# Subgroup analysis of the NORDIL trial

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In 2000, the prospective, randomized, open, endpoint-blinded NORDIL trial showed that the risk of the primary composite endpoint consisting of cardiovascular death, stroke and myocardial infarction was similar in hypertensive patients receiving the calcium-channel blocker diltiazem compared with conventional treatment based on diuretics and β-blockers [1]. These findings are in agreement with a recent meta-analysis showing that all antihypertensive drugs have similar beneficial effects on the overall cardiovascular prognosis [2]. However, these findings do not rule out the possibility that the newer classes of antihypertensive drugs might be particularly effective in special subgroups of patients and/or in preventing cause-specific endpoints. In this issue of the journal, Kjeldsen *et al.* assessed whether the relative treatment effects in the NORDIL trial were influenced by characteristics of patients at entry, such as gender, age, level of systolic or diastolic pressure, pulse pressure or heart rate [3]. In all subgroups, the incidence of the primary composite endpoint was similar in the two treatment groups. However, compared with conventional first line treatment, diltiazem reduced the risk of stroke by approximately 25% ($P < 0.05$) in patients with high systolic ($> 170$ mmHg), diastolic ($\geq 105$ mmHg) or pulse ($\geq 66$ mmHg) pressure. By contrast, the risk of myocardial infarction was 38% higher ($P = 0.04$) in the diltiazem group than in the patients randomized to diuretics/β-blockers if heart rate at entry was less than 74 beats per minute. Nevertheless, differences in treatment effects between subgroups were not significant for any of the endpoints. On average, the on-treatment systolic blood pressure was approximately 3 mmHg higher on diltiazem than on conventional therapy [3].

The 38% higher risk of myocardial infarction on diltiazem versus conventional therapy in subjects with a baseline heart rate below the median might be explained by the blood pressure difference between the two treatment groups. Indeed, according to a recently published meta-regression analysis [2] in 136 124 patients enrolled in 27 outcome trials, a 3.8 mmHg higher systolic pressure was associated with a predicted relative risk of 1.24 [95% confidence interval (CI) 1.04–1.44]. This was not significantly ($P = 0.66$) different from the relative risk observed in the NORDIL patients with heart rate below the median (1.38; 95% CI 1.01–1.87). In contrast, the 3 mmHg gradient in systolic pressure between the two treatment groups obviously cannot explain the lower stroke risk in the NORDIL patients on diltiazem. Indeed, the relative risk of stroke according to the metaregression analysis was 1.14 (95% CI 0.97–1.45) whereas, for all NORDIL patients, the relative risk was significantly ($P < 0.01$) lower (0.80; 95% CI 0.65–0.99) [2]. Stroke was only a secondary endpoint in the NORDIL trial and therefore a chance finding cannot be ruled out. On the other hand, the beneficial effect of diltiazem in the prevention of stroke is in agreement with two recently published meta-analyses of randomized outcome trials [2,4]. The first meta-analysis [4] included five trials that compared calcium-channel blocker-based regimens with diuretic or β-blocker-based therapy, 23 454 patients, 985 strokes and 1077 coronary heart disease events. Compared with old drug classes (diuretics and β-blockers), calcium-channel blockers significantly reduced the risk of stroke by an additional 13% (95% CI 2–23), but tended to increase the risk of coronary heart disease by 12% (95% CI 0–26). The second meta-analysis [2] included six trials, 24 322 patients, 974 strokes and 843 myocardial infarctions. Compared with old drugs, calcium-channel blockers provided more reduction in the risk of stroke (13.5%, 95% CI 1.3–24.2) and less reduction in the risk of myocardial infarction (19.2%, 95% CI 3.5–37.3), resulting in a similar overall cardiovascular benefit. Calcium-channel blockers might therefore be especially effective in stroke prevention.

The interactions between treatment effects and subgroups were not significant for any of the endpoints. There may be several interpretations for this finding. First, it could indicate that the relative differences between the two treatment groups are not influenced by sex, age and the severity of hypertension. The fact that the relative risks for stroke were significant in the more severe hypertensive patients (systolic blood pressure $> 170$ mmHg, diastolic blood pressure $\geqslant 105$ mmHg or pulse pressure $\geqslant 66$ mmHg) and not significant in the less severe hypertensive patients could be due to the lower underlying stroke risk in the latter subgroups, meaning that the analyses in the less severe hypertensive patients had less statistical power. Second, the NORDIL trial was not designed to test differences between the randomized first-line treatments in specific subgroups. For stroke, the relative difference between the two treatment groups was approximately 25% in the more severe hypertensive patients but only approximately 10% in the less severe hypertensive patients. The NORDIL trial may have had insufficient statistical power to detect interactions between treatment and patient characteristics, such as the blood pressure level at baseline. Third, in patients with a high heart rate, the risk of myocardial infarction may not be influenced by blood pressure-lowering treatment. Fourth, it remains possible that the diuretic/β-blocker-based therapy and treatment initiated with a calcium-channel blocker are both more effective at higher blood pressure levels. However, most placebo-controlled studies in moderate to severe hypertensive patients did not find an interaction between blood pressure level at randomization and the benefit derived from active treatment [5].

