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Cardiovascular Outcomes in Autonomous Cortisol Secretion and Nonfunctioning Adrenal Adenoma: A Systematic Review

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There is growing evidence that autonomous cortisol secretion (ACS), previously known as subclinical Cushing syndrome, is associated with greater prevalence of cardiovascular (CV) risk factors. However, it is unclear whether ACS is associated with greater prevalence of CV outcomes compared with nonfunctioning adrenal adenomas (NFAAs). The objective of this study is to evaluate CV outcomes and CV risk factors in patients with adrenal adenoma with ACS compared with NFAA. A literature review was performed in Embase, Medline, Cochrane Library, and reference lists within selected articles. The study protocol was registered with PROSPERO. A literature search yielded six studies that met the inclusion criteria. Studies varied in their definitions of ACS and CV outcomes. Two retrospective longitudinal studies further demonstrated higher incidence of new CV events (ACS 16.7% vs NFAA 6.7%, $P = 0.04$) and higher CV mortality in patients with ACS (ACS 22.6% vs 2.5%, $P = 0.02$). The prevalence of CV outcomes in ACS was more than three times greater than in patients with NFAA. Three of five studies found that ACS was associated with higher prevalence of diabetes and hypertension. There was no difference in dyslipidemia or body mass index demonstrated in any study. There is heterogeneity among the few studies evaluating the association between ACS and CV outcomes. Although these studies suggest a higher risk of CV outcomes in patients with ACS, many did not adjust for known confounders. Larger, high quality, prospective studies are needed to evaluate this association and to identify modifiable risk factors.

Freeform/Key Words: Cushing syndrome, autonomous cortisol secretion, nonfunctional adrenal adenoma, cardiovascular outcomes

With radiological advancements, the frequency of incidentally discovered adrenal adenomas has increased, with studies quoting an incidence 3% in middle age and ≤10% in older adults [1–3]. Adrenal incidentalomas (AIs), although usually benign and nonfunctional, may be associated with cortisol excess. They are currently classified as Cushing syndrome, autonomous cortisol secretion (ACS), possible ACS, and nonfunctioning adrenal adenoma (NFAA).

Abbreviations: ACS, autonomous cortisol secretion; AI, adrenal incidentaloma; BMI, body mass index; CHD, coronary heart disease; CV, cardiovascular; CVE, cardiovascular event; DST, dexamethasone suppression test; MI, myocardial infarction; NFAA, nonfunctioning adrenal adenoma; pACS, possible autonomous cortisol secretion; SCS, subclinical Cushing syndrome; T2DM, type 2 diabetes mellitus.

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ACS, previously known as subclinical Cushing syndrome (SCS) or subclinical hypercortisolism, is a condition of biochemical cortisol excess in the absence of classic clinical features of Cushing syndrome [3–5]. The definition was modified in the 2016 European guidelines to distinguish ACS and overt Cushing syndrome as separate conditions with significantly different morbidity and mortality [6]. The prevalence of ACS is estimated to be 1% to 29% in those with AI [5, 6]. Serum cortisol levels after 1-mg overnight dexamethasone suppression test (DST) were used to categorize patients with AI ≤50 nmol/L (≤1.8 μg/dL) as NFAA, 51 to 138 nmol/L (1.9 to 5.0 μg/dL) as possible ACS (pACS), and >138 nmol/L (>5.0 μg/dL) without overt features of Cushing syndrome as ACS [6].

There is clear evidence that Cushing syndrome is associated with severe morbidity and elevated cardiovascular (CV) mortality [7–9]. Although most studies agree that ACS and NFAA rarely develop into overt Cushing syndrome [8, 10–14], there is evidence that ACS is associated with an elevated risk of CV outcomes and metabolic abnormalities [15–19], with studies supporting similar findings in patients with NFAA [20–22]. Although limited by cross-sectional data, these studies suggest that NFAAs secrete low levels of glucocorticoids and may not be truly "nonfunctional." Although there have been several attempts to streamline the management of patients with AI, much remains controversial as a consequence of limited research, especially with regard to the role of adrenalectomy and follow-up in those who do not have overt signs and symptoms of Cushing syndrome. A better understanding of CV outcomes in ACS compared with NFAA will help guide the management of patients with AIs, including those that initially present as "nonfunctional." Moreover, comparing the prevalence and incidence of traditional CV risk factors in relation to CV outcomes will help clarify the causal vs noncausal relationship between excess cortisol and the risk of CVD. This study aims to systematically review and summarize the literature on CV risk factors and outcomes in patients with NFAA and ACS.

1. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [23]. The study protocol was registered with PROSPERO (registration number CRD42017053153).

A. Literature Search

The search strategy was developed with the guidance of an information specialist. We used the Ovid Medline©, Embase, and Cochrane Reviews electronic databases. We searched the database for primary research studies evaluating CV outcomes in patients with adrenal adenomas, published between 1946 and February 2018. We limited the search to English-language publications. Additional publications were identified by a manual search through reference lists of articles identified by this search strategy.

B. Study Selection

We included all primary research studies (prospective and retrospective observational studies and randomized controlled trials) aimed at comparing CV risk factors and outcomes in NFAA and ACS. For this study, we included studies only if they reported at least one primary outcome (CV outcome). If the study reported only on CV risk factors (our secondary outcome), the study was not included. We included studies that enrolled participants with adrenal adenomas found incidentally on imaging (*i.e.,* incidentalomas) and studies that grouped participants into NFAA and ACS based on definitions predetermined by the authors. The definitions of ACS and NFAA chosen for this systematic review were based on original definitions used in the included studies on the basis of morning cortisol after 1-mg DST: patients with ACS were defined as those with AI with morning cortisol after 1-mg DST >50 nmol/L or >138 nmol/L without any overt Cushing features. Patients with NFAA

were defined as those with AI who did not meet the cortisol cutoff point for ACS. Suppressed ACTH, increased urinary free cortisol, and elevated midnight cortisol were also used in the studies as composite criteria for ACS. However, because these levels were not standardized between the studies, we opted to only include overnight 1-mg DST. Detailed description of the criteria for AI subcategories are available in Table 1.

We excluded nonoriginal studies and case reports. Titles and abstracts of potentially eligible studies were screened, and articles were rejected when the eligibility criteria were clearly not met. For the remaining articles, two investigators (J.P. and A.D.) independently assessed the full texts for eligibility. Differences in assessments were resolved by discussion to reach consensus.

C. Study Outcomes

The predefined primary outcome was the difference in CV outcome prevalence, incidence, and mortality between the two groups: NFAA and ACS. CV outcome was defined as any major CV event, including acute coronary syndrome, stable angina, coronary artery disease, stroke, and congestive heart failure. A broad definition was chosen because of potential heterogeneity regarding study outcome definition. Secondary outcomes included differences in prevalence and incidence of CV risk factors including body mass index (BMI), hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia.

D. Data Extraction and Validity Assessment

Two authors (J.P. and A.D.) independently extracted data from each included study. Discrepancies were resolved by discussion and adjudication with the other reviewers.

E. Data Synthesis and Analysis

The outcomes were organized into evidence tables for narrative synthesis. It was anticipated that the majority of included studies would be nonrandomized studies and that heterogeneity would exist between studies. For example, we anticipated that the included patient populations, definitions of NFAA and ACS, and definitions and type of CV outcomes and risk factors in each study would vary significantly. Based on this expectation, it was thought that a pooled analysis would be inappropriate. Instead, a detailed narrative synthesis of the included studies was planned.

F. Risk of Bias

Two investigators independently appraised each study for quality by using an assessment form based on the Newcastle Ottawa Scale (Appendix 2) [24]. The Newcastle Ottawa Scale assesses the risk of bias in nonrandomized studies (case-control and cohort studies) by using the following main categories: study group selection, comparative group selection, outcome assessment, and adequacy of follow-up.

For cohort studies, a maximum score of 9 stars was assigned, with a low risk of bias defined as a score of $\geq$8, moderate risk of bias 5 to 7, and high risk of bias $\leq$4. For cross-sectional studies, a maximum score of 7 stars was assigned, with a low risk of bias defined as a score of $\geq$6, moderate risk of bias 3 to 5, and high risk of bias $\leq$2. Discrepancies were resolved by discussion and adjudication with the other reviewers.

