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REVIEW

Controversial cardiovascular and hematologic comorbidities in atopic dermatitis

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Abstract

Atopic dermatitis' (AD) systemic involvement is wide-reaching. The cardiovascular and hematological comorbidities of AD have potential for considerable economic and physical burden; however, data surrounding the association between these comorbidities and AD is controversial. This review discusses the cardiovascular and hematological comorbidities of AD, detailing the conflicting evidence, pathophysiology, and connection to medications. A PubMed search was conducted for studies detailing the association of cardiovascular and hematological comorbidities with AD, providing approximately 30 results. Additional searches were conducted for studies discussing the pathophysiology of these comorbidities and possible connections to AD medications. Various studies highlight either positive, negative, or no association of AD with hypertension, stroke, myocardial infarction, heart failure, and thrombosis. Coronary heart disease, angina, peripheral artery disease, and anemia are consistently positively associated with AD. However, the attributable risks of AD for stroke, myocardial infarction, heart failure, and atrial fibrillation are low (25 per 100,000 persons [99% CI 6–44], 12 per 100,000 persons [99% CI − 4–27], 40 per 100,000 persons [99% CI 22–57], and 37 per 100,000 persons [99% CI 15–55]), respectively. The pathophysiology underlying these potential associations is not entirely clear. Corticosteroids, cyclosporine, and antimetabolites, all used to treat AD, may also be associated with many of these comorbidities. AD's controversial associations with cardiovascular and hematological diseases complicates management as it is difficult to define recommendations for screening of these comorbidities. A better understanding may help lessen the economic and physical burden of these comorbidities in AD patients.

Keywords Atopic dermatitis · Cardiovascular · Comorbidities · Controversial · Eczema · Risk factors

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects 15 to 20% of children and 1 to 3% of adults globally and has many systemic comorbidities [1]. AD is a well-established component of the "atopic march," which details the progressive development of AD, allergic rhinitis, and asthma starting in early childhood. The comorbidities and associations of AD are wide-reaching, as AD's systemic involvement is postulated to influence the development of various malignant, autoimmune, neuropsychiatric, cardiovascular, and hematological diseases. Some of these diseases are disproportionately prevalent globally and potentially fatal. For example, cardiovascular disease accounts for the death of one individual every 37 s, and billions suffer from thromboses and anemia, common comorbidities associated with AD [2–4]. Thus, understanding the cardiovascular and hematological comorbidities of AD may help lessen the associated burden of these comorbidities in AD patients. Additionally, although often overlooked in the evaluation of comorbidities, medications involved in the treatment of AD may also affect the propensity for development of certain cardiovascular and hematological conditions.

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The uncertainty and evolving recommendations regarding the management of such controversial associations add to the complexity of AD treatment. Failed treatment strategies may lead to increased physician visits, medication changes, and worsening side effects with the escalation of treatment; these variables may increase the economic and physical burdens of AD. Additionally, patients with AD utilize the healthcare system more frequently than comparatively healthy individuals, often spending upwards of $300 a month to manage their AD [5]. Currently, conflicting evidence exists regarding the cardiovascular and hematologic comorbidities associated with AD; understanding this data will help providers lessen patient's disease burdens, focus future research, and provide empathetic patient care by acknowledging the potential systemic associations of AD. This paper will discuss the controversies surrounding cardiovascular and hematologic comorbidities of AD, detailing the conflicting evidence, pathophysiology, and possible connection to medications.

Cardiovascular and hematologic comorbidities

Cardiovascular comorbidities in AD patients include hypertension (HTN), stroke, myocardial infarction (MI), coronary heart disease, angina, peripheral artery disease, heart failure (HF), atrial fibrillation (AF), thrombosis, and anemia (Table 1). Though the pathophysiology is not completely understood, AD's inflammatory effects may predispose to such comorbidities due to underlying pathophysiologic mechanisms, genetic differences, environmental factors, or shared risk factors. Such risk factors include increased body mass index, alcohol and tobacco use, sleep disturbance, and decreased physical activity [6–8].

