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Πρόγραμμα Μεταπτυχιακών Σπουδών (ΠΜΣ)

"Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική
και Κλινική Βιοπληροφορική"

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Αξιολόγηση της Αποτελεσματικότητας της Χειρουργικής Προσέγγισης στη Θεραπεία Ασθενών με Τυχαιώματα Επινεφριδίων και Ήπια Αυτόνομη Έκκριση Κορτιζόλης: Πρωτόκολλο μιας Τυχαιοποιημένης, Ελεγχόμενης Κλινικής Δοκιμής.

Assessing the Effectiveness of Surgical Approach in the Treatment of Patients with Adrenal Incidentalomas and Mild Autonomous Cortisol Secretion: A Randomized Controlled Trial Protocol.

ΜΑΝΤΑ ΑΣΠΑΣΙΑ
Ιατρός

Τριμελής Συμβουλευτική Επιτροπή:
Δοξάνη Χρυσούλα, Στεφανίδης Ιωάννης, Ζιντζαράς Ηλίας

Λάρισα, Σεπτέμβριος 2023

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PROTOCOL INFORMATION PAGE

Trial title	Assessing the Effectiveness of Surgical Approach in the Treatment of Patients with Adrenal Incidentalomas and Mild Autonomous Cortisol Secretion: A Randomized Controlled Trial
Trial identification number	XXX
Protocol version number	Protocol version 1.0
Date prepared	15 September 2023
Investigational Product	Surgical Treatment (Adrenalectomy)
Phase	Phase III
Sponsor	XXX
Study Centers	
Coordinating center	Endocrine Unit, Second Propaedeutic Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Greece
Collaborating centers	Endocrinology Departments and Surgical Departments specialized in endocrine gland surgery in Greece and countries of the European Union

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DISCLOSURE OF PRINCIPAL INVESTIGATOR

Protocol Study Title: Assessing the Effectiveness of Surgical Approach in the Treatment of Patients with Adrenal Incidentalomas and Mild Autonomous Cortisol Secretion: A Randomized Controlled Trial.

The herein protocol became known to myself by the Study Sponsor. I understand that the protocol remains as yet unpublished; I certify that all disclosed information to myself for this protocol will remain strictly confidential.

The Principal Investigator,

Print Name

Signature Date

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1. LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
AEs: Adverse Events
ACTH: Adrenocorticotropic Hormone
ALP: Alkaline phosphatase
AIs: Adrenal Incidentalomas
CRA: Clinical Research Associate
CRF: Case report form
CT: Computed tomography
CTX: C-telopeptide of type I collagen
DHEAS: Dehydroepiandrosterone sulfate
DM: Diabetes mellitus
DMC: Data Monitoring Committee
DST: Dexamethasone suppression test
DXA: Dual energy X-ray absorptiometry
ECG: Electrocardiogram
ESE: European Society of Endocrinology
FDG-PET: Positron emission tomography with [18F]2-deoxy-D-glucose
FSH: Follicle stimulating hormone
FT3: Free triiodothyronine
gGT: Gamma-glutamyl transferase
GCP: Good clinical practice
GDPR: General EU Data Protection Regulation
Hb: Hemoglobin
HbA1c: Hemoglobin A1c
Hct: Hematocrit
HDL: High-density lipoprotein
HTN: Hypertension
HUs: Hounsfield units
IB: Investigator's brochure
ICH-GCP: International Conference on Harmonization Guidelines for Good Clinical Practice
IEC: Independent Ethics Committee
IRB: Institutional Review Board
LA: Laparoscopic adrenalectomy
LDL: Low-density lipoprotein
LH: Luteinizing hormone
MACS: Mild autonomous cortisol secretion
MCH: Mean corpuscular hemoglobin
MCHC: Mean corpuscular hemoglobin concentration
MCV: Mean corpuscular volume
MRI: Magnetic resonance imaging
NTX: N-telopeptide of type I collagen

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RBC: Red blood cells
RCT: Randomized controlled trial
RDW: Red cell distribution width
RSI: Reference safety information
PACS: Possible autonomous cortisol secretion
PI: Primary investigator
PINP: Procollagen type I N-terminal propeptide
PLT: Platelets
PTH: Parathyroid hormone
SAEs: Serious adverse events
SGOT: Serum glutamic oxaloacetic transaminase
SGPT: Serum glutamic pyruvic transaminase
SHBG: Sex hormone-binding globulin
SUSAR: Suspected unexpected serious adverse reaction
TSH: Thyroid-stimulating hormone
T4: Thyroxine
WBC: White blood cells