2. Results

A. Study Selection

The search of the OVID Medline©, Embase, and Cochrane Reviews electronic databases, and review of the reference lists of included articles, provided total of 1847 citations. After we

Table 1. Characteristics of Included Studies

Author	Study Design	Country	Population	Participants	Cutoff Values for Subgroups			Follow-Up Duration
					ACS	pACS	NFAA	
Yener *et al.* (25)	Cross-sectional	Turkey	AI (2002–2009)	273	Overnight 1-mg DST >50 nmol/L At least 1 of: • ACTH <1.1 pmol/L (5 pg/mL) • Urinary free cortisol 110 μg/d • Midnight cortisol >207 nmol/L (>7.5 μg/dL)		Overnight 1 mg DST ≤50 mmol/L At least 1 of: • Morning DHEAS levels >40 μg/dL • Plasma ACTH >1.1 pmol/L (>5 pg/mL) • Urinary free cortisol <110 μg/d • Midnight cortisol <207 nmol/L (<7.5 μg/dL)	24 mo only for NFAA group
Debono *et al.* (26)	Cohort	United Kingdom	AI (2005–2013)	206	Overnight 1-mg DST >138 nmol/L	Overnight 1-mg DST 50–137 nmol/L	Overnight 1-mg DST ≤0 mmol/L	Mean 4.2 y
Di Dalmazi *et al.* (18)	Cohort	Italy	AI (1995–2010)	198	Overnight 1-mg DST >138 nmol/L	Overnight 1-mg DST 50–137 nmol/L	Overnight 1-mg DST ≤50 mmol/L	Mean 7.5 y (range 26 mo–5 y)
Morelli *et al.* (19)	Cohort	Italy	AI (1996–2012)	206	Overnight 1-mg DST >138 nmol/L OR At least two: • ACTH 2.2 pmol/L (<10 pg/mL) • Elevated urinary free cortisol (above upper limit of normal of assay) • 1-mg DST >83 nmol/L (>3.0 μg/dL)		Overnight 1-mg DST <137 nmol/L	Mean 83 mo (range 60–186 mo)
Morelli *et al.* (28)	Case-control	Italy	AI (1996–2016)	518	Overnight 1-mg DST >50 nmol/L		Overnight 1-mg DST ≤50 mmol/L	Mean: 161.8 ± 45.1 (range 120–426 mo)
Patrova *et al.* (27)	Cohort	Sweden	AI (2003–2010)	365	Overnight 1-mg DST >138 nmol/L	Overnight 1-mg DST 50–137 nmol/L	Overnight 1-mg DST ≤50 mmol/L	Mean 5.2 ± 2.3 y (range 0.6–13.7 y)

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removed duplicates and screened titles, abstracts, and full text, a total of six studies met the eligibility criteria and were included in this systematic overview (Fig. 1).

B. Study Characteristics

Table 1 lists the characteristics of all six included studies [18, 19, 25–28]. Four studies were retrospective cohort studies [18, 19, 26, 27]. One study was a prospective design for one study group; however, only cross-sectional data were reported when the two reported study groups were compared [29]. One study used a case-control design [28]. The duration of the cohort studies ranged from 4 to 15 years. A total of 1766 participants were included in the six included studies, of which 363 were ACS, 279 were pACS, and 1124 were NFAA. There was an overlap of 95 subjects in Morelli's 2012 and 2017 studies [19, 28], resulting in a total of 1671 unique individuals.

All studies included participants with adrenal lesions discovered incidentally by abdominal ultrasound, CT scan, or MRI and excluded patients with overt Cushing syndrome, suspected hormonally active lesion, or adrenal malignancy.

The definitions of ACS and NFAA varied between the studies, with differing cutoff values of serum cortisol after overnight 1-mg DST. These values are summarized in Table 1. Different criteria were used to define ACS, with the two most common criteria being secreted cortisol >138 nmol/L or >50 nmol/L after 1-mg DST. Three studies included an intermediate phenotype or possible ACS, defined as cortisol levels 50 to 138 nmol/L [18, 26, 27]. Two of the six studies also included suppressed ACTH, elevated 24-hour urinary free cortisol, and elevated midnight cortisol level as part of the composite criteria for ACS. The cutoff numbers for these tests were not standardized between the studies and therefore not used to determine participant categories [19, 25].

