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Mifepristone in the treatment of the ectopic adrenocorticotropic hormone syndrome

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Summary

Objectives: Mifepristone, a glucocorticoid receptor antagonist, can be used to manage hypercortisolism in patients with ectopic adrenocorticotropic hormone syndrome (EAS) when surgical cure is not feasible. Outcomes of EAS patients treated with mifepristone have been limited to reports of isolated cases. We aimed to determine the efficacy and limitations of mifepristone in the treatment of EAS and to compare outcomes with those of patients who underwent bilateral adrenalectomy.

Method: A retrospective cohort study of EAS patients from the University of Michigan between 1997 and 2017 was conducted.

Results: Of the 55 patients with EAS, 16 were treated with mifepristone: eight neuroendocrine tumours, two carcinomas and six occult tumours. Treatment with mifepristone was most commonly prompted by psychosis, uncontrolled glucose and/or hypertension. The median maintenance dose was 600 mg/d. Amelioration of psychosis was observed within 48 hours in 3/3 patients, and the glycaemic control was improved in 14/16 patients. The median duration of treatment was 9 months, and three patients were treated for more than 24 months. The overall survival at 24 months was equivalent between patients with EAS treated with mifepristone vs bilateral adrenalectomy (N = 12) (P = 0.6).

Conclusions: Mifepristone is effective in treating EAS for over 2 years, and survival was not different from that of patients treated with bilateral adrenalectomy. Aggressive concomitant therapy for hypokalaemia and hypertension is necessary.

KEYWORDS

bilateral adrenalectomy, cortisol, Cushing's syndrome, ectopic ACTH, ectopic Cushing's syndrome, glucocorticoid receptor antagonist, mifepristone

1 | INTRODUCTION

Adrenocorticotropin (ACTH)-dependent hypercortisolism, or Cushing's syndrome, is most commonly caused by a corticotropin-secreting pituitary adenoma (Cushing's disease). Ectopic ACTH syndrome (EAS) occurs in a small fraction of patients with endogenous hypercortisolemia, due to extra-pituitary sources of corticotropin or, rarely, CRH.[1,2] EAS is associated with various benign and malignant tumours, most commonly bronchial/pulmonary, thymic or pancreatic neuroendocrine tumours (NET) and, rarely, small cell lung carcinoma (SCLC), pheochromocytoma and medullary thyroid carcinoma (MTC). Cushing's syndrome is associated with cardiovascular, metabolic, infectious and skeletal complications, regardless of aetiology.[3-7] In particular, EAS can be fulminant, leading to altered mental status, thromboembolism and/or opportunistic infections.[3] The first-line treatment for all forms of clinically overt Cushing's syndrome is surgical removal of the hormonally active tumour. Not uncommonly, however, EAS originates in occult tumours, which are

difficult to localize despite extensive imaging.[8-13] Furthermore, surgical cure is achieved in less than half of EAS patients,[9,10] with persistent hypercortisolism.

Medical therapy can be used preoperatively in patients who require immediate control of hypercortisolism, in poor surgical candidates or when the source of Cushing's syndrome is occult.[14,15] Bilateral adrenalectomy is typically reserved for patients with surgically incurable Cushing's syndrome and difficult to control hypercortisolism.[16-18] Nevertheless, bilateral adrenalectomy leads to permanent adrenal insufficiency and creates the need for lifelong glucocorticoid and mineralocorticoid replacement, with the risk of fatal adrenal crises.[17,18]

Mifepristone, a glucocorticoid receptor antagonist, was approved by US Food and Drug Administration in 2012 for the management of hypercortisolism-induced hyperglycaemia in patients with endogenous Cushing's syndrome who have failed or are not candidates for surgical cure.[19] Circulating ACTH and cortisol concentrations cannot serve as indicators for disease control and commonly increase in some forms of Cushing's syndrome during treatment with mifepristone.[20,21] A prospective, multicentre trial conducted to assess the efficacy and safety of mifepristone in endogenous Cushing's syndrome focused mainly on patients with Cushing's disease (86%) and showed robust improvement in clinical and metabolic parameters.[22] Outcomes of patients with EAS treated with mifepristone, however, have been only reported in isolated cases and for short intervals of time.[23-26] Because EAS is often more aggressive clinically and also more difficult to cure due to occult or metastatic sources of ACTH, we aimed to assess the efficacy and safety of mifepristone in the treatment of EAS.

