



ARTERIAL THROMBOEMBOLIC EVENTS DURING IMMUNE CHECKPOINT INHIBITOR THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Amar Nath Pandey¹, Virender Verma^{2*}, Dr Kunal Das³, Dr (Col) Anil Malik⁴, Alok Kumar⁵, Dr Pankaj Garg⁶, Dr Sanjay Sadhu⁴

¹Associate Professor, General Medicine, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

²Associate Professor, Pediatrics, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

³DNB Medical Oncology, Max Superspeciality Hospital Vaishali, Ghaziabad (UP), India.

⁴Professor, Plastic Surgery, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

⁵Professor and Head, Nephrology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

⁶Professor and Head, Surgical Oncology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

Corresponding Author*: Dr Virender Verma, Associate Professor, Pediatrics, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, India.

Email ID: vadrenaline@gmail.com

DOI: <https://doi.org/10.59551/IJHMP/25832069/2026.7.2.126>

How to cite this article: Pandey AN, Verma V, Das K et al. Arterial Thromboembolic Events during Immune Checkpoint Inhibitor Therapy: A Systematic Review and Meta-Analysis. *Indian J. Health Care, Med. Pharm. Pract.* 2026;7(2):166-173.

COPYRIGHT@ 2026, IJHMP | This work is licensed under a [Creative Commons Attribution 4.0 International Licence](https://creativecommons.org/licenses/by/4.0/) 

Received: 05 June, 2026, Decision for Acceptance: 16 July, 2026

ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have changed the way many solid tumours are treated, but they also carry a recognised risk of thromboembolism. Most published work has looked at venous thromboembolism. Arterial thromboembolic events (ATE), which include myocardial infarction, ischaemic stroke and peripheral arterial occlusion, have received comparatively less attention despite their serious clinical consequences.

Objective: To systematically review and bring together the published evidence on the incidence, risk factors and clinical outcomes of arterial thromboembolic events occurring during ICI therapy.

Methods: Fifteen studies were assembled for this review. These included two systematic reviews with meta-analysis, six retrospective or observational cohorts, two pharmacovigilance or disproportionality analyses, and other primary reports describing arterial thromboembolic outcomes in patients receiving ICIs. The review followed Cochrane and PRISMA-informed methodology. Data on cumulative incidence, hazard, odds or relative risk estimates, and identified risk factors were extracted and brought together narratively, with quantitative pooled estimates drawn from the two included meta-analyses.

Results: Pooled arterial event rates across advanced solid tumours ranged from 1.0% to 1.1% (Solinas et al., 95% CI 0.5-2.1%), and stood at 1% in a lung cancer specific meta-analysis (Yang et al., 95% CI 1-2%, $I^2=80.9\%$). Cumulative incidence in an Austrian cohort rose from 1.0% at six months to 1.8% at twenty-four months. A Dutch cohort found a three-fold higher risk of myocardial infarction and stroke compared with the general population, along with a 2.2-fold higher mortality risk in patients who developed arterial events. Risk factors that appeared consistently across studies included prior thromboembolic or cardiovascular disease, smoking, obesity, poor performance status, combination ICI regimens, concurrent chemotherapy, and an elevated Khorana score, although the Khorana score performed less well in this population than it usually does in general oncology practice.

Conclusion: Arterial thromboembolic events affect roughly one in a hundred patients receiving ICIs, a rate two to three times above background risk, and they carry a noticeably higher mortality burden once they occur. Cardiovascular risk assessment before starting therapy, along with vigilance during treatment, particularly in patients on combination regimens or with prior vascular disease, appears sensible. Prospective trials designed specifically to test prophylactic strategies in this setting are still needed.

KEYWORDS: Immune Checkpoint Inhibitors, Arterial Thromboembolism, Myocardial Infarction, Ischaemic Stroke, Cancer-associated Thrombosis, Meta-analysis.

Introduction

Cancer on its own raises the chance of blood clotting, and this risk climbs further once systemic treatment begins. Immune checkpoint inhibitors include antibodies against programmed cell death protein 1 (PD-1), its ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). When these drugs first entered clinical use, they were widely seen as gentler than cytotoxic chemotherapy with respect to vascular side effects. Early pharmacovigilance work soon changed that picture, flagging venous thromboembolism as an adverse event worth watching in patients receiving these agents[1]. A single-institute retrospective study went a step further and reported acute vascular events, arterial in nature, as a possibly related adverse effect of immunotherapy. This was among the first clear signals that the arterial side of clotting risk also deserved attention[2].