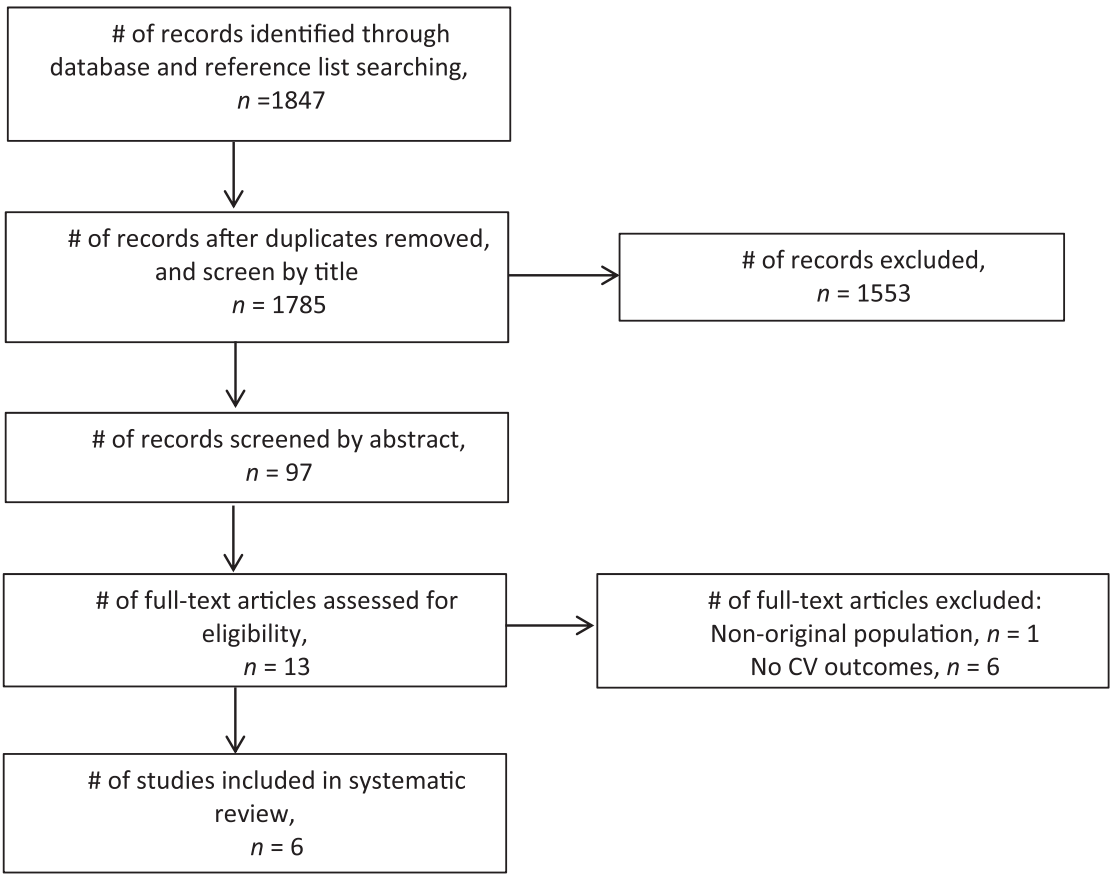

Figure 1. Study selection process.

C. Risk of Bias

Of the six included studies, two studies were rated as having low risk of bias [18, 28] and four studies were rated as moderate risk of bias [18, 25–27] The results are summarized in Table 2.

D. Cardiovascular Outcomes

The primary outcomes are summarized in Table 3. The difference in prevalence of CVD was reported in four of six studies [18, 19, 25, 28]. The prevalence was statistically greater by twofold to threefold in the ACS group compared with the NFAA group in all four studies, with all studies' P values <0.05. Di Dalmazi *et al.* [18] reported the differences in coronary heart disease (CHD) prevalence and stroke prevalence independently, which revealed 11% more CHD ($P < 0.03$) and 9% more stroke ($P = 0.03$) in ACS than in NFAA.

