Title:

Influence of Rivaroxaban for Intermittent Claudication and Exercise Tolerance in Patients With Symptomatic PAD

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STATISTICAL ANALYSIS PLAN

1. Randomization

Due to the limited number of studied groups, randomization of patients will be carried out using the minimization or equivalent principle, which allows maintaining similarity of groups in terms of known prognostic factors.

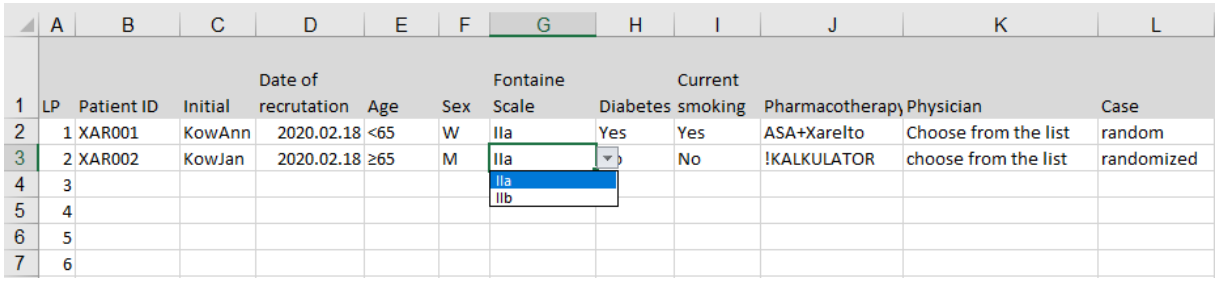
The minimization principle by Taves (1974), independently developed and generalized by Pock and Simon (1975), takes into account the previous distribution of patients with specific prognostic factors in particular groups. It is based on the algorithm of assigning another patient to one of the arms in such a way as to reduce the total differentiation of groups with respect to selected features. The following parameters will be taken into account as stratifying factors: age (<65 vs. ≥65), gender (women vs. men), degree of disease (Fountaine IIa vs. IIb scale), diabetes (yes vs. no), current smoking (yes vs. no). The number of analyzed factors is consistent with the recommendations of the authors, who recommend including no more than five stratifying factors. The advantage of minimization is the fact that it is a "dynamic" method, which does not require prior preparation of randomization lists but allows to select treatment "on the fly" on the basis of updated data analysis.

In order to carry out the randomization, a calculator and database have been developed, which will be available online for cooperating physicians (Fig. 1 and 2). This will allow for real-time randomization by researchers, including patients in the study at the same time. The prototype table contains personal data, while the final version will provide anonymized data.

Figure 1. The calculator developed for randomization.

		Treatment A	Treatment B
Parameter	Value	ASA	ASA+ Xarelto
Age	<65	1	0
	≥65	0	0
Sex	W	0	0
	M	0	1
Fontaine Scale	IIa	0	1
	IIb	0	0
Diabetes	Yes	1	0
	No	0	0
Current smoking	Yes	1	0
	No	0	0
	Number of cases	0,6	0,4
Age	≥65	1	1
Sex	M	0	2
Fontaine Scale	IIa	0	2
Diabetes	Yes	0	0
Current smoking	No	0	0
	Variability of features	1	5
RESULT OF RANDOMIZATION	Drug	ASA	

Figure 2. The database used to perform randomization.



	A	B	C	D	E	F	G	H	I	J	K	L
1	LP	Patient ID	Initial	Date of recrutation	Age	Sex	Fontaine Scale	Diabetes	Current smoking	Pharmacotherapy	Physician	Case
2	1	XAR001	KowAnn	2020.02.18	<65	W	IIa	Yes	Yes	ASA+Xarelto	Choose from the list	random
3	2	XAR002	KowJan	2020.02.18	≥65	M	IIa		No	!KALKULATOR	choose from the list	randomized
4	3						IIa					
5	4						IIb					
6	5											
7	6											

2. The statistical power of the study

This study, in which 60 participants are planned to participate, 30 in each study group, is a pilot study to obtain preliminary data on the variability of the parameters studied within and between groups. The zero hypothesis of this study (H0) assumes no effect of rivaroxaban on the claudication distance and effort tolerance in PAD patients. The study will be continued until 80-90% of statistical power is obtained to detect 5% differences in Δ DCH and Δ DMAX values between groups treated with rivaroxaban and aspirin compared to aspirin.

After obtaining preliminary results, the power of the test will be analyzed to determine the adequate sample size. An example of such an analysis for test-t for independent samples is given in Figure 3. A sample of 30 people per test group (Required N (per group) value) would meet the above statistical power assumptions. For example, in group I, the mean percentage difference Δ DCH (change in claudication distance after three months) would be 3.667% (Mu1 value), and in group II the mean would be -1.333% (Mu2 value), giving a total of 5% difference in Δ DCH between groups (the standardized effect in this case is Es=0.8621%) with a standard deviation value for the whole population of SD=5.800 (Figure 6a). The key to obtaining statistical significance will be the observed internal variability within the study groups, because in the case of double the standard deviation for the results from the whole study population (SD=11.6), the success of this project would already require gathering 115 people in each study group (Figure 3b).

