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**Comparative efficacy and safety of treatments for secondary Raynaud's phenomenon:
systematic review and network meta-analysis of randomized trials**

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Abstract

Background: Several pharmacological treatments are currently available for secondary Raynaud's phenomenon (RP) but there is uncertainty regarding the best options. We aimed to assess and compare the benefits and harms of treatments available for secondary RP.

Method: We searched for systematic reviews published in MEDLINE and the Cochrane Database of Systematic Reviews up to January 2017, for randomized controlled trials (RCTs) from inception to September 2019 in MEDLINE, Embase and clinicaltrials.gov. We obtained individual patient data of one unpublished RCT. We included double-blind RCTs comparing two or more pharmacological treatments or placebo in patients with secondary RP. Three researchers independently performed data extraction. Efficacy outcomes included severity, daily frequency and cumulative duration of RP attacks. We also examined tolerability and acceptability. Pairwise meta-analyses and Bayesian random-effects network meta-analyses were used to synthesize data (CRD42017057518).

Findings: We selected 58 RCTs (3794 patients, 93% with secondary RP). Phosphodiesterase-5 inhibitors (PDE5i) were more effective than placebo on the three efficacy outcomes, with low-to-moderate level of evidence. Calcium channel blockers (CCB) were superior to placebo for frequency and severity of attacks, with low level of evidence. Selective serotonin reuptake inhibitor and oral prostacyclin-receptor agonists were superior to placebo for severity of attacks, with low level of evidence. PDE5i and CCB were less well tolerated than placebo.

Interpretation: PDE5i and CCBs are the most effective pharmacological options, but their efficacy is moderate and the level of evidence is low. Moreover, current evidence does not support the use of any other drug in secondary RP.

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Research in context

Evidence before this study

Raynaud's phenomenon can be secondary to connective tissue diseases, especially systemic sclerosis (SSc), where it represents the most frequent and earliest sign of vasculopathy. The updated European League against Rheumatism (EULAR) guidelines recommend oral calcium channel blockers (CCBs) or phosphodiesterase type 5 inhibitors (PDE5i) as first-line therapy for systemic sclerosis (SSc)-related RP. Yet, whether one treatment is superior over the other is unknown, owing to the lack of direct/indirect comparisons. Moreover, other drugs have been proposed, such as endothelin receptor antagonists, prostacyclin analogs, or non-prostanoid IP-receptor agonists, but the place of these options within the treatment strategy remains unclear. We searched Pubmed for meta-analyses on the treatment of secondary RP published between database inception and August 8, 2019. Using the search terms "Raynaud's phenomenon" AND ("meta-analysis" or "network meta-analysis"), we found several meta-analyses have assessed the efficacy of the different treatments used in SSc-related RP, especially CCBs and PDE5i. However, to our knowledge, none has combined direct and indirect comparisons through a network meta-analysis approach, to assess and compare the efficacy and tolerability of all available treatments for secondary RP. We thus conducted a network meta-analysis combining direct and indirect comparisons to assess and compare the efficacy and tolerability of all available treatments for secondary RP.

Added value of this study

This network meta-analysis includes 58 RCTs and 15 classes of drugs. We also had access to the full dataset of the largest, unpublished trial on a PDE5i in RP (NCT01090492),

which we have re-analyzed and included in our meta-analysis. Overall, 3794 patients were included among whom 93% had secondary RP, and 84% were women. Our results show that both CCBs and PDE5i are both superior to placebo for most outcomes, with similar, yet moderate, treatment effect; and with low-to-moderate level of evidence. For all other oral treatments, the efficacy is not consistent across outcomes, and/or the level of evidence is low to very low.

Implications of all the available evidence

The two treatments recommended as first-line therapy (i.e. CCBs and PDE5i) are both superior to placebo but the treatment effect is below the minimal clinically important difference. For all other drugs, our results highlight that the available evidence is too weak to support any recommendation. Our results thus challenge the clinical relevance of these treatments, emphasizing the pressing need for the development of new therapeutic strategies, including non-pharmacological interventions.

Introduction

Raynaud's phenomenon (RP) is the occurrence of paroxysmal episodes of a localized deficiency in cutaneous perfusion, most often in response to cold or emotional stress.¹ It affects 3 to 5% of the general population, with substantial geographic variations.² RP can be primary (idiopathic) or secondary to a connective tissue disease, especially systemic sclerosis (SSc). In the latter case, RP is present in up to 95% of patients,² and is the earliest sign of the vasculopathy. SSc-related microvascular impairment is associated with significant morbidity (e.g. ulcers and gangrene) and functional disability.³

Recently, the updated European League against Rheumatism (EULAR) recommendations advised oral calcium channel blockers (CCBs) as first-line therapy for SSc-related RP, and phosphodiesterase type 5 inhibitors (PDE5i) for patients with SSc with severe RP and/or those who do not respond to CCBs.⁴ CCBs and PDE5i have both been shown to have moderate efficacy in reducing the frequency and the severity of RP in patients with SSc.^{5,6} Intravenous iloprost also reduces the frequency and severity of attacks, and is recommended for severe RP secondary to SSc when oral therapies (including CCBs and PDE5i) have failed.^{4,7} Other treatments such as fluoxetine have been tested in patients with SSc-related RP. However, whether a treatment is superior to another remains unknown. Indeed, very few randomized controlled trials (RCTs) have directly compared these different treatments. In addition, the place of newer agents such as endothelin receptor antagonists, oral prostacyclin analogs / non-prostanoid IP-receptor agonists among treatment options remains unclear.^{8,9}

In order to compare the efficacy and safety of all pharmacological treatments that have been tested in SSc-related RP, we performed a systematic review of RCTs with network meta-analyses.

Methods

This systematic review complies with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement guidelines.^{10,11} The protocol and systematic search strategy are available online (PROSPERO registry, CRD42017057518, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017057518). On publication of this article, the full dataset will be made freely available online through the Open Science Framework.

Literature Searches

We searched for narrative or expert reviews, systematic reviews, and meta-analyses indexed in MEDLINE and/or the Cochrane Database of Systematic Reviews on treatments for secondary RP or for SSc-related digital ulcers, published from inception to January 2017. We screened all trials included in the reviews we had found. In addition, we searched for RCTs published from inception to September 2019 in MEDLINE, Embase, the clinicaltrials.gov registry, and the AdisInsight database. Finally, we asked key opinion leaders in the field. No language restriction was applied. Details of the search strategy are available as supplementary material (appendix p3).

Study selection and data extraction

Double-blind randomized controlled trials were eligible if they (1) had a parallel or crossover design, (2) included patients with secondary RP, (3) compared two or more pharmacological treatments or a treatment versus placebo, (4) reported at least one outcome of interest. A crossover trial was eligible only if there was a washout period of one week or more. Trials including both primary and secondary RP patients were eligible if outcome data were reported separately for secondary RP patients, or if more than 50% of patients had secondary RP.

All reviews we found were screened independently by two investigators for relevance and all RCTs identified. Titles abstracts, and subsequently the full-text of all RCTs (from reviews and our de novo search) were evaluated independently for eligibility by three investigators. Disagreements were solved by consensus.

The following data were extracted for each selected RCT: RCT characteristics (year of publication, country(ies) and latitude where the study was conducted (latitude was not considered for multi-country studies), funding source, follow-up duration, study design, primary outcome); participant characteristics (age, sex ratio, etiology of RP, percentage of smokers, disease duration, baseline frequency, severity and mean duration of RP attacks); and details of the intervention (add-on therapy, dosage, treatment duration, therapeutic class).

We found unpublished results for two RCTs in clinicaltrials.gov. For one RCT of a PDE5 inhibitor, posted results pertain to the *per protocol* population. We obtained access to the individual patient data through the sponsor (www.pfizer.com/science/clinical_trials/trial_data_and_results/data_requests) and we re-analyzed the intention-to-treat population (appendix p5).

Outcomes

We pre-specified the following efficacy outcomes: 1. Mean daily frequency of RP attacks. 2. Mean severity of RP attacks measured using the Raynaud's Condition Score (RCS), a visual analog scale (VAS) or any other severity score. When several measures were used we prioritized RCS because it is a more comprehensive measure of RP severity, taking into account disability and impact on quality of life.^{12,13} If RCS was not reported, other severity scores were extracted and converted into the 10-point scale used for the RCS. 3. Mean daily cumulative duration of attacks.

Tolerability was defined as the proportion of patients who reported a serious adverse event or dropped out early because of adverse events. Finally, we assessed acceptability, defined as all-cause discontinuation, which encompasses both efficacy and tolerability.

Data synthesis

All pharmacological treatments were grouped into 15 therapeutic classes: α -adrenoceptor antagonists; anti-oxidants; anti-interleukin-6 (IL6); angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARB); Botulinum Toxin type A (BTA); CCBs; endothelin receptor antagonist (ERA); PDE5i; phosphodiesterase-3 inhibitors (PDE3i); intravenous prostacyclin analogs (IV PGI₂); oral prostacyclin analogs/non-prostanoid IP-receptor agonists (Oral IP agonists); selective serotonin reuptake inhibitor (SSRI); soluble Guanylate Cyclase stimulators (SGCs); topical nitric oxide donor (Topical NO); and thromboxane synthase inhibitors (TSI). When a study reported several arms with different doses of the same drug, these groups were merged.

We measured treatment effect using the mean difference (MD) for efficacy outcomes and incidence rate ratios (IRR) for safety outcomes. We first conducted pairwise meta-analyses of placebo controlled RCTs to estimate the effect of each drug class versus placebo. We then performed network meta-analyses to summarize direct and indirect evidence. We used a Bayesian approach using Markov Chain Monte Carlo simulation with non-informative prior distributions. A normal likelihood was used for continuous outcomes and the Poisson distribution with a logarithm link function for safety outcomes. Given the heterogeneity in RCTs and in-patient characteristics included in the meta-analyses we used random-effect models to draw results (appendix p 6).