Two studies compared the difference in incidence of CV events (CVEs) between ACS and NFAA [18, 19]. In one cohort, the incidence of CVEs in ACS was 20.5% compared with 8.4% in NFAA, with an odds ratio of 2.7 (95% CI, 1.0 to 7.1), $P < 0.04$ [19]. Likewise, the Di Dalmazi *et al.* [18] cohort demonstrated that there was a greater incidence of CVEs in ACS (16.7%) when compared with NFAA (6.7%), $P = 0.04$, with an unadjusted hazard ratio for new CVEs of 3.01 (95% CI, 1.04 to 8.72), $P = 0.04$. The definitions of CVEs varied between the two studies: Morelli *et al.* [19] defined CVE as CHD or ischemic or hemorrhagic stroke, whereas Di Dalmazi *et al.* [18] defined CVE as nonfatal acute myocardial infarction (MI), percutaneous transluminal coronary angioplasty and surgical bypass for ischemic heart disease, or ischemic stroke.

Two separate studies used multivariate regression analysis to test for incidence of CVEs and post–1-mg overnight DST serum cortisol level as a continuous variable [27, 28]. Both found that CVE occurrence was significantly associated with post–1-mg DST cortisol levels independently from other CV risk factors. Based on the regression analysis, Morelli *et al.* [28] determined that a serum cortisol level >50 nmol/L after overnight 1-mg DST predicted increased CVE risk by 2.5-fold.

Survival rates in patients with ACS were reduced (ACS 6.9 years vs NFAA 8.4 years, $P < 0.01$) [25], CV-specific mortality at 15 years was elevated (ACS 22.6% vs NFAA 2.5%, $P < 0.02$), and all-cause mortality at 15 years (ACS 43.0% vs NFAA 8.8%, $P = 0.005$) [18] and at 12 years were elevated (ACS 18.2% vs NFAA 7.8%) [27] in comparison with patients with NFAA [18, 26, 27].

Cause of death was reported in the three studies. In Debono *et al.*'s cohort [26], the main causes of death were CVD and respiratory infections. Similarly, Di Dalmazi *et al.* [18] also reported that their main cause of mortality was CVD. However, in Patrova *et al.*'s [27] cohort, the rate of death due to malignancies was higher than that of CVD.

Table 2. Risk of Bias for Observational Studies Evaluating the Difference Between Patients With ACS and NFAA and CVEs Based on the Newcastle-Ottawa Scale for Nonrandomized Clinical Studies and Stratified by Type of Study

	Study Design	Selection	Comparability	Outcome	Risk of Bias
Cohort studies					
Debono *et al.* (26)	RC	XXXX	X	XX	Moderate
Di Dalmazi *et al.* (15)	RC	XXXX	X	XXX	Low
Morelli *et al.* (19)	RC	XXX		XXX	Moderate
Patrova *et al.* (27)	RC	XXX	X	XXX	Moderate
Cross-sectional and case-control studies					
Yener *et al.* (25)	CS	XXXX		X	Moderate
Morelli *et al.* (28)	CC	XXXX	X	X	Low

Each X represents a point awarded for each numbered item within the selection, comparability, and outcome or exposure.

Abbreviations: CC, case-control study; CS, cross-sectional study; RC, retrospective cohort study.

Table 3. Comparison of CV Outcomes in Patients With ACS Compared With Those With NFAA