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2. TRIAL SYNOPSIS

Full title	Assessing the Effectiveness of Surgical Approach in the Treatment of Patients with Adrenal Incidentalomas and Mild Autonomous Cortisol Secretion: A Randomized Controlled Trial
Study design	Prospective multicenter, randomized, Phase III clinical trial
Objectives	<u>Primary Objective:</u> - Major cardiovascular events: acute myocardial infarction, stroke, cardiovascular mortality <u>Secondary Objectives:</u> - Resolution of cortisol hypersecretion - Improvement in metabolic parameters (blood pressure, glucose, lipid profile, body weight) - All-cause mortality - Quality of life - Bone health parameters: bone mineral density, vertebral fractures, bone turnover markers - Adverse events related to treatment
Inclusion criteria	1. Adult patients (age ≥ 18 years) 2. Unilateral adrenal incidentaloma detected on imaging 3. Mild autonomous cortisol secretion, as defined by the latest ESE criteria as follows: a. Serum cortisol levels > 50 nmol/L or 1.8 g/dL following 1-mg overnight dexamethasone suppression test b. Absence of signs and symptoms of overt Cushing's syndrome: facial plethora, abdominal striae (especially if reddish-purple in color and > 1 cm wide), proximal myopathy, skin atrophy/easy bruising 4. Ability to provide informed consent
Exclusion criteria	1. Patients with signs and symptoms of overt hypercortisolism/Cushing's syndrome 2. Intake of medications that affect the metabolism of cortisol and dexamethasone or the release of cortisol 3. Chronic conditions, including hypogonadism, thyrotoxicosis, chronic kidney disease and liver disease, alcoholism, eating, rheumatologic or hematological disorders 4. Possible metastatic disease 5. Radiologic characteristics not compatible with adrenocortical adenoma at imaging studies

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	6. Diagnosis of pheochromocytoma or aldosteronoma 7. Non-adrenal autonomous cortisol secretion 8. Bilateral adrenal tumors 9. Contraindications for surgical intervention 10. Previous adrenal surgery 11. Inability to provide informed consent 12. Pregnant women
Treatments	Group A: Surgical intervention (adrenalectomy) Group B: Conservative management
Endpoints *Primary Endpoint* *Secondary Endpoints*	● Cardiovascular endpoint: Decrease in the occurrence of major cardiovascular events (acute myocardial infarction, stroke, cardiovascular mortality) ● Resolution of cortisol hypersecretion, as indicated by 1 mg DST from baseline to study completion ● Improvement in metabolic parameters (blood pressure, glucose, lipid profile, body weight) from baseline to study completion. These include: ○ Changes in blood pressure (systolic/diastolic/mean) ○ Changes in fasting glucose and insulin ○ Changes in HbA1c ○ Changes in total cholesterol, HDL, LDL, triglycerides ○ Changes in body weight and waist-hip ratio ● Time until the occurrence of all-cause mortality ● Changes in quality-of-life scores using the SF-36 questionnaire ● Changes in bone health parameters. These include: ○ Changes in bone mineral density, as measured by Dual energy X-ray absorptiometry (DXA scan) ○ Occurrence of vertebral fractures ○ Changes in bone turnover markers ● Occurrence of adverse events related to treatment
Statistical methods	The patients' data will be analyzed using the intention-to-treat principle. The needed number of patients needed is based on the following hypothesis: ● A statistical significance level of 5% (two-sided) is used ● A 80% statistical power is desired ● 1:1 randomization applies ● Relative hazard (Group A/Group B) = 0.8

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	● The incidence of major cardiovascular events in MACS patients was found to be approximately 16.7% ● A decrease of 30% in major cardiovascular events is considered clinically significant According to the criteria above, 1522 patients are needed (761 in each group).

3. ABSTRACT

Background: Adrenal incidentalomas (AIs) are adrenal tumors identified when evaluating unrelated conditions. A considerable number of AI patients exhibit Mild Autonomous Cortisol Secretion (MACS), which has been linked to key cardiometabolic risk factors, posing clinical dilemmas regarding proper management.
Aim: This randomized controlled trial aims to evaluate the effectiveness of a surgical approach in improving outcomes for this patient population.
Methods: A multicenter, randomized controlled trial will be conducted involving patients with AIs and MACS. Patients will be randomly assigned to either a surgical intervention or a conservative management group. The primary endpoint will be the decrease in the occurence of major cardiovascular events over a defined follow-up period. Secondary endpoints will include hormonal control, improvement in metabolic and bone parameters, and quality of life. Appropriate statistical analyses will be performed to assess differences between the two groups.
Results: We anticipate that the surgical approach will lead to a significant reduction in major cardiovascular events compared to non-surgical management. Secondary outcomes will provide additional insights into the benefits and risks associated with each approach.
Conclusion: This clinical trial will provide valuable evidence regarding the optimal management strategy for patients with AIs and MACS. The results will help inform clinical decision-making and contribute to improved patient outcomes in this challenging patient population.

Keywords: adrenal incidentalomas, autonomous cortisol secretion, hypercortisolism, adrenalectomy, cardiovascular events, metabolic risk factors, bone health, quality of life

ΠΕΡΙΛΗΨΗ

Εισαγωγη: Τα τυχαιώματα των επινεφριδίων (AIs) είναι όγκοι των επινεφριδίων που εντοπίζονται κατά την αξιολόγηση μη σχετικών καταστάσεων. Ένας σημαντικός αριθμός ασθενών με AI εμφανίζουν ήπια αυτόνομη έκκριση κορτιζόλης (MACS), η οποία έχει συνδεθεί με σημαντικούς καρδιομεταβολικούς παράγοντες κινδύνου, θέτοντας κλινικά διλήμματα σχετικά με την κατάλληλη διαχείριση.
Σκοπός: Αυτή η τυχαιοποιημένη ελεγχόμενη δοκιμή στοχεύει να αξιολογήσει την αποτελεσματικότητα της χειρουργικής προσέγγισης για αυτόν τον πληθυσμό ασθενών.
Μέθοδοι: Θα διεξαχθεί μια πολυκεντρική, τυχαιοποιημένη ελεγχόμενη κλινική δοκιμή που θα περιλαμβάνει ασθενείς με AI και MACS. Οι ασθενείς θα ταξινομηθούν τυχαία είτε σε

