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META-ANALYSIS
Heart failure and cardiomyopathies

Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis

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See page 4978 for the editorial comment for this article 'Immune checkpoint inhibitors and cardiovascular events among patients with cancer: a window into the critical role of the immune system in cardiovascular biology', by L. Kondapalli and T.G. Neilan, https://doi.org/10.1093/eurheartj/ehab708.

Aims The risk and incidence of cardiovascular (CV) immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs) in cancer patients remain unknown.

Methods and results We systematically reviewed all randomized clinical trials (RCTs) including at least one ICI-containing arm and available CV adverse event (CVAE) data in cancer patients in the ClinicalTrials.gov registry, Medline, and the Cochrane CENTRAL Register of Controlled Trials, up to 31 August 2020 (CRD42020165672). The primary outcome was the summary risk of 16 different CVAEs associated with ICI exposure vs. controls (placebo and non-placebo) in RCTs. CVAEs with an increased risk associated with ICI exposure were considered as CV irAEs. Summary incidences of CV irAEs identified in our primary outcome analyses were computed using all RCTs including at least one ICI-containing arm. We used a random-effects meta-analysis to obtain Peto odds ratios (ORs) with 95% confidence intervals (CIs) and logit transformation and inverse variance weighting to compute summary incidences. Sixty-three unique RCTs with at least one ICI-containing arm (32 518 patients) were retrieved, among which 48 (29 592 patients) had a control arm. Among the 16 CVAEs studied, ICI use was associated with an increased risk of 6 CV irAEs including myocarditis, pericardial diseases, heart failure, dyslipidemia, myocardial infarction, and cerebral arterial ischaemia with higher risks for myocarditis (Peto OR: 4.42, 95% CI: 1.56–12.50, $P < 0.01$; $I^2 = 0\%$, $P = 0.93$) and dyslipidemia (Peto OR: 3.68, 95% CI: 1.89–7.19, $P < 0.01$; $I^2 = 0\%$, $P = 0.66$). The incidence of these CVAEs ranged from 3.2 (95% CI 2.0–5.1) to 19.3 (6.7–54.1) per 1000 patients, in studies with a median follow-up ranging from 3.2 to 32.8 months.

Conclusion In RCTs, ICI use was associated with six CV irAEs, not confined to myocarditis and pericarditis.

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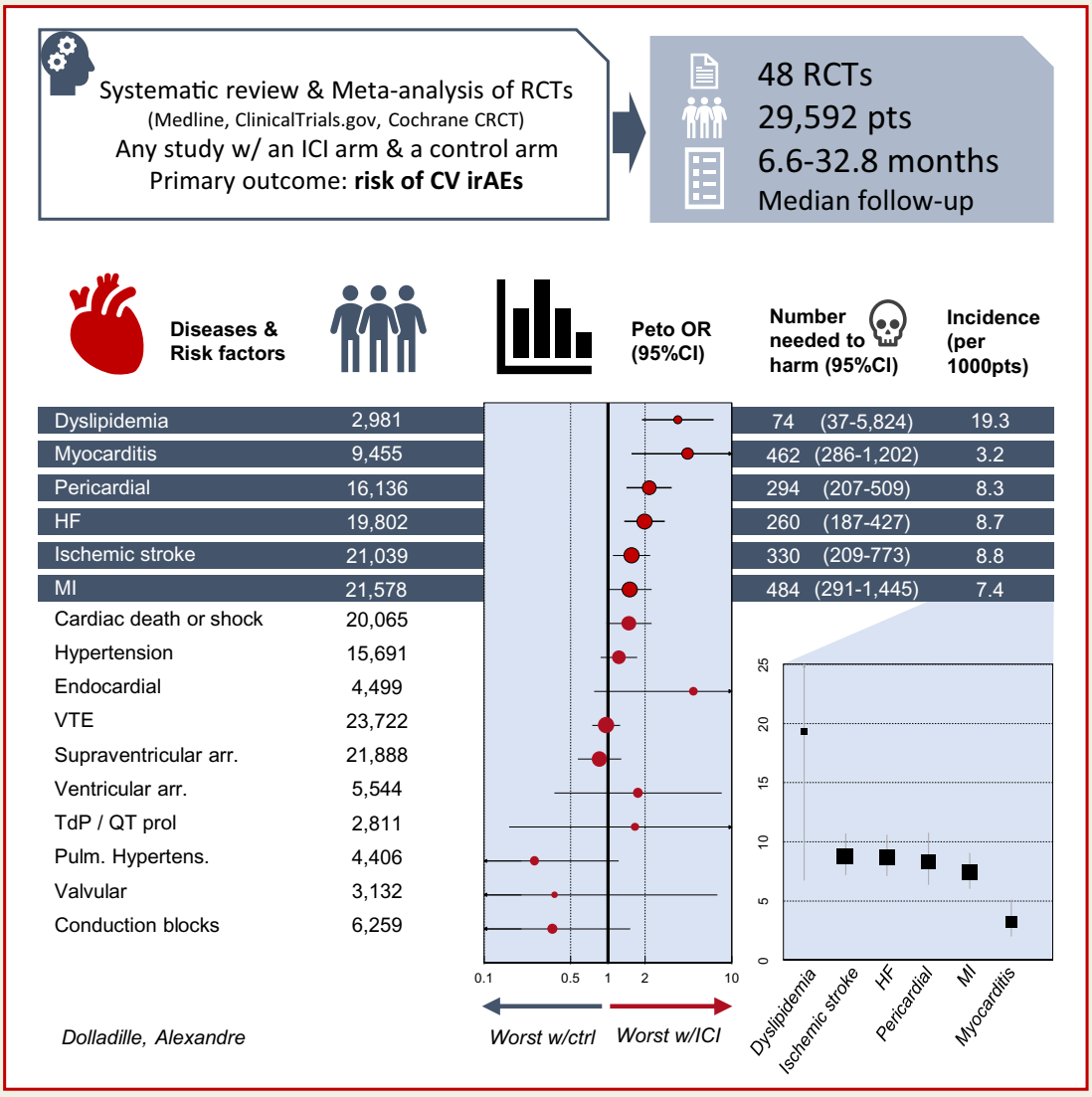
Graphical Abstract



Cardiovascular immunotoxicities (risk and incidence) of immune checkpoint inhibitors from randomized controlled trials.

