Supplementum

Methods

Study cohort and design (Figure 1)

The endocrine outpatient clinics at the regional hospitals of Randers, Silkeborg, Viborg, and Aarhus University Hospital participated in the study representing a total catchment population of 816,691 persons (226,253, 95,488, 141,310, and 353,640, respectively). The project was initiated at Silkeborg Regional Hospital (September 2019) with enrollment starting at Viborg Regional Hospital in December 2019, Aarhus University Hospital in May 2020, and Randers Regional Hospital in August 2020. The inclusion period was 12 months from the start of inclusion in each center. Patients were followed until a conclusion was reached regarding their malignancy status and hormonal hypersecretion, or until end of pathway due to patient wish or death.

Controls: The historical control cohort consisted of retrospectively identified patients with adrenal incidentalomas investigated at either Viborg or Silkeborg regional hospital during 2018 (n = 103), all following the "*Care as usual*" pathway with attendance at the clinic.
Cases: Cases were consecutively and prospectively registered. All patients were adults, referred with adrenal incidentalomas described as ≥ 10 mm to one of the four participating outpatient endocrine clinics. Cases were assigned to one of three pathways; NNTS, "*Attendance-pathway*" (AP), or "*Other"* based on the patient's individual risk profile as follows:
NNTS: Low-risk patients defined as follows:

- Older than 40 years of age, since adrenal incidentalomas are rare before 40 years of age
- Without recent (as assessed by the clinician handling the referral taking into account tumor type and cancer stage before intended curative treatment) or current malignancy
- Without hypokalemia except what is explainable by diuretics or hypomagnesemia.
- Without treatment-resistant hypertension (blood pressure above goal despite concurrent use of three antihypertensive agents of different classes taken at maximally tolerated doses, one of which should be a diuretic).
- Treated with less than four antihypertensive agents irrespective of type.
- No hypertension before the age of 35 years.

A subgroup of the NNTS group was subclassified as "*Converted to attendance at clinic*" if the endocrinologist undertaking the investigation/deemed it necessary to evaluate the patient physically

based on incoming laboratory results, an unenhanced CT attenuation value > 10 Hounsfield units (HU), or the patient requesting an attendance consultation.
Attendance pathway: In this pathway attended patients not designated as low-risk patients.
Other: Patients not meeting the NNTS pathway criteria and who did not attend the clinic due to, e.g., critical comorbidities.
Patients could be assigned to *Attendance at the clinic* at any time if the endocrinologist handling the referral deemed this necessary.
A Shiny app (https://www.shinyapps.io/) based decision support web application was developed using the R package shiny (https://CRAN.R-project.org/package=shiny) and documented in Gitkraken Version XX (Axosoft, Arizona). The web application guides the clinician's handling of the referral and his or her assessment of incoming laboratory and imaging results. An English translation is available (https://incidentaloma.shinyapps.io/Incidentalom_UK).

A patient pathway flowchart is available in Figure 1. At referral, a physician screened the referral notice and radiological report to decide on allocation to the NNTS or the attendance pathway.
The Shared Medication Record provided access to information on citizen's medication including glucocorticoid and estrogen use. The Shared Medication Record bring together updated medicine information from all health professionals treating the patient. [1]
All participants received standardized patient information via secure email or surface mail on how to perform biochemical testing, information on CT procedures, and, if available, information about the nature of the tumor. If all tests were normal, patients assigned to the NNTS pathway were discharged without seeing an endocrinologist and subsequently received a standardized patient information letter explaining the results and recommending that they consult their general practitioner for blood pressure measurement/control. The patient's general practitioner received a discharge letter summarizing the results including guidelines about when a hypertensive patient should be referred for evaluation if the aldosterone-renin ratio had not previously been evaluated.

Adrenal CT

All centers used a scanning protocol consisting of unenhanced CT and contrast-material-enhanced and delayed-enhanced CT for patients with unenhanced CT attenuation ≥ 10 HU. Data on attenuation values and enhancement washout calculations were obtained from enhanced CT imaging (60 seconds after intravenous administration of contrast material and followed by delayed enhanced CT imaging at 15 minutes). The parameters for the unenhanced and delayed enhanced

examinations with both helical units included at maximum 3 mm collimation, 120 kVp, and more than 125 mAs.

