Prognostic Value of Combined Target-Organ Damage in Patients With Essential Hypertension

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BACKGROUND
Whether the combination of chronic kidney disease (CKD) and left ventricular hypertrophy (LVH) affects the cardiovascular (CV) risk in patients with uncomplicated hypertension is poorly investigated. The aim of this study was to assess the effects of LVH, CKD, and their combination on CV events in hypertension.

METHODS
This study analyzed 1,078 patients with essential hypertension.

RESULTS
LVH was present in 104 (9.6%) patients, CKD was present in 556 (51.5%) patients, and the combination of LVH and CKD was found in 174 (16.1%) patients. During the follow-up (median = 84 months), 52 CV events were observed (0.64 events/100 patient-years): 6 (2.4%) in patients without target-organ damage (TOD), 6 (5.7%) in patients with LVH, 20 (3.6%) in patients with CKD, and 20 (11.4%) in patients with combined LVH+CKD. Adjusted hazard ratio (HR) for CV events was 1.62 (P = 0.34) for LVH, 0.951 (P = 0.94) for CKD, and 2.45 (P = 0.03) for LVH+CKD. After multivariable Cox proportional hazard analysis, the combination of LVH+CKD was significantly associated with risk of CV events, when the model was adjusted for sex and age (HR = 2.447; P = 0.03) and for the presence of 1 CV risk factor (HR = 3.226; P = 0.02). In contrast, the association of LVH+CKD was no longer significant when the model was adjusted for sex, age, and the presence of ≥2 CV risk factors.

CONCLUSIONS
The results of this study highlight the relevance of the interactions between TODs and hemodynamic, anthropometric, and metabolic abnormalities in the CV risk stratification of patients with essential hypertension.

Keywords: blood pressure; cardiovascular risk; chronic kidney disease; essential hypertension; hypertension; left ventricular hypertrophy; myocardial infarction; stroke.

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The heart and kidney represent 2 target organs of essential hypertension. Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular (CV) morbidity and mortality; similarly, microalbuminuria and chronic kidney disease (CKD) are independent predictors of CV events in patients with hypertension.2,3

Both end-stage renal disease4 and heart failure5 are characterized by simultaneous cardiac and renal damage. This association has also been described in the early phases of organ damage in patients with hypertension. In particular, in a substudy of the LIFE trial, an association between increased left ventricular (LV) mass and urine albumin/creatinine ratio has been reported.6 Moreover, patients with hypertension and stage 2–5 CKD showed a high prevalence of LVH.7 It is important to underline that these studies were performed in a population of patients selected for the presence of LVH or CKD. The association of LVH and CKD in unselected patients with hypertension has been evaluated by few studies.5–10 Moreover, it is still marginally explored whether the combination of CKD and LVH further increases the prognostic power on CV outcome compared with LVH and CKD alone. In this regard, two studies5,10 have documented that simultaneous presence of LVH plus CKD further increases the risk of CV events compared with LVH or CKD alone. However, these studies mainly included patients with advanced CKD or with a previous CV event. Therefore, whether the combination of LVH plus CKD further increases the risk of CV events in hypertensive patients with a low CV risk profile remains poorly investigated. This information is not trivial because it may allow for a better stratification of CV risk in patients with hypertension.

The aim of this study was to assess in a cohort of patients with uncomplicated hypertension (i) the prevalence of LVH, CKD, and their association and (ii) the effects of LVH, CKD, and their combination on CV risk.

METHODS
Study design and population
We screened all patients with essential hypertension who were referred to the Hypertension Center of the Federico II University of Naples from October 1998 to September 2009 and prospectively evaluated those never treated for
hypertension at the time of their first visit to the center. Patients were included in the Campania Salute Network, which is a community-wide collaboration between general practitioners, 23 local hospitals, and the Hypertension Center aiming to provide a platform to study the causes and complications of hypertension. Patients had a minimum 3-year follow-up period.

