

# Exploratory Review of the Role of Statins, Colchicine, and Aspirin for the Prevention of Radiation-Associated Cardiovascular Disease and Mortality

Maria Isabel Camara Planek, MD; Adam J. Silver, MD; Annabelle Santos Volgman, MD; Tochukwu M. Okwuosa, DO

Cardiovascular disease (CVD) is the primary cause of mortality in cancer survivors.<sup>1</sup> In particular, radiation-associated cardiovascular disease (RACVD) is the leading cause of morbidity and mortality in cancer survivors who have undergone radiation therapy (RT), particularly mediastinal radiation.<sup>2–4</sup> Mediastinal RT has successfully reduced both the recurrence of many thoracic malignancies and mortality rates, particularly for breast cancer (the most common cancer in women), Hodgkin lymphoma, and some head and neck cancers, thus making up about a third of the current  $\approx 17$  million cancer survivors in the United States.<sup>5,6</sup> However, survivors of mediastinal RT are at risk of developing RACVD, especially those treated for Hodgkin lymphoma and breast cancer before the early 2000s.<sup>7</sup> In recent times, patients with lung cancer have much improved survival attributable to advances in cancer therapy, but the cardiovascular side effects of mediastinal radiation therapy loom large. The consequences of increased longevity include a wide range of complications from RACVD, many of which have been well studied.<sup>3</sup>

## Introduction to Radiation-Associated Cardiovascular Disease—Types and Clinical Sequelae

Coronary artery disease (CAD) is a well-known consequence of RT. RT causes capillary luminal stenosis and endovascular cell membrane disruption, leading to thrombosis, vessel wall

rupture, and reduced capillary density. Subsequently, a microvascular inflammatory cascade both accelerates and induces de novo medium- and large-vessel disease, resulting in atherosclerotic plaque instability and fibrocalcific ostial and proximal segment coronary artery stenosis. These sequelae manifest over 30 years as progressive chronic stable angina, myocardial infarction (MI), and ultimately ischemic cardiomyopathy.<sup>8–10</sup> Patients treated with high-dose regimens ( $>30$  Gy) are at risk for extensive ascending aorta and arch fibrocalcification, leading to the so-called porcelain aorta and CAD, which could lead to transient ischemic attacks or strokes in up to 7.4% of patients with Hodgkin lymphoma. Peripheral arterial disease involving the carotid arteries after head and neck radiation, and renal, iliac, and femoral arteries after pelvic radiation have also been reported.<sup>8,10</sup>

Other manifestations of RACVD include pericardial, myocardial, conduction system, valvular disease, and autonomic dysfunction. Acutely, RT-associated inflammation most often presents as transient ventricular repolarization abnormalities and mild myocardial dysfunction. However, between 5 and 30 years after RT, myocardial disease develops both directly by the effects of RT-mediated myocardial fibrosis and indirectly because of the subsequent impact of ischemia-related scarring from radiation-associated CAD.<sup>8,10</sup> Second, RT-associated necrosis of tumors anatomically proximal to the heart may contiguously migrate to the pericardium, leading to a potentially fulminant myo-pericarditis.<sup>8</sup> More often, a delayed acute pericarditis that occurs within weeks and up to 1 year of RT completion manifests as asymptomatic pericardial effusions or symptomatic pericarditis, which could lead to pericardial calcification, fibrosis, and effusive constriction.<sup>8,10</sup> Radiation-associated inflammation and calcification eventually causes subvalvular, annular, and leaflet fibrosis. Up to 30 years after RT, valve dysfunction results from a narrowed stenotic orifice, restricted leaflet mobility, and incompetence.<sup>8,11</sup> Finally, up to 75% of long-term blood cancer survivors who received mediastinal radiation develop some form of conduction defects on ECG.<sup>10</sup> Right bundle

From the Rush Heart Center for Women, Rush University Medical Center, Chicago, IL.

