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Original Research

Long-term cardiac effects of adrenalectomy versus surveillance in mild cortisol excess: 5-year results from the prospective ITACA study

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Abstract

Objective **To determine whether cardiac remodelling associated with mild autonomous cortisol secretion (MACS) is reversible after treatment and how trajectories compare with non-functioning adrenal incidentalomas (NFAI).**

Design **Five-year prospective cohort study (ITACA; NCT04127552).**

Methods **Sixty patients (35 MACS, 25 NFAI) underwent clinical, biochemical, and echocardiographic evaluations at baseline and after 1 and 5 years. MACS was managed with either active surveillance (AS, $n = 22$) or unilateral adrenalectomy (ADRX, $n = 13$). Longitudinal changes were analysed with linear mixed-effects models.**

Results **At baseline, MACS had a higher prevalence of left-ventricular (LV) hypertrophy (46% vs 16%, $P = .013$) and diastolic dysfunction (34% vs 12%, $P = .050$), and greater LV mass index (LVMi) (median 100 vs 85 g/m^2, $P = .011$). Over time, the change in LVMi differed between NFAI, MACS-AS and MACS-ADRX ($P = .004$). At 1 year, LVMi fell by −14.8 g/m^2 (95%CI −28.7 to −0.9) after ADRX and rose by 13.7 g/m^2 (0.8 to 26.5) under AS. By 5 years, LVMi returned to baseline in both MACS subgroups, whereas NFAI increased by 22.4 g/m^2 (12.3 to 32.5; $P < .001$). Right-ventricular systolic excursion (TAPSE) improved only in AS (3.6 mm, 1.8 to 5.4; $P = .001$). Global LV systolic and diastolic indices deteriorated similarly across groups. Major adverse cardiac events occurred in 13.3% of MACS-AS, 12.5% of ADRX, and 5.6% of NFAI patients.**

Conclusions **MACS is associated with early concentric LV remodelling that regresses after adrenalectomy but rebounds within 5 years, leaving surgical and surveillance patients with comparable cardiac geometry. Under AS, remodelling stabilizes, whereas NFA continue a slow, progressive hypertrophic course. These findings support serial echocardiographic monitoring and underscore the need to test other cortisol-lowering therapies, alone or in combination with surgery, for durable cardioprotection.**

Keywords MACS, cardiovascular, echocardiography, adrenal incidentaloma, adrenalectomy

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Significance

This study provides the first long-term, prospective evidence on cardiac outcomes in patients with mild autonomous cortisol secretion. By systematically comparing adrenalectomy and active surveillance against non-functioning adrenal incidentalomas over 5 years, we show that cortisol excess drives early structural cardiac remodelling, with only transient regression after surgery and steady progression in conservatively managed or "non-functioning" lesions. These findings emphasize echocardiography as a practical tool for risk stratification and monitoring, challenge the durability of surgical benefit, and highlight an unmet need for sustained cortisol-lowering strategies. The results directly inform clinical decision-making in the growing population of patients with adrenal incidentalomas.

Background

Adrenal incidentalomas are increasingly identified in routine abdominal imaging studies.[1-3] Among these, non-aldosterone-producing adrenocortical adenomas (NAPACAs) account for over 80% of incidentally detected adrenal lesions.[4,5] According to the most recent European Society of Endocrinology/European Network for the Study of Adrenal Tumors guidelines,[4] NAPACAs are classified based on post-dexamethasone suppression serum cortisol levels: non-functioning adrenal incidentalomas (NFAI), defined by a 1 mg overnight dexamethasone suppression test (1mg-DST) result ≤50 nmol/L, and mild autonomous cortisol secretion (MACS), defined by cortisol levels >50 nmol/L.

By definition, patients with MACS lack the overt clinical features of Cushing's syndrome (CS). However, they present a higher frequency of cortisol-related comorbidities compared to NFAI,[6] including hypertension, dysregulated glucose and lipid metabolism, impaired bone health, infectious diseases,[7] and coagulative alterations.[8-11] These alterations contribute to increased overall and cardiovascular mortality among affected individuals.[4] Interestingly, few studies have suggested that MACS may also be associated with cardiac morpho-functional alterations, including increased ventricular mass, interventricular septal thickness, and diastolic dysfunction,[12,13] similar to those observed in patients with CS. These changes are believed to result from chronic glucocorticoid exposure,[14] independently of traditional cardiometabolic risk factors and, importantly, are only partially reversible following remission of overt CS.[12] Despite growing awareness of the cardiovascular implications of MACS, the evolution of cardiac impairment following successful treatment has never been investigated. To note, while treatment of overt CS with surgical tumour removal is recommended,[15,16] management of MACS remains controversial. The latest guidelines emphasize an individualized, centre-specific approach when deciding the therapeutic approach to MACS, weighing surgical intervention against conservative monitoring.[4] In this context, the prospective, longitudinal ITACA trial ("Impact of Adrenal Incidentalomas and Possible Autonomous Cortisol Secretion on Cardiovascular and Metabolic Alterations") was designed to evaluate the cardiometabolic status of patients with NAPACAs, both at the time of diagnosis and after different treatment strategies.

The present study aims to report mid- to long-term outcomes from the ITACA cohort, comparing echocardiographic parameters, cardiovascular event incidence, and cardiometabolic comorbidities between patients with NFAI and MACS. Additionally, we explore the impact of unilateral adrenalectomy against active surveillance on these parameters.

Methods

Patients and study design

This prospective, observational study is part of the ITACA trial (NCT04127552) and included all consecutive patients diagnosed with unilateral adrenal incidentaloma referred to the adrenal outpatient clinic at the Department of Experimental Medicine, Policlinico Umberto I, Sapienza University of Rome, between September 2019 and April 2023. All adrenal lesions were >10 mm and incidentally discovered during computed tomography or magnetic resonance imaging performed due to unrelated clinical indications. Exclusion criteria included (1) a confirmed diagnosis of overt CS, defined according to current biochemical criteria, in combination with clinical signs of hypercortisolism[17]; (2) biochemical and/or histological diagnosis of adrenal masses other than NAPACA; (3) congenital adrenal hyperplasia, and other rare adrenal diseases; (4) patients taking drugs or affected by diseases known to alter corticosteroid metabolism or cortisol secretion, such as oral oestrogens; (5) previous history of major adverse cardiac events (MACEs), defined according to the 5-point classification[18]; (6) unavailable echocardiography follow-up after initial diagnosis; and (7) bilateral adrenal masses. After the baseline evaluation, patients were stratified as MACS or NFAI according to 1 mg-DST results following current guidelines.[4] Namely, MACS diagnosis was based on 2 consecutive abnormal 1-mg DST results, and the test closest to the baseline echocardiographic evaluation was used in the baseline analysis. Patients with borderline values underwent a low-dose Liddle test (0.5 mg dexamethasone every 6 hours × 2 days); patients with discordant results were excluded from the analysis. Adrenocorticotropic hormone (ACTH) levels equal or lower than 15 pg/mL were considered indicative of ACTH-independent cortisol secretion. The choice of management strategy for adrenal lesions was based on a combination of factors following multidisciplinary evaluation, including patient age, number and severity of clinical comorbidities, tumour size, presence and degree of cortisol excess, according to a predefined in-house decision-making algorithm (detailed in Figure 1) consistent with the guidelines available at the time of study conception and approval.[19] Patients with NFAI were managed conservatively with active surveillance (AS). The therapeutic management of MACS was individualized, with patients undergoing either AS or unilateral adrenalectomy (ADRX). Active surveillance consisted of periodic follow-up consultations follow-up in our endocrine outpatient clinic: twice-yearly for patients with MACS, and yearly for patients with NFAI. Obesity, diabetes, hypertension, dyslipidemia, and

