Outcomes of transcatheter aortic valve implantation with Medtronic's Evolut PRO compared to Evolut R. Systematic review and meta-analysis of observational studies.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
	Reporting of background should include	
1	Problem definition	1
2	Hypothesis statement	NA
3	Description of study outcome(s)	1
4	Type of exposure or intervention used	1
5	Type of study designs used	1
6	Study population	1
	Reporting of search strategy should include	
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	4, Figure 1
9	Effort to include all available studies, including contact with authors	2
10	Databases and registries searched	2
11	Search software used, name and version, including special features used (eg, explosion)	NA
12	Use of hand searching (eg, reference lists of obtained articles)	NA
13	List of citations located and those excluded, including justification	NA
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
	Reporting of methods should include	
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	NA
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	NA
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	NA
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Supplementary Table 2
22	Assessment of heterogeneity	3
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	3
24	Provision of appropriate tables and graphics	yes
	Reporting of results should include	
25	Graphic summarizing individual study estimates and overall estimate	NA
26	Table giving descriptive information for each study included	Table 2

27	Results of sensitivity testing (eg, subgroup analysis)	Supplementary Figure 4
28	Indication of statistical uncertainty of findings	NA
Item No	**Recommendation**	**Reported on Page No**
	Reporting of discussion should include	
29	Quantitative assessment of bias (eg, publication bias)	NA
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Supplementary Table 2
	Reporting of conclusions should include	
32	Consideration of alternative explanations for observed results	10
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11
34	Guidelines for future research	NA
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA 2000;283:2008-2012.

Supplementary Table S2. Bias assessment

Study (matched)	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Forrest JK et al. 2020 [21]	Serious	Critical	Low	Low	Moderate	Serious	Low	MODERATE-
Hellhammer K et al. 2018 [22]	Serious	Critical	Low	Low	Low	Moderate	Low	MODERATE+
Loewenstein I et al. 2022 [25]	Serious	Critical	Low	Low	Low	Serious	Low	MODERATE

Study (unmatched)	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Alvarado T et al. 2021 [19]	Serious	Cirtical	Low	Low	Low	Low	Low	MODERATE++
Dallan LAP et al. 2021 [20]	Serious	Cirtical	Low	Low	Low	Serious	Low	MODERATE
Kalogeras K et al. 2020 [23]	Serious	Critical	Low	Low	Low	Serious	Moderate	MODERATE-

Kroon HG et al. 2021 [24]	Serious	Cirtical	Low	Low	Low	Moderate	Moderate	MODERATE
Modolo R et al. 2020 [26]	Serious	Critical	Low	Low	Low	Low	Low	MODERATE++
Rao G et al. 2019 [27]	Serious	Critical	Low	Low	Serious	Moderate	Low	MODERATE-
Regazzoli D et al. 2019 [28]	Serious	Critical	Low	Low	Low	Serious	Moderate	MODERATE-
Schmidt S et al. 2022 [29]	Serious	Critical	Low	Low	Low	Serious	Low	MODERATE

Supplementary Table S3. Inclusion (choice of procedure type), exclusion criteria and choice of valve type.			
Study [ref]	Inclusion criteria/ Selection criteria for the procedure	Exclusion criteria	Selection criteria for the valve
Alvarado T et al. 2021 [19]	Patients presenting symptomatic (NYHA class >2) severe aortic stenosis (defined as aortic valve area (AVA) <1 cm^2 or indexed AVA <0.6 cm^2/m^2 who were deemed intermediate or high risk (STS >3) for SAVR.	Severe mitral regurgitation and presence of an aortic annulus size outside the limits recommended for the implant (perimeter derived diameter <18 mm or >26 mm).	Not reported.
Dallan LAP et al. 2021 [20]	Data from patients who underwent a TAV-in-SAV procedure using an Evolut R or Evolut PRO valve between April 2015 and June 2019 retrieved from the TVT Registry.	Not reported.	Not reported.
Forrest JK et al. 2020 [21]	TVT Registry database for patients with native tricuspid aortic valve stenosis treated with Medtronic self-expanding transcatheter aortic valves from January 2014 to September 2017 with follow-up through December 2017.	Data for the 31mm CoreValve and the 34mm Evolut R valve and patients with primary aortic insufficiency, with pre-existing surgical or transcatheter valves, and with bicuspid or other nontrileaflet native aortic anatomy.	Not reported.
Hellhammer K et al. 2018 [22]	Patients who underwent transfemoral TAVR with the MCV system from September 2015 to January 2018.	Patients with a valve size Evolut R 34mm and Evolut R 23mm.	Not reported.
Kalogeras K et al. 2020 [23]	Patients treated with either Evolut R or the Evolut PRO prostheses were included in the study.	Patients requiring the large 34 mm device (annulus perimeter N 81.7 mm) were excluded from the analysis, as the large size prosthesis is only available for the Evolut R platform and not the PRO. All patients with bicuspid valve were also excluded to avoid confounding the results.	Not reported.
Kroon HG et al. 2021 [24]	All patients who underwent transfemoral or transsubclavian TAVI with one of the three SEVs for severe aortic stenosis between January 2012 and December 2018 were entered into our prospective database.	Patients with a pacemaker at baseline were excluded (n = 37).	Not reported.