**Correspondence to:** Tochukwu M. Okwuosa, DO, FACC, FAHA, Cardio-Oncology Program, Rush University Medical Center | 1717 West Congress Parkway, Kellogg Bldg, Suite 328 | Chicago, IL 60612. E-mail: tokwuosa@rush.edu  
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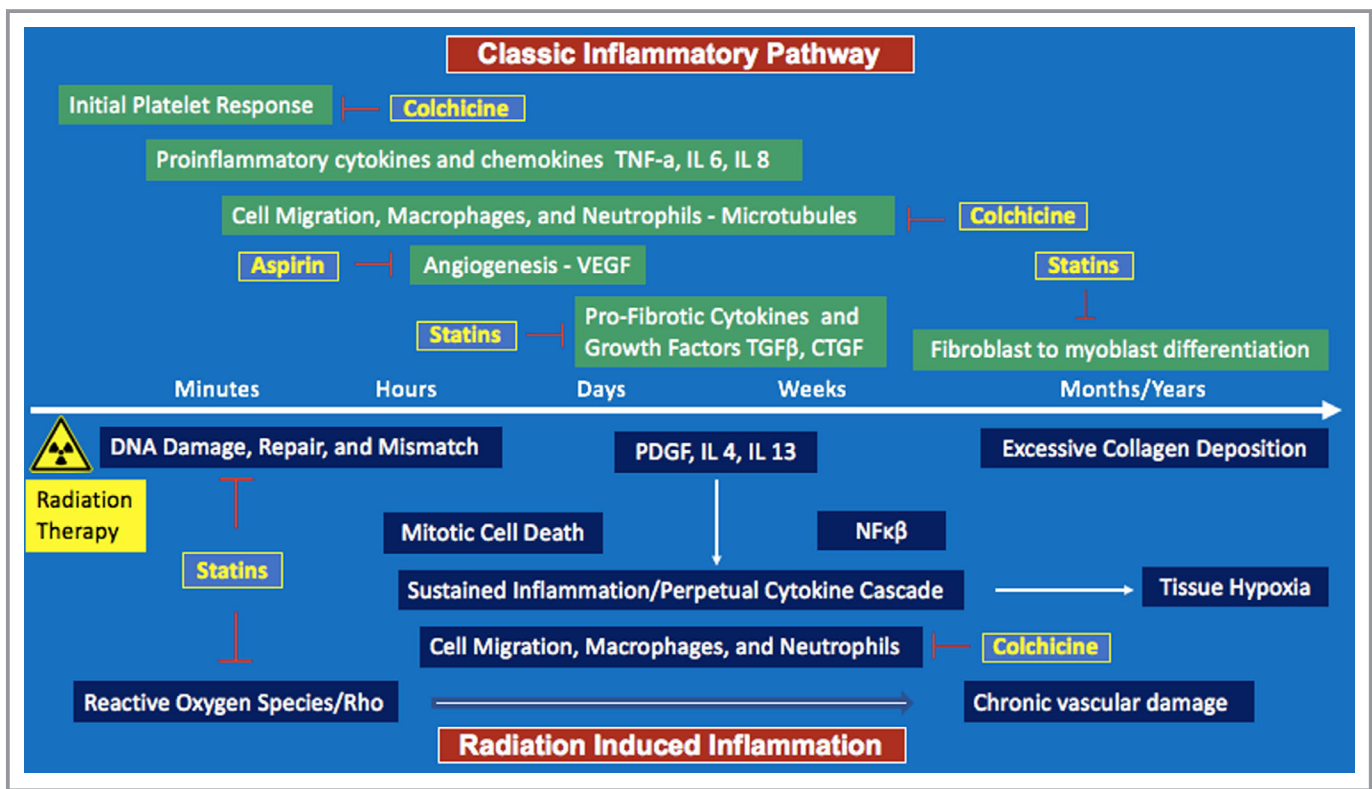
branch block is the most common late-manifesting conduction abnormality.<sup>8,10</sup>

### Molecular Pathophysiology of Radiation-Associated CAD

Most of our understanding of the pathophysiology of RACVD, in particular the RT sequelae of CAD, comes from preclinical work in animal studies. RT alters multiple biological pathways, including the acute and chronic inflammatory pathways, recruitment of cytokines and adhesion molecules, myocyte ischemia, and fibrosis, as shown in the Figure. More recently studied mechanisms of atherosclerosis in RT include the activation of reactive oxygen species (ROS) and rho signaling.<sup>12</sup>