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χειρουργική παρέμβαση είτε σε ομάδα συντηρητικής αντιμετώπισης. Το κύριο καταληκτικό σημείο θα είναι η μείωση στην εμφάνιση μειζόνων καρδιαγγειακών συμβαμάτων σε μια καθορισμένη περίοδο παρακολούθησης. Τα δευτερεύοντα καταληκτικά σημεία θα περιλαμβάνουν ορμονικό έλεγχο, βελτίωση των μεταβολικών και οστικών παραμέτρων και της ποιότητας ζωής. Θα πραγματοποιηθούν κατάλληλες στατιστικές αναλύσεις για την αξιολόγηση των διαφορών μεταξύ των δύο ομάδων.

Αποτελέσματα: Αναμένουμε ότι η χειρουργική προσέγγιση θα οδηγήσει σε σημαντική μείωση των μειζόνων καρδιαγγειακών συμβαμάτων σε σύγκριση με τη μη χειρουργική αντιμετώπιση. Τα δευτερεύοντα αποτελέσματα θα παρέχουν πρόσθετες πληροφορίες για τα οφέλη και τους κινδύνους που σχετίζονται με κάθε προσέγγιση.

Συμπέρασμα: Αυτή η κλινική μελέτη θα παράσχει πολύτιμα στοιχεία σχετικά με τη βέλτιστη στρατηγική διαχείρισης για ασθενείς με AIs και MACS. Τα αποτελέσματα θα βοηθήσουν στη λήψη κλινικών αποφάσεων και θα συμβάλουν στη βελτίωση των αποτελεσμάτων των ασθενών αυτών.

Λέξεις-κλειδιά: τυχαιώματα επινεφριδίων, αυτόνομη έκκριση κορτιζόλης, υπερκορτιζολαιμία, επινεφριδεκτομή, καρδιαγγειακά συμβάματα, μεταβολικοί παράγοντες κινδύνου, υγεία των οστών, ποιότητα ζωής.

4. INTRODUCTION

4.1. Background

4.1.1. Adrenal Incidentalomas

Adrenal Incidentalomas (AIs) are adrenal tumors discovered during the evaluation of medical conditions unrelated to adrenal disease. AIs do not include adrenal neoplasms detected in patients with a diagnosed malignancy, when undergoing imaging tests for disease staging, or in the context of investigating hereditary diseases.[1]

The prevalence of AIs varies depending on the source of the data and the selection of the population. There is, however, a clear rise with age and the ever-increasing use of diagnostic imaging tests with improved clarity. AIs are uncommon in people under the age of 30, while the majority are found in people over the age of 50. Overall, in a large number of studies, the median prevalence in autopsies was estimated at 2% and in imaging studies at 1.9%.[2]

According to current European Society of Endocrinology (ESE) Guidelines, the detection of an AI must be followed by a thorough clinical and laboratory workup and evaluation for the possibility of hormone hypersecretion and/or malignancy.[1]

The etiology of AIs varies and includes lesions derived from the adrenal cortex or medulla as well as masses of extra-adrenal origin. AIs are distinguished according to hormonal activity and benign or malignant character and may be unilateral or bilateral. Approximately 80% of AIs are benign adrenocortical adenomas, with the vast majority considered nonfunctioning. Hormone-secreting adenomas may secrete cortisol, aldosterone, catecholamines (pheochromocytoma), and sex steroids (androgens or estrogens). AIs of a

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malignant nature include adrenocortical carcinoma, primary adrenal lymphoma, metastases from extra-adrenal malignancies, and metastatic/malignant pheochromocytoma.[2]

Three main imaging techniques are used for the evaluation of AIs: Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and positron emission tomography with [18F]2-deoxy-D-glucose (FDG-PET), mostly used with CT (FDG-PET/CT). CT and MRI scans are primarily used to detect benign tumors and are not intended to rule out adrenal cancer. FDG-PET/CT, on the other hand, is utilized to detect malignant disease.[3] Noncontrast CT is the most reliable imaging technique for adrenal tumors currently, and it is suggested as the primary method of imaging in the diagnostic workup. No additional imaging is necessary if the noncontrast CT is compatible with a benign adrenal mass (homogeneous and lipid-rich appearance with HUs ≤10). In the event that imaging does not clearly demonstrate a mass with benign features and laboratory test results are not compatible with hormone hypersecretion, an individualized approach is required in order to make the decision for further investigation, follow-up and re-evaluation in 6-12 months, or immediate management.[1]

Due to tumor heterogeneity and variable biological behavior, decision-making for therapeutic intervention in AIs demands a multidisciplinary approach and individualization. Adrenalectomy is generally regarded as the gold standard of treatment for unilateral adrenal tumors with clinically substantial hormone excess, particularly when employing a minimally invasive method (i.e., laparoscopic adrenalectomy). In individuals with an asymptomatic, nonfunctional unilateral adrenal mass and evident benign characteristics on imaging examinations, surgery is not suggested.[1]

