

Testing the Restrictiveness and Generalizability of Randomized Controlled Trial Population Sampling using a Failed Perioperative Beta-Blocker Trial

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Abstract

Background

The limited applicability of evidence from randomized controlled trials in real word practice is considered a potential bottleneck for evidence-based practice but rarely systematically assessed. Using our failure to recruit patients into a perioperative beta-blocker trial, we set out to analyse the restrictiveness and generalizability of trial eligibility criteria in a real-world cohort.

Methods

We included adult patients scheduled for elective major non-cardiac surgery at an academic tertiary care facility who were screened for inclusion in a planned perioperative beta-blocker RCT, which was terminated due to recruitment failure. Primary outcome was the proportion of screened patients who matched the eligibility criteria of 36 published RCTs included in a large Cochrane meta-analysis on perioperative beta-blocker therapy. The PRECIS-2 tool was used to assess the pragmatism/explanatory level of each RCT.

Results

A total of 2,241 patients were included for the assessment of trial-eligibility. Overall, eligibility proportions were low and ranged from 53% to 0%. The average proportion of patients who did match the eligibility criteria of all 36 RCTs was 6.5% (n=145, 95% confidence interval 6.3 to 6.6). There was no major criterion causing trial-ineligibility of study patients. A higher PRECIS-2 score was associated with a higher proportion of matching patients (p<0.001).

Conclusions

Trial eligibility criteria in perioperative beta-blocker therapy trials are overly restrictive and not generalizable to a real-world population.

Background

Well-conducted randomized controlled trials (RCTs) are the gold standard for medical evidence and the basis for clinical decision-making. The applicability of evidence from RCTs in real word practice, however, may be limited [1, 2] but is rarely systematically assessed. Patients enrolled in RCTs are commonly highly selected using restrictive eligibility criteria to reduce subject variability and bias [3]. However, restrictive eligibility criteria may impair a study's generalizability.

Generalizability refers to the external validity of study inferences and represents the extent to which study results can be extrapolated to different circumstances and populations. The pragmatic-explanatory continuum indicator summary 2 (PRECIS-2) tool has been developed to support the assessment of the pragmatic or explanatory level of a given RCT [4]. This is essential if trial results are to be translated

adequately into clinical practice but rarely assessed by investigators [5]. Systematic assessment of the applicability of current evidence from RCTs may allow clinicians for a better interpretation of RCT-evidence to real world practice.

The current study was driven by our inability to recruit patients into an RCT due to restrictive eligibility criteria. The RCT aimed to determine efficacy and safety of perioperative beta-blocker therapy in patients with a high risk of cardiovascular mortality. In the trial's screening phase we noticed that the potentially eligible trial population was very small (only one patient out of more than 2200 patients screened could be enrolled within a three months period). The inability to recruit patients at one of the largest tertiary care centres in Europe raised the concern that the generalizability of beta-blocker trial populations in a real-world cohort of patients may be limited.

We aimed to test this hypothesis by systematically assessing the proportion of patients of the screening cohort who matched the eligibility criteria of 36 RCTs included in a large Cochrane meta-analysis [6].

Methods

Study setting and patients

This prospective cohort study was conducted at the Department of Anaesthesia, Medical University of Vienna at the General Hospital of Vienna, Austria, one of the largest tertiary care facilities in Europe. We screened adult patients (>45 years) scheduled for elective major non-cardiac surgery for eligibility for a planned perioperative beta-blocker RCT (EudraCT number: 2015-002366-23). Eligibility criteria were chosen based on literature available by 2015. Inclusion criteria were: no history of beta-blocker treatment within 30 days prior to enrolment, increased cardiovascular risk due to coronary artery disease or a combination of ≥ 2 of the following risk factors: ≥ 70 years, congestive heart failure (NYHA \leq II), chronic renal failure, smoking history, hypertension, diabetes, lipid-lowering drug treatment or hypercholesterolemia and severe obesity (BMI $\geq 35\text{kg/m}^2$). Patients with a history of stroke, severe asthma or chronic obstructive pulmonary disease, congestive heart failure NYHA class III/ IV and patients in cardiogenic shock were excluded. A complete list of eligibility criteria is available with an additional text file (see additional file).

Primary endpoint was the proportion of screened patients matching the eligibility criteria of 36 RCTs included in a large Cochrane meta-analysis. Secondary endpoints included the relation of eligibility proportions to the sample size and the PRECIS-2 score of each RCT.

