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ORIGINAL ARTICLE

Atherosclerotic Cardiovascular Events in Cancer Patients Treated With Immune Checkpoint Inhibitors: A Retrospective Cohort Study

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Background Immune checkpoint inhibitors (ICIs) are effective therapies for numerous cancers, but have been associated with atherosclerotic cardiovascular disease (ASCVD). This study aimed to identify predictors for ASCVD events among cancer patients treated with ICIs and the cardiovascular risk factor (CVRF) control of those who developed ASCVD.

Method A single-centre retrospective study of 366 cancer patients who received ICIs from 2018 to 2020 was performed. Demographic, baseline CVRF, cancer history, and ICI regimen data were obtained from medical records. The primary end point of ASCVD events was defined as myocardial infarction, coronary revascularisation, ischaemic stroke, or acute limb ischaemia. Cox proportional multivariable modelling and competing risks analysis were performed to assess ASCVD predictors. Descriptive analysis was performed to describe CVRF management among those who developed ASCVD events.

Results Over a median follow-up of 3.4 years (2.8–4.3), 26 patients (7.1%) experienced 27 ASCVD events (seven myocardial infarction, one coronary revascularisation, 13 ischaemic stroke, and six acute limb ischaemia events). There were 226 (61.8%) cancer-related deaths and no cardiac deaths. History of ASCVD before ICI initiation was independently associated with ASCVD events on traditional Cox modelling (hazard ratio [HR] 4.00; 95% confidence interval [CI] 1.79–8.91; $p<0.01$) and competing risks analysis (HR 4.23; 95% CI 1.87–9.60; $p<0.01$). A total of 17 patients developed ASCVD events after ICI cessation (median 1.4 years). Among those with ASCVD events, 12 had prior ASCVD, 16 had hypertension, nine had hypercholesterolaemia, and four had diabetes, and nine were actively smoking. Variable prescription of cardiovascular preventative therapies was noted.

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Conclusions History of ASCVD was associated with subsequent ASCVD events among patients treated with ICIs, which could occur even after active treatment was stopped. Identification and aggressive management of modifiable CVRFs should be considered throughout cancer survivorship in patients who received ICI treatment.

Keywords Immune checkpoint inhibitors • Immunotherapy • Medical oncology • Cardio-oncology • Cardiotoxicity

Introduction

Immune checkpoint inhibitors (ICI) are a class of immune-stimulating therapies that have revolutionised the treatment of cancer [1], achieving durable responses even in a subset of patients with widespread metastatic disease. As of February 2023, seven ICIs are available through the Pharmaceutical Benefits Scheme of Australia for the treatment of 14 different tumour types, across both (neo)adjuvant and metastatic settings [2]. However, the pro-inflammatory effects of ICIs have been associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) in cancer patients [3–6]. It is proposed that the ICI-mediated inhibition of PD-1 (programmed cell death 1), PD-L1 (programmed cell death 1 ligand 1), and CTLA4 (cytotoxic T-lymphocyte associated protein 4) promotes endothelial dysfunction and induces a predominantly T cell–driven inflammatory response in atherosclerotic plaques, leading to progression towards clinically unfavourable plaque phenotypes [7]. Of particular relevance is the use of ICI in adjuvant/curative settings, where increasing the risk of ASCVD may be especially undesirable.

Although screening for standard modifiable cardiovascular risk factors (CVRF) is recommended for all patients treated with ICIs [8–10], previous studies investigating predictors for ASCVD events following ICI therapy have reported conflicting results [4,11–13]. In this study, we assessed predictors for ASCVD events in an unselected cohort of cancer patients treated with ICIs, and described the CVRF profile and management of those who developed ASCVD events.

Materials and Methods

Study Design

This was a single-centre retrospective analysis of consecutive ambulatory patients with cancer treated with ICIs at Monash Health, Melbourne, Australia between January 2018 and December 2020. Institutional ethical approval was obtained for the study.

Study Population

All patients with a cancer diagnosis who were treated with ICIs at the institution's day oncology centre were included. Patients were identified from the hospital's pharmacy database, using prescription data comprising available ICIs through the Pharmaceutical Benefits Scheme of Australia during the study period: ipilimumab, nivolumab, pembrolizumab, durvalumab, and atezolizumab. Newer ICIs such as cemiplimab and avelumab were not available in Australia during the study period. Patients treated with ICIs as part of a clinical trial were excluded. There were no other exclusion criteria for the study.

