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ORIGINAL ARTICLE

Efficacy of very low dose perindopril 2 mg/indapamide 0.625 mg combination on left ventricular hypertrophy in hypertensive patients: the P.I.C.X.E.L. study rationale and design

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The PICXEL study is designed to evaluate the effects of long-term administration of very low-dose combination perindopril 2 mg/indapamide 0.625 mg (Per/Ind) *vs* enalapril in reducing left ventricular hypertrophy (LVH) in hypertensive patients. This multicentre, controlled, randomised, double-blind, parallel group study is carried-out to assess the variation of left ventricular mass index (LVMI) after treatment, using a centralised control of M-mode echocardiography determinations, and a dedicated software for semi-automatic measurement. Following a 4-week placebo run-in period, hypertensive outpatients aged ⩾18 years, with LVH (LVMI >120 and 100 g/m² for men and women, respectively), are randomised to receive once daily, over 52 weeks, either Per/Ind or enalapril. According to blood pressure levels, the dose may be adjusted. In addition to clinical examinations, ECG, blood pressure, heart rate and laboratory assessments echocardiographic determinations are performed for selection, at baseline, after 24 weeks and at the end of the study. The main outcome criteria is the change from baseline in LVMI which is considered the primary efficacy criterion; changes in blood pressure and echo-Doppler parameters constitute secondary criteria. Two-sided Student's *t*-test for independent samples will be used to differentiate the effects of the treatment between groups with $\alpha = 5\%$, and the inter-group difference of LVMI variation will be analysed with a power of 90%. A sample size of 500 patients is required making it necessary to randomise at least 550 patients, based on a 10% proportion of potentially non-assessable patients. The results of this study, obtained after applying strict methodological procedures and requirements, are expected to provide valuable and reliable information on the effects of long-term administration of Per/Ind on LVH, and on its potential superiority over enalapril.

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Introduction

Echocardiographic left ventricular hypertrophy (LVH) is a major contributor to the risk of stroke, cardiovascular events, and total mortality.[1–5] LVH regression with antihypertensive treatment seems to improve outcome although available data remain limited.[6,7]

It is therefore expected that antihypertensive treatments should not only normalise blood pressure[8] but also decrease myocardial hypertrophy.[9,10] Angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and calcium channel blockers have dem-

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onstrated their ability to promote LVH regression.[11,12] However, due to many limitations related to methodology (small number of patients, short treatment duration, non-comparative design and unblinded echocardiogram analysis) these studies have yielded no definite conclusions on the comparative efficacy of treatments in LVH regression. Four meta-analysis[13] suggest a higher effectiveness of ACE inhibitors over β-blockers, diuretics, or calcium antagonists in reducing LV mass (LVM)[14–17] but according to the lack of sufficiently powered comparative trials and publication bias their results must be taken with due caution. Recently, the LIVE study, conducted in 505 hypertensive patients with LVH, has shown that a full dose of the diuretic indapamide SR 1.5 mg could be significantly more effective than the ACE inhibitor enalapril in reducing LVM inded (LVMI).[18] A very low dose ACE inhibitor/diuretic combination has been proposed as a first-line therapy to improve blood pressure (BP) control in hypertensive patients.

The very low-dose combination perindopril 2 mg (ACE inhibitor)/Indapamide 0.625 mg (diuretic) combination (Per/Ind) Per 2/Ind 0.625 mg has shown a superior antihypertensive efficacy in comparative study *vs* atenolol, losartan and irbesartan[19–23] and studies in elderly patients and patients with renal impairments.[24,25] In long-term studies (1 year), Per/Ind combination has demonstrated a sustained efficacy with a high normalisation rate and a superiority to atenolol on systolic mean and pulse pressure.[19,26,27] In different pharmacological models of LVH, Per/Ind combination has shown its capacity to reverse left ventricular mass.[28–31] A preliminary double-blind controlled study comparing the low-dose combination Per/Ind and atenolol has shown the higher capacity of Per/Ind to decrease the LVM in hypertensive patients.[32] The current ongoing multicentre study evaluates the long-term treatment strategy based on the very low-dose **P**er 2 mg/**I**nd 0.625 mg combination in **C**ontrolled study **V**ersus **E**nalapril in the regression of echocardiographic LVH (PICXEL), in a large population of hypertensive patients. This study which is one of the few which includes optimal design features for such trials combines two originalities: a quality control of all recordings all along the study as performed for the first time in the LIVE study[18] and the use of a dedicated software to measure semi-automatically LVM and reduce interreader variability (Figure 1).

