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FOR

PRIMARY CARE

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APOLIPOPROTEIN B/APOLIPOPROTEIN A RATIO—A BETTER RISK MARKER [7-1]

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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 JULY 2008

The ApoB/ApoA Ratio Was The Most Powerful Marker Associated With MI. It Should Be Introduced Into Routine Clinical Practice.

7-1 LIPIDS, LIPOPROTEINS, AND APO-LIPOPROTEINS AS RISK MARKERS OF MYOCARDIAL INFARCTION IN 52 COUNTRIES

“Perhaps no issue in lipodology has been as contentious as whether ApoB and ApoA are better markers than are their cholesterol counterparts of risk of vascular disease.”

The American Diabetes Society and the American College of Cardiology have stated (2008) that ApoB is the test of choice to assess the adequacy of statin treatment, and should therefore be introduced into routine clinical practice.

This large case-control study included over 9000 cases of acute MI and over 12 000 controls—age and sex matched in 52 countries. It included all major ethnic groups. Non-fasting blood samples were available in all to determine levels of apo-lipoproteins and cholesterol. (ApoA and ApoB are unaffected by the non-fasting state, as are total cholesterol and HDL cholesterol.)

The investigators calculated odds ratios and population attributable risk (**PAR**) for acute MI for each measurement overall, and for each ethnic group.

Patients with MI had higher total cholesterol (**T-c**), non-HDL-cholesterol (**non-HDL-c**), and Apo B (*the Bad guy*) than controls.

With each decile increase in the ApoB/ApoA ratio, the risk of MI was greater than for each decile increase in the T-c/HDL-c ratio.

A one standard deviation (**SD**) difference in ApoA (*the Advantageous guy*) was associated with a 33% reduction in risk of MI, compared with a reduction of 15% for one SD of the T-c/HDL-c ratio.

The ApoB/ApoA ratio was the most powerful marker associated with MI in both sexes.

The overall PAR for acute MI for the ApoB/ApoA ratio was 54%; for the T-c/HDL-c ratio was 32%. For comparison, the PAR for smoking was 44%

“In all ethnic groups, and both sexes, the ApoB/ApoA ratio was a better risk marker for myocardial infarction than was the ratio of total cholesterol/HDL cholesterol.”

The clinical measurement of apo-lipoproteins is standardized, simple, inexpensive, and can be done non-fasting. “Our data provide broad and straightforward support that ApoB and ApoA should be introduced into clinical practice for the assessment of risk of vascular disease.”

Conclusion: The non-fasting ApoB/ApoA ratio was superior to any of the cholesterol ratios in estimation of risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages.

“Treat Now By Treating Comorbidities”

7-2 HEART FAILURE WITH PRESERVED EJECTION FRACTION

Nearly half of all patients with HF have a preserved ejection fraction (**HFPEF**; *formerly termed “diastolic HF”*). These patients have a high all-cause mortality after hospitalization for HF. Mortality within 1 year is about 25%; and 65% within 5 years. The implication is that adverse outcomes in these patients are driven by worsening HF. This is not necessarily accurate.

Data from observational studies and clinical trials suggest that these outcomes are driven by important comorbidities that are common in patients with HFPEF. These patients are typically elderly (mean age = 75 years), more often are women, and frequently have multiple comorbidities including hypertension, coronary artery disease, atrial fibrillation, diabetes, chronic kidney disease, cerebrovascular disease, obesity, and anemia.

In one trial, during approximately 3 years of follow-up, mortality in patients with HFPEF was due to cardiovascular causes in 72%, and non-cardiovascular causes in 28%. Of those who died of cardiovascular causes, 38% died of sudden cardiac death, 32% due to progressive HF, 7% due to myocardial infarction, and 9% due to stroke. “These results suggest that HF is not the most frequent cause of mortality in patients with HFPEF.”

“Because patients with HFPEF often have important comorbid conditions, and because these comorbidities strongly influence outcomes, clinicians should aggressively identify and treat conditions such as hypertension, CAD, atrial fibrillation, diabetes, chronic kidney disease, and cerebrovascular disease in these patients rather than waiting for new HFPEF-specific treatments to emerge.” Controlling BP is a class-1 recommendation from practice guidelines of the AHA and ACC for patients with HFPEF. One of the most significant beneficial aspects of improved BP control is the reduction in hospitalizations for HF. This benefit has been extended to the elderly who comprise the majority of patients with HFPEF. In the Hypertension in the Very Elderly Trial, aggressive treatment of hypertension in patients over 80 years of age resulted in a decrease in cardiovascular events and improved survival, with the most profound benefit occurring for the HF endpoint.

For practicing clinicians who provide care for patients with HFPEF, the greatest reductions in overall morbidity and mortality may result from treating comorbidities with therapies available now.

Cardiac output (adequate minute volume) is the determinant of HF, not ejection fraction. Unfortunately we do not now have ability to measure cardiac output easily and at low cost.

Controlling BP in the elderly essentially means controlling systolic pressure.

This is another good example of emphasis on treatment rather than prevention. Interventions should be made early in the course of disease, at a much younger age, rather than waiting until decompensation occurs.

The burden falls heavily on primary care.

7-3 ANKLE BRACHIAL INDEX COMBINED WITH FRAMINGHAM RISK SCORE TO PREDICT CARDIOVASCULAR EVENTS AND MORTALITY

Major cardiovascular and cerebrovascular events often occur in individuals without known preexisting cardiovascular disease. Prevention of these events starts with the accurate identification of those at risk. The Framingham risk score (**FRS**; risk of cardiovascular events over the following 10 years) is often considered the reference standard, but has limited accuracy. It tends to overestimate risk in low risk populations and underestimate risk in high risk populations. The FRS includes age, total cholesterol, high-density cholesterol, BP, diabetes, and smoking status.

The ankle/brachial index (**ABI**), the ratio between systolic BP in the ankle and systolic BP in the arm, is easily measured.

This study determined if the ABI provides information on risk independently of the FRS, and can improve risk prediction.