4.1.2. Adrenal Incidentalomas and Mild Autonomous Cortisol Secretion

Among AI patients, a significant proportion exhibit hypercortisolism, despite the absence of clinical signs or symptoms of Cushing's syndrome. This disorder, for which the terms “subclinical Cushing’s syndrome”, or “Possible Autonomous Cortisol Secretion (PACS)” have been extensively used, has lately become a matter of considerable research. It has been linked to long-term health outcomes, including diabetes mellitus (DM), hypertension (HTN) and a higher mortality risk. [4–9]

Because this disorder is now regarded as distinct from Cushing's syndrome and these individuals seldom acquire overt Cushing's syndrome, these formerly used terms are now being replaced by the term “Mild Autonomous Cortisol Secretion” (MACS).[1]

The diagnosis of MACS is based on a 1 mg dexamethasone suppression test (DST). In patients without overt Cushing's syndrome, a post-dexamethasone serum cortisol concentration greater than 50 nmol/L or 1.8 g/dL should be considered MACS without further classification based on cortisol levels after DST. ACTH independence should also be proven in these cases. Overall, MACS is confirmed in 20-50% of all AIs. While MACS patients are not regarded to be at a significant risk of developing overt Cushing's syndrome, the prevalence of DM, HTN, and dyslipidemia was 15-40% higher in MACS patients, and some studies have reported increased mortality.[10] Some studies have also found an increased incidence of asymptomatic vertebral fractures in patients with MACS. Lastly, several studies have shown that recovery from MACS is related to amelioration of DM, HTN, and possibly obesity.[11]

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The surgical approach should be explored in individuals with MACS. Age, gender, health status, degree and duration of cortisol secretion following DST, severity of comorbidities, and patient choice should all be considered. In all circumstances, the decision to conduct surgery should be made by an experienced multidisciplinary committee.

To date, the effectiveness of the surgical approach for MACS has been examined in a limited number of studies, the majority of them being retrospective cohort studies. Overall, most studies reported improvements in glycemic control, blood pressure control, and dyslipidemia.[12–15]

Among the studies that have compared surgical and conservative management in patients with AIs and MACS, only two were randomized controlled trials (RCTs). Toniatto et al., compared laparoscopic adrenalectomy to conservative management over a 7.7-year follow-up period. Diabetes improved in 62.5% of patients, hypertension in 67%, hyperlipidemia in 37.5%, and obesity in 50% in the surgical group. In subclinical Cushing's syndrome patients with osteoporosis, there were no significant alterations in bone metrics following surgery. Conversely, modest worsening of diabetes, hypertension, and hyperlipidemia was observed in conservatively treated individuals.[16]

Morelli et al., also demonstrated significant benefits from adrenalectomy in patients with MACS in a recent RCT. Overall, participants that underwent adrenalectomy demonstrated significant improvement in blood pressure and glycemic control compared to patients that were conservatively managed (68% and 13% improvement in BP control for surgical and conservative approaches, respectively, $p = 0.001$; 28% and 3.3% improvement in glycometabolic control for surgical and conservative approaches, respectively, $p = 0.02$).[17]

4.2. Study Rationale

The current body of research on the effect of a surgical approach in the treatment of patients with AIs and MACS is mostly based on retrospective cohort studies with substantial variation in the criteria used to define autonomous cortisol secretion. Despite the fact that these studies have investigated certain significant cardiovascular risk factors (blood pressure, glucose levels, lipid levels, and body weight), none of them reported on the risk of major cardiovascular events or mortality, and the overall quality of the evidence is rated low to very low.[1] Thus, the exact indications for surgery for patients with MACS cannot be defined.

The present study will be the first clinical trial designed in a randomized and controlled manner to assess the outcomes of adrenalectomy in patients with AIs and MACS based on precisely defined criteria for MACS, as outlined by the latest ESE Guidelines, with an emphasis on cardiovascular morbidity and mortality. The results of this study will provide valuable insights into the optimal management of this patient population and contribute to evidence-based clinical decision-making.

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4.3. Risk-Benefit assessment

4.3.1. Risks

Adrenalectomy is a relatively safe surgical operation. Potential risk factors for perioperative complications include the patient's gender, the reason for the surgery, the tumor's laterality, the surgical method, and the surgeon's experience.[18]

Laparoscopic adrenalectomy (LA) is currently the most effective treatment for the majority of adrenal diseases. The list of indications for its applicability has been expanded to include oncologic surgeries, large tumors, and pheochromocytomas.[19]

Compared to open adrenalectomy, LA had a considerably reduced perioperative morbidity and a shorter length hospitalization. Other minimally invasive approaches include retroperitoneoscopic and robotic techniques, which have similar outcomes to transabdominal lateral LA. No matter the method, research has demonstrated that experienced surgeons of the adrenal glands with a large number of cases had better results than less experienced surgeons. Overall, perioperative complication rates of 0% to 0.8% have been reported with minimally invasive techniques.[18]

Neoplastic tumors involving nearby organs continue to be the sole absolute contraindication for LA, where open surgery is still the most suitable approach.[20] However, tumor size of 6 cm or larger was independently associated with postoperative complications, longer operative time, and hospitalization time, as well as a higher likelihood of requiring conversion to an open procedure.[19]

The type of adrenal lesion seems to also play a significant role in the perioperative outcomes. Patients with malignant adrenal tumors and pheochromocytomas exhibited considerably greater rates of perioperative problems than those with benign, nonpheochromocytoma tumors.[21]

In the present study, patients who are randomly assigned to get surgical treatment will have their operations performed at an experienced facility by high-volume, skilled surgeons who specialize in treating adrenal tumors. Unless otherwise determined by the surgical team, a minimally invasive method will be applied.

