| Clinical Study Report Synopsis | |
|---|---|
| Drug Substance | None |
| Study Code | NIS-CEU-DUM-2006/1 |
| Edition Number | 2.0 |
| Date | May 7, 2009 |

# PANDORA Study

## Prevalence of peripheral Arterial disease in subjects with a moderate CVD risk, with No overt vascular Diseases nOR diAbetes mellitus. A non-interventional, cross-sectional, multi-centre, international survey.

| | |
|---|---|
| **Study dates:** | First subject enrolled: 24 May 2007<br>Last subject completed: 8 July 2008 |
| **Phase of development:** | Not applicable |
| **International Co-ordinating Investigator:** | Not applicable |
| **Sponsor's Responsible Medical Officer:** | ASTRAZENECA SpA<br>Via Sforza, Palazzo Volta<br>I-20080 Basiglio (MI)<br>Italy |

This study was performed in compliance with Good Clinical Practice.

| | | | |
|---|---|---|---|
| Drug Product | None | **SYNOPSIS** | |
| Drug Substance | None | | |
| Study Code | NIS-CEU-DUM-2006/1 | | |
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## Prevalence of peripheral Arterial disease in subjects with a moderate CVD risk, with No overt vascular Diseases nOR diAbetes mellitus. A non-interventional, cross-sectional, multi-centre, international survey.

**International Coordinating Investigators**

Not Applicable

**Study centre(s)**

The study was conducted in 591 centres across 6 countries (Italy, Belgium, France, the Netherlands, Greece and Switzerland).

**Publications**

There were no publications at the time of this report.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First subject enrolled** | 24 may 2007 | Not applicable |
| **Last subject completed** | 8 July 2008 | |

**Objectives**

The primary objective was to evaluate the prevalence of peripheral arterial disease (PAD), defined as Ankle-Brachial Index (ABI) $\leq$0 90, in subjects with at least two Cardiovascular Disease (CVD) risk factors, with no overt cardiovascular disease or diabetes mellitus.

**Study design**

This was a single visit, non interventional, cross sectional, international, multicentre study.

**Target subject population and sample size**

Male subjects aged ≥45 years or female subjects aged ≥55 years (age related risk factor), with at least one other CVD risk factor among cigarette smoking (any cigarette smoking during the past month), hypertension (arterial blood pressure ≥140/90 mmHg or on antihypertensive medication), low HDL-Cholesterol (HDL-C) <40 mg/dL or high LDL-Cholesterol (LDL-C) ≥130 mg/dL within 3 months of study entry, family history of premature Coronary heart Disease (CHD) (clinical CHD or sudden death in father or other male first-degree relative <55 years of age, CHD in mother or other female first-degree relative <65 years of age) or elevated waist circumference (≥102 cm for male, ≥88 cm for female) who provided written informed consent, could be included.

Subjects could not be included if they had symptoms of PAD, or if they had type 1 or 2 diabetes mellitus, established CHD, other CHD risk-equivalents, no lipid data (at least triglycerides, total cholesterol, and HDL-C) collected in the last twelve months, or serious or unstable medical or psychological conditions that, in the opinion of the Investigator, would compromise the subject's safety or successful participation in the study.

**Criteria for evaluation (main variables)**

The primary outcome variable was the percentage of subjects with PAD, defined as a pathological ABI (≤0.90 on left or right side).

Secondary outcome variables included frequency of smoking (as defined), family history of premature CHD, arterial hypertension, dyslipidemia, elevated waist circumference, physical activity (≥30 min of continuous/intermittent moderate intensity exercise ≥5 days/week), and alcool intake.

Patient reported outcomes included a 14-item subject questionnaire on awareness of CVD risk factors, knowledge and awareness of PAD, CVD risk perception and treatment, and visit frequency. In addition a 31-item investigator questionnaire (demographic/professional data, and information on knowledge and behaviour in CVD diagnosis and management, quantity of CVD cases experienced, attitudinal statements on general aspects, guidelines and goals, treatment, treatment review) was used.