Hypertension

Systolic blood pressure in the 90th percentile, after controlling for age, sex, family history, and history of prednisone or cyclosporine use, was positively associated with AD (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.09–3.90) in a 2012 case–control study in the United States [7]. Increased severity of AD, as determined by the Investigator's Global Assessment scale, was positively associated with HTN (OR 3.14, 95% CI 1.13–8.70) [7]. However, in a 2017 cross-sectional study, AD was negatively associated with HTN (OR 0.87; 95% CI 0.83–0.90) [9]. Additionally, AD patients had a subsequent negative association with MI (OR 0.87; 95% CI 0.75–1.00) and stroke (OR 0.79, 95% CI 0.66–0.95). Yet, in an alternate meta-analysis, HTN was negligibly associated with AD (OR 1.16, 95% CI 0.98–1.37) [10]. For diseases with a high incidence, such as HTN, it is difficult to fully assess the potential impact of AD on HTN without data presented as attributable risk (AR), as it is not uncommon for diseases with a high incidence to have a high AR while other means of representing risk, such as relative risk (RR), may be low [11].

Pathophysiologically, T lymphocytes, specifically T helper type 1 (T_H1) cells found in chronic AD lesions despite classically being a T_H2-driven disease, can potentiate the development of HTN via renal damage and vascular remodeling [12, 13]. However, a 2020 randomized controlled clinical trial (RCT) reported an increased number of T_H1 cells in older patients both with and without AD, suggesting that the relationship between AD and HTN may be based on age rather than the underlying pathophysiology of AD [14]. However, when comparing proinflammatory markers of atherosclerosis and cardiovascular risk in the same study, AD patients 60 years or older had greater numbers of these markers compared to younger AD patients and age-matched controls ($p < 0.05$) [14]. Although the data are conflicting, the pathophysiological connection between T_H1 cells, AD, and potential vascular and renal damage or remodeling suggests an association between HTN and AD. Understanding the relationship between AD and HTN may additionally explain the potential associations between AD and other conditions such as stroke, MI, angina, and peripheral arterial disease.

Stroke, MI, coronary heart disease, angina, and peripheral arterial disease

Stroke, MI, coronary heart disease, angina, and peripheral arterial disease can all be severely debilitating and potentially fatal. In a 2018 meta-analysis, increased severity of AD in men was associated with an increased risk of stroke (hazard ratio [HR] 1.33, 95% CI 1.14–1.56) and MI (HR 2.01, 95% CI 1.31–3.08) [15]. These associations were not present in females (stroke HR 1.02, 95% CI 0.77–1.35; MI HR 0.98, 95% CI 0.72–1.32). A 2019 meta-analysis also reported an increased risk of MI (RR 1.14, 95% credible interval [CrI] 1.05–1.23), angina (RR 1.16, CrI 1.07–1.26), and cardiovascular death (RR 1.25, 95% CrI 1.13–1.38) with increased AD severity [16]. In a 2019 cohort study assessing self-reported AD and mortality from cardiovascular disease, patients who self-reported flaring "often" had a 1.30 times greater risk of mortality due to coronary heart disease than patients who self-reported flaring "seldom or sometimes" (95% CI 1.01–1.56) [17]. However, there was no increased risk of stroke with self-reported "often" flares in AD (HR: 1.03, 95% CI 0.87–1.22). Another 2018 cohort study in which disease severity was classified based on the medications prescribed reported a 20% increased risk of stroke (99% CI 1.01–1.48) and a 40 to 50% increase in the risk of MI (99% CI 1.15–1.71), angina (99% CI 1.08–2.03), and cardiovascular death (99% CI 1.17–1.62) in patients with severe

Table 1 Summary of controversial cardiovascular and hematologic comorbidities in AD

