

In the cohort of 632 patients who underwent screening with EBCT, both the absolute calcium score and the calcium score percentile (sex- and age-adjusted percentiles from a large series scanned at the authors' center) were predictors of adverse outcomes. The majority of the events occurred in the middle 2 quartiles of scores, and the highest quartile of calcium scores had the highest event rate. Because of the small number of patients with scores in this highest quartile, the total proportion of events that occurred in this quartile was low. According to the authors, the calcium score percentile appeared to be a better measure in this study than the raw calcium score because of the former's ability to identify a greater proportion of the events that occurred. Thus, evaluating calcium scores as a percentile may be a better means to apply this test as a screening tool in an asymptomatic population. In this study, with respect to the population evaluated shortly after MI, a significant proportion would have been identified as being at risk for adverse outcomes had they been screened before their MIs.

This article is representative of much of the EBCT literature. Published data in limited series suggest that EBCT:

- Strongly correlates with the amount of atherosclerotic burden present.
- Predicts the presence of CAD in selected populations.
- Is an excellent independent predictor of adverse outcomes.

Several major flaws, however, continue to haunt the EBCT literature. To date, the data published tend to be based on preselected populations with significant referral bias, and the populations tend to be small and inadequate for evaluating the end points the authors select.

Further, the analyses performed tend to be statistically flawed, particularly with respect to whether EBCT is more valuable than other information. In the current manuscript, information known about the patient prior to the EBCT is not adjusted for in the analyses. How many additional events would have been detected by EBCT after patients who were unlikely to experience events (based on their clinical information) were excluded? In addition, the authors of this and other EBCT manuscripts tend to use quartiles of scores. These quartiles are extremely sensitive to the population selected; it is difficult to apply results based on quartiles of 1 cohort to another population unless the cohorts are very similarly matched. Since the event rates in asymptomatic populations tend to be very low, the event rate in the

lowest quartile will be extremely low, while it will be relatively high in the highest quartile. Although EBCT undoubtedly stratifies a population, is the relative risk high because of the test's performance or because of the analysis?

There is much to be optimistic about regarding EBCT's possible applications in the clinical community. Until the evidence is brought forth in well-analyzed, sufficiently powered cohorts, however, the support of this modality by guidelines will be delayed.

Hypertension

Scrutinizing Systolic Blood Pressure

Reviewed by Joseph L. Izzo, Jr, MD

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Systolic blood pressure (BP) is now achieving widespread attention as the more relevant clinical end point in hypertension. A recent Clinical Advisory update from the National Heart, Lung, and Blood Institute emphasizes this paradigm shift. Also included is a major criticism of a recent paper suggesting that systolic hypertension is benign.

A Clinical Advisory Statement: The Importance of Systolic Blood Pressure in Older Americans

Izzo JL Jr, Levy D, Black HR, for the Coordinating Co-mittee of the National High Blood Pressure Education Program

Hypertension. 2000;35:(5).

A Clinical Advisory Statement on the importance of systolic BP was issued in May from the Coordinating Committee of the National High Blood Pressure Education Program as an adjunct to the recommendations of *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI, 1997)*. Based on the large amount of evidence currently available, the committee recommended a major paradigm shift in urging that systolic BP become the major criterion for diagnosis, staging, and therapeutic

management of hypertension, particularly in middle-aged and older Americans.

Several lines of strong pathophysiologic evidence were quoted to support the initiative to emphasize systolic BP, including the strong associations among aging, increased stiffness of large arteries, increased systolic BP, increased pulse pressure, and the prevalence of cardiac and vascular disease. Isolated systolic hypertension, which is present in about two thirds of hypertensive individuals over age 60, was highlighted as the most common form of hypertension. Using JNC VI criteria, the diagnosis, classification, and staging of hypertension are more precise using systolic rather than diastolic BP. Risk stratification for major complications of hypertension (stroke, myocardial infarction, heart failure, and kidney failure) is actually confounded by the use of diastolic BP, because in persons with systolic hypertension, diastolic BP is *inversely* related to cardiovascular risk. Clinical benefits of treatment of isolated systolic hypertension are known to include reductions in stroke, myocardial infarction, heart failure, kidney failure, and overall cardiovascular disease morbidity and mortality. Unfortunately, only 1 in 4 Americans with hypertension has the disease controlled at JNC VI-recommended values of 140/90 mm Hg in uncomplicated hypertension or 130/85 mm Hg in persons with renal disease or diabetes. Hypertension control rates are poorest in older persons, primarily as a result of inadequate systolic BP control. The strategic value of risk stratification and the clinical benefit of vigorous BP management at all ages were reemphasized, and the use of age-adjusted BP targets was discouraged. Angiotensin-converting enzyme inhibitors were added to the list of drugs (thiazide diuretics, with or without β -blockers, and calcium antagonists) for which compelling evidence exists concerning reduced morbidity and mortality in older people.

Systolic Blood Pressure and Mortality

Port S, Demer L, Jennrich R, et al.
Lancet. 2000;355:175-180.

Port and colleagues from the mathematics department of the University of California at Los Angeles reanalyzed the impact of systolic BP on total mortality (cardiovascular and noncardiovascular deaths) in the 18-year database from the Framingham Heart Study, which represented clinical care in the 1950s and 1960s. Their purpose was to develop a 2-component analysis to identify threshold values for systolic BP in that database, which is known for its curvilinear relationship between systolic BP and mortality. From this analysis came the sweeping conclusion that

hypertension treatment is unnecessary unless systolic BP exceeds a threshold value of 160 to 180 mm Hg, depending on age and gender. This highly biased, clinically dangerous study has several major flaws that may mislead readers who are not thoroughly familiar with the subject.