The authors did not specify whether the number of patients to be treated to prevent one cardiovascular complication differed according to the patient characteristics at entry. Because absolute benefit is proportional to the underlying risk, it may be expected that the absolute number of patients needed to be treated with diltiazem to prevent one additional stroke is much smaller in the more severe hypertensive patients compared with the less severe hypertensive patients. The absolute difference between the two treatment groups could also have been different between older ($= 60$ years) and younger ($< 60$ years) patients and between women and men. Indeed, two meta-analyses of outcome trials in elderly hypertensive patients have shown that, although the relative benefit of active treatment versus no treatment was similar in men and women and in younger and older patients, the absolute benefit was much smaller in the lower risk groups [5,6]. The number of patients needed to be treated for 5 years to prevent one fatal or non-fatal cardiovascular complication was 18 in men versus 38 in women, and 19 in patients aged 70 years or older versus 39 in those aged 60–69 years [5].

A considerable number of the NORDIL patients (7% of the total population; $n = 727$) had non-insulin-dependent diabetes mellitus at baseline. The main mortality and morbidity results in this important subgroup have been reported elsewhere [1]. In patients with type 2 diabetes mellitus, the risks of the primary and all secondary endpoints were similar in the two treatment groups. Initially, these results might appear to contradict the combined findings of the double-blind, randomized, placebo-controlled Systolic Hypertension in the Elderly Program (SHEP) [7] and Systolic Hypertension in Europe (Syst-Eur) trial [8]. These two studies included patients with isolated systolic hypertension and normal renal function (serum creatinine $< 2$ mg/dl). In the SHEP trial, treatment starting with the thiazide diuretic chlorthalidone decreased the incidence of all cardiovascular complications to the same extent in 583 patients with diabetes mellitus (34%, 95% CI 6–54) and in 4149 patients without diabetes mellitus (34%, 95% CI 21–45). However, in the Syst-Eur trial, antihypertensive treatment starting with the calcium-channel blocker nitrendipine reduced the incidence of all cardiovascular endpoints significantly more ($P = 0.01$) in the diabetic patients (69%, 95% CI 41–84) than in the non-diabetic patients (26%, 95% CI 6–41). On the basis of the disparate effects between these two trials and the additional benefit in the prevention of proteinuria observed in the diabetic Syst-Eur patients [9], it may be speculated that dihydropiridine-derived calcium-channel blockers are more effective than thiazide diuretics in preventing cardiovascular complications in older patients with diabetes mellitus and normal renal function. Why, in the NORDIL trial, the outcome was similar in diabetic patients randomized to diltiazem and in those given conventional therapy remains to be elucidated. In the Syst-Eur trial, a dihydropiridine was used while in the NORDIL trial a calcium-channel blocker of a different class was employed. It might be that, in diabetic patients, dihydropyridine-derived calcium-channel blockers are more effective in preventing cardiovascular complications. However, blood pressure control may also play an important role. The NORDIL investigators did not specify whether the blood pressure differences between the diltiazem and conventional therapy groups were similar in the diabetic and non-diabetic patients. This information appears to be crucial for a correct interpretation of the relative risks. Finally, it is important to know the type of antihypertensive drugs effectively taken by the diabetic patients who were randomized to diltiazem and conventional therapy. In the total NORDIL population, only a limited number of patients ($< 39\%$) took a thiazide diuretic and a considerable number of patients used antihypertensive drugs other than diuretics or β-blockers [1].

Although the additional benefit of diltiazem-based

therapy versus diuretic/β-blocker-based therapy on the incidence of fatal plus non-fatal stroke in severe hypertensive patients is estimated to be approximately 25%, the confidence intervals are compatible with a difference of only 1–3%. Further research should therefore be performed to increase the precision of the estimate of the possible differential therapeutic effects of calcium-channel blockers and diuretics or β-blockers on cause-specific cardiovascular complications. More data are also required to draw firm conclusions on the use of older and newer drug classes according to patients' characteristics. Meanwhile calcium-channel blockers might be considered for the treatment of hypertension in patients at high risk for stroke, such as the elderly.

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