	Sample Size				Cardiovascular Outcomes
Author	ACS[a]	pACS[b]	NFAA	Outcome	ACS vs NFAA
Yener *et al.* (25)	42		231[c]	CVE (acute coronary syndrome, CAD, CABG, PAD, cerebrovascular disease, PCI, or stroke)	Prevalence of CVE: ACS 19.5% vs NFAA 6.7%, $P < 0.016$
Debono *et al.* (26)	19	92	95[d]	All-cause mortality	All-cause mortality: ACS vs NFAA, HR 22.0 (95% CI, 2.6–188.3)
				Mean survival	Survival ACS 6.9 y (95% CI, 5.6–8.3) vs pACS 7.3 (95% CI, 6.8–7.8) vs NFAA 8.4 (95% CI, 8.2–8.6), $P < 0.001$
Di Dalmazi *et al.* (18)	10	59	129[d]	CHD	CHD prevalence: ACS 18% vs NFAA 7%, $P < 0.03$
				Stroke	Stroke prevalence: ACS 13% vs NFAA 4%, $P = 0.03$
				MI	CVE incidence: ACS 16.7% vs NFAA 6.7%, $P < 0.004$
				CVD-specific mortality	CVE incidence: ACS vs NFAA unadjusted HR 3.01 (95% CI, 1.04–8.72), $P = 0.04$ CVD-specific mortality at 15 y (unadjusted) ACS 22.6% vs NFAA 2.5%, $P = 0.02$ All-cause mortality (unadjusted) at 15 y: ACS 43.0% vs NFAA 8.8%, $P = 0.005$
Morelli *et al.* (19)	39		167[c]	CVE (CHD, ischemic or hemorrhagic stroke)	CVE prevalence: ACS 20.5% vs NFAA 6.0%, $P < 0.05$ CVE incidence: ACS 20.5% vs NFAA 8.4%, $P = 0.04$ CVE incidence in ACS vs NFAA OR: 2.7 (95% CI, 1.0–7.1); $P < 0.04$
Morelli *et al.* (28)	220[e]		298[d]	CVE (MI, stroke, TIA, angina pectoris, PE, ICH, PAD)	CVE prevalence: ACS 26.8% vs NFAA 10.4%, $P < 0.001$
Patrova *et al.* (27)	33	128	204[d]	All-cause mortality	All-cause mortality: ACS 18.2% vs pACS 11.7% vs 7.8% NFAA, $P = 0.019$; HR 1.27 (95% CI, 0.86–2.12)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, cardiovascular heart disease; HR, hazard ratio; ICH, intercranial hemorrhage; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; TIA, transient ischemic attack.
[a]Serum cortisol levels after 1-mg DST >138 mmol/L.
[b]Serum cortisol levels after 1-mg DST 51–138 mmol/L.
[c]Serum cortisol levels after 1-mg DST ≤138 mmol/L.
[d]Serum cortisol levels after 1-mg DST ≤50 mmol/L.
[e]Serum cortisol levels after 1-mg DST >50 mmol/L.

E. CV Risk Factors

The secondary outcomes are summarized in Table 4. Five studies looked at the prevalence of CV risk factors at baseline. In three of five studies, there was significantly more baseline hypertension [25, 26, 28] and T2DM [18–20] documented in subjects with ACS compared with NFAA. One of the four studies found dyslipidemia to be more prevalent in the ACS group [28].

Of the five studies, two examined the incidence of CV risk factors at follow-up interval [18, 19]. One of two studies also reported an increased risk of hypertension at follow-up in those with ACS compared with NFAA [19]. Both studies reported higher T2DM rates at follow-up. None of the studies showed differences in dyslipidemia at follow-up [18, 19]. None of the studies demonstrated a difference in BMI between the ACS and NFAA groups at baseline or at follow-up [18, 19, 25, 26, 28].

Table 4. Comparison of CV Risk Factors in ACS vs NFAA in Patients With AI

	Diabetes (%)				Dyslipidemia or on Treatment (%)				Hypertension (%)				BMI (Mean)			
	ACS		NFAA		ACS		NFAA		ACS		NFAA		ACS		NFAA	
Author	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
Yener *et al.* (25)	16.6		18.7		—	—	—	—	68.2[a]	—	51.7		29.5	—	28.6	—
Di Dalmazi *et al.* (18)	40[a]	38[a] (ACS + pACS)	18	19	30	25 (ACS + pACS)	14	28	90	77 (ACS + pACS)	73	73	29.2	27.5[a] (ACS + pACS)	28.5	28.9
Morelli *et al.* (19)	33.3[a]	43.6[a]	16.8	22.2	53.8	69.2	41.9	53.9	66.7	87.2[a]	53.9	62.9	28.3	29.2	27.9	28.2
Patrova *et al.* (27)	9.1	—	12.3	—	12.1	—	17.2[a]	—	57.6[a]	—	39.2	—	25.7	—	28.7	—
Morelli *et al.* (28)	25.9[a]	—	18.5	—	41.4[a]	—	32.9	—	74.5[a]	—	60.7	—	27.4	—	27.8	—

Abbreviations: BL, baseline; FU, follow-up.
[a]Statistically significant difference between ACS and NFAA, $P < 0.05$.