Exclusion criteria were the following: carotid atherosclerotic plaques, secondary hypertension, congestive heart failure, significant aortic and/or mitral regurgitation, CKD at stage 5 or requiring dialysis, permanent atrial fibrillation, history of cerebro-vascular disease, and coronary artery disease. Patients who had a poor-quality ultrasound recording and/or incomplete medical history and/or laboratory tests were excluded from the analysis.

The research protocol was approved by the Ethics Committee of our institution. At the time of the inclusion in the study protocol, all patients provided written consent for subsequent analysis of their data. The study was conducted according to the consolidated standards for observational trials and was written according to the STROBE guidelines for Observational Studies in Epidemiology.

Before analysis, all data were checked for missing or contradictory entries and values out of the normal range. At the time of enrollment, all patients had a diagnosis of hypertension. The duration of hypertension was established after cross-checking the patients’ histories and records from their general practitioners.

Office blood pressure (BP) was measured with a mercury sphygmomanometer after the patient sat for 210 minutes. The average of 3 consecutive measurements was considered for the analysis.

Glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease formula. CKD was defined and stratified according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative classification. Type 2 diabetes mellitus and hypercholesterolemia were diagnosed as reported elsewhere. Metabolic syndrome was defined on the basis of the modified Adult Treatment Panel (ATP-III) criteria and diagnosed as previously reported. Patients were defined as obese if they had a body mass index ≥30.0 kg/m². Target values of BP were considered <140/90 mm Hg in nondiabetic patients and <130/80 mm Hg in diabetic patients. The presence of LVH and/or stage 2–4 CKD were considered manifestations of hypertension-induced target-organ damage (TOD).

Follow-up and endpoints

As the primary endpoint, we considered major CV events, including death due to cardiac causes, new-onset coronary artery disease (myocardial infarction, stable and unstable angina, sudden cardiac death, coronary revascularization procedures), stroke, transient cerebral ischemic attack, symptomatic aorto-iliac occlusive disease verified with angiography, thrombotic occlusion of a retinal artery documented with fluoroangiography, progressive heart failure requiring hospitalization, stage 5 CKD, renal transplantation, and renal failure requiring dialysis.

All eligible participants underwent at least 2 control visits after the basal evaluation. Time to occurrence of major CV events was ascertained with follow-up visits at the Hypertension Center, by interaction with general practitioners, and/or by phone interviews with patients. For the patients who developed a major CV event, hospital record forms and other available original source documents were reviewed.

Echocardiography

Echocardiograms were performed using ultrasound machines (Hewlett-Packard, SONOS 1500 from 1998 to 2005; SONOS 2500 from 2005 to 2008; Philips SONOS 5500, from 2008 to 2009) with dedicated transducers of 2.5 MHz, with the patients supine in the left lateral position according to the American Society of Echocardiography recommendations. All echocardiograms were performed and analyzed at the Hypertension Center. LV mass was calculated from a necropsy-validated formula and normalized for height (LVMi) in meters to the power of 2.7. LVH was defined as LVMi ≥ 51 g/m².

Carotid ultrasound

B-mode ultrasonography of carotid arteries was performed with patients in the supine position with the neck extended in mild rotation with an ultrasound device (Hewlett-Packard SONOS 1500, from 1998 to 2005; SONOS 2500, from 2005 to 2008; Philips SONOS 5500, from 2008 to 2009) equipped with a 7.5-MHz high-resolution transducer. All measurements were performed and analyzed at the Hypertension Center, as previously reported. The maximal arterial intima-media thickness was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery. Evidence of an intima-media thickness value >1.3 mm was considered as plaque.

Sample size

On the basis of a previous study, we predicted a 30% prevalence of LVH and a CV event rate of 2 per 100 person-years in the absence of LVH vs 4.5 per 100 person-years in the presence of LVH. On this basis, a sample size of 1,053 patients with an average follow-up time of 3 years per patient was estimated to detect a significant difference between the groups (2-tailed test) with a type I error of 5% and a type II error of 10%. Because we found a lower incidence of CV events than expected, the observation period was prolonged.