Loewenstein I et al. 2022 [25]	Diagnosis of aortic stenosis based on clinical and echocardiographic criteria of symptomatic patients with an aortic valve area (AVA) of ≤1 cm^2 or an indexed AVA of ≤0.6cm^2	Patients with missing valve-type data, treated with valves produced by other manufacturers than Medtronic, patients treated via non-femoral artery vascular access	Choice of senior interventional cardiologist according to valve availability.
Modolo R et al. 2020 [26]	Not reported.	Not reported.	Not reported.
Rao G et al. 2019 [27]	Severe symptomatic (NYHA ≥2) aortic stenosis (orifice area <1cm^2 continuity equation and a mean aortic valve gradient >40 mmHg or a max. velocity >4 m/s at rest on transthoracic echocardiography) in patients deemed high risk for SAVR.	Any previous aortic valve implantation, bicuspid aortic valves and patients requiring subclavian access.	Not reported.
Regazzoli D et al. 2019 [28]	Diagnosis of aortic stenosis and small aortic annuli treated with transcatheter implantation of current-generation SEVs (Evolut R, Evolut PRO, Acurate, Portico). A small aortic annulus was defined as annular area <400 mm^2 and/or annular perimeter <72 mm on computed tomography.	TAVR for pure aortic regurgitation and a lack of pre-procedural computed tomographic data.	Prosthesis type and size selection, as well as implantation technique and subsequent antithrombotic therapy, were left to discretion of the treating physician at each center.
Schmidt S et al. 2022 [29]	Successful TAVR with one of the dedicated valves (S3, ER, Neo), the integrity of pre-procedural CT measurements as well as availability of post-intervention echocardiography.	Patients undergoing valve-in-valve TAVR.	Prosthesis selection was at the discretion of the local heart team at each site.

Supplementary Table S4. Patients' baseline characteristics

Study [ref]	Intervention	HT (%)	DM (%)	PVD (%)	CKI (%)	COPD (%)	PM/ICD (%)	AF (%)	CAD (%)	MI history (%)	Stroke/CVD history (%)	Heart surgery history (%)	NYHA III/IV (%)	LVEF (%)	Mean aortic valve gradient [mmHg]	Aortic valve area (cm^2)	Aortic valve annulus diameter (mm)
Alvarado T et al. 2021 [19]	EvP	85	21	6	15	9	6	24	NR	3	15	6	48	63.0±14.0	42.0±13.0	0.70±0.16	23.0±1.8.0
	EvR	84	34	4	34	16	10	42	NR	8	14	12	68	62.0±10,6	45.0±18.0	0.70±0.18	24.0±4.3
Dallan LAP et al. 2021 [20]	EvP	90	32.3	25.1	NR	44.7	2	NR	NR	17.6	11.9	NR	79,7	NR	NR	NR	NR
	EvR	89.3	34.5	27.3	NR	44	3.7	NR	NR	21.1	13	NR	80,4	NR	NR	NR	NR
Forrest JK et al. 2020 [21]	EvP	92.3	37.6	26.2	NR	41.6	16.6	35.5	NR	NR	12.6	18.3	75.5	56.7±12.9	42.4±14.4	0.70±0.22	NR
	EvR	92.3	35.8	26.8	NR	41.7	15.2	35.5	NR	NR	12.8	19.5	78.1	56.6±13.4	43.3±15.2	0.69±0.21	NR
Hellhammer K et al. 2018 [22]	EvP	87.8	20.2	9.5	NR	18.9	12.1	50	71.6	NR	NR	NR	NR	NR	NR	0.79±0.18	73.0±5.4
	EvP	89.1	24.3	16.2	NR	33.1	10.8	33.1	70.9	NR	NR	NR	NR	NR	NR	0.62±0.20	73.0±6.2
Kalogeras K et al. 2020 [23]	EvR	NR	20.7	NR	29.3	NR	10.7	28	17.1	11.7	NR	11.9	NR	NR	40.3±19.9	0.72±0.48	NR
	EvP	NR	25.4	NR	33.5	NR	7.6	22.6	25.6	14.9	NR	57	NR	NR	46.5±18.8	0.69±0.32	NR
Kroon HG et al. 2021 [24]	EvP	NR	20.7	NR	29.3	NR	10.7	28	17.1	11.7	NR	11.9	NR	NR	NR	NR	23.7±1.8
	EvR	NR	25.4	NR	33.5	NR	7.6	22.6	25.6	14.9	NR	57	NR	NR	NR	NR	23.7±1.9
Loewenstein I et al. 2022 [25]	EvP	90.8	37.3	8.6	NR	NR	13.6	27.7	36.4	15.1	NR	NR	NR	58.4±9.7	NR	0.67±0.2	NR
	EvR	86.1	37.9	10.1	NR	NR	13.1	28.7	44,9	15.5	NR	NR	NR	56.1±11.0	NR	0.69±0.2	NR
Modolo R et al. 2020 [26]	EvP	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	EvR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Rao G et al. 2019 [27]	EvP	88.5	29.5	NR	NR	NR	NR	NR	NR	24.6	NR	NR	NR	NR	NR	NR	NR
	EvR	94.6	37.5	NR	NR	NR	NR	NR	NR	17.9	NR	NR	NR	NR	NR	NR	NR
Regazzoli D et al. 2019 [28]	EvP	81.9	24.1	19.1	NR	3.6	14.5	25	28.6	9.6	9.5	NR	81	NR	51.6±1.9	0.61±0.02	21.4±0.1
	EvR	85.4	26.2	18.1	NR	13.1	9.4	20.6	38.4	11.1	8.6	NR	74.1	NR	50.6±0.8	0.65±0.01	21.2±0.1
Schmidt S et al. 2022 [29]	EvP	85.4	25	NR	54.5	NR	NR	31.2	56.7	NR	NR	7.5	NR	NR	48.1±19.5	NR	23.4±1.7
	EvR	89.9	30.6	NR	62.3	NR	NR	43.2	62.6	NR	NR	17.8	NR	NR	34.9±20.7	NR	23.8±2.5
P, Evolut PRO; R, Evolut R; HT, hypertension; DM, diabetes mellitus; PVD, peripheral vascular disease; CKI, chronic kidney injury; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PM/ICD, pacemaker/implantable cardioverter-defibrillator; AF, atrial fibrillation; CAD, coronary artery disease; MI, miocardial infarction; LVEF, left ventricle ejection fraction; NR, not reported.																	