2 | MATERIALS AND METHODS

We conducted a cohort study of all patients with EAS evaluated at the University of Michigan between January 1997 and December 2017. Patients' demographics, clinical presentation, imaging, laboratory, and pathological and treatment data were retrospectively reviewed. The study was conducted with the University of Michigan Institutional Review Board approval (HUM0091004). A waiver of consent was granted for this retrospective study.

The diagnosis and source of Cushing's syndrome were based on the clinical and hormonal evaluation, in accordance with the Endocrine Society guidelines.[4] Occult primary tumours were defined as unidentified sources of Cushing's syndrome despite comprehensive investigations by cross-sectional imaging [computed tomography (CT) and magnetic resonance imaging (MRI)] and functional imaging [octreotide scan, [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) and [^{68}Ga]-DOTATATE PET/CT]. The efficacy of mifepristone was assessed based on the amelioration of psychotic symptoms, glucose and hypertension.

Statistical differences in measured parameters between groups were evaluated using the Mann-Whitney *U*-test. The Kaplan-Meier analysis was applied to evaluate the median overall survival between patients with EAS treated with mifepristone vs bilateral adrenalectomy. A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

From January 1997 to December 2017, 55 patients with EAS were evaluated in our institution. Of these, five patients, who were referred to our center for inferior petrosal sinus sampling and lacked treatment and follow-up data, were excluded. Of the remaining 50 patients, 16 were treated with mifepristone, whereas 34 patients received other therapies (12 bilateral adrenalectomy, 11 primary tumour resections, five other medical treatment and six combined medical modalities) (Figure 1). Mifepristone was used as the initial medical agent in eight patients; the remaining eight patients were previously treated with ketoconazole (8), metyrapone

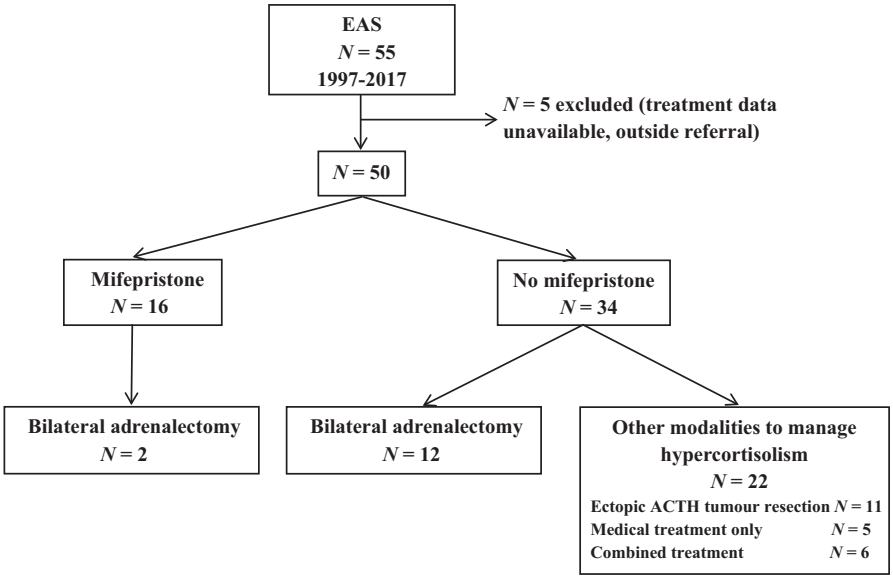

FIGURE 1 Patients with ectopic adrenocorticotropic hormone syndrome (EAS) evaluated at the University of Michigan (1997-2017) and treatment modalities

TABLE 1 Patient characteristics

	All patients N = 50	Patients treated with mifepristone N = 16	Patients who underwent bilateral adrenalectomy N = 12	*P* value (mifepristone vs bilateral adrenalectomy)
Sex (M/F)	18/32	3/13	5/7	0.14
Age (range), y	48 (11-75)	49 (25-75)	38 (11-64)	0.14
Solitary/metastatic	20/30	8/8	3/9	0.13
Occult source	10	6	2	
ACTH (pg/mL)	173 [111-310]	169 [113-310]	209 [133-508]	0.45
24 h-UFC (μg/24 h)	1229 [633-3469]	1000 [423-3935]	1613 [671-3650]	0.50

Data are expressed as medians [interquartile range]. To convert ACTH to pmol/L, multiply by 0.222. To convert UFC to nmol/24 h, multiply by 2.76.