These investigators conducted a literature search which identified 16 population cohort studies fulfilling their inclusion criteria. All subjects were derived from a general population (over 48 000 individuals; men and women in equal numbers; mean age varied from 47 to 78).

A meta-analysis was conducted in individuals who had no previous history of coronary heart disease (**CHD**). All had ABI and FRS measured at baseline.

Determined hazard ratios (**HRs**) for ABI, subdivided into 10 categories compared to a reference ABI of 111/100 to 120/100

Median follow-up ranged from 3 to 17 years (most more than 10 years) to determine total cardiovascular mortality and morbidity.

The HRs for death for different levels of ABI compared with the reference (111/100 to 120/100) increased consistently for men and women with decreasing ABI:

For 101-110/100 there was a slightly higher HR above reference.

For each 10 mm lower ABI, HR rose steadily to 4 at < 60/100.

The prevalence of a low ABI increased with age.

The ABI provided independent risk information in addition to the FRS. A low ABI (<90/100) approximately doubled the risk of total mortality, cardiovascular mortality, and major cardiovascular events as predicted by the FRS.

In predicting the 10-year risk of total CHD, these results indicate that measurement of ABI would change the risk determined by the FRS alone in approximately 1 of 5 men.

Conclusion: Measurement of ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

I believe addition of other risk factors, easily determined in primary care, would improve prognosis more efficiently. These would include: BMI, family history, waist circumference, and possibly apolipoprotein B and apolipoprotein A. (See the following article.)

I believe addition of ABI would increase costs to the public, especially the Medicare program, with little benefit. Primary care's challenge is to encourage patients to respond to the risk factors we already have instead of adding others.

Our efforts should be on prevention (eg, preventing the atherosclerotic disease which causes the decrease in ABI) rather than informing the patient that his ABI indicates disease already present.

“A Successful Translation From Research To Clinical Practice.”

7-4 EFFECT OF DISSEMINATION OF EVIDENCE IN REDUCING INJURIES FROM FALLS

Falling is a common, morbid, and expensive health condition among elderly persons. Effective strategies to prevent falls have been identified, but are underutilized. Falls account for about 10% of ED visits, and 6% of hospitalizations among persons age 65 and older, and are major determinants of functional decline, nursing-home placement, and restricted activity.

This study encouraged clinicians and facilities to incorporate evidence of intervention techniques into practice. The study compared rates of serious fall-related injuries and use of medical services following interventions for prevention vs usual care among persons age 70 and over.

Using a non-randomized design, compared two large regions in Connecticut:

- 1) Region where clinicians had been exposed to interventions to change clinical practice (intervention region)
- 2) Region where clinicians had not been exposed to such interventions (usual-care region).

The intervention region included 212 primary care offices (with 522 primary care clinicians including physician assistants and advanced practice nurses). The region also included 133 outpatient rehabilitation facilities, 26 home care agencies, 7 acute care hospitals, and 43 senior centers.

The recommended strategies for preventing falls included a reduction in medications, management of postural hypotension, management of visual and foot problems, hazard reduction, and balance gait, and strength training. Clinicians were encouraged to incorporate assessments, treatments, and referrals into their practices, as appropriate to their discipline and setting.

Enlisted help of media attention (TV, radio, and newspapers), web sites, posters, brochures, educational materials for patients, and advertising on buses to increase awareness; enlistment of opinion leaders to influence colleagues, and visits (outreach) to everyone in the main group of clinicians and facilities to explain evidence-based fall-related practices, and demonstrate how to incorporate fall prevention into their practices.

Rates of serious fall-related injuries per 1000 person years:

- A. Pre-intervention—31.2 in the usual care region, and 31.9 in the intervention region.
- B. During the intervention period—31.4 in the usual care region, and 29.6 in the

intervention region.

This represents an adjusted 9% decline in the rate of serious fall-related injuries.

Differences between regional rates persisted after the reported study period. Three years after the intervention, and one year after the evaluation period, rates of serious fall-related injuries per 1000 person-years were 30.9 in the usual care region and 28.6 in the intervention region.

“Relative rate reductions of 9% in serious fall-related injuries and 11% in fall-related use of medical services represent a successful translation from research to clinical practice.” The 11% reduction represents about 1800 fewer emergency department visits or hospital admissions.

“Our findings . . . suggest that the dissemination of evidence to clinicians about fall prevention when coupled with practice-change interventions results in the adoption of effective strategies to prevent falls and may reduce the number of falls and injuries.”

Conclusion: Dissemination of evidence about fall prevention, coupled with interventions to change clinical practice, may reduce injuries in elderly persons.

This is a remarkable community-wide effort. I congratulate everyone concerned.

I doubt the lone primary care clinicians could fully apply these efforts to their patients. It would be an added burden without adequate compensation.

This requires a team effort. Perhaps local Public Health Services or Hospice-Palliative Care could intervene to apply these interventions in a select number of elderly persons and their families.

Long-Acting Beta-Agonists Have A Narrow Therapeutic Window. They Deserve Caution

7 -5 EFFECTS OF ADDING SALMETEROL TO INHALED CORTICOSTEROIDS ON SERIOUS ASTHMA-RELATED EVENTS.

Early guidelines recommended that all patients with persistent asthma receive regular treatment with inhaled corticosteroid. For patients whose asthma is not controlled, adding a long-acting beta-agonist was recommended.

Subsequently there has been conflicting evidence about safety of combined inhaled LABA + inhaled corticosteroids.

This study examined whether the incidence of severe asthma-related events (including hospitalizations, intubations, deaths, and severe exacerbations) differed in persons receiving inhaled salmeterol + inhaled corticosteroids vs inhaled corticosteroid alone. It included 66 randomized, controlled trials (over 26 000 patients with moderate to severe persistent asthma) comparing inhaled corticosteroid + LABA (usually administered as twice-daily fluticasone/salmeterol (*Advair*; GlaxcoSmithKline), often by means of a single device), vs inhaled corticosteroid (*Flovent*; fluticasone; GSK) alone in patients with persistent asthma.

All trials were reported by GlaxcoSmithKline. Only 26 trials were longer than 12 weeks.