Supplementary Table S5. Procedural characteristics

Study [ref]	Intervention	Anesthesia (%)	Access site (%)	Valve sizes implanted (%) or mean±SD	Pre-dilatation (%)	Post-dilatation (%)	Contrast volume (ml)	Fluoroscopy time (minutes)	Procedure duration (minutes)
Alvarado T et al. 2021 [19]	EvP	general 45	femoral 100	NR	NR	NR	NR	NR	NR
	EvR	general 88	femoral 94	NR	NR	NR	NR	NR	NR
Dallan LAP et al. 2021 [20]	EvP	general 53.5	femoral 95.4	23 - 40.7 26 - 37.9 29 - 21.4 34 - 0	NR	NR	NR	NR	110.7±58.5
	EvR	general 59.9	femoral 95	23 - 50.7 26 - 33.4 29 - 12.6 34 - 3.3	NR	NR	NR	NR	110.1±57.5
Forrest JK et al. 2020 [21]	EvP	general 59.7	femoral 94.1 subclavian 2.9 direct aortic 2.0	23 - 3.2 26 - 33.6 29 - 63.3	NR	NR	NR	NR	100.9± 53.9
	EvR	general 55.9	femoral 93.5 subclavian 4.2 direct aortic 0.8	23 - 4.6 26 - 35.4 29 - 60	NR	NR	NR	NR	109.4± 53.5
Hellhammer K et al. 2018 [22]	EvP	NR	NR	26 - 51.4 29 - 48.6	28.3	18.9	101.7±32.5	17.4 ±6.5	83.4 ±25.9
	EvR	NR	NR	26 - 47.3 29 - 52.7	77.7	4.1	125.9 ±41.4	21.4 ± 8.8	105.5±31.2
Kalogeras K et al. 2020 [23]	EvP	general 0	femoral 100	NR	7.4	33.8	NR	NR	NR
	EvR	general 26.2	femoral 94 subclavian 5.6	NR	9.5	21.8	NR	NR	NR
Kroon HG et al. 2021 [24]	EvP	NR	femoral 97	23 - 2 26 - 33 29 - 65	12	41	NR	NR	NR
	EvR	NR	femoral 89	23 - 4 26 - 31 29 - 49	8	42	NR	NR	NR