The I^2 statistic was used to assess heterogeneity between trials in the pairwise meta-analysis using the Higgins-Thompson categorizations (low heterogeneity 25%, moderate

50%, high 75%)¹⁴. Publication bias was investigated by constructing funnel plots in a pairwise meta-analysis when $k > 10$ studies, and by using Egger's regression test to assess for funnel plot asymmetry. In addition, the influence of a small-study effect was investigated using a network meta-regression model according to sample size.

Treatment classes were ranked according to the lower boundary of the mean rank 95% Credibility Interval (CrI), as previously described.¹⁵

We performed a trial sequential network meta-analysis to assess if the amount of information to date was sufficient to support the conclusions.¹⁶

All statistical analyses were conducted using R version 3.3.4 (R Project for Statistical Computing) with R packages (gemtc, sequentialnma, meta, netmeta and rjags), and JAGS version 3.4.0.¹⁶⁻²¹

More details on statistical analysis are available on supplementary material (appendix p6).

Quality of Evidence assessment

Quality assessment was performed by two reviewers, independently. Discrepancies were discussed to reach a consensus. We judged the quality of each study using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs. RCTs were classified as having low risk of bias if none of the Cochrane domain-specific bias were rated as high risk of bias and three or less were rated as unclear risk; moderate if only one or none were rated as high risk of bias but four or more were rated as having an unclear risk, and all other cases were considered to have a high risk of bias (all remaining situations).²²

We assessed the quality of the comparison between each therapeutic class and placebo in the network using the Grading of Recommendation Assessment, Development and

Evaluation (GRADE) recommendations for network meta-analysis (appendix p 7), and the Confidence in Network Meta-Analysis Software (CINeMA) for network risk of bias.²³ Finally, we rated the quality of evidence for each therapeutic class as very low, low, moderate or high.

Heterogeneity and network consistency

Most of the comparisons showed little or no heterogeneity in pairwise meta-analyses. A moderate heterogeneity was found for 3 out of the 51 comparisons versus placebo (α -adrenoceptor antagonists and oral IP agonist for the frequency outcome; and IV PGI₂ analogs for severity). To assess the consistency of the 5 network meta-analyses we compared the model fitting statistics between consistent and inconsistent models. A consistent model was adopted for all outcomes (appendix p7). We also performed a node-splitting analysis to test for inconsistency and heterogeneity (appendix p8-11)²⁴.

Sensitivity analyses and subgroup meta-regressions

We conducted three pre-planned sensitivity analyses: i) studies including only patients with secondary RP; ii) studies assessing severity only with the RCS; iii) the exclusion of studies with a high risk of bias.

Meta-regressions were performed to assess the potential influence of pre-determined variables of interest: i) latitude (given the strong influence of climate on RP prevalence and severity); ii) age; iii) sex; iv) duration of the disease; v) follow-up period; vi) efficacy outcomes at baseline; vii) study sample size; viii) study design (parallel vs crossover). Two unplanned additional meta-regressions were conducted to assess the influence of add-on status, and smoking.

Role of the funding source

There was no funding source for this study

Results

The search yielded 58 double-blind RCTs^{8,9,25-76}, of which 35 were parallel and 25 were crossover studies, found in 78 reviews or from our de novo search (Figure 1; appendix p12-17). The studies had been published between 1982 and 2019, and compared 15 classes of drug, often against placebo (appendix p18). Two trials were unpublished: for one the results were available on clinicaltrials.gov (NCT00822354). The other was the largest clinical trial testing the efficacy of a PDE5 inhibitor in secondary RP (NCT01090492, n=243 patients), for which we re-analysed the individual patient data.

Study sample sizes ranged from 8 to 289 patients. The main characteristics of included studies are presented in the appendix, p. 19-24. Overall, 3794 patients were included among whom 93% had secondary RP and 84% were women. The median study follow-up was 6 weeks (Q1-Q3 4–12). Among efficacy outcomes, the frequency, severity and duration of RP attacks were available for 41 (70.1%) RCTs and 2193 (57.8%) patients, 45 (77.6%) RCTs and 3503 (92.3%) patients, and 23 (39.7%) RCTs and 1416 (37.3%) patients, respectively. Tolerability and acceptability were reported in 55 (94.8%) RCTs and 3535 (93.2%) patients and 56 (96.4%) RCTs and 3698 (97.5%) patients, respectively (appendix p25-28). The baseline characteristics of patients included in trials by drug class are summarized in Table 1.

Results of pairwise meta-analyses of each drug class versus placebo are presented in Appendix Table 6 (appendix p26).

Graphical representations of the network of comparisons for each efficacy outcome are shown in Figure 2. There was at least one placebo-controlled trial for all drug classes, except

for SSRI. Global heterogeneity was low to moderate for all outcomes, ranging from 0 to 41 % (appendix p 6). The results show that direct and indirect evidence is consistent for all outcomes.

Forest plots of all comparisons vs. placebo are presented in Figure 3. PDE5i were the only class statistically more effective than placebo for all three efficacy outcomes: -0.34 (-0.66, -0.03) for severity, -0.36 (-0.69, -0.04) for the frequency and -3.42 (-6.62, -0.29) for the duration of attacks, with a low to moderate levels of evidence. CCBs were also superior to placebo for the severity [-0.84 (-1.25, -0.45)] and the frequency [-0.35 (-0.67, -0.02)] of attacks, with a low level of evidence. Besides CCBs and PDE5i, two classes were superior to placebo for the severity of RP: SSRI [-1.54 (-2.68, -0.41)], and oral IP agonists [-0.48 (-0.80, -0.16)]; but the level of evidence was low to very low.

PDE5i ranked best in reducing the frequency and duration of attacks based on the upper limit of the 95% CrI for the mean rank, while CCBs ranked best for severity. However, considering the breadth of the mean rank 95% CrI, those results do not seem to be clinically meaningful.

PDE5i and oral IP agonists had lower acceptability and tolerability than placebo; CCBs also showed significantly worse tolerability than placebo.

League tables with all comparisons from the network meta-analyses, for efficacy and safety outcomes, are presented in the appendix (appendix p 32-36).

The risk-benefit profile of the different drug classes as well as the level of evidence are summarized in Figure 4.

The overall risk of bias was judged to be low, high or unclear in 22 (37.9%), 10 (17.2%) and 26 (44.8%) RCTs, respectively. High or unclear Cochrane domain-specific bias

was lowest for blinding (8.6%), and highest for incomplete outcome data (50%) (appendix p 37). The risk of bias for each RCT is summarized in Figure 5. More than half of the studies were supported by one or more pharmaceutical companies. Risk of bias for pairwise comparisons with placebo for efficacy outcomes are shown in appendix p 38-40. Network plots for the three efficacy outcomes show the risk of bias for all direct comparisons (appendix p 41-44). The highest levels of evidence were found for PDE5i, whereas studies on SSRI, anti-oxidants, α -adrenoceptor antagonists, and ACEi/ARB provided very low levels of evidence (appendix p 44-52).

Meta-regressions were consistent for the effect magnitude and direction for all efficacy outcomes (appendix p 53). Age was significantly correlated with a reduction in drug efficacy for severity and, while not significant, also tended to affect drug efficacy for other outcomes. Sponsorship of studies by commercial companies, treatment used as add-on therapy, smoking, and sample size did not have any significant impact on the results. Latitude, sex, disease duration, and follow-up period were not significantly associated with variations in effect size. Meta-regressions on baseline characteristics were not significant, however, they consistently showed a trend towards a positive correlation with efficacy for all three outcomes. As a *post hoc* sensitivity analyses, we adjusted the results on baseline values (appendix p 54-56). Notably, these showed that PDE5i and CCBs did not significantly lower the frequency of RP in patients with less than 5 attacks per day.

Results of pre-planned subgroup and sensitivity analyses are presented in appendix p 58-60. The most significant changes concern CCBs, for which the effect size is smaller when restricting analyses to secondary RP patients only, or to high quality trials. We added an unplanned sensitivity analysis to consider IV iloprost and other IV PGI₂ analogs separately (appendix p 60). However, it does not modify the main results. Trial sequential analyses

revealed that the optimal information size was reached only by CCB for severity; and the results remained significant after a threshold adjustment for frequency. Results for PDE5i remained significant after threshold adjustment for all three outcomes (appendix p 61).

Discussion

This systematic review and network meta-analyses provide a comprehensive synthesis of currently available data from randomized studies of pharmacological treatments for secondary Raynaud's phenomenon. CCBs and PDE5i both significantly decrease the frequency and severity of attacks in secondary RP patients, with comparable, but small effect sizes. It should be noted that PDE5i were the only drugs to significantly decrease the cumulative daily duration of RP attacks, which is in line with previous observations.^{6,77} Moreover, the level of evidence is stronger for PDE5i than CCBs. On the other hand, CCBs were better accepted than PDE5i.

Although these results support current recommendations about the use of CCB or PDE5i as first line treatments for secondary RP,⁴ they challenge their clinical relevance. Indeed, the improvement in mean severity on a 10-point scale was only -0.84 (-1.25, -0.45) for CCBs, and -0.34 (-0.66, -0.03) for PDE5i; in both cases this is far below the minimal clinically important difference for RCS in this population, which is considered to be about 1.5 points.¹² In addition, results from our meta-regressions suggest that patients with less than five attacks per day, or with severity below four on a 10-point scale, are not expected to have a significant benefit from these treatments. However, credibility intervals were large indicating the need for more data.

There was no evidence that IV PGI₂ analogs are superior to placebo, whether IV iloprost is considered separately or with other analogs. This result disagrees with a previous

meta-analysis that found, for iloprost versus placebo, a pooled mean difference of -0.69 (-1.12, -0.26) for the severity score and no significant effect on other outcomes.⁷ Since the same studies were included in both meta-analyses, this discrepancy may be explained by differences in the methodological approach: we used post-treatment data, and used baseline measurements as a covariate, while the meta-analysis by Pope et al. used changes from baseline, which is no longer recommended⁷⁸. The network approach also provides additional information, which may influence the final results.

