SUPPLEMENTARY MATERIALS

Supplementary Table SI. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Table III
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
MATERIAL AND METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Table SI
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3

Section and Topic	Item #	Checklist item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was	Page 4

Section and Topic	Item #	Checklist item	Location where item is reported
		performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 4
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Figure S1
Results of	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect	Table II

Section and Topic	Item #	Checklist item	Location where item is reported
individual studies		estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 5-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figures
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figures
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figures
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7
	23b	Discuss any limitations of the evidence included in the review.	Page 9
	23c	Discuss any limitations of the review processes used.	Page 9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 10
Competing interests	26	Declare any competing interests of review authors.	Page 10
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 2

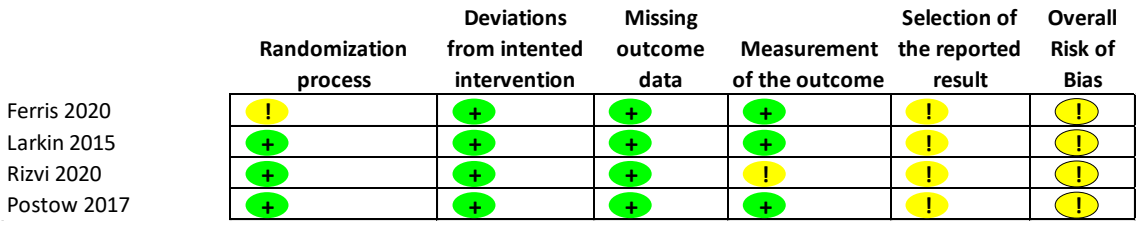
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Table SII. Search strategies

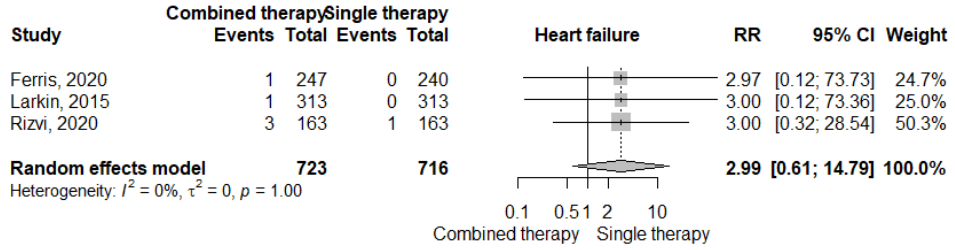
PubMed	("Immune Checkpoint Inhibitors"[Mesh] OR "Immune Checkpoint Inhibitors"[Tiab] OR CTLA-4 Antigen[Mesh] OR CTLA-4[Tiab] OR CTLA4[Tiab] OR CD152[Tiab] OR "Cytotoxic T Lymphocyte Associated Antigen 4"[Tiab] OR "Cytotoxic T-Lymphocyte Antigen 4"[Tiab] OR Ipilimumab[Mesh] OR Ipilimumab[Tiab] OR Tremelimumab[Tiab] OR Programmed Cell Death 1 Receptor[Mesh] OR "Programmed Cell Death 1"[Tiab] OR "Programmed death receptor 1"[Tiab] OR "PD-1"[Tiab] OR PD1[Tiab] OR "Programmed death ligand 1"[Tiab] OR "PD-L1"[Tiab] OR nivolumab[Tiab] OR pembrolizumab[Tiab] OR atezolizumab[Tiab] OR durvalumab[Tiab] OR cemiplimab[Tiab] OR toripalimab[Tiab] OR sintilimab[Tiab] OR avelumab[Tiab] OR Camrelizumab[Tiab] OR Pidilizumab[Tiab] OR Spartalizumab[Tiab] OR Keytruda[Tiab] OR Opdivo[Tiab] OR Libtayo[Tiab] OR Tecentriq[Tiab] OR Bavencio[Tiab] OR Imfinzi[Tiab]) AND (Neoplasms[Mesh] OR Neoplasm*[Tiab] OR carcinoma[Mesh] OR carcinoma[Tiab] OR cancer[Mesh] OR cancer[Tiab] OR tumo*[Tiab] OR malignan*[Tiab]) AND (random*[Tiab] OR placebo[Tiab] OR trial[Tiab])
Embase	("Immune Checkpoint Inhibitors":ti,ab OR CTLA-4:ti,ab OR CTLA4:ti,ab OR CD152:ti,ab OR "Cytotoxic T Lymphocyte Associated Antigen 4":ti,ab OR "Cytotoxic T-Lymphocyte Antigen 4":ti,ab OR Ipilimumab:ti,ab OR Tremelimumab:ti,ab OR "Programmed Cell Death 1":ti,ab OR "Programmed death receptor 1":ti,ab OR "PD-1":ti,ab OR PD1:ti,ab OR "Programmed death ligand 1":ti,ab OR "PD-L1":ti,ab OR nivolumab:ti,ab OR pembrolizumab:ti,ab OR atezolizumab:ti,ab OR durvalumab:ti,ab OR cemiplimab:ti,ab OR toripalimab:ti,ab OR sintilimab:ti,ab OR avelumab:ti,ab OR Camrelizumab:ti,ab OR Pidilizumab:ti,ab OR Spartalizumab:ti,ab OR Keytruda:ti,ab OR Opdivo:ti,ab OR Libtayo:ti,ab OR Tecentriq:ti,ab OR Bavencio:ti,ab OR Imfinzi:ti,ab) AND (Neoplasm*:ti,ab OR carcinoma:ti,ab OR cancer:ti,ab OR tumo*:ti,ab OR malignan*:ti,ab) AND (random*:ti,ab OR placebo:ti,ab OR trial:ti,ab)
Scopus	TITLE-ABS-KEY (("Immune Checkpoint Inhibitors" OR CTLA-4 OR CTLA4 OR CD152 OR "Cytotoxic T Lymphocyte Associated Antigen 4" OR "Cytotoxic T-Lymphocyte Antigen 4" OR Ipilimumab OR Tremelimumab OR "Programmed Cell Death 1" OR "Programmed death receptor 1" OR "PD-1" OR PD1 OR "Programmed death ligand 1" OR "PD-L1" OR nivolumab OR pembrolizumab OR atezolizumab OR