Statistical analysis

Normally distributed, continuous variables are expressed as means ± SDs and compared by the use of the Student t test. Categorical variables are expressed as proportions and
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compared by use of the χ² test with risk ratios and 95% confidence intervals (CIs) quoted. Normality was tested using the Kolmogorov–Smirnov test. One-way analysis of variance or the nonparametric test was used to analyze differences among groups with no TOD, LVH alone, CKD alone, and CKD plus LVH. The Pearson's correlation coefficient was calculated to assess correlation between data. The prevalence of LVH, CKD, and their association was calculated, and the rates of CV events were presented as the number of events per 100 patient-years based on the ratio of the number of events observed in the total number of patient-years of exposure up to the terminating event or censor. For the patients without events, the date of censor was that of the last visit of the patient or that of the phone interview. For the patients who experienced multiple events, analysis was restricted to the first event.

To assess the effects of single (LVH or CKD) or combined TOD on CV risk, a multivariable Cox proportional hazard model with a different degree of TOD (no TOD, LVH alone, CKD alone, or LVH plus CKD), adjusted for age and sex, was tested. To assess the effects on CV risk of the degree of LVH and of CKD, a Cox proportional hazard analysis including LVMi and GFR as continuous variables was performed. A sensitivity analysis, including an interaction between LVH and CKD and an interaction between LVMi and GFR, was performed. A second multivariable Cox proportional hazard analysis that included TOD (LVH plus CKD vs. no TOD) and as covariables age, sex, metabolic syndrome, obesity, diabetes, hypercholesterolemia, initial systolic BP (SBP) and diastolic BP (DBP), follow-up SBP and DBP, and treatment with renin-angiotensin system blockers was performed. Finally, to assess the independent prognostic value of TOD (no TOD, LVH alone, CKD alone, LVH plus CKD) over conventional CV risk factors, 3 multivariable Cox proportional hazard models, adjusted for age and sex, were tested: (i) a model with TOD and without CV risk factors; (ii) a model with TOD and 1 risk factor; and (iii) a model with TOD and ≥2 CV risk factors. The following were considered as CV risk factors: age (men: >55 years; women: >65 years), obesity, diabetes, hypercholesterolemia, low high-density lipoprotein cholesterol (men: <40 mg/dl; women: <50 mg/dl), and metabolic syndrome.

Hazard ratios (HRs) and 95% CIs were calculated with no TOD as the reference group vs. single TOD or combined TODs.

All data were analyzed by SPSS software (version 20; SPSS, Chicago, IL) and STATA software (version 12.0; StataCorp, College Station, TX). Statistical significance was accepted at P < 0.05.

RESULTS

From the initial study population of 9,978 patients with essential hypertension, we evaluated 1,078 patients. The selection criteria of the study cohort are reported in Figure 1. TOD was detected in 834 (77.3%) patients. In particular, LVH was observed in 104 (9.6%) patients, and CKD was detected in 556 (51.5%) patients, whereas the combination of LVH and CKD was detected in 174 (16.1%). Patients were categorized in 4 groups according to the absence of TOD and presence of CKD, LVH, and combination of CKD plus...
LVH. Table 1 shows the baseline clinical characteristics of the 4 study groups. In the CKD group, stage 2 was observed in 520 (93.5%) patients and stage 3 was seen in 36 (6.5%) patients, and in the LVH plus CKD group, stage 2 was detected in 146 (83.9%) patients, stage 3 was detected in 26 (14.9%) patients, and stage 4 was detected in 2 (1.1%).

Antihypertensive therapy prescribed at the time of enrollment is reported in Table 2. Renin-angiotensin system blockers were prescribed to >50% of patients with TOD.