Comorbidity	Study	Study type	Study results	Statistical strength
HTN	Silverberg et al [7]	Case-control	Positive association with systolic blood pressure in the 90th percentile and AD	OR 2.06, 95% CI 1.09–3.90
	Drucker et al [5]	Cross-sectional	Negative association with AD	OR:0.87, 95% CI 0.83 – 0.90
	Thyssen et al [10]	Meta-analysis	No association with AD	OR 1.16, 95% CI 0.98–1.37
Stroke, MI, Coronary Heart Disease, Angina Pectoris, and Peripheral Arterial Disease	Yuan et al [15]	Meta-analysis	Increased risk of stroke in men with AD	HR: 1.33, 95% CI 1.14–1.56
			Increased risk of MI in men with AD	HR: 2.01, 95% CI 1.31–3.08
			No association of stroke in females with AD	HR: 1.02, 95% CI 0.77–1.35
			No association of MI in females with AD	HR: 0.98, 95% CI 0.72–1.32
	Nishida et al [17]	Cohort study	Greater risk of mortality from coronary heart disease in self-reported flaring "often"	HR: 1.30, 95% CI 1.01–1.56
			No associated risk of stroke with self-reported flaring "often"	HR: 1.03, 95% CI 0.87–1.22
	Silverwood et al [18]	Cohort study	Increased risk of stroke in patients with increased severity of AD	HR: 1.22, 99% CI 1.01–1.48
			Increased risk of MI with AD	HR: 1.41, 99% CI 1.15–1.71
			Increased risk of unstable angina with AD	HR: 1.48, 99% CI 1.08–2.03
			Increased risk of AF with AD	HR: 1.38, 99% CI 1.17–1.62)
			Increased risk of cardiovascular death with AD	HR: 1.38, 99% CI 1.17–1.62
	Standl et al [17]	Cohort study	No increased risk of MI with AD	RR: 1.04, 95% CI 0.99–1.12
			No increased risk of stroke with AD	RR: 1.02, 95% CI 0.98–1.07
			Increased risk of angina pectoris with AD	RR: 1.17, 95% CI 1.12–1.23
			Increased risk of peripheral arterial disease with AD	RR: 1.15, 95% CI 1.11–1.19
	Drucker et al. [5]	Cross-sectional	Negative association with MI and AD	OR 0.87, 95% CI 0.75–1.00
			Negative association with stroke and AD	OR 0.79, 95% CI 0.66–0.95
Heart Failure	Ascott et al [6]	Meta-analysis	Increased risk of heart failure in AD patients in cohort studies	RR: 1.26, 95% CI 1.05–1.51
			Increased risk of heart failure with increasing AD severity	RR: 1.20 95% CI 1.06–1.36
			No association between heart failure and AD in cross-sectional studies	OR 1.32, 95% CI 0.70–2.48

Table 1 (continued)

Comorbidity	Study	Study type	Study results	Statistical strength
AF	Schmidt et al [24]	Cohort study	Increased long-term risk of AF in hospital-diagnosed AD	HR 1.2, 95% CI 1.0–1.6
	Silverwood et al [8]	Cohort study	Increased risk of AF with increasing severity of AD	Non-AD patients HR: 1.11, 99% CI 1.04–1.18). Moderate AD HR : 1.17, 99% CI 1.08–1.27). Severe AD HR : 1.38, 99% CI 1.17–1.62).
Thrombosis	Tomagawa -Mineoka et al [27]	RCT	A positive correlation between beta-thromboglobulin and platelet factor 4 with AD	$r = 0.31$, $p = 0.04$ and $r = 0.38$, $p = 0.01$ ($p < 0.05$)
	Nastalek et al [28]	RCT	Prolonged fibrinolysis time in AD patients	9.26 ±1.47 vs. 7.81 ± 1.17 minutes; $p < 0.0001$
Anemia	Rhew et al [32]	Cross-sectional	Positive association with iron deficiency anemia and AD	OR 1.42, 95% CI 1.37–1.47
	Drury et al [7]	Cross-sectional	Positive association of anemia with any severity of AD	OR 1.83, 95% CI 1.58–2.13

AD atopic dermatitis, *AF* atrial fibrillation, *CI* confidence interval, *HR* hazard ratio, *HTN* hypertension, *MI* myocardial infarction, *OR* odds ratio, *RCT* randomized controlled trial, *RR* relative risk

AD compared to patients with milder disease after accounting for body mass index, smoking, and alcohol consumption, factors more prevalent in AD patients [18]. The AR of stroke and MI in AD patients was 25 per 100,000 persons (99% CI 6–44) and 12 per 100,000 persons (99% CI − 4–27), respectively. On the other hand, in a 2017 cohort study, there was no increased risk of MI (RR: 1.04, 95% CI 0.99–1.12) or stroke (RR: 1.02, 95% CI 0.98–1.07) in patients with AD, although, there was an increased risk of angina (RR: 1.17, 95% CI 1.12–1.23) and peripheral arterial disease (RR: 1.15, 95% CI 1.11–1.19) [19]. Due to the conflicting data, it is unclear whether AD increases the risk of these debilitating cardiovascular comorbidities.