(1) and/or octreotide (2). Of the patients treated with mifepristone, two patients eventually underwent bilateral adrenalectomy, 8 and 28 months after the initiation of mifepristone, respectively, due to the poor control of hypertension and hypokalaemia.

The median age at the time of EAS diagnosis was 49 years (range 25-75 years) in patients treated with mifepristone, and 13 (81%) patients were women. EAS was caused by: NET in eight patients (two medullary thyroid cancers, two bronchial, two thymic and two gastroenteropancreatic NET); carcinoma in two patients (one nasopharyngeal and one non-small cell lung cancer); and occult primary tumour in six patients. Metastases were present at the time of the initial evaluation in eight (50%) patients. Baseline urinary free cortisol and plasma ACTH concentrations were similar between patients treated with mifepristone and bilateral adrenalectomy (Table 1).

The baseline clinical characteristics of the 16 patients with EAS treated with mifepristone are presented in Table 2. The most common metastatic sites were lymph nodes, liver and lung. Mifepristone was used in three patients with severe Cushing's syndrome prior to surgical resection of the primary tumour; in 13 patients, curative surgery was not feasible (metastatic disease in seven patients and occult EAS in six patients). With one exception, all patients had clinical signs of Cushing's syndrome: facial fullness, plethora, purplish striae, easy bruising, proximal muscle weakness, central obesity, dorsocervical hump and/or supraclavicular fullness. Neurocognitive symptoms were noted in 6/16 (38%) of patients and varied from memory impairment to depression and acute psychosis. Abnormal glycaemic status was present in all patients (nine poorly controlled diabetes mellitus and seven patients with new onset hyperglycaemia), and insulin therapy was initiated in three patients. All patients had hypertension and hypokalaemia prior to the initiation of mifepristone.

Mifepristone was initiated at the dose of 300 mg/day in all patients and subsequently increased every 2-4 weeks based on the clinical response and side effects' assessment. The median maintenance dose used without adverse events was 600 mg/day (range 300-1200 mg). The median duration of mifepristone treatment was 9 months (range 0.25-28 months, Table 3). Mifepristone was withheld in two patients due to hypotension and hypoglycaemia, and treatment with dexamethasone was promptly initiated (patients 5 and 14, Table 3). In one patient treated with 600 mg/d for 2 months, mifepristone therapy was interrupted during a urinary tract infection, reinitiated after resolution and subsequently titrated up to 1200 mg without further side effects. The other patient developed a haemothorax and respiratory failure following thoracentesis for a recurrent pleural effusion. She required sedation and intubation, and mifepristone therapy was therefore changed to intravenous etomidate.

Following the treatment with mifepristone, two patients subsequently underwent bilateral adrenalectomy. After 28 months of mifepristone therapy, patient number 14 suffered a seizure of unknown aetiology with acute kidney injury, poorly controlled hypertension and serum potassium fluctuations. The source of ACTH remained occult, and at that time, replacement therapy for adrenal insufficiency was deemed safer than medical management of hypercortisolism for her chronic care. Patient number one had widely metastatic medullary thyroid cancer, which initially responded to cabozantinib, but her tumour burden and hypercortisolism later progressed. She developed proximal muscle weakness, pedal oedema and severe hypertension during treatment with mifepristone 1200 mg/d plus spironolactone, amiloride and potassium supplements. Because her reliance on multiple drugs for hypercortisolism would compromise potential oncologic therapies, her adrenals were removed. Both patients improved clinically with glucocorticoid replacement following bilateral adrenalectomy, although patient number one later died due to progression of her cancer metastases.