	durvalumab OR cemiplimab OR toripalimab OR sintilimab OR avelumab OR Camrelizumab OR Pidilizumab OR Spartalizumab OR Keytruda OR Opdivo OR Libtayo OR Tecentriq OR Bavencio OR Imfinzi) AND (Neoplasm* OR carcinoma OR cancer OR tumo* OR malignan*) AND (random* OR placebo OR trial))
Web of Science	TS=((“Immune Checkpoint Inhibitors” OR CTLA-4 OR CTLA4 OR CD152 OR “Cytotoxic T Lymphocyte Associated Antigen 4” OR “Cytotoxic T-Lymphocyte Antigen 4” OR Ipilimumab OR Tremelimumab OR “Programmed Cell Death 1” OR “Programmed death receptor 1” OR “PD-1” OR PD1 OR “Programmed death ligand 1” OR “PD-L1” OR nivolumab OR pembrolizumab OR atezolizumab OR durvalumab OR cemiplimab OR toripalimab OR sintilimab OR avelumab OR Camrelizumab OR Pidilizumab OR Spartalizumab OR Keytruda OR Opdivo OR Libtayo OR Tecentriq OR Bavencio OR Imfinzi) AND (Neoplasm* OR carcinoma OR cancer OR tumo* OR malignan*) AND (random* OR placebo OR trial))

Supplementary Figure S1. Risk of bias of included RCTs. RoB2 assessment of included randomized controlled trials. RoB2 domains: D1: randomization process; D2: deviations from intended interventions; D3: missing outcome data; D4: measurement of outcome; D5: selection of the report result. Red (-) describes a high risk of bias; yellow (!) describes some concerns about bias; and green (+) describes a low risk of bias

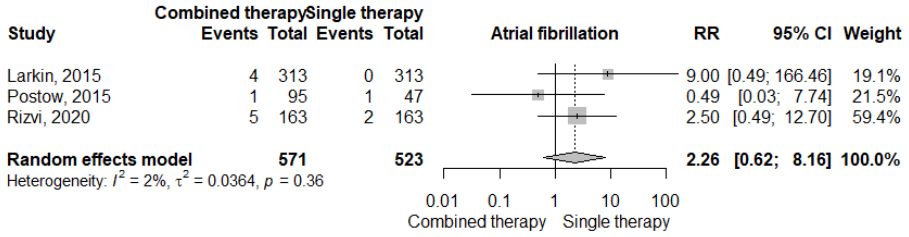


Supplementary Figure S2. Effects of combined versus single immunotherapy on heart failure



