Supporting Information

Text S1

Type I diabetes

This NMA evaluates the safety and effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes and represents a small dataset[1]. The authors evaluated glycosylated hemoglobin (A_{1c}), severe hypoglycemia, and weight gain outcomes. The analyses included 26 randomized clinical trials (RCTs) with 6776 patients and 8 treatments for A_{1c}, 16 RCTs with 5797 patients and 8 treatments for severe hypoglycemia, and 13 RCTs with 3396 patients and 5 treatments for gain weight. The results were presented in terms of pairwise mean differences and 95% confidence intervals (CIs) for A_{1c} and gain weight outcomes, and of odds ratios and 95% CIs for severe hypoglycemia. In Appendix Table 1 we present the SUCRA values as estimated in the original paper [1] that correspond to the three outcomes and eight treatments in total.

Appendix Table 1. SUCRA values (%), as calculated in the original paper [1], corresponding to long acting and intermediate acting insulin regiments for patients with type 1 diabetes in A_{1c}, severe hypoglycemia, and gain weight outcomes.

Type I diabetes			
Treatment	**Severe hypoglycemia**	**Gain weight**	**A_{1c}**
NPH[od/bid]	15.2	51.4	55.3
NPH[qid]	NA	NA	13.8
NPH[od]	51.4	0.3	9.2
Detemir[od/bid]	48.6	98.3	67.1
Detemir[qid]	18.3	NA	67.5
Detemir[od]	79.6	24.7	45.2
Glargine[bid]	87.4	NA	68
Glargine[od]	49.4	75.3	74.1

Abbreviations: A_{1c}: glycosylated hemoglobin, bid: twice daily, NA: Not available, Od: once daily, qid: four times daily, SUCRA: surface under the cumulative ranking curve

Serotonin (5-HT3) receptor antagonists for patients undergoing surgery

The empirical example we selected to represent the medium-sized empirical dataset is a systematic review and NMA published by Tricco et al.[2, 3] The authors evaluate the comparative safety and efficacy for 5-HT_3 receptor antagonists with each other, placebo, and/or other antiemetic agents for patients undergoing surgery. We use the SUCRA results for the treatment hierarchy in five studied outcomes: arrhythmia, delirium, nausea, vomiting, and postoperative nausea and vomiting (PONV). The NMA for arrhythmia included 31 RCTs with 6623 patients and 9 treatments, for delirium included 18 RCTs with 3652 patients and 6 treatments, for nausea included 195 RCTs with 24230 patients and 15 treatments, for

vomiting included 238 RCTs with 12781 patients and 15 treatments, and for PONV included 125 RCTs with 16667 patients and 13 treatments. The results were presented in terms of pairwise odds ratios and 95% CIs for all studied outcomes. In Appendix Table 2 we present the SUCRA values calculated in the original NMAs [2, 3] corresponding to the five outcomes and 15 treatments in total.

Appendix Table 2. SUCRA values (%), as calculated in the original NMAs[2, 3], corresponding to serotonin (5-HT_3) receptor antagonists for patients undergoing surgery in arrhythmia, delirium, nausea, vomiting and PONV outcomes.

5-HT_3 surgery					
Treatment	**Vomiting**	**Nausea**	**PONV**	**Delirium**	**Arrhythmia**
Placebo	4.6	0.8	0.1	51.9	42.8
Ondansetron	29.4	25.4	20.1	64.9	54.6
Granisetron	54.3	44.8	42.5	93.5	40.7
Dolasetron	22.0	13.3	37.7	27.7	81.5
Tropisetron	42.2	23.2	16.3	35.3	54.6
Ondansetron+Dexamethasone	76.0	71.9	63.0	NA	83.3
Palonosetron	30.1	54.9	72.3	NA	NA
Ramosetron	48.4	51.3	34.9	NA	35.3
Ondansetron+Droperidol IV	84.6	65.4	76.9	NA	NA
Ondansetron+Metoclopramide IV	78.8	52.8	NA	NA	NA
Granisetron+Dexamethasone	84.3	81.2	86.3	NA	2.9
Palonosetron+Dexamethasone	7.8	43.7	67.0	NA	NA
Dolasetron+Dexamethasone	73.9	72.8	NA	26.6	NA
Dolasetron+Droperidol IV	68.8	76.8	71.9	NA	54.2
Granisetron+Droperidol IV	44.8	71.7	61.1	NA	NA

