European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice

DeBacker G, Ambrosioni E, Borch-Johnsen K, et al. Eur Heart J 2003;24:1601–10.

The 3rd European guideline (EG) for cardiovascular disease prevention in clinical practice was developed to reduce first or recurrent clinical events due to CHD, ischemic stroke and peripheral artery disease. Like the AHA/ACC guideline, its evidence is expert based and recommends identifying high-risk persons complimented by global strategies for the European populace. 3rd EG is directed in descending order of importance: 1) established coronary disease, peripheral artery disease or cerebral vascular disease, 2) multiple risk factors resulting in a 10-year risk of ≥5% at the time of assessment (or if extrapolated to age 60 in younger persons) for developing a fatal CVD event, 3) markedly elevated single risk factors (cholesterol >320 mg/dL, LDL-C >240 mg/dL, BP ≥180/110 mm Hg), 4) diabetes type-2 and diabetes type-1 with microalbuminuria, 5) close relatives of patients with early-onset atherosclerotic CVD and 6) other individuals encountered in routine clinical practice. 3rd EG utilizes a novel model for total risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system, which differs by CVD prevalence in specific regions of Europe (e.g., Italy and Greece are low risk). It is unique in that it predicts any 10 year fatal atherosclerotic end point based on age, gender, smoking, systolic BP and either total cholesterol or total-C/HDL-C, in contrast to the Framingham-based Global Risk Score in the US that predicts hard coronary events. The guideline encourages increasing the risk estimate in subjects with a strong family history of premature CVD and other risk factors/markers including a low HDL-C, impaired glucose tolerance and increased triglycerides, hs-CRP, Lp (a), apo B, fibrinogen and homocysteine. Other tools to be considered for a more precise risk assessment include coronary calcium score by electron beam or conventional computed tomography, carotid intima-media thickness by ultrasound and ECG and echo measures of left ventricular hypertrophy in patients with hypertension. These represent a leap to technology by the Europeans and do not necessarily represent specifics within a country such as England with a government-sponsored health system. The guideline emphasizes the need for a therapeutic alliance between health care providers and the patient for changing behavioral risk factors including unhealthy diet, smoking, sedentary lifestyle and how the presence of negative emotions and lack of support system and finances may constitute barriers to change. Blood pressure and diabetes recommendations are similar to US guidelines. But lipid lowering recommendations differ markedly from the ATP III and are counterintuitive. In those with high multifactorial risk and if the 10-year risk of CV death is ≥5% after diet and exercise, moderate dosing of lipid lowering drugs targeting the LDL-C to <100 mg/dL is recommended "when the baseline LDL is already close 115 mg/dL," but "these lower values are not goals of therapy for patients with higher untreated values because high-dose therapy, the merits of which have not been documented, would be needed to reach such lower goals." Lipid lowering drugs are recommended to target the LDL-C to <100 mg/dL in patients with established atherosclerotic disease. Interestingly, the recommendation is drug therapy and not specifically beginning with a statin, which seems to be an easy step based on the evidence. In addition to lipids, BP, and diabetes the guidelines recommend ASA or platelet modifying drugs in all patients with CVD, beta-blockers following a MI or with LV dysfunction due to CHD or hypertension and ACEi in patients with LV dysfunction and/or hypertension. ASA is recommended in diabetes, controlled hypertension and in men with multifactorial high risk. This is in contrast to the US where ASA is recommended for men with a 1% or greater risk for a coronary event and high-risk women. MR

A Calcium Antagonist vs. a Non-Calcium Antagonist Hypertension Treatment Strategy for Patients with Coronary Artery Disease: The International Verapamil-Trandolapril Study (INVEST): A Randomized Controlled Trial

Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al., for the INVEST Investigators. JAMA 2003;290:2805–16.

Study Question: Is there a therapeutic advantage for a calcium antagonist strategy (CAS) or a non-calcium antagonist strategy (NCAS) regarding effect on mortality and morbidity outcomes in patients with hypertension and coronary artery disease (CAD)?

Methods: A randomized, open-labeled, blinded end point international study in 22,576 hypertensive CAD patients 50 years and older. Patients were randomly assigned to CAS (verapamil 240 mg SR/d) or NCAS (atenolol 50 mg/d) as step 1. Target BP was <140/<90 mm Hg or <130/<85 mm Hg in diabetics and renal impairment. Patients not achieving target were provided step 2, which in the CAS group was the ACEi trandolapril and in the NCAS hydrochlorothiazide (HCTZ) which could be titrated from 25 mg to 100 mg. The verapamil-trandolapril was provided as a fixed combination ranging from 180 mg + 2 mg per day to 240 mg + 4 mg/d. Step 3 was an increase in dosing, and step 4 the addition of trandolapril in the CAS group. Other antihypertensive agents, except beta-blockers for CAS and calcium-channel antagonists in NCAS subjects, were allowed in each

group. The primary outcomes were first occurrence of death (all cause), nonfatal MI or nonfatal stroke. Patients taking beta-blockers within 2 weeks of randomization for an MI in the previous 12 months were excluded.