Although RT may affect all 3 layers of the coronary artery, its main effect seems to be in the media layer, causing inflammatory cell and fibrin deposits, leading to atherosclerotic plaques.<sup>7</sup> In vitro studies show that the first phase of RACVD involves early endothelial dysfunction. Increased

endothelial permeability leads to recruitment of proinflammatory cytokines attributable to increased intercellular and vascular adhesion molecule expression and neutrophil recruitment. Extravasation of tumor necrosis factor, interleukin-6, platelet-derived growth factor, interleukin-4, interleukin-13, and transforming growth factor- $\beta$  (TGF- $\beta$ ) not only initiate the acute inflammatory pathway but also activate both the coagulation pathway via fibrin deposits and chronic fibrosis.<sup>14</sup> Activation of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells then results in sustained inflammation,<sup>14</sup> which subsequently promotes differentiation of fibroblasts into activated myofibroblasts via TGF- $\beta$ . The final common pathway in the pathophysiology of RT-associated fibrosis is then activated by TGF- $\beta$  signaling fibroblasts to activate into myofibroblasts that synthesize and deposit fibrin into the extracellular matrix of connective tissues. The critical step of sustained inflammation is the recruitment of macrophages and neutrophils to the tunica intima via nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells, which causes fatty streak formation even in the absence of preexisting



**Figure.** The proposed mechanism of statins, colchicine, and aspirin on the reduction of radiation-associated cardiovascular disease (RACVD). The normal inflammatory pathway is enhanced and perpetuated by the radiation-induced inflammatory pathway. Statins have been shown to counteract DNA damage repair, reactive oxygen/rho species in RACVD, while counteracting the normal inflammation pathway recruitment of transforming growth factor- $\beta$  (TGF- $\beta$ ), and connective tissue growth factor (CTGF). Colchicine is proposed to counteract the initial platelet response, as well as have a role in blocking inflammation-associated monocyte recruitment. Aspirin is proposed to specifically counteract the angiogenesis portion of inflammation, especially when paired with vascular endothelial growth factor-A inhibitors. Adapted from Donis et al,<sup>7</sup> and Williams, et al.<sup>13</sup>. NF $\kappa$ B, nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells; PDGF, platelet-derived growth factor; rho, part of Ras superfamily of guanosine triphosphate; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

atherosclerosis.<sup>5,15</sup> On the basis of these findings, it is proposed that RT alone can both initiate and accelerate preexisting conditions of atherosclerosis.<sup>5,15</sup>

Another key process studied in RACVD, specifically radiation-associated CAD, is chronic endothelial dysfunction from ROS and reactive nitrogen species. Oxidation of low-density lipoprotein cholesterol is one of the key first steps in the development of atherosclerosis.<sup>12</sup> This process is dependent on ROS, which is furthermore mitochondria dependent. RT has been shown to increase mitochondrial membrane permeability, which may increase ROS.<sup>16</sup> ROS also increases with acute inflammatory macrophage recruitment to the damaged endothelium. This highly unstable process promotes sustained inflammation, progression to atherosclerosis, and acceleration of RT-associated atherosclerosis.

These multiple pathways of endothelial dysfunction, acute and sustained inflammation, and ROS ultimately lead to chronic fibrosis, which is the critical process through which RT induces CVD.<sup>2,7</sup> Thus, targeting both early inflammation and oxidative stress with known anti-inflammatory agents is likely a promising target for the reduction of RACVD.<sup>13</sup>

## Current State of Radiation Therapy and Prevention of Radiation-Associated CVD

Modern RT shows promise in limiting cardiotoxicity, but cardiovascular morbidity persists.<sup>17</sup> To reduce the deleterious effects of RT, current changes to RT protocols include computed tomography planning models, 3-dimensional conformal RT, enhanced localization, gated techniques, deep inspiration breath hold, and proton versus photon therapy.<sup>5,18,19</sup> However, these newer radiation techniques have not been shown to reduce RACVD. In particular, there remains uncertainty regarding the cardiovascular effects of radiation with proton therapy, which has strong potential to minimize RACVD by allowing for radiation doses  $\leq 1$  Gy.<sup>20</sup> Darby et al<sup>17</sup> showed that each 1-Gy increase in radiation dose was associated with a 7.4% increase in coronary events in women with breast cancer who were treated with RT. Thus, further research on the impact of proton therapy on reducing RACVD is currently being conducted by an ongoing clinical trial (RadComp [Pragmatic Randomized Trial of Proton Versus Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness Consortium Trial], NCT02603341: PCORI). In this trial, patients with locally advanced breast cancer are randomized to proton versus photon therapy with planned 10-year follow-up. Primary end points include cardiovascular morbidity and mortality.<sup>21,22</sup> Though the eventual prevention goal is to develop RT protocols to minimize RACVD, the risk factors for developing RACVD highlight the call for earlier intervention on populations who are already at high risk.