Abbreviations: NA: Not available, PONV: postoperative nausea and vomiting

Chronic Obstructive Pulmonary Disease

The large-sized empirical dataset we selected is a systematic review and NMA evaluating the comparative safety and effectiveness of long-acting inhaled agents for adults with chronic obstructive pulmonary disease (COPD) [4]. We use the same SUCRA values as reported by the authors to present the treatment hierarchy in five studied outcomes: arrhythmia, pneumonia, cardiovascular mortality, mortality, and moderate-to-severe exacerbations. The NMA for arrhythmia included 26 RCTs with 27407 patients and 12 treatments, for pneumonia included 54 RCTs with 61551 patients and 21 treatments, for cardiovascular mortality included 195 RCTs with 24230 patients and 15 treatments, for mortality included 89 RCTs with 98447 patients and 28 treatments, and for moderate-to-severe exacerbations included 112 RCTs with 77749 patients and 26 treatments. The results were presented in terms of pairwise odds ratios and 95% CIs for all studied outcomes. In

Appendix Table 3 we present the SUCRA values calculated in the original NMA [4] corresponding to the five outcomes and the 30 distinct treatments across all outcomes.

Appendix Table 3. SUCRA values (%), as calculated in the original NMA [4], corresponding to long-acting inhaled agents for COPD compared in arrhythmia, pneumonia, cardiovascular mortality, mortality and moderate-to-severe exacerbations outcomes.

COPD					
Treatment	**Moderate-to-severe exacerbations**	**Cardiovascular mortality**	**Mortality**	**Pneumonia**	**Arrhythmia**
ACLI	33.8	28.2	66.9	77.4	62.8
AZD3199	67.7	70.2	67.7	NA	NA
BECL/FORM	66.3	NA	60.8	46.3	NA
BUDE	40.7	49.4	64.9	74.6	39.1
FLUT	36.6	61.4	41.2	18.4	NA
FLUT/TIOT	NA	NA	52.8	NA	NA
FORM	57.6	58.5	28.2	61.8	46.9
FORM/BUDE	81.3	27	43.1	34.7	20.8
FORM/BUDE/TIOT	NA	NA	26.9	NA	NA
FORM/MOME	51.8	NA	66.8	60.5	NA
FORM/TIOT	35.2	NA	63.6	NA	NA
GLYC	44.5	83.4	70.2	70.2	45.8
GSK961081	79.9	NA	NA	NA	NA
INDA	32.1	63.4	64.2	55.8	48.6
INDA/GLYC	70.2	77	60.5	66.5	40.9
INDA/TIOT	77.5	32.3	46.6	NA	NA
MOME	46.6	NA	29.7	40	NA
Placebo	13.7	50.5	44.7	52.8	74.3
SALM	37.3	75.9	58.2	NA	69.4
SALM/FLUT	44.1	65.3	70.6	11.2	74.8
SALM/TIOT	48.8	NA	30.3	41.8	NA
TIOT	63.4	40.2	50.5	59	62.5
TIOT/BUDE/FORM	96.2	NA	NA	54.8	NA
TIOT/FLUT/SALM	72.9	NA	28.5	33.7	NA
TIOT+Resp	NA	32	49.8	NA	NA
TRIAM	NA	19.2	64.7	NA	NA
UMEC	16.5	48.8	44.6	62.7	NA
VILA	16.8	35.5	27.9	45.1	NA
VILA/FLUT	51	54.6	39.2	11.5	14.1
VILA/UMEC	17.4	27.4	37.1	71.3	NA

Abbreviations: ACLI: aclidinium bromide, AZD3199: AZD3199 (ultra LABA), BECL/FORM: beclomethasone/formoterol, BUDE: budesonide, COPD: chronic obstructive pulmonary disease, FLUT: fluticasone, FLUT/TIOT: fluticasone/tiotropium, FORM, formoterol, FORM/BUDE: formoterol/budesonide, FORM/TIOT/BUDE: formoterol/budesonide/tiotropium, FORM/MOME: formoterol/mometasone, FORM/TIOT: formoterol/tiotropium, GLYC: glycopyrronium bromide, INDA:

indacaterol, INDA/GLYC: indacaterol/glycopyronium, INDA/TIOT: indacaterol/tiotropium, MOME: mometasone, NA: not available, SAML: salmeterol, SALM/FLUT: salmeterol/fluticasone, SALM/TIOT: salmeterol/tiotropium, TIOT: tiotropium, TIOT/BUDE/FORM: tiotropium/budesonide/formoterol, TIOT/FLUT/SALM: tiotropium/ fluticasone /salmeterol, TIOT+Resp: Tiotropium Respimat (Soft Mist Inhaler), TRIAM: triamcinolone acetonide, UMEC: umeclidinium, VILA: vilanterol, VILA/FLUT: vilanterol/fluticasone, VILA/UMEC: vilanterol/umeclidinium

Text S2

The R code to produce the rank-heat plot is provided in an extra txt file (rankheat plot function.txt)

Rank-heat plot: A graphical tool for treatment hierarchy

Version: 1.0

Description: The rank-heat plot is a visual representation of the treatment hierarchy estimated in a network meta-analysis across multiple outcomes. Several ranking statistics can be displayed within a rank-heat plot, including the probability of being the best, mean/median ranking, and the surface under the cumulative ranking (SUCRA) curve.

