JACC: CARDIOONCOLOGY VOL. 4, NO. 5, 2022

ORIGINAL RESEARCH

Pre-Existing Autoimmune Disease Increases the Risk of Cardiovascular and Noncardiovascular Events After Immunotherapy

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ABSTRACT

BACKGROUND The use of immune checkpoint inhibitors (ICI) is associated with cardiovascular (CV) events, and patients with pre-existing autoimmune disease are at increased CV risk.

OBJECTIVES The aim of this study was to characterize the risk for CV events in patients with pre-existing autoimmune disease post-ICI.

METHODS This was a retrospective study of 6,683 patients treated with ICIs within an academic network. Autoimmune disease prior to ICI was confirmed by chart review. Baseline characteristics and risk for CV and non-CV immune-related adverse events were compared with a matched control group (1:1 ratio) of ICI patients without autoimmune disease. Matching was based on age, sex, history of coronary artery disease, history of heart failure, and diabetes mellitus. CV events were a composite of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, transient ischemic attack, deep venous thrombosis, pulmonary embolism, or myocarditis. Univariable and multivariable Cox proportional hazards models were used to determine the association between autoimmune disease and CV events.

RESULTS Among 502 patients treated with ICIs, 251 patients with and 251 patients without autoimmune disease were studied. During a median follow-up period of 205 days, there were 45 CV events among patients with autoimmune disease and 22 CV events among control subjects (adjusted HR: 1.77; 95% CI: 1.04-3.03; $P = 0.0364$). Of the non-CV immune-related adverse events, there were increased rates of psoriasis (11.2% vs 0.4%; $P < 0.001$) and colitis (24.3% vs 16.7%; $P = 0.045$) in patients with autoimmune disease.

CONCLUSIONS Patients with autoimmune disease have an increased risk for CV and non-CV events post-ICI. (J Am Coll Cardiol CardioOnc 2022;4:660-669) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.11.008

Immune checkpoint inhibitors (ICIs) have expanded the therapeutic options for patients with cancer.[1,2] As expected, the expanded use of ICIs has also led to a need for the increased understanding of the related potential toxicities, broadly termed immune-related adverse events (irAEs).[3] These irAEs can affect any organ, and the most recognized toxicities include dermatitis, colitis, hepatitis, thyroiditis, hypophysitis, and pneumonitis.[3] Our understanding of the cardiovascular (CV) toxicities of ICI therapy is incomplete.[4] Recognized CV toxicities include myocarditis, pericardial effusions, arrhythmias, accelerated atherosclerosis, atherosclerosis-related CV events, and thromboembolic events.[5-13] With the expanded use of ICIs and the increased recognition of a broader potential for CV events, it will become increasingly important to identify those populations most at risk for these CV events.[4,11] Given concerns for toxicity from enhanced immune activation and decreased efficacy from baseline immunosuppression,[14] patients with pre-existing autoimmune disease[15] have been largely excluded from clinical trials of ICIs. Patients with autoimmune disease are at increased risk for CV events via both traditional and nontraditional risk factors.[16-19] Although there have been several retrospective studies linking underlying autoimmune disease to heightened risk for non-CV irAEs,[20-22] there are currently no data on whether patients with pre-existing autoimmune disease have an increased risk for CV events. We therefore conducted a retrospective analysis to better understand the clinical CV safety of using ICIs in patients with pre-existing autoimmune disease.

METHODS

PATIENTS. Cases and control subjects were derived from patients treated with ICIs as either standard therapy or as part of a clinical trial at a single academic hospital network (Massachusetts General Brigham). The study was approved by the Institutional Review Board at Massachusetts General Brigham. Subjects were identified by leveraging a pharmacy database to identify all patients treated with ICIs between May 31, 2015, and March 8, 2019. This resulted in a total of 6,683 unique potential cases and control subjects. Pre-existing autoimmune disease was defined a priori by generating a list of selected International Classification of Diseases-Ninth Revision and International Classification of Diseases-10th Revision codes for autoimmune disease (Supplemental List 1). Each patient initially flagged by International Classification of Diseases-10th Revision codes that occurred at least twice in the chart was then manually chart-reviewed to confirm the diagnosis, type of autoimmune disease, and treatments for that disease. Patients with and without pre-existing autoimmune disease were matched 1:1 without replacement. Patients were matched exactly for sex, history of coronary artery disease, history of heart failure, and diabetes mellitus, and age was matched using a caliper with a floating age ±2 years.