Data Sources and Variables

Clinical data were collated from the patients' electronic medical records, including demographics, baseline CVRFs, drug history, cancer history, and ICI regimen. Baseline CVRFs, including hypertension, hypercholesterolaemia, and diabetes, were patient-reported. History of smoking was defined as either active or prior smoking at time of ICI initiation. History of ASCVD was defined as prior myocardial infarction (MI), ischaemic stroke, or peripheral vascular disease. Cancer type and stage were identified from oncology multidisciplinary team meeting notes. The pooled cohort equation (PCE) was used to establish baseline cardiovascular risk in those without a history of ASCVD [14], while the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention (TRS2P) was used in those with previous MI [15]. Lipid profile, renal function, and glycated haemoglobin A1c (HbA1c) results from 1 year before ICI initiation were used for baseline cardiovascular risk assessment.

The primary outcome of the study was atherosclerotic cardiovascular disease (ASCVD) events, defined as a composite of non-fatal MI, coronary revascularisation, ischaemic stroke, and acute limb ischaemia. Data on cancer-related and cardiac-related mortality were also collected from recorded death certificates and presented. ASCVD events, cancer-related mortality, and cardiac-related mortality were adjudicated independently by two authors (S.T. and J.C.), with discrepancies resolved by a third reviewer (A.J.N.).

Statistical Analysis

Categorical data are displayed as absolute numbers with percentages and compared with the chi-square test. Continuous data are presented as mean±standard deviation if normally distributed or median (Q1–Q3) if non-Gaussian, and compared with *t*-tests or Wilcoxon rank-sum tests as appropriate. Cox proportional multivariable modelling was performed to identify predictors for ASCVD events using significant variables on univariate analysis ($p<0.10$). Time to

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Table 1 Baseline demographics stratified by development of atherosclerotic cardiovascular disease events.

Characteristics	All patients (N=366)	No ASCVD events (n=340)	ASCVD events (n=26)	p Value
Age, yr	66 [58–73]	65 [58–73]	68 [61–72]	0.27
Male sex	230 (62.8)	212 (62.4)	18 (69.2)	0.48
Hypertension	156 (42.6)	140 (41.2)	16 (61.5)	0.04
Diabetes mellitus	59 (16.1)	55 (16.2)	4 (15.4)	0.92
Hypercholesterolaemia	121 (33.1)	112 (32.9)	9 (34.6)	0.86
History of smoking	297 (81.2)	272 (80.0)	25 (96.2)	0.04
Medical history				
Heart failure	9 (2.5)	8 (2.4)	1 (3.9)	0.64
ASCVD	65 (17.8)	53 (15.6)	12 (46.2)	<0.01
Cancer type				
Non-small-cell lung cancer	238 (65.0)	219 (64.4)	19 (73.1)	0.37
Melanoma	36 (9.8)	33 (9.7)	3 (11.5)	0.76
Head and neck	31 (8.5)	29 (8.5)	2 (7.7)	0.88
Renal cell carcinoma	26 (7.1)	24 (7.1)	2 (7.7)	0.90
Small-cell lung cancer	15 (4.1)	15 (4.4)	0 (0.0)	0.27
Urothelial cancer	7 (1.9)	7 (2.1)	0 (0.0)	0.46
Other	13 (3.6)	13 (3.8)	0 (0.0)	0.31
Cancer stage				
I	3 (0.8)	3 (0.9)	0 (0.0)	0.63
II	14 (3.8)	11 (3.2)	3 (11.5)	0.03
III	128 (35.0)	115 (33.8)	13 (50.0)	0.10
IV	221 (60.4)	211 (62.1)	10 (38.5)	0.02
Immune checkpoint inhibitor				
Nivolumab	132 (36.1)	123 (36.2)	9 (34.6)	0.87
Pembrolizumab	114 (31.2)	105 (30.9)	9 (34.6)	0.69
Durvalumab	50 (13.7)	45 (13.2)	5 (19.2)	0.39
Atezolizumab	45 (12.3)	44 (12.9)	1 (3.9)	0.17
Ipilimumab and nivolumab	25 (6.8)	23 (6.8)	2 (7.7)	0.86
Number of doses	6 [3–12]	6 [3–12]	12 [6–23]	<0.01
Duration of therapy, days	112 [42–259]	108.5 [41.5–238.5]	265.5 [149–363]	<0.01