4.3.2. Benefits

As mentioned above, it is now well established that patients with AIs and MACS experience significant morbidity and even mortality. They are especially vulnerable to a number of serious cardiovascular risk factors, including high blood pressure, DM, dyslipidemia, and obesity. According to some studies, they also experience deterioration of bone microarchitecture with the development of vertebral fractures.

These parameters have significantly improved after MACS treatment, which could lead to the prevention of a number of serious long-term events. The surgical approach should be taken into consideration in every patient with a personalized strategy, according to current recommendations; nevertheless, more conclusive proof of the criteria for surgery is deemed necessary. Therefore, participants of the present study are expected to benefit from the surgical approach for MACS.

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5. STUDY OBJECTIVES

5.1. Primary objective

The primary objective of this trial is to compare the effectiveness of surgical intervention (adrenalectomy) with conservative treatment in patients with AIs and MACS regarding the decrease in the occurrence of major cardiovascular events (acute myocardial infarction, stroke, cardiovascular mortality).

5.2. Secondary objectives

The secondary objectives of this trial are to compare the effectiveness of surgical intervention (adrenalectomy) with conservative treatment in patients with AIs and MACS regarding the following outcomes:

- Resolution of cortisol hypersecretion
- Improvement in metabolic parameters (blood pressure, glucose, lipid profile, body weight)
- All-cause mortality
- Quality of life
- Bone health parameters: bone mineral density, vertebral fractures, bone turnover markers
- Adverse events related to treatment

6. STUDY DESIGN

6.1. Study type

This is a randomized, controlled Phase III trial aiming to assess the effectiveness of a surgical approach in treating patients with AIs and MACS in comparison to conservative treatment.

6.2. Study duration

The trial will be completed once the required number of patients has been collected for the primary objective. The anticipated enrollment and follow-up period is 5 years.

6.3. Randomization

Eligible participants will be randomized into the following two groups:

- Group A: Surgical intervention (adrenalectomy)
- Group B: Conservative management

A block randomization strategy will be utilized to reduce bias and create balance in the distribution of participants to treatment groups. At the initial visit, patients will be randomly assigned to either group A or group B using a randomization algorithm.

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6.4. Blinding

Due to the design of this clinical trial and the comparison of a surgical procedure to a non-surgical treatment, both researchers (including the surgeons performing the adrenalectomies and those conducting the follow-up visits) and patients will be unblinded to the approach received. However, in order to eliminate potential bias, researchers analyzing the data will be blinded to the approach followed for each participant.

7. SUBJECT SELECTION

7.1. Study population

The study population will consist of patients with AI from the Endocrine Outpatient Clinic of the Attikon University Hospital, as well as Endocrinology Departments and Surgical Departments specialized in endocrine gland surgery in Greece and countries of the European Union.

7.2. Inclusion criteria

1. Adult patients (age ≥ 18 years)
2. Unilateral adrenal incidentaloma detected on imaging
3. Mild autonomous cortisol secretion, defined by the latest ESE criteria as follows:
    c. Serum cortisol levels > 50 nmol/L or 1.8 g/dL following 1-mg overnight dexamethasone suppression test
    d. Absence of signs and symptoms of overt Cushing's syndrome: facial plethora, abdominal striae (especially if reddish-purple in color and > 1 cm wide), proximal myopathy, skin atrophy/easy bruising
4. Ability to provide informed consent

7.3. Exclusion criteria

1. Patients with signs and symptoms of overt hypercortisolism/Cushing's syndrome
2. Intake of medications that affect the metabolism of cortisol and dexamethasone or the release of cortisol
3. Chronic conditions, including hypogonadism, thyrotoxicosis, chronic kidney disease and liver disease, alcoholism, eating, rheumatologic or hematological disorders
4. Possible metastatic disease
5. Radiologic characteristics not compatible with adrenocortical adenoma at imaging studies
6. Diagnosis of pheochromocytoma or aldosteronoma
7. Non-adrenal autonomous cortisol secretion
8. Bilateral adrenal tumors
9. Contraindications for surgical intervention
10. Previous adrenal surgery

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11. Inability to provide informed consent
12. Pregnant women

7.4. Premature withdrawal of participants

Participants may withdraw from the study for any reason at any time. Possible reasons for early termination include consent withdrawal, noncompliance with the research protocol, or safety concerns.

8. STUDY PROCEDURES

8.1. Summary of study procedures

Group A (Surgical Intervention):

- Adrenalectomy, preferably minimally invasive or open as deemed appropriate by the surgical team.
- Post-operative management as per standard surgical care protocols.
- Monitoring of clinical and laboratory parameters and quality of life at the determined time points post-operatively.

Group B (Conservative Management):

- Monitoring of clinical and laboratory parameters, and quality of life at the determined time points.
- No surgical intervention during the study period.
- Initiation or continuation of appropriate medication as needed.