COVARIATES. Data on covariates of interest were extracted retrospectively from electronic medical records using the Research Patient Data Registry, which included standard demographics (age and gender), cancer-specific covariates (cancer type and ICI treatments, including programmed death-1 [PD-1], programmed death-ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated antigen-4 [CTLA-4]), CV history prior to ICI, and CV medications prior to ICI therapy. These also included the use of baseline active immunosuppression at the time of starting an ICI. This list included the use of corticosteroids (prior to starting an ICI) and any disease-modifying immunosuppressive agents.

DEFINITIONS AND OUTCOMES OF INTEREST. The primary endpoint was the occurrence of a CV event, which was a composite of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CTLA-4 = cytotoxic T lymphocyte-associated antigen-4

CV = cardiovascular

DVT = deep venous thrombosis

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

MI = myocardial infarction

PCI = percutaneous coronary intervention

PD-1 = programmed death-1

PD-L1 = programmed death-ligand 1

PE = pulmonary embolism

SMD = standardized mean difference

TIA = transient ischemic attack

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Paaladinesh Thavendiranathan, MD, MSc, served as the Guest Associate Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 19, 2022; revised manuscript received November 3, 2022, accepted November 8, 2022.

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
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artery bypass graft (CABG), stroke, transient ischemic attack (TIA), deep venous thrombosis (DVT), pulmonary embolism (PE), and myocarditis. These were chosen as data have linked ICIs to an increase in each of these events.[4] The individual components were key secondary endpoints. Events were initially identified using a key word search, and then all potential clinical events were independently adjudicated using standard definitions by a study team blinded to all other variables. The following clinical endpoints (MI, PCI, CABG, stroke, and TIA) were based on 2017 cardiovascular and stroke endpoint definitions for clinical trials from the Standardized Data Collection for Cardiovascular Trials Initiative.[23] DVT and PE were defined using standard radiographic findings, with PE identified via computed tomography and DVT identified via ultrasound or computed tomography; post-ICI events represent new events. Myocarditis was diagnosed by: 1) standard histologic features on endomyocardial biopsy or autopsy; and 2) a guideline-recommended scoring system for clinically suspected myocarditis that incorporates several variables, including clinical biomarkers and imaging features.[24] Non-CV adverse events post-ICI were identified using a key word search that included "colitis," "dermatitis," "hepatitis," "hypopituitarism," "myositis," "nephritis," "pancreatitis," "pneumonitis," "psoriasis," and "thyroiditis," all using standard definitions, and steroid use for an adverse event was also identified.[25]

STATISTICAL ANALYSES. Continuous variables are presented as mean ± SD or median (IQR) and categorical variables as frequencies (percentages). Comparisons were tested using paired Student's *t*-tests for continuous variables and the McNemar exact test for categorical variables. The primary measures of interest in this study were rates of CV events (MI, PCI, CABG, TIA, stroke, DVT, PE, and myocarditis) after ICI compared between those with and without pre-existing autoimmune disease. The secondary outcomes of interest were the rates of non-CV adverse events after ICI in these cohorts. Patient with and without pre-existing autoimmune disease were matched 1:1 without replacement. Patients were matched exactly for sex, history of coronary artery disease, history of heart failure, and diabetes mellitus, and age was matched using a caliper with a floating age ±2 years. These factors were chosen given prior studies identifying these as potentially important for ICI-induced CV events.[5,26,27]

TABLE 1 Baseline Characteristics of Patients With Prior Autoimmune Disease and No Prior Autoimmune Disease