Values represented as median (Q1–Q3) or number (percentage).
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; Q, quartile.

first ASCVD event analysis was undertaken with the date of ICI initiation used as the time of study entry. If a patient experienced more than one ASCVD event during follow-up, such as ischaemic stroke followed by non-fatal MI, the first event defined the ASCVD event recorded and the time of study exit. In patients without ASCVD events, date of death or last follow-up was used as the censoring date. A competing risks analysis was also undertaken by constructing cause-specific hazard models for ASCVD events, treating cancer-related death as a competing risk [16]. Multicollinearity between covariates was excluded by assessing variance inflation factors. Conditional proportional hazards assumptions were visually inspected by plotting Schoenfeld residuals. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Subgroup analysis was performed among those with stage 1–3 cancer, who are expected to have favourable cancer-related prognoses, and thus greater competing cardiovascular risk. Descriptive analysis was performed within the cohort with ASCVD events to describe the time from ICI initiation to the event, number of patients who subsequently succumbed to cancer, prevalence of CVRFs, and use of preventative therapies for CVRF control. A two-sided $p \leq 0.05$ was deemed statistically significant in all analyses. Statistical analysis was performed using Stata MP/14 (StataCorp, College Station, TX, USA).

Results

Patient Demographics, Comorbidities, and Cancer Data

The study cohort included 366 patients. Baseline demographics are presented in Table 1. The median age was 66 years (58–73) and 230 (62.8%) patients were male. A total of 156 patients (42.6%) had hypertension, 59 (16.1%) diabetes

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mellitus, 121 (33.1%) hypercholesterolaemia, 297 (81.2%) history of smoking, and 65 (17.8%) history of ASCVD (41 prior MI, 25 stroke, 9 peripheral vascular disease). Non-small-cell lung cancer was the most common type of malignancy in the cohort (238 patients, 65.0%), and most patients were treated for stage 4 disease (221 patients, 60.4%). The most common ICIs prescribed were single-agent PD-1 inhibitors, nivolumab (36.1%), and pembrolizumab (31.2%). Dual combination ICI therapy consisting of CTLA4 (ipilimumab) and PD-1 (nivolumab) inhibitors was used in only 25 patients (6.8%).

Cardiometabolic Screening and Risk Profile

Fasting lipid profile results within 1 year of starting ICI therapy were available in 17 patients (4.6%). Of these, nine had pre-existing hypercholesterolaemia, three prior MI, one stroke, and one peripheral vascular disease. The median total cholesterol, high-density lipoprotein, and low-density lipoprotein levels were 3.6 mmol/L (3.2–4.9), 1.0 mmol/L (0.7–1.2), and 2.0 mmol/L (1.8–3.3), respectively. A total of 58 patients (15.8%) had their HbA1c checked within a year of ICI initiation, with a median of 6.5% (6.0–7.5); of these, 27 were known to have a history of diabetes.

Among the 301 patients without a history of ASCVD, baseline PCE was determinable in 13 patients (4.3%) at the time of ICI initiation, with a median 10-year risk of 12.8% (6.3–27.8) (increased PCE risk is defined as ≥7.5% [17]). Baseline TRS2P was ascertainable for all 41 patients with a history of MI at the time of ICI initiation, with a median score of 2 [2,3] (increased TRS2P is defined as ≥5 [18]).

Primary Outcome and Mortality

A total of 26 patients (7.1%) experienced 27 ASCVD events (seven non-fatal MI, one coronary revascularisation, 13 ischaemic stroke, and six acute limb ischaemia events) over a median follow-up of 3.4 years, translating to an event rate of 2.1 events per 100 person-years. There were 226 deaths (61.8%) during the study period; all deaths were cancer-related and none were cardiac-related. The median time to cancer-related death from initiation of ICIs was 282 days (97–555). There were no differences in death rates between patients with and those without ASCVD events (17 [65.4%] vs 209 [61.5%]; p=0.69), although patients who developed ASCVD events had longer median overall survival from ICI initiation (565 vs 268 days; p<0.01).