Keywords Cardiovascular adverse event • Immune checkpoint inhibitor • Cancer • Safety meta-analysis • Randomized clinical trials

Introduction

With indications spanning multiple tumour types, immune checkpoint inhibitors (ICIs) used in monotherapy have become the standard of care for many types of cancer.[1] Although these novel immunotherapies were initially designed to treat advanced, refractory, or relapsed cancers, numerous ICIs, most commonly targeting programmed death-1 (PD-1), its ligand (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), are increasingly being used in early disease settings.[2] The number of patients receiving ICIs has increased in recent years and will continue to grow because indications for these therapies are ever expanding.[1,2] Due to the mechanism of action of ICIs, immune-related adverse events (irAEs) against normal tissue were anticipated.[3] With the growing number of treated patients, adverse events (AEs) associated with ICI use represent a real challenge for physicians, especially rare events for which standardized guidelines have not been established.[3]

Cardiovascular AEs (CVAEs) represent major issues for patients with cancer, during and after cancer treatment, and the frequency of CVAEs is higher in the cancer patient population.[4,5] The majority of

randomized controlled trials (RCTs) studying ICIs underestimated the risk of cardiovascular (CV) irAEs (i.e. myocarditis, pericarditis, and vasculitis), which have secondarily emerged as uncommon but potentially life-threatening AEs.[6–8] More recently, several CVAEs (i.e. myocardial infarction, heart failure, stroke, Takotsubo syndrome, arrhythmia)[9–15] were associated with ICI exposure in postmarketing surveillance studies. However, these studies only provide a low level of evidence by design and cannot infer direct causality between ICI use and CVAEs. Further evidence is mandatory to identify among all CVAEs reported in ICI RCTs, which CVAEs are at increased risk and are therefore to be considered as CV irAEs.

The aim of this study was to estimate the risk and incidence of CV irAEs associated with ICI exposure among all CVAEs reported in RCTs using a systematic review and a safety meta-analysis.

Methods

Registration

The study protocol was prospectively registered to the International Prospective Register of Systematic Reviews (registration number: CRD42020165672) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary material online, *Table S1*).[16] No ethics committee approval or subject informed consent was obtained as this was a retrospective analysis of already published studies.

Data sources, search strategy, and data extraction

A systematic review of the literature was performed in Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and the ClinicalTrials.gov register by two reviewers (J.Al. and P.-M.M.) according to prespecified selection criteria from inception to 7 April 2020. We used both controlled terms (i.e. MeSH terms in MEDLINE) and free-text terms related to ICIs with language restricted to English. Terms related to ICIs [anti-PD-1 antibodies (nivolumab, pembrolizumab, and cemiplimab), anti-PD-L1 antibodies (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 antibodies (ipilimumab and tremelimumab)] in the title or abstract (or both) were considered as the sole research domain, and the search strategy included the Cochrane Highly Sensitive Search Strategy for identifying RCTs in Medline.[17] Ongoing surveillance was performed up to 31 August 2020, to identify newly published studies (Medline) or posted results (ClinicalTrials.gov) that might affect the findings of the review. RCTs including at least one ICI-containing arm (including ICI in monotherapy, combination of ICI and ICI associated with other anticancer drugs) in adult patients (age ≥18 years) with cancer and available information on CVAEs were eligible for inclusion. Case reports or case series, case–control studies, observational studies, single-arm studies, and nonrandomized trials were excluded. We used a comprehensive stepwise method to capture all available CVAE cases. We described this method previously.[18] First, all available CVAEs classified according to the Common Terminology Criteria for Adverse Events (CTCAE) in RCTs on ICIs reported on ClinicalTrials.gov were extracted.[19,20] Second, if reported CVAEs were not available on ClinicalTrials.gov, all reported CVAEs were extracted from published RCTs. Last, regarding RCTs for which we had neither available CVAEs on ClinicalTrials.gov nor available CVAEs in publications, corresponding authors or sponsors of the study were contacted by e-mail to provide the required information. We checked each RCT identified to avoid double counting, and only RCTs for which CVAEs were available were retained in our final analyses. RCTs without data related to the CVAEs of interest were not included. We translated from CTCAE to the Medical Dictionary for Regulatory Activities (MedDRA) terminology, which was an exact match for CVAEs.

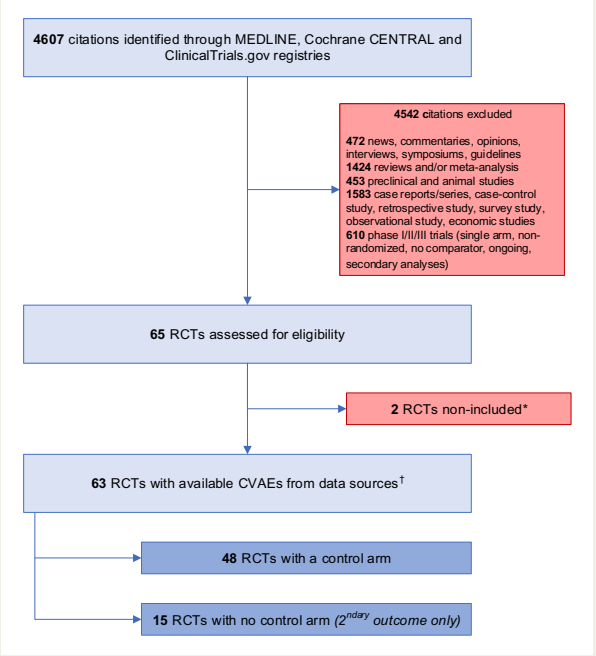


Figure 1 Study flow diagrams. PRISMA flow diagram of systematic review and meta-analysis in ClinicalTrials.gov registries, Medline, and Cochrane CENTRAL up to 7 April 2020. Ongoing surveillance was done up to 31 August 2020. CVAEs, cardiovascular adverse events; ICI, immune checkpoint inhibitors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials. *NCT02685059 (placebo RCT without available data from ClinicalTrials.gov and from publications) and NCT00527735 (placebo RCT with sequential administration of ICI and placebo in each arm). †Including 55 RCTs with available CVAEs from ClinicalTrials.gov and 8 supplementary RCTs with available CVAEs provided during ongoing surveillance.

Additional data from eligible studies were collected, including ICI regimen, control arm regimen, median age (years), previous lines of chemotherapy, intervention model, masking, median/mean follow-up (months), and overall number of patients analysed. All results including follow-up data posted on ClinicalTrials.gov were collected at the time of the searches.

Two authors (J.Al. and P.-M.M.) evaluated the risk of bias in individual studies using the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (also known as PROTECT) checklist tool specially designed to assess bias in safety meta-analyses.[21] In case of disagreements, a third author (C.D.) was consulted. Publication bias was assessed graphically by constructing a funnel plot. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Outcomes

The primary outcome of our meta-analysis was the summary risk of CVAEs associated with ICI exposure (any ICI regimen, including ICI in monotherapy, combination of ICI and ICI associated with other

Table 1 Characteristics of the randomized clinical trials included in the safety meta-analysis