AD increases blood platelet activation and oxidative stress while reducing fibrinolysis, which can potentially result in downstream atherothrombosis [15]. However, a 2016 cohort study reported no relationship between cardiovascular risk factors in AD patients and metabolite levels of various amino acids, sugars, acylcarnitines, glycerophospholipids, and sphingolipids associated with AD [19]. This suggests that AD may not contribute to the development of cardiovascular disease, as these metabolites contribute to cardiovascular oxidative stress. Another avenue worth exploring is the potentially conflicting role of T helper type 2 (T_H2) associated cytokines in the pathophysiology of atherosclerosis, a risk factor for both stroke and MI. For instance, inhibition of interleukin (IL)-5 and IL-13, two T_H2-specific cytokines, increases the progression of atherosclerosis [20–22]. However, inhibition of other T_H2 cytokines, such as IL-4, decreases the progression of atherosclerosis [23]. This suggests that an imbalance of T_H2 cytokines may contribute to the development of atherosclerosis. Understanding of the connection between T_H2 cell-related cytokines and AD may help explain the pathophysiological relationship between AD and stroke, MI, and other complications of atherosclerosis. Further understanding of AD in these cardiovascular comorbidities may help focus cardiovascular screening efforts in AD patients.

Heart failure

In a 2019 meta-analysis of two longitudinal cohort studies, AD was associated with an increased risk of HF (RR: 1.26, 95% CI 1.05–1.51) [16]. There was also an increased risk of HF with increasing severity of AD (RR: 1.20, 95% CI 1.06–1.36). Additionally, a 2018 cohort study of AD patients reported a 70% increase in the risk of HF (99% CI 1.38–2.06) with an AR of 40 per 100,000 persons (99% CI 22–57) [18]. However, in the 2019 meta-analysis, there was no association between HF and AD in cross-sectional studies (OR 1.32, 95% CI 0.70–2.48) [16]. The pathophysiology behind this potential connection is also not fully understood. AD's possible effects on oxidative stress and increased platelet activation in stroke and MI may contribute to this potential relationship.

Atrial fibrillation

AF's association with AD has only recently been investigated. In a 2019 cohort study, patients with hospital-diagnosed AD had a 20% increased risk of AF compared to the general population (95% CI 1.0–1.6) [24]. In a 2018 cohort study, the greatest risk of AF was in patients with severe AD (HR: 1.38, 99% CI 1.17–1.62) compared to patients with less severe AD with an AR of 37 per 100,000 persons (99% CI 15–55) [18]. As inflammation is an established risk factor of AF [24], the systemic inflammation in AD may predispose patients to AF, similarly to patients with psoriasis and rheumatic disorders [24, 25]. A better understanding of AD's association with AF may help understand the possible increased risk of stroke in AD patients, specifically the embolic type.

Thrombosis

Few studies establish a relationship between thrombosis and AD; however, an AD-induced hypercoagulable state as a result of increased platelet activation may result in increased thrombosis [26]. A 2008 RCT reported a positive correlation between beta-thromboglobulin ($r = 0.31$, $p = 0.04$) and platelet factor 4 levels ($r = 0.38$, $p = 0.01$), two platelet activation markers, and increasing AD severity ($p < 0.05$) assessed via the SCORing AD index, suggesting a prominent role of platelets in the chronic inflammation of AD [27]. However, in the same study, platelet aggregation function was not impaired in AD patients. In a 2010 RCT, 130 individuals with AD had reduced efficiency of fibrinolysis (prolonged fibrinolysis time: 9.26 ± 1.47 vs. 7.81 ± 1.17 min, $p < 0.0001$) [28]. Yet, other studies suggest opposite effects of AD on hemostasis. In a 1986 case–control study, patients with asthma and other concomitant allergen-induced inflammatory diseases had only a mild hemostatic defect and no increase in the risk of thrombosis despite platelet activation [29, 30]. Increased activity of proinflammatory mast cells and tryptases decreases the risk of thrombosis via tryptase-mediated degradation of fibrinogen, a mediator of thrombosis, and formation of a complex between heparin and tryptase resulting in anticoagulation [28, 31]. Appreciating the underlying mechanism behind thrombosis in AD patients may help future management in at-risk individuals.