Severe asthma exacerbations requiring systemic corticosteroids:

Combined therapy	5%
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Inhaled corticosteroid alone 8%

(Combined therapy prevented some severe exacerbations of severe asthma.)

Asthma-related hospitalizations (combined therapy vs corticosteroid alone) = 35 vs 34.

A subset of 24 trials showed a decreased risk of severe asthma-related exacerbations for combined therapy vs corticosteroid alone.

Few deaths and intubations limited the ability to measure risks for these outcomes. However, the number of asthma-related deaths has declined steadily since 1996 in the USA since salmeterol was introduced (1994) and then salmeterol + fluticasone became available in a single device (2001).

Conclusion: In patients with persistent asthma, salmeterol combined with inhaled corticosteroid may reduce the risk of severe asthma exacerbations, as compared with corticosteroids alone. The combination does not alter the risk of asthma-related hospitalizations, and may not affect the risk for asthma-related deaths or asthma-related intubations.

Regrettably, when we read about trials supported and reported by large drug companies we almost automatically look for bias. I believe the authors of this study took great pains to avoid the appearance of bias.

The message for primary care:

- 1) Try inhaled corticosteroids first.*
- 2) If not effective, add a inhaled LABA*
- 3) Do not use inhaled LABA alone as first-line therapy.*
- 4) If combination therapy fails, high dose oral or parenteral corticosteroids may be required.*

Would it be appropriate to prescribe a short-term of high dose oral corticosteroid for select patients with persistent, troublesome asthma? This could be held in reserve and be taken immediately when experiencing a severe exacerbation, as a bridge until the patient could access emergency treatment.

An Unrecognized Complication Of Diabetes. May Be Stronger Among Younger Persons With Diabetes.

7-6 DIABETES AND HEARING IMPAIRMENT

The present study used recent national survey data to examine the relationship between diabetes and hearing impairment. The NHANES (National Health and Nutrition Examination Study) 1999-2004 included over 5000 persons who completed an audiometric examination and diabetes questionnaire.

Pure tone air conduction thresholds were obtained for each ear at frequent frequencies (500 Hz or less were considered low frequency; 1000 to 2000 Hz mid-range frequency; and tones over 3000 Hz were considered high frequency).

Prevalence of hearing impairment (hearing loss [HL] in the worse ear:

	Diabetes (%)	No Diabetes (%)
Mild or greater severity (> 25 dB HL)		
Low or mid-frequency	21	9

High frequency	54	32
Moderate or greater severity (> 40 dB HL)		
Low or mid frequency	9	3
High frequency	37	16

Prevalence (%) of low or mid-frequency hearing impairment of greater severity according to age:

	Diabetes	No diabetes
20-49	16	5
50-59	32	14
60-69	36	30

“We estimate a prevalence of low- or mid-frequency hearing impairment of mild or greater severity of 28% among people with diabetes.” Proportionally, loss is greater in persons under age 60.

Conclusion: Hearing impairment may be an unrecognized complication of diabetes, especially in younger persons. Diabetes seems to be an independent risk factor. Screening for hearing loss among persons with diabetes may be justified.

This is my first encounter with this relationship.

That hearing loss is more common in younger persons is an important clinical point. Younger persons may not recognize their hearing loss.

The question remains—will tighter control at an earlier age prevent hearing loss?

“The Inability To Sustain Weight Loss Appears To Mirror The Inability To Sustain Physical Activity.”

7-7 EFFECT OF EXERCISE ON 24-MONTH WEIGHT LOSS MAINTENANCE IN OVERWEIGHT WOMEN

This study examined the effect of exercise of varying duration and intensity on weight loss in overweight adult women during a 24-month period.

Recruited 201 obese and overweight women in 1999 -2003 from a hospital-based weight loss research center. BMI = 27 to 40 (mean = 32); ages 21-45 (mean = 37).

Randomized to 1 of 4 groups based on prescribed leisure time physical activity (**LTPA**) energy expenditure (moderate 1000 kcal/wk; high 2000 kcal/wk) and exercise intensity (moderate; vigorous):

- 1) 1000 kcal/wk – moderate exercise
- 2) 1000 kcal/wk – vigorous exercise
- 3) 2000 kcal/wk – moderate exercise
- 4) 2000 kcal/wk – vigorous exercise

Participants were told to reduce intake to 1200-1500 kcal/day. They were encouraged to attend group meetings and receive telephone calls periodically focused on strategies for maintaining eating and exercise behavior.

Weight loss did not differ among the randomized groups. The mean weight loss overall at 6 months was 8%-10% of initial weight, and at 24 months was 5% of initial weight.

The LTPA increased by a mean of 1235 kcal/wk from baseline to 6 months and declined to a mean of only 720 kcal/wk at 24 months. The prescribed differences in LTPA were not sustained in any randomized group.

About 25% of subjects did achieve a loss of 10% at 6 months and sustained the loss for 24 months. This group reported performing more LTPA (1835 kcal/wk; 275 min/wk; 55 min per day for 5 days a week above baseline level) compared with those who sustained a loss of less than 10%. They were also more compliant with dietary restrictions.

. “Thus, the inability to sustain weight loss appears to mirror the inability to sustain physical activity.”

A level of LTPA that may be necessary to sustain weight loss in relatively sedentary overweight adults for as long as 24 months is approximately twice the public health recommendations. “This confirms the level of physical activity that should be targeted for successful weight loss.”

Conclusion: The addition of 275 min/wk of LTPA, in combination with reduction in energy intake, was important in allowing overweight women to sustain weight loss of 10% over a period of 24 months

This report is discouraging. Despite a high degree of support, (much higher than would generally be available in primary care), the great majority of participants did not maintain the set goals of diet and LTPA. However, a loss of 5% may reduce risk factors in some patients.

It does reset the levels of energy intake and expenditure necessary to maintain weight loss.

Despite the discouragement, primary care clinicians must continue to encourage weight control, first by maintaining it themselves.

I wonder—how long after the initial 2 years would weight loss be maintained?

ABSTRACTS JULY 2008

The ApoB/ApoA Ratio Was The Most Powerful Marker Associated With MI. It Should Be Introduced Into Routine Clinical Practice.