Patients and methods

Sample size

The sample size was calculated from the change in LVMI (g/m^2) between the last observation carried forward (LOCF) and baseline in the full analysis set required to differentiate between the treatment groups using a two-sided Student's *t*-test for independent samples with $\alpha = 5\%$. To detect an inter-group difference on LVMI variation with a power of 90%, given a standard deviation of 20 g/m^2, 233 patients per group are necessary. Anticipating 10% of patients potentially non-assessable according to previous experience on 1-year studies, a total number of 550 randomised patients appears necessary in order to obtain a final set of at least 500 patients with assessable echocardiographic data.

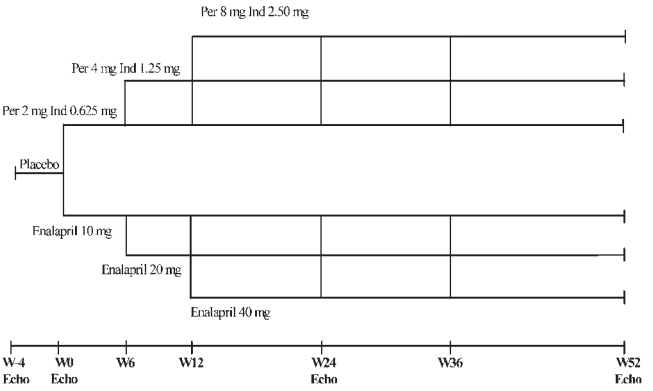

Figure 1 PICXEL study design.

Design

This phase III, multicentre, international study is conducted in 60 echocardiographic centres located in nine countries (Austria, Belgium, France, Germany, Hungary, Italy, Russia, Spain, The Netherlands) following a controlled, randomised, double-blind design in two parallel groups, one receiving the Per/Ind combination, and the other enalapril. After written informed consent, patients undergo a 4-week placebo run-in period, and then enter a 52-week double-blind active treatment period with either the very low-dose perindopril 2 mg/indapamide 0.625 mg once daily (OD), or enalapril 10 mg OD. Visits are scheduled on weeks 6, 12, 24, 36, and 52. According to BP control, doses may be doubled at any visit from W6, becoming perindopril 4 mg/indapamide 1.25 mg OD and enalapril 20 mg OD, then perindopril 8 mg/indapamide 2.5 mg OD and enalapril 40 mg OD when a further adjustment is needed.

Inclusion/non-inclusion criteria

Male and female outpatients $\geqslant$18 years may be included provided they present with both essential systolic hypertension (isolated or non-isolated), defined as 140 mm Hg $\leqslant$ sitting SBP $<$210 mm Hg, and echocardiographic LVH defined as LVMI $>$120 g/m^2 for men, and $>$100 g/m^2 for women, according to Penn convention criteria for LVM measurements. LVH has to be confirmed by the Central Echocardiography Committee prior to inclusion on the W-4 echocardiography.