8.2. Concurrent Medications

All participants will receive the standard of care treatment, as determined by the relevant guidelines. All concomitant medications administered during the study will be recorded by the investigators.

9. VISITS AND EVALUATIONS

9.1. Visits

9.1.1. Scheduled visits

Participants will be examined at baseline and followed up at 6 months, 12 months, and annually thereafter for a minimum of 2 years.

The following table shows in detail the procedures that will be carried out in each visit.

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Visit	Procedures
Screening visit	- Inclusion/Exclusion criteria - Informed consent - Recording of medical history and concurrent medications - Pregnancy test for women of reproductive age
Baseline visit	- Clinical examination - Recording of vital signs and electrocardiogram (ECG) - Recording of somatometric characteristics (height, body weight, waist and hip circumference) - Collection of peripheral blood and urine for laboratory examination - Pregnancy test for women of reproductive age - SF-36 quality of life questionnaire - Adrenal CT if not previously performed - Bone Mineral Density measurement using DXA scan - Recording of vertebral or other fractures - Randomization and allocation to Group A (surgical approach) or Group B (conservative management)
6-month visit	- Clinical examination - Recording of vital signs and electrocardiogram (ECG) - Recording of somatometric characteristics (height, body weight, waist and hip circumference) - Collection of peripheral blood and urine for laboratory examination - SF-36 quality of life questionnaire - Adrenal CT - Bone Mineral Density measurement using DXA scan - Recording of vertebral or other fractures - Recording of concurrent medications - Recording of major cardiovascular or other events during follow-up - Recording of adverse events related to treatment
12-month visit	- Clinical examination - Recording of vital signs and electrocardiogram (ECG) - Recording of somatometric characteristics (height, body weight, waist and hip circumference) - Collection of peripheral blood and urine for laboratory examination - SF-36 quality of life questionnaire - Adrenal CT

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	- Bone Mineral Density measurement using DXA scan - Recording of vertebral or other fractures - Recording of concurrent medications - Recording of major cardiovascular or other events during follow-up - Recording of adverse events related to treatment
Annual visits for a minimum of 2 years	- Clinical examination - Recording of vital signs and electrocardiogram (ECG) - Recording of somatometric characteristics (height, body weight, waist and hip circumference) - Collection of peripheral blood and urine for laboratory examination - SF-36 quality of life questionnaire - Adrenal CT - Bone Mineral Density measurement using DXA scan - Recording of vertebral or other fractures - Recording of concurrent medications - Recording of major cardiovascular or other events during follow-up - Recording of adverse events related to treatment
End of study visit	- Clinical examination - Recording of vital signs and electrocardiogram (ECG) - Recording of somatometric characteristics (height, body weight, waist and hip circumference) - Collection of peripheral blood and urine for laboratory examination - SF-36 quality of life questionnaire - Adrenal CT if > 6 months from last visit - Bone Mineral Density measurement using DXA scan if > 6 months from last visit - Recording of vertebral or other fractures - Recording of concurrent medications - Recording of major cardiovascular or other events during follow-up - Recording of adverse events related to treatment

9.1.2. Unscheduled visits

In the event that any participants appear outside of the scheduled visits for any reason, a visit will be conducted according to the standards of the rest and the reason that led to the need for this visit will be recorded.

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9.2. Study evaluations

For each participant, the following evaluations will be carried out:

1. Recording of demographic characteristics (age, sex, race)
2. Recording of medical history and current medications
3. Clinical examination
4. Recording of vital signs (systolic/diastolic/mean blood pressure, heart rate, respiratory rate, palmic oxymetry, temperature)
5. Electrocardiogram (ECG)
6. SF-36 quality of life questionnaire
7. Recording of vertebral or other fractures

9.3. Laboratory examinations

For each participant, the following laboratory examinations will be carried out:

1. Complete blood count: RBC count, Hb, Hct, MCV, MCH, MCHC, RDW, WBC, PLT
2. Biochemical profile: glucose, insulin, urea, creatinine, sodium, potassium, SGOT, SGPT, γ-GT, ALP, uric acid, calcium, phosphorus, magnesium, vitamin D (25OHD)
3. Hemoglobin A1c (HbA1c)
4. Lipid profile: total cholesterol, HDL, LDL, triglycerides
5. Hormonal profile: TSH, FT3, T4, PTH, FSH, LH, cortisol, ACTH, DHEAS, SHBG, testosterone, estradiol
6. 1-mg overnight dexamethasone suppression test (DST)
7. Pregnancy test (serum or urine) for women of reproductive age
8. 24h urine sample: urine free cortisol, albumin, sodium, potassium, urea, creatinine
9. Markers of bone metabolism/ Bone turnover markers: osteocalcin, bone ALP, Procollagen type I N-terminal propeptide (PINP), C-telopeptide of type I collagen (CTX), N-telopeptide of type I collagen (NTX)

9.4. Imaging studies

1. Dual energy X-ray absorptiometry (DXA scan) for the evaluation of bone mineral density
2. Adrenal CT, for the evaluation of tumor size and characteristics, as well as the follow-up of patients post-operatively.