R Packages required to be installed: `'fields', 'RColorBrewer', 'circlize'`

Usage

```
rankheatplot (data, format, lab.plot, color, title.name, legend.treatment="TRUE", cex=0.65,
              pos.outcome.label=c(0.01,-0.4), pos.treatment.label=c(-0.25,-0.4),
              asterisk="TRUE", show.numbers = "TRUE")
```

Required arguments

data Data-frame with rows corresponding to the treatments included in the network meta-analysis and columns corresponding to the studied outcomes. The first row should present the names of the outcomes, and the first column should present the names of the treatments.

Optional arguments

format Ranking statistics, with "percentage" (with values ranging between 0 and 100) (e.g., 54) referring to SUCRA values or the probability of being the best, and "rank" (e.g., 5.4) referring to median or mean rank of the included treatments (default is "percentage").

lab.plot Labels referred to the included treatments across the sectors of circles. Should be one of:

	"numbers", for numerical values
	"vector", for titles given by the user
	"default.titles", the first column of the dataset (names of the treatments) (default)
vector.outcomes	Labels referred to the included outcomes. Should be one of:
	"vector.outcome.names", for titles given by the user
	"default.titles", the first row of the dataset (names of the outcomes) (default)
color	Color palette of the plot, with options:
	"color": the scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%) (default)
	"grey": a dark grey corresponds to the smallest ranking value (0%) and a light grey corresponds to the highest ranking value (100%).
	"color.blind": the scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%) associated with a specific pattern.
title.name	Title of the plot
cex	Font size for **lab.plot** (default is 0.65)
legend.treatment	To present the legend with the names of the treatments (default is "FALSE")
pos.outcome.label	The x and y coordinates referring to the position of the legend for the outcomes.
pos.treatment.label	The x and y coordinates referring to the position of **legend.treatment**.
asterisk	Indicates whether a sector refers to treatments without data on the outcome within the circle (default is "FALSE")
show.numbers	Indicates whether to show the ranking statistic of each sector (default is "TRUE")

Details

In the rank-heat plot, circles from outside in refer to the outcomes in the same order as presented in the dataset by the user (column 2, 3, etc.). Note that the number of outcomes included in the rank-heat plot should be ≤ 13.

Care is needed for the correct selection between "rank" and "percentage" in the **format** argument, so as to avoid erroneous results! Also, the "color.blind" option in the **color** argument is not available when the "rank" format is used and the numerical values of the ranking statistic are always provided in each colored sector. In the "rank" format, the color in each sector is customized according to the number of treatments provided in the specific outcome. For example, in T1DM the weight gain outcome includes 5 treatments, whereas the A1c outcome includes 8 treatments in total. In such a case, the treatment that was ranked 5th in the weight gain outcome will have the same color with the 8th ranked treatment in A1c. Therefore, the colored bar presented at the bottom of the rank-heat plot does not present numerical values, but instead it provides only an indication of how the best and worst treatments are colored.