Clinical Trials.gov Identifier	Study	Study design	Comparison	Type of cancer	Advanced or metastatic cancer	Prior systemic therapy (%)	Mean age (years)	Follow-up (months)	No. patients in monotherapy ICI group	No. patients in combination therapy ICI group	No. patients in ICI + chemotherapy	No. patients in ICI + targeted therapy	No. patients in ICI + other anticancer drug(s) regimen(s)	No. patients in the control group
NCT00636168	Eggermont, *Lancet Oncol*, 2015	Phase 3 RCT	Ipilimumab 10 mg/kg vs. placebo	Melanoma	No	0	51.1	32.8[b]	471	–	–	–	–	474
NCT00861614	Kwon, *Lancet Oncol*, 2014	Phase 3 RCT	Ipilimumab 10 mg/kg vs. placebo	Prostate cancer	Yes	100	67.6	9.3[b]	393	–	–	–	–	396
NCT01057810	Beer, *J Clin Oncol*, 2017	Phase 3 RCT	Ipilimumab 10 mg/kg vs. placebo	Prostate cancer	Yes	0	69.0	24[a]	399	–	–	–	–	199
NCT01585987	2016	Phase 2 RCT	Ipilimumab 10 mg/kg vs. fluoropyrimidine	Gastric or gastroesophageal junction carcinoma	Yes	100	64.0	–	57	–	–	–	–	51
NCT01642004	Brahmer, *N Engl J Med*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg vs. docetaxel 75 mg/m^2	Squamous-cell non-small-cell lung cancer	Yes	100	63.3	11[a]	131	–	–	–	–	129
NCT01668784	Motzer, *N Engl J Med*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg vs. everolimus 10 mg	Renal-cell carcinoma	Yes	100	61.3	14[a]	406	–	–	–	–	397
NCT01673867	Borghaei, *N Engl J Med*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg vs. docetaxel 75 mg/m^2	Non-squamous non-small-cell lung cancer	Yes	100	61.6	13.2[a]	287	–	–	–	–	268
NCT01704287	Ribas, *Lancet Oncol*, 2015	Phase 2 RCT	Pembrolizumab 2 or 10 mg/kg vs. chemotherapy (paclitaxel + carboplatin, paclitaxel, carboplatin, dacarbazine, or temozolomide)	Melanoma	Yes	46–50	60.1	10[b]	357	–	–	–	–	171
NCT01721746	Weber, *Lancet Oncol*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg vs. chemotherapy (dacarbazine 1000 mg/m^2 or carboplatin AUC6 + paclitaxel 175 mg/m^2)	Melanoma	Yes	100	59.2	8.4[b]	268	–	–	–	–	102
NCT01721772	Robert, *N Engl J Med*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg + placebo vs. dacarbazine 1000 mg/m^2 + placebo	Melanoma	Yes	16.8	62.7	5.2[a]	206	–	–	–	–	205
NCT01843374	Maio, *Lancet Oncol*, 2017	Phase 2 RCT	Tremelimumab 10 mg/kg vs. placebo	Malignant mesothelioma	Yes	100	65.6	–	382	–	–	–	–	189
NCT01844505	Larkin, *N Engl J Med*, 2015	Phase 3 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg vs. Ipilimumab 3 mg/kg	Melanoma	Yes	0	59.6	12.2[b]	624[c]	313	–	–	–	–

Continued

Table 1 *Continued*

Clinical Trials.gov Identifier	Study	Study design	Comparison	Type of cancer	Advanced or metastatic cancer	Prior systemic therapy (%)	Mean age (years)	Follow-up (months)	No. patients in monotherapy ICI group	No. patients in combination therapy ICI group	No. patients in ICI + chemotherapy	No. patients in ICI + targeted therapy	No. patients in ICI + other anticancer drug(s) regimen(s)	No. patients in the control group
NCT01903993	Fehrenbacher, *Lancet*, 2016	Phase 2 RCT	Atezolizumab 1200 mg vs. docetaxel 75 mg/m^2	Non-small-cell lung cancer	Yes	100	61.6	14.8[b]	142	–	–	–	–	135
NCT01905657	Herbst, *Lancet*, 2016	Phase 2/3 RCT	Pembrolizumab 2 or 10 mg/kg vs. docetaxel 75 mg/m^2	Non-small-cell lung cancer	Yes	100	62.0	13.1[b]	682	–	–	–	–	309
NCT01927419	Postow, *N Engl J Med*, 2015	Phase 3 RCT	Ipilimumab 3 mg/kg + placebo vs. nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Melanoma	Yes	0	63.7	11[a]	46	94	–	–	–	–
NCT01928394 (1)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Breast cancer	Yes	100	–	–	18	21	–	–	–	–
NCT01928394 (2)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Gastric or gastroesophageal junction carcinoma	Yes	100	–	–	59	104	–	–	–	–
NCT01928394 (3)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Pancreatic cancer	Yes	100	–	–	18	51	–	–	–	–
NCT01928394 (4)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Small-cell lung cancer	Yes	100	–	–	245	215	–	–	–	–
NCT01928394 (5)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Bladder cancer	Yes	100	–	–	78	196	–	–	–	–
NCT01928394 (6)	Antonia, *Lancet Oncol*, 2016	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Ovarian cancer	Yes	100	–	–	–	126	–	–	–	–
NCT01984242	2019	Phase 2 RCT	Atezolizumab 1200 mg vs. sunitinib 50 mg vs. Atezolizumab 1200 mg + bevacizumab	Renal cell carcinoma	Yes	0	60.3	–	103	–	–	101	–	100
NCT02008227	Rittmeyer, *Lancet*, 2017	Phase 3 RCT	Atezolizumab 1200 mg vs. docetaxel 75 mg/m^2	Non-small-cell lung cancer	Yes	100	62.8	21[b]	608	–	–	–	–	579
NCT02041533	Carbone, *N Engl J Med*, 2017	Phase 3 RCT	Nivolumab 3 mg/kg vs. platinum-based chemotherapy	Non-small-cell lung cancer	Yes	11	63.1	13.5[b]	267	–	–	–	–	263

Continued

Table 1 *Continued*

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NCT02105636	Ferris, *N Engl J Med*, 2016	Phase 3 RCT	Nivolumab 3 mg/kg vs. chemotherapy (methotrexate, docetaxel, or cetuximab)	Squamous-cell carcinoma of the head and neck	Yes	100	59.1	5.1[a]	236	–	–	–	–	111
NCT02125461	Antonia, *N Engl J Med*, 2018	Phase 3 RCT	Durvalumab 10 mg/kg vs. placebo	Non-small-cell lung cancer	Yes	100	62.9	25.2[b]	475	–	–	–	–	234
NCT02142738	Reck, *N Engl J Med*, 2016	Phase 3 RCT	Pembrolizumab 200 mg vs. platinum-based chemotherapy (carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + gemcitabine, cisplatin + gemcitabine, or carboplatin + paclitaxel)	Non-small-cell lung cancer	Yes	0.7–1.9	64.2	11.2[b]	154	–	–	–	–	150
NCT02220894	Mok, *Lancet*, 2019	Phase 3 RCT	Pembrolizumab 200 mg vs. platinum-based chemotherapy (carboplatin + paclitaxel or pemetrexed)	Non-small-cell lung cancer	Yes	3–4	62.8	12.8[b]	636	–	–	–	–	615
NCT02252042	Cohen, *Lancet*, 2019	Phase 3 RCT	Pembrolizumab 200 mg vs. chemotherapy (methotrexate, docetaxel, or cetuximab)	Squamous-cell carcinoma of the head and neck	Yes	100	60.2	7.5[b]	246	–	–	–	–	234
NCT02256436	Bellmunt, *N Engl J Med*, 2017	Phase 3 RCT	Pembrolizumab 200 mg vs. chemotherapy (paclitaxel, docetaxel or vinflunine)	Urothelial carcinoma	Yes	100	65.5	14.1[b]	266	–	–	–	–	255
NCT02267343	Kang, *Lancet Oncol*, 2017	Phase 3 RCT	Nivolumab 3 mg/kg vs. placebo	Gastric cancer	Yes	100	62.0	8.9[b]	330	–	–	–	–	163
NCT02302807	Powles, *Lancet*, 2018	Phase 3 RCT	Atezolizumab 1200 mg vs. chemotherapy (vinflunine 320 mg/m^2, paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2)	Urothelial carcinoma	Yes	100	66.0	17.3[b]	459	–	–	–	–	443
NCT02319044	Siu, *JAMA Oncol*, 2019	Phase 2 RCT	Durvalumab 10 mg/kg vs. durvalumab 20 mg/kg + tremelimumab 1 mg/kg vs. tremelimumab 10 mg/kg	Squamous-cell carcinoma of the head and neck	Yes	≥73.8	61.0	5.2[b]	130[c]	133	–	–	–	–