10. ENDPOINTS

10.1. Primary endpoint

- Cardiovascular endpoint: Decrease in the occurrence of major cardiovascular events (acute myocardial infarction, stroke, cardiovascular mortality)

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10.2. Secondary endpoints

- Resolution of cortisol hypersecretion, as indicated by 1 mg DST from baseline to study completion
- Improvement in metabolic parameters (blood pressure, glucose, lipid profile, body weight) from baseline to study completion. These include:
    - Changes in blood pressure (systolic/diastolic/mean)
    - Changes in fasting glucose and insulin
    - Changes in HbA1c
    - Changes in total cholesterol, HDL, LDL, triglycerides
    - Changes in body weight and waist-hip ratio
- Time until the occurrence of all-cause mortality
- Changes in quality-of-life scores using the SF-36 questionnaire
- Changes in bone health parameters. These include:
    - Changes in bone mineral density, as measured by Dual energy X-ray absorptiometry (DXA scan)
    - Occurrence of vertebral fractures
    - Changes in bone turnover markers
- Occurrence of adverse events related to treatment

11. STATISTICAL ANALYSIS

11.1. Patient population analysis

The statistical analysis will be performed on individuals who had either surgical or conservative therapy and for whom relevant data are available. The patients' data will be analyzed using the intention-to-treat principle. Patients will be examined based on the treatment groups they were assigned to, regardless of the actual treatment they received or their compliance.

11.2. Statistical methods for data analysis

Depending on the size of the sample for each variable, the Shapiro-Wilk or Kolmogorov-Smirnov test will be used to determine the normality of the distribution. Continuous variables will be expressed as mean±standard deviation or as median [interquartile range]. The categorical variables will be expressed as absolute and relative frequencies (n, %). All baseline quantitative characteristics between the two groups of treatment will be compared by the Student’s t-test for parametric variables and by the Mann-Whitney U test for non-parametric variables. The chi-square test will be applied in the case of a categorical variable.

For comparisons between the baseline and completion of the study in each group, the t-test for dependent samples or the Wilcoxon's Signed Rank test, depending on the normality of the distribution, will be employed. In the case of a categorical variable, the McNemar test will be applied. Any p-value below 0.05 will be considered significant.

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11.3. Sample size

The needed number of patients needed is based on the following hypothesis:

- A statistical significance level of 5% (two-sided) is used
- A 80% statistical power is desired
- 1:1 randomization applies
- Relative hazard (Group A/Group B) = 0.8
- The incidence of major cardiovascular events in MACS patients was found to be approximately 16.7%
- A decrease of 30% in major cardiovascular events is considered clinically significant

According to the criteria above, 1522 patients are needed (761 in each group).

11.4. Interim analysis

When two-thirds of the total number of primary endpoints have been observed, an interim analysis will be conducted. The analysis will be carried out by a blinded statistician, who will report the findings to DMC. If the interim analysis demonstrates a clear benefit in the surgical therapy group, the committee may suggest that the trial be terminated earlier.

11.5. Statistical packages

The statistical analyses will be conducted using the statistical packages IBM SPSS Statistics for Macintosh, Version 28.0 and R Project for Statistical Computing for Macintosh, Version 4.3.1.

12. ADVERSE EVENTS AND OTHER SAFETY ASPECTS

12.1. Definition of Adverse Events (AEs)

An adverse event (AE) is any unwanted medical event in a trial participant. The adverse event does not necessarily have a causal relationship with the treatment.

12.2. Definition of Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any unwanted medical event that is considered serious at any dose if it:

1. leads to death
2. is life-threatening
3. necessitates hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly/birth defect

12.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that

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meets three criteria: suspected, unexpected and serious.

• Suspected: There is a fair likelihood that the adverse drug reaction was caused by the drug.

• Unexpected: An adverse reaction, whose nature or intensity is not consistent with the applicable product information.

• Serious: See above for SAE.

12.4. Adverse Drug Reaction (ADR)

- In the pre-approval clinical experience with a new investigational product or its new applications: unwanted and unintended responses, such as a sign (e.g., laboratory results), symptoms or disease related to any dose of a medicinal product where a causal relationship between a medicinal product and an adverse event is a reasonable possibility. The degree of certainty that an adverse medication response is attributable to an experimental product varies. If the ADR is strongly considered to be connected to a medical product, it should be mentioned in the reference safety information (RSI) and/or the Investigator's Brochure (IB).
- For marketed medicinal products: an unpleasant and unanticipated response to a medicine that occurs at levels routinely used in people for disease prevention, diagnosis, or therapy, or to modify physiological function.

12.5. Procedures for Recording Adverse Events

All AEs (both serious and non-serious) should be documented, whether patient-reported or observed by the researcher. The researchers are responsible for monitoring the safety of the study patients and notifying the sponsor in the case of any unexpected event. All AEs should be treated and monitored carefully until they are resolved or stabilized. If the researcher deems it essential, treatment may involve closer monitoring, and administration of medicinal or non-medicinal treatment.

All AEs must be recorded and documented in the patient's medical record, alongside the type of AE (symptom, clinical sign, disease, paraclinical examination finding), date of onset and progression, severity, association with the investigational treatment, outcome. In case of SAE, the following information will also be recorded: SAE description, dates and duration of hospitalization, probable cause of death.