The study was approved by the Ethics Committee of the Medical University of Vienna and conducted in accordance with Helsinki declarations.

RCTs included in the Cochrane meta-analysis

A large Cochrane meta-analysis was used as reference for high-quality evidence on the effect of perioperative beta-blockers in patients undergoing surgery [6]. Two authors (MT, CK) independently extracted inclusion and exclusion criteria of each RCT (n=36, Table 1) and systematically assessed the eligibility proportions of our screening cohort.

Statistical methods

Data are presented as mean \pm standard deviation (SD) or median with the 25-75% interquartile range (IQR), as appropriate. We determined proportions of screened patients matching the eligibility criteria for each available RCT together with 95% Jeffreys intervals. To estimate the average proportion of matches across all studies we used Poisson regression with a robust cluster variance estimator to calculate 95% confidence intervals. The pragmatic-exploratory continuum PRECIS-2 tool was used to assess the pragmatic/explanatory level of each RCT. The PRECIS-2 tool gives an estimate of the pragmatism/explanatory level of a trial ranging from a minimum of 9 points (very explanatory study) to a maximum of 45 points (very pragmatically conducted study). It contains 9 domains, which address the most relevant features of a trial, and was developed to support researchers in planning trial designs and to evaluate the impact of design decisions on applicability [4, 7, 8]. The domains include eligibility criteria, recruitment, setting, organization, flexibility delivery, flexibility adherence, follow-up, primary outcome and primary analysis [8, 9].

We plotted proportions of matches versus RCT's sample sizes and their PRECIS-2 scores and used regression analysis to quantify the association. We report p-values from the Wald test. Stata Statistical Software: Release 14, StataCorp. 2017 College Station, TX: StataCorp LLC was used for data analysis and Prism 8 for OS X Version 8.3.0 to draw figures. Generally, we considered a two-sided p-value <0.05 statistically significant.

Results

A total of 2,241 patients (mean age 52years \pm 20, 54% female (n=1,215)) were included for the assessment of trial-eligibility between October 2015 and January 2016 (Table 2).

Only a small proportion of patients matched the eligibility criteria for each of the 36 RCTs ranging from 53% to 0%. 6.5% of patients (n=145) were eligible for all 36 RCTs (95% confidence interval 6.3 to 6.6, Figure 1) and $<10\%$ of patients were eligible for 31 studies. For nine published studies not a single patient from our cohort met the eligibility criteria. There was no major criterion causing trial-ineligibility of study patients.

The median PRECIS-2 score of the RCTs was 18 points (IQR 17 to 20), indicating that the majority of RCTs were quite explanatory, less pragmatic studies. Figure 2 shows the nine domains of the PRECIS-2 tool and the PRECIS-2 scores of four representative RCTs included in the Cochrane meta-analysis.

A higher PRECIS-2 score was associated with a higher proportion of matching patients ($p < 0.001$) (Figure 3).

The individual study sample sizes were not related to trial-eligibility ($p = 0.84$; Figure 4).

Discussion

This study was based on the inability to recruit patients into a perioperative beta-blocker trial at one of the largest tertiary care centres in Europe. The recruitment failure raised the concern that the generalizability of beta-blocker trial populations in a real-world cohort of patients may be limited. We analysed the restrictiveness and generalizability of the trial eligibility criteria of a large Cochrane meta-analysis on perioperative beta-blockers in patients undergoing non-cardiac surgery in a real-world cohort. The proportions of matching patients were related to the sample size and the PRECIS-2 score of each RCT to determine the patients' detail matching.

As expected, only a small number of patients matched the eligibility criteria for each of the 36 RCTs. The sample size of individual studies was not related to trial-eligibility. It may be questioned whether the clinical impact of a trial should mainly be based on its sample size, as frequently observed in scientific conversations, or additionally include a tool to rate the pragmatic and explanatory characteristics of a clinical trial design. Using the PRECIS-2 tool we found that very pragmatically conducted studies, which are designed to be externally valid, are missing in the field of perioperative beta-blocker therapy. The focus on exploratory studies is a suitable explanation for the lack of applicability of available evidence to our screening cohort. Standardized assessment and reporting of the PRECIS-2 score or equivalent tools [10, 11] by trial investigators may support readers in appraising a trial's degree of pragmatism and help clinicians to estimate the applicability of study findings to their patients in clinical practice [12]. Unfortunately, sufficient details are rarely provided. Real world evidence, however, is defined by the degree of pragmatism. Pragmatic studies are designed to represent routine practice care. Even the most effective treatment is useless if it does not work in the normal clinical setting.