Known risk factors for RACVD include age at the time of RT  $< 50$  years old; anterior or left chest radiation; concomitant chemotherapy with anthracyclines; high cumulative dose of radiation fractions ( $> 2$  Gy/day) or total dose  $> 30$  Gy; and, perhaps most importantly, preexisting CAD.<sup>3</sup> RT has been shown to increase the relative risk of ischemic CVD in those with preexisting CAD by up to 60%.<sup>23</sup> Thus, targeting this elevated risk of CAD with prompt management upon initiating RT is essential.

## Current Role of Anti-Inflammatory Agents (Statins, Colchicine, and Aspirin) for CVD Prevention

Statins and aspirin are well established in the prevention of adverse CVD outcomes.<sup>24,25</sup> Moderate- and high-intensity statins reduce atherosclerotic CVD risk (ASCVD).<sup>26</sup> The strong data behind statin use is the reason current American College of Cardiology/American Heart Association guidelines recommend statins as primary prevention in various populations of patients.<sup>26,27</sup>

Aspirin is a well-known therapy for both primary and secondary prevention of ASCVD events. Low-dose aspirin (75–100 mg) has been used for many years for ASCVD prevention. However, the recent studies—ASCEND (A Study of Cardiovascular Events in Diabetes) and ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events)—have shown that there may be lack of net benefit of the use of aspirin in primary prevention because of major bleeding risk.<sup>28,29</sup> ASPREE (Aspirin in Reducing Events in the Elderly), however, has shown that low-dose aspirin as primary prevention in older adults does not result in a more significant reduction of CVD than placebo.<sup>30</sup> Thus, current recommendations are that aspirin may be considered for primary prevention of ASCVD in adults aged 40 to 70 with both higher ASCVD risk and no increased risk of bleeding.

Colchicine is established to have anti-inflammatory and anticoagulant properties that have shown promise in secondary prevention of CAD.<sup>31</sup> There is currently no recommendation for the use of colchicine in either primary or secondary prevention of ASCVD events. However, there is growing evidence that these anti-inflammatory agents' pleiotropic effects extend to the prevention of RACVD.

In the recent PROBE (Prospective, Randomized, Observer-Blinded Endpoint) trial, colchicine—in addition to statins and other standard secondary prevention therapies—was associated with reduced composite rate of acute coronary syndrome in those with stable CAD. The ongoing larger LoDoCo2 (Low Dose Colchicine2) and COLCOT (Colchicine Cardiovascular Outcomes Trial) studies<sup>32</sup> recently produced promising results in meeting its primary end point. After recent acute MI in 4745 patients, 0.5 mg/day of colchicine compared with placebo was shown to reduce death from cardiovascular causes, MI, stroke,

resuscitated cardiac arrest, and urgent hospitalization for angina leading to percutaneous coronary intervention (hazard ratio [HR], 0.77, 5.5% in the colchicine group, 7.1% in the placebo group, respectively). Given the mechanism of colchicine, this trial shows potential for the role of colchicine in management of ASCVD beyond current guidelines.

To date, there are no current guidelines for the use of anti-inflammatories in the prevention of radiation-associated adverse cardiovascular events. However, there is growing interest in the role of anti-inflammatory medication against the long-term effects of radiation therapy, particularly statins, aspirin, and colchicine.

## Radioprotective Role of Anti-Inflammatory Agents—Preclinical Data

### Statins

Statins have the most preclinical data supporting their radioprotective role. Statin therapy has been proven to provide benefit even at the earliest stages of the endothelial damage when recognized in CAD and RACVD.<sup>12</sup> They have been shown to ameliorate endothelial dysfunction that leads to both atherosclerosis and fibrosis. Statins have also been shown in multiple studies to reduce the effects of TGF- $\beta$  in animal studies.<sup>25,33</sup> Atorvastatin and simvastatin have been shown to reduce cardiac dysfunction and radiation-associated capsular fibrosis in silicone implants in irradiated rats by reducing