Since then, a growing body of literature has examined thromboembolism during ICI therapy, but most of it has centred on venous events, with arterial events described only as a secondary finding in larger reviews. A systematic review covering sixty-eight studies and more than twenty thousand patients with advanced solid tumours put the overall arterial event rate at roughly one in a hundred patients, with ischaemic stroke and myocardial infarction contributing in fairly equal measure[3]. Cohort data from Vienna, following 672 patients prospectively, showed that this risk builds up over time rather than staying fixed. It moved from about one percent at six months to nearly two percent by two years, and a prior history of thromboembolism stood out as the single strongest predictor[5].

A retrospective cohort of melanoma patients found that adding ipilimumab to a single-agent ICI regimen more than tripled the rate of thromboembolic events when compared with monotherapy. This points to treatment intensity itself as a factor that clinicians can, to some extent, work with[4]. Biomarker work from a Cleveland-based cohort has pointed towards younger age at diagnosis and metastatic disease as clinical predictors, alongside laboratory markers such as myeloid-derived suppressor cells, interleukin-8 and soluble vascular cell adhesion molecule-1. These findings hint at an underlying immune-mediated mechanism rather than a purely mechanical one[6].

Real-world pharmacovigilance databases add another layer to this picture. An analysis of the United States FDA Adverse Event Reporting System found a reporting odds

ratio of 1.44 for overall arterial events associated with ICIs, rising to 1.76 for cerebral arterial events, with myocardial infarction alone accounting for close to a quarter of all thromboembolic reports[7]. A related review of venous thromboembolism in cancer and cancer immunotherapy placed these arterial signals within the wider context of cancer-associated thrombosis. It also noted that pancreatic and ovarian malignancies carry disproportionately high venous rates, a pattern that may well be relevant to arterial risk given the shared prothrombotic pathways involved[8]. Data from the World Health Organization's VigiBase told a similar story, with arterial events making up over a quarter of thromboembolic reports linked to checkpoint inhibitors, and myocardial infarction the leading contributor within that group[9].

A retrospective comparison from Louisville found that adding platinum-based chemotherapy to an ICI regimen raised the twelve-month probability of an arterial event more than three-fold compared with ICI monotherapy alone. This finding lines up well with the combination-regimen data from the melanoma literature described above[10]. A meta-analysis focused on the link between immune-related venous thromboembolism and treatment efficacy, though centred on venous outcomes, reinforced the broader point that thromboembolic complications during ICI therapy occur often enough, and matter enough, to deserve dedicated review[11]. A comprehensive narrative review by Wang and Carrier brought much of this literature together, and additionally discussed management questions, such as anticoagulant choice, cardiac monitoring, and the still-debated role of primary prophylaxis, that remain unresolved for this specific patient group[12].

Two more recent meta-analyses have sharpened the quantitative picture for arterial events specifically. One, restricted to non-small-cell lung cancer and pooling fifty-seven studies, arrived at a pooled arterial event rate of one percent, though with considerable heterogeneity and a clear dose-response relationship according to regimen intensity[13]. Another, examining risk factors across thirteen studies and more than ten thousand patients, identified smoking, obesity, poor performance status, prior thrombosis, and an elevated Khorana score as independent predictors[14]. Most recently, a Dutch cohort study measured the excess risk against the general population directly, reporting roughly three-fold higher rates of both myocardial infarction and stroke, along with a more than doubled mortality risk once

an arterial event had taken place[15].

Given this growing but still scattered body of evidence, a dedicated systematic review and meta-analysis of arterial thromboembolic events during ICI therapy seemed timely. This review brings together the incidence data, risk factor analyses, and outcome data from the sources above, with the aim of building a clearer and more usable picture for clinicians managing patients on these agents.

Methods

Protocol and Reporting

This review followed the general methodological principles set out by Khan and colleagues for systematic reviews[16] and the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5[17]. The reporting structure covers question formulation, eligibility criteria, search and selection, data extraction, quality appraisal, and synthesis, in keeping with standard practice for systematic reviews in the biomedical literature.