				34 - 26					
Loewenstein I et al. 2022 [25]	EvP	NR	femoral 100	NR	NR	NR	124.1±54.5	17.5±9.5	NR
	EvR	NR	femoral 100	NR	NR	NR	151.9±138.2	19.2±11.4	NR
Modolo R et al. 2020 [26]	EvP	NR	NR	NR	NR	NR	NR	NR	NR
	EvR	NR	NR	NR	NR	NR	NR	NR	NR
Rao G et al. 2019 [27]	EvP	general 98.3	femoral 100	23 - 5 26 - 46.7 29 - 48.3	9.8	26.7	NR	NR	NR
	EvR	general 82.1	femoral 100	23 - 3.5 26 - 27.3 29 - 33.9 34 - 30.4	5.4	25	NR	NR	NR
Regazzoli D et al. 2019 [28]	EvP	NR	femoral 91.7	25.8±0.14	32.5	42.2	132.4±6.8	NR	NR
	EvR	NR	femoral 92.4	25.8±0.08	31.1	35.7	147.5±4.0	NR	NR
Schmidt S et al. 2022 [29]	EvP	NR	NR	NR	45.1	32.8	NR	NR	NR
	EvR	NR	NR	NR	30.4	26.6	NR	NR	NR
EvP, Evolut PRO; EvR, Evolut R; NR, not reported									

Supplementary figures legend:

Supplementary Figure S1: Risk Ratios (RRs) and corresponding 95% Confidence Intervals (CIs) for the comparison of Evolut PRO and Evolut R devices; A) more than 1 valve implanted; B) other TAVI-related complications. Each square represents study point estimate; diamonds reflect the overall effect. IV, inverse variance.

Supplementary Figure S2: A) Mean Differences (MDs) and corresponding 95% Confidence Intervals (CIs) for the comparison of Evolut PRO and Evolut R devices in terms of mean transprosthetic gradient; B) Risk Ratios (RRs) and corresponding 95% Confidence Intervals (CIs) for the comparison of Evolut PRO and Evolut R devices in terms of patient-prosthesis mismatch. Each square represents study point estimate; diamonds reflect the overall effect. IV, inverse variance.

Supplementary Figure S3: Risk Ratios (RRs) and corresponding 95% Confidence Intervals (CIs) for the comparison of Evolut PRO and Evolut R devices; A) 30-day mortality; B) myocardial infarction; C) cerebrovascular accident. Each square represents study point estimate; diamonds reflect the overall effect. IV, inverse variance.

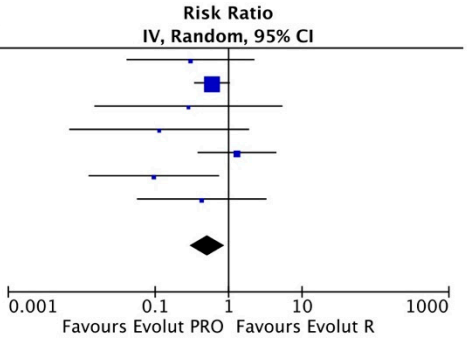
Supplementary Figure S4: Sensitivity analysis for the endpoints moderate-to-severe paravalvular leak (A) and major bleeding (B) after exclusion of single studies one at time and repeating the calculations. Risk difference (RD) analysis for all endpoints including studies reporting “0” events: patient prosthesis mismatch (C); major vascular complications (D); other TAVI related complications (E); 30-day mortality (F); myocardial infarction (G) and stroke (H).

Supplementary Figure S1:

A

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Dallan LAP et al. 2021	1	836	20	5061	6.9%	0.30 [0.04, 2.25]
Forrest JK et al. 2020	19	1500	32	1500	56.2%	0.59 [0.34, 1.04]
Hellhammer K et al. 2018	0	74	3	148	3.3%	0.28 [0.01, 5.42]
Kalogeras K et al. 2020	0	175	12	498	3.6%	0.11 [0.01, 1.91]
Kroon HG et al. 2021	4	82	6	160	16.8%	1.30 [0.38, 4.48]
Loewenstein I et al. 2022	1	222	10	213	6.6%	0.10 [0.01, 0.74]
Regazzoli D et al. 2019	1	84	11	397	6.7%	0.43 [0.06, 3.28]
Total (95% CI)		**2973**		**7977**	**100.0%**	**0.52 [0.30, 0.89]**
Total events	26		94			

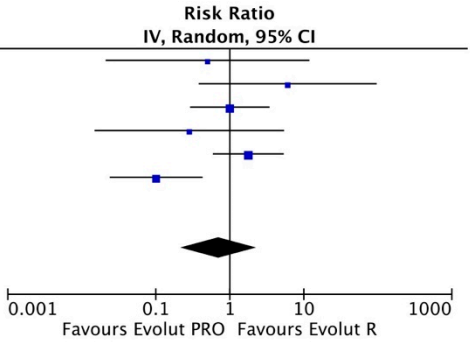
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.51$, df = 6 (P = 0.37); $I^2 = 8\%$
Test for overall effect: Z = 2.40 (P = 0.02)