Other drug classes, such as SSRI, oral IP agonists and anti-oxidants showed superiority over placebo in terms of reducing the severity of RP but the level of evidence was low or very low, and this outcome was less robust, as discussed below. Heterogeneity in their effect on the different outcomes raises concern about their actual efficacy. Current evidence is insufficient to support the use of fluoxetine, which was added as a grade C recommendation in the 2017 update⁴.

Overall, pharmacological interventions had only a modest effect (PDE5i, CCBs) or failed to show any efficacy. Several recent trials have shown a strong placebo effect on frequency, severity and duration of attacks that may mitigate active treatment efficacy.^{8,9,41} Whether this placebo effect is related to a physiological improvement in cold tolerance or to behavioural changes during the trial remains to be further explored.⁷⁹ Moreover, several projects are ongoing to develop more robust outcomes in the field.⁸⁰⁻⁸²

Some of the patients' characteristics may also be important determinants of treatment efficacy. Surprisingly, age was the only significant modifier of treatment effect in this meta-analysis. Indeed, no significant effect of CCB or PDE5i was found above the age of 40. This may be related to disease duration with progressive structural vascular damage. Disease

duration did not significantly affect our results, probably due to lack of power. This deserves to be further explored through individual patient meta-analyses.

Indeed, several patient characteristics may influence treatment effects, but they are difficult to identify in the context of a rare condition. This is particularly true when dealing with secondary RP considering the large within-patient and between-patient variability. To address this issue, we recently proposed to evaluate treatments in RP using an individualized approach, by conducting N-of-1 trials.⁶⁰ The strength of this approach is to estimate the treatment efficacy and safety for each patient, and to consider the individual patient's preference.

Our systematic review has several limitations. Many comparisons were judged as being of low or very low quality according to the GRADE framework, which restricts the validity of our results. Indeed, several small trials with poor methodology were the unique representatives in the network of drug classes such as thromboxane synthase inhibitors, selective serotonin reuptake inhibitor or anti-oxidants.

Secondly, there was a large degree of uncertainty, with only a small number of trials for many of the comparisons, and the available evidence may be insufficient to draw firm conclusions. In addition, our analyses combine intent-to-treat and per protocol data; in a few cases, we were not able to clearly distinguish the number of patients included in the final analysis from the number of patients initially randomized, and lowered the quality of these trials. Finally, our findings are limited by a potential bias due to selective reporting. Indeed, 63 trials were excluded because their outcomes of interest could not be included in the final analysis (e.g. when results were expressed as dichotomous variables).

Our findings suggest that several trials should be planned to explore areas of uncertainty in the field: selective serotonin reuptake inhibitor versus placebo, endothelin receptor antagonists versus placebo using the frequency of attacks as efficacy outcome, or recommended CCBs versus PDE5i (e.g. nifedipine versus sildenafil). Although the impetus for conducting new trials involving CCBs or PDE5i versus placebo may be weak given the information already available on these drugs (i.e. pharmaceutical companies are unlikely to sponsor such clinical trials), and the difficulties inherent in running clinical trials in RP, they are needed for several reasons. While PDE5i rank as the best treatment for two out of three outcomes, and have the highest level of evidence, they are not approved in RP in several countries such as United States, France or United Kingdom. Moreover, it is worth noting that CCB trials have approximately 25% of primary RP, and sensitivity analysis restricting data to trials including only patients with secondary RP may substantially influence the results. It is possible that CCBs are actually inferior to PDE5i, but this needs to be addressed in a head-to-head trial. This network meta-analysis may serve as a basis for planning such trial in the future, through conditional trial design methods.⁸³

A strong heterogeneity among the scales and scores used to assess the severity of attacks (from a severity score graded 0-3 to the RCS, and SHAQ or VAS for pain) limits the validity and extrapolation of our results. Disturbingly, in the subgroup meta-analysis restricted to trials that used RCS as outcome, no drug class had proven efficacy over placebo.

Finally, clinical efficacy and safety were evaluated by drug class, rather than by individual drugs. Although this substantially increased the power to detect treatment effects, this could be an issue, particularly for those classes in which data for different drugs were pooled, such as anti-oxidants. However, between-study heterogeneity within drug classes was low in the pairwise meta-analysis, suggesting little variability of treatment effects.

In conclusion, the findings of this network meta-analysis provide no evidence for recommending any treatment with certainty in secondary RP. Yet, the level of evidence is low. Notwithstanding these caveats, CCB and PDE5i, might still be relevant when a pharmacological treatment is indicated, especially in patients with severe RP. Our findings emphasize the pressing need for the development of new therapeutic strategies for secondary RP, including non-pharmacological interventions.

Contributors

Substantial contributions to the conception and design: Study concept and design was conducted by C.K., M.R. and J.-L. C. Acquisition of data was done by C. K., M. L and M.R. Analysis and interpretation of data was done by C. K., M. R., S. B. and J.-L. C. Drafting of the manuscript was completed by C. K and M. R. Critical revision of the manuscript for important intellectual content was completed by C. K., M. R., M. L., S. B., S. B., A. H., Y. A., M. M.-C., L. T. and J.-L. C. Approval of the final manuscript was completed by C. K., M. R., M. L., S. B., S. B., A. H., Y. A., M. M.-C., L. T. and J.-L. C.

All authors have signed a statement attesting that they fulfil the authorship criteria of the ICMJE recommendations, have approved the version to be submitted, and agree to be accountable for all aspects of the study.

Declaration of interests

MR has received research grants from United Therapeutics for other studies. JLC have received research grants from Pfizer, United Therapeutics, Topadur Pharma, and Bioprojet for other studies. ALH has consultancy relationships with Boehringer-Ingelheim, Gesynta and Camurus, has received research funding from Actelion and Gesynta, and speaker's fees from Actelion. MM-C has consultancy relationships and/or has received grant/research support from Pfizer, Bristol-Myers Squibb,

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Figure legends

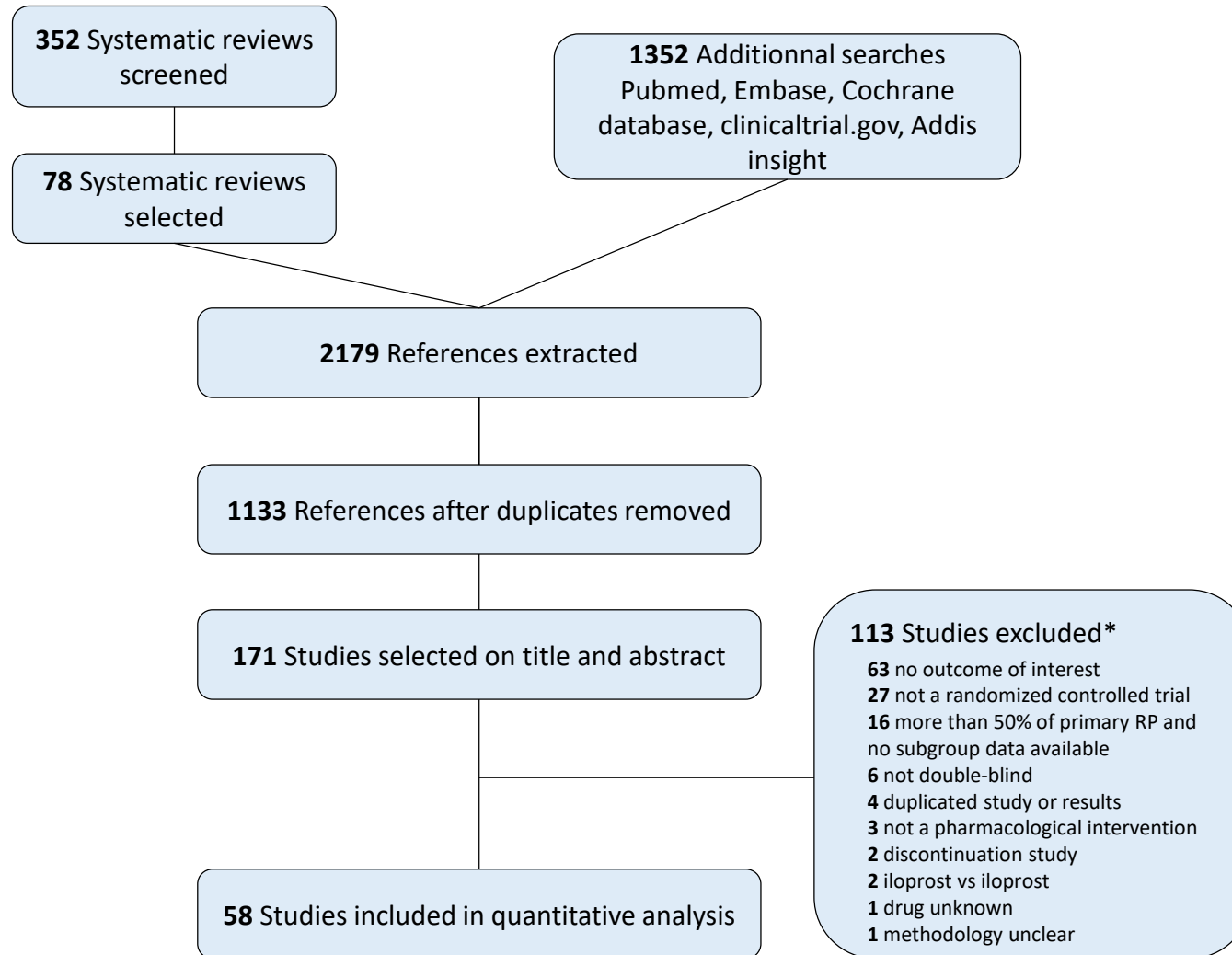
Figure 1. Flow diagram of the study selection process. * There was more than one reason for some studies.