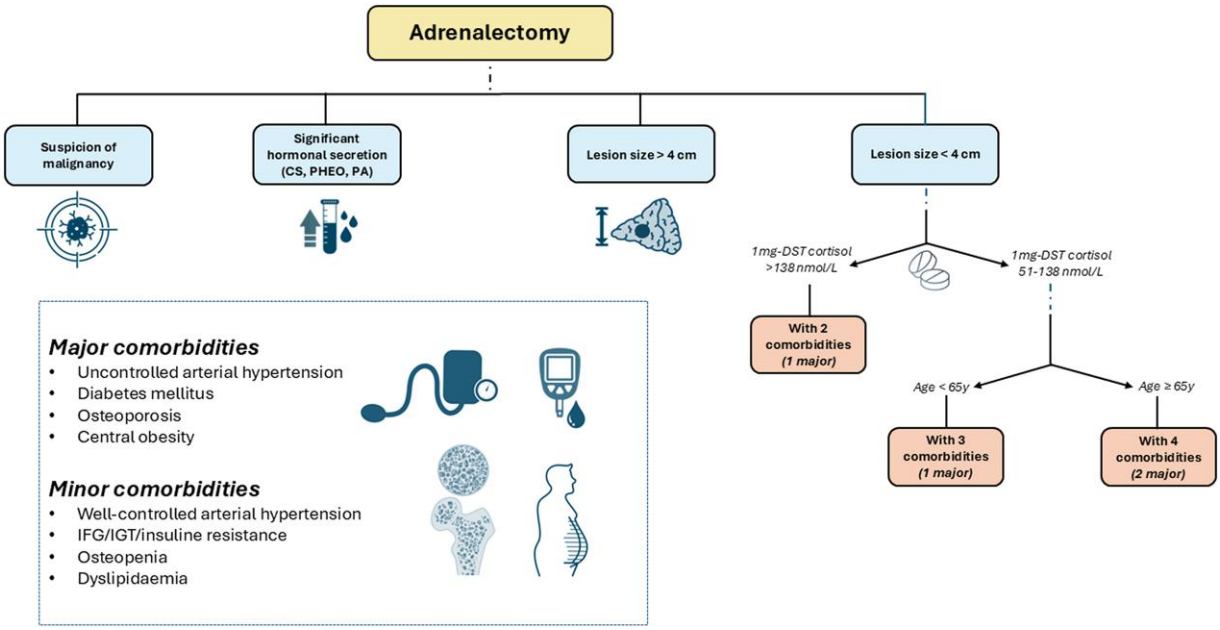

Figure 1 The ITACA algorithm for the management of adrenal lesions at our centre. Abbreviations: CS, Cushing's Syndrome; PHEO, Pheochromocytoma; PA, Primary hyperaldosteronism; 1mg-DST, post-1 mg dexamethasone suppression; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

osteoporosis were systematically assessed and managed by endocrinologists. Cardiovascular risk management was performed in collaboration with cardiologists. Adherence and treatment response were evaluated at each visit through clinical review, medication reconciliation, and laboratory or imaging data as appropriate. Although no fixed prescription protocol was adopted, treatment adjustments for each comorbidity were made in accordance with contemporary clinical guidelines and applied consistently across all groups. All adrenalectomies were performed by a single expert surgeon (A.M.P.) through a laparotomic or laparoscopic approach, depending on tumour size and patient characteristics. All patients underwent post-operative hypothalamic-pituitary-adrenal axis assessment at definite intervals until hormonal recovery, as per in-house protocol.[20] Regardless of treatment strategy, all patients underwent subsequent complete study evaluations at 1-year, and/or 5-year follow-up. The study was approved by the Local Ethics Committee of Sapienza University in Rome (reference number 5279) and was conducted in accordance with the Declaration of Helsinki (1964) and its subsequent amendments. All patients provided their written informed consent.

Study procedures

At each study visit, patients underwent the following assessments.

Medical history evaluation

Detailed medical history was collected with particular attention to cardiovascular complications and MACEs; all the other non-fatal cardiac, thrombotic, and arrhythmic events were classified as minor cardiac adverse events. Smoking status was classified as current (patients smoking any tobacco during the observation period), former (patients who previously quit smoking) or never smoker.[21] The main cortisol-related comorbidities (ie, arterial hypertension, diabetes mellitus, dyslipidaemia, osteoporosis, and obesity) were systematically monitored at each study visit. Diabetes mellitus and dyslipidaemia were diagnosed according to current guidelines, or via the reported use of glucose and lipid-lowering drugs[22,23]; insulin resistance was defined by the Homeostasis Model Assessment of Insulin Resistance $\geq$2.5.[24] Clinical worsening was defined as the new onset of the comorbidity or the need for treatment intensification, either via dose increase or in the number of drugs.

Anthropometrics and vital signs

Clinical assessments made by expert endocrinologists focused on signs or symptoms suggestive of adrenal hormone excess. Anthropometric measurements included body mass index, waist circumference, and hip circumference. Obesity was defined by body mass index values greater than 30 kg/m^2. Vital signs were also collected, with arterial hypertension being defined by ambulatory systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg on repeated evaluations and/or by the reported use of antihypertensive medication.[25]

Biochemical and hormonal analyses

Fasting baseline blood samples were collected between 8.00 and 9.00 h AM. Laboratory analyses included glucose and lipid profiles, electrolytes, renal and liver function, along with an endocrine workup, including baseline serum cortisol, ACTH, 24-hour urinary free cortisol (UFC), and dehydroepiandrosterone sulphate (DHEAS) levels. In patients with MACS and NFAI under

active surveillance, 1mg-DST was also performed and reassessed at each study time point.

Serum and 24-hour urinary cortisol levels were quantified by radioimmunoassay using Beckman Coulter reagents (IM1841). The assay's dynamic range was 8.60-2000 nM. The method demonstrated high specificity, with negligible or undetectable cross-reactivity towards other endogenous steroids and commonly administered pharmacological agents. Plasma ACTH concentrations were determined by immunoradiometric assay employing Beckman Coulter reagents (IM2030, B89463) as previously described.[26] The assay's measurement range extended from 0.31 to approximately 1500 pg/mL. High specificity was confirmed by minimal or absent cross-reactivity with structurally related peptides. DHEAS concentrations were assessed by chemiluminescent microparticle immunoassay using the ARCHITECT DHEAS kit by Abbott (8K27), with an analytical range of 3.0 μg/dL to 1500.0 μg/dL. The assay was designed to exhibit ≤10% cross-reactivity with structurally similar steroid compounds.

Echocardiography

Transthoracic echocardiography was performed by trained, blinded sonographers (S.M. and F.M.) using the same ultrasound machine and scanning protocol (Aplio CV Toshiba with a 3 MHz transducer in 2D, Doppler, colour-Doppler, and Tissue Doppler Imaging. Cardiac structure was assessed by measuring left atrial volume, left ventricle end-diastolic diameter (LV-EDD), interventricular septal thickness (IVST), and posterior wall thickness (PWT) at end-diastole. Left ventricular mass was then calculated by the corrected American Society of Echocardiography method: $LVM = 0.8\ (1.04\ ((LV\text{-}EDD + IVST + PWT)^3 - (LV\text{-}EDD)^3) + 0.6)$ and was later indexed by body surface area (LVMi). Left ventricle hypertrophy (LVH) was defined by LVMi measurements greater than 102 g/m^2 and 88 g/m^2 in male and female patients, respectively.[27] Normal reference limits for IVST, PWT, and LV-EDD were defined according to chamber quantification guidelines, which specify sex-adjusted normal ranges of 6-10 mm (men) and 6-9 mm (women) for both IVST and PWT, and 42-58 mm (men) and 38-52 mm (women) for LV-EDD.[27] Relative wall thickness (RWT) was calculated as (IVST + PWT)/LV-EDD; in patients with LVH, an RWT value greater than 0.42 suggested concentric hypertrophy, whereas values lower than 0.42 reflected eccentric hypertrophy.[27] Left ventricle systolic function was assessed via left ventricular ejection fraction (LVEF), determined by manual tracing using Simpson's biplane method; LV-EF was considered normal at ≥52% in men and ≥54% in women, following chamber quantification standards.[27] Tricuspid annular peak systolic excursion (TAPSE) was used to assess right ventricle systolic activity, with values <17 being suggestive of right ventricular systolic dysfunction.[27] Diastolic function was evaluated by pulse-wave tissue Doppler imaging, using the following parameters: Left atrial volume indexed to body surface area (which was defined as increased by values >35 mL/m^2),[28] the ratio of early (E) to late (A) mitral inflow velocity, early relaxation velocity (e') averaged from the septal, and lateral mitral annulus, the ratio of E/e' as an indicator of left ventricle filling pressures. Normal left ventricular filling pressures were defined by an average E/e′<8, while values >14 were considered indicative of elevated pressures, in accordance with recent recommendations.[29] A normal mitral inflow pattern was defined by an E/A ratio between 0.8 and 2.0, whereas an E/A < 0.8 with E < 50 cm/s indicated impaired relaxation and an E/A ≥ 2.0 indicated restrictive filling.[29] Left ventricle diastolic dysfunction was classified as grade I (mild), II (moderate), or III (severe) based on current recommendations.