7-1 LIPIDS, LIPOPROTEINS, AND APO-LIPOPROTEINS AS RISK MARKERS OF MYOCARDIAL INFARCTION IN 52 COUNTRIES

Developing countries already account for most of the cases of coronary heart disease (**CHD**).

The INTERHEART study^{1,2} showed that the same nine modifiable risk factors account for almost all the population-attributable risk (**PAR**) of myocardial infarction (**MI**)—smoking, exercise, fruit and vegetables, alcohol, hypertension, diabetes, abdominal obesity, psychosocial, high apo-lipoprotein B100 / apo-lipoprotein A1 ratio). [**ApoB/ApoA ratio**]. Of these, the ApoB/ApoA ratio—a ratio of the pro-atherogenic to anti-atherogenic lipoproteins in plasma—accounted for half the PAR. (*ApoB is a risk factor for CVD; ApoA is protective. As ApoB increases, risk increase; as ApoA increases, risk decreases.*)

“Perhaps no issue in lipidology has been as contentious as whether ApoB and ApoA are better markers than are their cholesterol counterparts of risk of vascular disease.”

The American Diabetes Society and the American College of Cardiology have stated (2008) that ApoB is the test of choice to assess the adequacy of statin treatment, and should therefore be introduced into routine clinical practice.

This study compared the apo-lipoproteins and cholesterol as indices for risk of acute MI.

Conclusion: Non-fasting ApoB/ApoA ratio was superior to any of the cholesterol ratios.

STUDY

1. This large case-control study included over 9000 cases of acute MI and over 12 000 controls—age and sex matched in 52 countries. It included all major ethnic groups. Non-fasting blood samples were available in all to determine levels of apo-lipoproteins and cholesterol. (ApoA and ApoB are unaffected by the non-fasting state, as are total cholesterol and HDL cholesterol.)
2. Calculated odds ratios and PAR for acute MI for each measurement overall, and for each ethnic group.

RESULTS

1. Patients with MI had higher total cholesterol (**T-c**), non-HDL-cholesterol (**non-HDL-c**), and Apo B (*the Bad guy*) than controls.
2. With each decile increase in the ApoB/ApoA ratio, the risk of MI was greater than for each decile increase in the T-c/HDL-c ratio.
3. A one standard deviation (**SD**) difference in ApoA (*the Advantageous guy*) was associated with a 33% reduction in risk of MI, compared with a reduction of 15% for one SD of the T-c/HDL-c ratio.

4. For non-HDL-c and T-c, a one SD difference showed a weaker association with MI than did ApoB.
5. The ApoB/ApoA ratio was the most powerful marker associated with MI in both sexes.
8. The area under the receiving operating characteristic curve (ROC) was higher for the ApoB/ApoA ratio than for all the other cholesterol ratios.
9. The protective effect of the ApoB/ApoA ratio, although remaining high at all ages, was reduced with age.
10. The overall PAR for acute MI for the ApoB/ApoA ratio was 54%; for the T-c/HDL-c ratio was 32%. For comparison, the PAR for smoking was 44%

DISCUSSION

1. "In all ethnic groups, and both sexes, the ApoB/ApoA ratio was a better risk marker for myocardial infarction than was the ratio of total cholesterol/HDL cholesterol."
2. The ApoB/ApoA ratio was associated with greater risk at all ages than were any of the cholesterol ratios (T-c/HDL-c; non-HDL-c/HDL-c; and LDL-c/HDL-c), although the risk associated with the ApoB/ApoA ratio decreases with age.
3. Indeed, the PAR of ApoB/ApoA ratio was almost double that of the total cholesterol/HDL cholesterol ratio.
4. "An important feature of our results is that ApoB was better than total-cholesterol, LDL-cholesterol, and non-HDL-cholesterol in predicting myocardial infarction, and ApoA was better than HDL-cholesterol in predicting myocardial infarction." For each decile of rise in ApoB, the risk rose to a greater extent than for the cholesterol. ApoB is a strong risk factor for MI
5. For each decile rise in ApoA, the risk of MI declined to a greater extent than it declined with each decile rise in HDL-c. ApoA is a strong protective factor for MI.
6. The pathological basis of why the ApoB/ApoA ratio is better than the cholesterol ratios at risk prediction is not completely understood. Each atherogenic lipoprotein particle contains one molecule of ApoB. Therefore, the number of plasma ApoB molecules equals the total number of atherogenic particles, of which LDL predominates. Small dense, cholesterol depleted LDL particles are common, and when present, LDL-cholesterol underestimates the number of LDL particles. Unlike HDL-cholesterol, ApoA has several physiological roles. It guides reverse cholesterol transport, is an antioxidant, and anti-inflammatory, and helps to produce nitric oxide (*all protective factors*).
7. The clinical measurement of apo-lipoproteins is standardized, simple, inexpensive, and can be done non-fasting. "Our data provide broad and straightforward support that ApoB and ApoA should be introduced into clinical practice for the assessment of risk of vascular disease."

CONCLUSION

The non-fasting ApoB/ApoA ratio was superior to any of the cholesterol ratios in estimation of risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages.

Lancet July 19, 2008; 372: 224-33 Original investigation by the INTERHEART study investigators, first author Matthew J McQueen, McMaster University, Hamilton, Ontario, Canada

1 Am Heart Journal 2001; 141: 711

2 Lancet 2004; 364: 957

“Treat Now By Treating Comorbidities”

7-2 HEART FAILURE WITH PRESERVED EJECTION FRACTION

Among patients older than 65 years, heart failure (HF) has become the most common discharge diagnosis and the primary cause of readmission within 60 days.

Nearly half of all patients with HF have a preserved ejection fraction (HFPEF; *formerly termed “diastolic HF”*). These patients have a high all-cause mortality after hospitalization for HF. Mortality within 1 year is about 25%; and 65% within 5 years.

Few large randomized trials have been specifically designed for patients with HFPEF. These trials have shown minimal benefit. There is little evidence on which to base treatment. The implication is that adverse outcomes in these patients are driven by worsening HF. This is not necessarily accurate.