Figure 2. Graphical representation of the network of included trials for each outcome. The thickness of lines between nodes is proportional to the number of trials comparing the treatments. The sizes of the nodes are proportional to the number of patients in each treatment group.

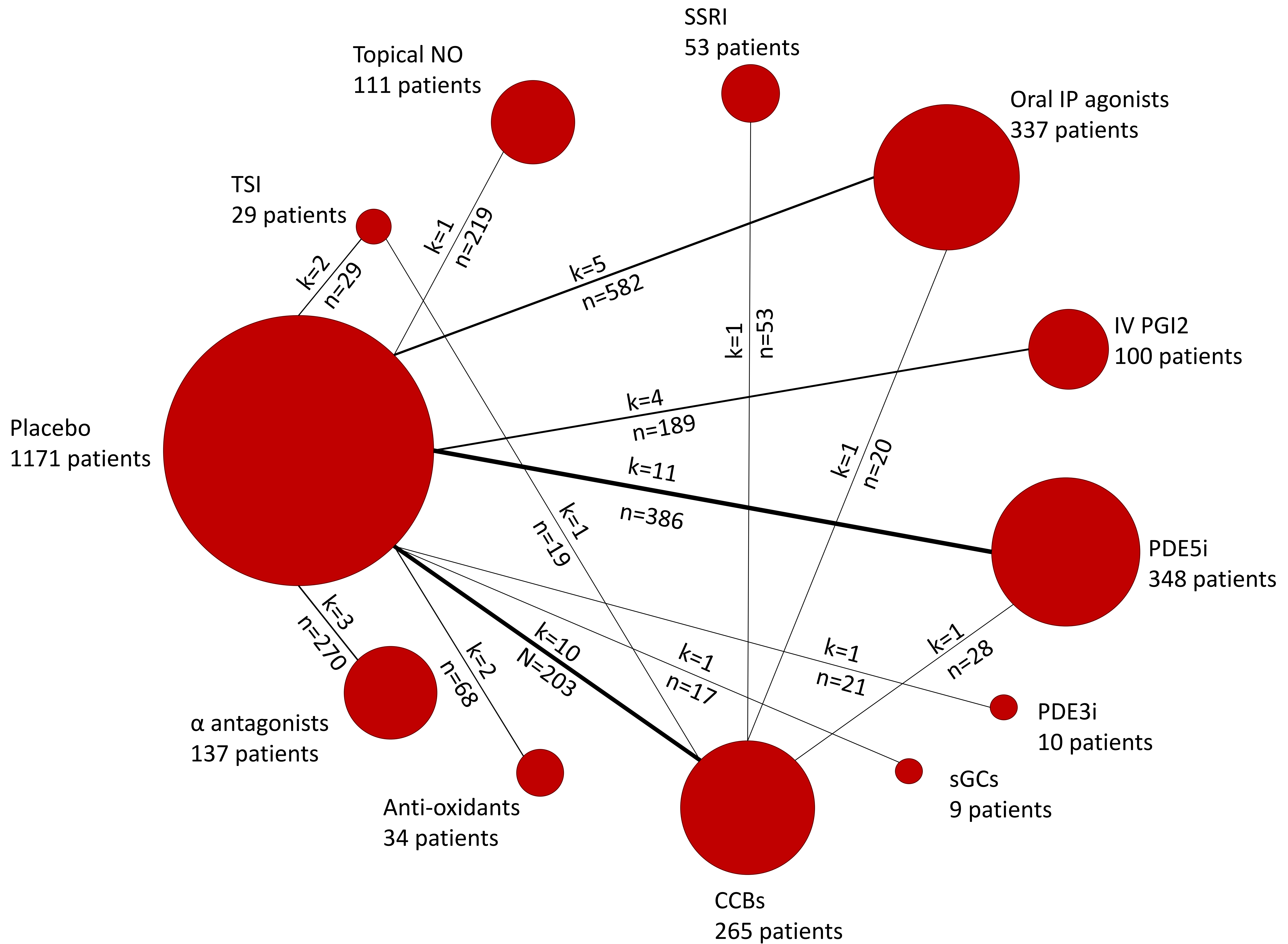
Figure 3. Forest plots of the network meta-analysis results. Drug classes are hierarchized according to the lower boundary of the mean rank 95% Credibility Interval (CrI) Data are Mean Differences (95% CrI) for efficacy outcomes and Incidence Rate Ratios (95% CrI) for safety outcomes. The colour depends of the average level of evidence according to GRADE: red: very low; orange: low; green: moderate.

Figure 4. Graphical representation of the network meta-analysis according to a mean difference summary of each drug class tested for the daily frequency of Raynaud's phenomenon crisis and the Incidence Rate Ratio for tolerability. The size of the nodes is proportional to the number of patients in each drug class. The colour depends of the average level of evidence according to GRADE: red: very low; orange: low; green: moderate.

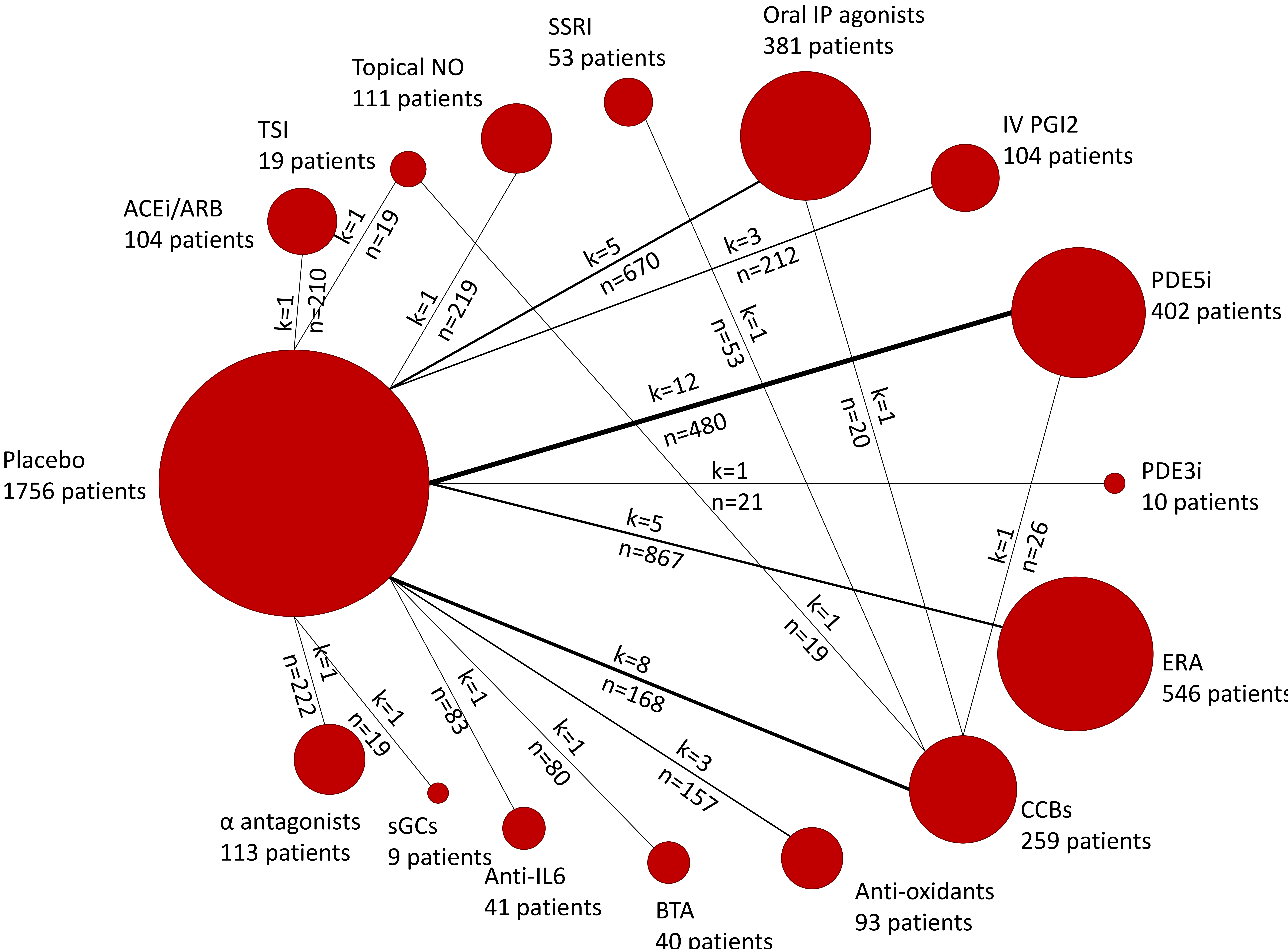
Figure 5. Circular plot representing the Cochrane domain-specific risk of bias according to each drug class. We considered a study as being “supported by a pharmaceutical company” when it was indicated anywhere in the text that the trial was at least partly funded and/or sponsored by the company which manufactured or marketed the drug being assessed, or if one or more authors were affiliated with the company in question.