TGF- $\beta$ .<sup>33,34</sup> Specifically, TGF- $\beta$ 1-mediated  $\alpha$ -smooth muscle actin production and fibroblast-to-myofibroblast differentiation are inhibited in RT, which demonstrates the reduction in the critical checkpoint from the radiation-associated proinflammatory response to the profibrotic response.<sup>35,36</sup> Statins also act on rho-mediated pathways in radiation, decreasing fibrosis via connective tissue growth factor.<sup>37</sup>

Another potential novel role of anti-inflammatory medications in the setting of RACVD protection is their role against known protective mechanisms against chemotherapy-associated cardiovascular damage. In a recent review studying anthracycline-induced cardiovascular toxicity, statins showed promise as anthracycline toxicity prophylaxis via their ability to work against rhoA and Rac1 signaling.<sup>38</sup> These signals are key in the ROS pathway that is central to not only anthracycline toxicity but also RACVD. Second, anthracycline use concomitant with RT is an already well-studied high-risk factor for RACVD development.<sup>3</sup> The approach to decrease both anthracycline toxicity and RACVD at the same time may be a novel angle in future studies on the role of all anti-inflammatories in RACVD.

These findings, as well as supporting preclinical studies, are summarized in Table 1.<sup>39–44</sup>

### Aspirin

The preclinical data for the role of aspirin in the prevention of RACVD has been mixed, but overall favorable. One study

**Table 1.** Summary of Preclinical Studies Investigating the Role of Statins on Reduction of Radiation-Induced Cardiovascular Disease

Statin	Observation	Reference
Atorvastatin	Atorvastatin reduces TGF- $\beta$ 1 and Smad2/3 levels and reduces cardiac dysfunction in irradiated rats	Zhang et al (2015) <sup>34</sup>
Lovastatin	Inhibits TGF- $\beta$ 1-mediated $\alpha$ -smooth muscle actin production and fibroblast-to-myofibroblast differentiation	Meyer-Ter Vehn et al (2008) <sup>35</sup>
Lovastatin	Attenuates radiation-induced proinflammatory and profibrotic response in different tissues	Ostrau et al (2009) <sup>36</sup>
Pitavastatin	Radiosensitizes tumor and potentiates radiation benefit by delaying DNA repair and enhancing tumor senescence in vitro and in vivo	Efimova et al (2018) <sup>39</sup>
Pravastatin	Pravastatin reduces radiation-induced normal tissue apoptosis without apoptosis reduction in tumor tissue	Doi et al. (2017) <sup>40</sup>
Pravastatin	Inhibits radiation-induced enteropathy by inhibiting extracellular matrix deposition in human fibrotic cells, without tumor protection	Haydont et al (2007) <sup>41,42</sup>
Simvastatin	Reduces radiation-induced capsular fibrosis in silicone implants in irradiated rats, significantly reducing TGF- $\beta$ and connective tissue growth factor	Chung et al (2016) <sup>33</sup>
Simvastatin	Decreases connective tissue growth factor production by rho-mediated pathways in radiation	Eberlein et al (2001) <sup>37</sup>
Simvastatin	Decreases radiation-induced apoptosis in the thymus via the Akt/sirtuin 1 pathway, thus exerting protective effect	Yang et al (2017) <sup>43</sup>
Simvastatin, lovastatin	Statins reduce the mRNA expression of proinflammatory and profibrotic cytokines stimulated by ionizing radiation in vitro and alleviate ionizing radiation-induced inflammation and fibrosis in vivo	Fritz et al (2011) <sup>25</sup>
Simvastatin	Mitigates periarterial fibrosis, severity of myocardial infarction, and increase in low-density lipoprotein levels in rat models irradiated >10 Gy	Lenarczyk et al (2015) <sup>44</sup>

TGF- $\beta$ 1 indicates transforming growth factor-  $\beta$ 1.



showed the radioprotective effect of aspirin via reduction of oxidative damage in rats that received lung radiation, showing promise for aspirin as a radioprotector in the clinical setting.<sup>45</sup> On the other hand, one particular study differentiates between the natural atherosclerotic pathway and the accelerated atherosclerotic pathway in RACVD.<sup>46</sup> In animal models, aspirin was shown to reduce age-related CAD in nonirradiated apolipoprotein E null rats, but did not inhibit atherosclerosis in apolipoprotein E null rats that received RT (14 Gy).<sup>47</sup>

Other preclinical studies show potential for other mechanisms of aspirin in prevention RACVD. For example, the vascular endothelial growth factor pathway is known to be directly affected by RT.<sup>2</sup> Aspirin use with vascular endothelial growth factor inhibition may be a possible modality to reduce RACVD.<sup>48</sup> In a recent review of tumor microenvironment resistance of radiation immunotherapy, targeting vascular endothelial growth factor-A in radiation immunotherapy was shown to be largely enhanced when combined with cyclooxygenase-1 inhibitors.<sup>49</sup> Further research is necessary to study this mechanism of aspirin on RT.