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Table I *Continued*

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NCT02337491	2019	Phase 2 RCT	Pembrolizumab 200 mg vs. pembrolizumab 200 mg + bevacizumab	Glioblastoma multiforme	No	–	51.1	25[b]	30	–	–	50	–	–
NCT02351739	2019	Phase 2 RCT	Pembrolizumab 200 mg vs. pembrolizumab 200 mg + acalibrutinib	Urothelial bladder cancer	Yes	100	66.1	–	35	–	–	40	–	–
NCT02352948 (1)	Planchard, *Ann Oncol*, 2020 (1)	Phase 3 RCT	Durvalumab 10 mg/kg vs. chemotherapy (erlotinib 150 mg or gemcitabine 1000 mg/m^2 or vinorelbine 30 mg/m^2)	Non-small-cell lung cancer	Yes	100	63.4	9.1[b]	62	–	–	–	–	64
NCT02352948 (2)	Planchard, *Ann Oncol*, 2020 (2)	Phase 3 RCT	Durvalumab 10 mg/kg vs. durvalumab 20 mg/kg + tremelimumab 1 mg/kg vs. tremelimumab 10 mg/kg vs. chemotherapy (erlotinib 150 mg or gemcitabine 1000 mg/m^2 or vinorelbine 30 mg/m^2)	Non-small-cell lung cancer	Yes	100	63.4	9.1[b]	177[c]	174	–	–	–	118
NCT02358031	Burtness, *Lancet*, 2019	Phase 3 RCT	Pembrolizumab 200 mg vs. chemotherapy (cetuximab plus a platinum and 5-fluorouracil) vs. pembrolizumab 200 mg + chemotherapy (platinum and 5-fluorouracil)	Squamous-cell carcinoma of the head and neck	Yes	0	61.0	11.5[b]	300	–	276	–	–	287
NCT02362594	Eggermont, *N Engl J Med*, 2018	Phase 3 RCT	Pembrolizumab 200 mg vs. placebo	Melanoma	No	0	53.8	15[b]	509	–	–	–	–	502
NCT02366143	Socinski, *N Engl J Med*, 2018	Phase 3 RCT	Atezolizumab 1200 mg + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel	Non-small-cell lung cancer	Yes	0	63.0	9.5[a]	–	–	–	–	356	336
NCT02369874	2020	Phase 3 RCT	Durvalumab 10 mg/kg vs. durvalumab 20 mg/kg + tremelimumab 1 mg/kg vs. standard of care	Squamous-cell carcinoma of the head and neck	Yes	100	59.4	–	237	246	–	–	–	240

Continued

Table 1 *Continued*

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			(cetuximab, taxane, methotrexate, or fluoropyrimidine)											
NCT02370498	Shitara, *Lancet*, 2018	Phase 3 RCT	Pembrolizumab 200 mg vs. paclitaxel 80 mg/m^2	Gastric or gastro-oesophageal junction cancer	Yes	100	60.2	7.9[b]	294	–	–	–	–	276
NCT02374242	Long, *Lancet Oncol*, 2018	Phase 2 RCT	Nivolumab 3 mg/kg vs. Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Melanoma	Yes	–	61.1	14[b]	25	35	–	–	–	–
NCT02395172	Barlesi, *Lancet Oncol*, 2018	Phase 3 RCT	Avelumab 10 mg/kg vs. docetaxel 75 mg/m^2	Non-small-cell lung cancer	Yes	100	63.5	18.3[b]	393	–	–	–	–	365
NCT02425891	Schmid, *N Engl J Med*, 2018	Phase 3 RCT	Atezolizumab 840 mg + nab-paclitaxel 100 mg/m^2 vs. placebo + nab-paclitaxel 100 mg/m^2	Breast cancer	Yes	0	56.0	12.9[b]	–	–	452	–	–	438
NCT02453282	Rizvi, *JAMA Oncol*, 2020	Phase 3 RCT	Durvalumab 10 mg/kg vs. platinum-based chemotherapy vs. durvalumab 20 mg/kg + tremelimumab 1 mg/kg	Non-small-cell lung cancer	Yes	0	63.7	–	369	371	–	–	–	352
NCT02454179	2019	Phase 2 RCT	Pembrolizumab 200 mg vs. pembrolizumab 200 mg + acalibrutinib	Squamous-cell carcinoma of the head and neck	Yes	100	61.8	–	39	–	–	37	–	–
NCT02477826	Hellman, *N Engl J Med*, 2019	Phase 3 RCT	Nivolumab 240 mg vs. chemotherapy	Non-small-cell lung cancer	Yes	0	64.0	29.3[a]	–	576	–	–	–	570
NCT02481830	2020	Phase 3 RCT	Nivolumab 240 mg vs. topotecan + amrubicin	Small-cell lung cancer	Yes	100	61.6	15.8[a]	282	–	–	–	–	265
NCT02494583	2020	Phase 3 RCT	Pembrolizumab 200 mg vs. pembrolizumab 200 mg + chemotherapy (cisplatin 80 mg/m^2 + 5-fluorouracil 800 mg/m^2) vs. chemotherapy (cisplatin 80 mg/m^2 + 5-fluorouracil 800 mg/m^2)	Gastric or gastroesophageal junction adenocarcinoma	Yes	0	60.5	–	254	–	250	–	–	244
NCT02538666	Owonikoko, *Ann Oncol*, 2019	Phase 3 RCT	Nivolumab 240 mg vs. placebo vs. Nivolumab	Small-cell lung cancer	Yes	100	63.9	9[a]	279	278	–	–	–	273