All SAEs should be notified to the sponsor as soon as possible (when the investigator becomes reasonably aware of the incident). In compliance with appropriate regulatory standards, some SAEs may not need rapid reporting, such as death or other endpoint events. More information should be supplied as a follow-up report as needed. For reported fatalities, the investigator should provide any further required information (e.g., autopsy reports and terminal medical reports) to the sponsor, the IRB/IEC, and, if relevant, the regulatory authority as soon as it becomes available.

12.6. Follow-up to Adverse Events

Patients who encountered an AE and/or withdrew from the study as a result of that AE will be observed on a regular basis, and special monitoring reports will be prepared under the researcher's supervision, which will subsequently be submitted to the sponsor.

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12.7. Procedure in case of pregnancy

At the screening visit, women of reproductive age should have a negative pregnancy test (serum or urine). Any pregnancy in a female study patient should be reported to the sponsor by the researcher. If a participant becomes pregnant during the course of the study, her participation in the study should be terminated. The health condition of the mother and fetus will be reported monthly by the study researchers after contacting the participant until the pregnancy is completed or terminated.

13. MONITORING AND AUDIT

13.1. Independent Data Monitoring Committee (DMC)

An independent data monitoring committee (DMC) has been established by the Sponsor to examine the progress of the current clinical trial, the safety data, and the critical efficacy endpoints at regular intervals. The DMC will suggest to the Sponsor whether to continue, amend, or discontinue the trial.

Meetings of the DMC will be held prior to the commencement of the trial and at predetermined time periods corresponding to 40%, 70%, and 100% enrolment. DMC will be blinded to the difference between the two arms of treatment for the main endpoint and SAEs at the meetings at 40% and 70% enrollment. At the end of each meeting, all members will sign the minutes and a declaration indicating whether the trial may proceed based on the agreed-upon criteria. The DMC will finally meet after the final analysis is available.

13.2. Monitoring

The Sponsor is responsible for monitoring the trial's procedures, in order to protect the participants' rights, safety and well-being and the reliability of trial results as the trial progresses. The Sponsor will establish and maintain regular contact with the investigators through Clinical Research Associates (CRAs). CRAs will assess the study center's competency, informing the sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, the Sponsor is responsible for ensuring that written informed consent has been acquired from all participants correctly according to principles of Declaration to Helsinki, GCP, and applicable regulatory requirements and that data are recorded accurately and thoroughly. The Sponsor will additionally monitor protocol adherence. During monitoring visits, source data will be verified and all entries in the CRFs will be compared with the original source documents. The investigators must agree to meet with the CRAs on a frequent basis and to cooperate in resolving any queries or findings that arise throughout the monitoring process.

13.3. Audit

The purpose of a Sponsor's audit, which is independent of and distinct from regular monitoring or quality control functions, is to determine if the procedures that are used to

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manage and conduct the trial are effective and compliant. The Sponsor should appoint individuals who are not associated with the clinical trial under audit. The Sponsor will guarantee that the auditors are suitably trained and experienced to perform audits.

14. ETHICAL ASPECTS

14.1. General statements

The procedures outlined in this protocol for the organization and conduct of the present clinical trial are in compliance with ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP), as well as the EU Clinical Trials Directive. Participants' personal information will be collected in accordance with the General EU Data Protection Regulation (GDPR).

14.2. Approval from regulatory authorities

Prior to trial commencement, the protocol will be submitted to the relevant Institutional Review Board (IRB) and Independent Ethics Committees (IECs) of all study centers. Specifically for the coordinating center, the protocol will be submitted to the IRB of the Attikon University Hospital, as well as the Bioethics Committee of the National and Kapodistrian University of Athens.

14.3. Informed Consent

Prior to trial participation, each patient will freely provide informed consent, which will be documented. Potential participants who are unable to offer informed consent should have their legally appropriate representative provide consent. A signed and dated informed consent form, either paper or electronic, will be used to document informed consent.

If new information becomes available that may be important to the participant's interest in continuing the trial participation, the participant or the participant's legally appropriate representative should be notified as soon as possible. The communication of this information, as well as confirmation of intent to continue trial participation, should be noted.

14.4. Funding

- The study is funded by XXX.
- Investigators will declare any potential conflicts of interest.

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15. DATA MANAGEMENT, DOCUMENTATION AND ARCHIVING

15.1. Data documentation and management

The primary investigator (PI) and sub-investigators of each center are in charge of collecting and documenting patient data. The PI is responsible for ensuring that the data is accurate and comprehensive. Initially, all data will be recorded in a predetermined manner in written case report forms (CRF) and will then be registered electronically on an appropriately formatted database.

15.2. Data archiving and confidentiality

Access to patient data will be limited to PI, sub-investigators and the Sponsor. All paperwork will be collected and stored in the patient's personal file under the PI's responsibility. All patient files will be kept in a secure location under the PI's supervision for 5 years after trial termination.

15.3. Publication policy

Information regarding the present trial will be published by the Sponsor on Clinical Trials online platform (www.clinicaltrials.gov) and the study will receive a unique coding number (NCT XXXXXXXX). The relevant data, results and their copyrights will be the property of the Sponsor, who will be able to use them in various ways, such as for submission to government regulators or sharing with other researchers. The results of the study will be reviewed by both the investigators and the sponsor before their publication. The results will not be announced or shared with third parties in any way until an agreement is signed by the sponsor. The results of the study will be published in recognized peer-reviewed scientific journals.

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