B

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Alvarado T et al. 2021	0	33	1	50	9.5%	0.50 [0.02, 11.92]
Dallan LAP et al. 2021	1	836	1	5061	11.4%	6.05 [0.38, 96.69]
Forrest JK et al. 2020	5	1500	5	1500	23.1%	1.00 [0.29, 3.45]
Hellhammer K et al. 2018	0	74	3	148	10.5%	0.28 [0.01, 5.42]
Kalogeras K et al. 2020	5	175	8	498	24.3%	1.78 [0.59, 5.36]
Loewenstein I et al. 2022	2	222	19	213	21.1%	0.10 [0.02, 0.43]
Rao G et al. 2019	0	60	0	56		Not estimable
Total (95% CI)		**2900**		**7526**	**100.0%**	**0.71 [0.22, 2.32]**
Total events	13		37			

Heterogeneity: $Tau^2 = 1.16$; $Chi^2 = 12.61$, df = 5 (P = 0.03); $I^2 = 60\%$
Test for overall effect: Z = 0.56 (P = 0.57)

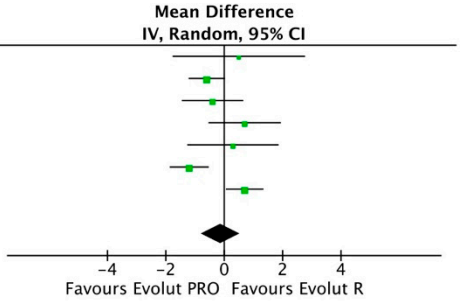


Supplementary Figure S2

A

Study or Subgroup	EvPRO Mean	EvPRO SD	EvPRO Total	EvR Mean	EvR SD	EvR Total	Weight	Mean Difference IV, Random, 95% CI
Alvarado T et al. 2021	8.9	3.7	33	8.4	6.8	50	6.3%	0.50 [-1.77, 2.77]
Dallan LAP et al. 2021	14.9	8.4	836	15.5	9.1	5061	19.0%	-0.60 [-1.22, 0.02]
Hellhammer K et al. 2018	7.5	3.7	74	7.9	3.9	148	14.6%	-0.40 [-1.45, 0.65]
Loewenstein I et al. 2022	9.5	7.5	222	8.8	5.6	213	12.8%	0.70 [-0.54, 1.94]
Rao G et al. 2019	8.5	4.6	60	8.2	4	56	10.1%	0.30 [-1.27, 1.87]
Regazzoli D et al. 2019	6.9	3	84	8.1	2	397	18.5%	-1.20 [-1.87, -0.53]
Schmidt S et al. 2022	8.4	4.5	268	7.7	4.2	546	18.8%	0.70 [0.06, 1.34]
Total (95% CI)			**1577**			**6471**	**100.0%**	**-0.11 [-0.78, 0.56]**

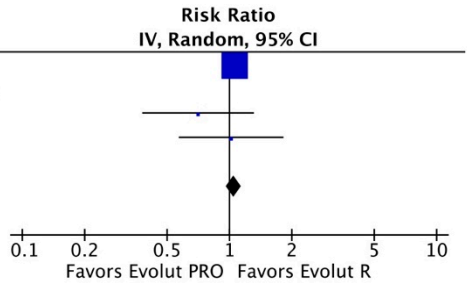
Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 20.50$, df = 6 (P = 0.002); $I^2 = 71\%$
Test for overall effect: Z = 0.33 (P = 0.74)



B

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Dallan LAP et al. 2021	356	836	2035	5061	96.1%	1.06 [0.97, 1.15]
Rao G et al. 2019	0	60	0	56		Not estimable
Regazzoli D et al. 2019	10	84	67	397	1.8%	0.71 [0.38, 1.31]
Schmidt S et al. 2022	16	268	32	546	2.1%	1.02 [0.57, 1.82]
Total (95% CI)		**1248**		**6060**	**100.0%**	**1.05 [0.97, 1.14]**
Total events	382		2134			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.62$, df = 2 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 1.15 (P = 0.25)

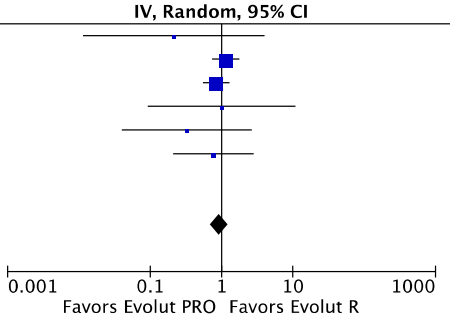


Supplementary Figure S3

A

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Alvarado T et al. 2021	0	33	3	50	1.0%	0.21 [0.01, 4.02]
Dallan LAP et al. 2021	23	836	122	5061	44.4%	1.14 [0.74, 1.77]
Forrest JK et al. 2020	37	1500	44	1500	46.1%	0.84 [0.55, 1.29]
Hellhammer K et al. 2018	1	74	2	148	1.5%	1.00 [0.09, 10.85]
Kroon HG et al. 2021	1	82	6	160	1.9%	0.33 [0.04, 2.66]
Loewenstein I et al. 2022	4	222	5	213	5.1%	0.77 [0.21, 2.82]
Rao G et al. 2019	0	60	0	56		Not estimable
Total (95% CI)		**2807**		**7188**	**100.0%**	**0.93 [0.69, 1.25]**
Total events	66		182			