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Table I *Continued*

Clinical Trials.gov Identifier	Study	Study design	Comparison	Type of cancer	Advanced or metastatic cancer	Prior systemic therapy (%)	Mean age (years)	Follow-up (months)	No. patients in monotherapy ICI group	No. patients in combination therapy ICI group	No. patients in ICI + chemotherapy	No. patients in ICI + targeted therapy	No. patients in ICI + other anticancer drug(s) regimen(s)	No. patients in the control group
			1 mg/kg + Ipilimumab 3 mg/kg											
NCT02546986	2020	Phase 2 RCT	Pembrolizumab 200 mg vs. pembrolizumab 200 mg + oral azacitidine	Non-small-cell lung cancer	Yes	100	63.9	11.3[b]	49	–	51	–	–	–
NCT02558894	O'Reilly, *JAMA Oncol*, 2019	Phase 2 RCT	Durvalumab 1500 mg vs. durvalumab 1500 mg + tremelimumab 75 mg	Pancreatic ductal adenocarcinoma	Yes	100	61.5	3.2[b]	32	32	–	–	–	–
NCT02576977	Mateos, *Lancet Haematol*, 2019	Phase 3 RCT	Pembrolizumab 200 mg + pomalidomide and dexamethasone vs. pomalidomide and dexamethasone	Relapsed or refractory multiple myeloma	Yes	100	65.0	8.1[b]	–	–	125	–	–	124
NCT02579863	Usmani, *Lancet Haematol*, 2019	Phase 3 RCT	Pembrolizumab 200 mg + lenalidomide and dexamethasone vs. lenalidomide and dexamethasone	Multiple myeloma	No	0	74.0	6.6[b]	–	–	151	–	–	150
NCT02580058	Pujade-Lauraine, *Future Oncol*, 2018	Phase 3 RCT	Avelumab 10 mg/kg + pegylated liposomal doxorubicin vs. pegylated liposomal doxorubicin vs. avelumab 10 mg/kg	Ovarian cancer	Yes	100	60.3	12.4[b]	187	–	182	–	–	177
NCT02613507	Wu, *J Thorac Oncol*, 2019	Phase 3 RCT	Nivolumab 3 mg/kg vs. docetaxel 75 mg/m^2	Non-small-cell lung cancer	Yes	99	59.1	10.4[b]	337	–	–	–	–	156
NCT02625623	Bang, *Ann Oncol*, 2018	Phase 3 RCT	Avelumab 10 mg/kg vs. chemotherapy (paclitaxel 80 mg/m^2 or irinotecan 150 mg/m^2)	Gastric or gastroesophageal junction adenocarcinoma	Yes	100	59.5	10.6[b]	184	–	–	–	–	177
NCT02684006	Motzer, *N Engl J Med*, 2019	Phase 3 RCT	Avelumab 10 mg/kg + axitinib 5 mg vs. sunitinib 50 mg	Renal cell carcinoma	Yes	0	62.0	13[a]	–	–		442	–	444
NCT02702401	Finn, *J Clin Oncol*, 2020	Phase 3 RCT	Pembrolizumab 200 mg vs. placebo	Hepatocellular carcinoma	Yes	0	65.2	13.8[b]	279	–	–	–	–	134

Continued

Table I *Continued*

Clinical Trials.gov Identifier	Study	Study design	Comparison	Type of cancer	Advanced or metastatic cancer	Prior systemic therapy (%)	Mean age (years)	Follow-up (months)	No. patients in monotherapy ICI group	No. patients in combination therapy ICI group	No. patients in ICI + chemotherapy	No. patients in ICI + targeted therapy	No. patients in ICI + other anticancer drug(s) regimen(s)	No. patients in the control group
NCT02788279	Eng, *Lancet Oncol*, 2019	Phase 3 RCT	Atezolizumab 1200 mg vs. regorafenib 160 mg vs. atezolizumab 1200 mg + cobimetinib	Colorectal cancer	Yes	100	57.8	7.3[b]	90	–	–	179	–	80
NCT03036488	Schmid, *N Engl J Med*, 2020	Phase 3 RCT	Pembrolizumab 200 mg + paclitaxel and carboplatin vs. placebo	Breast cancer	Yes	0	49.0	15.5[b]	–	–	784	–	–	390
NCT03933449	2020	Phase 3 RCT	Pembrolizumab 200 mg vs. chemotherapy (paclitaxel or docetaxel or irinotecan)	Gastric or gastroesophageal junction carcinoma	Yes	100	59.9	–	62	–	–	–	–	59

RCT was classified according to their NCT. For studies only available on ClinicalTrial.gov, the year corresponds to the last update posted.
ICI, immune checkpoint inhibitor; RCT, randomized controlled trial; SOC, standard of care;
[a]Median follow-up duration.
[b]Minimum follow-up duration.
[c]ICI monotherapy arm included both an anti-PD-1/PDL-1 and an anti-CTLA4.

Reaction	n/N ICI	n/N ctrl	Peto OR (95%CI)	N stud/I2
Dyslipidemia	39/2,047	2/934	3.68 (1.89-7.19)	4/0%
Myocarditis	14/5,366	1/4,089	4.42 (1.56-12.50)	12/0%
Pericardial diseases	71/9,263	22/6,873	2.16 (1.42-3.29)	24/0%
Heart Failure	89/11,714	29/8,088	1.98 (1.36-2.88)	32/0%
Cerebral arterial ischemia	98/12,336	41/8,703	1.56 (1.10-2.20)	33/0%
Myocardial infarction	70/12,698	31/8,880	1.51 (1.01-2.26)	31/0%
Cardiac death or shock	67/11,943	29/8,122	1.48 (0.98-2.25)	30/0%
Hypertension	498/9,479	295/6,212	1.23 (0.87-1.73)	23/73%
Endocardial disorders	5/2,880	0/1,619	4.93 (0.78-31.29)	5/0%
Venous thromboembolic events	246/13,965	172/9,757	0.97 (0.75-1.26)	39/28%
Cardiac supra-ventricular arrhythmias	98/13,028	65/8,860	0.86 (0.57-1.28)	34/24%
Cardiac ventricular arrhythmias	6/3,368	2/2,176	1.75 (0.37-8.31)	8/13%
Torsade de pointes / QT prolongation	3/1,720	1/1,091	1.66 (0.16-17.26)	4/23%
Pulmonary hypertension and rel. card. inv.	2/2,710	5/1,696	0.26 (0.05-1.23)	6/3%
Cardiac valve disorders	1/1,769	2/1,363	0.37 (0.02-7.64)	3/41%
Cardiac conductive disorders	3/3,832	5/2,427	0.36 (0.08-1.51)	8/0%

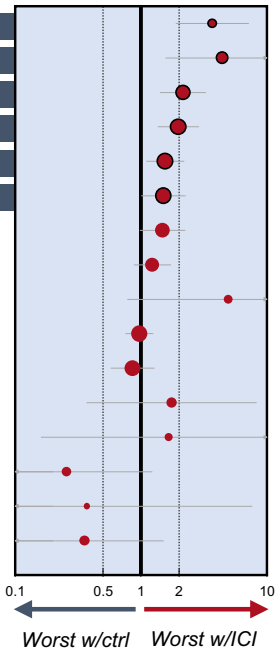

Figure 2 Summary pooled analysis forest plot on the risk of ICI therapy-associated cardiovascular adverse events vs. controls in randomized controlled trials. *n/N* refers to the number of events (*n*) observed for the outcome in regard to the overall number of patients (*N*) in each group. Circle size is proportional to the number of studies used to estimate the summary Peto OR. CI, confidence interval; ctrl, control; ICI, immune checkpoint inhibitor; OR, odds ratio; rel. card. Inv, related cardiac involvement; stud, study(ies).