In all three patients with acute psychosis, the symptoms improved within 48 hours after initiating mifepristone. Amelioration of depressive symptoms and memory impairment occurred over a few weeks in 3/3 patients. Glycaemic control was improved in 14/16 patients: five with newly diagnosed hyperglycaemia and nine with uncontrolled diabetes, three of whom stopped all antidiabetic agents. While on mifepristone treatment, four patients had improved blood pressure control; seven patients required intensification of the antihypertensive regimen, particularly by adding a mineralocorticoid receptor antagonist; and five patients had worsening hypertension despite more aggressive treatment (Table 3).

Minor side effects of mifepristone were reported during treatment, most commonly fatigue (50%), anorexia (31%), nausea

TABLE 2 Characteristics of mifepristone-treated patients (before initiation)

	Sex	Age (y)	Primary tumours	Distant metastasis	Psychiatric symptoms	Glycaemic status	Previous medications	MRA(mg/d) and K^+ supplements (mEq/d)
1	F	49	MTC	LN, Liver, Bone	No	New-onset hyperglycaemia	Ketoconazole, octreotide	SPL 25, K 120
2	F	32	MTC	LN, Lung, Liver, Bone	No	Uncontrolled DM	None	SPL 50, K 40
3	F	75	Bronchial NET	None	Psychosis	Uncontrolled DM	Ketoconazole	SPL 100
4	F	66	Bronchial NET	LN, Cutaneous	Memory loss	Uncontrolled DM	Ketoconazole	SPL 50, K 20
5	M	49	Pancreatic NET	LN, Liver	No	Uncontrolled DM	None	SPL 200, K 160
6	F	67	Ileal NET	Lung, Peritoneum, Ovary, Pancreas	No	New-onset hyperglycaemia	Octreotide	SPL 25, K 20
7	M	37	Thymic NET	LN	Psychosis	Uncontrolled DM	None	SPL 50, K 60
8	M	25	Thymic NET	LN, Brain, Bone	No	New-onset hyperglycaemia	Ketoconazole, metyrapone	EPL 100, K 100
9	F	47	Nasopharyngeal carcinoma	Lung, Bone	No	New-onset hyperglycaemia	Ketoconazole	SPL 100
10	F	60	NSCLC	None	No	New-onset hyperglycaemia	None	SPL 25
11	F	33	Occult	None	Depression	Uncontrolled DM	Ketoconazole	SPL 50
12	F	74	Occult	None	Psychosis	Uncontrolled DM	None	SPL 50, AMI 5, K 80
13	F	56	Occult	None	No	Uncontrolled DM	Ketoconazole	SPL 50, K20
14	F	28	Occult	None	No	New-onset hyperglycaemia	None	SPL 200
15	F	65	Occult	None	Depression	New-onset hyperglycaemia	None	SPL 50, K 20
16	F	46	Occult	None	No	Uncontrolled DM	None	SPL 50

Age, age in years; AMI, amiloride; EPL, eplerenone; F, female; IFG, impaired fasting glucose; K+, potassium replacement in mEq/d; LN, lymph node; M, male; MRA, mineralocorticoid receptor antagonist; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; NSCLC, nonsmall cell lung cancer; PG, plasma glucose; psychiatric symptoms, included psychosis, depression and memory loss; SPL, spironolactone.

and vomiting (31%), and oedema (19%) (Table 4). Worsening hypokalaemia and increased blood pressure were observed in 31% of mifepristone-treated patients, but only one patient experienced severe hypokalaemia (serum potassium level ≤2.5 mmol/L). Hypokalaemia was more common in patients receiving >600 mg/d of mifepristone. The antihypertensive medications, especially mineralocorticoid receptor antagonist, and oral potassium replacement were adjusted during mifepristone treatment. Patients were treated with up to 300 mg of spironolactone or eplerenone, 20 mg of amiloride and 200 mEq/d of potassium. The median maintenance dose of spironolactone was 200 mg/d (range 50-300 mg/d). Mifepristone dose reduction was required in two patients due to symptoms of glucocorticoid withdrawal, such as persistent anorexia.