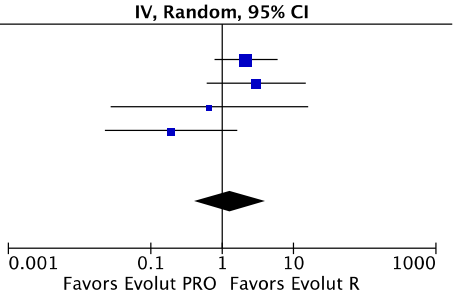
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.06$, df = 5 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 0.48 (P = 0.63)



B

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Alvarado T et al. 2021	0	33	0	50		Not estimable
Dallan LAP et al. 2021	5	836	14	5061	42.0%	2.16 [0.78, 5.99]
Forrest JK et al. 2020	6	1500	2	1500	28.0%	3.00 [0.61, 14.84]
Hellhammer K et al. 2018	0	74	1	148	10.5%	0.66 [0.03, 16.06]
Loewenstein I et al. 2022	1	222	5	213	19.5%	0.19 [0.02, 1.63]
Rao G et al. 2019	0	60	0	56		Not estimable
Total (95% CI)		**2725**		**7028**	**100.0%**	**1.31 [0.42, 4.05]**
Total events	12		22			

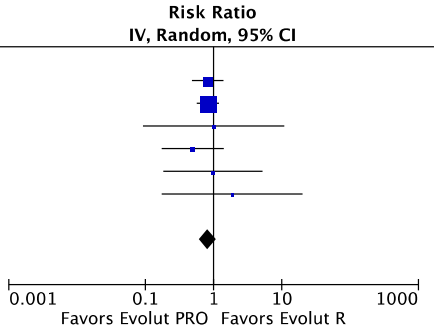
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 5.00$, df = 3 (P = 0.17); $I^2 = 40\%$
Test for overall effect: Z = 0.46 (P = 0.64)



C

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Ratio IV, Random, 95% CI
Alvarado T et al. 2021	0	33	0	50		Not estimable
Dallan LAP et al. 2021	15	836	111	5061	28.7%	0.82 [0.48, 1.40]
Forrest JK et al. 2020	48	1500	58	1500	58.0%	0.83 [0.57, 1.20]
Hellhammer K et al. 2018	1	74	2	148	1.4%	1.00 [0.09, 10.85]
Kalogeras K et al. [ATLAS] 2020	4	175	23	498	7.5%	0.49 [0.17, 1.41]
Kroon HG et al. 2021	2	82	4	160	2.9%	0.98 [0.18, 5.22]
Rao G et al. 2019	2	60	1	56	1.5%	1.87 [0.17, 20.02]
Total (95% CI)		**2760**		**7473**	**100.0%**	**0.81 [0.61, 1.08]**
Total events	72		199			

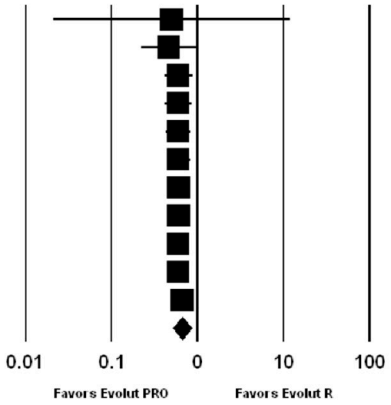
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.42$, df = 5 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 1.45 (P = 0.15)



Supplementary Figure S4:

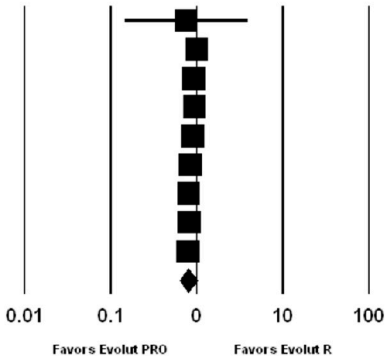
A

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Alvarado T et al. 2021	0.500	0.021	11.916	-0.428	0.668
Dallan LAP et al. 2021	0.463	0.220	0.973	-2.031	0.042
Forrest JK et al. 2020	0.603	0.420	0.866	-2.741	0.006
Hellhammer K et al. 2018	0.599	0.419	0.858	-2.793	0.005
Kalogeras K et al. [ATLAS] 2020	0.588	0.424	0.816	-3.179	0.001
Kroon HG et al. 2021	0.600	0.440	0.819	-3.217	0.001
Loewenstein I et al. 2022	0.606	0.449	0.818	-3.275	0.001
Modolo R et al. 2020	0.605	0.455	0.805	-3.451	0.001
Rao G et al. 2019	0.598	0.452	0.791	-3.608	0.000
Regazzoli D et al. 2019	0.596	0.452	0.787	-3.647	0.000
Schmidt S et al. 2022	0.665	0.516	0.856	-3.160	0.002
	0.665	0.516	0.856	-3.160	0.002