Patients with ASCVD events were more likely to have hypertension (61.5% vs 41.2%; p=0.04), history of smoking (96.2% vs 80.0%; p=0.04), prior ASCVD (46.2% vs 15.6%; p<0.01), stage 1–3 disease (61.5% vs 37.9%; p=0.02), higher median number of ICI doses (12 vs 6 doses; p<0.01), and longer duration of ICI therapy (265.5 vs 108.5 days; p<0.01) (Table 1).

The final included covariates in the multivariable analysis were hypertension, history of smoking, prior ASCVD, stage 1–3 cancer, and median number of ICI doses. The incidence of ASCVD events was found to be independently associated with history of ASCVD (HR 4.00; 95% CI 1.79–18.91; p<0.01) (Table 2).

Table 2 Multivariable analysis for atherosclerotic cardiovascular disease events.

Variables	Hazard ratio	95% CI	p Value
Hypertension	2.10	0.92–4.82	0.08
History of smoking	3.65	0.48–27.74	0.21
History of ASCVD	4.00	1.79–8.91	<0.01
Stage 1–3 disease	1.20	0.53–2.73	0.66
Median number of doses	0.99	0.96–1.02	0.68

Hazard ratio for median number of doses was calculated per one increase in number of doses.

Abbreviations: CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease.

When competing risks analysis was performed using cause-specific hazard modelling, the estimated cause-specific HR for ASCVD events was significant only for prior ASCVD (HR 4.23; 95% CI 1.87–9.60; p<0.01) (Table 3). Comparatively, the cause-specific HRs for cancer-related death were significant for stage 1–3 cancer (HR 0.61; 95% CI 0.46–0.82; p<0.01) and median number of ICI doses (HR 0.93; 95% CI 0.91–0.95; p<0.01).

Subgroup Analysis

A total of 145 patients (39.6%) were treated with ICIs for stage 1–3 cancer. Comparisons between patients with stage 1–3 and stage 4 cancer are demonstrated in Supplementary Table 1. A total of 16 patients (11.0%) with stage 1–3 cancer experienced ASCVD events during follow-up, while 78 (53.8%) died of cancer. Patients who developed ASCVD events were more likely to be older (median age, 70 vs 63 years; p=0.05) and have a history of ASCVD (43.8% vs 17.1%; p=0.01), higher median number of ICI doses (16 vs 7 doses; p=0.02), and longer duration of ICI therapy (290 vs 125 days; p=0.01) (Supplementary Table 2).

Descriptive Analysis of the ASCVD Events Cohort

Among the 26 patients with ASCVD events, the median age was 68 years (61–72), and most had non-small-cell lung cancer (19 patients, 73.1%); 13 had stage 3 and 10 had stage 4 cancers (Table 1). The median duration of ICI treatment was 266 days (149–363). Eight patients developed other non-cardiac immune-related adverse events during treatment. The median time from ICI initiation to ASCVD event development was 1.1 years (0.5–2.3). Seventeen (17) patients developed ASCVD events after cessation or completion of ICI therapy (median 1.4 years), while ASCVD events occurred in nine patients during active treatment. A total of 17 (65.4%) patients eventually succumbed to cancer during follow-up (Figure 1).

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Table 3 Cause-specific hazard models for atherosclerotic cardiovascular disease events and cancer-related death.

