

## Supplementary material

**Table S1:** Description of packages used in R

| Name                                                                      | Maintainer         | Brief description                                                                                                                                                                               | Link                                                                                                      |
|---------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| simmer: Discrete-Event Simulation for R                                   | Iñaki Ucar         | A process-oriented and trajectory-based Discrete-Event Simulation (DES) package for R.                                                                                                          | <a href="https://CRAN.R-project.org/package=simmer">https://CRAN.R-project.org/package=simmer</a>         |
| Rfast: A Collection of Efficient and Extremely Fast R Functions           | Manos Papadakis    | A collection of fast (utility) functions for data analysis.                                                                                                                                     | <a href="https://CRAN.R-project.org/package=Rfast">https://CRAN.R-project.org/package=Rfast</a>           |
| Runuran: R Interface to the 'UNU.RAN' Random Variate Generators           | Josef Leydold      | Interface to the 'UNU.RAN' library for Universal Non-Uniform RANdom variate generators.                                                                                                         | <a href="https://CRAN.R-project.org/package=Runuran">https://CRAN.R-project.org/package=Runuran</a>       |
| extraDistr: Additional Univariate and Multivariate Distributions          | Tymoteusz Wolodzko | Density, distribution function, quantile function and random generation for a number of univariate and multivariate distributions.                                                              | <a href="https://CRAN.R-project.org/package=extraDistr">https://CRAN.R-project.org/package=extraDistr</a> |
| EnvStats: Package for Environmental Statistics, Including US EPA Guidance | Alexander Kowarik  | Graphical and statistical analyses of environmental data, with focus on analyzing chemical concentrations and physical parameters, usually in the context of mandated environmental monitoring. | <a href="https://CRAN.R-project.org/package=EnvStats">https://CRAN.R-project.org/package=EnvStats</a>     |
| Rcpp: Seamless R and C++ Integration                                      | Dirk Eddelbuettel  | The 'Rcpp' package provides R functions as well as C++ classes which offer a seamless integration of R and C++.                                                                                 | <a href="https://CRAN.R-project.org/package=Rcpp">https://CRAN.R-project.org/package=Rcpp</a>             |
| dplyr: A Grammar of Data Manipulation                                     | Hadley Wickham     | A fast, consistent tool for working with data frame like objects, both in memory and out of memory.                                                                                             | <a href="https://CRAN.R-project.org/package=dplyr">https://CRAN.R-project.org/package=dplyr</a>           |
| purrr: Functional Programming Tools                                       | Lionel Henry       | A complete and consistent functional programming toolkit for R.                                                                                                                                 | <a href="https://CRAN.R-project.org/package=purrr">https://CRAN.R-project.org/package=purrr</a>           |

|                                                                   |                       |                                                                                                                                                                                                       |                                                                                                         |
|-------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| stringr: Simple, Consistent Wrappers for Common String Operations | Hadley Wickham        | A consistent, simple and easy to use set of wrappers around the fantastic 'stringi' package.                                                                                                          | <a href="https://CRAN.R-project.org/package=stringr">https://CRAN.R-project.org/package=stringr</a> ;   |
| svMisc: 'SciViews' - Miscellaneous Functions                      | Philippe Grosjean     | Miscellaneous functions for 'SciViews' or general use: manage a temporary environment attached to the search path for temporary variables you do not want to save() or load().                        | <a href="https://CRAN.R-project.org/package=svMisc">https://CRAN.R-project.org/package=svMisc</a>       |
| ggpubr: 'ggplot2' Based Publication Ready Plots                   | Alboukadel Kassambara | 'ggpubr' provides some easy-to-use functions for creating and customizing 'ggplot2'- based publication ready plots.                                                                                   | <a href="https://CRAN.R-project.org/package=ggpubr">https://CRAN.R-project.org/package=ggpubr</a>       |
| survival: Survival Analysis                                       | Terry M Therneau      | Contains the core survival analysis routines, including definition of Surv objects, Kaplan-Meier and Aalen-Johansen (multi-state) curves, Cox models, and parametric accelerated failure time models. | <a href="https://CRAN.R-project.org/package=survival">https://CRAN.R-project.org/package=survival</a>   |
| survminer: Drawing Survival Curves using 'ggplot2'                | Alboukadel Kassambara | Contains the function 'ggsurvplot()' for drawing easily beautiful and 'ready-to-publish' survival curves with the 'number at risk' table and 'censoring count plot'.                                  | <a href="https://CRAN.R-project.org/package=survminer">https://CRAN.R-project.org/package=survminer</a> |