During the follow-up period, 11 patients died: five patients treated with mifepristone and six patients who underwent bilateral adrenalectomy. Of the five patients treated with mifepristone, four had widely metastatic malignancies (bronchial, thymic, nasopharyngeal and medullary thyroid carcinoma) and one patient with metastatic thymic carcinoma died from acute respiratory failure. Of the six patients who had undergone bilateral adrenalectomy, all died with widely metastatic malignancies (three gastrinoma, one medullary thyroid carcinoma, one thymic carcinoma and one pancreatic neuroendocrine tumour). The overall survival at 24 months was equivalent between patients with EAS treated with mifepristone vs those with bilateral adrenalectomy (58% vs 55%, respectively, $P = 0.625$ Figure 2).

4 | DISCUSSION

Herein, we present our experience with mifepristone in the treatment of EAS, compared to previous experience limited to very few reports. EAS is often clinically fulminant, and effective medical therapies are important in managing hypercortisolism and its complications in preparation for curative surgery. Furthermore, because ectopic corticotropin-secreting tumours can be occult, medical therapy can be continued until the source of EAS is identified, obviating the need for bilateral adrenalectomy. Our data demonstrate the efficacy of mifepristone in resolving psychotic symptoms within 48 hours of initiation. In addition, mifepristone improved glycaemic control and blood pressure in 88% and 69% of the EAS patients, respectively. A previous study showed improved glycaemic control in 60% of patients, with nearly half being able to reduce the intensity of

TABLE 3 Clinical data during mifepristone treatment

	Primary tumours	Maintenance dose (mg/d)	Duration of mifepristone treatment (mo)	Reason for cessation mifepristone	Clinical and biochemical improvement after treatment			MRA(mg/d) and K^+ supplements (mEq/d)
					Psychiatric symptoms	Glycaemic control	HTN	
1	MTC	1200	8	Bilateral adrenalectomy	-	Yes	No	SPL 300, AMI 5, K 80 (^)
2	MTC	600	1	Death*	-	Yes	Yes	SPL 150, K 40 (^)
3	Bronchial NET	300	8	Cure	Yes	Yes*	Yes	SPL 100
4	Bronchial NET	300	4	Death*	Yes	Yes	Yes	SPL 200 (^)
5	Pancreatic NET	300	0.5	Etomidate	-	Yes*	Yes	SPL 300, K 90 (^)
6	Ileal NET	300	10	Cure	-	Yes	Yes	K 20 (ˇ)
7	Thymic NET	900	12	Cure	Yes	Yes*	No	EPL 100, K 240 (^)
8	Thymic NET	1200	16	Death*	-	No	No	EPL 300, AMI 20, K 200 (^)
9	Nasopharyngeal carcinoma	900	1.5	Death*	-	Yes	Yes	SPL 250 (^)
10	NSCLC	1200	27	Ongoing	-	Yes	No	SPL 300 (^)
11	Occult	600	13	Ongoing	Yes	Yes	Yes	SPL 50
12	Occult	300	0.25	Ongoing	Yes	Yes	Yes	SPL 100, AMI 5 (^)
13	Occult	600	10	Ongoing	-	Yes	Yes	SPL 50
14	Occult	1200	28	Bilateral adrenalectomy	-	Yes	No	SPL 300, K 120 (^)
15	Occult	600	7	Ongoing	Yes	No	Yes	SPL 100, K 40 (^)
16	Occult	300	28	Ongoing	-	Yes	Yes	SPL 200, K 100 (^)

–, Negative; AMI, amiloride; BA, Clinical signs, signs of cushing syndrome (plethora, purplish striae, round face, etc.); Death*, death from tumor progression; EPL, eplerenone; Etomidate, changed treatment to etomidate; K^+, potassium replacement in mEq/d; MRA, mineralocorticoid receptor antagonist; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; Psychiatric symptoms, included psychosis, depression and memory loss; SPL, spironolactone; Yes*, improved glycemic control with cessation of all antidiabetic agents.
During therapy with mifepristone, changes in K supplements and MRA are indicated by (^) for dose increase and (ˇ) for dose decrease.

TABLE 4 Adverse effect of mifepristone

Adverse events	Number of patients
Fatigue	8
Oedema	3
Nausea and vomiting	5
Anorexia	5
Glucocorticoid treatment	2
Increased dose of MRA and potassium supplementation	12
Abnormal vaginal bleeding, of 13 women	1

MRA, mineralocorticoid receptor antagonist.

antidiabetic regimen.[22] In our cohort, hyperglycaemia was improved in 14/16 patients, and in three patients, all antidiabetic agents were discontinued.