An adenoma was diagnosed as benign in case of a:

- homogenous mass with HU ≤ 10 on unenhanced CT
- benign enhancement washout value (absolute ≥ 60% and relative ≥ 40%) and follow-up CT at six months or more without growth and tumor < 4 cm.
- previous CT showing tumor without growth for more than two years irrespective of the presence of adrenal CT.

Biochemical workup

Biochemical work-up included plasma fractionated metanephrines and a 1 mg overnight dexamethasone suppression test (1mg DST).

Plasma renin activity and aldosterone were recommended according to the decision aid in hypertensive patients who were not well regulated on three antihypertensive drugs, patients receiving more than three antihypertensive drugs, patient with hypertension before 35 years of age, unexplained hypokalemia or large potassium supplement, or when this was deemed relevant by the investigating endocrinologist who took into account comorbidities and advanced age.

Urinary free cortisol (UFC), adrenocorticotropic hormone (ACTH) and/or dehydroepiandrosterone sulfate (DHEAS) were recommended in patients with insufficient suppression on the 1mg DST, if deemed clinically relevant by the investigating endocrinologist.

Mild autonomous cortisol secretion was defined following the European Society of Endocrinology guidelines [2]:

- Cortisol levels 50-138 nmol/L after the 1mg DST in combination with one of the following three:
    1. ACTH below the lower limit of normal
    2. DHEAS below the lower limit of normal
    3. Elevated UFC
- Cortisol levels > 138 nmol/L after the 1mg DST.

Hormonal determinations were condunenhanced CTed with routinely available reagents as follows:

P-Cortisol (competitive immunometric assay, Siemens Atellica, all hospitals).

P-DHEA-S (LC-MS/MS, Aarhus University Hospital).

P-ACTH (Cobas ECLIA electrochemiluminescence, Roche, Aarhus University Hospital).

Plasma aldosterone and renin concentrations were analyzed by automated chemiluminescence immunoassay (CLIA, iSYS, Immuno Diagnostic Systems, Aarhus University Hospital). P-fractionated metanephrines (LC-MS/MS, Aarhus University Hospital). UFC (LC-MS/MS, Aalborg University Hospital).

Data collection

Data from all hospitals were retrieved from the regional electronic clinical information system (Columna Clinical Information System, Systematic) and entered into an electronic case report form using Epidata 3.0 Denmark. CT images were retrieved from the regional and national Danish picture archiving and communication system. Radiology reports were retrieved manually from the radiology systems and from regional electronic patient records.