**Table S2:** Parameters for modeling the time of occurrence of simulated events

| Parameters                                   | Probability distribution | Values                     | Sensitivity analysis                                                                                      | Source |
|----------------------------------------------|--------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------|--------|
| Occurrence of IC                             | Exponential              | rate = 0.021               | Exponential parameter varied by ± 20% with uniform distribution                                           | [1]    |
| Occurrence of CLI (PAD to CLI)               | exponential              | rate = 0.004               | Exponential parameter varied by ± 20% with uniform distribution                                           | [1]    |
| Occurrence of CLI (IC to CLI)                | exponential              | rate = 0.064               | Exponential parameter varied by ± 20% with uniform distribution                                           | [1]    |
| Occurrence of amputation (Fontaine IIa, IIb) | Weibull                  | shape=0.40, scale=2010     | Varying only scale parameter Variation of the scale parameter; uniform distribution within ± 20% interval | [2]    |
| Occurrence of amputation (Fontaine III, IV)  | Weibull                  | shape=0.46, scale=73.44    |                                                                                                           | [2]    |
| Time to death (female)                       | Weibull                  | shape=3.52, scale=31.98    |                                                                                                           | [3]    |
| Time to death (male)                         | Weibull                  | shape=2.64, scale=36.84    |                                                                                                           | [3]    |
| Death after amputation                       | Weibull                  | shape=0.61, scale=5.48     |                                                                                                           | [4]    |
| <i>Vessel patency</i>                        |                          |                            |                                                                                                           |        |
| Primary PTA (IC)                             | Weibull                  | shape = 0.87 scale= 28.13  | Variation of the scale parameter; uniform distribution within ± 20% interval                              | [5–8]  |
| Primary PTA (CLI)                            | Weibull                  | shape = 0.93 scale = 10.17 |                                                                                                           |        |
| Primary PTA/S (IC)                           | Weibull                  | shape = 0.80 scale = 28.19 |                                                                                                           |        |
| Primary PTA/S (CLI)                          | Weibull                  | shape = 0.88 scale = 9.37  |                                                                                                           |        |
| Primary (autologous; IC)                     | Weibull                  | shape = 1.04 scale = 31.37 |                                                                                                           |        |
| Primary (autologous ;CLI)                    | Weibull                  | shape = 1.16 scale = 11.66 |                                                                                                           |        |
| Primary (graft; IC)                          | Weibull                  | shape = 1.22 scale = 20.78 |                                                                                                           |        |
| Primary (graft; CLI)                         | Weibull                  | shape = 1.42 scale = 9.01  |                                                                                                           |        |
| Secondary PTA (IC)                           | Weibull                  | shape = 0.79 scale = 67.10 |                                                                                                           |        |
| Secondary PTA (CLI)                          | Weibull                  | shape = 0.82 scale = 21.74 |                                                                                                           |        |
| Secondary PTA/S (IC)                         | Weibull                  | shape = 0.83 scale = 47.21 |                                                                                                           |        |
| Secondary PTA/S (CLI)                        | Weibull                  | shape = 0.87 scale = 16.09 |                                                                                                           |        |
| Secondary (autologous; IC)                   | Weibull                  | shape = 0.96 scale = 56.49 |                                                                                                           |        |
| Secondary (autologous; CLI)                  | Weibull                  | shape = 1.01 scale = 21.96 |                                                                                                           |        |
| Sekundární (graft; IC)                       | Weibull                  | shape = 0.97 scale = 33.00 |                                                                                                           |        |
| Sekundární (graft; CLI)                      | Weibull                  | shape = 1.21 scale = 14.38 |                                                                                                           |        |
| <i>Time to next examination</i>              |                          |                            |                                                                                                           |        |