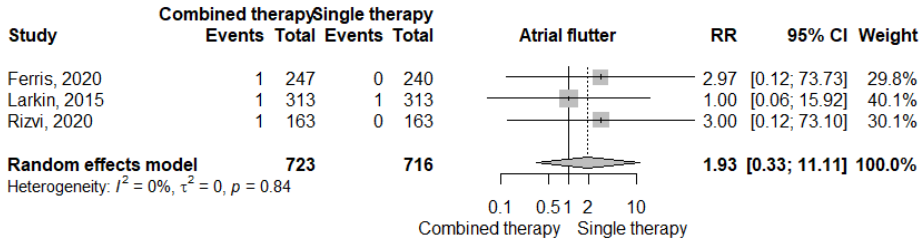
Effects of combined immunotherapy (Combined therapy) on heart failure compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S3. Effects of combined versus single immunotherapy on atrial fibrillation



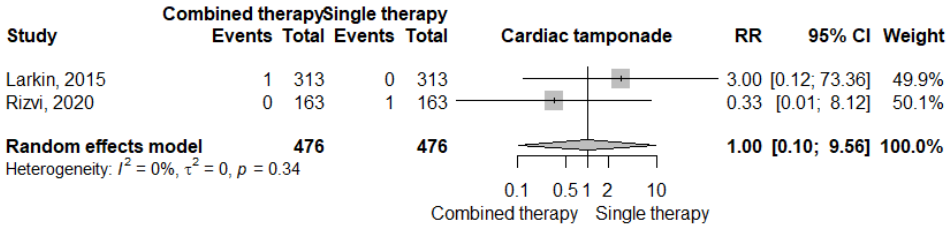
Effects of combined immunotherapy (Combined therapy) on atrial fibrillation compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S4. Effects of combined versus single immunotherapy on atrial flutter



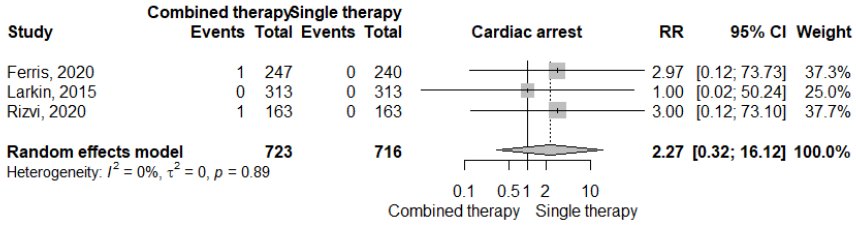
Effects of combined immunotherapy (Combined therapy) on atrial flutter compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S5. Effects of combined versus single immunotherapy on cardiac tamponade



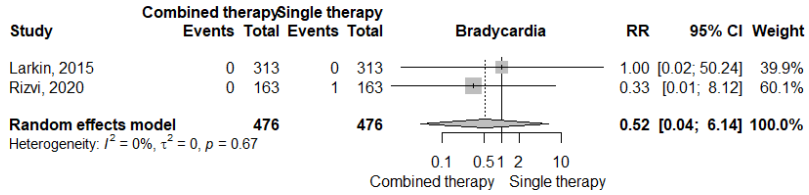
Effects of combined immunotherapy (Combined therapy) on cardiac tamponade compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S6. Effects of combined versus single immunotherapy on cardiac arrest



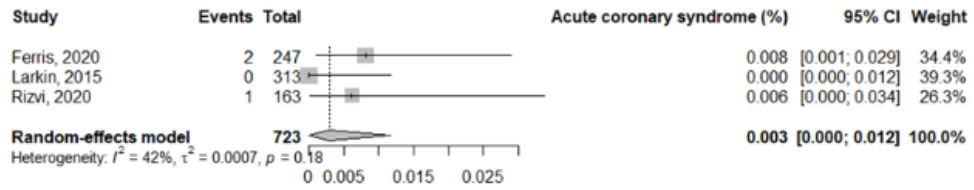
Effects of combined immunotherapy (Combined therapy) on cardiac arrest compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S7. Effects of combined versus single immunotherapy on bradycardia



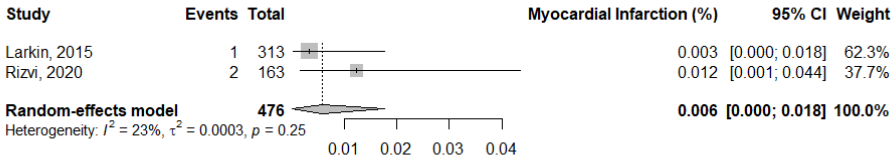
Effects of combined immunotherapy (Combined therapy) on bradycardia compared to control (Single therapy). Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S8. Prevalence of acute coronary syndromes in combined immunotherapy arms