anticancer drug(s)) vs. controls in RCTs. CVAEs with an increased risk associated with ICI exposure were considered as CV irAEs. Controls were classified as placebo or non-placebo. Non-placebo drugs were defined as any anticancer drug(s) regimen(s) not containing ICIs and included cytotoxic agents, targeted therapies [including kinase inhibitors, vascular endothelial growth factor-pathway inhibitors, and related agents (everolimus)], and other anticancer drug(s). CVAEs of interest were cardiac death or shock, cardiac conductive disorders, cardiac supra-ventricular arrhythmias, cardiac valve disorders, cardiac ventricular arrhythmias, cerebral arterial ischaemia, dyslipidemia, endocardial disorders, heart failure (HF), hypertension, myocardial infarction (MI), myocarditis, pericardial diseases, pulmonary hypertension (PH), torsade de pointe/QT prolongation, and venous thromboembolic events (VTE). All cases of myocarditis were considered, disregarding their aetiology. We gathered CVAEs using the MedDRA terminology (see the detailed list of MedDRA terms in the Supplementary material online, *Table S2*).

The secondary outcome was the summary incidence of CV irAEs identified in our primary outcome analyses using all RCTs including at least one ICI arm. A *post hoc* secondary outcome was the risk of CV irAEs for ICI combination therapy vs. monotherapy.

Statistical analysis

We performed a random-effects meta-analysis to compute Peto odds ratios (ORs) with 95% confidence intervals (CIs), which has been described as the most accurate method for binary studies with rare events (<1%) by Morton and colleagues.[22] Assuming CV irAEs were not frequent events (incidence <10%), we interpreted OR as a measure of the risk.[23,24] The incidence of CV irAEs was computed with logit transformation and inverse variance weighting. Prespecified sensitivity analyses of the primary outcome were computed to assess the robustness of the results, by recalculating the combined Peto OR after removing (i) each study sequentially, (ii) higher weighted RCTs (which had a weight percentage ≥75th percentile), (iii) smallest RCTs (which had sample size <300 patients), and (iv) RCTs that were judged to be at high risk of bias.

We assessed between-study heterogeneity using the inconsistency index I^2 statistic and the χ^2 test with its *P*-value. Substantial between-study heterogeneity was defined by an I^2 value of >50%, and significant heterogeneity was defined by a χ^2 *P*-value of <0.10 per the Cochrane Handbook for Systematic Reviews of Interventions.[17] Prespecified subgroup analyses on ICI regimen, control regimen, and cancer type were performed, as well as *post hoc* analyses on median follow-up (including linear meta-regression), tobacco use, sex ratio, age, and cancer stage. Additional *post hoc* measurements using the risk difference (Mantel–Haenszel method) and number needed to harm were also computed. Data management and meta-analysis of the pooled data (Peto method) were done with R (version 3.5.3) and the R package meta and presented in forest plots. A two-sided *P*-value of <0.05 in *Z*-tests (for overall effect) or χ^2 tests (for overall subgroup comparison) in all analyses was considered statistically significant.

Results

Descriptions of included studies

The PRISMA flow diagram of study selection is presented in *Figure 1* and the search strategy is presented in Supplementary material online, *Table S3*. Details of the study characteristics are presented

Cardiovascular AE	n/N	Summary incidence per 1000 pts (95%CI)	N stud/I2
Dyslipidemia	69/2,453	19.3 (6.7-54.1)	5/92%
Heart Failure	103/14,662	8.7 (7.1-10.6)	44/6%
Cerebral arterial ischemia	116/15,446	8.8 (7.2-10.7)	46/10%
Pericardial diseases	79/11,837	8.3 (6.3-10.8)	33/22%
Myocardial infarction	87/15,429	7.4 (6.0-9.1)	43/0%
Myocarditis	14/6,497	3.2 (2.0-5.1)	18/0%

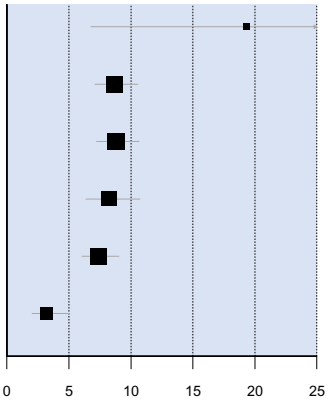

Figure 3 Summary pooled incidence analysis of cardiovascular immune-related adverse events associated with immune checkpoint inhibitor therapy (per 1000 patients). *n/N* refers to the number of events (*n*) observed for the outcome in regard to the overall number of patients (*N*) in patients treated with immune checkpoint inhibitor therapy. Square size is proportional to the number of studies used to estimate the summary incidence. CI, confidence interval; stud, study(ies).

in *Table 1*. Sixty-three unique RCTs reported between 2010 and 2020 (45 phase 3 RCTs and 18 phase 2 RCTs; 13 placebo-RCTs and 50 non-placebo-RCTs) with available CVAEs met the predefined criteria. These 63 RCTs were registered with 57 unique identifiers on ClinicalTrials.gov (2 NCTs used for >1 RCT). Nine RCTs had more than two arms. Risk of bias assessments for each of the included studies is summarized in Supplementary material online, *Table S4*. According to the GRADE scale, the certainty of evidence was high for all RCTs (Supplementary material online, *Table S5*). Among the 63 unique RCTs retrieved, 48 had a control arm and were therefore used for our primary outcome analyses (risk of CVAEs associated with ICI exposure). Among these 48 RCTs, 9 RCTs had >2 arms. A total of 29 592 adult patients were enrolled, of whom 17 199 were in the ICI-containing arms (58.1%) and 12 393 were in the control arms (41.9%). The mean age for the entire population ranged from 51 to 74 years and the follow-up ranged from 6.6 to 32.8 months (available in 30). The administered ICIs (ICI alone, ICI + other anticancer drug(s), other than ICI) were nivolumab in 25.0%, pembrolizumab in 31.2%, atezolizumab and durvalumab in 10.4%, ipilimumab in 10.4%, avelumab in 8.3%, and tremelimumab in 2.1% of the studies. ICI-containing arms were: ICI in monotherapy alone in 41/48 RCTs, combination of ICI (nivolumab + ipilimumab or durvalumab + tremelimumab) in 5/48, ICI monotherapy + cytotoxic chemotherapy(ies) in 7/48, ICI monotherapy + targeted therapy(ies) in 3/48, and ICI monotherapy + another anticancer drug(s) regimen(s) in 1/48. Non-small-cell lung cancer and melanoma were the most frequent cancer types in 37.5% (18/48) and 10.5% (5/48) of studies, respectively.