Eligibility Criteria

A PICO framework guided the review question. Population: adult patients with solid tumours receiving immune checkpoint inhibitor therapy, whether anti-PD-1, anti-PD-L1, or anti-CTLA-4 agents, alone or in combination. Intervention or exposure: ICI therapy. Comparison: where data allowed, non-ICI systemic therapy, the general population, or ICI monotherapy against combination regimens. Outcome: arterial thromboembolic events, defined as myocardial infarction, ischaemic stroke, transient ischaemic attack, or peripheral and acute limb arterial occlusion, reported alongside incidence, risk-factor, or comparative effect data. Studies reporting only venous thromboembolism without arterial data were retained where they offered risk-factor or mechanistic information relevant to the broader thromboembolic picture of ICI therapy, though these were excluded from the arterial-specific quantitative synthesis.

Study Identification and Selection

Fifteen distinct primary and review-level sources meeting the criteria above were identified and retained for this synthesis. These comprised two systematic reviews with meta-analysis of arterial or overall thromboembolic outcomes[3,13], one further meta-analysis addressing risk factors across thirteen studies[14], one narrative review with clinical management guidance,¹² five retrospective or prospective cohort studies[2,4,5,6,15], two pharmacovigilance disproportionality analyses[7,9], one further retrospective comparative cohort[10], one meta-analysis of venous events and treatment efficacy[11], and one broader narrative review of venous thromboembolism in cancer immunotherapy providing background data[8]. Selection followed the usual two-stage process in systematic review work: an initial screen against the eligibility criteria above, followed by a full assessment of each report for extractable arterial

thromboembolic data.

Data Extraction

A structured form was used to extract the following details from each included study: first author and year, study design, sample size, cancer type or types, ICI regimen, definition and method of ascertaining arterial events, cumulative incidence or event rate with time frame where stated, comparator group and its rate, and any hazard ratio, odds ratio, relative risk, or reporting odds ratio with its 95% confidence interval and p-value. Risk-factor data reported for venous or arterial outcomes were extracted separately, as several studies analysed the two outcomes together using shared covariates.

Quality and Heterogeneity Considerations

The included studies spanned randomised trial data embedded within larger reviews, single- and multi-centre retrospective cohorts, and spontaneous-report pharmacovigilance databases. Given this mix, applying one formal risk-of-bias tool across every design was not attempted. Instead, design-appropriate caution guided the weighing of evidence. Cohort and registry data were judged using considerations similar to the Newcastle-Ottawa framework, covering selection of cohort, comparability, and outcome ascertainment. Pharmacovigilance data were interpreted keeping the inherent limits of disproportionality analysis in view, chiefly reporting bias and the absence of a denominator of total exposed patients.

Statistical Synthesis

Where the original authors had already carried out independent meta-analytic pooling using random-effects models[3,13], those pooled estimates and their heterogeneity statistics (I^2) are reported here directly rather than re-derived, since study-level event and denominator data for every contributing trial were not uniformly available for re-extraction. For the remaining single studies, point estimates with 95% confidence intervals are presented exactly as reported. A narrative synthesis approach was used to bring these figures together across designs, following Cochrane guidance for situations where statistical re-pooling across heterogeneous designs, whether trial-embedded, cohort, or pharmacovigilance in nature, is not appropriate[17].

Results

Overview of Included Studies

Table 1 sets out the design, population, and key arterial findings of the studies contributing quantitative data to this review. Sample sizes ranged from a single-centre cohort of 406 patients[10], to a meta-analysis pooling 20,273 patients across sixty-eight studies[3]. The cancer types represented included non-small-cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, gynaecological cancers, and mixed advanced solid tumours, with melanoma and lung cancer the most frequently represented populations.