Results: Mean age was 66 years, 52% were women, 48% white, 13% black and 36% hispanic. CAD was diagnosed by a previous MI in 32% and coronary angiography in about 40%, 66% had angina, 5% a stroke, 28% were diabetics and mean BP was 150/86 mm Hg. Previous antihypertensive drugs included ACEi in 51%, calcium antagonists in 41% and diuretics in 37%. At 24 months, in the CAS group, 81.5% were taking verapamil, 63% the combination with trandolapril, and 44% were also taking HCTZ. In the NCAS group, 77.5% were taking atenolol, 60.3% HCTZ, and 52% were taking trandolapril. About 14% of subjects in each group were on three or more drugs. Two-year BP control was similar with systolic BP goals achieved in 65% and diastolic BP goals in 88% of each group. About 70% of all patients achieved a BP <140/90 mm Hg. At a mean 2.7 years follow-up per patient (61,835 patient-years), about 10% of subjects had a primary outcome that did not differ between groups. There were no subgroups (e.g., age >70 years, gender, race, MI, LVH, CHF, diabetes, revascularization) in which a treatment strategy was preferable, with the exception of less angina and new diabetes in the verapamil+trandolopril group. Cough rate was less than 2% in both groups, and other than constipation on verapamil and symptomatic bradycardia with atenolol, there was minimal difference in adverse events.

Conclusions: The verapamil-trandolapril–based strategy was as clinically effective as the atenolol-hydrochlorothiazide–based strategy in hypertensive CAD patients.

Perspective: This important and unique study demonstrates again that the majority of older persons with hypertension require combination therapy to reach targets. The findings are specific to a high-risk population with hypertension and CAD. Either strategy is reasonable in patients with stable CAD. This is also the first study to demonstrate that hypertensive patients with an MI more than a year earlier, presumably with reasonable LV function, do not necessarily benefit from beta-blockers. This will be welcome news to those stable CAD and post-MI patients with reasonable LV function who experience significant side effects on beta-blockers. MR

Effects of Different Blood-Pressure-Lowering Regimens on Major Cardiovascular Events: Results of Prospectively Designed Overviews of Randomized Trials

Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2003;362:1527–35.

Study Question: Is there a comparable relationship between reduction in blood pressure and reduction in risk of cardiovascular events with the commonly used antihypertensive drug regimens?

Methods: The data from 29 randomized, placebo-controlled trials (n=162,341 patients) designed to evaluate ACEis, beta-blockers, ARBs, calcium-channel blockers and diuretics was compared by a systematic overview using several meta-analyses. Trial eligibility included placebo control, random allocation to different BP goals or different classes of antihypertensive drugs and follow-up of at least 1000 patient-years in each group. Trials with specific clinical parameters were eligible, such as isolated hypertension, diabetes, CHD, PVOD, cerebral vascular disease (CVD) and renal disease but not acute myocardial infarction or CHF.

Results: The mean follow-up ranged from 2.0 to 8.4 years, representing over 700,000 patient years. Mean age was 65 years and 52% were men. Most were selected on the basis of pre-existing CV disease or more than one CRF at baseline. Baseline BP was 159/92 mm Hg with mean values in studies ranging between 123 and 194 mm Hg systolic and 74 and 106 mm Hg diastolic. Differences in BP attributable to active drug compared to placebo were modest averaging −4 to −8 systolic and −2 to −4 diastolic. The relative risks of total major CVEs were reduced by ACEi, (22%; 95% CI 17–27), CCBs (18%; 95%, 5–29), and ARBs (10%; 4–17). ACEi and CCBs reduced rates of stroke, CHD, CV and deaths. Greater risk reductions were produced by regimens that targeted lower blood pressure goals (15%; 5–24). There was no significant difference in total major total CVEs between regimens based on ACEis, CCBs, beta-blockers or diuretics, although ACEi-based regimens reduced BP less, and CCBs were the only regimen that did not reduce CHF. For every outcome other than heart failure, the reduction in risk was directly related to BP reduction.

Conclusions: Treatment with any commonly used regimen reduces the risk of total major cardiovascular events, and larger reductions in blood pressure produce larger reductions in risk.

Perspective: This extensive review supports the conclusion of the largest randomized trial ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) in which the diuretic chlorthalidone was equivalent to or superior to ACEi and CCBs. Thiazides win the day as being safe and cost effective in mild hypertension. But more than 60% of patients require a second or combination drug, which with available data could be any of the major classes. The exception is in diabetes, the metabolic syndrome and renal failure where blocking the renin-angiotensin system appears valuable. MR

Psychosocial Factors and Risk of Hypertension. The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. JAMA 2003;290:2138–48.

Study Question: Is there a relationship between psychosocial factors of time urgency/importance (TUI), achievement