Data from observational studies and clinical trials suggest that these outcomes are driven by important comorbidities that are common in patients with HFPEF. These patients are typically elderly (mean age = 75 years), more often are women, and frequently have multiple comorbidities including hypertension, coronary artery disease, atrial fibrillation, diabetes, chronic kidney disease, cerebrovascular disease, obesity, and anemia.

In one study, 91% of patient with patients with HFPEF had a diagnosis of hypertension, CAD, or diabetes. In another study, in which CAD was documented by angiography, the presence and extent of CAD was a major determinant of prognosis.

Two randomized clinical trials showed that angiotensin receptor blockers and digoxin did not improve survival.

In one trial, during approximately 3 years of follow-up, mortality in patients with HFPEF was due to cardiovascular causes in 72%, and non-cardiovascular causes in 28%. Of those who died of cardiovascular causes, 38% died of sudden cardiac death, 32% due to progressive HF, 7% due to myocardial infarction, and 9% due to stroke. “These results suggest that HF is not the most frequent cause of mortality in patients with HFPEF.”

In another study, 24% of patients with HF had an ejection fraction greater than 50% (ie, HFPEF). During a 6-month follow-up 44% of these patients were rehospitalized. But only 50% were a result of HF. The other half were hospitalized for non-HF causes.

Independent predictors of death included age, stroke, chronic obstructive pulmonary disease, cancer, diabetes, low glomerular filtration rate, and hyponatremia.

“Because patients with HFPEF often have important comorbid conditions, and because these comorbidities strongly influence outcomes, clinicians should aggressively identify and treat conditions such as hypertension, CAD, atrial fibrillation, diabetes, chronic kidney disease, and cerebrovascular disease in these patients rather than waiting for new HFPEF-specific treatments to emerge.” Controlling BP is a class-1 recommendation from practice guidelines of the AHA and ACC for patients with HFPEF. One of the most significant beneficial aspects of improved BP control is the reduction in hospitalizations for HF. This benefit has been extended to the elderly who comprise the majority of patients with HFPEF. In the Hypertension in the Very Elderly Trial, aggressive treatment of hypertension in patients over 80 years of age resulted in a decrease in cardiovascular events and improved survival, with the most profound benefit occurring for the HF endpoint.

For practicing clinicians who provide care for patients with HFPEF, the greatest reductions in overall morbidity and mortality may result from treating comorbidities with therapies available now.

JAMA July 23/30 2008; 300: 431-433 “Commentary” editorial, first author Sanjiv J Shah, Northwestern University Feinberg School of Medicine, Chicago, IL

7-3 ANKLE BRACHIAL INDEX COMBINED WITH FRAMINGHAM RISK SCORE TO PREDICT CARDIOVASCULAR EVENTS AND MORTALITY

Major cardiovascular and cerebrovascular events often occur in individuals without known preexisting cardiovascular disease. Prevention of cardiovascular events starts with the accurate identification of those at risk. The Framingham risk score (**FRS**; risk of cardiovascular events over the following 10 years) is often considered the reference standard, but has limited accuracy. It tends to overestimate risk in low risk populations and underestimate risk in high risk populations. The FRS includes age, total cholesterol, high-density cholesterol, BP, diabetes, and smoking status.

Other risk markers have been incorporated in studies to improve prognostic power (eg, metabolic syndrome, plasma C- reactive protein, coronary artery calcium score, and carotid arterial intima-media thickness).

The ankle/brachial index (**ABI**), the ratio between systolic BP in the ankle and systolic BP in the arm, is easily measured. ABI has been used for years to confirm the diagnosis and severity of peripheral vascular disease.

The ABI is a marker of generalized atherosclerosis, and may have the potential to improve prediction.

This study determined if the ABI provides information on risk independently of the FRS, and can improve risk prediction.

Conclusion: Measurement of ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

STUDY

1. These investigators conducted a literature search which identified 16 population cohort studies fulfilling their inclusion criteria. All subjects were derived from a general population (over 48 000 individuals; men and women in equal numbers; mean age varied from 47 to 78).
2. A meta-analysis was conducted in individuals who had no previous history of coronary heart disease (**CHD**). All had ABI and FRS measured at baseline.
3. The FRS varied across studies from 11% to 32% in men, and from 7% to 15% in women.
4. Determined hazard ratios (**HRs**) for ABI, subdivided into 10 categories compared to a reference ABI of 111/100 to 120/100. And determined if adding ABI to the FRS would improve prediction.
5. Median follow-up ranged from 3 to 17 years (most more than 10 years) to determine total cardiovascular mortality and morbidity.

RESULTS

1. The HRs for death for different levels of ABI compared with the reference (111/100 to 120/100) increased consistently for men and women with decreasing ABI:
 - For 101-110/100 there was a slightly higher HR above reference.
 - For each 10 mm lower ABI, HR rose steadily to 4 at < 60/100.
 - The prevalence of a low ABI increased with age.
2. HR for total mortality for ABIs of less than 90/100 in men was 3.33 compared to the reference. For women = 2.70.
3. For cardiovascular mortality and major cardiovascular events, the HR for each decreasing ABI rose consistently to 3.45 for an ABI of less than 60/100.
4. Values for ABI less than 90/100 have been taken traditionally as a measure of increased risk. In nearly all studies in men, HRs for total mortality have been statistically higher in individuals with an ABI less than 90/100 compared with the reference of 110-120/100.
5. The ABI provided independent risk information in addition to the FRS. A low ABI (less than 90/100) approximately doubled the risk of total mortality, cardiovascular mortality, and major cardiovascular events as predicted by the FRS.
6. In predicting the 10-year risk of total CHD, these results indicate that measurement of ABI would change the risk determined by the FRS alone in approximately 1 of 5 men.

DISCUSSION

1. "The ABI is potentially a useful tool for prediction of cardiovascular risk." In contrast to measurement of coronary artery calcium and carotid intima-media thickness, ABI has the advantage of ease of use in primary care physician's offices and in community settings. It is now widely used in specialist vascular clinics, but rarely used in primary care.