Risk of CVAEs associated with ICI exposure

As shown in the *Graphical abstract* and *Figure 2*, ICIs significantly increased the risk of 6 CV irAEs including myocarditis (Peto OR: 4.42, 95% CI: 1.56–12.50, $P < 0.01$; $I^2 = 0\%$, $P = 0.93$), dyslipidemia (Peto OR: 3.68, 95% CI: 1.89–7.19, $P < 0.01$; $I^2 = 0\%$, $P = 0.66$), pericardial diseases (Peto OR: 2.16, 95% CI: 1.42–3.29, $P < 0.01$; $I^2 = 0\%$, $P = 0.49$), HF (Peto OR: 1.98, 95% CI: 1.36–2.88, $P < 0.01$; $I^2 = 0\%$, $P = 0.74$), cerebral arterial ischaemia (Peto OR: 1.56, 95% CI: 1.10–2.20, $P = 0.01$; $I^2 = 0\%$, $P = 0.63$), and MI (Peto OR: 1.51, 95% CI: 1.01–2.26, $P = 0.047$; $I^2 = 0\%$, $P = 0.96$). Sensitivity analyses were consistent with the main result (Supplementary material online, *Table S6*). In a *post hoc* analysis, ICI combination therapy showed a higher risk of cerebral arterial ischaemia than ICI monotherapy, and a non-significantly higher risk of MI, HF, myocarditis, and pericardial diseases (Supplementary material online, *Figure S1*). The inverted funnel plot for the primary outcome did not suggest publication bias (Supplementary material online, *Figure S2*). Subgroup analyses with regard to cancer types, control regimens, ICI regimens, the median follow-up, tobacco use, sex ratio, age, and cancer stage are presented in Supplementary material online, *Table S7*. There were no between group differences, except for HF, which was more frequently observed in studies with a mean age <61.5 years than in those with a mean age >61.5 years. No interaction between follow-up length and CVAE reporting was found (Supplementary material online, *Figure S3*). *Post hoc* analyses using the risk difference are shown in Supplementary material online, *Table S8*.

Incidence of CV irAEs with an increased risk associated with ICI exposure

A total of 32 518 adult patients were enrolled in the 63 included RCTs, of whom 20 125 were in the ICI-containing arms (61.9%) and 12 393 were in the control arms (38.1%). The mean age for the entire population ranged from 49 to 74 years (available in 55 studies) and the follow-up ranged from 3.2 to 32.8 months. The administered ICIs (ICI alone, ICI + other anticancer drug(s), other than ICI) were nivolumab in 31.7%, pembrolizumab in 30.2%, atezolizumab and durvalumab in 11.1%, ipilimumab in 7.9%, avelumab in 6.4%, and tremelimumab in 1.6% of the studies. ICI-containing arms were: ICI as

monotherapy alone in 55/63 RCTs, combination of ICI (nivolumab + ipilimumab or durvalumab + tremelimumab) in 16/63, ICI monotherapy + cytotoxic chemotherapy(ies) in 8/63, ICI monotherapy + targeted therapy(ies) in 6/63 and ICI monotherapy + another anticancer drug(s) regimen(s) in 1/63. Non-small-cell lung cancer and melanoma were the most frequent cancer types in 28.6% (18/63) and 12.7% (8/63) of studies, respectively.

The incidence of the 6 CV irAEs identified in the primary analysis was calculated in the 63 RCTs and ranged from 3.2 (95% CI 2.0–5.1, I^2 = 0%) for myocarditis to 19.3 (6.7–54.1, I^2 = 92%) for dyslipidemia per 1000 patients during a follow-up ranging from 3.2 to 32.8 months (available in 35 studies) (*Graphical abstract*, *Figure 3*).

Discussion

To our knowledge, this study is the first large-scale analysis with an exhaustive and comprehensive capture of CVAEs in ICI RCTs documenting an increased risk of six individual CV irAEs associated with ICI therapy. Based on a comprehensive safety meta-analysis, we highlight that ICI therapy increases the risk of myocarditis, dyslipidaemia, pericardial diseases, HF, cerebral arterial ischaemia, and MI and that such CV irAEs occur in ∼3 to 20 per 1000 patients treated by ICIs during a follow-up ranging from 3.2 to 32.8 months.

Recently, a meta-analysis attempted to address the risk of CV irAEs associated with ICIs and did not find any increased risk, including for myocarditis,[25] but several limitations inherent to the methodology used in this meta-analysis were noticed.[26] Having exhaustive access to RCT safety results is challenging as the published manuscript of efficacy studies in public citation databases often do not report on rare AEs.[27] This difference between efficacy and safety meta-analysis is critical; therefore, an 'efficacy-like' methodology applied to a safety meta-analysis appears to be not fully appropriate.[27] ClinicalTrials.gov (https://clinicaltrials.gov/, U.S. National Institutes of Health) is the largest clinical trial register website, holding registrations from over 353 000 trials from 209 countries since 1997.[28] In 2008, reporting both efficacy and safety results became mandatory.[28] The ClinicalTrials.gov register therefore represents a powerful tool to study AEs in RCTs and is considered more comprehensive than the published manuscripts for this objective.[20] Agostinetto *et al.*,[25] using a usual 'efficacy-like' approach based only on an extraction of public citations databases, captured 230 CVAEs associated with ICI exposure from 66 RCTs (total of 34 664 patients). Using a previously validated stepwise approach based first on the ClinicalTrials.gov register,[18] we comprehensively captured 419 CVAEs encountering the same definition as Agostinetto and colleagues from 48 RCTs (total of 29 592 patients). In addition, the use of the Peto OR method has been proven to be the most appropriate method to detect rare events.[22]