F. Subjects With Progression or Normalization of Disease

Our search identified three studies that described a subgroup of patients who progressed in their disease, with rising cortisol levels after 1-mg DST [18, 19, 27]. In these studies, progression of NFAA to pACS or pACS to ACS was noted in 3% to 12% of participants. Di Dalmazi *et al.* [18] also demonstrated in its subgroup analysis that participants with progression of disease had the worst mortality and CVD outcomes compared with the other groups. Moreover, Morelli *et al.* [19] demonstrated that tumor size >2.4 cm was associated with the development of ACS from NFAA (OR 2.97; 95% CI, 1.37 to 6.44; $P < 0.006$). In contrast, one study reported normalization of disease to pACS or NFAA in 12% to 15% [27]. This finding of normalization was not reported in the other two studies. Progression to overt Cushing syndrome was not reported in any of the studies [18, 19, 25–28].

G. Other Related Outcomes

Several studies have suggested a possible correlation between tumor size and the degree of alterations in adrenal function [19, 25, 26, 28]. However, there were inconsistent data regarding a direct correlation between the tumor size and cortisol secretion [18, 27]. Moreover, one study that looked at adenoma size and its effect on CVEs found no significant differences [28].

3. Discussion

With advances in imaging techniques, the incidental discovery of adrenal adenoma is rising, leading to increased detection of ACS. Recent evidence suggests greater morbidity and mortality associated with ACS when compared with the general population. The management of this patient group remains largely controversial, however [30]. There have been multiple clinical practice guidelines from various societies in the past 10 years, including the National Institutes of Health in 2003, Endocrine Society in 2008, French Society of Endocrinology in 2008, American Association of Clinical Endocrinologists in 2009, Italian Association of Clinical Endocrinologists in 2011, and most recently, European Society of Endocrinology in 2016 [6, 31–36]. There has been nonconformity between the clinical practice guidelines especially with regard to classification of AI based on 1-mg DST morning cortisol cutoffpoints, as well as the role of adrenalectomy and follow-up in ACS and NFAA.

The current European guidelines from 2016 suggest an individualized approach for surgical management for those with ACS based on comorbidities, age, and degree of cortisol excess. Surgery and repeat hormonal workup are not recommended for those with NFAA and benign features on imaging [6]. In the Italian Association of Clinical Endocrinologists 2015 guidelines, adrenalectomy is suggested for those for whom adequate medical therapy does not achieve treatment goals associated with comorbidities possibly linked to cortisol excess [36]. Similarly, the American Association of Clinical Endocrinologists 2009 guidelines recommend surgery in ACS with worsening hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis [35]. By contrast, the National Institutes of Health (2003) and French Society of Endocrinology (2008) clinical practice guidelines did not recommend adrenalectomy [24, 31].

This systematic review suggests that that there is greater CVE prevalence, mortality, and reduced survival in patients with ACS when compared with those with NFAA. These findings, although limited by heterogeneity of data, suggest that despite both ACS and NFAA groups having more CVD risks and outcomes compared with the general population, the degree of cortisol secretion plays a role in the risk of developing CVD outcomes. This finding is further supported by two studies that showed a direct correlation between the incidence of CVEs and post–1-mg overnight DST serum cortisol level as a continuous variable. This correlation supports the notion that serum cortisol levels after 1-mg overnight DST should be a continuous variable rather than categorical entities. This notion is in agreement with the European guidelines from 2016 [6]. Moreover, our results indicate that there is a greater

relative indication for surgery in those with ACS when compared with NFAA. However, the absolute indication for adrenalectomy in both ACS and NFAA hinges on future prospective and randomized controlled studies comparing adrenalectomy with conservative management on CV outcomes.