Anemia

In a 2019 Korean cross-sectional study, AD was positively associated with iron deficiency anemia (OR 1.42, 95% CI 1.37–1.47) [32]. In a 2016 U.S. cross-sectional study, the odds of developing anemia were increased with any severity of AD (OR 1.83, 95% CI 1.58–2.13) [33]. However, additional factors such as selection bias likely contribute to this association, as healthy individuals are infrequently screened for anemia. Yet, the complications of AD and risk factors of anemia are similar. Chronic inflammation, use of systemic medications, malnutrition, obesity, use of alternative medicines, and avoidance of food are shared characteristics of patients with anemia and AD [33]. However, the pathophysiology of this relationship is not fully understood. The importance of the management of anemia is emphasized in its many effects on a patient's life: increased morbidity, negative affect on school performance, and psychosocial comorbidities [33]; these negative outcomes are also present in many patients with AD.

Attributable risks

Knowledge of the ARs conferred by AD gives perspective and defines quantitatively the impact of AD on the development of these comorbidities [11]. The ARs of AD for some of these comorbidities are low; the AR of stroke, MI, HF, and AF were 25 per 100,000 persons (99% CI 6–44), 12 per 100,000 persons (99% CI − 4–27), 40 per 100,000 persons (99% CI 22–57), and 37 per 100,000 persons (99% CI 15–55), respectively [18]. Although some of the RR and OR presented are large, based on ARs the clinical impact of AD on stroke, HF and AF is minimal and there is no clinical impact of AD on MI. Additionally, the overall incidence of such comorbidities should be considered as well; diseases with low incidence may have a small AR despite a large RR and vice versa for diseases with a large incidence. Thus, although this article presents the association between many comorbidities and AD in terms of RR and OR, clinicians should consider the differences between these forms of data presentation and actual absolute or AR before considering making changes to disease management.

Medications and AD comorbidities

Medications used in the treatment of AD—short-term medications such as corticosteroids, cyclosporine, and antimetabolites—may have serious adverse effects (Table 2). In a 2017 cohort study analyzing AD patients based on the type of medication usage, individuals using topical medications had the highest risk of MI (excess risk per 10,000 person-years [ER]: 3.05) and patients using systemic medications had the highest risk of stroke (ER: 5.8) [19]. Thus, non-biologic oral and systemic medication usage may contribute to the development of various AD comorbidities to a greater extent than the inherent pathophysiologic mechanisms of AD.

Severe AD is often treated with potent medications like cyclosporine and oral systemic corticosteroids; these

Table 2 Summary of adverse effects associated with AD medications

Adverse effects	Study	Medication	Study results	Statistical strength
HTN	Lee et al [35]	Corticosteroids	Positive association with HTN	OR 1.42, 95% CI 1.23–1.64
	Panoulas et al [37]		Higher corticosteroid dose resulted in higher prevalence of HTN	$P = 0.028$
	Lee et al [35]	Cyclosporine	Positive association with HTN	OR 7.13, 95% CI 1.85–27.49
	Hijnen et al [36]		Use of cyclosporine in AD resulted in new diagnosis of HTN in 11 of 73 patients	
Stroke	Standl et al [17]	Systemic AD medications	Increased risk of stroke	Excess risk per 10,000 person-years: 5.8
MI	Standl et al [17]	Topical AD medications	Increased risk of MI	Excess risk per 10,000 person-years: 3.05
Cardiovascular Morbidity	Naranjo et al [40]	Corticosteroids	Decreased risk of cardiovascular morbidity	HR: 0.95, 95% CI 0.92–0.98
Heart Failure	Ng et al [41]	Corticosteroids	Mineralocorticoid effects of corticosteroids like prednisone can exacerbate heart failure	
	Bernatsky et al [42]	Methotrexate	Decreased risk of heart failure in rheumatoid arthritis patients	RR 0.8, 95% CI 0.6–1.0