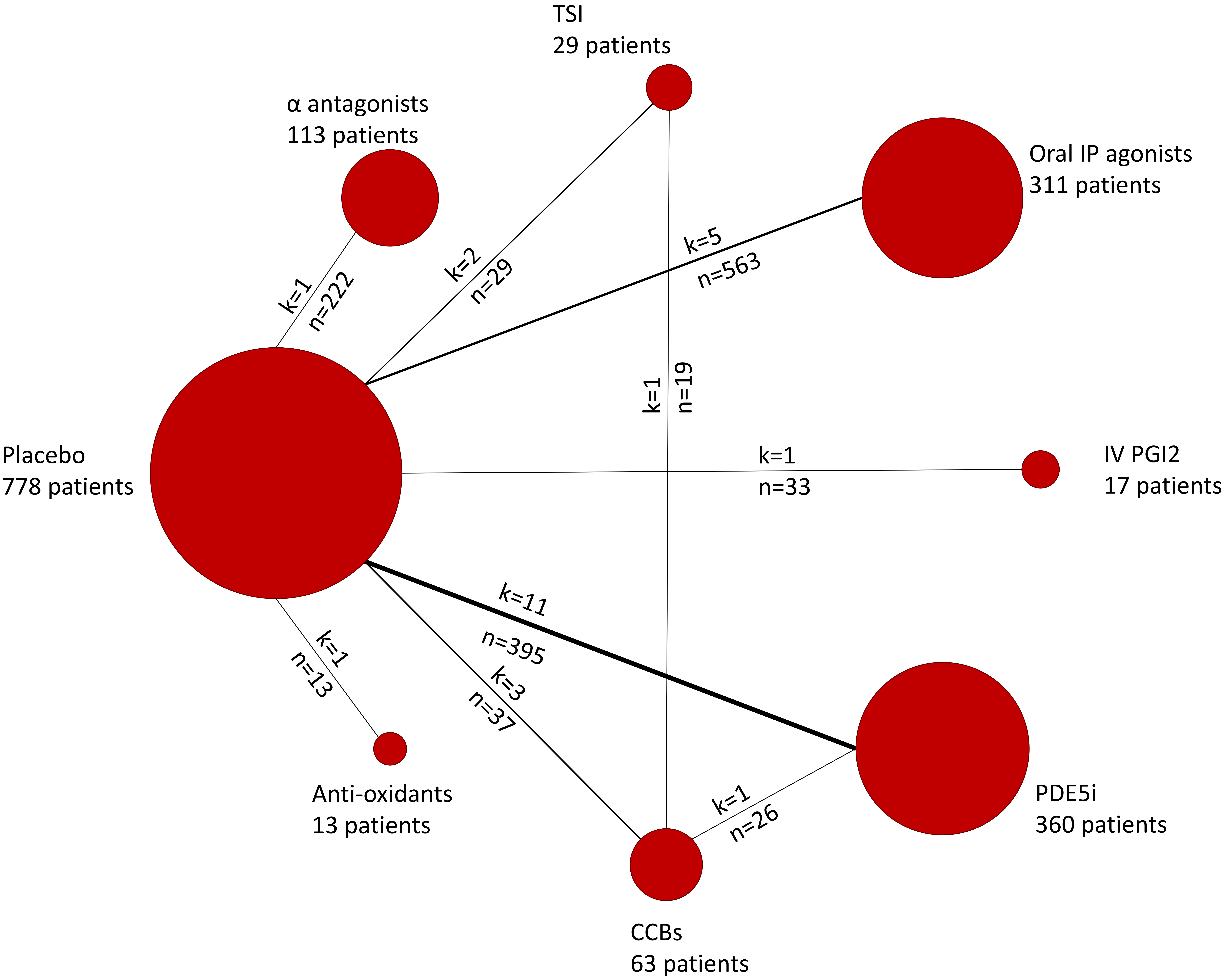
A. Frequency of RP attacks



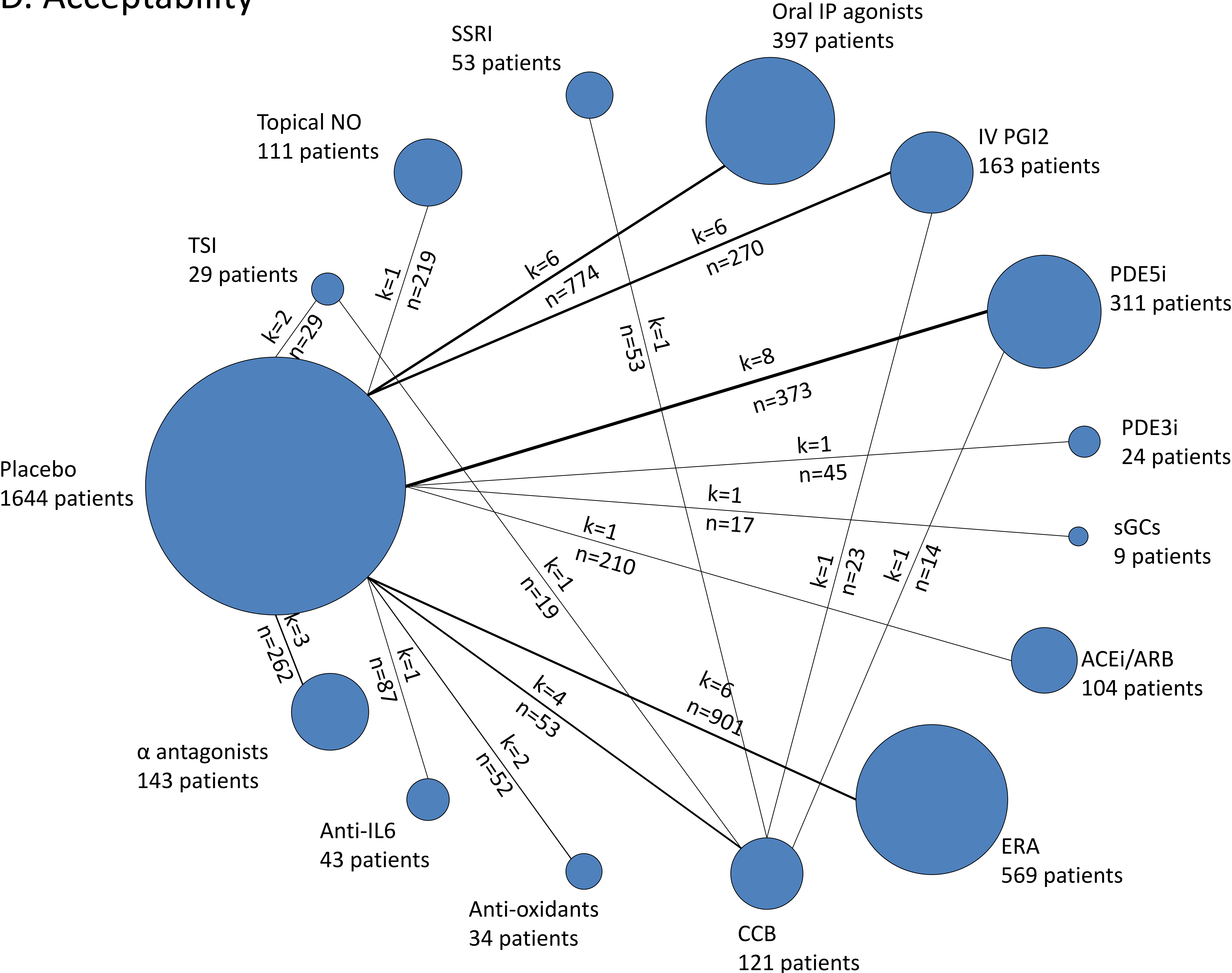
B. Severity of RP attacks



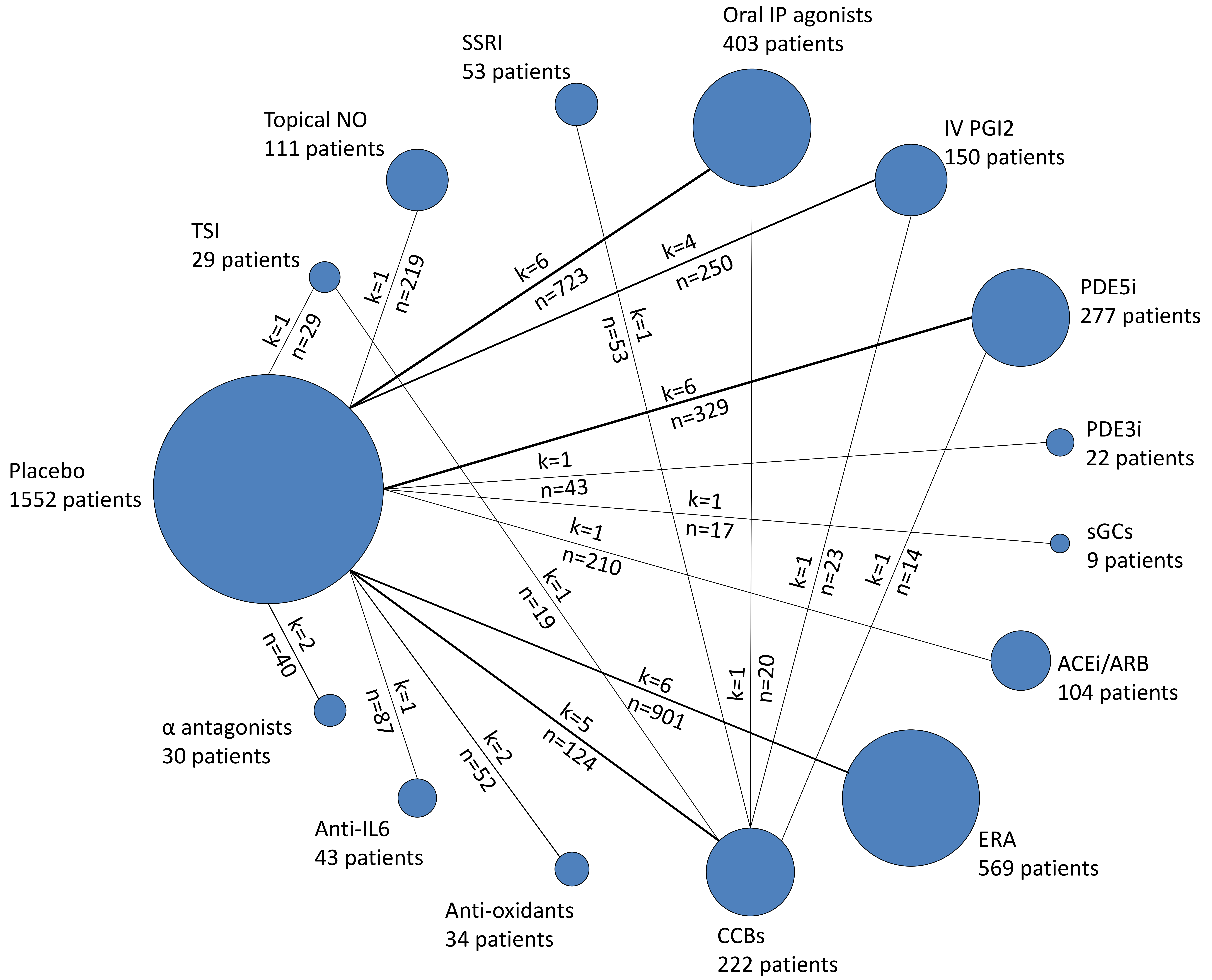
C. Duration of RP attacks