Variable	ASCVD events			Cancer-related death		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Hypertension	2.07	0.91–4.72	0.09	1.03	0.77–1.36	0.85
History of smoking	1.15	0.63–2.12	0.65	1.00	0.84–1.19	0.98
History of ASCVD	4.23	1.87–9.60	<0.01	1.03	0.70–1.51	0.89
Stage 1–3 disease	1.29	0.56–2.93	0.55	0.61	0.46–0.82	<0.01
Median number of doses	0.99	0.96–1.02	0.68	0.93	0.91–0.95	<0.01

Hazard ratio for median number of doses was calculated per one increase in number of doses.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

Twelve (12) patients had a history of ASCVD (seven prior MI, three stroke, and two peripheral vascular disease) at the time of ICI initiation. Of these, 10 were taking antithrombotic therapy and nine were on statin therapy; none were prescribed other lipid-lowering therapies (Figure 2). Sixteen (16) patients had pre-existing hypertension, with 13 treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, seven with beta blockers, one with a calcium channel blocker, and one with a thiazide diuretic. One patient with known hypertension was not on regular antihypertensive therapy. Nine patients had hypercholesterolaemia, and all were treated with statins at baseline. Four patients had a known history of type 2 diabetes mellitus at the time of ICI initiation. One was treated with metformin and insulin, one with monotherapy dipeptidyl peptidase IV inhibitor, and two were not on any diabetic drugs at the time of ICI initiation. Nine patients were actively smoking at the time of ICI initiation. Documentation on smoking counselling and cessation rates after initiation of ICI therapy was incomplete.

None of the patients had calculable baseline PCE risk scores at the time of ICI initiation; among seven patients with prior MI, the median TRS2P was 2 [1,3]. There was no documentation on whether modifiable CVRFs were monitored and treated appropriately to target throughout ICI therapy. There were no documented changes in prescription of antithrombotic, statin, or antihypertensive therapy throughout ICI treatment; one patient had up-titration of insulin for diabetes during ICI treatment. At the time of ASCVD event diagnosis, six patients had their lipid profile checked, while HbA1c was assessed in five patients.

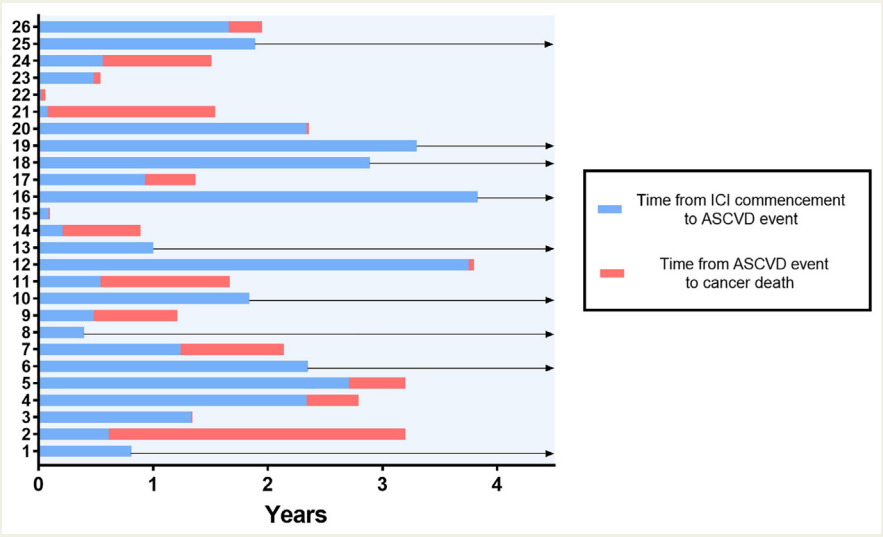

Figure 1 Time to event among patients with ASCVD events. The blue bar charts represent the amount of time from ICI initiation to development of ASCVD events. In those who subsequently succumbed to cancer death, the red bar charts represent the amount of time between development of ASCVD events and cancer death. The black arrows indicate continuing survival at study censoring date. ASCVD events were found to occur at variable time points after ICI initiation. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ICI, immune checkpoint inhibitor.