B

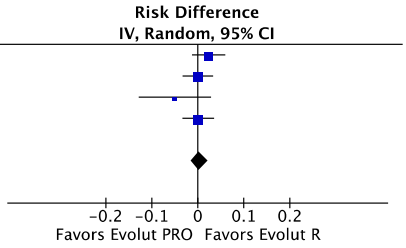
Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Alvarado T et al. 2021	0.758	0.147	3.903	-0.332	0.740
Dallan LAP et al. 2021	1.000	0.749	1.335	0.000	1.000
Forrest JK et al. 2020	0.929	0.701	1.231	-0.515	0.607
Hellhammer K et al. 2018	0.944	0.714	1.247	-0.409	0.683
Kalogeras K et al. [ATLAS] 2020	0.900	0.689	1.176	-0.773	0.440
Kroon HG et al. 2021	0.840	0.649	1.088	-1.319	0.187
Loewenstein I et al. 2022	0.807	0.633	1.030	-1.725	0.084
Rao G et al. 2019	0.816	0.641	1.038	-1.657	0.097
Regazzoli D et al. 2019	0.800	0.631	1.015	-1.838	0.066
	0.800	0.631	1.015	-1.838	0.066



C

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Dallan LAP et al. 2021	356	836	2035	5061	28.6%	0.02 [−0.01, 0.06]
Rao G et al. 2019	0	60	0	56	34.0%	0.00 [−0.03, 0.03]
Regazzoli D et al. 2019	10	84	67	397	6.1%	−0.05 [−0.13, 0.03]
Schmidt S et al. 2022	16	268	32	546	31.3%	0.00 [−0.03, 0.04]
Total (95% CI)		**1248**		**6060**	**100.0%**	**0.00 [−0.02, 0.02]**
Total events	382		2134			

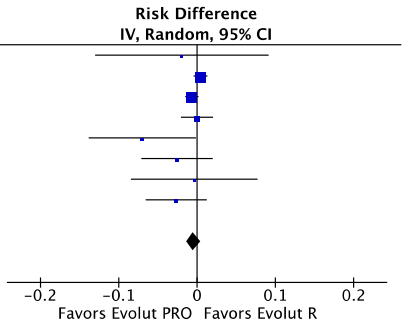
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.03$, df = 3 (P = 0.39); $I^2 = 1\%$
Test for overall effect: Z = 0.41 (P = 0.68)



D

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Alvarado T et al. 2021	2	33	4	50	0.6%	−0.02 [−0.13, 0.09]
Dallan LAP et al. 2021	13	836	56	5061	36.3%	0.00 [−0.00, 0.01]
Forrest JK et al. 2020	16	1500	26	1500	37.7%	−0.01 [−0.02, 0.00]
Hellhammer K et al. 2018	0	74	0	148	14.1%	0.00 [−0.02, 0.02]
Kroon HG et al. 2021	4	82	19	160	1.6%	−0.07 [−0.14, −0.00]
Loewenstein I et al. 2022	11	222	16	213	3.6%	−0.03 [−0.07, 0.02]
Rao G et al. 2019	3	60	3	56	1.2%	−0.00 [−0.08, 0.08]
Regazzoli D et al. 2019	2	84	20	397	4.8%	−0.03 [−0.07, 0.01]
Total (95% CI)		**2891**		**7585**	**100.0%**	**−0.00 [−0.01, 0.00]**
Total events	51		144			

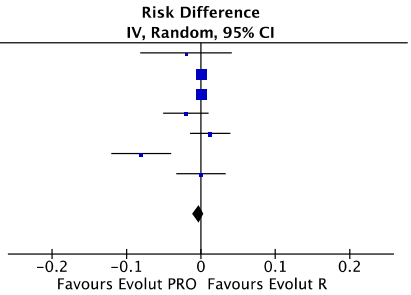
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.65$, df = 7 (P = 0.21); $I^2 = 27\%$
Test for overall effect: Z = 0.97 (P = 0.33)



E

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Alvarado T et al. 2021	0	33	1	50	1.4%	−0.02 [−0.08, 0.04]
Dallan LAP et al. 2021	1	836	1	5061	41.0%	0.00 [−0.00, 0.00]
Forrest JK et al. 2020	5	1500	5	1500	37.8%	0.00 [−0.00, 0.00]
Hellhammer K et al. 2018	0	74	3	148	5.3%	−0.02 [−0.05, 0.01]
Kalogeras K et al. [ATLAS] 2020	5	175	8	498	6.6%	0.01 [−0.01, 0.04]
Loewenstein I et al. 2022	2	222	19	213	3.2%	−0.08 [−0.12, −0.04]
Rao G et al. 2019	0	60	0	56	4.6%	0.00 [−0.03, 0.03]
Total (95% CI)		**2900**		**7526**	**100.0%**	**−0.00 [−0.01, 0.00]**
Total events	13		37			