Statistical analysis

The distribution of continuous variables was tested with the Shapiro–Wilk test; linearity was established by visual inspection of a scatterplot. Categorical variables were expressed as percentages and frequencies; continuous variables were reported as mean and standard deviation or median and interquartile range (25th–75th percentile), according to the data distribution. For group comparisons, unpaired Student's *T*-test, Mann–Whitney, and χ^2 tests were used, as appropriate. Continuous variables were compared between groups via an analysis of covariance (ANCOVA), including the presence or absence of autonomous cortisol secretion and unilateral adrenalectomy as fixed effects, and factors known to affect cardiovascular status (age, smoking, body mass index, diabetes mellitus, dyslipidaemia, hypertension) as covariates. The assumptions of the general linear model were verified prior to analysis. Independence of observations was assumed, and multicollinearity was checked using the Variance Inflation Factor, with a threshold of 5. Homogeneity of regression slopes was verified, and Bonferroni correction was applied to account for multiple comparisons. Correlations between continuous variables were analysed using Spearman's rank correlation coefficients. Linear regression analysis was performed, applying a stepwise predictor selection to identify baseline predictors of changes in cardiac parameters at the subsequent study time points. Longitudinal intra-patient changes over time were evaluated using a mixed-effects model with Restricted Maximum Likelihood estimation, accounting for within-subject correlations while managing the missing data under the Missing At Random assumption. Effect sizes were calculated for all group comparisons: Cohen's d for t-tests, partial eta-squared (η^2) for ANCOVA, and standardized β coefficients for linear regression models. Statistical significance was set at $P < .05$. *P*-values between .05 and .10 were considered to indicate a trend towards significance. All analyses were performed using SPSS, version 29 (IBM, Chicago, IL), and GraphPad Prism 10.0 software package (GraphPad Software, La Jolla, CA). Sample size was calculated at study conception; our analysis estimated a sample of 57 subjects (inflated to 68 to account for a 15% chance of dropout during the longitudinal phase) as suitably powered, based on a previous longitudinal echocardiography study performed on patients with CS before and after remission.[30]

Results

Baseline characteristics

One hundred and fifty-three consecutive patients with adrenal incidentalomas were referred to our Centre during the enrolment period. Of those, 63 were excluded due to the following: established diagnosis of overt CS ($n = 7$), bilateral adrenal lesions ($n = 21$), adrenal mass other than NAPACA ($n = 18$), previous history of myocardial infarction or unstable angina ($n = 7$), and medications affecting cortisol secretion or metabolism ($n = 10$). A

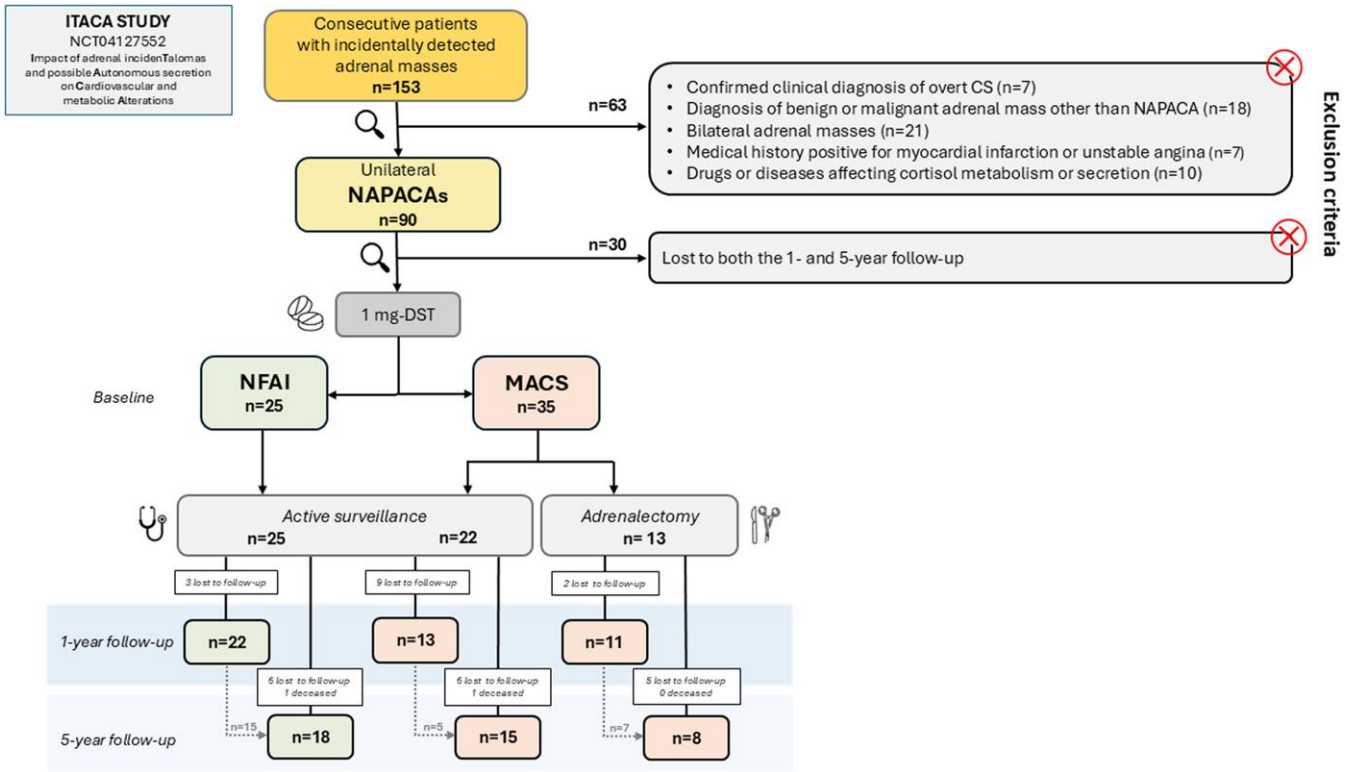

Figure 2 Flow-chart detailing the patient selection process. Abbreviations: CS = Cushing's Syndrome; NAPACA = non-aldosterone producing adrenocortical adenomas; 1mg-DST = 1 mg overnight dexamethasone suppression test; NFAI = non-functioning adrenal incidentalomas; MACS = mild autonomous cortisol secretion.

total of 90 eligible patients were screened for cortisol excess and stratified in NFAI and MACS. Thirty patients were either lost to follow-up or refused to perform the allocated procedures and were therefore excluded from the final analysis. Sixty patients (35 MACS, 25 NFAI) were included. The patient selection process is detailed in Figure 2. The baseline characteristics of the 2 groups are shown in Table 1. Patients with MACS and NFAI were comparable in age, sex distribution, and prevalence of the main cardiometabolic comorbidities. As expected, patients in the MACS group presented with larger maximum lesion diameter ($P = .001$), higher post-DST serum cortisol levels ($P < .001$), and lower ACTH and DHEAS levels ($P = .006$ for both). After adjusting for age, smoking, and the main cardiometabolic comorbidities (hypertension, diabetes, and dyslipidemia), baseline cardiac parameters revealed higher LVMi ($P = .011$), IVST ($0 = 0.050$), PWT ($P = .032$), and RWT ($P = .050$) in patients with MACS, who also showed a higher prevalence of LVH ($P = .013$) and diastolic dysfunction ($P = .050$), compared to the NFAI group. In the whole cohort, baseline post-DST cortisol levels were positively, albeit weakly, associated with baseline IVST ($r = 0.256$, $P = .027$) and PWT ($r = 0.338$, $P = .006$), while showing a trend towards a positive correlation with LVMi ($r = 0.205$, $P = .080$). Baseline ACTH levels inversely, though again weakly, correlated with baseline LVMi ($r = -0.237$, $P = .023$), RWT ($r = -0.261$, $P = .031$), ISVT ($r = -0.266$, $P = .027$), and PWT ($r = -0.337$, $P = .009$). Among the 35 patients with MACS, 13 underwent ADRX, while 22 were managed with AS. Patients undergoing ADRX had higher UFC levels (0.99 ± 0.43 vs $0.57 \pm 0.28 \times$ULN, $P = .005$) and a larger lesion diameter [36 (30.5-41.5) vs 24 (13.0-28.0) mm, $P < .001$]. Patients managed with AS showed a trend towards a higher prevalence of hypertension ($P = .061$) and a higher median number of antihypertensive drugs ($P = .022$); conversely, patients undergoing ADRX showed a trend towards a higher rate of uncontrolled dyslipidaemia ($P = .061$). Nevertheless, baseline cardiac parameters were comparable, with a trend towards lower IVST in the ADRX group [9.8 (8.7-10.9) vs. 11.0 (10.1-11.8) mm, $P = .098$] (Table 2). Nine ADRX patients developed transient postoperative adrenal insufficiency requiring replacement therapy. Full axis recovery occurred within 18 months in all but one patient. No significant differences in cardiac parameters were observed between patients with or without postoperative adrenal insufficiency (data not shown).