	No Prior Autoimmune Disease (n = 251)	Prior Autoimmune Disease (n = 251)	*P* Value
Demographics			
Age at ICI initiation, y	67.2 ± 11.0	67.3 ± 11.0	0.34
Sex			1.00
Female	127 (50.6)	127 (50.6)	
Male	124 (49.4)	124 (49.4)	
CV risk factors			
Chronic kidney disease	27 (10.8)	23 (9.2)	0.62
Chronic obstructive pulmonary disease	23 (9.2)	21 (8.4)	0.86
Diabetes mellitus	28 (11.2)	28 (11.2)	1.00
Stroke	25 (10.0)	15 (6.0)	0.13
Smoking	32 (12.8)	19 (7.6)	0.066
Hypertension	119 (47.4)	71 (28.3)	<0.001
Prior CV disease			
Coronary artery disease	23 (9.2)	23 (9.2)	1.00
Heart failure	17 (6.8)	17 (6.8)	1.00
Deep venous thrombosis	14 (5.6)	7 (2.8)	0.13
Pulmonary embolism	22 (8.8)	10 (4.0)	0.023
VTE (DVT or PE)	31 (12.4)	15 (6.0)	0.011
Prior CV medications			
Statins	83 (33.1)	93 (37.1)	0.38
ACE inhibitors/ARBs	62 (24.7)	96 (38.3)	0.002
Aspirin	72 (28.7)	89 (35.5)	0.10
Beta-blockers	55 (21.9)	103 (41.0)	<0.001
Diuretic agents	61 (24.3)	90 (35.9)	0.007
Cancer types			
Gastrointestinal	19 (7.6)	20 (8.0)	1.00
Gynecologic	7 (2.8)	12 (4.8)	0.36
Breast	11 (4.4)	5 (2.0)	0.18
Brain	1 (0.4)	7 (2.8)	0.070
Genitourinary	16 (6.4)	24 (9.6)	0.24
Head and neck	23 (9.2)	24 (9.6)	1.00
Hematologic	6 (2.4)	15 (6.0)	0.078
Thoracic	87 (34.7)	93 (37.1)	0.63
Melanoma	79 (31.5)	49 (19.5)	0.004
Sarcoma	0 (0.0)	2 (0.8)	0.50
Other	2 (0.8)	0 (0.0)	0.50
ICI therapy			
Monotherapy			
PD-L1	26 (10.4)	37 (14.7)	0.17
PD-1	179 (71.3)	208 (82.9)	0.002
CTLA-4	27 (10.8)	0 (0.0)	<0.001
Combination therapy			
PD-1/CTLA-4	19 (7.6)	6 (2.4)	0.007

Values are mean ± SD or n (%). *P* values are from paired Student's *t*-tests or McNemar exact tests.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CTLA-4 = cytotoxic T lymphocyte-associated antigen-4; CV = cardiovascular; DVT = deep venous thrombosis; ICI = immune checkpoint inhibitor; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PE = pulmonary embolism; VTE = venous thromboembolism.

Univariable and multivariable Cox proportional hazards regression models were used to calculate HRs and 95% CIs to assess the relationship between pre-existing autoimmune disease to the time to the first clinical event (or censoring) for the composite endpoint. To account for the paired data structure and thus within-group correlation, we use shared-frailty Cox models. To account for remaining heterogeneity among the matched patients, analyses were adjusted using a set of predefined covariates including CV risk factors (stroke, smoking, and hypertension) and medications (statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aspirin, beta-blockers, and diuretic agents). As a robustness check, we also calculated the standardized mean difference (SMD) and considered any variable with SMD >10% in the regression analysis. Because of the limited event numbers, we used univariable Cox regression models for each variable with SMD >10% and included variables with P values <0.20 in univariable analysis in a multivariable model. Findings were similar to our main analysis and are thus shown in the Supplemental Appendix (Supplemental Tables 2 and 3). In a sensitivity analysis, we calculated subdistribution HRs using Fine and Gray competing risks regression models in which the competing risk was all-cause mortality. Proportional hazards assumptions were tested using Schoenfeld residuals. Incidence rates were computed using the Kaplan-Meier method and cumulative incidence rates using Fine and Gray's method. All statistical tests were 2-sided, and P values <0.05 were considered to indicate statistical significance. Analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing) and Stata version 16.1 (StataCorp).

RESULTS

Of the 6,683 patients, 251 had diagnoses of autoimmune disease prior to ICI and were able to be matched to patients without pre-existing autoimmune disease. Baseline clinical characteristics are shown in **Table 1**. Patients without autoimmune disease were more likely to have histories of hypertension (28.3% vs 47.4%; $P < 0.001$) and tended toward a history of smoking (7.6% vs 12.8%; $P = 0.066$). Those with pre-existing autoimmune disease were more likely to have histories of either DVT or PE (12.4% vs 6.0%; $P = 0.011$). In contrast, those with autoimmune disease were more likely to have been prescribed specific CV medications prior to starting ICI therapy, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (38.3% vs 24.7%; $P = 0.002$), beta-blockers (41.0% vs 21.9%; $P < 0.001$), and diuretic agents (35.9% vs 24.3%; $P = 0.007$). To better understand disease severity of the underlying autoimmune disease, we found that 41% of patients were on active immunosuppressive drugs at time of ICI therapy, and 31% were on active immunosuppression within 30 days of ICI therapy, suggesting that there was a cohort of patients with more severe disease requiring baseline therapy.