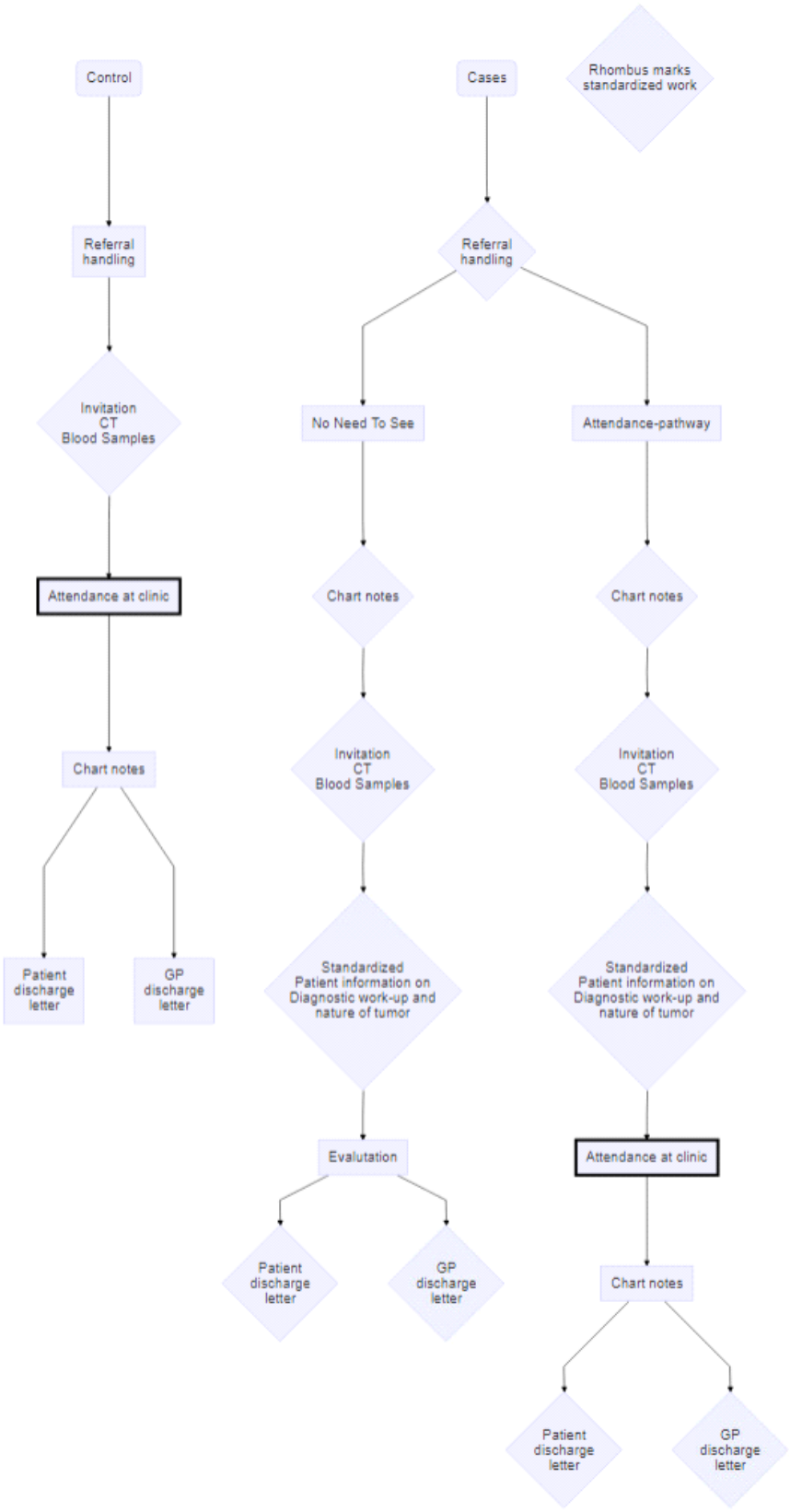
Up-to-date information on presently prescribed medicine was obtained from the Shared Medication Record to which all prescribing physicians may add information on prescribed medicine. [1] Electronic patient records were scrutinized for available data on BP, diagnosis of osteoporosis, type 2 diabetes, and hypokalemia.

The research and reporting methodology adhered to the SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence) [3].