Main non-inclusion criteria were: severe, secondary, or complicated hypertension, previously known

ECG abnormalities (atrioventricular block 2nd-or-3rd degree, ventricular arrhythmia, rhythm disturbance such as atrial flutter or atrial fibrillation), poor echogenicity, asymmetric septal hypertrophy defined as an interventricular septal wall thickness (IVSWT)/posterior wall thickness (PWT) >1.5, dilated left ventricle defined as an end-diastolic left ventricular internal diameter (LVIDd) >60 mm, left ventricular fractional shortening <25%, segmental or global kinetic abnormality, valvular disease, concomitant liver or renal disease, significant abnormalities in laboratory parameters. Contraindication to study treatments, obesity, alcohol or drug abuse, pregnancy or possibility of pregnancy are also criteria for non-selection.

Scheduled visits and follow-up

At all visits from inclusion to discharge, patients undergo a complete clinical examination, including weight and calculation of the waist/hip ratio, an assessment of BP and heart rate, and a screening for tolerability. Full laboratory tests are scheduled on W0, W24 and W52. Short laboratory tests are scheduled at other visits. Genetic risk factors associated with the occurrence of LVH and its regression after antihypertensive treatment are also identified; the ACE gene and the gene for the angiotensin II type I receptor are determined from the blood sampling of W0. Ancillary studies such as ABPM, 24 h holter ECG and QT dispersion are optional for patients and performed prior to W0, W24 and W52 visits. Ambulatory BP monitoring is performed to confirm the relationship between ABPM and LVM since several studies have reported that LVH is more closely correlated to ABPM than to casual BP measurement.[33] In hypertension with LVH loss of baroreceptor sensitivity is even more marked and accompanied by loss of variability. If heart rate variability has been shown to be significantly reduced in patients with LVH, in fact almost everything remains to be done due to the lack of controlled studies.[34] To assess the relationship between heart rate variability and LVMI, a holter ECG is performed over 24 h three times during the study. As LVH is also a risk factor for ventricular arrhythmias, 12-lead QT dispersion ECGs are performed to test the correlation of QT dispersion with LVMI baseline and regression.[35,36] A control ECG review will permit to evaluate in a prospective way the correlation between ECG LVH and Cornell voltage or Sokolow–Lyon voltage and echocardiographic LVH at baseline and their variation under treatment.

Assessment of efficacy

The echocardiography parameters are first measured and calculated by investigators according to the Penn Convention.[37] The mean of the measurements from three to five cardiac cycles for each of the indices is considered.

The primary efficacy criterion in this study is the change between baseline (W0) and the last observation carried out (LOCF) in the LVMI (calculated as the ratio: LVM/body surface area). The LVM is calculated according to Devereux formula: LVM = 1.04 [(IVSWTd + LVIDd + PWTd)^3 – (LVIDd)^3] – 13.6 g).[37,38] To assess efficacy, echocardiography is performed on three occasions: at baseline (W0), at W24, and at discharge (W52).

The secondary echocardiographic efficacy criteria are changes observed between W0 and LOCF in end-diastolic and systolic LV posterior wall thickness (PWTd, PWTs), end-diastolic and end-systolic interventricular septal wall thickness (IVSWTd, IVSWTs), end-diastolic and end-systolic LV internal diameter (LVIDd, LVIDs), the LVM, the LV mass/height$^{2.7}$,[39] the LV fractional shortening (FS) and the relative wall thickness (RWT = PWTd + IVSWTd/LVIDd).

Blood pressure is measured at each visit from W-4 to W52 in each patient by the same investigator, using the same arm and equipment. End points are the changes in sitting and standing systolic BP (SBP) and diastolic BP (DBP) between baseline and the last observation. Safety is assessed by monitoring clinical events, laboratory test abnormalities and 12-lead ECGs.

Echocardiography procedures

Equipment: Echocardiography with Super VHS recording is performed in the M-mode owing to the easiness of this technique, its reproducibility and reliability. The ultrasound source (phase-shift electronic or mechanical sector scanner) has to allow simultaneous Doppler recording.