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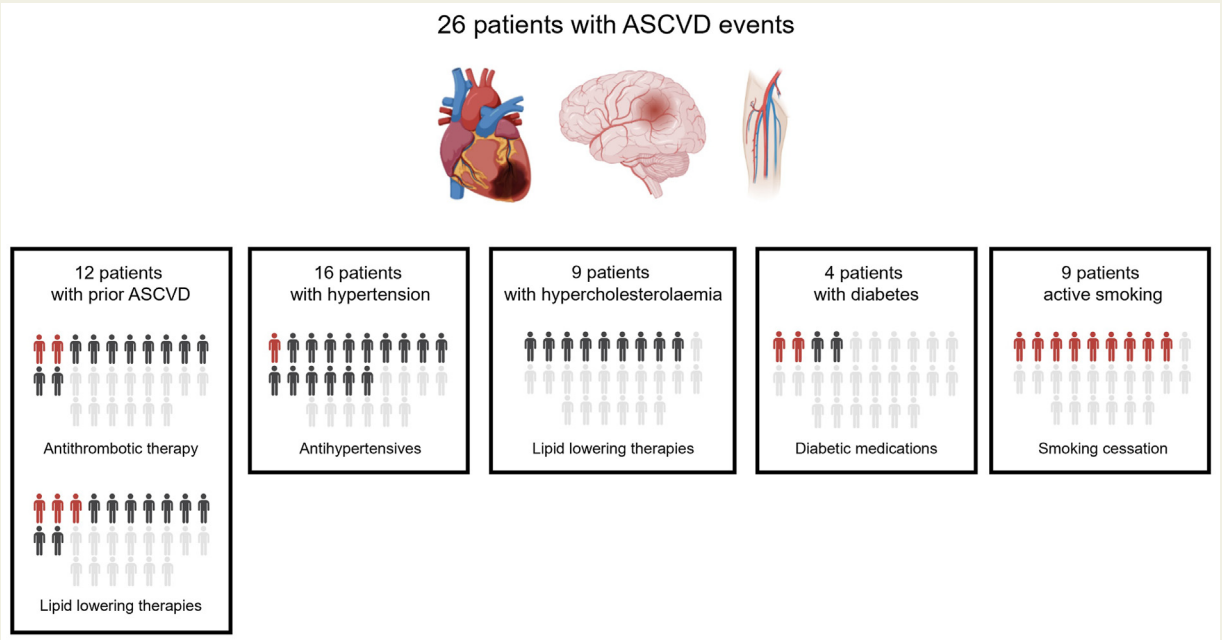

Figure 2 Management of modifiable CVRFs among patients with ASCVD. The black figures represent the number of patients with the highlighted CVRF, as established by patient-reported medical history. The red figures represent the number of patients who were untreated for that particular CVRF. In those who were treated with cardiovascular preventative therapies, it was unclear if control and treatment targets were achieved during cancer survivorship.
Abbreviations: CVRF, cardiovascular risk factor; ASCVD, atherosclerotic cardiovascular disease;

Discussion

In this analysis of 366 patients with cancer receiving ICI therapy, we report a 7.1% incidence of ASCVD events over a median 3.4-year follow-up (2.1 events per 100 person-years). Additionally, there was an association between history of ASCVD and the development of ASCVD events both on conventional Cox proportional modelling and competing risk analysis. When restricted to those with stage 1–3 cancer with more favourable prognoses, there was an increased incidence of ASCVD events of 11.0%. Development of ASCVD events occurred more commonly after cessation of ICI therapy rather than during active treatment. Among patients who developed ASCVD events, CVRFs were not uncommon, and prescription of preventative therapies was variable. Baseline estimation of cardiovascular risk using conventional scoring instruments was only calculable in a minority of patients because of lack of routine cardiometabolic screening. This is the largest Australian study to date to report the incidence and predictors of ASCVD events as well as modifiable CVRFs among patients with cancer treated with ICIs.

The association between ICIs and ASCVD events has been well described in the literature, with comparable event rates found in our study. An Australian study of 289 melanoma patients treated with ICIs reported increased risk of ASCVD events compared with patients who received non-ICI treatments, with an incidence of 3.6 events per 100 person-years [19]. In a retrospective analysis of 5,684 patients, Drobni et al. [4] also described a three-fold increased risk of ASCVD events among cancer patients treated with ICIs, with an incidence of 6.6 events per 100 person-years. Similar findings were reported in a meta-analysis of 28 ICI trials consisting of 29,592 patients, where patients treated with ICIs were found to have a 1.5-fold (0.7 events per 100 person-years) and 1.6-fold (0.9 events per 100 person-years) increased risk of MI and stroke, respectively [20]. As these estimates relied on adverse event reporting during trial follow-up rather than analysing ASCVD events as a pre-specified end point, these results could have underestimated the real-world risk of ASCVD with ICIs [21]. Furthermore, cancer trials often exclude patients with pre-existing ASCVD, thus leading to selection bias towards healthier study populations and lower ASCVD event rates [22,23].