Natural history of cardio-metabolic features in NAPACAs

Throughout the 5-year study timeframe, 3 patients with MACS (13.0%) experienced a MACE compared to one patient with NFAI (5.6%, $P = .423$). Similarly, the rate of minor cardiac events was higher in MACS (21.7%) compared to NFAI (11.1%), although non-significantly ($P = .369$). Event types are summarized in Table 3. No significant differences were observed when stratifying patients with MACS by treatment strategy: at the 5-year timepoint, 2 patients (13.3%) managed with AS developed major cardiac events (1 unstable angina, 1 congestive heart failure, respectively) and 4 (26.6%) developed minor events (2 atrial fibrillation, 2 deep venous thrombosis). Conversely, 1 patient (12.5%) who underwent ADRX developed acute myocardial infarction and

Table 1 Baseline characteristics and comorbidities of the whole cohort and after stratifying for 1 mg dexamethasone suppression test.

	MACS ($n = 35$)	NFAI ($n = 25$)	
Clinical parameters			
Sex (M/F)	12/23	10/15	0.651
Age, years	62.8 ± 8.0	63.9 ± 9.0	0.626
BMI, kg/m^2	27.3 (23.8-30.8)	24.2 (23.3-26.9)	0.127
Previous MACEs, *n* (%)	2 (5.7)	0 (0.0)	0.087
Previous minor cardiac events, *n* (%)	0 (0.0)	1 (4.0)	0.393
Obesity, *n* (%)	8 (22.9)	4 (16.0)	0.513
Hypertension, *n* (%)	23 (65.7)	17 (68.0)	0.853
Patients treated ≥ 3 anti-hypertensive drugs, *n* (%)	5 (14.2)	2 (8.0)	0.455
Duration of hypertension, years	11.4 ± 9.2	7.7 ± 7.3	0.201
ACE-inhibitors, *n* (%)	7 (20.0)	6 (24.0)	0.524
Sartans, *n* (%)	10 (28.6)	4 (16.0)	0.375
Diuretics, *n* (%)	7 (20.0)	4 (16.0)	0.866
Alpha-blockers, *n* (%)	3 (8.5)	1 (4.0)	0.562
Beta-blockers, *n* (%)	7 (20.0)	6 (24.0)	0.524
Calcium-antagonists, *n* (%)	8 (22.8)	6 (24.0)	0.706
Diabetes mellitus, *n* (%)	3 (8.6)	0 (0.0)	0.133
Dyslipidemia, *n* (%)	21 (60.0)	14 (56.0)	0.757
Active smoking, *n* (%)	17 (48.6)	10 (40.0)	0.511
Maximum diameter, mm	29.0 (20.0-36.7)	19.0 (11.7-25.5)	**0.001**
1mg-DST cortisol, nmol/L	79.5 (66.2-97.3)	35.2 (29.7-42.9)	**<0.001**
UFC xULN	0.77 ± 0.41	0.75 ± 0.32	0.824
ACTH, pg/mL	15.0 (11.2-18.7)	18.9 (14.8-34.0)	**0.006**
DHEAS, mcg/dL	50.8 (27.0-81.9)	83.6 (59.8-124.3)	**0.006**
Echocardiographic parameters			
Cardiac remodelling indexes			
Left ventricle mass index, g/m^2	83.9 (77.6-90.2)	70.9 (63.7-78.2)	**0.011**
Inter-ventricle sept thickness, mm	10.6 (10.0-11.1)	9.7 (9.1-10.4)	**0.050**
Posterior wall thickness, mm	9.1 (8.5-9.7)	8.1 (7.5-8.8)	**0.032**
Left ventricle end-diastole diameter, mm	44.2 (42.7-45.8)	45.2 (43.4-47.0)	0.420
Relative wall thickness	0.43 (0.41-0.46)	0.39 (0.36-0.42)	**0.050**
Left ventricle hypertrophy, *n* (%)	9 (25.7)	1 (4.0)	**0.013**
Concentric hypertrophy, *n*	6/9	1/1	
Eccentric hypertrophy, *n*	3/9	0/1	
Diastolic function parameters			
E/A ratio	0.96 (0.81-1.10)	0.89 (0.73-1.05)	0.583
Left atrium volume index, mL/m^2	24.6 (21.1-28.2)	23.0 (19.4-26.6)	0.526
Average E/e' ratio	8.4 (7.5-9.2)	7.8 (7.0-8.6)	0.369
Diastolic dysfunction, *n* (%)	19 (54.2)	9 (36.0)	**0.050**
Systolic function parameters			
TAPSE	20.4 (19.2-21.7)	22.3 (21.1-23.6)	**0.039**
Left ventricle ejection fraction, %	63.8 (61.8-65.7)	61.5 (59.2-63.7)	0.134

Continuous data are expressed as mean ± SD or median (interquartile range), as appropriate. Categorical variables are expressed as number and frequency (%). Echocardiographic parameters are compared between groups via an ANCOVA model with mild autonomous cortisol secretion (MACS) as a fixed factor and the following as covariates: age, BMI, hypertension, diabetes, dyslipidaemia, and current and/or previous smoking. Values represent the estimated marginal means (lower-upper limit of 95% CI). Significant *P*-values are highlighted in bold.
Abbreviations: MACS, mild autonomous cortisol secretion; NFAI, nonfunctioning adrenal incidentaloma; M, male; F, female; BMI, body mass index; MACE, major adverse cardiovascular events; ACE, angiotensin-converting enzyme; 1 mg-DST, serum cortisol following 1 mg dexamethasone suppression test; UFC, 24-h urinary free cortisol; ACTH, adrenocorticotropic hormone, DHEAS, dehydroepiandrosterone sulphate; E/A, early to late ventricular filling velocity, e′=early diastolic mitral annular velocity, TAPSE, tricuspid annular plane systolic excursion.

1 (12.5%) developed atrial fibrillation. The differences in the incidence of major and minor events between the 2 groups were not statistically significant ($P = .935$ and $P = .429$, respectively). Moreover, the 3 groups did not show any significant differences in the evolution of the main cardiometabolic comorbidities, including arterial hypertension, T2DM, and dyslipidemia, aside from a higher prevalence of obesity development in patients with MACS managed with AS compared to those with NFAI ($P = .008$) (Figure 3). To evaluate whether defining worsening solely by treatment intensification might have led to misclassification, we

Table 2 Baseline characteristics and comorbidities in patients with MACS after stratifying for treatment approach.

	AS ($n = 22$)	ADRX ($n = 13$)	*P* value
Clinical parameters			
Sex (M/F)	8/14	4/9	.732
Age, years	63.9 ± 8.9	60.9 ± 6.3	.291
BMI, kg/m^2	27.2 (25.65-29.5)	27.4 (23.31-33.7)	.880
Obesity, *n* (%)	4 (18.2)	4 (30.8)	.392
Hypertension, *n* (%)	17 (77.3)	6 (46.2)	.061
Controlled hypertension, *n* (%)	12/17 (70.5%)	5/6 (83.3%)	.342
Antihypertensive drugs, *n*	2.0 (0.0-3.0)	1.0 (0.0-2.0)	**.022**
Diabetes mellitus, *n* (%)	2 (9.1)	1 (7.7)	.866
Controlled diabetes, *n* (%)	1/2 (50%)	0/1 (0%)	—
Antidiabetic drugs, *n*	1.0 (1.0-2.0)	1.0 (1.0-1.0)	.980
Dyslipidaemia, *n* (%)	14 (63.6)	7 (53.8)	.568
Controlled dyslipidaemia, *n* (%)	7/14 (50%)	2/7 (28.5%)	.061
Lipid-lowering drugs, *n*	1.0 (1.0-1.0)	1.0 (1.0-2.0)	.850
Osteoporosis/osteopenia, *n* (%)	6 (27.3%)/10 (45.5%)	3 (23.1%)/9 (69.2%)	.290
Cortisol-related comorbidities, *n*	2.0 (1.5-3.0)	2.5 (2.0-3.0)	.749
Active smoking, *n* (%)	11 (50.0)	6 (46.2)	.826
Maximum diameter, mm	24.0 (13.0-28.0)	36.0 (30.5-41.5)	**<.001**
1mg-DST cortisol, nmol/L	79.5 (65.6-89.7)	84.5 (66.2-100.0)	.862
UFC xULN	0.57 ± 0.28	0.99 ± 0.43	**.005**
ACTH, pg/mL	15.4 (11.2-21.0)	14.7 (11.1-17.2)	.573
DHEAS, mcg/dL	53.2 (31.3-92.5)	37.5 (19.6-72.7)	.170
Echocardiographic parameters			
Cardiac remodelling indexes			
Left ventricle mass index, g/m^2	81.4 (71.4-91.3)	82.9 (69.5-96.3)	.856
Inter-ventricle sept thickness, mm	11.0 (10.1-11.8)	9.8 (8.7-10.9)	.098
Posterior wall thickness, mm	9.1 (8.3-9.9)	8.8 (7.6-10.0)	.711
Left ventricle end-diastole diameter, mm	43.8 (41.8-45.8)	44.9 (42.2-47.7)	.511
Relative wall thickness	0.44 (0.41-0.49)	0.41 (0.36-0.46)	.282
Left ventricle hypertrophy, *n* (%)	5 (22.7)	4 (30.8)	.258
Diastolic function parameters			
E/A ratio	0.97 (0.74-1.21)	1.00 (0.64-1.36)	.892
Left atrium volume index, mL/m^2	24.6 (19.8-29.4)	26.5 (16.4-36.7)	.732
Average E/e' ratio	8.2 (7.0-9.4)	9.5 (7.6-11.4)	.263
Diastolic dysfunction, *n* (%)	10 (45.4)	9 (69.2)	.213
Systolic function parameters			
TAPSE	20.2 (18.6-21.9)	21.0 (18.4-23.6)	.637
Left ventricle ejection fraction, %	63.2 (60.9-65.5)	64.8 (61.7-67.9)	.404