Methods: The recording is performed in patients in the left lateral supine position after a 15-min rest and a left parasternal space is selected allowing the ultrasound beam to be perpendicular to the LV long axis. The same intercostal space must be used at the initial and each subsequent visit. M mode recordings of LV are performed at the tip of mitral valves guided by two-dimensional (2D) long axis and short axis views. The M-mode cursor positions in both the long- and short-axis 2D views are recorded on single frame. At least five consecutive cardiac cycles are recorded to eliminate respiratory influence on LV dimensions. The preferential recording speed of 100 mm/s is defined, but if impossible, the maximal speed available is recommended.

Recordings: All echocardiograms are recorded on separate tapes of 3–4 min duration. Each recording tape includes: parasternal long- and short-axis scans each showing the M-mode cursor, at least five consecutive cycles with M mode tracings of LV from both 2D views, an apical four-chamber 2D view including the LV long axis and pulsed Doppler imaging of mitral flow and an apical two-chamber-

aortic view including pulsed Doppler imaging of aortic flow in the outflow tract.

Echocardiography quality control procedures

During the course of the study a Central Echocardiography Committee of independent echocardiographers perform quality control all echocardiograms to ensure their conformity with the procedures required. At the end of the study, all echocardiograms will be blindly reviewed for statistical analysis.

All echocardiographic and Doppler recordings are reviewed by the Central Echocardiography Committee using a Iô 3.4 unit from IôDP company (Paris, France). This unit is a computerised system with multiple pre-existent functions for data acquisition, storing, transfer, analysis and export, and enables additional dedicated quantification functions to be included. This semi-automated measurement method allows automatic edge detection which are to be validated by the experts. This method was proved to give reliable and reproducible measurements of LVM.[40]

During the control of quality, the reviewer selects and digitises with Iô 3.4 unit the best images and sequences according to the protocol. This quality control is aimed at selection to confirm that LVH criteria are present and at all visits that the quality of recordings complies with the requirements of the protocol. All data are saved on digital optical disks and stored on a dedicated computer.

At the end of the study a final review of all randomised echocardiograms blinded for treatment, centre, visit date and patient identification will be performed. Each patient's scans will be stored on the same digital optical disk in a random order which will be sent to a reviewer for quantification of LVH parameters. A set of final scans will jointly be reviewed by two members of the Central Echocardiography Committee to assess the reproducibility of LVM in this study using the same Iô 3.4 unit.

Preliminary baseline data of the first 500 randomised patients

Table 1 summarises selected characteristics of the first 500 randomised patients at the inclusion visit. The average age was 56 years, and 46% of patients were men and 54% were women. Systolic and diastolic blood pressures at baseline averaged 164 mm Hg and 98 mm Hg, respectively. Among the first 500 randomised patients 87% took treatment for hypertension before the study. The average LVM was 300 g for men and 240 g for women). Mean LVMI was 153 g/m^2 for men and 138 g/m^2 for women.

Table 1 Baseline characteristics of the first 500 randomised patients

Baseline characteristics	*Mean ± s.d.*
Sex Ratio (M/F)	46/54
Age (years)	56±10.2
Weight (kg)	76±11.5
Height (cm)	167±8.7
Systolic BP (mm Hg)	164±14.4
Diastolic BP (mm Hg)	98±8.6
Medical and surgical history (Yes)	81%
Treatment for hypertension (Yes)	87%
LVM (g)	300±63.3 (M) 240±51.9 (F)
LVMI (g/m^2)	153±31.6 (M) 138±25.9 (F)

Discussion

This study is ongoing and all patients required have already been included. Among the 1019 patients selected, 679 were included and 340 non included. Nearly two-thirds of the non-inclusion reasons were related to the non-validation of echocardiography (poor echogenicity, one-third). The first results are planned at the beginning of 2003. Conclusive and reliable information on the ability of the very low-dose combination Per/Ind to reverse LVH in comparison with the standard ACE inhibitor enalapril may be expected from this large-scale trial conducted in a large population of hypertensive patients with LVH.