Treatment with ICIs could be perceived as a non-modifiable CVRF for ASCVD given that patients require treatment with these agents for their malignancies. This emphasises the importance of baseline cardiovascular risk estimation and identification and control of other standard modifiable CVRFs among patients treated with ICIs for prevention of ASCVD events in cancer survivorship (Figure 3), in keeping with recommendations from the 2022 European Society of Cardiology Cardio-Oncology Guidelines [8]. However, this is not commonly performed in real-world standard cancer care, possibly because of an understandable clinician and patient focus on the cancer diagnosis

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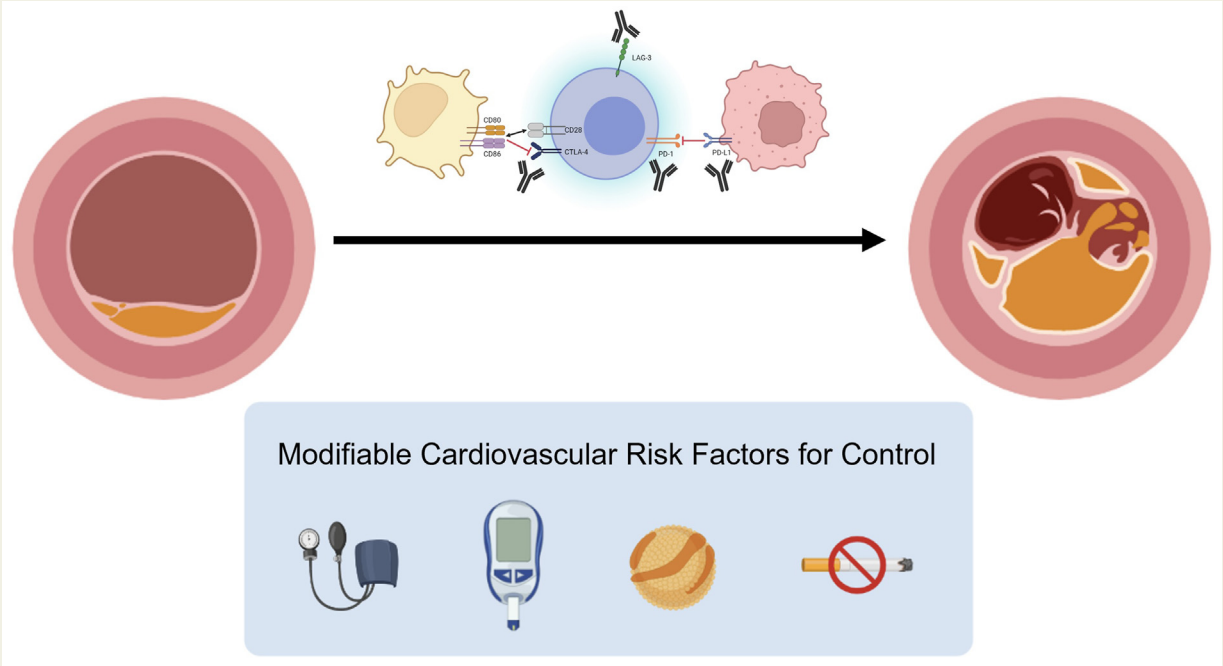

Figure 3 Modifiable CVRFs for control to prevent atherosclerotic cardiovascular disease with immune checkpoint inhibitors. Immune checkpoint inhibitors could be perceived as a non-modifiable CVRF for atherosclerotic cardiovascular disease. Hence, emphasis should be directed towards identification and aggressive control of standard modifiable CVRFs, such as hypertension, diabetes, hypercholesterolaemia, and smoking.
Abbreviations: CVRF, cardiovascular risk factor; CTLA-4, cytotoxic T-lymphocyte associated protein 4; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1.