Continuous data are expressed as mean ± SD or median (interquartile range), as appropriate. Categorical variables are expressed as number and frequency (%). Echocardiographic parameters are compared between groups via an ANCOVA model with unilateral adrenalectomy as a fixed factor and the following as covariates: age, BMI, hypertension, diabetes, dyslipidaemia, and smoking. Values represent the estimated marginal means (lower-upper limit of 95% CI). Significant *P*-values are highlighted in bold.
Abbreviations: MACS, mild autonomous cortisol secretion; AS, patients with MACS treated with active surveillance, ADRX, patients with MACS treated with unilateral adrenalectomy; M, male; F, female; BMI, body mass index; 1 mg-DST, serum cortisol following 1 mg dexamethasone suppression test; UFC, 24-h urinary free cortisol; ACTH, adrenocorticotropic hormone, DHEAS, dehydroepiandrosterone sulphate; E/A, early to late ventricular filling velocity, e′=early diastolic mitral annular velocity, TAPSE, tricuspid annular plane systolic excursion.

analysed longitudinal cardiometabolic parameters in patients whose therapy remained unchanged. No significant differences were observed in systolic (132 ± 14 vs 130 ± 15, $P = .557$) or diastolic (82 ± 11 vs 80 ± 9, $P = .216$) blood pressure levels, nor between HbA1c (5.6 ± 0.3 vs 5.5 ± 0.3, $P = .230$), glucose levels (94 ± 12 vs 90 ± 14, $P = .085$), or between total cholesterol (185 ± 42 vs 178 ± 27, $P = .431$), HDL cholesterol (55 ± 14 vs 60 ± 16, $P = .073$), LDL cholesterol (104 ± 34 vs 101 ± 22, $P = .681$) and triglyceride (116 ± 38 vs 101 ± 31, $P = .093$) levels.

Longitudinal echocardiography analysis

Cardiac remodelling indexes

A linear mixed-effects model revealed a significant time-by-subgroup interaction for LVMi ($P = .004$). At 1 year, LVMi diverged sharply: ADRX showed a fall of −14.8 g/m^2 (95% CI −28.7 to −0.9; $P = .036$), whereas NFAI and AS increased by +12.0 g/m^2 (2.6 to 21.5; $P = .012$) and +13.7 g/m^2 (−1.3 to 26.1; $P = .030$), respectively. By 5 years, NFAI exhibited further hypertrophy (+22.4 g/m^2, 12.3 to

Table 3 Cardiometabolic outcomes over a 5-year follow-up in patients with NAPACAs.

	NFAI (18)	AS ($n = 15$)	ADRX ($n = 8$)	*P* value
Major adverse cardiac events, *n* (%)	1 (5.6) Stroke (1)	2 (13.3) Unstable angina (1), congestive heart failure (1)	1 (12.5) Acute myocardial infarction (1)	.577
Minor adverse cardiac events, *n* (%)	2 (11.1) Atrial fibrillation (1) Retinal infarction (1)	4 (26.6) Atrial fibrillation (2), Deep venous thrombosis (2)	1 (12.5) Atrial fibrillation (1)	.722

Incidence rates of major and minor adverse cardiac events over the 5-year study timeframe in patients with NAPACAs, stratified according to tumour subtype and treatment approach. Abbreviations: NFAI, non-functioning adrenal incidentalomas; AS, adrenal tumours with mild autonomous cortisol secretion managed with active surveillance; ADRX, adrenal tumours with mild autonomous cortisol secretion managed with unilateral adrenalectomy.

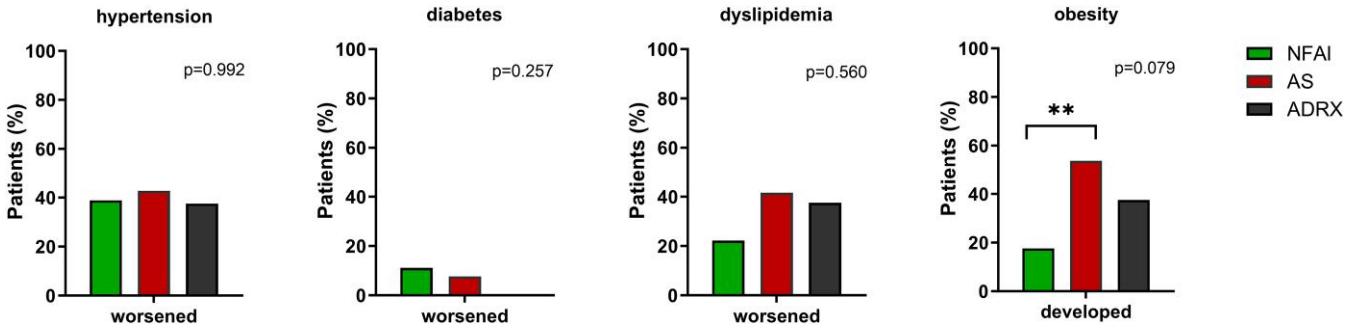

Figure 3 Trends of cardiometabolic comorbidities over a 5-year follow-up in patients with NAPACAs. The evolution of cardiometabolic comorbidities over the 5-year study timeframe, stratified according to tumour subtype and treatment approach. Clinical worsening was defined by the *ex-novo* development of the specific comorbidity, or by the requirement of treatment intensification to control said comorbidity. Abbreviations: NFAI, non-functioning adrenal incidentalomas; AS, adrenal tumours with mild autonomous cortisol secretion managed with active surveillance; ADRX, adrenal tumours with mild autonomous cortisol secretion managed with unilateral adrenalectomy. The *P* values within each graph refer to the overall χ^2 test. Between groups comparison is shown only for obesity which approached significance at the χ^2 test; $^{**}P < .01$.

32.5; $P < .001$), while AS plateaued (+7.5 g/m^2, −4.2 to 18.1; $P = .218$). The initial regression in ADRX was no longer evident (+4.8 g m^{-2}, −10.4 to 20.0; $P = .528$). The between-group contrast at 5 years remained sizeable (NFAI vs. ADRX differed by roughly +18.1 g/m^2, whereas AS sat in between), but only the NFAI trajectory reached statistical significance across time. Despite the absence of time-by-subgroup interaction for ISVT ($P = .615$), post-hoc within-group contrasts revealed a small thickening in the NFAI group (+1.3 mm, 95% CI −0.2 to 2.3; $P = .020$) at year 5. Similarly, LV-EDD showed no overall interaction effect ($P = .355$); however, ADRX patients experienced an early, transient reduction at 1 year (−2.7 mm, 95% CI −5.4 to −0.06; $P = .045$) that was no longer evident at 5 years. Longitudinal trends in cardiac structure parameters are shown in Figure 4 and Table 4. At 1-year post-adrenalectomy, markers of greater cortisol autonomy were associated with more pronounced structural improvement. Specifically, lower baseline ACTH levels correlated with greater reductions in LVMi (ρ=0.745, $P = .013$) and PWT (ρ=0.644, $P = .044$), and higher post 1mg-DST cortisol values were similarly associated with greater reductions in LVMi (ρ=−0.353, $P = .022$). No significant associations were found between baseline hormonal parameters and echocardiographic changes at the 5-year follow-up. Despite these short-term variations, cardiac measurements remained within physiological limits throughout follow-up (Figure 4). Consistently, the incidence of newly developing LVH did not differ significantly among the groups throughout follow-up. After 5 years, the prevalence of LVH was similar across groups (8/18 in NFAI, 6/15 in AS, and 3/8 in ADRX, $P = .937$). New-onset concentric LVH occurred in 14 patients (7 NFAI, 6 AS, 1 ADRX, $P = .518$), while only one ADRX patient showed regression of LVH.