The median follow-up period was 84 months for patients without TOD and those with CKD or LVH, whereas it was 72 months for the group of patients with combined LVH and CKD (P = not significant). During the follow-up period, the numbers of patient accesses to the Hypertension Center were 5.5 in patients without TOD, 384 (69%) patients with CKD, 64 (62%) patients with LVH, and 84 (48%) patients with LVH plus CKD.

During the follow-up period, target values of BP were found in 166 (68%) patients without TOD, 384 (69%) patients with CKD, 64 (62%) patients with LVH, and 84 (48%) patients with LVH plus CKD. At the end of the study period, target values of BP were found in 166 (68%) patients without TOD, 384 (69%) patients with CKD, 64 (62%) patients with LVH, and 84 (48%) patients with LVH plus CKD. At the last visit, the numbers of prescribed antihypertensive drugs were 2.2 ± 0.9 in patients without TOD, 2.1 ± 0.8 in patients with CKD, 2.5 ± 1.2 in patients with LVH (P < 0.05 vs. no TOD and CKD), and 2.6 ± 1.1 in patients with combined LVH plus CKD (P < 0.05 vs. no TOD and CKD).

During the follow-up period, 52 (4.8%) major CV events (0.64 events/100 patient-years) were observed. Crude incidence of CV events multiplied by 100 patients-years is reported in Figure 3. Six (2.4%) CV events were recorded in patients without TOD, the reductions of SBP and DBP were 18 ± 18 mm Hg and 12 ± 11 mmHg, respectively. In patients with CKD, the reductions were 18 ± 18 mm Hg for SBP and 12 ± 11 mm Hg for DBP; in those with LVH they were 18 ± 19 mm Hg and 13 ± 10 mm Hg, respectively; and in those with combined LVH plus CKD, they were 21 ± 22 mm Hg and 14 ± 14 mm Hg, respectively (Figure 2).

### Table 1. Baseline clinical characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No TOD n= 244</th>
<th>LVH n= 104</th>
<th>CKD n= 556</th>
<th>LVH + CKD n= 174</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42 ± 12</td>
<td>48 ± 13*</td>
<td>49 ± 11*</td>
<td>54 ± 10*,****</td>
</tr>
<tr>
<td>Duration of hypertension, mo</td>
<td>39 ± 12</td>
<td>44 ± 13</td>
<td>46 ± 11</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Male sex</td>
<td>171 (70)</td>
<td>86 (83)</td>
<td>317 (57)</td>
<td>110 (63)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>152 ± 14</td>
<td>157 ± 18</td>
<td>152 ± 14</td>
<td>161 ± 18*,**</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>95 ± 9</td>
<td>100 ± 10**</td>
<td>96 ± 9</td>
<td>99 ± 11*,**</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>75 ± 12</td>
<td>75 ± 12</td>
<td>74 ± 12</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 4</td>
<td>29 ± 4**</td>
<td>27 ± 3</td>
<td>29 ± 5*,**</td>
</tr>
<tr>
<td>GFR, ml/min/1.73 m²</td>
<td>104 ± 14</td>
<td>103 ± 15</td>
<td>75 ± 10*,***</td>
<td>73 ± 12*,***</td>
</tr>
<tr>
<td>LVMI, g/m²²</td>
<td>40 ± 5</td>
<td>56 ± 7*,**</td>
<td>42 ± 5</td>
<td>57 ± 8*,**</td>
</tr>
<tr>
<td>IMT max, mm</td>
<td>0.88 ± 0.05</td>
<td>0.96 ± 0.01</td>
<td>0.90 ± 0.06</td>
<td>0.96 ± 0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (1)</td>
<td>8 (8)*,**</td>
<td>11 (2)</td>
<td>5 (3)***</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>112 (46)</td>
<td>52 (50)</td>
<td>332 (58)*</td>
<td>110 (63)*</td>
</tr>
<tr>
<td>Obesity</td>
<td>32 (13)</td>
<td>34 (33)*,**</td>
<td>83 (15)</td>
<td>57 (33)*,**</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>41 (17)</td>
<td>26 (25)</td>
<td>100 (18)</td>
<td>49 (28)</td>
</tr>
</tbody>
</table>

Data are means ± SDs or no. (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HR, heart rate; IMT max, maximum carotid intima-media thickness; LVH, left ventricular hypertrophy; LVMI, indexed left ventricular mass; SBP, systolic blood pressure; TOD, target-organ damage.