## Colchicine

Preclinical studies are favorable for colchicine's role in RACVD prevention. Colchicine inhibits microtubule polymers, resulting in reduction of interleukin-6 and leukocyte adhesion molecules, thus suggesting a potential for this medication to inhibit the chronic inflammatory pathway and fibrosis induced by radiation.<sup>50,51</sup> Microtubules play a large role in the accumulation of acute-phase reactants and are also considered to be critical in platelet aggregation.<sup>52</sup> Colchicine's *in vitro* antiplatelet activity has been studied as well, and further studies are needed to determine if this would benefit RACVD prevention.<sup>52,53</sup>

## Radioprotective Role of Anti-Inflammatory Agents—Clinical Data

### Statins

Similar to preclinical studies, statins have the most data in clinical studies that support their overall radioprotective effect. However, limited data have evaluated the cardiovascular protective effects of these agents.

A recent retrospective cohort study of 5718 cardiac patients who received thoracic and/or head and neck RT showed a strong trend toward significant reduction in both cardiovascular and cerebrovascular events in patients on statin therapy.<sup>1</sup> Cardiac patients were defined as those who had a history of acute coronary syndrome or who had undergone any coronary revascularization procedure (percutaneous angioplasty or coronary artery bypass surgery).

Though the 15% relative risk reduction was nonsignificant after adjusting for patient demographics, the trend toward the study's primary outcome of cardiovascular event reduction was notable (HR, 0.85; 95% CI, 0.69–1.04;  $P=0.0811$ ). Of note, one of this study's main limitations is that the statin cohort had significantly increased underlying CAD and increased underlying comorbidities, which could bias the statin group toward higher risk of vascular events overall.<sup>1</sup>

While there is a paucity of data for cardiovascular protective effects of statin therapy in the setting of RT, a myriad of studies have evaluated the role of statins in cancer-related and overall morbidity and mortality after mediastinal or head and neck RT that may show promise for the cardioprotective role of statins. In a large population-based cohort of esophageal adenocarcinoma treated with surgery, RT, and chemotherapy from the National Cancer Registry of the United Kingdom, statin use after diagnosis was associated with reduced all-cause mortality.<sup>54</sup> After adjusting for covariates, statins were correlated with reduction in all-cause mortality in the cohort (HR, 0.63; 95% CI, 0.43–0.92). A strength of this study was the assessment of prediagnosis statin use as a confounder based on treatment modality (RT, surgery, chemotherapy).<sup>54</sup>

Most recently, in 2019, Gupta et al<sup>55</sup> conducted the first study to date correlating statin use and dyslipidemia with overall mortality in patients with head and neck cancer from the Surveillance, Epidemiology, and End Results and Medicare databases. In this study, 65.2% of patients received RT and 45.5% received chemotherapy. After adjusting for treatment modality covariates, Kaplan–Meier and multivariate Cox analysis regression analysis demonstrated that statin use in patients with dyslipidemia was associated with improved cancer-related and overall survival, compared with patients with dyslipidemia not treated with statins. Patients with dyslipidemia on statins had overall survival at 2 years of 73% (95% CI, 0.69–0.76), compared with patients with dyslipidemia not on statins (61.7%; 95% CI, 0.57–0.65). Notably, after subgroup multivariate Cox analysis on overall survival, those who received RT had an HR of 0.30 (95% CI, 0.19–0.49;  $P<0.01$ ).<sup>55</sup> Though these data are promising, as mortality reduction is consistently noted after adjusting for the covariate of RT alone across these studies, it is unclear how much of the overall mortality risk is directly related to RT itself. More direct studies are needed on the direct cardioprotective role of statins in RACVD.