Study (year)	Design; n	Population	ICI regimen	Key arterial TE finding
Bar et al. (2019) ²	Retrospective, single centre	Mixed solid tumours	Various ICIs	Acute vascular events reported as a possibly related adverse event; an early signal for arterial risk.
Solinas et al. (2020) ³	Systematic review and meta-analysis; 68 studies, n=20,273	Advanced solid tumours	PD-1/PD-L1/CTLA-4, mono- and combination	Pooled ATE rate 1.1% (95% CI 0.5-2.1%); ischaemic stroke 1.1% (95% CI 0.65-1.45%); MI 0.7% (95% CI 0.15-1.15%); RR versus non-ICI arms 1.86 (95% CI 0.7-4.9, P=.21).
Sussman et al. (2021) ⁴	Retrospective cohort	Melanoma	Monotherapy versus ipilimumab combination	TE incidence 16.7% (combination) versus 5.0% (monotherapy) at 6 months, P=.02.
Moik et al. (2021) ⁵	Retrospective cohort; n=672	Melanoma 30.4%, NSCLC 24.1%, RCC 11.0%	Nivolumab, pembrolizumab and others	Cumulative ATE incidence 1.0% at 6 months, 1.3% at 12 months, 1.8% at 24 months; prior VTE the strongest predictor (SHR 3.69, 95% CI 2.00-6.81).
Roopkumar et al. (2021) ⁶	Retrospective cohort	Mixed solid tumours	PD-1/PD-L1 inhibitors	Younger age (OR 0.99 per year, 95% CI 0.980-0.998) and metastatic disease (OR 1.71, 95% CI 1.12-2.61) predicted VTE; MDSC, IL-8 and sVCAM-1 elevations acted as biomarker predictors.
Li et al. (2021) ⁷	FAERS disproportionality analysis; 1,855 reports	All cancers reported to FAERS	Anti-PD-1, anti-PD-L1, anti-CTLA-4	Reporting odds ratio for overall ATE 1.44 (95% CI 1.37-1.52); cerebral ATE ROR 1.76 (95% CI 1.59-1.96); MI accounted for 21.56% of reports.
Alghamdi et al. (2022) ⁹	WHO Vigibase descriptive analysis; 161 serious cases	All cancers	ICIs (class not separately reported)	Arterial events made up 26.7% of reports; MI 24.8%, acute coronary syndrome 5.0%, embolic stroke 1.9%.
Maharaj et al. (2022) ¹⁰	Retrospective cohort; n=406	NSCLC 44%, GI 31%, melanoma 25%	ICI alone versus ICI+platinum versus platinum alone	12-month ATE probability 2.2% (ICI alone) versus 7.1% (ICI+chemotherapy) versus 6.8% (chemotherapy alone); P=.030 and P=.032 for pairwise comparisons.
Yang et al. (2024) ¹³	Systematic review and meta-analysis; 57 studies, 63 arms, n=16,602	NSCLC	PD-1/PD-L1/CTLA-4, mono- and combination	Pooled ATE rate 1% (95% CI 1-2%), range 0.1-7.7% across studies, I ² =80.9% (P=.00); combination therapy 4% versus monotherapy 2%; chemoradiotherapy combination 7%.
Song et al. (2024) ¹⁴	Systematic review and meta-analysis; 13 studies, n=10,608	Mixed solid tumours	ICIs, various classes	Smoking (OR 1.69), obesity (OR 1.68), ECOG ≥2 (HR 1.55), prior thrombus (OR 3.01) and Khorana score ≥2 (HR 1.5) were independent predictors.
van Lent et al. (2025) ¹⁵	Observational cohort; n=663	Melanoma 47%, NSCLC 24%, urothelial 12%, gynaecological 3%	Nivolumab, pembrolizumab, ipilimumab, combination	ATE in 2.1% (14/663); MI rate 5.9 and stroke rate 11.7 per 1,000 person-years; MI risk 3.0-fold and stroke risk 3.2-fold higher than the general population; ATE carried a 2.2-fold higher mortality risk.

Incidence of Arterial Thromboembolic Events

Across the two dedicated meta-analyses, the pooled arterial event rate settled into a fairly narrow band. Solinas and colleagues, pooling sixty-eight studies and 20,273 patients

with advanced solid tumours, reported an overall arterial rate of 1.1% (95% CI 0.5-2.1%), which split into 1.1% for ischaemic stroke (95% CI 0.65-1.45%) and 0.7% for myocardial infarction (95% CI 0.15-1.15%)[3]. Yang and

colleagues, restricting their fifty-seven-study meta-analysis to non-small-cell lung cancer, arrived at a nearly identical pooled rate of 1% (95% CI 1-2%), though individual study rates ranged widely from 0.1% to 7.7%, and heterogeneity was high ($I^2=80.9\%$, $P=.00$)[13]. Within the studies pooled by Solinas and colleagues, individual trial-level rates varied a good deal: a stroke rate of 0.2% in one large lung cancer trial stood in contrast to an arterial event rate of 6.5% in a retrospective lung cancer series, showing how much study design and population selection can shift the numbers seen[3].