Limitations: Although we identified an evidence gap for a clinically relevant topic potentially limiting the generalizability and applicability of trial results, we cannot rule out that trial results are also applicable to patients not included in the above trials. Moreover, looking at one example topic, we cannot generalize these findings to other fields, despite it is obvious that this may apply to all clinical research to some extent.

Conclusion

In conclusion we found that trial eligibility criteria in perioperative beta-blocker therapy trials are overly restrictive and not generalizable to a real-world population. Despite the availability of high-quality evidence from a large Cochrane meta-analysis, the applicability of results from perioperative beta-blocker trials may be limited. This may be partly explained by a lack of pragmatic studies in this field. Systematic

assessment and reporting of the applicability of trial results may allow clinicians for a better interpretation of data generalizability.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Medical University of Vienna and conducted in accordance with Helsinki Declarations.

Consent for publication

No individual patient data is reported that would require consent to publish from patients.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

Source of funding

No funding was received.

Authors' contributions

MT, CK, AD, PN, HH conceived and designed the study. MT, CK, DR, AD, PN collected patient data. MT, CK, AD, PN, HH analyzed data. MT, MS, NB, CS, HH interpreted data. HH did the statistical analysis. MS, NB, CS wrote the first draft of the manuscript, drew figures and tables. All authors critically revised the manuscript for important intellectual content and approved its current version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The manuscript has not been previously published and is not under consideration for publication in the same or substantially similar form in any other peer-reviewed media.

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Tables

Table 1. RCTs on non-cardiac surgery patients included in the Cochrane meta-analysis (n=36)

First author, year of publication	Inclusion criteria (n)	Exclusion criteria (n)	Enrolled patients (n/screened)	PMID
1# Apipan 2010	4	6	60/n.a.	20006165
2# Bayliff 1999	3	13	99/242	10086546
3# Burns 1988	4	2	86/n.a.	2972306
4# Coleman 1980	5	0	42/n.a.	7004251
5# Cucchiara 1986	3	15	74/n.a.	2877599
6# Juul 2006	4	6	921/2066	16793810
7# Gibson 1988	2	11	40/n.a.	2904310
8# Gupta 2011	4	8	66/n.a.	21712869
9# Inada 1989	3	7	40/n.a.	2697239
10# Jakobsen 1992	4	0	40/n.a.	1600972
11# Jakobsen 1997	3	0	35/n.a.	9422300
12# Kawaguchi 2010	5	13	56/n.a.	20118792
13# Lai 2006	2	0	60/n.a.	16687084
14# Lee 2010	4	8	60/n.a.	20877702
15# Liu 1986	4	6	30/n.a.	3768764
16# Liu 2006	2	0	30/n.a.	16706126
17# Magnusson 1986	4	4	30/309	3511930
18# Mangano 1996	6	0	200/n.a.	8929262
19# Marwick 2009	2	6	400/n.a.	19332211
20# Miller 1990	6	8	45/n.a.	n.a.
21# Miller 1991	6	9	548/n.a.	1683818
22# Moon 2011	4	8	54/n.a.	22117987
23# Neary 2006	6	7	38/2351	16764198
24# Oxorn 1990	4	11	48/n.a.	1968784
25# Brady 2005	2	8	103/151	15874923
26# Devereaux 2008	6	10	8351/n.a.	18479744

27# Raby 1999	3	2	26/n.a.	10071990
28# Sandler 1990	4	14	45/n.a.	n.a.
29# Shukla 2010	2	7	60/n.a.	n.a.
30# Stone 1988	3	7	128/n.a.	2895596
31# Suttner 2009	2	6	75/n.a.	19336536
32# Wallace 1998	5	3	200/n.a.	9447850
33# Whitehead 1980	2	0	60/n.a.	7004258
34# Yang 2006	2	7	496/n.a.	17070177
35# Yang 2008	2	0	102/n.a.	18953854
36# Zaugg 1999	2	8	63/n.a.	10598610

Detailed study characteristics are available at [13].

n.a., not available.

Table 2. Baseline characteristics of the study cohort assessed for trial-eligibility

	N	
Age (years)	2241	52 (\pm 20)
Sex (female)	2241	1215 (54)
Height (cm)	1826	169 (\pm 12)
Weight (kg)	1975	76 (\pm 21)
BMI (kg/m ²)	1826	27 (\pm 6)

Data are mean (\pm SD) or n (%).