2. Measurement is simple. Determination of ABI with use of a hand-held Doppler takes about 10 to 15 minutes. It can be taken by a suitably trained nurse or other health care professionals.
3. It causes minimal discomfort and is non-invasive. Patient's acceptability is high.
4. "Our results indicate that a proportion of men and women having an ABI test would be placed in a different risk category."

CONCLUSION

Measurement of ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

JAMA July 9, 2008; 300: 197-208 Review article and meta-analysis by the Ankle Brachial Index Collaboration, corresponding author Gerry Fowkes, University of Edinburgh, Scotland.

"A Successful Translation From Research To Clinical Practice."

7-4 EFFECT OF DISSEMINATION OF EVIDENCE IN REDUCING INJURIES FROM FALLS

Falling is a common, morbid, and expensive health condition among elderly persons. Effective strategies to prevent falls have been identified, but are underutilized. Falls account for about 10% of ED visits, and 6% of hospitalizations among persons age 65 and older, and are major determinants of functional decline, nursing-home placement, and restricted activity.

Positional hypotension, use of multiple medications, and impairments in cognition, vision, balance, gait, and strength increase the risk of falling and falling injuries.

Randomized, controlled trials support the effectiveness of multicomponent fall-prevention strategies in reducing risk.

Despite evidence and mandates, falls remain largely ignored in clinical practice.

Reported barriers to incorporating evidence about fall prevention into practice include ignorance, insufficient reimbursement, competing time demands, a perceived lack of expertise, and inadequate referral patterns.

This study encouraged clinicians and facilities to incorporate evidence of intervention techniques into practice. The study compared rates of serious fall-related injuries and use of medical services following interventions for prevention vs usual care among persons age 70 and over.

Conclusion: Dissemination of evidence about fall prevention, coupled with interventions to change clinical practice, may reduce injuries in elderly persons.

STUDY

1. Using a non-randomized design, compared two large regions in Connecticut:
 - 1) Region where clinicians had been exposed to interventions to change clinical practice (intervention region)

- 2) Region where clinicians had not been exposed to such interventions (usual-care region).
2. The intervention region included 212 primary care offices (with 522 primary care clinicians including physician assistants and advanced practice nurses). The region also included 133 outpatient rehabilitation facilities, 26 home care agencies, 7 acute care hospitals, and 43 senior centers.
3. The interventions encouraged primary care clinicians and staff members involved in home care to adopt effective risk assessments and strategies for the prevention of falls.
4. Outcomes were rates of serious fall-related injuries (hip and other fractures, head injuries, and joint dislocations) and fall-related use of medical services per 1000 person-years among persons age 70 and over.
5. Interventions occurred between 2001 and 2004; evaluations took place from 2004 to 2006
6. The recommended strategies for preventing falls included a reduction in medications, management of postural hypotension, management of visual and foot problems, hazard reduction, and balance gait, and strength training. Clinicians were encouraged to incorporate assessments, treatments, and referrals into their practices, as appropriate to their discipline and setting.
7. The main clinician groups were primary care, home care (nurses and physical and occupational therapists) outpatient rehabilitation (physical and occupational therapists), and emergency department clinicians.
8. Enlisted help of media attention (TV, radio, and newspapers), web sites, posters, brochures, educational materials for patients, and advertising on buses to increase awareness; enlistment of opinion leaders to influence colleagues, and visits (outreach) to everyone in the main group of clinicians and facilities to explain evidence-based fall-related practices, and demonstrate how to incorporate fall prevention into their practices.
9. Determined rates of fall-related injuries and use of medical services. Medicare beneficiaries were the chief source of this information. Serious fall-related injuries included visits to emergency departments, and admissions to study hospitals by persons age 70 and over.

RESULTS

1. Rates of serious fall-related injuries per 1000 person years:
 - A. Pre-intervention—31.2 in the usual care region, and 31.9 in the intervention region.
 - B. During the intervention period—31.4 in the usual care region, and 29.6 in the intervention region.
2. This represents an adjusted 9% decline in the rate of serious fall-related injuries.
3. Differences between regional rates persisted after the reported study period. Three years after the intervention, and one year after the evaluation period, rates of serious fall-related injuries per 1000 person-years were 30.9 in the usual care region and 28.6 in the intervention region.

DISCUSSION

1. During the evaluation period, the adjusted rate of serious fall-related injuries in the intervention region were 9% lower than that of the usual care region.
2. “Relative rate reductions of 9% in serious fall-related injuries and 11% in fall-related use of medical services represent a successful translation from research to clinical practice.” The 11% reduction represents about 1800 fewer emergency department visits or hospital admissions.
3. “Because no single intervention has proved to be exceptionally effective, we used multiple practice-change interventions. We cannot definitely state which components were most effective.”
4. A previous study reported that 50% of primary care clinicians reported referred patients for balance disturbances, and 88% performed medication reviews. Among home-care clinicians, more than 80% reported addressing postural hypotension, balance disturbances, multiple medications, and home hazards for at least some patients.
5. “Our findings . . . suggest that the dissemination of evidence to clinicians about fall prevention when coupled with practice-change interventions results in the adoption of effective strategies to prevent falls and may reduce the number of falls and injuries.”

CONCLUSION

Dissemination of evidence about fall prevention, coupled with interventions to change clinical practice, may reduce injuries in elderly persons.

NEJM July 17 2008; 359: 252-61 Original investigation, first author Mary E Tinetti, Yale University School of Medicine, New Haven Conn.

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Long-Acting Beta-Agonists Have A Narrow Therapeutic Window. They Deserve Caution

7-5 EFFECTS OF ADDING SALMETEROL TO INHALED CORTICOSTEROIDS ON SERIOUS ASTHMA-RELATED EVENTS.

Early guidelines recommended that all patients with persistent asthma receive regular treatment with inhaled corticosteroid. For patients whose asthma is not controlled, adding a long-acting beta-agonist was recommended.

Subsequently (2006), concern about long acting beta-agonists was raised in a randomized, observational study of over 25 000 patients. The study compared long-acting beta-agonists (**LABA** eg, salmeterol [xxxxx]) with placebo added to usual therapy. It showed a small, (but statically significant) increase in severe asthma-related events, including death associated with salmeterol.