European guidelines from 2016 also suggest using the cutoff point value of cortisol ≤50 nmol/L on post–1-mg DST to exclude the diagnosis of autonomous cortisol secretion [6]. This guideline was based on two studies that showed greater mortality and morbidity in ACS when compared with NFAA [18, 26]. Although our review agrees that ACS has greater risk of CVEs than NFAA, there are limitations to both the Debono *et al.* [26] and Di Dalmazi *et al.* [18,] categorical subgroups: NFAA and ACS. The groups were preselected based on existing definitions of AI: ≤50 nmol/L cortisol after 1-mg DST as NFAA. Both of these studies did not account for other cortisol cutoff values in grouping NFAA and ACS. Furthermore, in another study, post–1-mg DST cortisol of >41 nmol/L was the most sensitive to determine when CVE prevalence correlated with the level of excess cortisol (measured by 1-mg DST). Therefore, whether cortisol of 50 nmol/L after 1-mg DST should be the cutoff for "nonfunctioning" AI risk remains unclear.

Our systematic review also shows that ≤12% of patients progressed to worsened categories of AI, although none converted to overt Cushing syndrome. Although this progression has not been demonstrated in all studies, it supports the hypothesis that ACS is part of a biochemical spectrum. With the exception of one study that demonstrated an association between tumor size and disease progression, other predictors of progression vs normalization of adrenal function have not yet been described [19]. Based on Di Dalmazi *et al.*'s [18] subgroup analysis, which shows increased mortality in the group of patients who worsened in their cortisol secretion, it is possible that this group possesses phenotypical differences despite being on a biochemical continuum. This finding has not been confirmed in other studies.

Interestingly, despite all studies demonstrating more CVEs in the ACS group, not all studies showed a statistical difference in prevalence or incidence of traditional CV risk factors (diabetes, dyslipidemia, and hypertension). Thus, the mechanism of hypercortisolemia causing greater CV mortality may not work solely via traditional CV risk factors. Some studies have suggested that elevated post–1-mg DST cortisol itself is an independent risk factor for CVEs when adjusted for CV risk factors [18, 27, 28]. Other studies have demonstrated that patients with ACS had a higher prevalence of diastolic dysfunction, higher arterial stiffness, and greater left ventricular mass when compared with NFAA independent of other cardiac risk factors [37]. Additional work investigating the mechanism of cortisol on CV outcomes in patients with ACS and NFAA is warranted.

A. Limitations

Our systematic review includes only retrospective and cross-sectional studies, limiting the opportunity for assessing causality and introducing risks of bias and confounders. Based on the results, it is difficult to know whether ACS and CV risk factors or events are simply correlated or whether there is a causal relationship. Very few studies adjusted for known confounders, further limiting our ability to accurately interpret the data. Moreover, four of the six included studies had moderate risk of bias. Most studies had limitations that were related to patient selection, adequacy of control group, follow-up, and retrospective nature of the study.

Based on current European guidelines, patients with NFAA do not need any additional follow-up or screening for CV outcomes and metabolic complications [6]. Patients with pACS and ACS probably had more follow-up, more investigations, and more contact with the health care system. Given the retrospective design of the included studies, it is possible that CV events and outcomes were more likely to be reported for these patients than for patients with NFAA.

Heterogeneity in existing studies also made it challenging to interpret outcomes and synthesize conclusions. First, the definition of ACS varied between studies. Hormonal assays

mostly involved serum cortisol after 1-mg DST but sometimes in combination with other assays. Moreover, the definitions used for both ACS and CV outcomes differed between studies. The method of determining the cause of mortality also differed between studies. Some studies used the reports of general practitioners, cardiologists, or endocrinologists, whereas others used electronic medical records. One study used communication via telephone to family members to determine the cause of death, which could have resulted in inaccurate outcome information. These differences in methods and definitions of outcome measures limited our ability to pool data and analyze data. Qualitative analysis was also limited by studies differing in their definitions and measurement of CVEs.

B. Review Implications

Our review supports the current European guidelines regarding the biochemical continuous definition and diagnosis of adrenal incidentaloma using serum cortisol after 1-mg DST. It also indicates that until more definitive studies are performed, adrenalectomy should be offered only to those with established cortisol excess, on the basis of individualized risk-benefit assessment.

This review highlights the importance of future research in this area. Additional studies are needed to evaluate the use of cortisol after 1-mg DST as a continuous variable rather than distinct categories of AI. Large prospective studies are also warranted to better understand the progression in cortisol secretion, changes in tumor size, and the mechanisms by which excess cortisol may increase CVE risk independent of traditional CV risk factors.

Acknowledgments

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References and Notes

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