|                                     |            |                                  |                                             |     |
|-------------------------------------|------------|----------------------------------|---------------------------------------------|-----|
| Time to next preventive examination | Uniform    | Min=1,8<br>Max= 2,2              | Fixed                                       | [9] |
| Time of effect exercise therapy     | Triangular | Min= 1,5<br>Mode= 2<br>Max = 2,5 | Fixed                                       |     |
| Time between followed diagnostic    | -          | 1 year                           | Uniform distribution (min = 0.8, max = 1.2) |     |

Primary and secondary patency for endovascular interventions were simulated based on a study Vossen et al. [5]. No statistically significant effect of Fontaine classification was found in the study for primary patency. A significant effect was found for secondary patency, but the value of the effect was not reported in the study. In other studies, the effect of CLI on primary patency was reported, e.g., Nishibe et al. [6] reports an HR of 2.5 (95% CI 1.08-5.83). Probability distribution values for primary patency obtained from the analysis of published Kaplan–Meier curves from the study of Vossen et al. [5] were adjusted based on simulations, so that an HR between IC and CLI was required to be 2.5. An overview of the probability distribution settings simulated for IC and CLI based on the data of the study by Vossen et al. [5] can be seen in Table S1.

Primary bypass patency was derived from PTA data. A study by Antoniou et al. [7] (comparison of bypass and PTA) shows an odds ratio of 1.44 for IC and 0.95 for CLI (for 4-year primary patency). The OR values were converted to RR, and therefore a value of 1.11 is considered for IC and a value of 0.98 for CLI. The difference of autologous and artificial bypasses was simulated based on Cochrane's systematic search by Ambler and Twine [8]. The size of the effect was based on the data from a comparison of 5-year primary patency, and the OR of 0.47 was recalculated to an RR of 0.62. In the Ambler and Twine study [8], the data were not published separately for IC and CLI, and therefore the considered RR is the same for IC and CLI.

The same process was used for secondary throughput data. As a suitable study evaluating the effect of CLI on secondary patency versus IC was not found, the same magnitude of effect as reported by Nishibe et al. [6] for primary patency was used (HR 2.5 (95% CI 1.08-5.83)). The secondary bypass patency was again derived from PTA data. In a study by Antoniou et al. [7], an OR 0.9 (for 4-year secondary patency) without distinguishing between area of intervention and disease severity (IC vs. CLI) was used. The OR values were converted to RR, and the considered value was 0.97. Input parameters for autologous and artificial bypasses were again based on Cochrane's systematic search by Ambler and Twine [8]. The size of the effect was based on comparison of 5-year secondary patency and the OR 0.41 was recalculated to 0.59 RR.