*P < 0.05 vs. no TOD; **P < 0.05 vs. CKD; ***P < 0.05 vs. LVH; ****P < 0.05 vs. no TOD, CKD, and LVH.

### Table 2. Starting antihypertensive therapy: distribution of antihypertensive drugs among the 4 groups of patients

<table>
<thead>
<tr>
<th>Antihypertensive drug</th>
<th>No TOD</th>
<th>LVH</th>
<th>CKD</th>
<th>LVH + CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>53 (22)</td>
<td>38 (37)** ***</td>
<td>139 (25)</td>
<td>59 (34)** ***</td>
</tr>
<tr>
<td>AT₁ antagonists</td>
<td>63 (26)</td>
<td>22 (22)</td>
<td>166 (30)</td>
<td>74 (43)** ***</td>
</tr>
<tr>
<td>Ca²⁺ antagonists</td>
<td>26 (11)</td>
<td>29 (28) **</td>
<td>88 (16)</td>
<td>40 (23) **</td>
</tr>
<tr>
<td>β-blockers</td>
<td>46 (19)</td>
<td>33 (32) ***</td>
<td>111 (20)</td>
<td>34 (20)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>61 (25)</td>
<td>37 (36)</td>
<td>139 (26)</td>
<td>60 (38) **</td>
</tr>
</tbody>
</table>

Data are no. (%).

Abbreviations: ACE, angiotensin-converting enzyme; AT₁, angiotensin type 1 receptor; Ca²⁺, calcium; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; TOD, target-organ damage.

*P < 0.05 vs. no TOD; **P < 0.05 vs. CKD; ***P < 0.05 vs. no TOD, CKD, and LVH.
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without TOD, 20 (3.6%) in patients with CKD, 6 (5.7%) in patients with LVH, and 20 (11.4%) in patients with combined TOD. Sex and age HRs for major CV events were 0.951 (95% CI = 0.242–3.737; P = 0.94) for CKD, 1.62 (95% CI = 0.440–10.953; P = 0.34) for LVH, and 2.45 (95% CI = 1.090–5.494; P = 0.03) for LVH plus CKD (Figure 4). In addition, LVMi and GFR were also analyzed as continuous variables. LVMi (HR =1.042; 95% CI = 1.009–1.077; P = 0.01), but not GFR (HR = 0.993; 95% CI = 0.975–1.012; P = 0.49), was found to be an independent predictor of CV events. No interactions were found between LVH and CKD when these parameters were analyzed as either categorical or continuous variables. A second multivariable Cox hazard analysis showed that the occurrence of CV events was independently associated with age, sex (male), combined TOD, and metabolic syndrome (Table 3).

Multivariable Cox proportional hazard analysis showed that combination of LVH plus CKD was associated with significantly high risk of major CV events when the model was adjusted for both sex and age (model 1) and for the presence of 1 conventional CV risk factor (model 2). In contrast, the association of LVH and CKD was no longer significant when the model was adjusted for sex, age, and presence of ≥ 2 conventional CV risk factors (model 3) (Table 4).