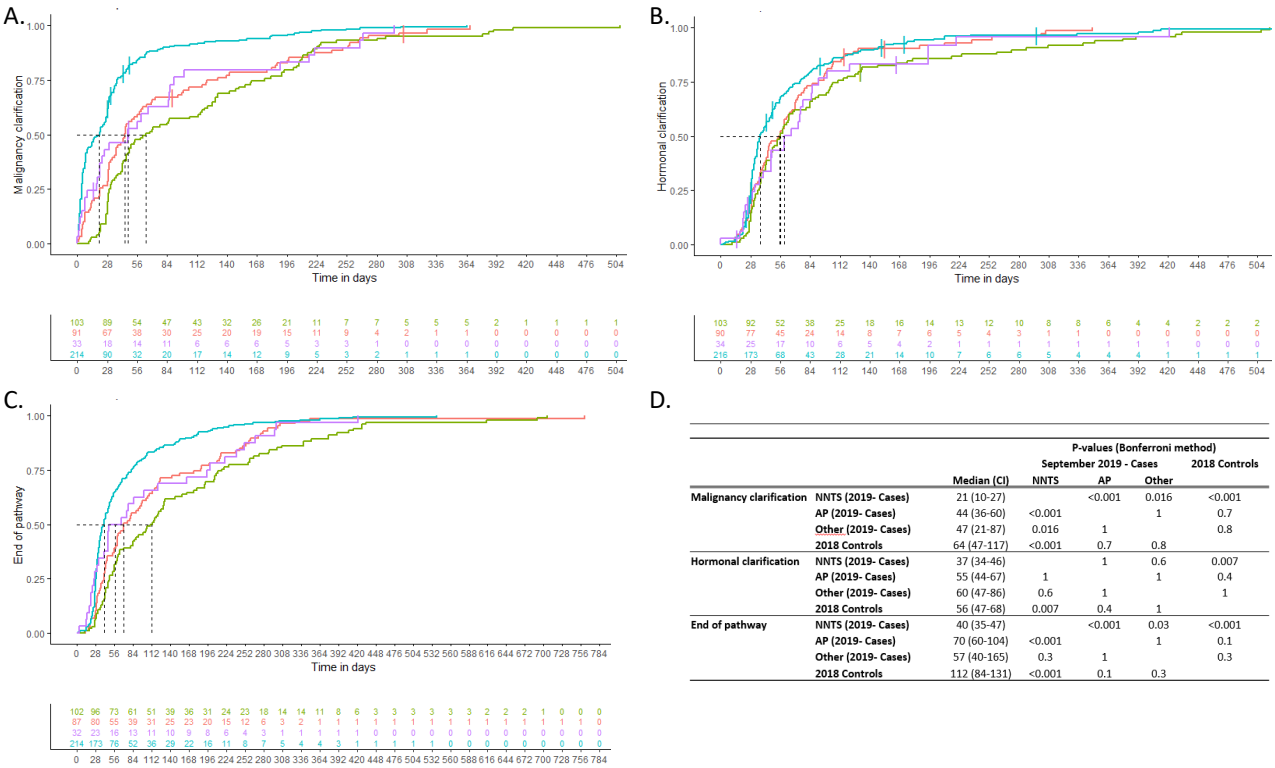
	2019 - Cases N (%)		2018 Controls N (%)	
Mild autonome cortisol secretion				
Yes	60	(17)	11	(11)
No	213	(61)	70	(68)
Insufficient data	49	(14)	19	(18)
NA	25	(7)	3	(3)
Total	347	(100)	103	(100)

Supplemental Table 1. Overall P-value 0.2 and 0.1 for data with and without missing values, respectively.

NA= Non-applicable



Supplemental Figure *1*. Overview of standardized work in the Control and new pathway (cases). Standardized work is marked by a rhombus. Left panel presents the Control pathway (used until 2018). The right panel presents the Case pathway (currently used).



D.

			P-values (Bonferroni method)		
			September 2019 - Cases		2018 Controls
		Median (CI)	NNTS	AP	Other	
Malignancy clarification	**NNTS (2019- Cases)**	21 (10-27)		<0.001	0.016	<0.001
	AP (2019- Cases)	44 (36-60)	<0.001		1	0.7
	Other (2019- Cases)	47 (21-87)	0.016	1		0.8
	2018 Controls	64 (47-117)	<0.001	0.7	0.8	
Hormonal clarification	**NNTS (2019- Cases)**	37 (34-46)		1	0.6	0.007
	AP (2019- Cases)	55 (44-67)	1		1	0.4
	Other (2019- Cases)	60 (47-86)	0.6	1		1
	2018 Controls	56 (47-68)	0.007	0.4	1	
End of pathway	**NNTS (2019- Cases)**	40 (35-47)		<0.001	0.03	<0.001
	AP (2019- Cases)	70 (60-104)	<0.001		1	0.1
	Other (2019- Cases)	57 (40-165)	0.3	1		0.3
	2018 Controls	112 (84-131)	<0.001	0.1	0.3	

Supplemental Figure 2. Kaplan-Meier time-to-event plot. The Y axis presents the proportion of patients with clarification or reaching end of pathway. The X axis represents time in days. Right-censored individuals are indicated by the vertical lines. Dotted black lines: medians. Blue line: No-Need-To-See. Purple line: Attendance pathway. Red line: Group *Other*. Green: 2018 Controls. The table below indicates the number at risk. **A** Time to malignancy clarification. **B.** Time to hormonal clarification. **C.** Time to end of pathway. **D.** Table of medians with 95% confidence interval and log rank test p-value adjusted for multiple comparison by the Bonferroni method.