**Table S3:** Parameters and assumptions used in the model

| Parameters                                            | Value                                                      | Sensitivity analysis                                             | Source       |
|-------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------|--------------|
| Time to death with PAD                                | RR = 1,6 relative to úmrtí                                 | Fixed                                                            | [10]         |
| Time to death with IC                                 | RR = 3,1 relative to úmrtí                                 | Fixed                                                            | [11]         |
| Time to death with CLI                                | RR = 2,0 relative to IC                                    | Fixed                                                            | [12]         |
| Effect of pharmacological treatment                   | HR = 0,75                                                  | Fixed                                                            | [13,14]      |
| Vein for bypass                                       | 60 % autologous<br>65 % regularly                          | beta(39.4, 26.27)                                                |              |
| Preventive examination                                | 25 % irregularly<br>10 % do not attend                     | Fixed                                                            | [15]         |
| Irregular check-ups – prob. of attending              | 50 %                                                       | beta(12, 12)                                                     |              |
| Fontaine class distribution in occurrence of IC       | IIa: 66,8 %<br>IIb: 33,2 %                                 | IIa: beta (32.53, 16.17)                                         | [16]         |
| Fontaine class distribution in occurrence oCLI        | III 66,7 %<br>IV 33,3 %                                    | III: beta (32.63, 16.29)                                         | [16]         |
| Exercise effect                                       | 21,8 % worsening<br>36,7 % unchanged<br>41,6 % improvement | worsening: beta (77.98, 280)<br>improvement: beta (57.98, 81.40) | [17]         |
| Efekt bez cvičení                                     | 19.4 % worsening<br>48.1 % unchanged<br>32.5 % improvement | worsening: beta(80.41, 334)<br>improvement: beta(67.18, 140)     | [17]         |
| Type of amputation                                    | BKA = 68,3 %<br>AKA = 31,7 %                               | BKA: beta(31.02, 14.40)                                          | [18]         |
| 30-day mortality PTA                                  | IC = 0,2 %<br>CLI = 2,8 %                                  | IC: beta(99.80, 49799)<br>CLI: beta(97.17, 3373)                 | [18]<br>[19] |
| 30-day mortality PTA/S                                | IC = 0,4 %<br>CLI = 2,8 %                                  | IC: beta(99.60, 24799)<br>CLI: beta(97.17, 3373)                 | [20]<br>[19] |
| 30-day mortality bypass                               | IC = 0,7 %<br>CLI = 3,3 %                                  | IC: beta(99.29, 14085)<br>CLI: beta(96.67, 2833)                 | [20]<br>[19] |
| 30-day mortality amputation                           | BKA = 8,9 %<br>AKA = 27,7 %                                | BKA: beta(91.01, 932)<br>AKA: beta(72.02, 188)                   | [4]<br>[4]   |
| 30-day morbidity PTA                                  | IC = 3,8 %<br>CLI = 35,8 %                                 | IC: beta(96.16, 2434)<br>CLI: beta(63.84, 114.49)                | [7]          |
| 30-day morbidity PTA/S                                | IC = 2,5 %<br>CLI = 35,8 %                                 | IC: beta(97.48, 3802)<br>CLI: beta(63.84, 114.49)                | [20]<br>[7]  |
| 30-day morbidity bypass                               | IC = 9,5 %<br>CLI = 46,3 %                                 | IC: beta(90.41, 861)<br>CLI: beta(53.24, 61.75)                  | [7]          |
| Distribution of complication for bypass according DRG | Mild:qa 43 %<br>Severe: 57 %                               | CC=2-3: beta(56.57, 74.99)                                       | [21]         |
| Reoperation possible                                  | IC = 95 %<br>CLI = 98,45 %                                 | IC: beta(4.05, 0.21)<br>CLI: beta(0.57, 0.009)                   | [18,22]      |
| DM                                                    | Male 13,34 %<br>Female 9,84 %                              | Male: beta(86.53, 562.10)<br>Female: beta(90.06, 825.20)         | [23]         |
| Hypertension                                          | Male 21,89 %<br>Female 22,26 %                             | Male: beta(183.42, 23.13)<br>Female: beta(77.52, 270.72)         | [24]         |
| Dyslipidemia                                          | 88,8 %                                                     | beta(10.31, 1.30)                                                | [23]         |
| Smoking status                                        | Male 35,2 %<br>Female 27,2 %                               | Male: beta(64.45, 118.64)<br>Female: beta(72.53, 194.12)         | [25]         |
| Technical success PTA                                 | 86.5 %                                                     | beta(15.16, 2.89)                                                | [26]         |
| Technical success PTA/S                               | 95 %                                                       | beta(10.38, 1.69)                                                | [27]         |
| Technical success Bypass                              | 100 %                                                      | Fixed                                                            | [28]         |
| Amputation in CVSP                                    | Yes = 46,32 %                                              | beta(53.22, 61.67)                                               | [10]         |