One major flaw of the study is that the authors used as their principal dependent variable *total mortality* instead of the more relevant end point of *total cardiovascular morbidity and mortality*, as had been used by the Framingham investigators. The erroneous choice ignores the stated public health goal of antihypertensive therapy, which is to reduce both morbidity and mortality. Rates of nonfatal myocardial infarction or stroke are 5- to 10-fold higher than the corresponding fatality rates for these events. By basing their results on mortality, the authors did an enormous injustice to those who may suffer the impact of kidney or heart failure and nonfatal strokes or heart attacks.

Another major flaw is the choice of the small, outdated 18-year Framingham database. Only about 5000 individuals were included in that cohort, which was divided subsequently into deciles for analysis. The event rate in these deciles was simply too low for statistical significance to be claimed. Furthermore, in the 2-component analysis employed, the lack of relationship between systolic BP and noncardiovascular mortality rates, especially at the lower pressure levels, exaggerated any potential threshold effect.

The authors' highly biased approach has led to faulty conclusions that are in direct opposition to more powerful and compelling clinical evidence. A more robust and representative database is the contemporaneous MRFIT (Multiple Risk Factor Intervention Trial) follow-up study, in which 316,000 men were followed for 12 years. In this database, there is a nearly linear relationship between systolic BP and coronary heart disease mortality *at all levels of systolic blood pressure, with no apparent systolic threshold*. In all probability, the hypothesis that a systolic threshold exists would have been rejected if the authors had used the MRFIT database. There is also irrefutable evidence from well-conducted clinical trials that treatment of isolated systolic hypertension improves morbidity and mortality. In particular, the SHEP (Systolic Hypertension in the Elderly Program) and Syst-EUR (Systolic Hypertension in Europe) studies demonstrate that reduction of systolic BP from the 170 mm Hg to the 140 mm Hg area reduces stroke, myocardial infarction, heart failure, and all-cause cardiovascular morbidity and mortality. Finally, Port and his nonclinician colleagues failed to recognize the increased risk caused by the interaction of systolic hypertension with other cardiovascular risk factors. The World

Health Organization and the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure strongly recommend the treatment of systolic hypertension to target values of 140 mm Hg or less in uncomplicated hypertension. Target BP in those with diabetes, kidney failure, or heart failure should be below 130/85 mm Hg.

Thus, Port's conclusions are not supported by his own data or the literature. These authors have violated acceptable academic practice by elevating selected observational data to the level of worldwide practice guidelines while ignoring information from more robust databases and randomized clinical trials. Their conclusions, if followed, would increase the global burden of cardiovascular disease.

Lipid Disorders

Reducing Risk of Stroke and Fracture

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News of possible risk-reducing measures for patients is always welcome. Three studies report on 2 areas of risk reduction: lowering risk of stroke in women by increasing physical activity; diminishing the risk of fractures with the use of statins.

Physical Activity and Risk of Stroke in Women

Hu FB, Stampfer MJ, Colditz GA, et al.

JAMA. 2000;283:2961-2967.

Physical activity has been shown to reduce the risk of coronary heart disease, but its value for lowering the risk of stroke has not been well established. Hu and coworkers report on the association between physical activity and the incidence of stroke in the Nurses' Health Study, a prospective observational study of subjects residing in 11 US states and lasting 8 years (560,087 person-years of follow-up). A total of 72,488 female nurses, aged 40 to 65 years, without evidence of cardiovascular disease, were divided into quintiles of physical activity, based on the

hours per week spent in moderate or vigorous recreational activities, such as walking, jogging, bicycling, aerobics. Relative to the lowest quintile of physical activity, the relative risk of all types of stroke in the highest quintile of physical activity was 0.66 ($P = .005$ across all quintiles), with intermediate risk reductions at lesser levels of physical activity. The reduced stroke risk was observed primarily for ischemic stroke (88% of events had CT or MRI evaluation), with a risk reduction in the highest physical activity group compared with the lowest of 0.52. Insignificant associations between physical activity and subarachnoid hemorrhage or intracerebral hemorrhage were found. The reduction in stroke risk was not limited to those nurses undergoing strenuous physical activity.

After multivariate adjustment, walking was associated with a reduced risk of total stroke (highest to lowest quintile ratio, 0.66). Interestingly, those nurses with the fastest walking paces had the greatest reduction in total and ischemic stroke compared with those with average or casual walking pace. The authors concluded that their data indicate that physical activity, including moderate-intensity exercise such as walking, is associated with substantial reduction in risk of total and ischemic stroke in a dose-dependent manner.

This study is one of several recent reports documenting that physical activity reduces cardiovascular risk. The findings that the benefit is proportional to the time spent exercising and that even intermediate-grade exertion, such as walking, is beneficial will be helpful arguments in inducing patients to exercise more. Whereas many patients are reluctant or unable to undertake strenuous physical activity for cardiovascular or orthopedic reasons, this study documents the benefit of more widely applicable activities such as walking. A reduction in stroke can now be added to the other benefits of physical activity for which there is a consensus on the reduction in coronary heart disease and type 2 diabetes. The protective effect of physical activity is probably mediated through alterations in various risk factors, including reductions in blood pressure, plasma fibrinogen level, and platelet aggregation, and increases in high-density lipoprotein cholesterol and plasma tissue plasminogen activator activity.

The major limitation of this study is its format, it was a prospective observational study rather than a randomized trial. It is always possible that unforeseen confounding factors account for the risk reduction, not the physical activity. Within this limitation, however, we can use this study for additional motivation for our patients to increase their physical activity.