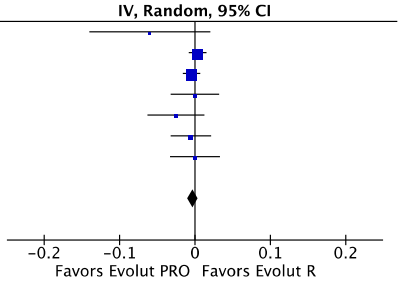
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.63$, df = 6 (P = 0.005); $I^2 = 68\%$
Test for overall effect: Z = 0.71 (P = 0.48)



F

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Alvarado T et al. 2021	0	33	3	50	0.8%	−0.06 [−0.14, 0.02]
Dallan LAP et al. 2021	23	836	122	5061	38.1%	0.00 [−0.01, 0.02]
Forrest JK et al. 2020	37	1500	44	1500	39.8%	−0.00 [−0.02, 0.01]
Hellhammer K et al. 2018	1	74	2	148	5.2%	0.00 [−0.03, 0.03]
Kroon HG et al. 2021	1	82	6	160	3.7%	−0.03 [−0.06, 0.01]
Loewenstein I et al. 2022	4	222	5	213	7.5%	−0.01 [−0.03, 0.02]
Rao G et al. 2019	0	60	0	56	4.9%	0.00 [−0.03, 0.03]
Total (95% CI)		**2807**		**7188**	**100.0%**	**−0.00 [−0.01, 0.00]**
Total events	66		182			

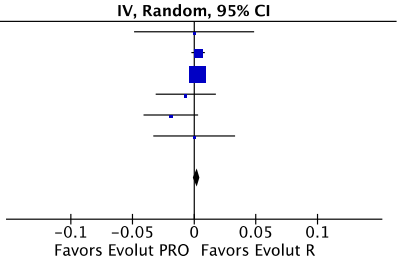
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.54$, df = 6 (P = 0.60); $I^2 = 0\%$
Test for overall effect: Z = 0.65 (P = 0.52)



G

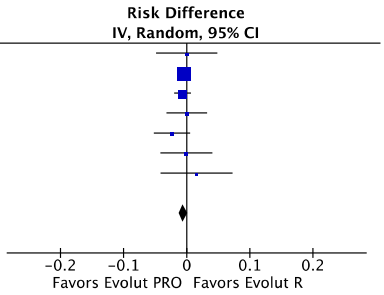
Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Alvarado T et al. 2021	0	33	0	50	0.4%	0.00 [−0.05, 0.05]
Dallan LAP et al. 2021	5	836	14	5061	30.2%	0.00 [−0.00, 0.01]
Forrest JK et al. 2020	6	1500	2	1500	65.3%	0.00 [−0.00, 0.01]
Hellhammer K et al. 2018	0	74	1	148	1.5%	−0.01 [−0.03, 0.02]
Loewenstein I et al. 2022	1	222	5	213	1.8%	−0.02 [−0.04, 0.00]
Rao G et al. 2019	0	60	0	56	0.8%	0.00 [−0.03, 0.03]
Total (95% CI)		**2725**		**7028**	**100.0%**	**0.00 [−0.00, 0.01]**
Total events	12		22			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.24$, df = 5 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 1.49 (P = 0.14)



H

Study or Subgroup	Evolut PRO Events	Evolut PRO Total	Evolut R Events	Evolut R Total	Weight	Risk Difference IV, Random, 95% CI
Alvarado T et al. 2021	0	33	0	50	2.2%	0.00 [−0.05, 0.05]
Dallan LAP et al. 2021	15	836	111	5061	52.7%	−0.00 [−0.01, 0.01]
Forrest JK et al. 2020	48	1500	58	1500	29.4%	−0.01 [−0.02, 0.01]
Hellhammer K et al. 2018	1	74	2	148	4.9%	0.00 [−0.03, 0.03]
Kalogeras K et al. [ATLAS] 2020	4	175	23	498	6.2%	−0.02 [−0.05, 0.01]
Kroon HG et al. 2021	2	82	4	160	3.0%	−0.00 [−0.04, 0.04]
Rao G et al. 2019	2	60	1	56	1.6%	0.02 [−0.04, 0.07]
Total (95% CI)		**2760**		**7473**	**100.0%**	**−0.01 [−0.01, 0.00]**
Total events	72		199			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.32$, df = 6 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 1.45 (P = 0.15)