Simvastatin has also been shown to reduce the effects of nonmodifiable CAD risk factors following total body irradiation >10 Gy in animal models. In this study by Lenarczyk et al,<sup>44</sup> total body radiation was shown to increase sustained triglycerides and low-density lipoprotein cholesterol. Not only did simvastatin significantly reduce periarterial fibrosis, it was also shown to decrease severity of induced MI 20 and 80 days after radiation.

These findings are summarized in Table 2, which includes supporting data on statins' role in the reduction of all-cause mortality in nonmediastinal cancers.<sup>56–61</sup>

### Aspirin

Clinically, aspirin has long been associated with a reduction in cancer mortality.<sup>62</sup> This has largely been studied in colorectal cancer.<sup>24</sup> Studies in mediastinal cancers are rarer. Fourteen smaller observational studies have reported a reduction in breast cancer mortality with use of aspirin (HR, 0.69; 95% CI, 0.53–0.90).<sup>62</sup> However, some of these studies included other anti-inflammatory agents with aspirin, including nonsteroidal anti-inflammatory drug anticoagulants.<sup>49,63</sup>

Similar to statin therapy, there are limited to no data on the role of aspirin in the modulation and prevention of RACVD. Prospective and randomized studies are currently

investigating the effect of aspirin in the prevention of both cancer and CVD, such as the ongoing substudies of ASPREE and ARRIVE reexamining the benefits of aspirin in CVD in an era of increased statin use<sup>30,64</sup>; however, clinical efforts to promote aspirin use in primary prevention of CVD should be made on the basis of a balanced evaluation of the benefit–risk ratio at the individual level.<sup>64</sup>

### Colchicine

Despite promising preclinical data, there are no *clinical* studies thus far on the use of colchicine in CAD reduction after RT. As noted previously, COLCOT shows that colchicine may have a role in secondary prevention of CAD after MI. Nonetheless, it should be noted that the anti-inflammatory properties of colchicine, as well as minimal cardiotoxicity risk compared with other anti-inflammatory drugs such as nonsteroidal anti-inflammatory

**Table 2.** Summary of Clinical Studies Investigating the Role of Statins on Reduction of Radiation-Induced Cardiovascular Disease and/or Cardiovascular Mortality

Specified Timing of Statin Use	Study Design	Primary Outcome	Study/Year
Within 6-mo prediagnosis of cancer	Retrospective cohort	Statins reduced all-cause mortality among patients with any type of cancer by 15% (95% CI, 13–17) in Danish Cancer Registry patients who received either RT or chemotherapy	Nielsen et al (2012) <sup>56</sup>
Within 1 y before initiation of RT	Retrospective cohort	Statin use after RT of the thorax, head, and neck associated with strong trend in cardiovascular event reduction	Boulet et al (2019) <sup>1</sup>
Postdiagnosis of esophageal cancer	Retrospective cohort	Statin use after a diagnosis of esophageal adenocarcinoma and further treatment with RT was associated with reduced esophageal cancer-specific and all-cause mortality	Alexandre et al (2016) <sup>54</sup>
During RT	Retrospective cohort	1. Simvastatin significantly increased 3-y local recurrence-free survival rate of inflammatory breast cancer and triple negative inflammatory breast cancer in patients who received adjuvant RT 2. Simvastatin radioprotects non-inflammatory breast cancer cell lines MCF-7 and SKBR3 3. Simvastatin radiosensitizes inflammatory breast cancer cell lines MDA-MBC3, SUM149, SUM190	Lacerda et al (2014) <sup>57</sup>
Timing not specified	Large case control	Statin use in patients with head and neck cancer in the Surveillance, Epidemiology, and End Results and Medicare database with hyperlipidemia was associated with improved overall survival at 2 y after adjusting for RT	Gupta et al (2019) <sup>55</sup>
During and after RT	Retrospective cohort	Statin nonuse associated with early biochemical failure following prostate RT, which in turn is associated with increased mortality of any cause	Zaorsky et al (2012) <sup>58</sup>
Postdiagnosis of prostate cancer	Retrospective cohort	Statin use associated with reduced risk of all-cause mortality in patients with prostate cancer who underwent RT	Katz et al (2010) <sup>59</sup>
During RT	Retrospective cohort study	1. Statin use during RT significantly predicted improvement on the American Joint Committee on Cancer grade 0 to 1 in patients with rectal cancer, which correlated with significant increase in <i>overall</i> survival 2. Statins significantly improve response of rectal cancer to neoadjuvant chemoradiation	Mace, et al (2013) <sup>60</sup>
During RT	Prospective cohort study	Statins increase prostate cancer recurrence-free survival in patients who received high-dose RT Statins may radio-sensitize prostate cancer to RT	Kollmeier et al (2011) <sup>61</sup>

RT indicates radiation therapy.

drugs, make this drug well-suited to further clinical investigation into its possible role in ameliorating the inflammatory cardiovascular milieu associated with RACVD.