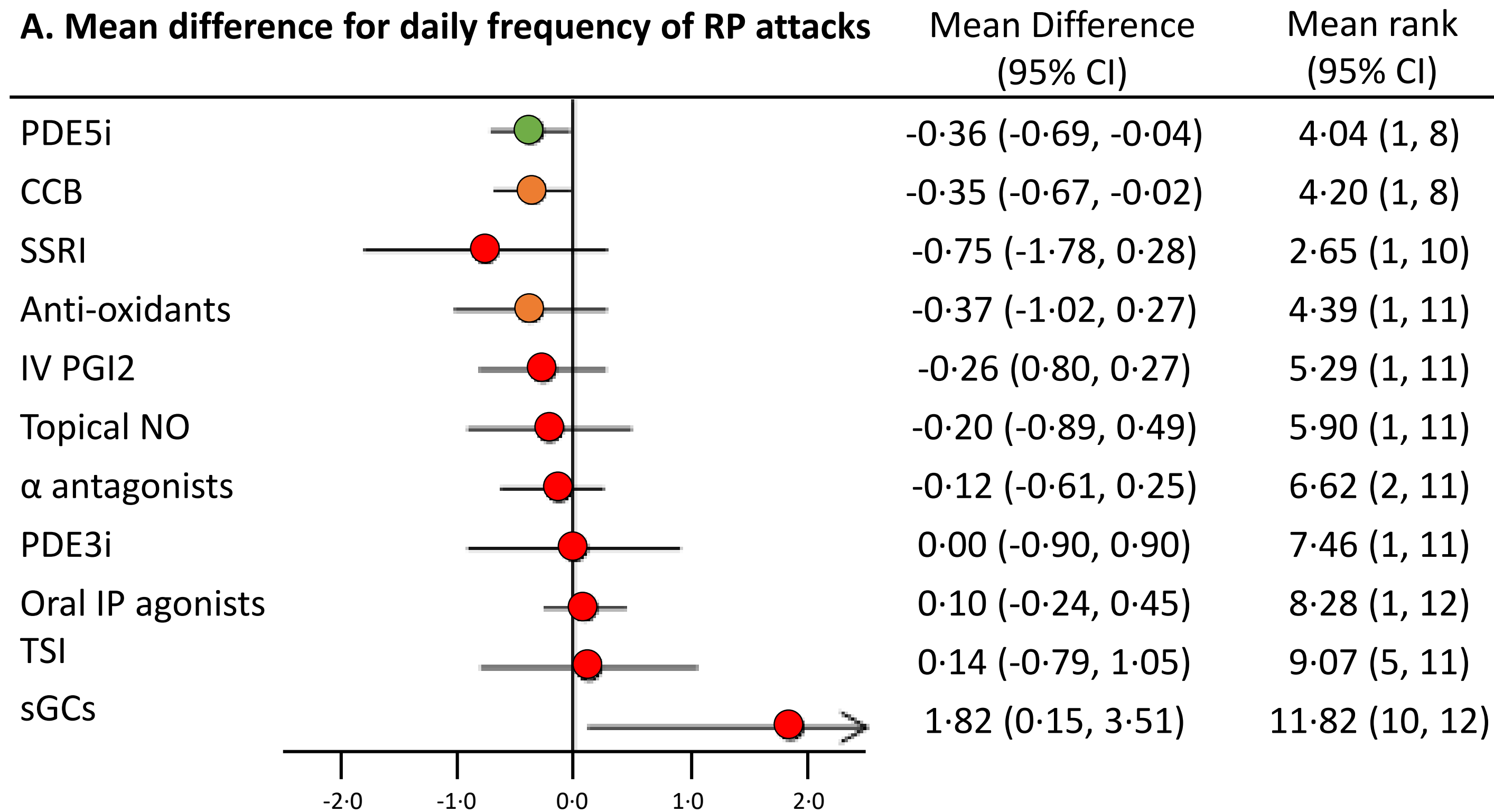
D. Acceptability



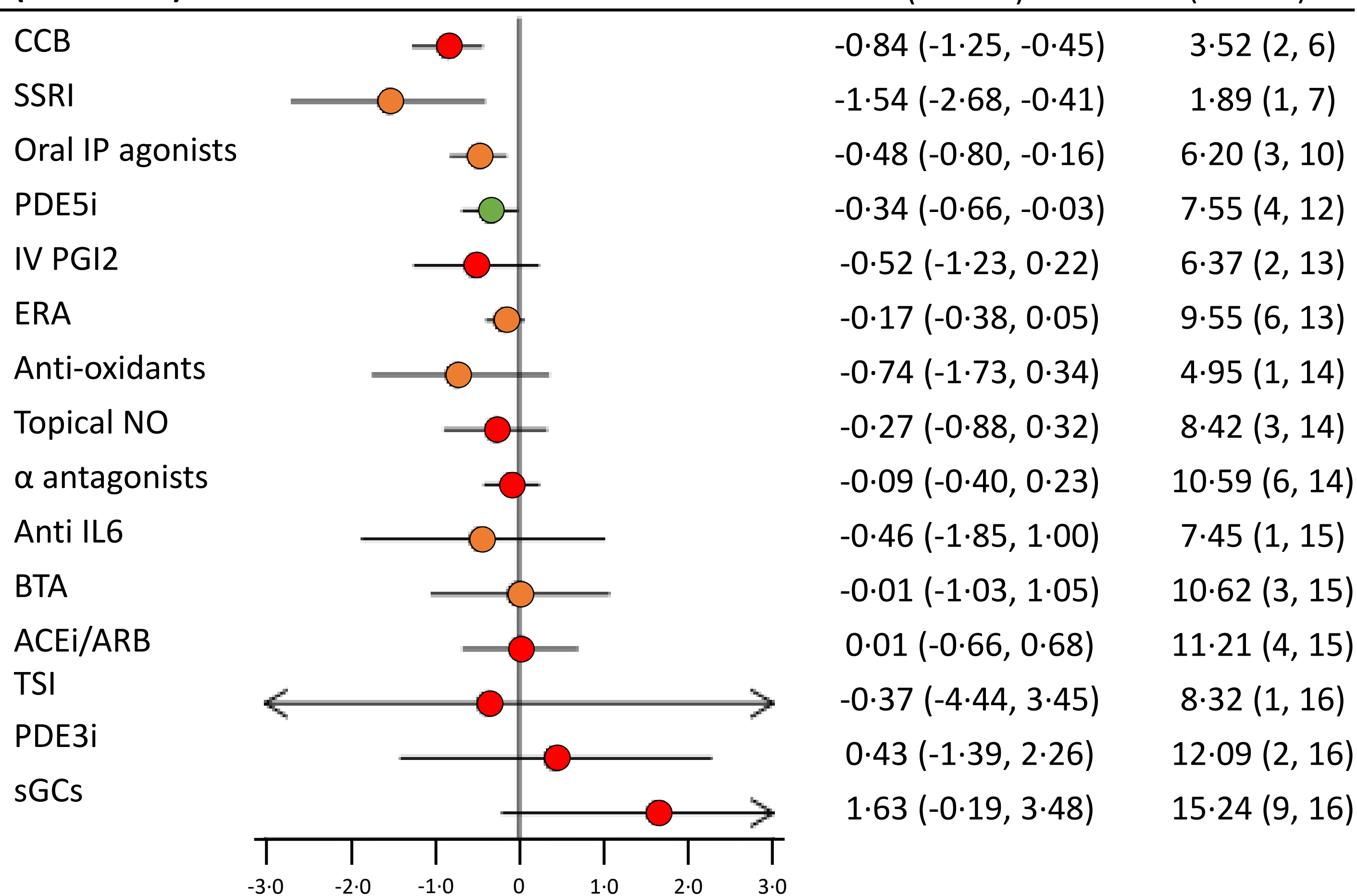
E. Tolerability



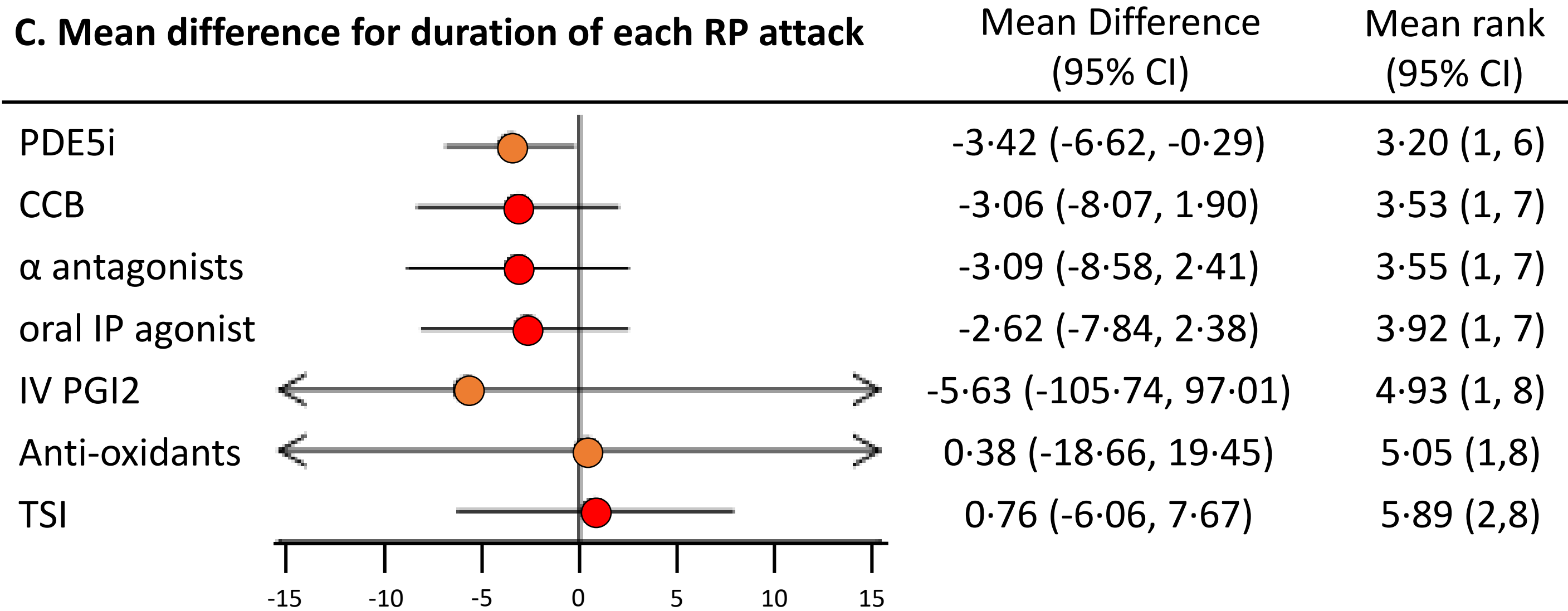
A. Mean difference for daily frequency of RP attacks