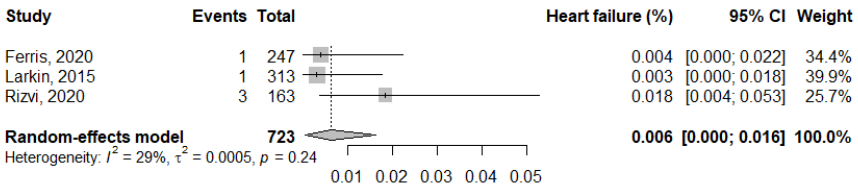
Prevalence of acute coronary syndromes in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S9. Prevalence of myocardial infarction in combined immunotherapy arms



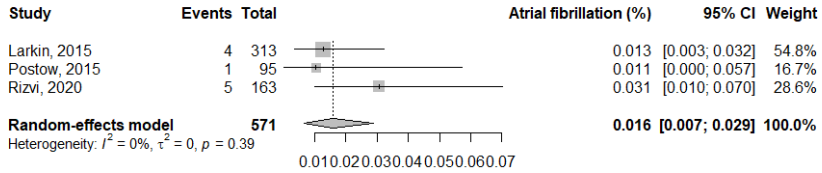
Prevalence of myocardial infarction in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S10. Prevalence of heart failure in combined immunotherapy arms



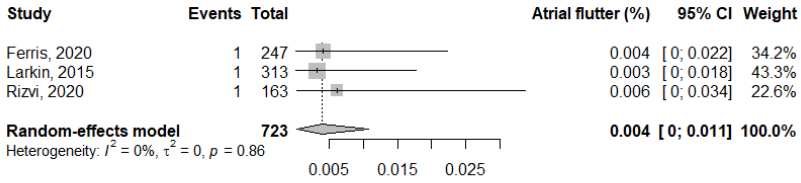
Prevalence of heart failure in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S11. Prevalence of atrial fibrillation in combined immunotherapy arms



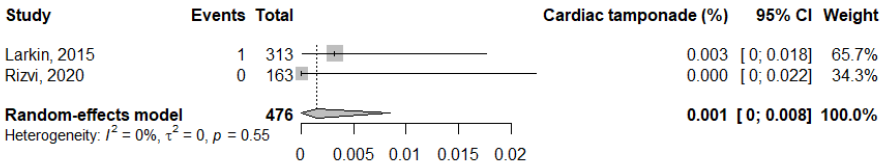
Prevalence of atrial fibrillation in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S12. Prevalence of atrial flutter in combined immunotherapy arms



Prevalence of atrial flutter in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

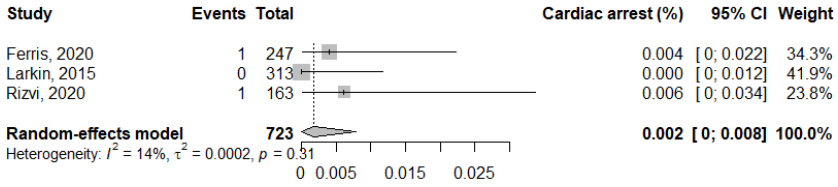
Supplementary Figure S13. Prevalence of cardiac tamponade in combined immunotherapy



arms

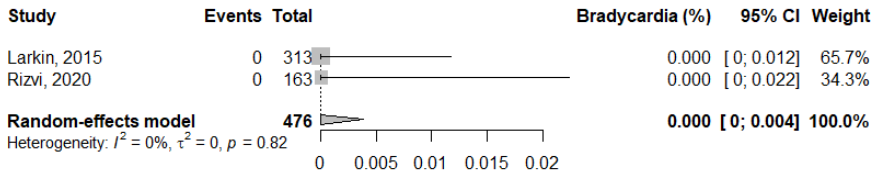
Prevalence of cardiac tamponade in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S14. Prevalence of cardiac arrest in combined immunotherapy arms



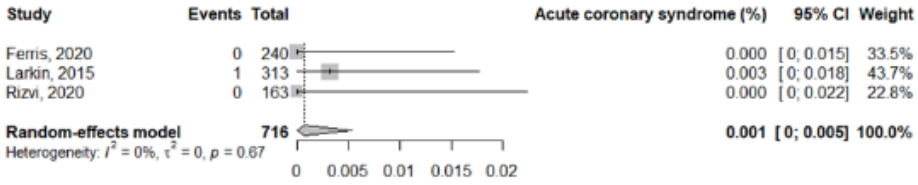
Prevalence of cardiac arrest in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S15. Prevalence of bradycardia in combined immunotherapy arms