For cancer types, the rates of melanoma were higher among patients without autoimmune disease (19.5% vs 31.5%; $P = 0.004$). There was also a difference in the type of ICI received, whereby patients with autoimmune disease were more likely to have received PD-1 inhibitors (82.9% vs 71.3%; $P = 0.002$) and less likely to be treated with CTLA-4 inhibitors (0% vs 10.8%; $P < 0.001$) or combination immunotherapy (2.4% vs 7.6%; $P = 0.007$) (**Table 1**).

The most common underlying autoimmune diseases were rheumatoid arthritis (23%), psoriasis (23%), and polymyalgia rheumatica (9.1%). These were followed by Hashimoto's thyroiditis, lupus, and ulcerative colitis (Supplemental Table 1). Most patients had 1 underlying autoimmune disease, with only a small subset having more than 1 autoimmune disease.

Over a median follow-up period of 205 days (IQR, 56-471 days) there were 45 events among patients with pre-existing autoimmune disease compared with 22 events among patients without autoimmune disease (unadjusted HR: 1.81; 95% CI: 1.09-3.02; $P = 0.023$) (**Table 2**). Comparing individual components of the composite CV event, we found that the rate of all individual CV events except CABG was higher in patients with pre-existing autoimmune

TABLE 2 Cardiovascular Events by Pre-Existing Autoimmune Disease Status

	No Prior Autoimmune Disease (n = 251)	Prior Autoimmune Disease (n = 251)	*P* Value
MI	3 (1.2)	6 (2.4)	0.51
PCI	2 (0.8)	3 (1.2)	1.00
CABG	1 (0.4)	0 (0.0)	1.00
TIA	0 (0.0)	5 (2.0)	0.063
Stroke	3 (1.2)	7 (2.8)	0.29
DVT	9 (3.6)	18 (7.2)	0.12
PE	6 (2.4)	7 (2.8)	1.00
Myocarditis	1 (0.4)	4 (1.6)	0.38
Composite event, excluding DVT and PE	9 (3.6)	22 (8.8)	0.047
Composite event, including DVT and PE	22 (8.8)	45 (17.9)	0.023

Values are n (crude %). *P* values are from McNemar exact tests for individual events and Cox model with shared frailty for composite event.

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; other abbreviations as in Table 1.

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TABLE 3 Univariable and Multivariable Cox Regression Analyses for the Composite Outcome (With Shared Frailty)

	Univariable Models			Multivariable Model		
	HR	95% CI	*P* Value	aHR	95% CI	*P* Value
Prior autoimmune disease	1.81	1.09-3.02	0.023	1.77	1.04-3.03	0.036
CV risk factors						
Stroke	1.25	0.54-2.91	0.60	1.15	0.48-2.79	0.76
Smoking	1.22	0.53-2.85	0.64	1.33	0.56-3.16	0.52
Hypertension	0.96	0.57-1.60	0.86	0.98	0.56-1.71	0.94
CV medications[a]	1.12	0.98-1.30	0.10	1.09	0.94-1.27	0.24

Cox model with shared frailty for composite outcome. [a]Medications included statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aspirin, beta-blockers, and diuretic agents.
aHR = adjusted HR; CV = cardiovascular.

disease, although not statistically significant (Table 2). We also compared the baseline characteristics of those patients with autoimmune disease who did and did not have CV events. Patients with pre-existing autoimmune disease who did develop CV events were less likely to have histories of diabetes mellitus but did not differ in other baseline characteristics.

There was a significant difference in event-free survival between those with pre-existing autoimmune disease and those without pre-existing autoimmune disease (Figure 1). Adjusting for CV risk factors as well as CV medications in a multivariable Cox proportional hazards model led to an almost 2-fold higher risk for developing a CV event in patients with pre-existing autoimmune disease (adjusted HR: 1.77; 95% CI: 1.04-3.03; $P = 0.0364$) (Table 3). When excluding patients on active immunosuppression at time of ICI therapy (31% of patients), results were significant in univariable analysis (HR: 1.99; 95% CI: 1.03-3.80; $P = 0.039$) but not significant in a multivariable analysis, likely because of the small sample size. Moreover, in a competing risks regression analysis, subdistribution HRs were significantly different between cases and control subjects with regard to CV events both in univariable and multivariable analyses (Supplemental Figure 1).