DST dynamics differed substantially between groups. NFAI patients showed consistently low DST values throughout follow-up (baseline 36.6 ± 8.3; 1 year 33.9 ± 11.3; 5 years 39.3 ± 10.5 nmol/L). In MACS, the AS group exhibited overall stability (baseline 83.6 ± 26.7; 1 year 90.5 ± 19.5; 5 years 88.1 ± 34.4 nmol/L), whereas in ADRX patients, albeit DST was not routinely performed, patients undergoing DST showed marked and sustained post-operative suppression ($n = 4$: baseline 83.3 ± 25.6; 1 year 41.0 ± 8.4; 5 year 35.6 ± 20.2 nmol/L). No DST rebound was observed, and DST changes did not parallel longitudinal variations in LVMi or other markers of cardiac remodelling.

Cardiac function parameters

The progression of the main parameters of systolic and diastolic function is shown in Figure 5 and Table 4. LVEF fell homogeneously across the cohort of −4.4% (95% CI −7.8 to −1.0; $P = .010$) in NFAI, −6.2% (−9.9 to −2.5; $P = .001$) in AS and −8.7% (−14.0 to −3.4; $P = .001$) in ADRX over the 5-year interval (time-by-subgroup interaction $P = .657$). No change was detectable at the 1-year mark. For TAPSE the interaction term approached significance ($P = .061$). Within-group contrasts showed an increase only in the AS group at one year (+3.7 mm; −1.6 to 5.8, $P = .004$) which maintained at 5 years

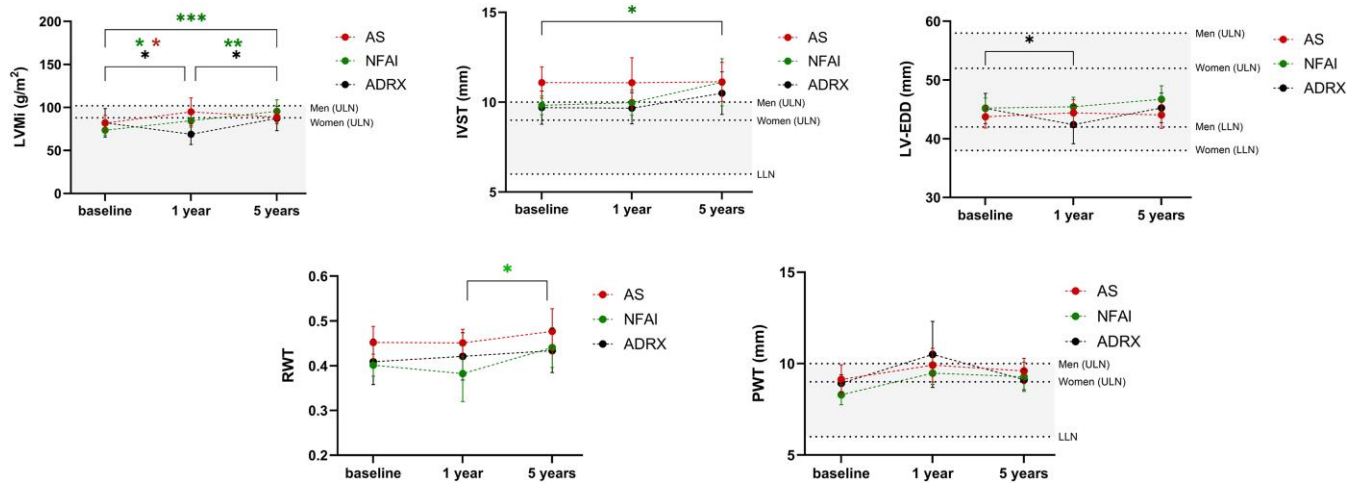

Figure 4 Trends of remodelling cardiac indexes in patients with adrenal incidentalomas over a 5-year follow-up. The black dashed line represents patients belonging to the ADRX group, the red dashed line represents patients with MACS under AS, and the green dashed line shows the patients with NFAI. Abbreviations: NFAI, non-functioning adrenal incidentalomas, AS, adrenal tumours with mild autonomous cortisol secretion managed with active surveillance, ADRX, adrenal tumours with mild autonomous cortisol secretion managed with unilateral adrenalectomy. LVMi, left ventricle mass index. IVST, interventricular sept thickness. LV-EDD, left ventricle end-diastole diameter. PWT, posterior wall thickness. RWT, relative wall thickness. ULN, upper limit of normal. LLN, lower limit of normal. Greyed areas represent normal intervals.

(+3.6 mm; 1.8 to 5.4, $P = .001$). The E/A ratio likewise showed no interaction ($P = .626$) but did display a modest uniform decline over time. At 5 years, the reductions were −0.1 (95% CI −0.3 to −0.01; $P = .035$) in NFAI and −0.2 (−0.4 to −0.05; $P = .012$) in AS, whereas the change in ADRX (−0.02, −0.6 to 0.1) was not significant. There was no change in left atrial volume and E/e′.

Discussion

This prospective clinical trial is the first study to serially map cardiac geometry and performance over 5 years in patients with adrenal incidentalomas diagnosed with MACS or NFAI, while comparing active surveillance and unilateral adrenalectomy. Surgery induced early improvement in LVMi at one year, but this was not sustained at 5 years, whereas surveillance plateaued and NFAI progressed. All groups showed a modest, likely age-related, decline in LVEF; only surveillance patients displayed a rise in TAPSE, an exploratory finding that warrants confirmation. At baseline, MACS already showed greater structural burden (higher LVMi, thicker septum, greater diastolic dysfunction) despite comparable cardiometabolic profiles, reinforcing that even mild cortisol excess promotes adverse cardiac remodelling.[12,13] Clinically, our findings indicate that echocardiography is useful to document short-term structural changes after adrenalectomy, but its long-term prognostic impact remains to be clarified.

Cardiac alterations in MACS mirror those observed in overt CS.[31-35] While hypertension, diabetes, and dyslipidaemia contribute, cortisol appears to independently drive remodelling,[13,14] as confirmed from baseline inter-group differences which persisted after adjustment for comorbidities and correlated with cortisol levels.[12,14,35] Successful treatment of CS has been shown to reduce left ventricular wall thickness,[35] as well as improve systolic and diastolic function,[30] in some but not all published series.[14,33] Nonetheless, evidence regarding the reversibility of cardiac alterations in patients with MACS following treatment is still lacking. In our cohort, adrenalectomy induced an 18% LVMi reduction at 12 months, contrasting with mass increase in AS and NFAI of about 17%, but this advantage waned by year 5 while NFAI showed progressive hyperthrophy. These findings suggest hypercortisolism removal confers an early benefit, most evident in patients with more severe MACS but durability is limited, whereas “non-functioning” lesions follow a slower, yet relentless, hypertrophic course. It should be noted, however, that despite the observed longitudinal changes, cardiac remodelling generally remained within the physiological range across all groups, with no significant differences in the onset of LVH. This suggests that the observed statistical variations might not necessarily translate into clinically relevant structural deterioration. TAPSE improvement in AS may reflect more aggressive cardiovascular management or non-muscular influences such as volume status, underscoring the need for confirmation with more reproducible techniques, including cardiac magnetic resonance imaging.

Overall, patients with MACS (both AS and ADRX) showed a gradual decline in systolic and diastolic function, but relative stability in cardiac morphology, whereas NFAI exhibited progressive functional (reduced LVEF and altered E/A ratio) and structural (increased LVMi and IVST) deterioration. On one hand, this could be attributable to the limited sample size, especially considering the ADRX group. However, it is important to note that the unequal size of the treatment subgroups reflects real-world clinical eligibility rather than methodological imbalance, as only a subset of MACS patients met surgical criteria during the recruitment window. While this limits the precision of subgroup comparisons, the longitudinal mixed-effects approach preserves the validity of overall trajectory estimates. Similarly, the modest differences in baseline comorbidities between patients with MACS managed conservatively and surgically likely reflect the fact that treatment allocation was not based solely on comorbidity burden. As per the prespecified clinical algorithm and prevailing guidelines,

Table 4 Change in cardiac parameters across the 3 patient groups over a 5-year follow-up.