Cohort data outside these two meta-analyses were broadly in line with this one to two percent range, and also showed that the risk builds up over time rather than staying at one fixed level. The Vienna cohort found cumulative arterial incidence rising from 1.0% at six months to 1.3% at twelve months and 1.8% at twenty-four months, with melanoma, lung cancer, and renal cell carcinoma subgroups all falling within overlapping confidence intervals of each other[5]. The Dutch cohort reported a similar overall rate of 2.1% (14 of 663 patients), which translated into a myocardial infarction rate of 5.9 and a stroke rate of 11.7 per 1,000 person-years, figures that were three-fold and 3.2-fold higher, respectively, than matched general-population rates[15].

Pharmacovigilance data cannot be compared directly to cohort incidence, since they lack a clear denominator of total exposed patients, but in relative terms they told a consistent story. The FAERS disproportionality analysis found a reporting odds ratio of 1.44 for overall arterial events and 1.76 for cerebral arterial events specifically, with anti-PD-L1 agents showing the strongest signal among the ICI classes[7]. The WHO VigiBase analysis found arterial events accounted for over a quarter of all thromboembolic reports, with myocardial infarction alone making up close to a quarter of these[9].

Effect of Regimen Intensity

A pattern seen repeatedly across the studies was that combination regimens carried a higher arterial risk than monotherapy. In the melanoma cohort, adding ipilimumab to single-agent therapy raised the thromboembolic rate from 5.0% to 16.7% by six months ($P=.02$)[4]. In the lung cancer meta-analysis, combined ICI regimens showed a pooled rate of 4% against 2% for monotherapy, and adding chemoradiotherapy on top of immunotherapy pushed this further to 7%[13]. The Louisville cohort found a similar gradient with chemotherapy rather than combination immunotherapy: the twelve-month arterial event probability was 2.2% with ICI alone, climbing to 7.1% with ICI plus platinum chemotherapy and 6.8% with platinum chemotherapy alone, differences that reached statistical significance ($P=.030$ and $P=.032$ respectively) [10]. Taken together, these findings suggest that treatment intensity, whether from combined immunotherapy or added

cytotoxic chemotherapy, acts as a consistent driver of arterial risk rather than an incidental finding confined to one dataset.

Risk Factors

Several patient-level and disease-level factors came up repeatedly across the included studies as predictors of thromboembolic risk during ICI therapy, though not every study separated venous from arterial predictors cleanly. A prior history of thromboembolism was the most consistently reported risk factor of all. The Vienna cohort reported a sub-distribution hazard ratio of 3.69 (95% CI 2.00-6.81, $P<.001$) for patients with such a history[5]. The risk-factor meta-analysis by Song and colleagues supported this finding, reporting an odds ratio of 3.01 (95% CI 1.53-5.92) for prior thrombus[14]. The same meta-analysis identified smoking history (OR 1.69, 95% CI 1.15-2.48), obesity defined as body mass index above 30 (OR 1.68, 95% CI 1.37-2.07), poor performance status of ECOG 2 or above (HR 1.55, 95% CI 1.02-2.36), and a Khorana score of 2 or higher (HR 1.5, 95% CI 1.23-1.84) as further independent predictors[14].

Age showed an inconsistent relationship across studies. Song and colleagues found no significant association for age 65 or above (OR 0.91, 95% CI 0.66-1.26)[14]. The Dutch cohort likewise found no clear age effect for either venous (adjusted HR 0.6, 95% CI 0.3-1.2) or arterial outcomes (adjusted HR 1.6, 95% CI 0.4-6.8)[15]. By contrast, the Cleveland cohort found that younger age at diagnosis was itself a predictor of venous thromboembolism (odds ratio 0.99 per one-year increase, 95% CI 0.980-0.998, $P=.015$), along with metastatic disease (OR 1.71, 95% CI 1.12-2.61, $P=.013$)[6]. This inconsistency probably reflects differences in population age structure and cancer type across the cohorts rather than a genuine contradiction, and is one area where future pooling of individual patient data would help clarify matters.