Hypokalaemia was present at the time of diagnosis in all EAS patients and remained problematic during mifepristone treatment, similar to what has been reported previously.[10,24] The massive glucocorticoid excess in patients with EAS exceeds the capacity of 11β-hydroxysteroid dehydrogenase type two to inactivate cortisol to cortisone, which thus activates the mineralocorticoid receptor.[21,22,27,28] An accurate assessment of mifepristone's contribution to hypokalaemia in our patients with EAS was difficult, due to overlapping factors, such as elevation of ACTH and cortisol due to the progression of tumours; concomitant tubular dysfunctions from chemotherapy; or severe vomiting and diarrhoea. Correction of hypokalaemia during treatment with mifepristone required up to 300 mg/d of spironolactone and/or up to 240 mEq/d of potassium, similar to a previous report.[22] These data suggest that serum potassium should be aggressively treated and closely monitored in patients with EAS during all stages and in particular when mifepristone is used.

A major consideration when using mifepristone in clinical practice is the inability to utilize serum or urine cortisol measurements as indicators of disease control. In addition, symptoms of glucocorticoid withdrawal are expected during mifepristone therapy, as well as continued clinical manifestations of hypercortisolism. In patients treated with mifepristone who experience hypotension, hypoglycaemia, nausea and vomiting, weakness and dizziness,

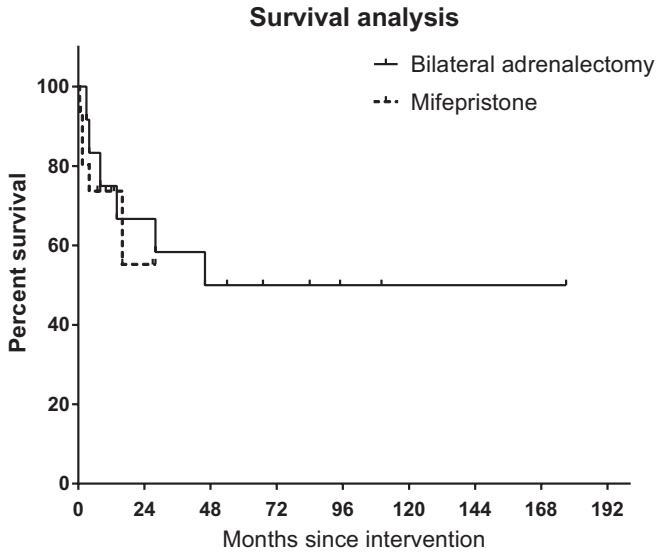

FIGURE 2 The Kaplan-Meier analysis was applied to evaluate the median overall survival between patients with ectopic adrenocorticotropic hormone syndrome (EAS) treated with mifepristone vs bilateral adrenalectomy. The mifepristone group included the two patients who subsequently had bilateral adrenalectomy; the survival difference remained not significantly different if these two were excluded from the analysis

mifepristone should be discontinued, and dexamethasone should be initiated promptly.[29] In our study, only two patients required interruption of mifepristone and dexamethasone treatment, and of these, one case had transient symptoms, precipitated by an episode of urinary tract infection. Nonetheless, a severe illness that demands augmented glucocorticoid activity should be promptly treated, and frequent clinical reassessment should be used to guide further therapy.

Our study substantiates the efficacy of mifepristone in the management of EAS, for both acute and extended management of hypercortisolism. Importantly, mifepristone was safely used for over 2 years in three of our patients. Survival for patients treated with mifepristone was similar to those managed with bilateral adrenalectomy, and tumour progression was the major cause of death. The small number of patients and the retrospective study design limit the extrapolation of our results. While the severity of hypercortisolemia was comparable between patients treated with mifepristone vs bilateral adrenalectomy, both groups were heterogeneous with respect to aetiology of EAS and clinical features, and treatment choice was not randomized. Mifepristone, along with a mineralocorticoid receptor antagonist and potassium supplementation, is effective in patients who cannot undergo bilateral adrenalectomy immediately or with occult tumours while searching for the source.

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CONFLICT OF INTEREST

RJA has received consulting fees from Corcept Therapeutics. TW and AFT report no conflict of interests in this work.

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