**Statistical methods**

In view of the observational nature of the study, a descriptive statistical analyses approach was applied. All collected data were described in total and by country. Continuous data were described by their mean, standard deviation, median, minimum and maximum values. Categorical data were described by the number and percentage of subjects in each category. The main statistical analysis was performed in evaluable subjects (i.e. all enrolled subjects who signed informed consent, showed no protocol violations, had ABI measurement and > 80% Subject Record Form data collected), with a confirmatory analysis performed in the total enrolled population. This latter analysis confirmed findings from the evaluable population

Statistical analyses were performed using the SAS system (SAS for Windows version 8.2, SAS Institute Inc., Cary / NC, USA) according to the Statistical Analysis Plan prepared prior to database lock.

**Subject population**

The subject population and disposition are shown in Table S1.

**Table S1 Number of subjects enrolled and evaluable in each country and in total**

| Country | Enrolled subjects n | Evaluable subjects | |
|---|---|---|---|
| | | n | % |
| Italy | 5298 | 5112 | 96.5 |
| Belgium | 1576 | 1510 | 95.8 |
| France | 1011 | 979 | 96.8 |
| Netherlands | 1011 | 917 | 90.7 |
| Greece | 840 | 789 | 93.9 |
| Switzerland | 551 | 509 | 92.4 |
| Total | 10287 | 9816 | 95.4 |

10287 subjects were enrolled and 9816 subjects had evaluable data. Most frequent reason(s) for exclusion from the evaluable subjects subset included absence of lipid data collected within last 12 months (1.7% of enrolled subjects), unmeasurable ABI (1.7%), or <80% of Subject Record Form data collected (1.3%).

The subject demographic characteristics are summarised in Table S2.

**Table S2 Demographic characteristics of enrolled and evaluable populations**

| Characteristic | | Enrolled subjects (n=10287) | Evaluable subjects (n=9816) |
|---|---|---|---|
| Age (years) | n | 10287 | 9816 |
| | Mean (SD) | 64.1 (9.1) | 64.3 (9.0) |
| | Median | 63 | 63 |
| | Interquartile range | 58 - 70 | 58 - 71 |
| Sex, n (%) | n | 10287 | 9816 |
| | Male | 5495 (53.4) | 5254 (53.5) |
| | Female | 4792 (46.6) | 4562 (46.5) |

| Characteristic | | Enrolled subjects (n=10287) | Evaluable subjects (n=9816) |
|---|---|---|---|
| Race, n (%) | n | 10287 | 9816 |
| | Caucasian | 10018 (97.4) | 9562 (97 4) |
| | Black | 31 (0 3) | 28 (0.3) |
| | Oriental | 48 (0.5) | 44 (0 5) |
| | Other | 190 (1.8) | 182 (1.8) |
| Civil Status, n (%)* | n | 9275 | 8836 |
| | Single (unmarried) | 502 (4.9) | 476 (4 8) |
| | Married or living together | 7092 (68.9) | 6754 (68 8) |
| | Widowed | 1094 (10 6) | 1060 (10 8) |
| | Divorced or separated | 579 (5 6) | 538 (5.5) |
| | Other | 8 (0.1) | 8 (0.1) |

*not collected in France, missing for 1 Swiss subject

## Study results

### PAD

The average percent frequency of subjects with PAD was 17.8%.

### CVD risk factors/lifestyle habits

Percent frequencies of lifestyle habits and CVD risk factors in evaluable subjects with and without PAD, with Odds Ratio, 95% CI and associated p value, are summarised in Table S3.

**Table S3** **Percent frequencies of lifestyle habits and CVD risk factors in subject with and without PAD.**

| Variable | | With PAD (n=1751) | Without PAD (n=8065) | OR (95% CI) p° |
|---|---|---|---|---|
| Smoking | Habitual smoker | 34.0 | 25.5 | 1.33 (1.20- |
| | Ex-smoker (%) | 23.0 | 25.7 | < 0.0001 |
| | Non smoker (%) | 43.0 | 48.8 | |
| | Total (n) | 1751 | 8065 | |
| Hypertension | No (%) | 20.3 | 26.4 | 1.46 (1.28- |
| | Yes (%) | 79 7 | 73.6 | < 0.0001 |
| | Total (n) | 1751 | 8065 | |

| Variable | | With PAD (n=1751) | Without PAD (n=8065) | OR (95% CI) p° |
|---|---|---|---|---|
| Family history | No (%) | 64.3 | 82.7 | 2.43 (2.16- |