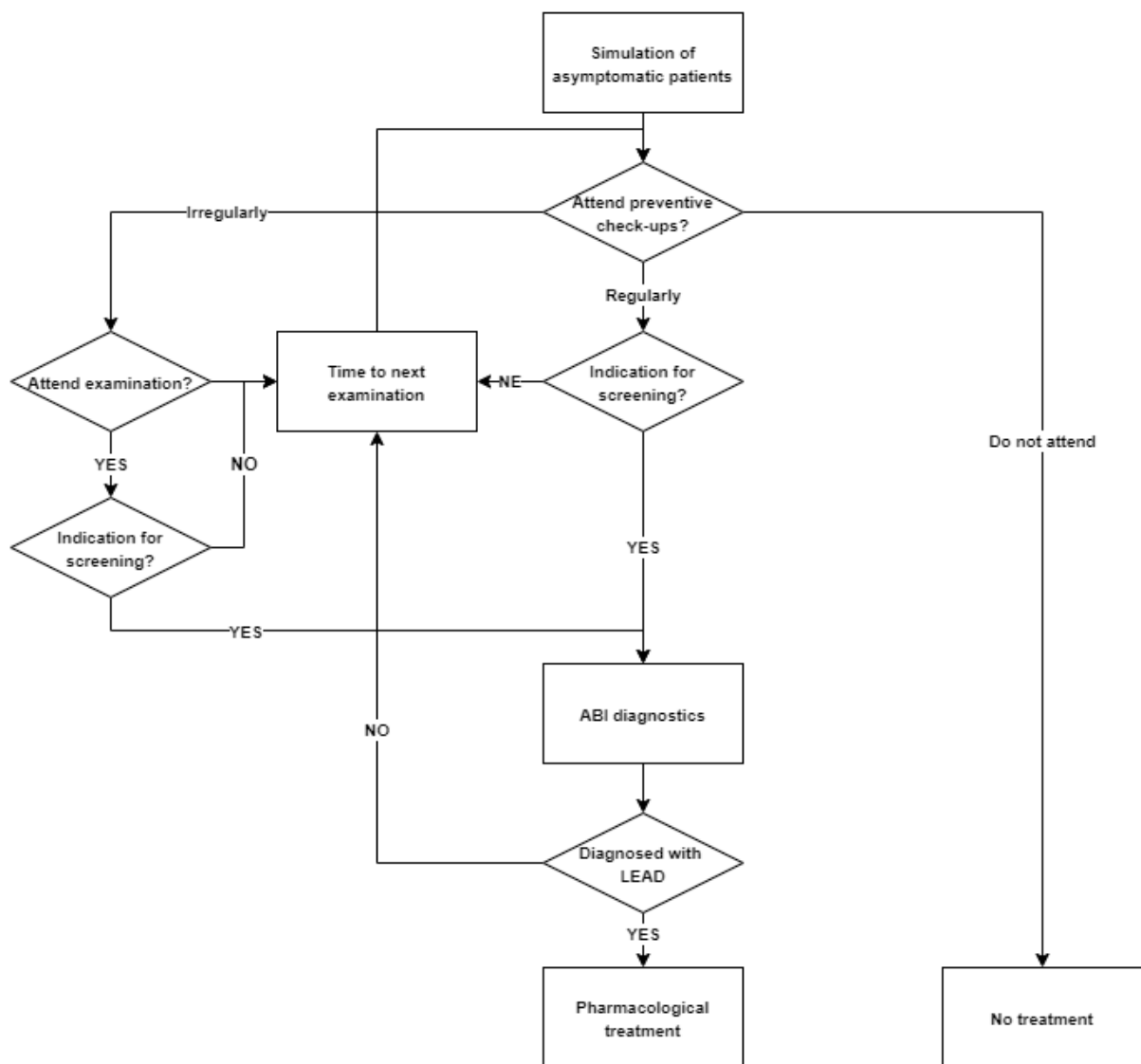
