Only 7.5% of Americans at Low Risk for Heart Disease

BY DIANA MAHONEY

The prevalence of a low-risk profile for cardiovascular disease among adults in the U.S. population has decreased in recent years, suggesting the "huge potential" for preventing cardiovascular disease is far from being realized, according to an analysis of NHANES data.

Using data from four National Health and Nutrition Examination Surveys, Dr. Earl S. Ford, medical officer of the U.S. Public Health Service at the Centers for Disease Control and Prevention, and his colleagues tracked cardiovascular risk data for American adults aged 25-75 years during 1971-1975, 1976-1980, 1988-1994, and 1999-2004, and showed that the prevalence of a low-risk profile increased from 4.4% at the time of the first survey to 10.5% by the third survey, but then decreased to 7.5% in the fourth survey (1999-2004).

Limited strides toward reducing heart risk 'during the 1970s and 1980s have more recently been negated by the obesity epidemic and increased rates of hypertension and diabetes.'

The low-risk-factor profile incorporated the following variables: not currently smoking, total cholesterol less than 200 mg/dL without cholesterol-lowering medications, systolic blood pressure less than 120 mm Hg and diastolic blood pressure less than 80 mm Hg without antihypertensive medications, body mass index less than 25 kg/m^2, and not having been previously diagnosed with diabetes (Circulation 2009 Sept. 14 [doi:10.1161/CirculationAHA.108.835728]).

"The limited strides that were made toward achieving low-risk status during the 1970s and 1980s have more recently been negated by the obesity epidemic and increased rates of hypertension and diabetes," Dr. Ford said in an interview. According to the results, "fewer than 10% of Americans are meeting the low-risk goals."

The low-risk-factor patterns were similar for men and women, but the prevalence of low-risk profiles was higher in women than in men in each of the surveys, the authors reported. Similarly, the low-risk-factor burden was much higher among survey respondents aged 25-44 years than among those aged 45-64 or 65-74 years in all the surveys, and it was higher among whites than blacks during each survey except 1976-1980. During 1988-1994 and 1999-2004 only, a larger percentage of whites had a low-risk-factor burden, compared with Mexican Americans, they wrote.

An analysis of the individual risk categories showed favorable trends for not currently smoking (60% at the time of the first survey and 74% by the fourth survey) and low concentrations of total cholesterol (35% and 43%, respectively). For blood pressure, the low-risk percentage was higher for the period 1988-1994 than for the 1971-1975 period, but it decreased for the period 1999-2004, "which is worrisome," the authors wrote. Similarly, "the distribution of body mass index progressively deteriorated over time," they reported, adding that the unfavorable trends "argue for vigorous population-based approaches to reverse the unhealthy shift in the distributions of blood pressure and body mass index and to sustain or accelerate the improvement in the distribution of total cholesterol."

Because the NHANES surveyed only noninstitutionalized adults, the true risk-factor burdens "may be even worse" than those reported, which is one of the limitations of the study, the authors noted. Additional limitations include the exclusion of physical activity and a dietary index as part of the risk determination, and changes in the wording of questions for use of current antihypertensive medication and physician-diagnosed diabetes that could potentially have affected the estimates, they wrote.

Despite the possible limitations of the study, "our results clearly demonstrate a great need for prevention; thus, health care providers should have adequate resources, time, and reimbursement to engage in the prevention of cardiovascular disease in individuals," they authors wrote, adding that those efforts should be in concert with those of state and national agencies charged with developing effective public health interventions.

In an editorial, Rob M. van Dam, Ph.D., of the Harvard School of Public Health in Boston, and Dr. Walter C. Willett of Brigham and Women's Hospital in Boston, commented that the trajectory of the risk factor trends is even more worrisome considering the analyses "do not yet reflect the effects of the current epidemic of childhood obesity, which causes an early onset of type 2 diabetes, hypertension, and dyslipidemia" (Circulation 2009 Sept. 14 [doi:10.1161/CirculationAHA.109.891507]).

The findings, they wrote, "provide an important signal that the health of Americans is at a crossroad. The current path leads toward increasing adiposity, diabetes mellitus, cardiovascular disease, and disability and an unfit, socially isolated population stuffed with pills and subjected to frequent palliative procedures." To change course, they stressed, physicians can help by working with their patients one on one, but "their help is needed even more as leaders in the effort to reshape policies and our environment."