Figures

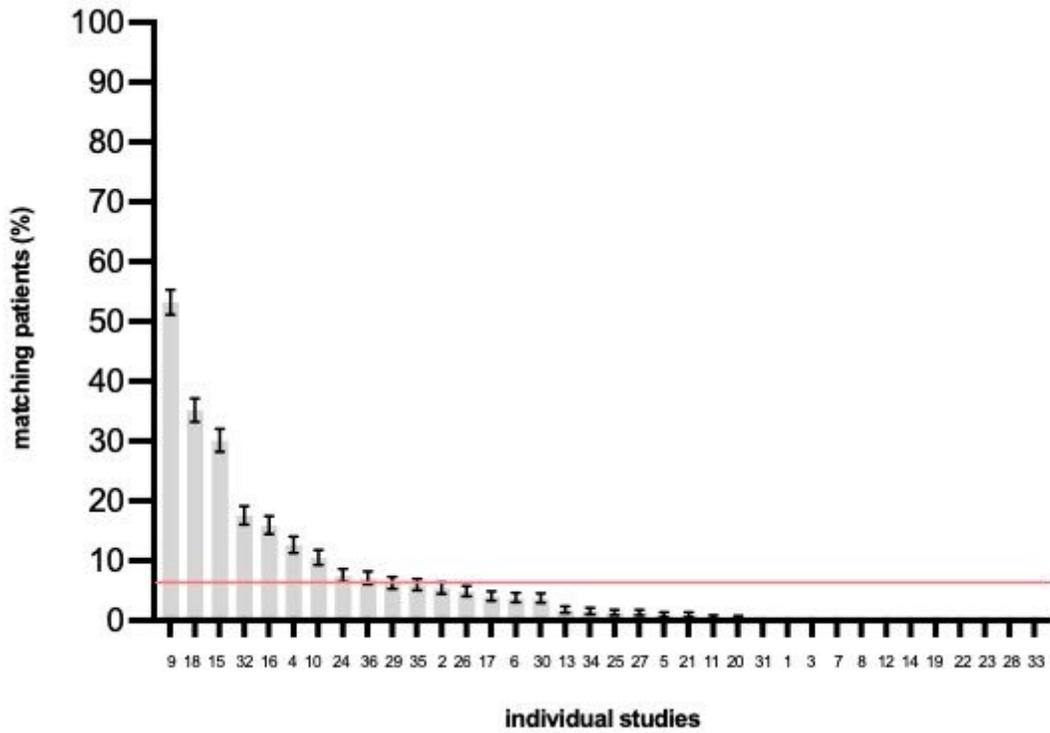


Figure 2

Proportions (with 95% Jeffreys intervals) of screened patients matching the eligibility criteria for each available RCT. The average proportion of matching patients was 6.5% (95% confidence interval 6.3 to 6.6) (red horizontal line). X-axis: individual RCTs in descending order of matches. Y-axis: proportion of matching patients (%).