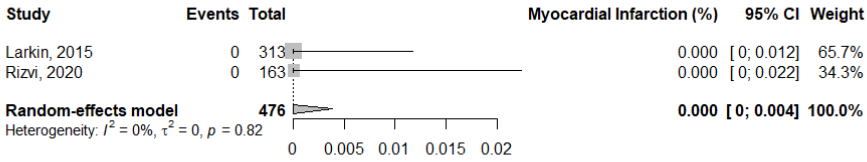
Prevalence of bradycardia in combined immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S16. Prevalence of acute coronary syndromes in single immunotherapy arms



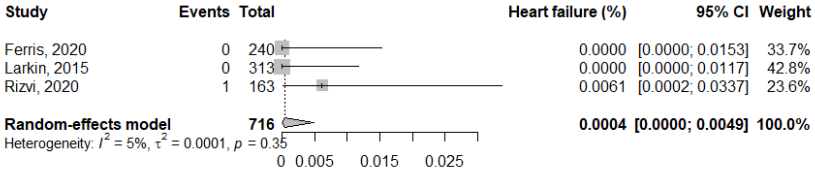
Prevalence of acute coronary syndromes in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S17. Prevalence of myocardial infarction in single immunotherapy arms



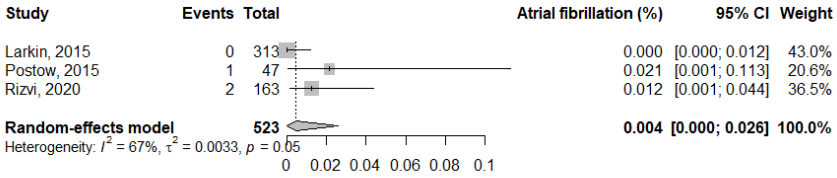
Prevalence of myocardial infarction in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S18. Prevalence of heart failure in single immunotherapy arms



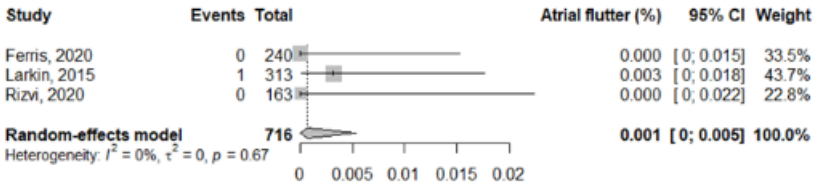
Prevalence of heart failure in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S19. Prevalence of atrial fibrillation in single immunotherapy arms



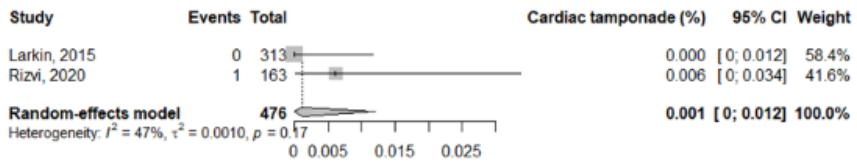
Prevalence of atrial fibrillation in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S20. Prevalence of atrial flutter in single immunotherapy arms



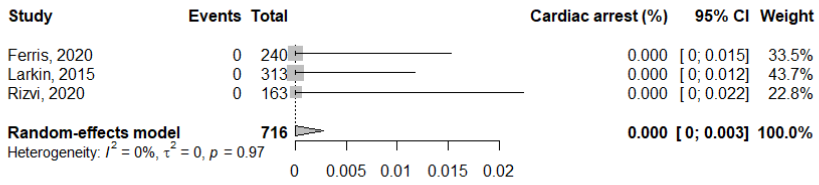
Prevalence of atrial flutter in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S21. Prevalence of cardiac tamponade in single immunotherapy arms



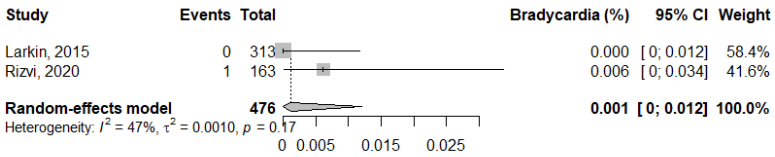
Prevalence of cardiac tamponade in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S22. Prevalence of cardiac arrest in single immunotherapy arms



Prevalence of cardiac arrest in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.

Supplementary Figure S23. Prevalence of bradycardia in single immunotherapy arms



Prevalence of bradycardia in single immunotherapy arms. Squares represent the mean difference (MD) of each RCT, horizontal lines represent the 95% confidence intervals (CI) of the MD, and diamonds are the MD of the overall random effects meta-analysis.