Cancer type itself carried weight in more than one dataset. Gynaecological malignancy stood out sharply in the Dutch cohort, with an adjusted hazard ratio of 6.7 (95% CI 1.4-31.4) for venous thromboembolism, and a broadly similar signal (sub-distribution hazard ratio 4.08, 95% CI 1.43-11.63) emerged from the Vienna cohort[5,15]. Biomarker-level predictors were reported in only one study: elevated myeloid-derived suppressor cells, interleukin-8, and soluble vascular cell adhesion molecule-1 measured before treatment began were all associated with subsequent venous thromboembolism in the Cleveland cohort, hinting at an immune-activation pathway distinct from the classical Virchow triad mechanisms behind malignancy-associated clotting[6].

Wang and Carrier, in their narrative review, drew together several further risk factors reported by studies not independently represented in this synthesis. These included current smoking and high PD-L1 expression in lung cancer patients, a history of coronary artery disease, poor performance status, and combination ICI-chemotherapy

regimens, along with early biomarker signals such as a sharp rise in C-reactive protein within the first month of treatment and elevated high-sensitivity troponin I before treatment as predictors of major adverse cardiac events[12].

Effect of ICI Drug Class

Differences between PD-1, PD-L1 and CTLA-4 inhibitor classes were examined only in the FAERS analysis. Anti-PD-L1 agents carried the strongest reporting signal for cerebral arterial events (ROR 1.64, 95% CI 1.25-2.15) and for overall thromboembolic reports relative to protein kinase inhibitors (ROR 1.08, 95% CI 0.99-1.18), with anti-PD-1 agents following (ROR 0.90) and anti-CTLA-4 agents lowest (ROR 0.85)[7]. Anti-PD-1 agents specifically carried a reporting odds ratio of 1.43 (95% CI 1.23-1.66) for overall arterial events[7]. Since this comes from a single pharmacovigilance dataset with the reporting biases inherent to such databases, this class-level difference is best read as hypothesis-generating rather than confirmatory.

Outcomes Following Arterial Events

Only the Dutch cohort directly measured the downstream consequence of an arterial event once it occurred, finding a 2.2-fold higher risk of all-cause mortality (95% CI 1.1-4.1) in patients who developed an arterial thromboembolic event during follow-up compared with those who did not[15]. This finding, though drawn from a single cohort, carries clinical weight. It suggests that an arterial event during ICI therapy is not simply an incidental finding but a marker of substantially worse overall prognosis, which strengthens the case for active cardiovascular risk management in this population rather than passive observation.

Management Considerations

Wang and Carrier's review, while focused mainly on treatment rather than incidence, offered the most complete synthesis of management data available. Direct oral anticoagulants and low-molecular-weight heparin remain the anticoagulants of choice, in line with practice for cancer-associated thrombosis more broadly, with the specific choice guided by bleeding risk, tumour site, patient preference, and cost[12]. The same review noted that thromboembolic risk does not plateau early but keeps accumulating with treatment duration, reaching a plateau only around thirty months in metastatic renal cell carcinoma and thirty-six months in metastatic urothelial cancer, an observation with direct bearing on how long clinicians should stay watchful[12]. It further noted that the 2022 European Society of Cardiology guidelines recommend troponin monitoring before every ICI cycle as a screening measure for arterial and cardiac complications, and that primary thromboprophylaxis in patients with a Khorana score of 2 or above remains an open question specific to this drug class, since the Khorana score itself performs less reliably in ICI-treated populations than it does in the wider oncology setting[12,14].

Discussion

This synthesis brings together fifteen sources spanning meta-analyses, cohort studies, and pharmacovigilance databases, and the overall picture is reasonably coherent despite the differences in design. Arterial thromboembolic events occur in roughly one to two percent of patients receiving ICI therapy, a rate that appears two to three times higher than what would be expected in an age-matched general population, and this excess risk seems to grow rather than shrink the longer treatment continues[3,13,15].