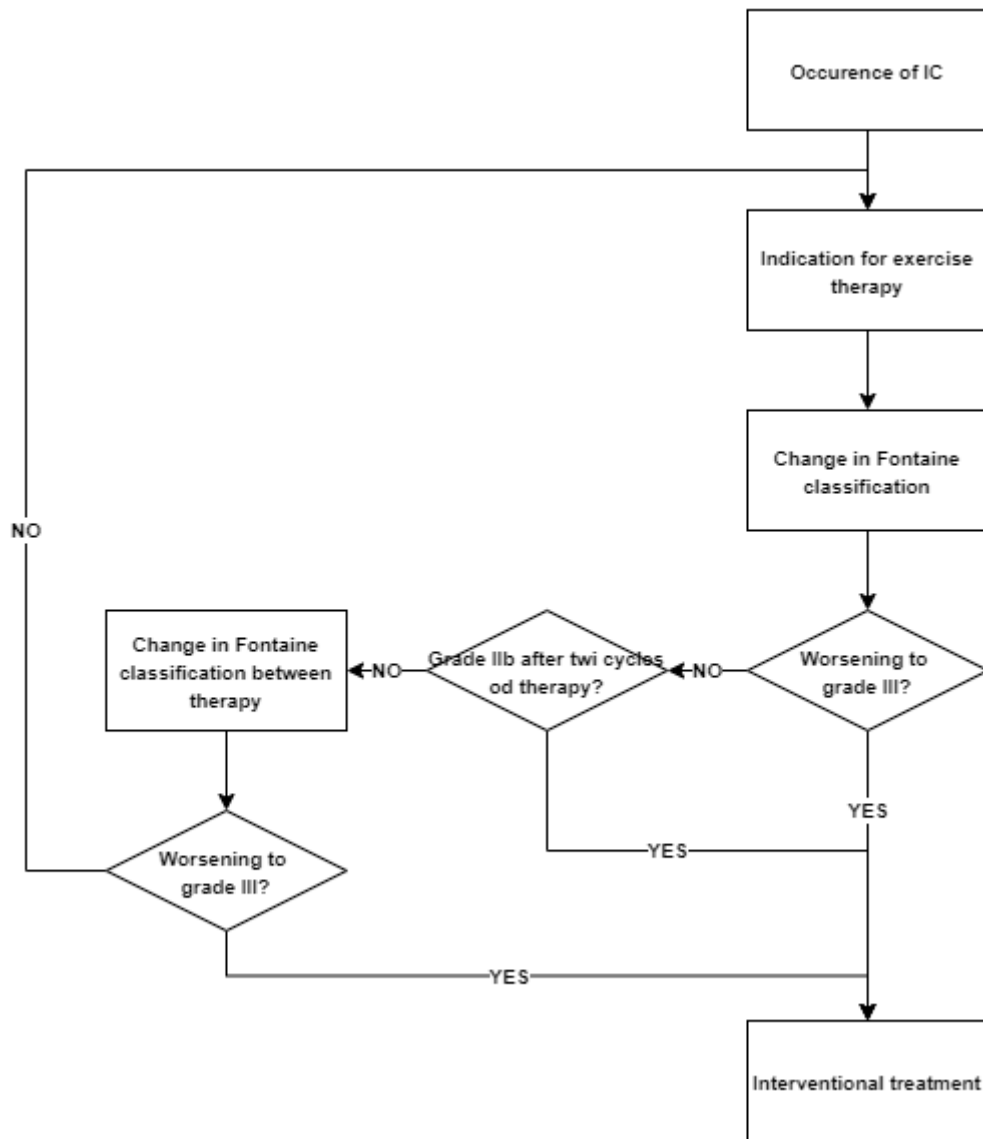