In contrast, a large case-control study of 532 asthma deaths concluded that LABA were *not* associated with asthma-related deaths.

The Cochrane Airways Group has published several meta-analyses of clinical trials that studied the combination of inhaled corticosteroids + LABA. It concluded that exacerbations of asthma were infrequent and occurred at similar or lower rates in participants receiving combined therapy than in those receiving inhaled corticosteroids alone.

Another meta-analysis (2006) examined life-threatening and fatal asthma exacerbations in participants using LABA. About 50% of the cohort did not receive concurrent inhaled corticosteroid. Results showed that, although rare, asthma-related hospitalizations and death occurred more frequently in patients receiving LABA without inhaled corticosteroids.

This study continues the controversy.

Conclusion: Salmeterol combined with inhaled corticosteroid, decreased risk of severe exacerbations requiring systemic corticosteroids.

STUDY

1. Examined whether the incidence of severe asthma-related events (including hospitalizations, intubations, deaths, and severe exacerbations) differed in persons receiving inhaled salmeterol + inhaled corticosteroids vs inhaled corticosteroid alone.
2. Included 66 randomized, controlled trials (over 26 000 patients with moderate to severe persistent asthma) comparing inhaled corticosteroid + LABA (usually administered as twice-daily fluticasone/salmeterol (*Advair*; GlaxcoSmithKline), often by means of a single device), vs inhaled corticosteroid (*Flovent*; fluticasone; GSK) alone in patients with persistent asthma.
3. All trials were reported by GlaxcoSmithKline. Only 26 trials were longer than 12 weeks.
4. Adjudicated case narratives on serious adverse effects that were reported by GSK.

RESULTS

1. Severe asthma exacerbations requiring systemic corticosteroids:

Combined therapy	5%
Inhaled corticosteroid alone	8%
2. Asthma-related hospitalizations (combined therapy vs corticosteroid alone) = 35 vs 34.
3. One asthma-related intubation and one asthma-related death occurred in patients receiving combined therapy. No such events occurred in patients receiving corticosteroids alone.
4. A subset of 24 trials showed a decreased risk of severe asthma-related exacerbations for combined therapy vs corticosteroid alone.
5. Few deaths and intubations limited the ability to measure risks for these outcomes.

DISCUSSION

1. "These results derived primarily from 66 GlaxcoSmithKline trials of 20 966 participants, suggest that the

addition of salmeterol to inhaled corticosteroids dose *not* alter the risk for asthma-related hospitalizations compared with corticosteroids alone.”

2. Addition of salmeterol may not alter the risk for asthma-related intubation and death. However, with only 2 intubations or death events, it is difficult to draw firm conclusions.
3. The low incidence of hospitalizations and intubations is reassuring because hospital admission is a recognized risk factor for asthma morbidity and mortality.
- 4 Treatment with LABA + inhaled corticosteroids, compared with corticosteroids alone decrease risk for some severe exacerbations, but may not alter the risk for asthma-related hospitalizations, intubations, and death.
- 5 Previous studies of inhaled LABA without corticosteroid led to the speculation that up to 5000 theoretical asthma-related deaths in the USA were due to the drug. Other studies did not support this conclusion. In fact, the number of asthma-related deaths has declined steadily since 1996 in the USA since salmeterol was introduced (1994) and then salmeterol + fluticasone became available in a single device (2001).
7. Inhaled corticosteroids added to LABA mitigate the risk of untoward asthma-related events that may be associated with use of LABA alone.

CONCLUSION

In patients with persistent asthma, salmeterol combined with inhaled corticosteroid may reduce the risk of severe asthma exacerbations, as compared with corticosteroids alone,. The combination does not alter the risk of asthma-related hospitalizations, and may not affect the risk for asthma-related deaths or asthma-related intubations.

Annals Int Med July 1, 2008; 149: 33-42 Original investigation, first author Eric Bateman, University of Cape Town, South Africa.

GSK sponsored this study (data collection, analysis, and data interpretation) and most of the trials included.

An editorial in this issue of Annals by Kevin B Weiss, American Board of Medical Specialties, Evanston IL comments:

“Ultimately, nearly all drugs have therapeutic windows within which physicians and patients must function. Like insulin and oral anticoagulation, long-acting beta-agonists have a narrow therapeutic window. They deserve the same caution and meticulous attention to detail that physicians expect of themselves when they prescribe potentially harmful drugs.”

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An Unrecognized Complication Of Diabetes. May Be Stronger Among Younger Persons With Diabetes.

7-6 DIABETES AND HEARING IMPAIRMENT

In the adult population, risk of hearing loss is associated with age, male sex, lower education, industrial and military occupation, leisure time noise exposure, and smoking. It is estimated to exceed 30% among that age 65 and older.

Diabetes affects about 10% of the adult population. It is associated with microvascular and neuropathic complications. These complications could injure the vasculature and neural system of the inner ear. Two studies have described evidence of such pathological changes.

The present study used recent national survey data to examine the relationship between diabetes and hearing impairment.

Conclusion: Hearing impairment is common in adults with diabetes. Diabetes seems to be an independent risk factor.