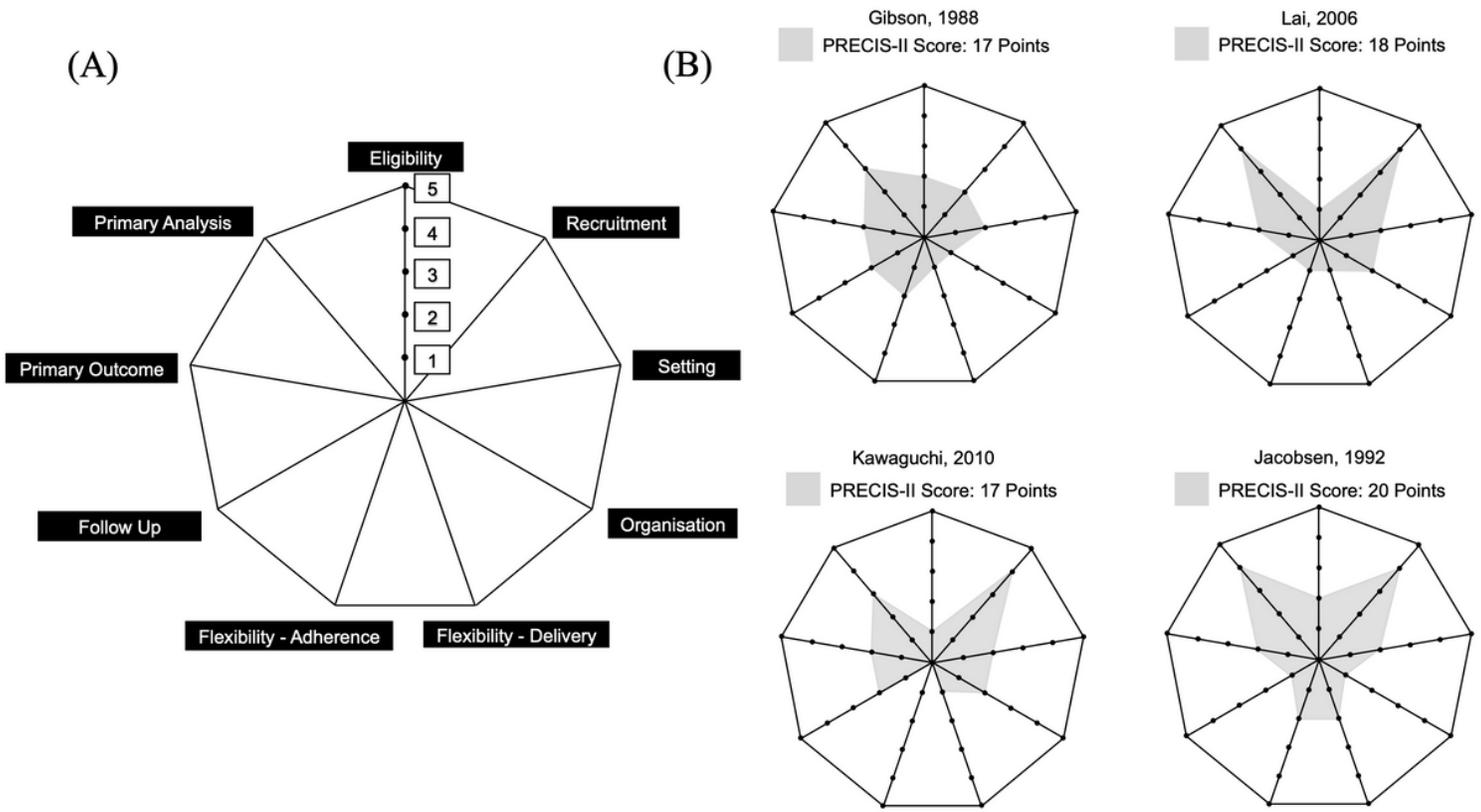


Figure 3

PRECIS-2 scores of four representative studies included in the Cochrane meta-analysis. (A) The nine PRECIS-2 domains represent the explanatory/pragmatic level of a trial on the pragmatic to explanatory continuum, ranging from a minimum of 9 points (very explanatory level) to a maximum of 45 points (very pragmatic level) [8, 9]. (B) PRECIS-2 scores of four RCTs, exemplifying the explanatory, less pragmatic design of studies included in the Cochrane meta-analysis. The median PRECIS-2 score of all 36 RCTs was 18 points (IQR 17 to 20).

