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Non-Interventional Study (NIS) Report Synopsis

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Observational non-interventional study – epidemiological survey "AchievemenT of goal resting HEart rate on beta-blockers in patients with stable angiNA and hypertension in routine practice" (ATHENA)

Study dates: 01.04.2011 - 31.08.2011

First Patient In: 01 April 2011

Last Patient Last Visit: 31 August 2011

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NIS REPORT SYNOPSIS

Observational non-interventional study – epidemiological survey "AchievemenT of goal resting HEart rate on beta-blockers in patients with stable angiNA and hypertension in routine practice" (ATHENA)

Sites and number of patients

Number of sites and subjects planned

388 patients (not less than 400 patients due to possible drop-outs) were planned to be included in the study in 20 participating institutions (a minimum of 10 patients from each institution was expected). Sample size was estimated based on the precision of the primary variable estimation within 90% confidence interval of ±5%, taking into consideration that the proportion of patients with achieved resting heart rate (HR) goals is about 8%. Sample size was also estimated in order to reveal significant differences of Seattle Angina Questionnaire (SAQ) score with the method of two means, for 5% of level of significance and 80% of study power, taking into consideration that 15 is standard deviation of SAQ score, and the assumed proportion of patients with target resting HR goals is 8%.

Number of subjects included in the analysis

Totally 400 patients were included in the study in 20 participating institutions.

Study design

Non-interventional multicenter prospective study. This is a multi-centre survey of patients who are currently using beta-blockers (BB) treatment for at least 2 months and with no dose change for a minimum of 4 weeks in the Russian Federation. During a single patient's visit, the data of BB treatment were collected before patient's participation in the study. No specific therapy or procedures outside routine clinical practice were planned for the study participants.

Study participants

Subject sample was extracted from the typical cardiologic population of patients with coronary heart disease (CHD) and concomitant arterial hypertension (AH) taking BB who visited their physician routinely and signed informed consent for study participation.

Inclusion criteria

- Subject must be 18 years of age or older of either gender or race;
- Stable angina I-III class by the Canadian Cardiovascular Society Classification and concomitant essential arterial hypertension;
- Subject is on beta-blockers treatment for at least 2 months prior to inclusion into survey, with no dose change for a minimum of 4 weeks;
- Subject must provide informed consent and comply with the survey procedures.

***Exclusion criteria**:*

- Subjects who are unwilling or unable to provide informed consent;
- Use of phenylalkylamine and benzothiazepine calcium channel blockers;
- Hemodynamic significant mitral and aortic valve disease;
- Acute myocardial infarction and unstable angina within 3 months before enrolment.

Evaluation variables

Demographic and clinical characteristics

Age, gender, stable angina class and duration, arterial hypertension grade and duration, current beta-blocker treatment, other antianginal and antihypertensive treatment, BP and HR level.

Primary variable:

- The number and percentage of subjects achieving HR goals, according to ACC/AHA/ACP–ASIM Guidelines for the management of patients with chronic stable angina and to all-Russian Scientific Cardiology Society (RSCS) guidelines on stable angina in real clinical practice.

According to ACC/AHA/ACP–ASIM Guidelines for the Management of patients with chronic stable angina, in the treatment of stable angina, resting HR goals are **55 to 60 beats per min**.

Secondary variables:

- The mean dose of each beta-blocker in patients who achieved and not achieved resting HR goals
- SAQ score in patients who achieved and non achieved resting HR goals
- The association between achievement of resting HR goals, according to the ACC/AHA/ACP–ASIM Guidelines for the management of patients with chronic stable angina and to RSCS guidelines on stable angina and achievement of blood pressure (BP) goals according to Reappraisal of European guidelines on hypertension management: a European Society of Task Force document and RSCS guidelines on hypertension diagnostic and treatment

Statistical analysis methods

General methods

Results were provided for the total sample and predefined subgroups (patients with achieved and not achieved the resting HR goals). Descriptive statistics were calculated for interval and categorical variables. Comparison between subgroups for the normally distributed interval variables was performed with t-test. Levene test was used to assess the equality of variances in different samples. Comparison between subgroups for categorical variables was performed using Chi-square test.

Primary variable

For assessment of percentage of subject that achieved target level of resting HR, both frequency and 95% confidence interval for frequency (calculated using Clopper-Peasron method) was calculated.

Secondary variables

Non-parametric Mann-Whitney test was used for comparison of the average daily doses of beta-clockers and scores of SAQ between subgroups.

Contingency tables including expected and observed frequencies were built in order to assess contingency between achieved HR level and achieved BP level. Statistical significance of this contingency was assessed using chi-square test, and grade of contingency (in case of its presence) was assessed using Cramer contingency coefficient and φ coefficient.

SUMMARY

Target analysis population

Statistical analysis was performed on a single "per protocol" population (n=399). One patient was excluded due to exclusion criteria violation. Predefined subgroups included patients with achieved the resting HR goals (n=62) and not achieved the resting HR goals (n=337).

Demographics and clinical characteristics

Overall, the gender ratio approximated 1:1. There were 200 (50.1%) males and 199 (49.9%) females.The patients' age ranged from 37 to 91, with mean and SD of 64 ± 10 years. 191 (48.0%) patients had II functional class of stable angina according to Canadian Cardiovascular Society. Median of the stable angina duration was 5.4 years. 182 (45.4%) patients had III grade of AH at the diagnosis. Median of the AH duration was 13.2 years.

Most of the patients were taking bisoprolol (48.9%) and metoprolol (36.1%). Concomitant medications included nitrates and other vasodilators, ACE inhibitors, sartans, diuretics, antiplatelets, anticoagulants, antiarrhythmics, hypolipidemic medications, other cardiovascular medications.

Patient demographics and clinical characteristics didn't differ between subgroups with achieved and not achieved resting HR goals with the exception of both systolic and diastolic BP that was significantly lower in the subgroup with achieved resting HR goals.

Primary objective

In real clinical practice study participants, 62 of 399 (15.5%) (95% CI: 0.121-0.195) achieved resting HR goals (55-60 beats/min) according to ACC/AHA/ACP–ASIM Guidelines for the management of patients with chronic stable angina and RSCS guidelines on stable angina.

Secondary objectives

1) The medians of doses of BBs (metoprolol, bisoprolol, carvedilol) were similar in both groups of patients with achieved target HR and not achieved target HR, except for metoprolol (median of metoprolol dose was 75 mg and 50 mg respectively). However, statistical analysis did not revealed significant difference in the average daily doses of these BBs (metoprolol, bisoprolol, carvedilol) between subgroups with achieved and not

achieved the resting HR goals. For other BBs (atenolol, nebivolol, sotalol, betaxolol) comparison have not been performed due to an inappropriate size of the subgroup(s).

2) Average scores for all SAQ scales (Physical limitation, Angina Stability, Angina Frequency, Treatment Satisfaction, Disease perception) and total score didn't differ between subgroups with achieved and not achieved the resting HR goals.

3) Statistically significant correlation (p=0.005) was confirmed between achievement of the resting HR goals according to the ACC/AHA/ACP–ASIM Guidelines for the management of patients with chronic stable angina and RSCS guidelines on stable angina (55-60 beats/min) and achievement of BP goals according to revised European guidelines 2009 and RSCS guidelines for AH management 2010 (<140/90 mmHg) with a moderate contingency coefficient values (0.144 for Cramer coefficient and 0.145 for φ coefficient).