The biological basis for this excess risk is still being worked out, but the data assembled here offer some clues. Prior thromboembolic disease is consistently the strongest single predictor, appearing in both the Vienna and Song datasets. This points towards a population with pre-existing vascular vulnerability being unmasked or accelerated by immune activation, rather than checkpoint inhibitors creating an entirely new prothrombotic state in previously healthy blood vessels[5,14]. At the same time, the biomarker findings from the Cleveland cohort, namely elevated myeloid-derived suppressor cells, interleukin-8, and soluble vascular cell adhesion molecule-1 measured before clinical events occurred, suggest an active immune-mediated component. This is plausibly related to T-cell-driven vascular inflammation, atherosclerotic plaque destabilisation, or endothelial activation, mechanisms that would not be expected from cytotoxic chemotherapy acting through simple endothelial injury alone[6]. The finding that combination immunotherapy regimens carry roughly three times the risk of monotherapy fits this immune-activation idea reasonably well, since combination regimens are known to produce a broader and more intense immune response than single-agent therapy[4,13].

From a clinical standpoint, the finding that mortality nearly doubles once an arterial event occurs deserves particular attention[15]. Oncologists have traditionally focused surveillance during ICI therapy on immune-related adverse events such as colitis, pneumonitis, and endocrinopathies, with cardiovascular monitoring often taking a back seat. The data reviewed here suggest this balance may need adjusting, at least for patients carrying recognised risk factors, whether prior vascular disease, smoking, obesity, poor performance status, or a high Khorana score, or for those receiving combination regimens. Baseline cardiovascular risk assessment before starting therapy, and closer follow-up thereafter, particularly with troponin monitoring as suggested by the 2022 European Society of Cardiology guidelines, seem like reasonable practical steps even ahead of dedicated prospective trials[12].

The question of primary anticoagulant prophylaxis remains genuinely unsettled. The Khorana score, developed and validated for chemotherapy-associated venous thromboembolism, does not translate cleanly to this population, and none of the studies reviewed here tested a prophylactic anticoagulation strategy directly against

arterial outcomes[12,14]. Until purpose-built risk-prediction tools and prospective prophylaxis trials become available, the most defensible approach for clinicians is probably individualised risk stratification using the factors identified in this review, combined with prompt recognition and treatment should symptoms of myocardial infarction or stroke arise during therapy.

Limitations

Several limitations temper how far these findings can be generalised. First, the studies included here differ substantially in design, ranging from randomised-trial-embedded safety data pooled within larger reviews to spontaneous-report pharmacovigilance databases. This heterogeneity, reflected in the [12] of 80.9% reported by Yang and colleagues, makes a single combined quantitative estimate somewhat artificial[13]. Second, pharmacovigilance data such as the FAERS and VigiBase analyses lack a true denominator of total exposed patients, so their reporting odds ratios describe relative reporting patterns rather than true incidence or absolute risk, and both remain vulnerable to reporting bias and background notoriety effects around checkpoint inhibitors as a drug class[7,9]. Third, most cohort studies included here were retrospective and single-centre, which raises the usual concerns about selection bias, incomplete ascertainment of asymptomatic events, and residual confounding by indication, since sicker patients with more comorbidities may have been directed towards or away from ICI therapy in ways not fully captured by adjustment[5,6,10,15]. Fourth, several risk factors reported in the narrative review by Wang and Carrier were themselves drawn second-hand from primary studies not independently represented in this synthesis, so those particular findings should be treated as supporting context rather than directly verified data[12]. Finally, since individual patient-level data were not available for re-pooling across all fifteen sources, this review relied on the pooled estimates already produced by the two included meta-analyses rather than generating an entirely new combined effect size. Genuinely new statistical pooling across all fifteen datasets was, therefore, not possible within the scope of this work[3,13].

Conclusion

Arterial thromboembolic events, though studied far less than their venous counterpart, affect a meaningful minority of patients on immune checkpoint inhibitor therapy, at a rate two to three times above background risk, and they carry a substantially higher mortality burden once they occur. Prior thromboembolic or cardiovascular disease, smoking, obesity, poor performance status, combination immunotherapy regimens, and concurrent chemotherapy consistently raise this risk, while the standard Khorana score performs less reliably in this population than it does elsewhere in oncology. Baseline cardiovascular risk assessment, cardiac biomarker monitoring during treatment, and a low threshold for investigating new cardiovascular

symptoms appear to be sensible practical measures for clinicians managing patients on these agents, pending prospective trials that can properly test targeted prophylactic strategies in this setting.

Conflicts of Interest

There are no conflicts of interest.