Variable	Groups	Δ (baseline-1year)	*P* value	Δ (baseline-5years)	*P* value	Time-by-subgroup *P* value
Cardiac remodelling parameters						
LVMi (g/m^2)	NFAI	+12.0 (2.6 to 21.5)	**.012**	+22.4 (12.3 to 32.5)	**<.001**	
	AS	+ 13.7 (+1.3 to 26.1)	**.030**	+ 7.5 (−4.2 to 18.1)	.218	**.004**
	ADRX	−14.8 (−28.7 to −0.9)	**.036**	+ 4.8 (−10.4 to 20.0)	.528	
PWT (mm)	NFAI	+1.2 (0.1 to 2.5)	.070	+1.0 (0.4 to 2.4)	.154	
	AS	+ 0.9 (−0.7 to 2.5)	.281	+ 0.5 (−1.0 to 2.0)	.530	.838
	ADRX	+ 1.4 (0.5 to 3.2)	.139	−0.1 (−2.2 to 1.9)	.912	
ISVT (mm)	NFAI	+0.1 (−0.3 to 0.6)	.491	+1.3 (−0.2 to 2.3)	**.020**	
	AS	+ 0.01 (−0.6 to 0.7)	.982	+ 0.04 (−1.2 to 1.3)	.942	.615
	ADRX	−0.03 (−1.1 to 1.0)	.946	+ 0.8 (−0.4 to 2.0)	.164	
LV-EDD (mm)	NFAI	+0.4 (−1.4 to 2.2)	.665	+1.5 (−0.4 to 3.6)	.119	
	AS	+ 0.1 (−2.2 to 2.4)	.920	+ 0.5 (−1.6 to 2.7)	.622	.355
	ADRX	−2.7 (−5.4 to −0.06)	**.045**	+ 0.4 (−2.6 to 3.3)	.796	
RWT	NFAI	−0.01 (−0.06 to 0.03)	.467	+0.04 (−0.01 to 0.1)	.144	
	AS	−0.01 (−0.06 to 0.06)	.978	+ 0.02 (−0.03 to 0.1)	.404	.894
	ADRX	+ 0.01 (−0.06 to 0.08)	.741	+ 0.02 (−0.05 to 0.1)	.528	
Systolic function parameters						
LV-EF (%)	NFAI	−0.2 (−3.4 to 2.9)	.868	−4.4 (−7.8 to −1.0)	**.010**	
	AS	−1.4 (−5.3 to 2.6)	.487	−6.2 (−9.9 to −2.5)	**.001**	.657
	ADRX	−1.8 (−6.2 to 2.6)	.420	−8.7 (−14.0 to −3.4)	**.001**	
TAPSE (mm)	NFAI	0.07 (−1.5 to 1.6)	.921	+1.0 (−0.5 to 2.7)	.186	
	AS	+ 3.7 (−1.6 to 5.8)	**.004**	+ 3.6 (1.8 to 5.4)	**.001**	.061
	ADRX	+ 0.7 (−1.6 to 3.1)	.535	+ 2.7 (−0.02 to 5.4)	.117	
Diastolic function parameters						
LAVI (mL/m^2)	NFAI	−0.3 (−4.3 to 3.5)	.848	+2.7 (−1.1 to 6.7)	.166	
	AS	+ 1.9 (−3.0 to 6.8)	.437	+ 3.1 (−1.3 to 7.6)	.167	.905
	ADRX	+ 0.8 (−6.3 to 7.8)	.832	+ 0.8 (−7.5 to 9.2)	.839	
E/A	NFAI	+0.06 (−0.04 to 0.1)	.3445	−0.1 (0.3 to 0.01)	**.035**	
	AS	−0.01 (−0.2 to 0.1)	.9635	−0.2 (0.4 to −0.05)	**.012**	.626
	ADRX	−0.09 (−0.3 to 0.1)	.4165	−0.2 (−0.6 to 0.1)	.106	
Average E/e’	NFAI	−1.1 (−2.2 to 0.03)	.060	0.3 (−1.2 to 1.9)	.856	
	AS	+1.5 (−0.3.to 3.5)	.104	−0.4 (−2.4 to 1.5)	.741	.501
	ADRX	+0.13 (−3.1 to 3.4)	.991	−2.1 (−36.7 to 32.5)	.655	

2-way analysis of variance (ANOVA) detailing the interaction of time and patient subgroup in our cohort. Values are expressed as least squares means (lower-upper limit of 95% confidence interval). Significant *P*-values are highlighted in bold. Abbreviations: NFAI, non-functioning adrenal incidentalomas; AS, patients with mild autonomous cortisol secretion managed with active surveillance; ADRX, patients with mild autonomous cortisol secretion managed with unilateral adrenalectomy; LVMi, left ventricle mass index; PWT, posterior wall thickness; IVST, interventricular sept thickness, LV-EDD, left ventricle end-diastole diameter; RWT, relative wall thickness; LV-EF, left ventricle ejection fraction; TAPSE, tricuspid annular peak systolic excursion; LAVI, left atrium volume index; E/A, early to late ventricular filling velocities. e′, early diastolic mitral annular velocity.

surgical procedure eligibility was principally determined by tumour size, radiological features, and biochemical severity, parameters that were indeed more pronounced in the ADRX group.

Several factors may explain why cardiac hypertrophy progressed in NFAI but remained broadly stable in MACS. One possibility is that MACS patients enter the disease trajectory with an earlier and more pronounced degree of concentric remodelling, so that mid-term changes naturally reach a plateau, whereas NFAI patients, whose baseline cardiac morphology is closer to normal, may still be undergoing age-related structural progression. Additionally, MACS patients typically undergo closer endocrine and cardiometabolic follow-up, with earlier optimization of blood pressure, glucose, and lipid profiles. This more intensive management may have mitigated the progression of LV hypertrophy despite persistent low-grade cortisol exposure. By contrast, NFAI patients are generally discharged from follow-up under current guidelines, and age-related cardiovascular worsening may be more likely to go unaddressed Moreover, growing evidence suggests that a proportion of non-functioning adenomas might exhibit subtle, cyclical or stress-related steroidogenic activity.[36,37] Even minimal fluctuations in cortisol secretion might exert a cumulative cardiometabolic burden,[36,38-42] reinforcing the concept of cortisol secretion as a continuum rather than a binary state.[42] Taken together, differing baseline remodelling stage, differences in follow-up intensity, and potential low-grade steroidogenic activity in NFAI, may all account for the divergent long-term trajectories observed in our cohort.

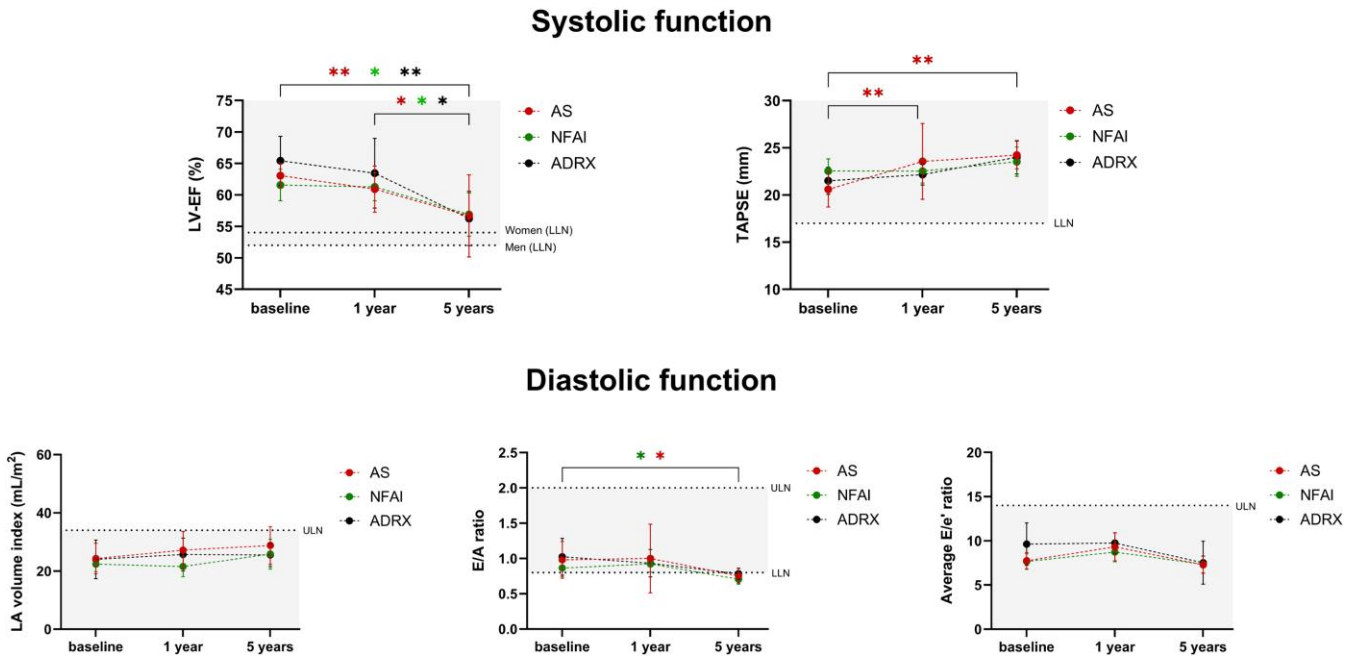

Figure 5 Trends of cardiac function indexes in patients with adrenal incidentalomas over a 5-year follow-up. The black dashed line represents the trend in systolic and diastolic function parameters in the ADRX group, the red dashed line represents the MACS group, and the green dashed line shows the trends in the NFAI group. Abbreviations: NFAI, non-functioning adrenal incidentalomas, AS, adrenal tumours with mild autonomous cortisol secretion managed with active surveillance, ADRX, adrenal tumours with mild autonomous cortisol secretion managed with unilateral adrenalectomy, LVEF, left ventricular ejection fraction, TAPSE, tricuspid annular peak systolic excursion. LAVI, left atrium volume index. E/A, early to late ventricular filling velocities. e′, early diastolic mitral annular velocity. ULN, upper limit of normal. LLN, lower limit of normal. Greyed areas represent normal intervals.