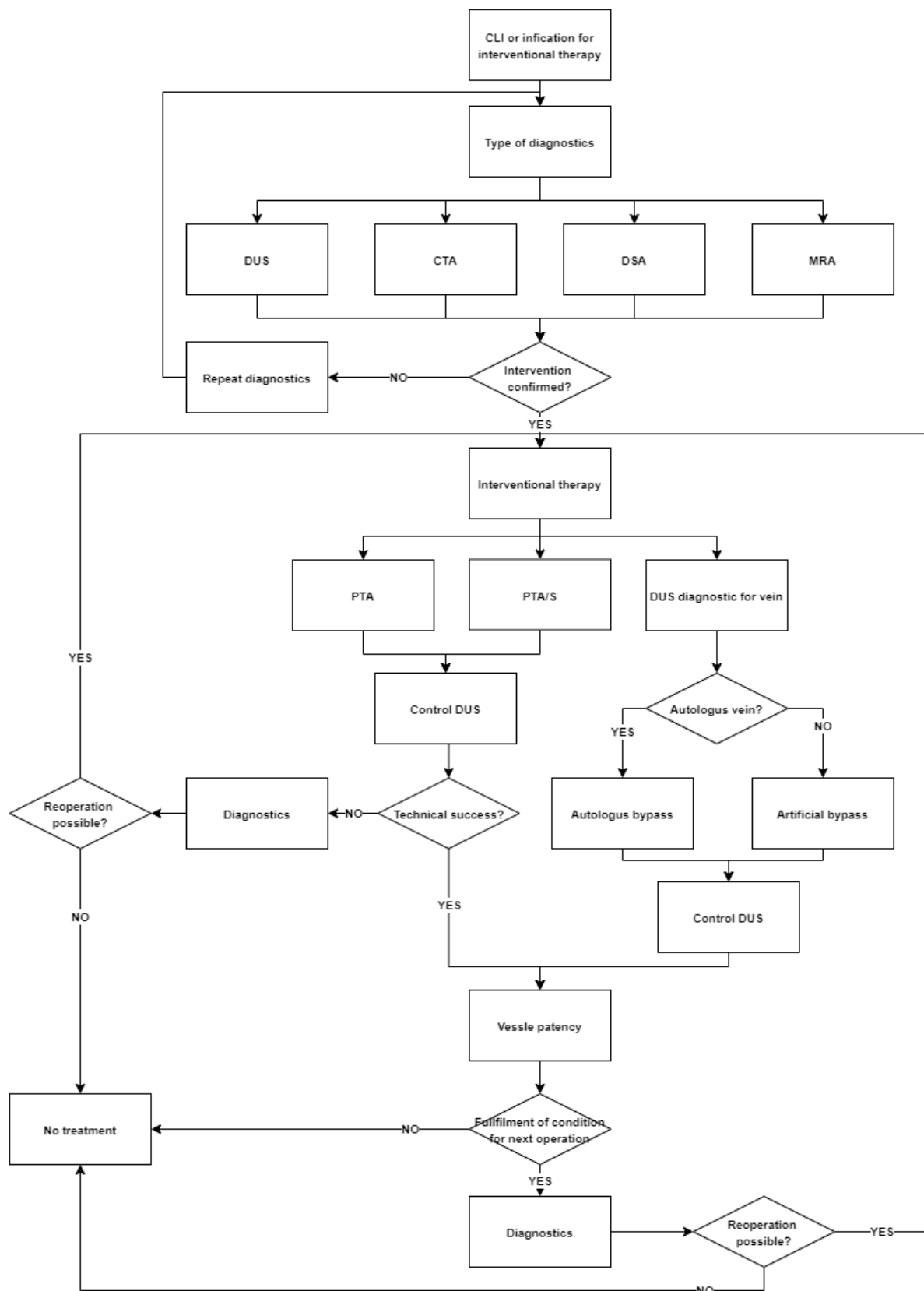