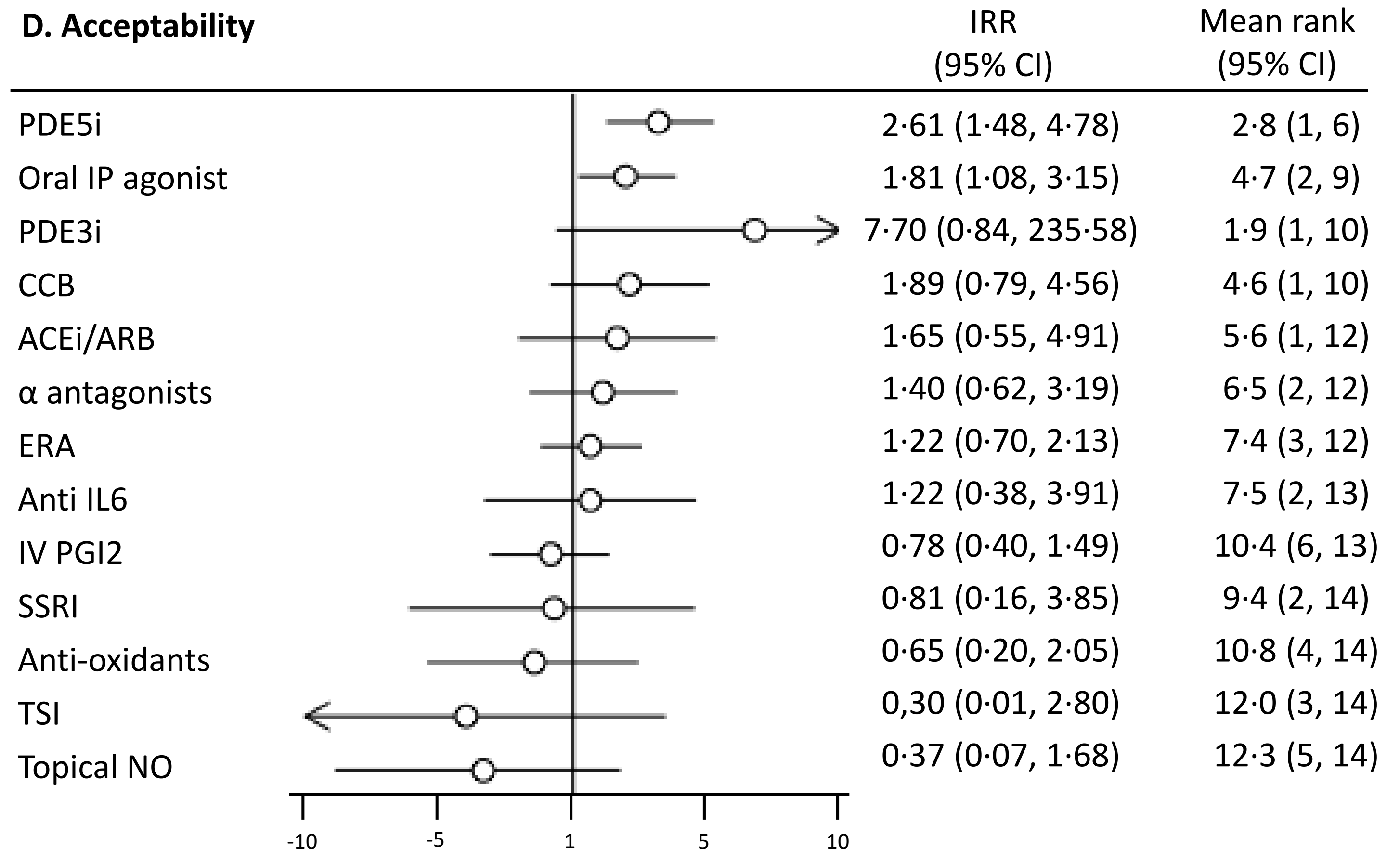
**B. Mean difference for severity of RP attacks
(scale 0-10)**



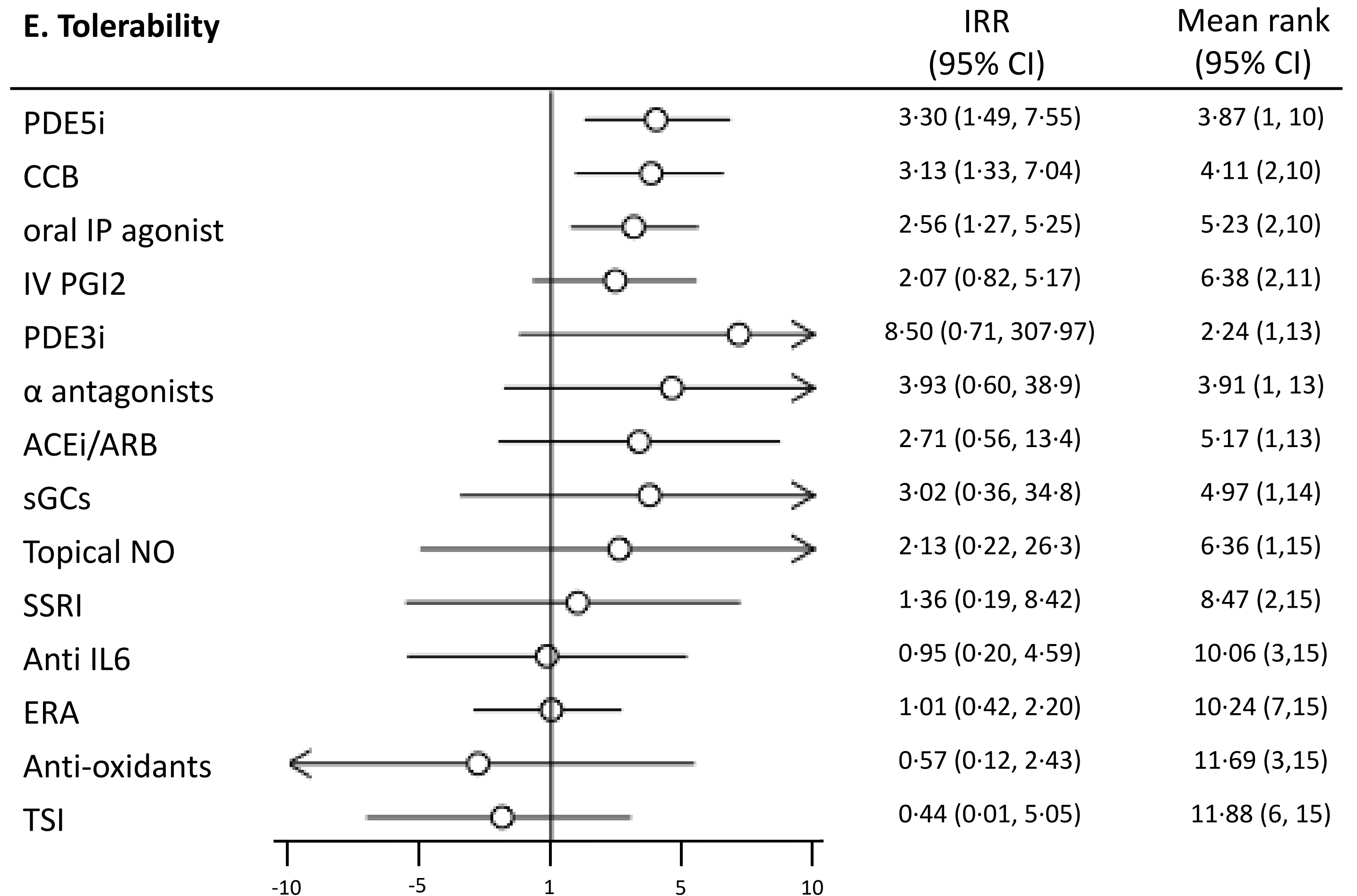
C. Mean difference for duration of each RP attack