Importantly, the transient nature of remodelling improvement after adrenalectomy in MACS does not contradict a cortisol-mediated mechanism. Rather, it mirrors what has been consistently observed in overt CS, where early postoperative regression of LVH often occurs, yet full normalization is not always achieved and residual structural or functional abnormalities may persist over time despite biochemical cure. This pattern has been documented in several prospective studies showing sustained but incomplete reversal of remodelling after treatment of overt hypercortisolism,[30,31] supporting the interpretation that cortisol excess acts as an early driver of cardiac changes, whereas long-term trajectories likely reflect additional age-related and cardiometabolic influences. However, given the limited number of operated patients, the comparisons drawn in the present should be regarded as exploratory, not allowing firm conclusion regarding differential cardiac trajectories.

Hard cardiovascular events were rare and therefore our analyses failed to reach statistical significance, but trends aligned with prior studies. Patients with MACS managed with active surveillance showed a 2-fold higher MACEs incidence than NFAI (13.3% vs 5.6%), consistent with NAPACA[43] and other cohorts reporting excess myocardial infarction, stroke, and cardiovascular mortality in MACS,[44,45] independent of risk factors.[44-47] A retrospective series also found a 3-fold higher annual event rate in MACS (3.1% vs. 1.2%), although the different cutoff to define MACS could have biased the results.[46] Importantly, cardiovascular risk correlates with cortisol levels,[44,45] with one multicenter study showing a 2.5-fold increase in overall event risk, which in turn increased 1.3-fold for every 28 nmol/L rise in post-DST cortisol.[45] We also observed a 2-fold incidence rate of minor, mainly thrombotic, events in AS, echoing our previous findings of a prothrombotic state.[11]

Prospective data on adrenalectomy and cardiovascular outcomes remain limited.[48] Meta-analyses show improvements in blood pressure and glycaemia in up to two-thirds of patients with MACS,[4,49-51] and the recent CHIRACIC trial demonstrated clear benefit in hypertensive unilateral MACS, with over half achieving remission of hypertension and nearly half reducing therapy.[52] In our cohort, however, long-term trajectory hypertension or diabetes did not differ between surgical and conservative groups. By contrast, dyslipidaemia outcomes and greater obesity incidence in non-operated MACS aligned with prior epidemiological reports,[4,50] supporting a modest lipid effect but a stronger weight signal. Although underpowered, these trends parallel larger studies, suggesting biological plausibility.[4] Importantly, while cardiometabolic risk factors evolved similarly, cardiac geometry diverged, underscoring cortisol excess itself, rather than classic risk factors, as the main driver of remodelling.

Baseline echocardiography may assist in characterizing cardiac status and identifying early signs of cortisol-related remodelling; however, its value for true risk stratification is not supported by the present data and requires further investigation. The transient LVMi regression after adrenalectomy highlights the potential of directly addressing cortisol excess, particularly in those with more severe baseline hypercortisolism. However, the loss of benefit by year 5, and lack of functional gains question long-term durability and point to the need to explore alternatives. Given the invasive and irreversible nature of unilateral adrenalectomy, future studies could compare surgical, medical and conservative strategies in terms of long-term cardiac and cardiometabolic

outcomes in patients with mild hypercortisolism. In this context, medical therapy with steroidogenesis inhibitors or glucocorticoid receptor antagonists, though not yet guideline-endorsed, is increasingly proposed for mild hypercortisolism,[26,53-59] especially in bilateral disease or when surgery is contraindicated,[49] with promising effects on blood pressure, insulin resistance, and other cardiometabolic parameters.[55-59] Nevertheless, our study was not designed to evaluate medical treatments and cannot inform therapeutic recommendations.

These findings should be interpreted with caution. The cohort was modest with some loss to follow-up at 1-year and mixed-effects models assume data are missing at random. Treatment allocation was not randomized, so residual confounding is possible. Serum dexamethasone was not measured, which may marginally affect DST interpretation; however, recent large-scale data indicate a very low prevalence of inadequate dexamethasone absorption,[60] and all patients with borderline 1-mg DST results in our cohort confirmed their functional status on low-dose dexamethasone suppression testing, making misclassification unlikely. Because unilateral adrenalectomy is expected to normalize cortisol secretion, postoperative 1-mg DST testing is not routinely repeated and was therefore not systematically performed in our cohort, precluding a stratification based on postoperative remission status in this subgroup. Conventional 2-dimensional echocardiography cannot capture subtle fibrosis or deformation like more sensitive modalities such as cardiac magnetic resonance imaging or speckle-tracking strain[61,62]; moreover, inter-observer variability between the 2 sonographers might represent a potential methodological limitation. Comorbidity worsening was defined by treatment escalation, which may miss cases of unaddressed deterioration in blood pressure, glucose, or lipid control. Although longitudinal analyses in patients without treatment changes did not show significant parameter worsening, subtle misclassification cannot be excluded. Finally, due to the absence of a lesion-free control group, absolute age-related cardiac changes had to be inferred from historical comparators rather than a contemporaneous reference population. Nevertheless, the study has several strengths, including its prospective design, systematically conducted within a registered trial (NCT04127552), with a solid overall 5-year enrolment rate. Moreover, groups were balanced for key cardiovascular risk factors, reducing confounding factors.

In conclusion, ITACA delivers the first long-term evidence that adrenalectomy induces an early but transient regression of left-ventricular hypertrophy in MACS, with surgical and conservatively managed patients showing similar cardiac outcomes at 5 years. Active surveillance was characterized by an initial rise that subsequently plateaus, whereas NFAI showed progressive hypertrophy. Echocardiography remains valuable for documenting cardiac phenotype at diagnosis and monitoring its evolution; however, our data do not establish a prognostic or risk-stratifying role. Dedicated longitudinal studies are required to determine whether specific echocardiographic features can predict long-term cardiac outcomes or identify patients who may benefit from sustained cortisol-lowering strategies.

Authors' contributions

Dario de Alcubierre (Data curation [equal], Formal analysis [lead], Investigation [lead], Writing—original draft [lead]), Davide Ferrari (Formal analysis [supporting], Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Alessandra Tomaselli (Data curation [supporting], Investigation [supporting], Writing—review & editing [supporting]), Federica Moscucci (Data curation [supporting], Investigation [equal], Writing—review & editing [supporting]), Ilaria Bonaventura (Investigation [supporting], Writing—review & editing [equal]), Aurora Francia (Data curation [supporting], Investigation [supporting], Writing—review & editing [supporting]), Elisabetta Vozza (Investigation [supporting], Writing—review & editing [supporting]), Ilaria Lospinuso (Investigation [supporting], Writing—review & editing [supporting]), Evaristo Ettorre (Supervision [supporting], Writing—review & editing [supporting]), Valeria Hasenmajer (Writing—review & editing [supporting]), Marianna Minnetti (Investigation [equal], Writing—review & editing [supporting]), Emilia Sbardella (Investigation [supporting], Writing—review & editing [supporting]), Marta Tenuta (Writing—review & editing [supporting]), Sergio Morelli (Methodology [supporting], Writing—review & editing [supporting]), Alessandro Paganini (Investigation [lead], Methodology [equal], Writing—review & editing [supporting]), Andrea Isidori (Conceptualization [lead], Funding acquisition [equal], Supervision [equal], Validation [equal], Writing—review & editing [supporting]), and Riccardo Pofi (Data curation [supporting], Formal analysis [supporting], Investigation [supporting], Methodology [equal], Project administration [lead], Supervision [lead], Validation [equal], Writing—original draft [supporting], Writing—review & editing [lead])

Conflict of interest: A.M.I. reports grants and personal fees from Recordati HRA, Pfizer, and Gedeon. The remaining authors have nothing to disclose.

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Data availability

Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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