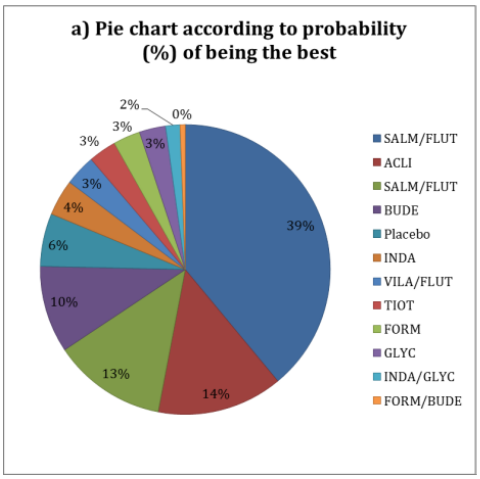
Examples

Below we present 2 empirical examples using the SUCRA values presented in a systematic review and NMA published by Tricco et al.[2-4] See Appendix 1 for further details.

```
######### COPD (grey scale) #########
library(fields)
library(RColorBrewer)
library(circlize)
treatments<-c("ACLI", "AZD3199", "BECL/FORM", "BUDE", "FLUT", "FLUT/TIOT", "FORM", "FORM/BUDE",
              "FORM/BUDE/TIOT", "FORM/MOME", "FORM/TIOT", "GLYC", "GSK961081", "INDA",
              "INDA/GLYC", "INDA/TIOT", "MOME", "Placebo", "SALM", "SALM/FLUT", "SALM/TIOT",
              "TIOT","TIOT/BUDE/FORM","TIOT/FLUT/SALM","TIOT+Resp","TRIAM","UMEC","VILA",
              "VILA/FLUT", "VILA/UMEC")
arrhythmia<- c(62.8, NA, NA, 39.1, NA, NA,46.9, 20.8,NA,NA,NA, 45.8,NA, 48.6, 40.9 ,NA , NA, 74.3 ,69.4,
              74.8,NA,62.5, NA, NA, NA, NA , NA, NA , 14.1, NA)
pneumonia<-c(77.4, NA,  46.3, 74.6, 18.4, NA,  61.8, 34.7, NA,  60.5, NA ,  70.2, NA ,  55.8 ,66.5, NA,  40,  52.8
              ,NA ,  11.2,41.8, 59 ,  54.8, 33.7 ,NA ,  NA ,  62.7, 45.1, 11.5, 71.3)
cvm<-c(28.2, 70.2 ,NA  , 49.4, 61.4, NA,  58.5 ,27  , NA ,  NA ,NA ,  83.4, NA ,  63.4, 77 ,  32.3 ,NA ,  50.5, 75.9,
              65.3,NA,  40.2, NA ,  NA ,  32,  19.2, 48.8, 35.5, 54.6 ,27.4)
mortality<-c(66.9, 67.7, 60.8, 64.9, 41.2, 52.8, 28.2, 43.1, 26.9, 66.8,63.6, 70.2, NA,  64.2 ,60.5, 46.6, 29.7 ,44.7,
              58.2 ,70.6,30.3 ,50.5 ,NA  , 28.5, 49.8, 64.7, 44.6, 27.9, 39.2, 37.1)
exacerbations<-c(33.8, 67.7, 66.3, 40.7, 36.6 ,NA ,  57.6 ,81.3, NA ,  51.8,35.2, 44.5, 79.9, 32.1, 70.2, 77.5, 46.6
              ,13.7 ,37.3, 44.1,48.8, 63.4, 96.2, 72.9, NA ,  NA ,  16.5 ,16.8, 51,17.4)
mydata<-data.frame(treatments, exacerbations, cvm, mortality, pneumonia, arrhythmia)
vector.outcome.names<-c("Moderate-to-severe exacerbations","Cardiovascular mortality","Mortality",
              "Pneumonia", "Arrhythmia")
rankheatplot(data=mydata,format="percentage",lab.plot="numbers",
              vector.outcomes="vector.outcome.names", color="grey", title.name="COPD - Rank-heat plot
              based on SUCRA", cex=0.65, legend.treatment="TRUE", pos.outcome.label=c(0.24,-0.50),
              pos.treatment.label=c(1,-0.45), asterisk="TRUE",show.numbers="false")
```

```
#########################################################################
                #### 5-HT3 surgery (colored scale) ########
library(fields)
library(RColorBrewer)
library(circlize)
#SUCRA values
treatments<-c("Placebo",                "Ondansetron","Granisetron",                "Dolasetron","Tropisetron",
              "Ondansetron+Dexamethasone",  "Palonosetron","Ramosetron",  "Ondansetron+DroperidolIV",
              "Ondansetron+MetoclopramideIV",                "Granisetron+Dexamethasone",
              "Palonosetron+Dexamethasone",  "Dolasetron+Dexamethasone",  "Dolasetron+DroperidolIV",
              "Granisetron+DroperidolIV")
Arrhythmia<- c(42.8, 54.6, 40.7, 81.5, 54.6, 83.3, NA, 35.3, NA, NA, 2.9, NA, NA, 54.2, NA)
Delirium<-c(51.9, 64.9, 93.5, 27.7, 35.3, NA, NA, NA, NA, NA, NA, NA, 26.6, NA, NA)
Nausea<-c(0.8, 25.4, 44.8, 13.3, 23.2, 71.9, 54.9, 51.3, 65.4, 52.8, 81.2, 43.7, 72.8, 76.8, 71.7)
Vomiting<-c(4.6, 29.4, 54.3, 22, 42.2, 76, 30.1, 48.4, 84.6, 78.8, 84.3, 7.8, 73.9, 68.8, 44.8)
PONV<-c(0.1, 20.1, 42.5, 37.7, 16.3, 63, 72.3, 34.9, 76.9, NA, 86.3, 67, NA, 71.9, 61.1)
mydata<-data.frame(treatments,Vomiting, Nausea, PONV, Delirium, Arrhythmia)
vector<-c("PLAC","ONDA","GRAN","DOLA",      "TROP","ONDA+DEX","PALO",      "RAMO",      "ONDA+DROP",
              "ONDA+MET", "GRAN+DEX", "PALO+DEX", "DOLA+DEX", "DOLA+DROP", "GRAN+DROP")
rankheatplot(data=mydata,format="percentage",lab.plot="vector",      color="color",      title.name="B.  5-HT3
              surgery",      cex=0.65,      legend.treatment="false",      pos.outcome.label=c(0.25,-0.5),
              pos.treatment.label=c(0.9,-0.45), asterisk="false",show.numbers="TRUE")
#########################################################################
```