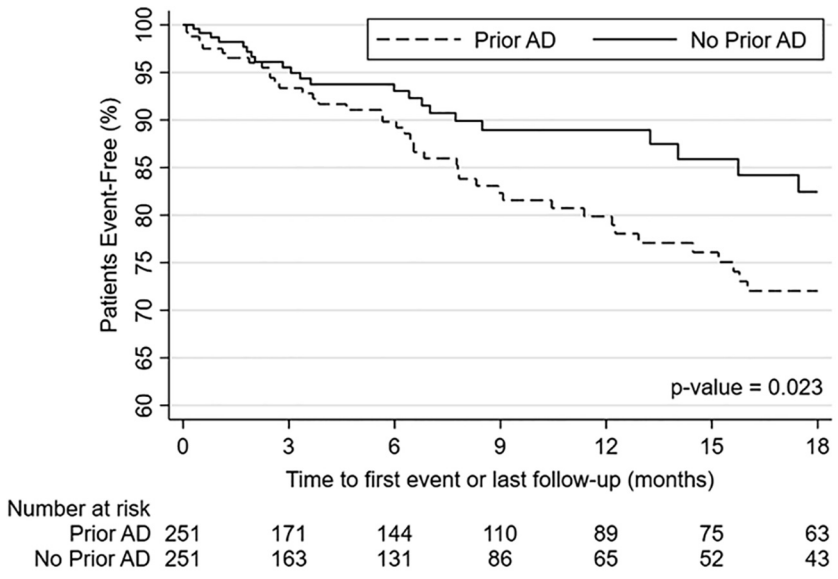
We also compared rates of non-CV irAEs between groups. Among the individual components of non-CV irAEs, the rates of psoriasis (11.2% vs 0.4%; $P < 0.001$) and colitis (24.3% vs 16.7%; $P = 0.045$) were higher in those with pre-existing autoimmune disease (Table 4). The use of steroids for any irAE did not differ significantly between those with and without histories of autoimmune disease.

DISCUSSION

This study presents, to our knowledge, the first evaluation of CV events post-ICI in a population with pre-existing autoimmune disease (Central Illustration). There are limited data sources to test this question, as pre-existing autoimmune disease has largely been excluded in clinical trials of ICIs. The exclusion of patients with pre-existing autoimmune disease is due in part to the use of immunosuppressive medications that may dampen the response, and conversely, the potential concern for a higher rate of irAEs from immune system overactivation.[28] Studies have posited that pre-existing autoimmune disease may be a risk factor for development of CV toxicities post-ICI,[29] although this had not yet been evaluated prior to this study. In our study, we found that approximately 4% of patients who received ICIs had underlying autoimmune disease, a rate similarly reported in other large cohort studies.[22] We also found that our patients with pre-existing autoimmune disease were less likely to have history of hypertension but were more likely to have been prescribed CV medications prior to ICI therapy. Our principal finding was that after matching for baseline differences in cohorts, patients with pre-existing autoimmune disease—despite having lower rates of traditional CV risk factors and having a lower proportion of patients that received combination immunotherapy and a CTLA-4 inhibitor—had significantly increased rates of CV events post-ICI. Of note, more than two-thirds of patients were on active immunosuppression at time of ICI, suggesting more than low-risk disease. These patients also had increased rates of specific non-CV toxicities—dermatologic and colitis—post-ICI. These findings suggest the importance of heightened surveillance for these events post-ICI.

Several studies have reported the spectrum of CV toxicities related to ICI; however, to our knowledge, no studies have tested the association between pre-existing autoimmune disease and CV events post-ICI. Historically, independent of ICIs, autoimmune diseases have been linked to an increased risk for CV disease, and the occurrence of a CV event with autoimmune disease is a recognized major cause of premature mortality.[19] The increase in risk is likely via up-regulation of inflammatory pathways leading to dyslipidemia, insulin resistance, hypercoagulability, and endothelial cell dysfunction; other factors have also been posited, including depression, hypothyroidism, hyperuricemia, low level or function of endothelial progenitor cells, and vitamin D deficiency.[30] Of note, both traditional and nontraditional risk factors have been reported to confer risk in this population, which may not have been fully encapsulated by baseline characteristics measured in this study.[30] In a recent observational population-based study, patients with autoimmune disease were

FIGURE 1 Kaplan-Meier Curves of Cardiovascular Events in Patients With and Without AD



There was a significant difference ($P = 0.02$) in event-free survival between those with pre-existing autoimmune disease (AD) (n = 251) and those without pre-existing AD (n = 251). *P* value based on Cox model with shared frailty for composite event.