The rationale for a combined antihypertensive regimen based on an ACE inhibitor and a diuretic has often been reported, such combination providing several advantages:[41] the diuretic-induced increase in plasma renin activity enhances the efficacy of the ACE inhibitor, the potential consequences of the increase in plasma renin activity are counteracted by ACE inhibition, and the lower diuretic dosage decreases adverse metabolic and electrolyte side effects. Furthermore the combined Per/Ind tested in this study was previously shown to provide a good BP control[27–29] with a sustained normalisation rate in 1 year of treatment and a superiority towards reference monotherapy like ATII-antagonists or β-blockers.

The duration of the 4-week placebo period is certainly not sufficient to reverse significantly the beneficial effect of prior therapy on LVM. Nevertheless, due to the randomisation, the number of patients previously treated should be the same in the two treatment groups which will unbiased the comparison. Furthermore, this 4-week period allows us to standardise the laboratory tests for safety and BP for efficacy at randomisation by wearing off the effects of previous treatment.[8] The 52-week period of treatment is in accordance with the duration of treatment recommended for such a study.[42]

Echocardiography is the most commonly used method for LVM measurement. Nevertheless, given the limited reproducibility of echocardiographic measurements,[43] and their close dependence on the quality of investigation, it is mandatory to standardise both the recording procedure and the reading of

the results, and above all to ensure that quality control is maintained throughout the study[44] to avoid a loss of available data at the end of the study.

Although MRI appears to be more precise and reliable for measuring LVM,[45] it is limited by cost, fixed facilities and claustrophobia. The echocardiography widely used permits the realisation of large-scale studies which can then include a representative population of hypertensive LVH patients. Furthermore M mode methods based on the cube function formula have been shown to predict LVM at necropsy in humans with reasonable accuracy (correlations coefficients generally in excess of 0.9).[38] Semi-automated measurements of left ventricular diameters and wall thickness from M mode recordings allow standardisation of the review process which is required in such a large-scale multicentric study where centralised review has to be made by several reviewers. It also saves time in answering investigators during the reviewing procedure. This is a critical step in on-line quality control review because an answer must be given to the investigators as soon as possible in order to record a new videotape if necessary. In addition, this semi-automatic software has other advantages for the final review such as preselection of the best images, removing the need for a recalibration step in the final review and allowing easier and faster blinding and randomisation of recordings due to digitised images and sequences.

Finally this study fulfills all requirements for a comparative study on LVH regression with echocardiography: randomised, double-blind comparative trial, adequate sample size (>200 pts/group), adequate duration (1 year), quality control performed all along the study to avoid lost patients or insufficient quality recordings.

Conclusion

As a result of the very strict methodological procedures used in the PICXEL study (ie, the on-line quality control, the specificity of the dedicated software, and the blinded review of all recordings), conclusive and reliable data on the ability of a long-term strategy based on a very low-dose Per/Ind combination to reverse LVH may be expected. This very low dose combination, which has already proven its antihypertensive efficacy, should present an additional therapeutic benefit that makes it suitable for the treatment of hypertensive patients with LVH.

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Appendix

The following persons participated in the PICXEL trial:

Steering Committee: B Dahlöf (International coordinator), JP Degaute (Belgium coordinator), G de Simone, (Italy coordinator), P de Leeuw (Netherlands coordinator), J Garcia Puig (Spain coordinator), P Gosse (France coordinator), Y Karpov (Russia coordinator), D Magometschnigg (Austria coordinator), L Matos (Hungary coordinator), R. Schmieder (Germany coordinator).

Central Echocardiographic Committee: P Gosse (Chairman, reviewer in quality/final review), O Dubourg (Reviewer – quality/final review), P Guéret (Reviewer – quality/final review), G de Simone (Reviewer – quality/reproducibility), R Schmieder (Reviewer – reproducibility). *Ancillary studies:* P Amouyel (genetic chair), R Asmar (ABPM chair), JY

Le Heuzey (holter ECG chair), M Nieminen (ECG QT dispersion chair).

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