## Need for Better Atherosclerotic Cardiovascular Disease Risk Stratification in Radiation Therapy Patients

Clinical evidence shows that there is a need for optimal cardiovascular preventive care in those who receive RT, especially in patients with cancer who have a high-baseline ASCVD risk.<sup>65</sup> In a large retrospective study of patients who received chemoradiation therapy for head and neck squamous cell carcinoma, 34% of patients without CAD had indications to be on statin therapy per American College of Cardiology/American Heart Association guidelines, yet statin therapy was not initiated in any patient in that subgroup.<sup>65</sup> Furthermore, of those in the cohort with known CVD, 30% were not taking statin therapy. Other retrospective data support these findings. In the largest study to date on the use of statins in patients with cancer, involving 18 721 patients who used statins in the Danish Cancer Registry, only 0.5% (n=244) of the 45 540 subjects in the nationwide cohort that underwent RT were receiving statin therapy.<sup>56</sup> This study suggests lack of optimization in both primary and secondary prevention of atherosclerotic disease in patients with cancer who receive RT, despite the known significantly higher risk of CAD and CVD after RT.

Compared with the major adverse cardiovascular events end points studied in patients with breast cancer and lymphoma receiving RT, a recent study observed a similar absolute risk of CVD (HR, 1.05/Gy; 95% CI, 1.02–1.08 Gy) in patients with non-small cell lung cancer who received RT.<sup>66</sup> In addition to this finding, database studies estimate that >40% of patients with lung cancer have preexisting CVD. Second, there is higher cancer-related mortality in individuals meeting guideline-based statin eligibility.<sup>67</sup> However, <50% of these eligible patients with lung cancer are treated with guideline-directed medical therapy according to American College of Cardiology/American Heart Association recommendations.<sup>27,66</sup> A large cohort study from the UK Clinical Practice Research Datalink primary care database confirms this trend as well—cancer survivors were found no more likely to receive statins than the general population, despite higher CVD risk.<sup>68</sup> This is a concerning finding, as patients with cancer are living longer and therefore calls for further research into the role of these anti-inflammatory agents on RACVD risk prevention and/or treatment.

## Conclusions

In conclusion, RT creates a chronic inflammatory milieu leading to a significant variety of CVD with associated

morbidity and mortality. As RACVD is the leading cause of mortality in the ever-growing population of cancer survivors who have undergone RT, improvement for effective preventive strategies is imperative. Anti-inflammatory medications—in particular, statins, colchicine, and aspirin—show great promise for the prevention of morbidity and mortality attributable to RACVD. There is increasing support for the radioprotective role of these medications in animal and clinical studies. Nonetheless, there are few preclinical and almost nonexistent clinical data on the role of statins, aspirin, and colchicine as anti-inflammatory therapies in the prevention of RACVD. The improved longevity of patients with cancer after treatment, and the significant morbidity and mortality attributable to the chronic inflammatory CVD process associated with RT, necessitates such studies, as they are crucial to the cardiovascular health, reduced morbidity, and improved survival of patients with cancer.

Clinical questions answered/clarified:

1. Do anti-inflammatory medications have a potential role in the reduction of cardiovascular events in radiotherapy?

Clinical questions remaining/future directions:

1. Statins have been consistently shown to decrease all-cause mortality and increase recurrence-free survival in patients with cancer who receive radiotherapy in both preclinical and clinical studies; however, only 1 clinical study to date has directly evaluated the potential role of statin therapy in prevention of RACVD.
2. Similarly, clinical data on the use of colchicine and aspirin for RACVD prevention are lacking but promising.
3. More direct studies on the role of these anti-inflammatory agents on CVD risk prevention after mediastinal RACVD are called for.

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## Disclosures

None.

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