DISCUSSION

The main finding of this study is that the association of LVH plus CKD increases the risk of major CV events compared with LVH or CKD alone. Interestingly, this phenomenon is not detectable in the presence of ≥2 conventional CV risk factors. Our observation is consistent with previous reports. In fact, Tsioufis et al. found that the presence of both LVH and CKD is associated with an increase in composite CV events compared with LVH alone.9 Similarly, Vernooij et al. found, in hypertensive patients with a previous CV event, that the presence of the combination of LVH plus CKD further increases CV risk compared with the presence of either LVH or CKD alone.10 The CV risk associated with the combination of LVH plus CKD reported by these studies is definitely higher compared with that found in this study. This difference can be explained by a lower CV risk profile of the study cohort. In fact, we excluded patients with previous CV events. Furthermore, the majority of patients had stage 2 CKD, whereas Tsioufis et al. enrolled patients starting at stage 3 CKD.9 Finally, the prevalence of diabetes was lower in this population than it was in the other studies. Our results are inconsistent with the data of Foguet et al. who found that, in newly diagnosed patients with hypertension, the prevalence of the combination of LVH plus CKD amounted to 38.1%.8 We believe that this difference can be explained because, in addition to GFR, Foguet et al. used the serum creatinine values to detect CKD.

We found that LVH and CKD alone do not increase the risk of CV events. This finding has varying explanations. First, in several studies, the LVH-related increase in CV risk was estimated without considering the concomitant presence
Table 4. Normalized hazard ratio for cardiovascular events in patients with combined target-organ damage

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>95% CI</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: sex and age</td>
<td>0.895</td>
<td>1.09–5.49</td>
<td>2.447</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 2: sex, age, 1 CV risk factor</td>
<td>1.171</td>
<td>1.20–8.66</td>
<td>3.226</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 3: sex, age, ≥ 2 CV risk factors</td>
<td>0.431</td>
<td>0.47–4.95</td>
<td>1.539</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Figure 4. Cox multivariable free-time events curves in relation to target-organ damage (TOD) groups. There was a significant difference in rate of cardiovascular events among patients with combined TOD (left ventricular hypertrophy (LVH) + chronic kidney disease (CKD)) vs. patients with no TOD, with LVH alone, and with CKD alone.
of other forms of TOD. Therefore, the increased CV risk attributed to LVH or CKD could be related to the presence of concomitant forms of subclinical organ damage. Similarly, the presence of anthropometric and metabolic abnormalities frequently associated with TOD in hypertension can increase the risk of CV events.26 Finally, it should be pointed out, that in many observational27,28 and interventional29,30 studies supporting the role of LVH as an independent CV risk factor, the presence of LVH was assessed by using echocardiography, which is less sensitive than echocardiography.31 However, it must be emphasized that we found that LVMi increased the risk of CV events. Together, these findings allow the speculation that enhanced CV risk ascribed to LVH could be related to the more severe forms of LVH. Similarly, in several studies, CKD was diagnosed using creatinine values, which are known to identify more severe forms of CKD.

A further aspect of the study that must be discussed is the low incidence of CV events in the study cohort. There are possibly 2 reasons for this finding. First, in the cohort a high percentage of patients (approximately 65%) achieved target values of BP. In addition, >50% of patients with TOD started antihypertensive treatment with renin-angiotensin system blockers, which are particularly effective at reducing LVH32 and CKD.33 The results of this study highlight the high relevance of the interactions between TODs and hemodynamic, anthropometric, and metabolic abnormalities in the CV risk stratification of patients with uncomplicated hypertension.

Some study limitations should be considered. In this study, the presence of TOD was investigated once—that is, when the patients were referred to the Hypertension Center for baseline stratification of CV risk. Salvetti et al. demonstrated that in addition to basal assessment, changes in both LVH and CKD during antihypertensive treatment allow a more accurate evaluation of CV risk.34 Therefore, the results of this study should be interpreted considering that a single evaluation of TOD may have a lower accuracy in the stratification of CV risk vs. multiple evaluations. Second, we applied several exclusion criteria. This strategy was adopted to minimize the influence of potential confounders that can influence the CV risk. Third, this study included local patients with hypertension; therefore, its results may not be automatically extended to other ethnic groups.

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DISCLOSURE

The authors declared no conflict of interest.

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1986; 2004; 1978; 134