and prognosis. In an Australian study of 333 patients admitted to a cardiology unit, patients with a history of cancer were found to have been prescribed less cardioprotective drugs for CVRF control despite having similar CVRF profiles to those without cancer [24]. Similarly, a study of 571 childhood cancer survivors reported underdiagnosis and undertreatment of CVRFs in up to 27.1% and 21.0% of the cohort, respectively [25]. The results from our study extend existing data and suggest that identification of CVRFs and prescription of preventative therapies could have been improved before the development of ASCVD events in a proportion of the cohort. This is paramount for patients with pre-existing ASCVD who may be at increased risk of further ASCVD events following ICI initiation. The determination of CVRFs in our study, as in most real-world settings, was reliant on patient-reported medical history because of a lack of routine cardiometabolic screening, which could have led to underestimation of the prevalence of CVRFs. Monitoring of CVRF control and achievement of treatment targets were not performed as part of standard cancer care in our cohort, and hence it remains unclear if patients were undertreated for CVRFs.

Our study suggests that the risks of ASCVD events with ICIs may not be limited to the ICI treatment period and may continue into long-term cancer survivorship following treatment cessation or completion. This could be biologically plausible, with several small studies suggesting that ICIs increase the risk of ASCVD events by altering atherosclerotic plaque composition and volume. In a post-mortem study of 22 patients, those treated with ICIs were found to have lymphocyte-predominant coronary artery plaque rather than conventional macrophage-driven atherosclerosis [7]. Additionally, Drobni et al. [4] demonstrated that ICIs were associated with increased progression of aortic plaque volume, particularly non-calcified plaque volume, in a retrospective study of 40 patients with melanoma. These changes in plaque morphology and volume provide mechanistic explanations for the persisting risks of ASCVD events even after ICI therapy is stopped, thus proposing the importance of continuing CVRF control throughout cancer survivorship.

Immune checkpoint inhibitors (ICIs) are increasingly used in the treatment of various cancers, with over 3,000 ongoing trials investigating new indications, including studies assessing curative-intent (neo)adjuvant regimens [26]. With improving overall cancer survival consequent to rapid expansion of ICI use, there are concerns that a larger proportion of patients may be at increased risk of ASCVD events during cancer survivorship. Implementation strategies for CVRF screening and control among cancer patients treated with ICIs are needed because current health systems are not designed to holistically address both oncological and cardiovascular aspects of these patients' care. Screening for

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hypercholesterolaemia and diabetes could be incorporated into routine pathology testing conducted as part of standard cancer care. Blood pressure measurements obtained during routine visits to hospital for cancer care could be used to screen for hypertension [27]. The accuracy of conventional cardiovascular risk scoring instruments should also be re-assessed in cancer-specific populations treated with ICIs to ensure their applicability. Streamlined referral systems to cardio-oncology services could be instituted to allow initiation and titration of cardiovascular preventative therapies for patients with newly identified CVRFs or pre-existing ASCVD, as well as counselling on lifestyle modification and smoking cessation.

Limitations

This study should be interpreted in the context of several limitations. The study was retrospective in design and relied on electronic medical record documentation. Although this is the largest Australian study on ASCVD events in patients treated with ICIs, it was performed in a single-centre setting and had a small patient population relative to conventional cardiovascular studies. Additionally, our cohort included an unselected population of patients with cancer (predominantly lung cancer), and thus results may not be generalisable to each individual tumour type. Finally, this study was not able to compare the incidence of ASCVD events between patients treated with ICIs and a control group receiving non-immunological therapies. However, this was not the purpose of the study, as ICIs have already been well demonstrated to be associated with ASCVD in earlier studies.

Conclusion

Cancer patients who developed ASCVD events after starting treatment with ICIs were more likely to have pre-existing ASCVD. These events were found to occur anytime during cancer survivorship, but commonly after completion or cessation of ICI treatment. Treatment of CVRFs was variable among patients who developed ASCVD events following initiation of ICI therapy. Implementation studies are required to improve the uptake of CVRF screening and control among patients with cancer treated with ICIs.

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Conflicts of Interest

There are no conflicts of interest to disclose.

Submission Declaration and Verification

This article has not been published previously and is currently not being considered for publication elsewhere.

Data Availability Statement

Data are available on request from the authors.

Appendices

Supplementary data associated with this article can be found, in the online version, at https://dx.doi.org/10.1016/j.hlc.2023.10.008.

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