found to be at a 1.4 to 3.6 times increased risk for CV disease than patients without autoimmune disease across a spectrum of diseases; in another meta-analysis of patients with rheumatoid arthritis and lupus, the investigators found a relative risk of 1.55 and close to 2, respectively, for symptomatic CV events including MI and ischemic cerebrovascular accident. Given our present results, this suggests that the CV effects of ICI therapy are likely synergistic with increased risk from underlying autoimmune disease.[31,32] Additionally, although our understanding of the association between ICIs and CV events is incomplete and requires further studies,[4] independently, ICIs may increase CV events.[10] These therapies have been associated with the occurrence of several CV events, which have also been noted to be increased in patients with autoimmune disease. Although the most fatal manifestation of ICIs' promoting CV events is myocarditis, other manifestations have been observed, including effects on the pericardium and vasculature, atherosclerosis, and promotion of thromboembolic events.[5,6,8,10,13,33,34]

On a mechanistic level, ICIs target the PD-1, PD-L1, and CTLA-4 pathways, which have been implicated in autoimmunity. These molecules are key in the T cell signaling pathway and are involved in central and peripheral tolerance. For example, interactions in PD-1 and PD-L1 pathways are important in diseases including type 1 diabetes mellitus, rheumatoid arthritis, and inflammatory bowel disease.[35] Furthermore, although CV effects of ICIs have not been studied in patients with autoimmune disease, drugs currently used in rheumatic diseases that modulate the immune system have been shown to have varying CV effects. For example, abatacept is an

TABLE 4 Noncardiovascular Events by Pre-Existing Autoimmune Disease Status

	No Prior Autoimmune Disease (n = 251)	Prior Autoimmune Disease (n = 251)	*P* Value
Colitis	42 (16.7)	61 (24.3)	0.045
Dermatitis	45 (17.9)	52 (20.7)	0.50
Hepatitis	10 (4.0)	18 (7.2)	0.17
Hypopituitarism	13 (5.2)	9 (3.6)	0.50
Myositis	4 (1.6)	3 (1.2)	1.00
Nephritis	10 (4.0)	7 (2.8)	0.63
Pancreatitis	3 (1.2)	6 (2.4)	0.51
Pneumonitis	22 (8.8)	22 (8.8)	1.00
Psoriasis	1 (0.4)	28 (11.2)	<0.001
Thyroiditis	7 (2.8)	10 (4.0)	0.63
Any irAE	113 (45.0)	128 (51.0)	0.21
Steroid use for any irAE	72 (28.7)	89 (35.5)	0.13

Values are n (crude %). *P* values are from McNemar exact tests.
irAE = immune-related adverse event.