| | | | | |
|---|---|---|---|---|
| of premature | Yes (%) | 35.7 | 17.3 | < 0 0001 |
| | Total (n) | 1751 | 8065 | |
| Elevated waist | Yes (%) | 60.2 | 60.0 | 0.99 (0 88- |
| circumference** | No (%) | 39.8 | 40.0 | 0 80 |
| | Total (n) | 1751 | 8064 | |
| Dyslipidemia | Yes (%) | 49 5 | 55.9 | 0.88 (0.79- |
| | No (%) | 50 5 | 44.1 | |
| | Total (n) | 1751 | 8065 | |
| High LDL-C *** | Yes (%) | 50.9 | 53 6 | 0.93 (0 82- |
| (untreated | No (%) | 49.1 | 46 4 | 0 29 |
| subjects) | Total (n) | 1198 | 5237 | |
| High LDL-C *** | Yes (%) | 53.9 | 42 7 | 1.20 (0 97- |
| (treated | No (%) | 46.1 | 57 3 | 0 09 |
| subjects) | Total (n) | 440 | 2409 | |
| Low HDL-C **** | Yes (%) | 17 8 | 12 8 | 1.40 (1 21- |
| | No (%) | 82 2 | 87.2 | <0.0001 |
| | Total (n) | 1751 | 8065 | |
| Physical activity | Inactive (%) | 63.7 | 57.2 | 1.11 (0.99- |
| | Active (%) | 36.3 | 42.8 | 0.07 |
| | Total (n) | 1751 | 8064 | |
| Alcohol intake | Moderate (%)^ | 60.2 | 53.3 | 1 53 (1.37- |
| | High (%)^^ | 8.9 | 7.4 | < 0.0001 |
| | None (%) | 30 9 | 39 3 | |
| | Total (n) | 1751 | 8065 | |

° from Cochran-Mantel-Haenszel test
*clinical CHD or sudden death in first degree male relative aged <55 years or female relative aged < 65 years
** ≥ 102 cm in males and ≥ 88 cm in females
*** ≥ 130 mg/dL (≥3.3 mmol/L) **** < 40 mg/dL (<1.0 mmol/L)
^ ≤ two glasses per day ^^ > two glasses per day

## Current medications

Frequency of current CV medications was significantly higher in subjects with PAD (79.0% *vs* 77.2%, OR 0.82, 95% CI 0.73-0.94, p=0.003 from Cochran-Mantel-Haenszel test). On the contrary, statin treatment was less frequent in subjects with PAD (16.5% *vs* 21.8%, OR 1.32, 95% CI 1.14-1 54, p=0.0004 from Cochran-Mantel-Haenszel test).

## CVD risk

Subjects with PAD showed a Framingham 10-yr CHD risk score higher than subjects without PAD (mean ± SD values 15.7±8.7% *vs* 12.3±7.6%, respectively). No major differences between groups were seen in terms of SCORE 10-yr CV death risk score.

**Logistic regression analysis of subject determinants**

The association between PAD and subjects determinants, including subject characteristics (country, age, sex, race, civil status), lifestyle habits and CVD risk factors, as well as statin treatment, was evaluated by means of a logistic regression analysis. Age was found to be significantly ($p<0.0001$) associated to PAD (OR 1.02, 95% CI 1.01-1.02). In addition, as far as civil status (reported from all countries except France), both divorced and widowed subjects were significantly ($p\leq 0.03$) more likely to show PAD than married subjects (OR 2.89, 95% CI 2.34-3.55, and 1.22, 95% CI 1.01-1.47, respectively).

Among risk factors, subjects with family history of premature CHD were more likely to show PAD than subjects without it (OR 2.43, 95% CI 2.15-2.76). Habitual smokers were more likely to have PAD than non-smokers (OR 1.55, 95% CI 1.34-1.79). Subjects with hypertension were more likely showing PAD than subjects without hypertension (OR 1.50, 95% CI 1.30-1.73). Subjects with low HDL-C more likely showed PAD than subjects without it (OR 1.38, 95% CI 1.18-1.61).

Among lifestyle habits, alcohol intake was significantly ($p\leq 0.0012$) associated with PAD, with both subjects with high intake and subjects with moderate intake more likely showing PAD than subjects with no intake (OR 1.47, 95% CI 1.16-1.84, and OR 1.37, 95% CI 1.20-1.56, respectively).

Finally, as for current medications, subjects on treatment with statins were less likely to show PAD than subjects not receiving it (OR 0.62, 95% CI 0.50-0.76).