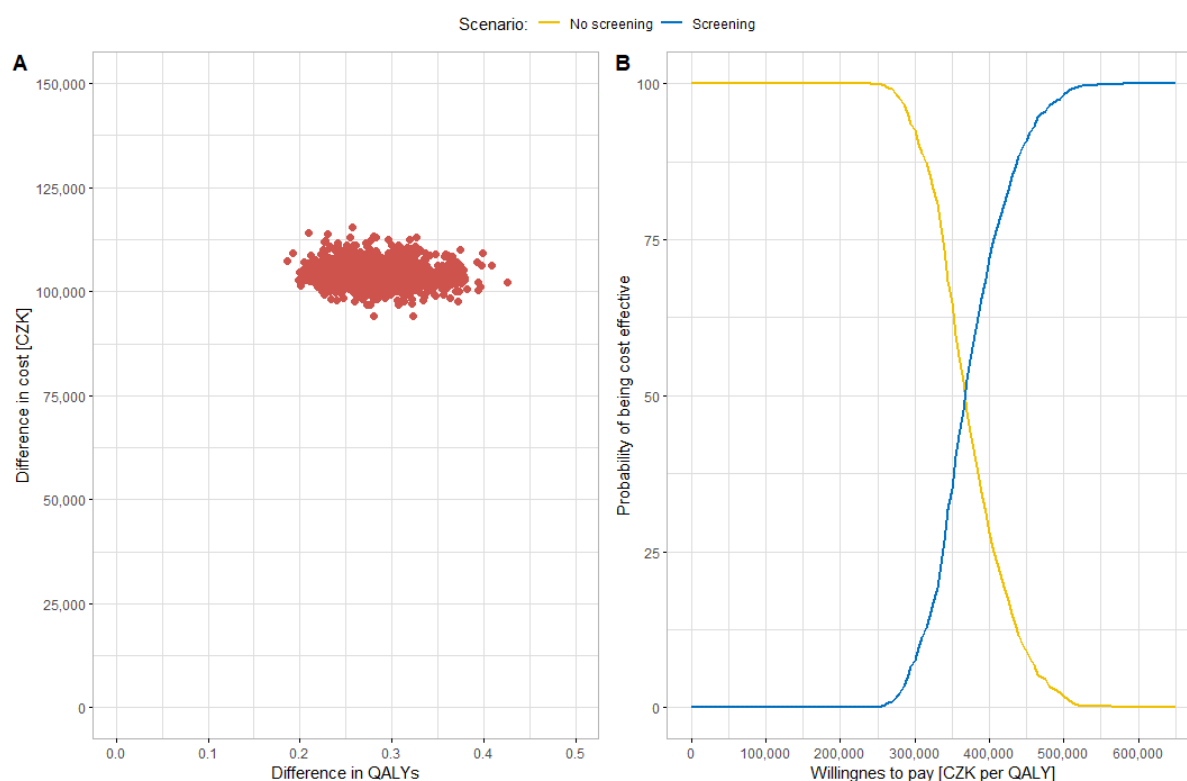
Figure S1: Model logic diagram – screening with ABI



**Figure S2:** Model logic diagram – Exercise therapy for Fontaine classification IIa and IIb



**Figure S3:** Model logic diagram – Interventional therapy decision



**Figure S4:** Cost-effectiveness scatter plane using different pseudo-random numbers; **B:** Cost-effectiveness acceptability curve for probabilistic analysis using different pseudo-random numbers.

The cost-effectiveness scatter plane in Figure S1 in Part A shows the resulting ICER values obtained using different pseudorandom numbers for each iteration. All results (red dots in figure S4) are again in the upper right quadrant, where screening is a more costly, while more effective, intervention. The ICER values were below the WTP for all iterations in this case as well, and therefore screening is a cost-effective intervention in all simulation iterations. The average mean value of the cost difference and the effect difference at a discount rate of 3% was CZK 104,304 and 0.29, respectively, and the resulting ICER value was CZK 363,642 per QALY. In part B Figure S1, it can be seen that from a WTP greater than CZK 550,000, that the ICER of all iterations are cost-effective.

## References

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