Figures



b) Rank chart according to probability of being the best

Rank according to P(best)	Treatment
1	SALM/FLUT
2	ACLI
3	SALM
4	BUDE
5	Placebo
6	INDA
7	VILA/FLUT
8	TIOT
9	FORM
10	GLYC
11	INDA/GLYC
12	FORM/BUDE

Figure S1. Pie chart (a) and rank chart (b) representing the probability for each treatment being the best in the chronic obstructive pulmonary disease (COPD) arrhythmia network. Each region in the pie chart (a) corresponds to a different treatment and is proportional to the respective ranking probability. Each section of the rank chart (b) corresponds to a different treatment, and NMA treatments are ordered from best (top of the chart) to worst (bottom of the chart) according to their probability best. *Abbreviations*: ACLI: aclidinium bromide, BUDE: budesonide, FLUT/TIOT: fluticasone/tiotropium, FORM: formoterol, FORM/BUDE: formoterol/budesonide, GLYC: glycopyrronium bromide, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, SAML: salmeterol, TIOT: tiotropium, VILA/FLUT: vilanterol/fluticasone

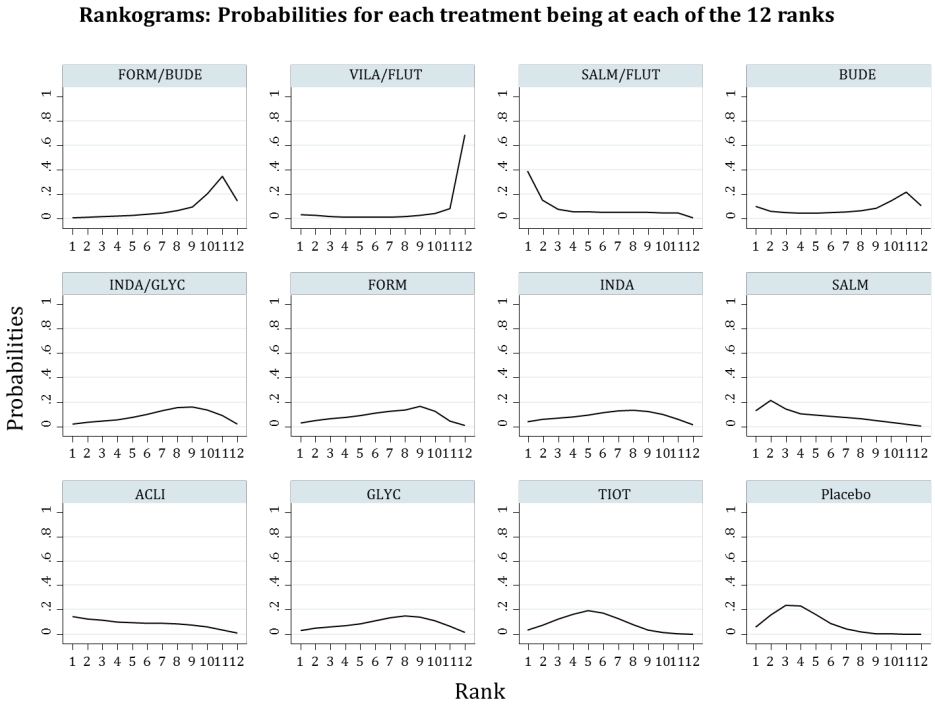


Figure S2. Rankograms for the 12 chronic obstructive pulmonary disease (COPD) treatments studied in arrhythmia outcome. On the horizontal axis the 12 possible ranks are displayed (from best to worst), whereas on the vertical axis the probability of each treatment being at each of the 12 ranks is presented. *Abbreviations*: ACLI: aclidinium bromide, BUDE: budesonide, FLUT/TIOT: fluticasone/tiotropium, FORM: formoterol, FORM/BUDE: formoterol/budesonide, GLYC: glycopyrronium bromide, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, SAML: salmeterol, TIOT: tiotropium, VILA/FLUT: vilanterol/fluticasone