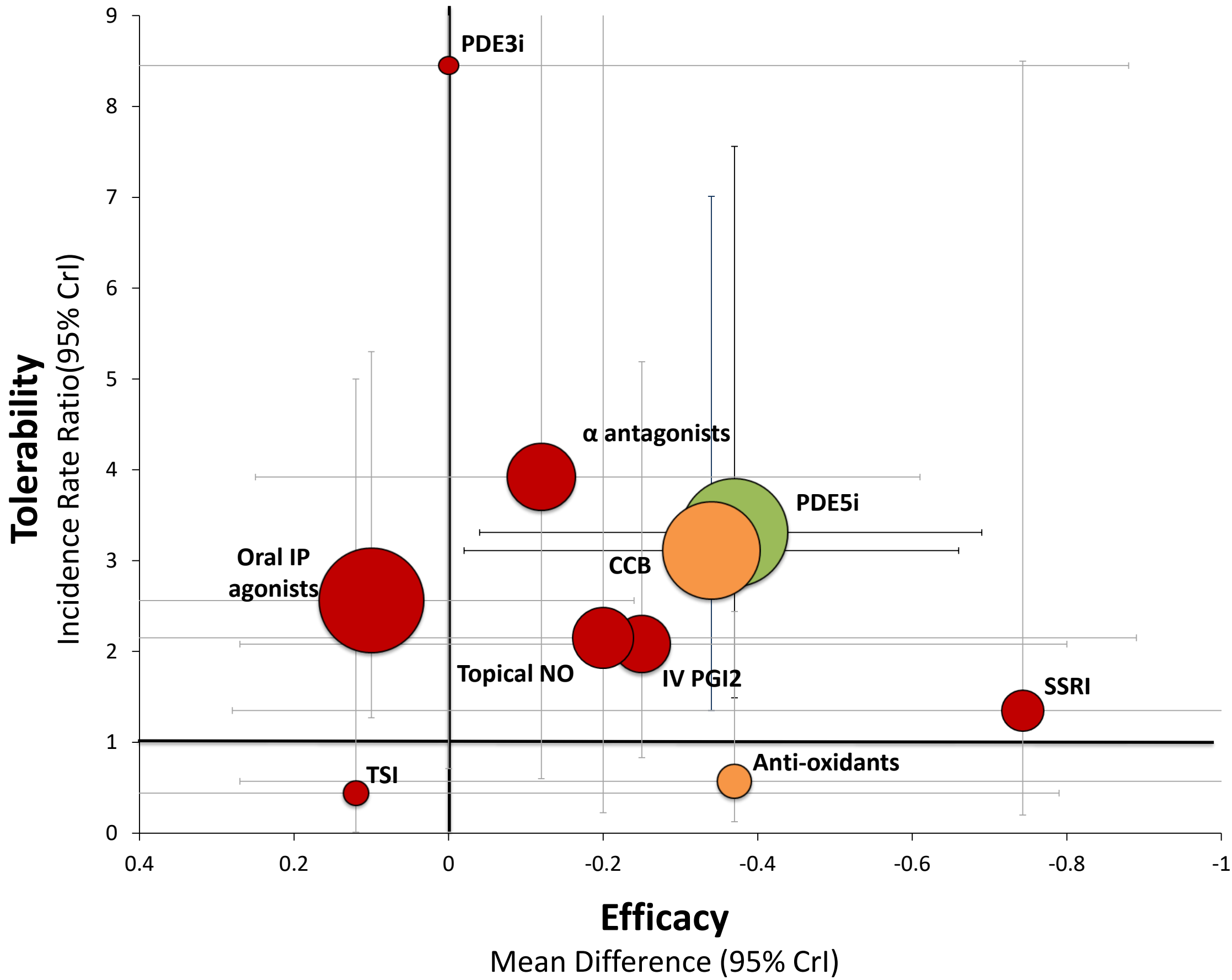


D. Acceptability



E. Tolerability





Risk of bias

- High Risk
- Low Risk
- Unclear risk

Supported by pharmaceutical companies

- No
- Yes
- Unclear

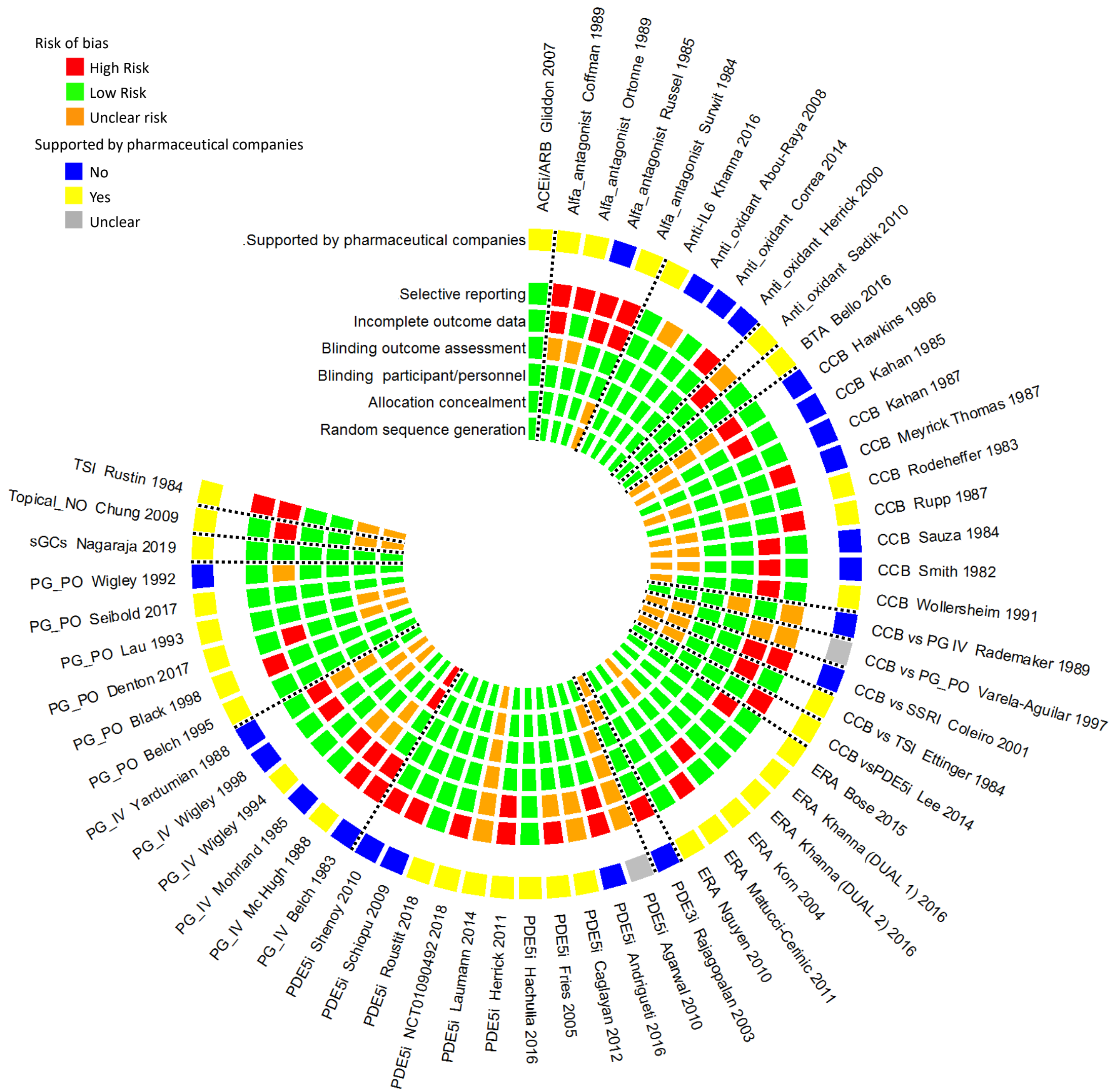


Table 1. Baseline characteristics of study participants, by drug class.

Drug class	Trials (n)	Patients (n)	Age, y Mean	Women (%)	Disease duration, y Mean (SD)	Secondary RP (%)	Severity (0 to 10) Mean (SD)	Frequency (daily) Mean (SD)	Duration (minutes) Mean (SD)
α antagonists	4	280	47.8	77	9.5	59	1.79 (0.46)	1.96 (1.88)	15.6 (10.81)
Anti oxidants	4	195	50.1	66	9.3	100	6.11 (2.88)	1.76 (1.97)	NR
Anti-IL6	1	87	49.5	77	NR	100	NR	NR	NR
ACEi/ARB	1	210	54.5	85	4.5	100	NR	NR	NR
Botulinum Toxin type A	1	40	51.9	78	15.6	100	NR	NR	NR
Calcium channel blockers	14	342	43.5	84	10.3	74	4.58 (2.19)	3.05 (6.26)	13.46 (8.57)
Endothelin receptor antagonists	6	901	50.4	83	10.8	100	3.84 (2.74)	NR	NR
Phosphodiesterase type 3 inhibitors	1	21	42	75	12	100	NR	NR	NR
Phosphodiesterase type 5 inhibitors	12	556	47.1	88	7.7	98	3.92 (2.50)	3.01 (2.16)	15.94 (17.42)
Intravenous prostacyclin analogs	7	295	48.6	79	11.2	88	4.69 (2.15)	3.62 (2.39)	NR
Oral prostacyclin analogs / non-prostanoid IP-receptor agonists	7	693	48.9	84	12.5	98	3.39 (1.73)	3.53 (2.09)	21.1593 (21.70)
Selective serotonin reuptake inhibitor	1	53	NR	79	NR	51	4.35 (2.84)	2.98 (2.26)	NR
Soluble Guanylate Cyclase stimulator	1	17	51	76	11	100	5.40 (1.60)	4.30 (1.70)	NR
Topical nitric oxide donor	1	219	45.9	93	NR	68	3.34 (2.07)	2.8 (1.81)	NR
Thromboxane synthase inhibitors	2	35	38	77	10	72	NR	NR	NR

ACEi/ARB : angiotensin-converting enzyme (*ACE*) inhibitor and an angiotensin receptor blocker (*ARB*); NR: not reported