STUDY

1. The NHANES (National Health and Nutrition Examination Study) 1999-2004 included over 5000 persons who completed an audiometric examination and diabetes questionnaire.
2. Pure tone air conduction thresholds were obtained for each ear at frequent frequencies (500 Hz or less were considered low frequency; 1000 to 2000 HZ mid-range frequency; and tones over 3000 were considered high frequency).
3. For each frequency range, a pure tone loss averaging greater than 25 decibels defined hearing impairment of mild or greater severity. A pure tone loss averaging greater than 40 decibels defined hearing impairment of moderate or greater severity.
4. Functional description of hearing impairment:

Frequency range	Severity of impairment
	A. Pure tone average threshold > 25 to 40 decibels hearing loss (dB HL).
Low or mid	Slight difficulty understanding speech under ideal listening conditions
High	Slight difficulty understanding speech under unfavorable conditions.
	B. Pure tone average threshold > 40 dB HL
Low or mid	Considerable difficulty understanding speech under ideal listening conditions
High	Considerable difficulty understanding speech under unfavorable conditions

RESULTS

1. Prevalence of diabetes = 399 subjects; no diabetes 4741.

2. Prevalence of hearing impairment in the worse ear:

	Diabetes (%)	No Diabetes (%)
Mild or greater severity (> 25 dB HL)		
Low or mid-frequency	21	9
High frequency	54	32
Moderate or greater severity (> 40 dB HL)		
Low or mid frequency	9	3
High frequency	37	16

3. Prevalence (%) of low or mid-frequency hearing impairment of greater severity according to age:

	Diabetes	No diabetes
20-49	16	5
50-59	32	14
60-69	36	30

DISCUSSION

1. “We estimate a prevalence of low- or mid-frequency hearing impairment of mild or greater severity of 28% among people with diabetes.” Associations were generally stronger between diabetes and high-frequency hearing impairment.
2. Prevalence of impairment was higher among individuals with diabetes in both sexes, all groups of race, ethnicity, education, and income-poverty ratio, and at all ages but age 60-69.
3. The association between diabetes and hearing impairment remained in analyses that adjusted for other factors that may contribute to impairment (eg, smoking, noise exposure, and ototoxic medications).
4. The relative contribution of diabetes to hearing impairment may be stronger among younger persons with diabetes.
5. Several biological mechanisms might explain the association: diabetes-related pathogenic changes in the microvasculature, degeneration of nerves of the ear with compromised cochlear function, narrowing of the internal auditory artery.

CONCLUSION

Hearing impairment may be an unrecognized complication of diabetes. Screening for hearing loss may be justified in persons with diabetes.

Annals Int Med July 1, 2008; 149: 1-10 Original investigation, first author Kathleen E Bainbridge, Social and Scientific Systems, Silver Springs, MD.

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“The Inability To Sustain Weight Loss Appears To Mirror The Inability To Sustain Physical Activity.”

7-7 EFFECT OF EXERCISE ON 24-MONTH WEIGHT LOSS MAINTENANCE IN OVERWEIGHT WOMEN

Behavioral interventions including diet and exercise can result in a weight loss of about 10% of body weight within 6 months. Leisure time physical activity (**LTPA**) is important in the maintenance of clinically significant weight loss.

The consensus of recommendations for LTPA is a minimum of 30 minutes of moderate physical activity on most days for the week (150 min/wk). There is growing consensus that more exercise may be necessary to enhance long-term weight loss.

This study examined the effect of exercise of varying duration and intensity on weight loss in overweight adult women during a 24-month period.

Conclusion: The addition of 275 min/wk of LTPA above baseline activity, in combination with a reduction in energy intake is important in allowing women to sustain weight loss of more than 10%.

STUDY

1. Recruited 201 obese and overweight women in 1999 -2003 from a hospital-based weight loss research center. BMI = 27 to 40 (mean = 32); ages 21-45 (mean = 37).
2. Randomized to 1 of 4 groups based on prescribed LTPA energy expenditure (moderate 1000 kcal/wk; high 2000 kcal/wk) and exercise intensity (moderate; vigorous):
 - 1) 1000 kcal/wk – moderate exercise
 - 2) 1000 kcal/wk – vigorous exercise
 - 3) 2000 kcal/wk – moderate exercise
 - 4) 2000 kcal/wk – vigorous exercise
3. Participants were told to reduce intake to 1200-1500 kcal/day. They were encouraged to attend group meetings and receive telephone calls periodically focused on strategies for maintaining eating and exercise behavior.
4. Subjects were encouraged to spread exercise over 5 days/wk, and to exercise for a minimum of 10 minutes each time.
5. A treadmill was issued to each subject to use at home.
6. 89% completed the 24-month study.

RESULTS

1. Weight loss did not differ among the randomized groups. The mean weight loss overall at 6 months was 8%-10% of initial weight, and at 24 months was 5% of initial weight.
2. About 25% of subjects did achieve a loss of 10% at 6 months and sustained the loss for 24 months. This group reported performing more LTPA (1835 kcal/wk; 275 min/wk) compared with those who

sustained a loss of less than 10%. They were also more compliant with dietary restrictions.

DISCUSSION

1. This study attempted to judge the amount and intensity of exercise that may be required to enhance long-term weight loss. The prescribed intensity of exercise (moderate vs vigorous) did not influence weight loss outcomes.
2. The results show that the initial weight loss of 10% of body weight at about 6 months was not generally maintained. Mean weight loss declined to a mean of 5% at 2 years regardless of the prescribed amount of intensity of exercise. (Mean weight regain from 6 months to 2 years was approximately 50%.)
3. The LTPA increased by a mean of 1235 kcal/wk from baseline to 6 months and declined to a mean of only 720 kcal/wk at 24 months. The prescribed differences in LTPA were not sustained in any randomized group.
4. "Thus, the inability to sustain weight loss appears to mirror the inability to sustain physical activity."
5. However, about ¼ of those randomized did maintain a 10% weight loss at 24 months.* This corresponds to a mean of 275 min/wk of LTPA (55 min per day for 5 days a week above baseline level. "This confirms the level of physical activity that should be targeted for successful weight loss."
(*This group was compliant in continuing connection with the study investigators and was also more compliant with prescribed eating behaviors.)
6. A level of LTPA that may be necessary to sustain weight loss in relatively sedentary overweight adults for as long as 24 months is approximately twice the public health recommendations.
7. "The results of this study are clinically relevant and provide guidance to health care professionals regarding the magnitude of physical activity that needs to be included in behavioral interventions for weight loss and weight loss maintenance."
8. LTPA did not function independently of diet control and willingness to maintain contact with the professional staff.

CONCLUSION

The addition of 275 min/wk of LTPA, in combination with reduction in energy intake, was important in allowing overweight women to sustain weight loss of 10% over a period of 24 months

Archives Int Med July 28, 2008; 168: 1550-59 Original investigation, first author John M Jakicic, University of Pittsburgh, PA.

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