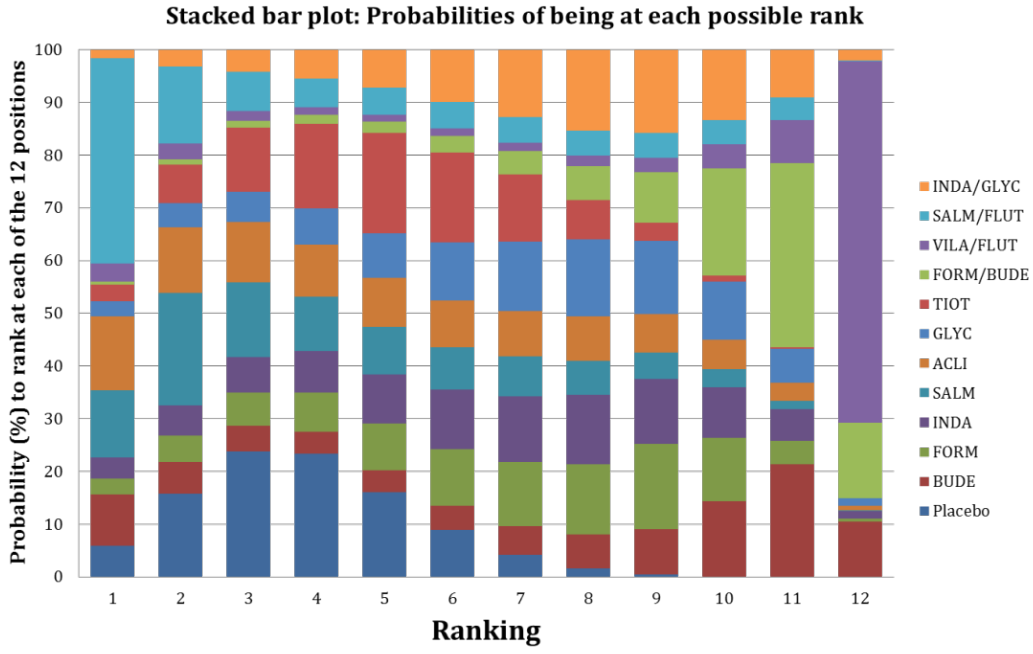


Figure S3. Stacked bar plot for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome. On the horizontal axis the 12 possible ranks are displayed (from best to worst), whereas on the vertical axis the probability of each treatment being at each of the 12 ranks is presented. Each bar represents one of the 12 possible ranks, and the

category of each bar corresponds to the probability of each treatment to be at the specific rank. *Abbreviations*: ACLI: aclidinium bromide, BUDE: budesonide, FLUT/TIOT: fluticasone/tiotropium, FORM: formoterol, FORM/BUDE: formoterol/budesonide, GLYC: glycopyrronium bromide, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, SAML: salmeterol, TIOT: tiotropium, VILA/FLUT: vilanterol/fluticasone

