum of acute coronary syndromes, the level of BNP measured in the first few days after an acute coronary event predicts long term risk of death and non-fatal coronary events. The prognostic usefulness persists after adjustment for the presence of HF and other important predictors of mortality.

The authors suggest that B-type natriuretic peptide should be measured after an acute coronary syndrome in order to identify the risk of adverse outcomes. Treatment should be adjusted accordingly.

NEJM October 4, 2001; 345: 1041-21 Original investigation from the Thrombolysis in Myocardial Infarction Study Group, first author James A de Lemos, University of Texas Southwestern Medical School, Dallas.

1 Called "brain" natriuretic peptide because it was first isolated from brain tissue. Later, the major site of production was found to be in the heart.

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Add BNP and CRP to your list

10-15 ACUTE CORONARY SYNDROMES & BEYOND MYOCYTE NECROSIS

The acute coronary syndromes comprise: 1) ST elevation acute myocardial infarction (MI), 2) Non-ST elevation MI, and 3) Unstable angina.

Recently, important advances have been made in both revascularization techniques and medical treatment. A typical approach includes multiple treatment options: aspirin, beta-blockers, low-molecular-weight heparin, intravenous glycoprotein IIb/IIIa receptor antagonists, the anti-platelet drug clopidogrel (*Plavix*), coronary stenting, thrombolytic agents, statins, and ACE inhibitors.

One of the most important challenges in this era of cost containment is to identify the subgroup of patients who are at highest risk of adverse events in order to target the most aggressive therapies to these patients.

Use of clinical characteristics, ECG findings, and levels of traditional serum markers of myocyte necrosis (CKMB, troponin I, myoglobin) is only partially successful in risk stratification. Some patients with unstable angina have no evidence of myocyte necrosis. They have underlying rupture or erosion of unstable plaques in the coronary arteries. These patients are also at increased risk.

Brain Natriuretic Peptide (BNP)

A preceding study reported that B-type natriuretic peptide (**BNP**) predicts the long-term risks of death in patients with coronary syndromes. This was independent of ECG changes, troponin levels, and presence or absence of heart failure. In patients with unstable angina who had no evidence of myocyte necrosis on the basis of troponin concentrations, elevated BNP portended an adverse prognosis.

BNP is a marker of neurohumoral activation. Beta-blockers and ACE inhibitors both counter neurohumoral activation. They are crucial for the secondary prevention of myocardial infarction. Although both the sympathetic nervous system and renin-angiotensin-aldosterone are activated by acute myocardial infarction, ACE inhibition does not alter the circulating levels of BNP or norepinephrine.

BNP is a potent predictor of the risk of death in patients with heart failure, regardless of cause. In patients with advanced left ventricular dysfunction treated with high dose ACE inhibitors and beta-blockers, levels of BNP remain independently related to risk of death and progression of the heart failure.

C-reactive Protein (CRP)

Inflammation has a critical role in the pathogenesis of acute coronary syndromes. Inflammation contributes to rupture of vulnerable atherosclerotic plaques. Many patients with acute myocardial infarction have multiple complex coronary plaques associated with adverse clinical outcomes. Inflammation may have widespread effects throughout the coronary vasculature. Several inflammatory serum markers have been linked to both coronary atherosclerosis and acute coronary syndromes. C-reactive protein (**CRP**) is the most widely studied. Elevated levels of CRP are associated with increased risk of recurrent events across the spectrum of acute coronary syndromes, independent of the presence or absence of myocyte necrosis. CRP may have direct atherothrombotic effects.

Statins are critical treatment of myocardial infarction for both primary and secondary prevention. Statins have a number of anti-inflammatory effects. They reduce CRP levels as well as stabilize atherosclerotic plaques by decreasing lipid content, lipid oxidation, and inflammation. They increase collagen content of plaques. Statins benefit patients with elevated CRP levels.

Tests for neurohumoral activation (elevated BNP) and inflammation (CRP) may augment our ability to identify patients at risk of adverse events, and potentially help to reserve the most expensive and aggressive therapies to individuals at highest risk.

NEJM October 4, 2001; 334: 1057-59 Editorial by LeRoy E Rabbani, Columbia University College of Physicians and Surgeons, NEW York. www.nejm.org

Comment:

I believe CRP and BNP will be used in the clinic more frequently for risk stratification. RTJ

Added to therapy – a naturally occurring peptide

10-16 CONGESTIVE HEART FAILURE TREATMENT

The FDA has approved nesiritide (*Natrecor*), a preparation of human B-type natriuretic peptide, for intravenous treatment of acutely decompensated congestive heart failure (ADCHF).

It has been studied in 10 trials. The largest trial enrolled over 450 patients who required hospitalization for management of ADCHF. At the end of 3 hours, nesiritide was associated with a significant lowering of pulmonary capillary wedge pressure compared with placebo. Dyspnea was significantly improved.

Hypotension was the major adverse reaction. The degree of hypotension depended on dose.

The effect of nesiritide on wedge pressure and dyspnea did not significantly differ from intravenous nitroglycerin.

JAMA October 3, 2001; 286: 1569 "From the Food and Drug Administration" news by Bernard A Schwetz, FDA, Rockville Md. www.jama.com

Comment:

This is an example of adding a naturally occurring physiological human substance to patients who already have increased levels of that substance. Similar to insulin in type 2 diabetes. RTJ

Why some are susceptible to duodenal ulcer; some to stomach cancer

10-17 EPIDEMIOLOGY AND DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION.

(This "Clinical Review" discusses aspects of H pylori infection: epidemiology; why it is a chronic infection; association with peptic ulcer and gastric cancer; and diagnosis. I abstracted a few highlights. RTJ)

H pylori is a small, highly mobile Gram negative bacillus that colonizes only the mucus layer of the stomach. Humans are the only known reservoir. It is one of the commonest bacterial pathogens in humans. Most infected persons are asymptomatic.

It is likely that infection is acquired from family members by the gastro-oral route. It is more common in the socioeconomically disadvantaged. It is an occupational hazard of gastroenterologists, associated with performing endoscopy.

H pylori induces an acute inflammatory gastritis. The immunologic response of the host is generally not sufficient to clear the infection, which persists for life. Infection with different strains is possible since infection with one strain does not protect against another. Each strain may be uniquely adapted to each host to an extent that, for some subjects, it may be considered as a commensal bacteria.

Infection in infancy is thought to lead to pangastritis. Acquisition later in childhood may lead to a predominantly antral gastritis. With antral gastritis, there is loss of regulatory feedback (but an intact acid secreting gastric corpus). This results in production of a high acid load which reaches the duodenum. Duodenal gastric metaplasia results. The islands of metaplasia are then colonized by *H pylori* leading to duodenitis and a high risk of ulcer. In contrast, pangastritis, with an inflamed corpus, is associated with loss of acid-secretion. this leads to increased risk of gastric ulcer and gastric cancer ó similar to that of the autoimmune gastritis of pernicious anemia.

The article goes on to discuss tests to diagnose the infection. It cites 8 different tests.

BMJ October 20, 2001; 323: 920-22 Review article, first author Robert P H Logan, University Hospital, Nottingham, UK www.bmj.com/cgi/content/full/323/7318/920