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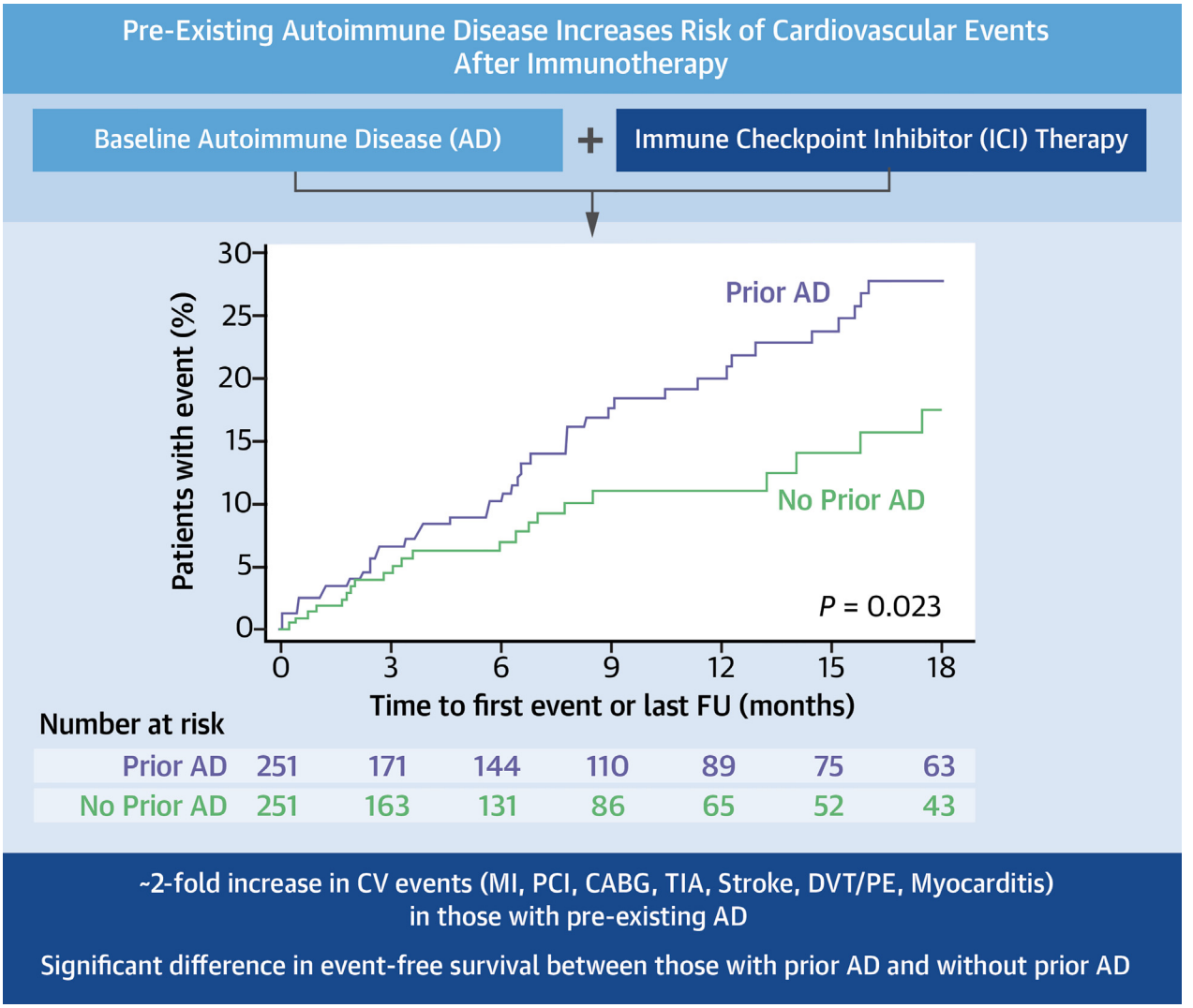
CENTRAL ILLUSTRATION **Baseline Autoimmune Disease Increases Risk for CV Events After Immunotherapy**



Lee C, et al. J Am Coll Cardiol CardioOnc. 2022;4(5):660–669.

Patients with autoimmune disease (AD) have increased cardiovascular (CV) risk. Immune checkpoint inhibitor (ICI) therapy can also increase CV events. There was a close to 2-fold increase in CV events in patients with baseline AD who received ICI therapy, suggesting need for close surveillance. CABG = coronary artery bypass graft; DVT = deep venous thrombosis; FU = follow-up; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; TIA = transient ischemic attack.

anti-CD80/CD86 fusion protein consisting of the extracellular domain of human CTLA-4 that inhibits T cell costimulation and is commonly used in rheumatoid arthritis; it has been shown to reduce CV risk in these patients compared with other therapies such as tumor necrosis factor inhibitors.[36,37] The costimulatory pathway inhibited by abatacept has been shown to have a role in atherosclerosis, and therefore inhibiting this pathway may be beneficial in CV risk reduction.[38] Given this prior research, we hypothesized that ICIs, which conversely up-regulate T cell signaling pathways, may increase CV risk.

Importantly, dysregulation of T cell signaling pathways likely produces distinctive CV events in different ways; for example, PD-L1-deficient mice have been shown to have proinflammatory and proatherogenic responses, which may explain MI and cerebrovascular events, whereas CTLA-4 deletion in mice leads to tissue inflammation and myocarditis.[10,39] The difference in impact may partially explain the difference in individual CV outcomes in our present study. In our study, we also found that patients with pre-existing autoimmune disease were more likely to be on CV medications prior to therapy despite a lower baseline CV risk. It is possible that those with underlying autoimmune disease are under closer CV surveillance with earlier preventive treatment, although there are currently no formal prevention guidelines.[32] A recent population-based observational study of 22 million individuals in the United Kingdom revealed an increased risk for developing CV disease in patients with autoimmune disease but showed that this was not explained by measured traditional risk factors; the investigators posited that chronic inflammation in itself drives these CV events, especially on the basis of prior research suggesting the effective use of anti-inflammatory therapies in reducing CV events.[32] Given this, it is possible that although CV medications were increasingly used in our pre-existing autoimmune disease cohort, these do not directly target underlying chronic inflammation that drives CV events.