Figure 3: Examples of analyses of the adequate sample size to obtain 90% of the statistical power to detect 5% differences in the percentage values of the parameter Δ DCH (changes of the claudication distance after three months expressed in %) depending on the different values of SD. With SD = 5.8%, a sample of 30 persons per test group (a) would be sufficient, and in the case of double, the variability within the group, 115 persons per test group (b), would have to be collected.

a)

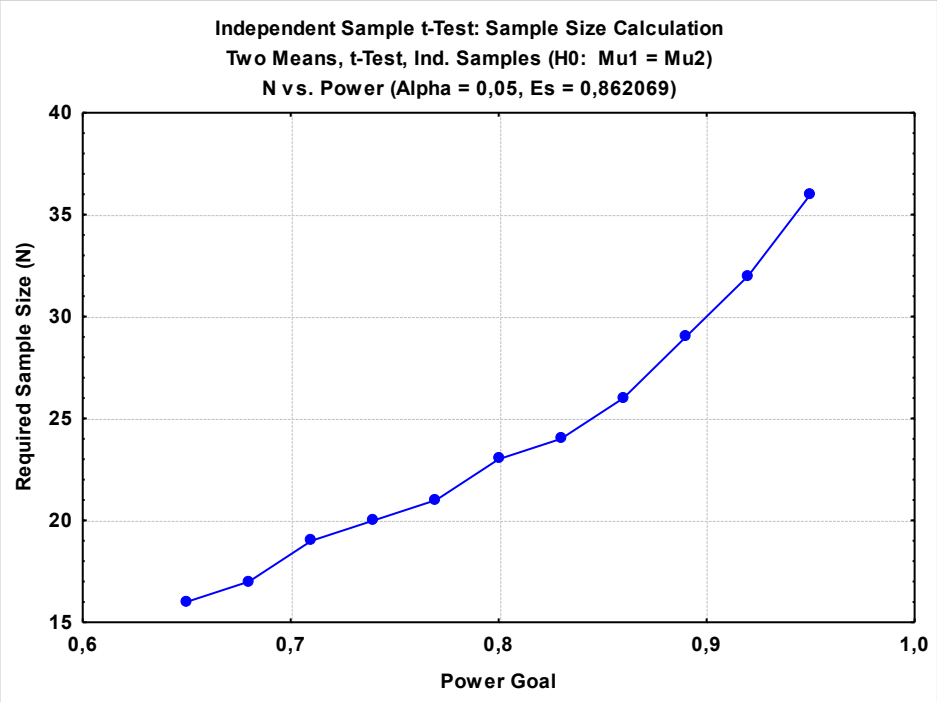
	Sample Size Calculation Two Means, t-Test, Ind. Samples H0: Mu1 = Mu2
	Value
Population Mean Mu1	3,6670
Population Mean Mu2	-1,3330
Population S.D. (Sigma)	5,8000
Standardized Effect (Es)	0,8621
Type I Error Rate (Alpha)	0,0500
Critical Value of t	2,0017
Power Goal	0,9000
Actual Power for Required N	0,9071
Required N (per group)	30,0000

b)

	Sample Size Calculation Two Means, t-Test, Ind. Samples H0: Mu1 = Mu2
	Value
Population Mean Mu1	3,6670
Population Mean Mu2	-1,3330
Population S.D. (Sigma)	11,6000
Standardized Effect (Es)	0,4310
Type I Error Rate (Alpha)	0,0500
Critical Value of t	1,9704
Power Goal	0,9000
Actual Power for Required N	0,9023
Required N (per group)	115,0000

If a statistically significant effect (80-90% test power) cannot be achieved with the assumed sample size, the test protocol will be modified by increasing the sample size and/or extending the observation period. For estimation of the sample size, the relationship between the test power and sample size will be analyzed. The results of such an analysis for the sample values contained in Figure 3a are given in Figure 4.

Figure 4: Example of a graph of test power versus sample size. Data for the example in Figure 3a



It is assumed that the study group will not exceed 100 participants (50 in each group), and the observation period will be extended to a maximum of 12 months. In the absence of significant results for extended observations, interpretation of the data will be based on indicating that it is impossible to reject the zero hypotheses (H0) that the tested drug does not affect the progress of the disease, with the indicated statistical power of the study.

The analysis of test power and sample size will be carried out using the module "Test Power Analysis" of STATISTICA v10.0.

3. Statistical analysis of the results

Statistical evaluation of the results will be carried out using standard statistical methods, single- and multi-factor tests. These analyses will be carried out using STATISTICA v10.0 and GraphPad Writings programs. Hypotheses will be verified at the significance level $P<0.05$. The evaluation of genotypes will take into account the Bonferroni correction for multiple comparisons.

LITERATURE

Pocock S.J., Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103–115.

Taves D.R. Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. 1974; 15: 443–453.