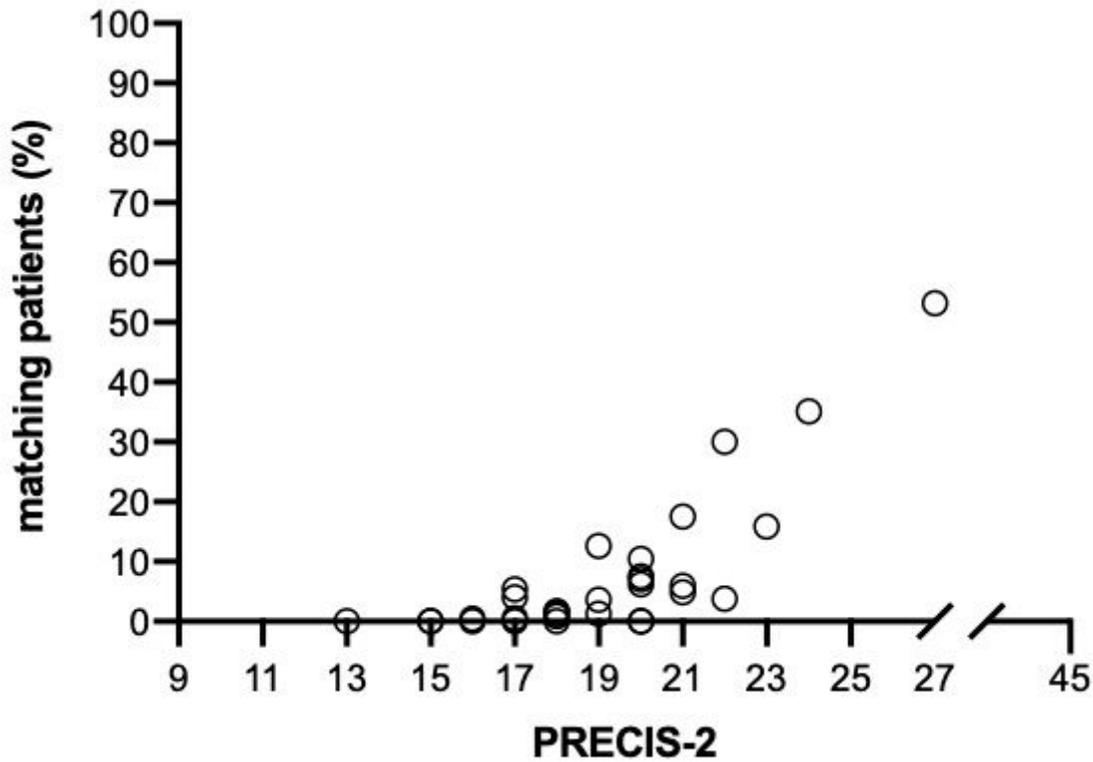


Figure 5

Proportions of matching patients versus PRECIS-2 scores of RCT's. A higher PRECIS-2 score was associated with a higher proportion of matching patients ($p < 0.001$). X-axis: PRECIS-2 scores of RCTs. Y-axis: proportion of matching patients (%).

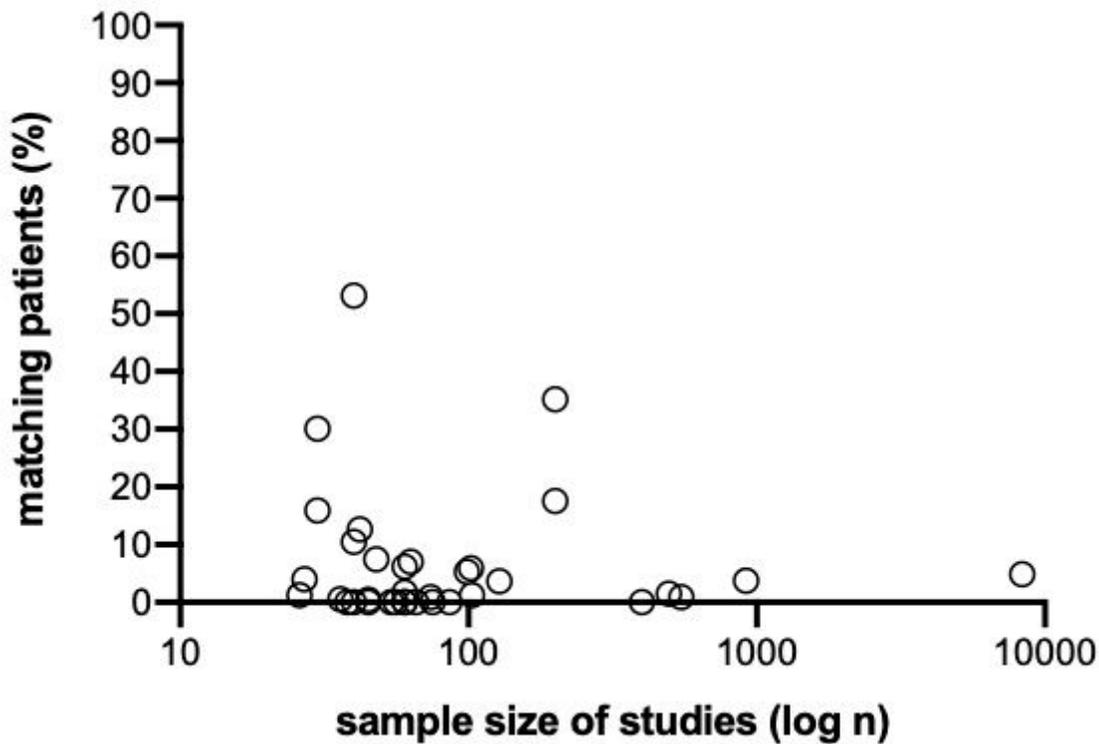


Figure 8

Eligibility proportions versus sample size of RCT's. Individual study sample sizes were not related to trial-eligibility ($p=0.84$). X-axis: sample size of RCTs on a logarithmic scale. Y-axis: proportion of matching patients (%).