This proportion would increase substantially if the stricter JNC VI guidelines of a target blood pressure of 130/85 mm Hg are used. Patients with blood pressures higher than this target should now be receiving antihypertensive therapy and guidelines already include ACE inhibitors as one of the first-line agents. Should the diabetic patient who smokes but has no other evidence of cardiovascular risk, be placed on ramipril as a result of this trial? Or the patient with isolated hypercholesterolaemia? Subgroup analyses did not reveal large differences between groups but, as the investigators rightly pointed out, the study was not powered to detect significant interactions. The risk of microvascular complications, in particular nephropathy, was also reduced. This finding reinforces the UKPDS findings, but uncertainty remains as to whether it is those with hypertension (as studied in the UKPDS) who are mainly responsible for these impressive results, or whether the diabetic patient who smokes, but is not hypertensive, would also benefit.

The HOPE study cannot be repeated because most of the type of diabetic patients included in that study should now be on some form of antihypertensive therapy. But the choice of agent remains uncertain, and HOPE has few answers here. Although the investigators cite the ABCD (Appropriate Blood Pressure Control in Diabetes) and CAPP studies to indicate that ACE inhibitors are superior to calcium-channel blockers, there are considerable concerns about the interpretation of these two studies. The choice is not helped by the UKPDS, in which ACE-inhibitors and β-blockers were found to be equivalent to each other. None of these studies was specifically designed or powered to compare the impact of different antihypertensive agents on vascular outcomes in people with diabetes, and any subgroup analysis must be interpreted with caution.

The clinical applicability of the findings of the HOPE study therefore seems more novel and easier to assess for patients with existing cardiovascular disease than for high-risk diabetic patients. Whether ACE inhibitors are superior to other agents remains unanswered. This issue may be addressed by the ALLHAT study, which is designed to test the efficacy of several agents, and includes a large number of people with diabetes. But in UKPDS, ABCD, CAPP, UKPDS, and ALLHAT has been restricted to those with relatively high blood pressures. What is now required is an examination of the impact of antihypertensive therapy in those diabetic patients without evidence of cardiovascular disease, in acknowledgment of their enhanced vulnerability to premature mortality.

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5 The Heart Outcomes Prevention Evaluation Study Investigators.
epidemiological studies in which the unit of investigation is the individual, and thus several confounding variables, such as smoking, bodyweight, physical activity, can be adjusted for, the ecological study uses populations in different geographic locations. There are no certain to be confounding and selection biases between these populations (ie, people living in one community may differ in several distinct ways from individuals living elsewhere). This concern has led some investigators to label these types of studies “ecologic fallacy” since the true relation between exposure and disease may be distorted by the inability to control for confounding variables. But ecological studies do have some advantages, in part because existing data sets can be used and the projects are relatively cost-efficient. Two studies in the USA and several in Europe have provided ecological evidence that exposure to fluoridated water over a lifetime can increase the risk of hip fractures.1

The study by Sharon Hillier and colleagues in today’s Lancet is extremely important because it joins only a handful of previous epidemiological investigations exploring the relation between fluoride ingestion to the risk of hip fractures. Indeed, in this population-based case-control study from Cleveland County, UK, the researchers show that the frequency of hip fractures correlates with low body-mass index (kg/m²) and physical inactivity. But, after adjustment for these and other confounders, the investigators could not find an increased risk of hip fracture among individuals with lifetime exposure to water containing fluoride at concentrations greater than 0·9 mg/L. Moreover, in this study, an ecological approach was also used to compare the risk of fracture among residents living in Hartlepool, a town with high natural concentrations of fluoride (>1 mg/L) in their drinking water, with residents of other communities of the county where fluoride concentrations are very low (<0·2 mg/L). Even by the ecological approach, the odds ratio for a hip fracture among Hartlepool residents was 1·0. These data, combined with those of Cauley and co-workers, provide compelling evidence that lifelong exposure to fluoridated water does not increase the risk of hip fracture. Yet, the controversy is likely to continue, as water fluoridation becomes more widespread, osteoporosis in the general population increases, and more case-control studies in larger cohorts are undertaken. For now, Hillier and colleagues’ study offers tremendous insight into the strengths and limitations of trial designs for establishing risk from population-based studies.

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New insights into role of microenvironment in multiple myeloma

Much has been learnt in the past few years about how the microenvironment influences bone destruction, tumour growth and survival, as well as drug resistance in multiple myeloma (MM). MM is a clonal B-cell neoplasm of fully differentiated B cells. MM apparently arises in a lymph node, and is characterised by extensive non-random somatic hypermutation in the complementarity-determining regions of the immunoglobulin heavy-chain genes, which indicates that the myeloma precursor cell had been extensively exposed to an antigen in a germinal centre. No further intraclonal variations occur as the disease progresses. It is generally accepted that, after switching of immunoglobulin class, MM cells travel from the lymph node into the blood stream and that, as they mature, they acquire a broad spectrum of adhesion molecules that facilitate their homing in to the bone marrow.

Adhesion of MM cells to stromal cells induces the latter cells to secrete osteoclast-activating factors, such as interleukin (IL)-1β, IL-6, and tumour-necrosis factor (TNF)-β. These osteoclast-activating factors prompt the stromal cells and osteoblasts to secrete TRANCE, a new member of the TNF family. TRANCE induces differentiation and maturation of osteoclast progenitors. Its activity can be blocked by osteoprotegerin, which acts as a decoy receptor for TRANCE. Osteoprotegerin, also called osteoclastogenesis-inhibitory factor, is a member of the TNF-receptor superfAMILY and is produced by many different cell types. In healthy people, osteoclastic activity is regulated by a delicate balance between TRANCE and osteoprotegerin. In MM, this balance is completely disturbed, not only by increased production of TRANCE, but also by inactivation of osteoprotegerin by syndecan-1 (CD138), which is present in large amounts on, and actively shed from, the surface of MM cells. Increased osteoclastic activity leads to release from the bone matrix of several cytokines, such as transforming growth factor-β, IL-6, basic fibroblast growth factors, and insulin-like growth factors. These cytokines will directly or indirectly stimulate MM cell growth as well as cause the MM cells to release parathyroid-hormone-related protein, which induces secretion of TRANCE (figure). The end result is a vicious circle, with MM cells stimulating bone resorption, and bone resorption leading to increased tumour growth.

This vicious circle can be broken by bisphosphonates. Second-generation bisphosphonates, such as pamidronate, plus conventional chemotherapy are superior to conventional chemotherapy alone in reducing skeletal events in MM patients with stage III disease. Pamidronate reduces IL-6 production by bone-marrow stroma in MM patients and induces apoptosis of osteoclasts by inhibiting the mevalonate pathway, which results in loss of geranylgeranylated proteins, such as Rho. The more potent bisphosphonates may also cause apoptosis of MM cells in a concentration and time dependent manner. This effect can be blocked by enforced expression of bel-2 protein.1

Proliferation and survival of myeloma cells is regulated through many different pathways, some of which are well established. IL-6 has been known for many years to be a major growth and survival factor for MM cells. IL-6 activates the JAK-STAT survival as well as the RAS growth pathways, which in turn activate nuclear-transcription-factor (NF-κB) and endogenous production of IL-6. NF-κB apparently is also activated through a different