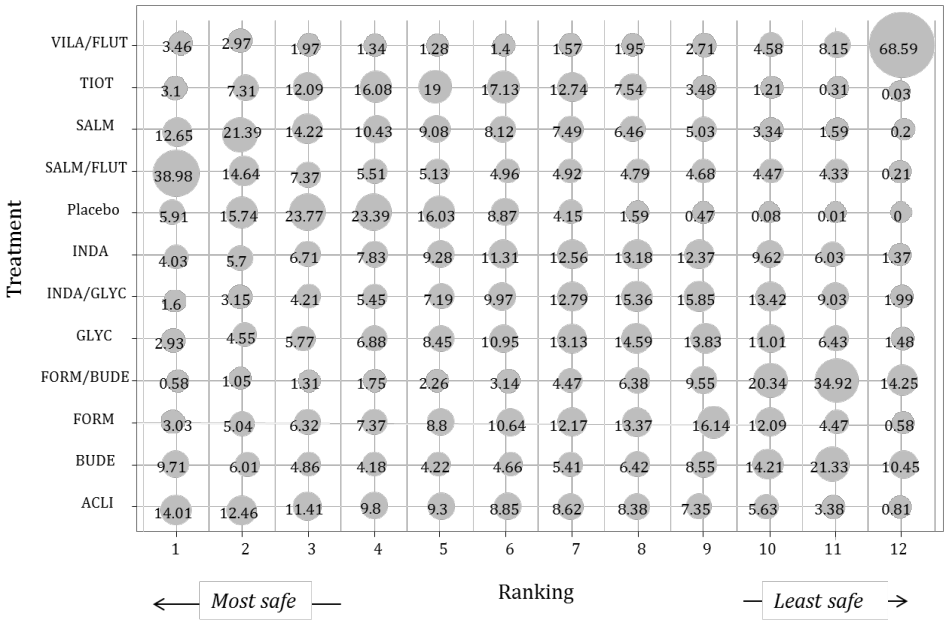


Figure S4. Bubble plot for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome. On the horizontal axis the probability of each treatment being at each possible ranking is displayed, whereas on the vertical axis the 12 treatments included in the network are presented. The area of each circle is proportional to the probability of each ranking, which is presented in the center of each circle. *Abbreviations*: ACLI: aclidinium bromide, BUDE: budesonide, FLUT/TIOT: fluticasone/tiotropium, FORM: formoterol, FORM/BUDE: formoterol/budesonide, GLYC: glycopyrronium bromide, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, SAML: salmeterol, TIOT: tiotropium, VILA/FLUT: vilanterol/fluticasone

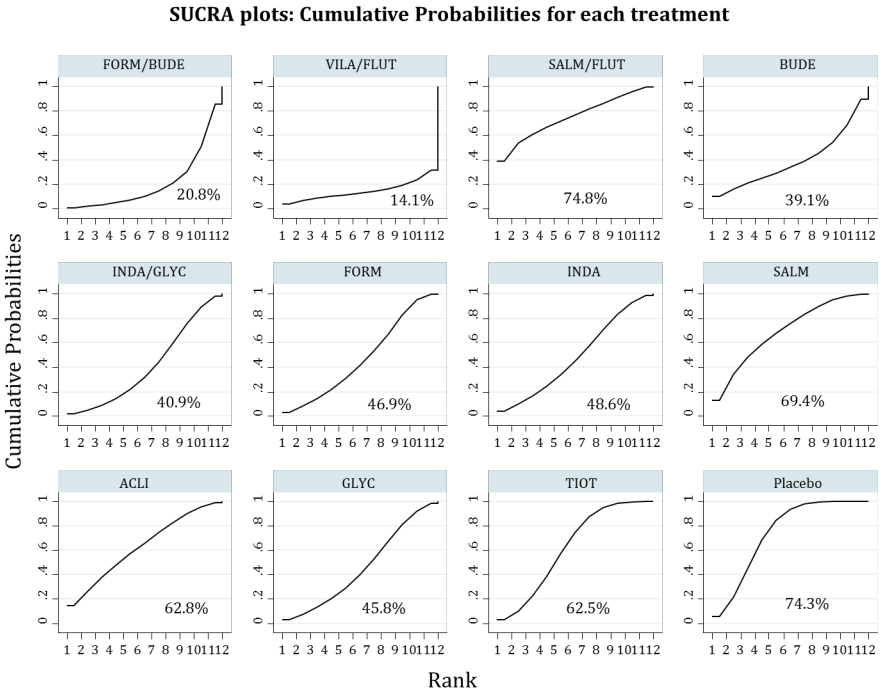


Figure S5. SUCRA plots for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome. On the horizontal axis the 12 possible ranks are displayed (from best to worst), whereas on the vertical axis the cumulative probability of each treatment is presented. The surface under the cumulative ranking curve is also depicted in percentage. *Abbreviations*: ACLI: aclidinium bromide, BUDE: budesonide, FLUT/TIOT: fluticasone/tiotropium, FORM: formoterol, FORM/BUDE: formoterol/budesonide, GLYC: glycopyrronium bromide, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, SAML: salmeterol, SUCRA: surface under the cumulative ranking curve, TIOT: tiotropium, VILA/FLUT: vilanterol/fluticasone