Most attention has been drawn to myocarditis and pericarditis, the first CV irAEs associated with ICI therapy.[6,12,29,30] More recently, translational and real-life data suggested an increased risk of other CV irAEs, including HF and MI.[9,13–15] A nationwide study in Denmark showed that patients treated with ICIs had increased rates of CVAEs; these CVAEs could be delayed from ICI initiation, contrasting with the early onset of myocarditis and pericarditis.[14] Within 6 months after the first ICI administration, the hazard ratios of CVAEs were 2.14 (95% CI 1.50–3.05) in patients with lung cancer and 4.30 (1.38–13.42) and 4.93 (2.45–9.94) in patients with malignant melanoma treated with PD-1 inhibitors and CTLA-4 inhibitors, respectively. After 6 months, the hazard ratios were 2.26 (1.27–4.02) for patients with lung cancer and 3.48 (1.91–6.35) for patients with malignant melanoma and CTLA-4 inhibitors. Similar results were found in a single academic medical centre cohort comparing 2842 ICI patients to 2842 controls matched by age, history of cardiovascular events, and cancer type.[13] In this study, there was a three-fold higher risk for atherosclerotic CV irAEs (defined as MI, coronary revascularization, and ischaemic stroke) after starting an ICI (hazard ratio 3.3 [95% CI: 2.0–5.5]; $P < 0.001$). Recently, some case reports supported by pharmacovigilance data provided convincing elements regarding a plausible causal association between ICI therapy and MI occurrence.[9] In the present study, we confirm that ICI therapy increases the risk of developing atherosclerotic CV irAEs including both MI and cerebral arterial ischaemia. The progression of atherosclerotic plaque is a robust predictor and surrogate of atherosclerotic CV irAEs, and it has been established that dyslipidemia contributes to this progression.[31] In our study, we also found a significant and strong association between ICI therapy and dyslipidaemia occurrence, which supports the biological plausibility of our observations between ICI use and atherosclerotic CV irAEs. Combined with other studies performed in both humans and animals,[13,32] our findings argue for an acceleration in atherosclerosis after ICI introduction through the occurrence of dyslipidemia. PD-1-deficient myeloid progenitors up-regulate genes involved in lipid synthesis, mainly cholesterol, and uptake and down-regulate genes promoting cholesterol metabolism, cumulatively leading to increased cellular cholesterol levels.[33] PD-1 appears to play a critical role in down-regulating proatherogenic T-cell responses and PD-1 blockade was associated with an exacerbation and acceleration of atherosclerotic lesions via a significant infiltration of activated CD4(+) and CD8(+) T cells in genetically modified mice deficient in both low density lipoprotein receptor and PD-1 (Ldlr(-/-)Pd1(-/-)).[34] In addition, aggravated hypercholesterolaemia was observed in Ldlr(-/-)Pd1(-/-) mice. This accelerated atherogenesis seems to appear quickly after PD-1 blockade with an increase in atherosclerotic lesions visible as early as 5 weeks in Ldlr(-/-)Pd1(-/-) mice.[35] Therefore, it could be interesting to monitor serum lipid levels, especially cholesterol levels, in dedicated ICI patient cohorts to precisely determine the onset and intensity of these acquired dyslipidemias. In addition, whether intensive lipid-lowering therapy could decrease atherosclerotic CV irAEs in ICI-treated patients is unknown. Statin use was previously associated with reduced progression of atherosclerotic plaque in 40 patients treated by ICI for melanoma who benefitted from computed tomography performed at 3 time points (annual progression rate of total plaque volume, 5.2% on statins vs. 8.3% not on statins; $P = 0.04$).[13] Dedicated RCTs are warranted to assess the impact of lipid-lowering therapies in patients treated with ICIs on the risk of atherosclerotic CV irAEs. In our study, it appears that the risk of dyslipidemia is higher in melanoma RCTs. Several hypotheses can be raised. Progression free survival is considered better in melanoma compared to other cancer localizations.[36] Time to onset of dyslipidemia is not available in included RCTs but we can hypothesize that longer survival may allow to detect more dyslipidemia.

Other cancer localizations such as lung cancer included patients at higher cardiovascular risk, particularly with a high proportion of tobacco use, that may be already treated with lipid-lowering agents.

Myocarditis is a challenging diagnosis.[37–40] Therefore, classification bias might interfere with the association between HF and ICI exposure we found. Although HF was previously associated with ICI use with a more delayed time to onset compared to myocarditis,[15] it should be noted that myocarditis often presented as HF symptomatology;[12] therefore, HF may be reported as an AE by investigators in ICI RCTs. Moreover, heterogeneous practices among trial centres may have led to missing the challenging diagnosis of myocarditis. This likely results in an underestimation of myocarditis incidence, which may reduce the association measures in our study (Peto OR). On the other hand, as all cases of myocarditis were considered disregarding their aetiology, there might have been cases of nonimmune-related myocarditis during RCTs; hence, we might have slightly overestimated the incidence of immune-related myocarditis.

Another important finding in our study is the absence of an increased risk of VTE associated with ICI therapy. Mainly due to the confounding role of the underlying cancer and the design of studies (retrospective cohorts), data regarding the risk of VTE associated with ICI therapy were conflicting.[41,42] Regarding arrhythmia occurrence, we also did not find any increased risk. The association between arrhythmias and ICI therapy is debated and appears complex. Several pharmacovigilance studies found a modest but significant association between supra-ventricular arrythmias and ICI therapy[6,43] and it should be noted that a high proportion of cases (>60%) were co-reported with at least one concomitant irAE or other favouring AEs.[43] Ventricular tachycardias and conduction disorders were previously reported in severe cases of myocarditis, but in ICI-treated patients these disorders are likely a consequence of myocarditis rather than direct immune reactions.[29]

Importantly, we computed the incidence for the six CV irAEs identified in our primary analysis. The most frequent CV irAE in our study was dyslipidemia with an incidence of 19.3 per 1000 patients. Conversely, myocarditis was the rarest CV irAE with an incidence of 3.2 per 1000 patients, which is in line with previous reports.[8,29] Interestingly, cerebral arterial ischaemia, HF and MI were 2–3 times more frequent than myocarditis. In a recent evaluation of pivotal clinical trials supporting the Food and Drug Administration approval of contemporary anticancer therapies, 37% of immunotherapy trials did not report any CVAEs in follow-up, as did 54% of skin and 37% of lung cancer trials.[44] Moreover, in trials reporting CVAEs, the noted rates of AEs were markedly lower than those observed among real-life populations.[44] These findings suggest a general underreporting and/or appreciation of CVAEs among cancer RCT participants that may affect our results, especially incidence computations and the authors hypothesized that our incidence findings in RCTs might be underestimated and not reflect real-life incidence.

Study limitations

Only reported CVAE cases were analysed in this study, and the authors acknowledged that these reported cases may not reflect all CVAEs encountered in clinical practice. Nonserious AE cases are usually not fully published on reporting websites and only AEs with a >5% frequency are listed. Some concerns about the inconsistent reporting of anticancer therapy-associated CVAEs in RCTs have been recently raised.[44] The absence of individual patient data precluded time-to-event analysis and reporting. Preexisting traditional CV risk factors are usually not reported in oncological RCTs, except the use of tobacco in lung and head and neck cancer RCTs. The possible difference in preexisting traditional CV risk factors between RCTs/cancer localization may influence our incidence analyses. Currently, there is no standardized consensus on the choice of surveillance strategies and management algorithms for CVAEs in patients participating in oncological RCTs. However, reported AEs represent a consistent definition used worldwide to collect AEs in clinical trials that are publicly available on uniform reporting websites and the adoption and adherence to systemic reporting of AEs is standard for the evaluation of clinical data.[45,46] Therefore, incumbent on these AEs registered on the reporting ClinicalTrials.gov register is the rigorous reporting of potentially limiting or impactful AEs to allow informed assessment.[47]

Conclusion

In RCTs, ICI use was associated with an increased risk of myocarditis, pericardial disorders, HF, dyslipidaemia, and atherosclerotic CV irAEs (MI and cerebral arterial ischaemia). The incidence of these CV irAEs ranged from ∼3 to 20 per 1000 patients during a median follow-up ranging from 3.2 to 32.8 months. These incidences might be underestimated in RCTs as cardiac monitoring is usually minimalist in oncologic trials. Clinicians must be aware that ICI use is associated with the occurrence of several CV irAEs, not confined to myocarditis and pericarditis. Dyslipidaemia associated with ICI therapy must be explored in dedicated studies and whether lipid-lowering therapy could decrease the rate of atherosclerotic CV irAEs in ICI-treated patients must be addressed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: J.Al. reports honoraria for presentations and consulting fees from Bayer, BMS, Pfizer, Amgen, and Bioserenity, outside the submitted work. J.M.L. reports honoraria from Novartis for participation on an advisory board, outside the submitted work.

Data availability

Data used in this meta-analysis are freely available from reporting websites.

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