AD atopic dermatitis, C*I* confidence interval, *HR* hazard ratio, *HTN* hypertension, *MI* myocardial infarction, *OR* odds ratio, *P p* value, *RR* relative risk

medications are associated with an increased risk of HTN [34]. In a 2016 case–control study of psoriasis patients, current use of cyclosporine (OR 7.13, 95% CI 1.85–27.49) and oral systemic corticosteroids (OR 1.42, 95% CI 1.23–1.64) was positively associated with newly diagnosed HTN [35]. Retention of water and sodium along with increased oxidative stress may be an underlying explanation for this relationship [35]. Additionally, a 2007 cohort study demonstrated a new diagnosis of arterial HTN in 11 out of 73 patients with the use of cyclosporine for AD [36]. The association between oral corticosteroids and HTN is preserved in diseases besides AD. In a 2008 cohort study comparing oral systemic corticosteroid use in rheumatoid arthritis and the development of HTN, the combination of medium-doses (> 7.5 mg) and long-term exposures of oral systemic corticosteroids was associated with a higher prevalence of HTN compared to the combination of low doses and long-term exposure of systemic corticosteroids ($p = 0.028$) [37]. Given the data, oral corticosteroids have a strong association with HTN, a risk factor of coronary artery disease, stroke, and MI [38, 39]. However, in a 2008 cross-sectional study comparing the risk of cardiovascular morbidity and the use of oral corticosteroids in rheumatoid arthritis patients, oral corticosteroids were associated with a decreased risk of cardiovascular morbidity after adjusting for traditional risk factors (HR: 0.95, 95% CI 0.92–0.98) [40].

Corticosteroids may also be associated with HF, as the mineralocorticoid effects of some corticosteroids such as prednisone, used in severe AD, may exacerbate HF [41]. This association should be considered in AD patients that are at risk for HF. Additionally, an increased frequency of thrombosis is associated with the use of systemic corticosteroids [34]; this may contribute to the potential increased risk of thrombosis and subsequent stroke and MI in AD patients. Systemic corticosteroids and cyclosporine, although popular treatments, require additional consideration beforeprescribing in patients with prior cardiovascular risk factors or who may be prone to cardiovascular disease. Therefore, cardiovascular and hematologic comorbidities in AD patients may be the result of the pathophysiologic effects of AD, the medications used for AD, or a combination of these factors.

Limitations

Many of the studies discussed present associations via RR and OR, which can overestimate the effect of AD on these comorbidities, as RR is a fractional comparison between an exposed and unexposed group. Measures like AR, on the other hand, describe the incidence of an event in a defined population when making comparisons [11]. Therefore, consideration of AR, accompanied by baseline risk and RR, provides a better picture to practitioners when determining guidance on screening and intervention. Additionally, the varying types of studies used in this article influence the interpretations stemming from the data. For

example, with meta-analyses, there is a lack of standardization in the assessment of disease severity. With cross-sectional studies, causation cannot be evaluated, as the outcome and exposure are simultaneously assessed. As demonstrated, several factors, such as a small AR, lack of data standardization, and the utilization of cross-sectional data, may call into question the application of this article's findings in clinical practice.

Conclusion

AD's controversial association with various cardiovascular and hematologic comorbidities may complicate AD management. Practitioners are faced with the responsibility of educating patients about potential risks to other body systems with the diagnosis of AD. As many studies cite relationships in terms of RR or OR, clinicians should be cognizant of what this may mean in terms of absolute or ARs for their patients. Screening AD patients for some of these cardiovascular and hematologic comorbidities at a greater level than normally recommended for patients of the same age may not be appropriate, as the ARs conferred by AD for these comorbidities may not be clinically significant. As it stands, it is difficult to determine whether the potential association of AD with these comorbidities is due to pathophysiological effects, adverse events associated with medications used to treat AD, or a combination of the two factors. A better understanding of these potential associations may aid in defining recommendations for screening and management of possible comorbidities while also lessening the economic and physical burdens of patients with AD.

Declarations

Conflict of interest Dr. Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Mr. Pandher, Ms. Ghamrawi, and Ms. Heron have no conflicts to disclose.

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