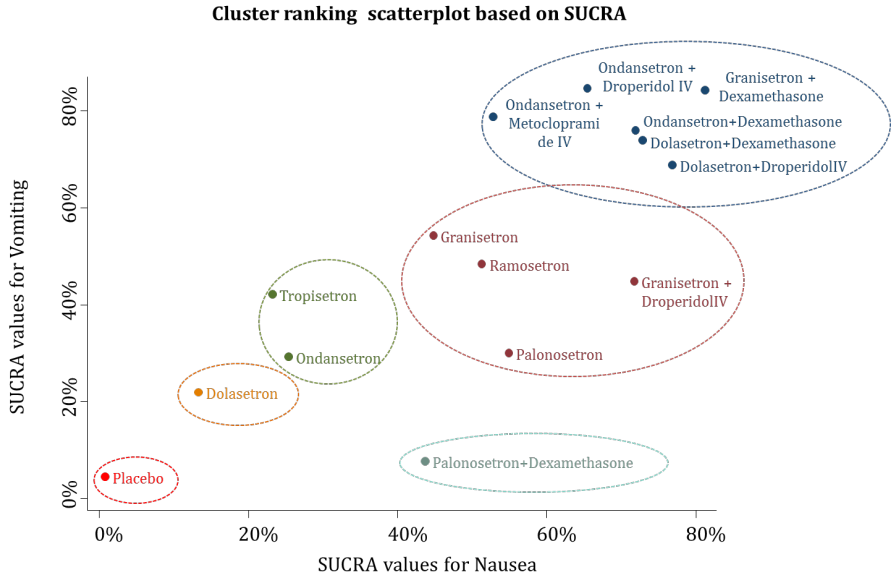


Figure S6. Cluster ranking scatterplot for 15 serotonin (5-HT$_3$) receptor antagonists according to SUCRA values for nausea (x-axis) and vomiting (y-axis) outcomes for patients undergoing surgery. Each color represents a group of treatments that belong to the same cluster (this is also shown by a separate dashed circle). Treatments lying on the upper right hand side are more effective for both outcomes. SUCRA: surface under the cumulative ranking curve.

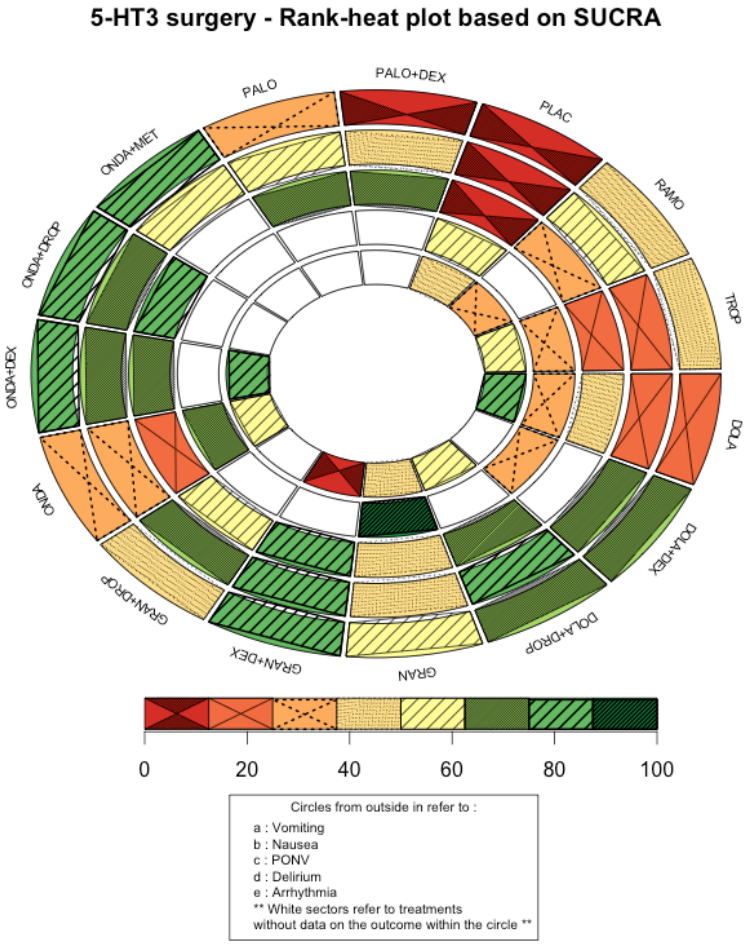


Figure S7. Rank-heat plot of 15 serotonin (5-HT$_3$) receptor antagonists for patients undergoing surgery in five outcomes. Each sector is colored according to the SUCRA value of the corresponding treatment and outcome. The scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%), and each color is associated with a different pattern. Uncolored sectors show that the underlying treatment was not included in the NMA for the particular outcome.

References

1. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W, Harrington A, Wilson C, Tsouros S, Soobiah C *et al*: **Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis**. *Bmj* 2014, **349**:g5459.
2. Tricco AC, Soobiah C, Blondal E, Veroniki AA, Khan PA, Vafaei A, Ivory J, Strifler L, Ashoor HM, MacDonald H *et al*: **Comparative efficacy of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis**. *BMC Medicine* 2015, **(in press)**:13.

3. Tricco AC, Soobiah C, Blondal E, Veroniki AA, Khan PA, Vafaei A, Ivory J, Strifler L, Ashoor HM, MacDonald H *et al*: **Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis**. *BMC Medicine* 2015, **(in press)**:13.
4. Tricco AC, Strifler L, Veroniki AA, Yazdi F, Khan PA, Scott A, Ng C, Antony J, Mrklas K, D'Souza J *et al*: **Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis**. *BMJ open* 2015, **5**(10):e009183.