	2019 - Cases			2018 Controls	P-value	P-value Excl. Nas
	NNTS	AP	Other			
n	219	94	34	103		
Proportion in each subgroup	63%	27%	10%			
Age [range]	63.5 [36.1-89.9]	66.2 [31.5-85.7]	67.3 [43.2-91.3]	66.4 [32.6-88.5]	0.4	
Sex (Male%)	50%	47%	27%	37%	0.02	
Tumor size [mm]	17 [9-50]*	20 [10-51]	19 [10-85]	18 [10-60]	< 0.001	
HU ≤ 10						
Yes	178 (81.3%)	43 (45.7%)	19 (55.9%)	64 (62.1%)	< 0.001	< 0.001
No	32 (14.6%)	49 (52.1%)	14 (41.2%)	34 (33.0%)		
NA	9 (4.1%)	2 (2.1%)	1 (2.9%)	5 (4.9%)		
Bilateral						
Yes	38 (17.4%)	23 (24.5%)	3 (8.8%)	22 (21.4%)	0.2	0.2
No	180 (82.2%)	71 (75.5%)	30 (88.2%)	80 (77.7%)		
NA	1 (0.5%)	0 (0.0%)	1 (2.9%)	1 (1.0%)		
Washout						
Yes	18 (56.2%)	29 (59.2%)	11 (78.6%)	14 (41.2%)	0.3	0.07
No	8 (25.0%)	13 (26.5%)	1 (7.1%)	14 (41.2%)		
NA	6 (18.8%)	7 (14.3%)	2 (14.3%)	6 (17.6%)		
Type 2 diabetes						
Antidiabetic medicine/elevated HbA1C	28 (12.8%)	17 (18.1%)	5 (14.7%)	13 (12.6%)	0.6	
No antidiabetic medicine & normal HbA1C	191 (87.2%)	77 (81.9%)	29 (85.3%)	90 (87.4%)		
Osteoporosis						
Treatment	22 (10.0%)	8 (8.5%)	7 (20.6%)	10 (9.7%)	0.4	0.3
No osteoporosis treatment	196 (89.5%)	86 (91.5%)	27 (79.4%)	92 (89.3%)		
NA	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.0%)		
Normal blood pressure measurement						
Yes	87 (39.7%)	47 (50.0%)	17 (50.0%)	25 (24.3%)	< 0.001	< 0.001
No	108 (49.3%)	43 (45.7%)	13 (38.2%)	76 (73.8%)		

NA	24 (11.0%)	4 (4.3%)	4 (11.8%)	2 (1.9%)		
Hypertensive status						
Before age 35 years	1 (0.5%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	< 0.001	< 0.001
Not within target range	2 (0.9%)	13 (13.8%)	2 (5.9%)	2 (1.9%)		
None of those above	183 (83.6%)	68 (72.3%)	24 (70.6%)	92 (89.3%)		
NA	33 (15.1%)	11 (11.7%)	8 (23.5%)	9 (8.7%)		
Hypokalemia						
Large potassium supplement	1 (0.5%)	3 (3.2%)	1 (2.9%)	2 (1.9%)	< 0.001	< 0.001
Spontaneous	8 (3.7%)	14 (14.9%)	9 (26.5%)	1 (1.0%)		
No	208 (95.0%)	77 (81.9%)	23 (67.6%)	99 (96.1%)		
NA	2 (0.9%)	0 (0.0%)	1 (2.9%)	1 (1.0%)		
Malignancy (recent or present)						
Yes	6 (2.7%)	36 (38.3%)	12 (35.3%)	8 (7.8%)	< 0.001	< 0.001
No	208 (95.0%)	58 (61.7%)	22 (64.7%)	93 (90.3%)		
NA	5 (2.3%)	0 (0.0%)	0 (0.0%)	2 (1.9%)		

Supplemental Table 2. Descriptives. Pre-intervention control cohort (2018) versus cases after intervention, by subgroup as follows: NNTS (No Need To See), AP (Attendance pathway), and Other.

NA = Non-applicable

1. **The Shared Medication Record** [https://sundhedsdatastyrelsen.dk/da/english/digital_health_solutions]
2. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM: **Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors**. *European journal of endocrinology / European Federation of Endocrine Societies* 2016, **175**(2):G1-G34.
3. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D: **SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process**. *BMJ Quality & Safety* 2016, **25**(12):986.