For non-CV irAE, retrospective studies of patients with well-controlled autoimmune disorders have noted that irAEs and autoimmune exacerbations occur in this population with a frequency ranging from 16% to 50%.[14] Our cohort represented a range of autoimmune diseases, with psoriasis and rheumatoid arthritis the most common diseases, a distribution similar to the largest retrospective cohort study to date investigating post-ICI flares and irAEs.[20] Our rates of psoriasis and colitis were increased in patients with pre-existing autoimmune disease. This finding is in line with prior retrospective studies but is the largest study to date analyzing irAEs in this population.[20,22]

STUDY LIMITATIONS. As mentioned, given that most clinical trials have traditionally excluded patients with pre-existing autoimmune disease, patients in this study represent a lower risk group with well-controlled disease for whom clinicians had believed it feasible to offer therapy. We also did not have baseline inflammatory markers on these patients as a marker of severity. However, we did find that about 40% were on active immunosuppression at the time of ICI therapy, suggesting that more than one-third of patients in the cohort were not completely asymptomatic and did require some form of therapy. Furthermore, although to our knowledge this is the largest published study to date, the sample size was overall small, and the number of clinical events was small; it may therefore have been underpowered to detect sizable differences, particularly in non-CV irAEs, which were not significantly different between the 2 populations. The population was also heterogeneous in the underlying type of cancer, ICI used, and underlying autoimmune disease. This was limited mainly by current practice and guidelines, in which only a small subset of autoimmune patients are treated with ICIs. However, we believe that this still provides an important understanding that overall CV risk is increased in these patients, and therefore careful monitoring is needed when giving ICIs to this population of patients, especially with future expanded eligibility criteria. Last, corticosteroid use for irAEs in our study was overall lower than expected given that our study may not have encapsulated all irAEs and because some of the irAEs identified may have been low grade or may not have required corticosteroid use given the type of irAE.

CONCLUSIONS

We observed an increased rate of CV events in patients with pre-existing autoimmune disease post-ICI after adjusting for age and history of hypertension, despite a lower CV risk profile at baseline. Our study contributes to the current body of research showing that even in those with overall well-controlled autoimmune disease, close monitoring is necessary both CV and non-CV events. Future studies of preventive measures prior to ICI will be needed for this patient population once risk factors are better identified, especially if patients with less well-controlled autoimmune diseases are to be enrolled in ICI-based trials.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Neilan is supported by gifts from A. Curt Greer and Pamela Kohlberg and from Christina and Paul Kazilionis, the Michael and Kathryn Park Endowed Chair in Cardiology, and a Hassenfeld Scholar Award; and is supported by grants from the National Institute of Health/National Heart, Lung, and Blood Institute (R01HL30539, R01HL137562, and K24HL150238). Dr Drobni was supported by the ÚNKP-22-4-II-SE New National Excellence Program of the Ministry for Innovation and Technology from the National Research, Development, and Innovation fund. Dr Neilan has been a consultant to and received fees from H3-Biomedicine, Abbvie, Roche, C-4 Therapeutics, Sanofi, CRO Oncology, Genentech, and Amgen, outside of the current work; has received consulting fees from Bristol Myers Squibb for advice focused on myocarditis related to ICIs; and has received grant funding from AstraZeneca and Bristol Myers Squibb. Dr Taron has received funding from Deutsche Forschungsgesellschaft (TA 1438/1-2.T); and is a member of the Speakers Bureaus of Siemens Healthineers and Bayer, unrelated to this work. Dr Hoffmann has received consulting fees from Abbott, Duke University (National Institutes of Health), and Recor Medical, outside the submitted work; and has received research grants from Medimmune, HeartFlow, AstraZeneca, and KOWA. Dr Sullivan has been a consultant to Asana, AstraZeneca, Bristol Myers Squibb, Eisai, Iovance, Merck, Novartis, Pfizer, OncoSec, and Replimune; and has received research funding from Amgen and Merck, all outside the present work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients receiving ICIs for cancer, the presence of preexisting autoimmune disease, even if well controlled, appears to increase the risk for CV events.

TRANSLATIONAL UTLOOOK: Further research is needed on the mechanisms underlying increased risk for CV events in patients with autoimmune disease receiving ICIs. In addition, future studies should explore what preventive measures can decrease this risk.

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KEY WORDS coronary artery disease, immunotherapy, myocarditis, thrombosis

APPENDIX For a supplemental figure, tables, and a supplemental list, please see the online version of this paper.