The authors said they had no financial disclosures related to this report. ■

Combo Antihypertensive Options Predicted to Increase

BY PATRICE WENDLING

CHICAGO — Two trends are emerging in the development of investigational antihypertensive drugs.

Look for more fixed-dose combinations and agents with beneficial effects beyond blood pressure lowering alone, said Dr. George Bakris, director of the hypertensive diseases unit and professor of medicine at the University of Chicago.

"There's going to be a lot more in the armamentarium of combination therapy," he said at a meeting sponsored by the International Society on Hypertension in Blacks. "Approximately 76% of all the 75 million hypertensives require two or more antihypertensive agents, and people are sick of taking pills."

Takeda Pharmaceuticals recently launched a phase III trial of its investigational compound TAK-491, an angiotensin receptor blocker (ARB), combined with the diuretic chlorthalidone in patients with moderate to severe hypertension. Takeda expects TAK-491 to show stronger antihypertensive action and to have a profile in improving insulin resistance and decreasing proteinuria that is superior to existing ARBs. The company also expects that it will succeed its current mainstay product candesartan, also an ARB.

"It's not your mother's ARB," Dr. Bakris said. "It could be the ARB tailored for the metabolic syndrome."

Boehringer Ingelheim recently announced effective 24-hour blood pressure control with its investigational combination of the ARB telmisartan and the calcium channel blocker amlodipine in hypertensive patients at risk of cardiovascular events and those not controlled with amlodipine alone.

In April 2009, the Food and Drug Administration approved Exforge HCT, the only antihypertensive agent to include three medications—amlodipine, valsartan, and hydrochlorothiazide—in a single pill.

Neutral Endopeptidase Inhibitors

Neutral endopeptidase (NEP) inhibitors also are being given a second look, this time in combination with ARBs. NEP is the major enzymatic pathway of degradation of natriuretic peptides, which are thought to have such beneficial effects in hypertension as vasodilation, natriuresis, and inhibition of the sympathetic nervous system.

The investigational drug omapatrilat (Vanlev), which combined inhibition of both ACE and NEP, appeared to be a powerhouse, beating such leading agents as losartan and amlodipine. But its new drug application was withdrawn for a second time in 2002 because of reports of life-threatening angioedema.

"Theoretically, the synergy from an ARB/NEP combination should be similar. And because of lesser bradykinin effects, the risk is lower for angioedema, as ARBs have about a 10% incidence of angioedema, compared with ACE inhibitors," Dr. Bakris explained in an interview. "The role of NEP is unclear since no one knows the mechanism of angioedema, but it is very rare in Caucasians and has an incidence of less than 0.01% in African Americans."

Several ARB/NEP inhibitors, including MDL 100240 and MDL 100173, are in development, with these combinations expected probably in late 2010-2011, he said.

Endothelin Inhibitors

Finally, researchers are investigating combined ARB and endothelin inhibition. Endothelin (ET-1) is an amino acid peptide produced by the vascular endothelium and increases angiotensin II, aldosterone, antidiuretic hormone, thrombin, and reactive oxygen species. Studies have shown ET-1 is a powerful vasoconstrictor (Radiology 2001;219:419-26) and plays a role in salt retention (Circulation 2001;103:263-8).

Dr. Bakris noted that Gilead Sciences made a splash earlier this year when it released interim results showing dramatic additional blood pressure reductions with its selective endothelin A receptor antagonist darusentan in patients who had resistant hypertension despite maximal doses of a three-drug regimen that included a diuretic.

The phase III DAR-311 trial, also known as DORADO, met its coprimary efficacy end points, reporting that 14 weeks of once-daily oral darusentan 50 mg, 100 mg, and 300 mg significantly reduced mean trough sitting systolic BP by 18 mm Hg at the two higher doses and mean trough sitting diastolic BP by 10 mm Hg at all three doses.

"I helped design this study and none of us thought we would get this kind of effect," he said. "This is definitely something that will be in the armamentarium for resistant hypertension," Dr. Bakris said.

He suggested darusentan could be available in 6-9 months, but cautioned that it should not be considered for first-line treatment.

"In case you think this is such a gorilla you should start with it, that is not how these studies were designed and you should not extrapolate to that," he said. "It would be wrong."

He noted that treatment-related peripheral edema/fluid retention of about 1 L was an issue in about one-third of patients at each dose.

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