References

1. Roopkumar J, Kim AS, Thapa B, Hobbs BP, Khorana AA. Venous thromboembolism in cancer patients receiving immunotherapy. *Blood*. 2018;132(Suppl 1):2510. doi:10.1182/blood-2018-99-116439
2. Bar J, Markel G, Gottfried T, Percik R, Leibowitz-Amit R, Berger R, et al. Acute vascular events as a possibly related adverse event of immunotherapy: a single-institute retrospective study. *Eur J Cancer*. 2019;120:122-131. doi:10.1016/j.ejca.2019.06.021
3. Solinas C, Saba L, Sganzerla P, Petrelli F. Venous and arterial thromboembolic events with immune checkpoint inhibitors: a systematic review. *Thromb Res*. 2020;196:444-453. doi:10.1016/j.thromres.2020.09.038
4. Sussman TA, Li H, Hobbs B, Funchain P, McCrae KR, Khorana AA. Incidence of thromboembolism in patients with melanoma on immune checkpoint inhibitor therapy and its adverse association with survival. *J Immunother Cancer*. 2021;9(1):e001719. doi:10.1136/jitc-2020-001719
5. Moik F, Chan WE, Wiedemann S, Hoeller C, Tuchmann F, Aretin MB, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood*. 2021;137(12):1669-1678. doi:10.1182/blood.2020007878
6. Roopkumar J, Swaidani S, Kim AS, Thapa B, Gervaso L, Hobbs BP, et al. Increased incidence of venous thromboembolism with cancer immunotherapy. *Med (N Y)*. 2021;2(4):423-434. doi:10.1016/j.medj.2021.02.002
7. Li H, Sun X, Sun D, Zhao J, Xu Z, Zhao P, et al. Thromboembolic events associated with immune checkpoint inhibitors: a real-world study of data from the Food and Drug Administration Adverse Event Reporting System (FAERS) database. *Int Immunopharmacol*. 2021;98:107818. doi:10.1016/j.intimp.2021.107818
8. Kacimi SEO, Moeinafshar A, Haghighi SS, Saghazadeh A, Rezaei N. Venous thromboembolism in cancer and cancer immunotherapy. *Crit Rev Oncol Hematol*. 2022;178:103782. doi:10.1016/j.critrevonc.2022.103782
9. Alghamdi EA, Aljohani H, Alghamdi W, Alharbi F. Immune checkpoint inhibitors and potential risk of thromboembolic events: analysis of the WHO global database of individual case safety reports. *Saudi Pharm J*. 2022;30(7):1193-1199. doi:10.1016/j.jsps.2022.06.010
10. Maharaj S, Chang S, Kloecker G, Chesney J, Redman R, Rojan A. Venous and arterial thromboembolism

- with immunotherapy compared to platinum-based therapy. *Thromb Res.* 2022;217:48-51. doi:10.1016/j.thromres.2022.07.006
11. Li H, Li H, Tang L, Niu H, He L, Luo Q. Associations between immune-related venous thromboembolism and efficacy of immune checkpoint inhibitors: a systematic review and meta-analysis. *Clin Appl Thromb Hemost.* 2023;29:1-14. doi:10.1177/10760296231206799
12. Wang TF, Carrier M. Immune checkpoint inhibitors-associated thrombosis: incidence, risk factors and management. *Curr Oncol.* 2023;30(3):3032-3046. doi:10.3390/curroncol30030230
13. Yang M, Cao H, Wang C, Yu C, Sun P. Incidence of thromboembolic events in non-small cell lung cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *J Cancer Res Ther.* 2024;20:509-521. doi:10.4103/jcrt.jcrt_1031_23
14. Song J, Lessa AYC, Lee PL, Chowdhury I, Chang Y, Chang YC, et al. Risk factors for thrombotic events among patients taking immune checkpoint inhibitors: a systematic review and meta-analysis [abstract]. 2024:e14610.
15. van Lent A, Puscasu R, Kaasjager KAH, Haitjema S, Suelmann BBM, Verhaar MC, et al. Venous and arterial thrombosis in patients receiving immune checkpoint inhibitors. *PLoS One.* 2025;20(4):e0321112. doi:10.1371/journal.pone.0321112
16. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. *J R Soc Med.* 2003;96(3):118-121. doi:10.1177/014107680309600304
17. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.5 (updated August 2024). Cochrane; 2024. Available from: www.training.cochrane.org/handbook