12° congresso Nazionale AME
6th Joint Meeting with AACE

Bari,
7-10 novembre 2013

Inquadramento di laboratorio della patologia corticosurrenalica

Il caso dell'aldosterone: fra certezze e pitfalls

Anna Frigo
Medicina Generale a Indirizzo Endocrinologico
Azienda Ospedaliera Universitaria Integrata
Verona

Aldosterone nella clinica

Bari,
7-10 novembre 2013

↑ PRA
↑ A

- Ipertensione nefrovascolare
- Uso di diuretici
- Tumori secernenti renina
- Ipertensione maligna
- Coartazione aortica

↓ PRA
↑ A

Aldo-PRA ratio ≥ 40
Aldo- ≥ 15 ng/dl

Ricerca Iperaldosteronismo Primario

↓ PRA
↓ A

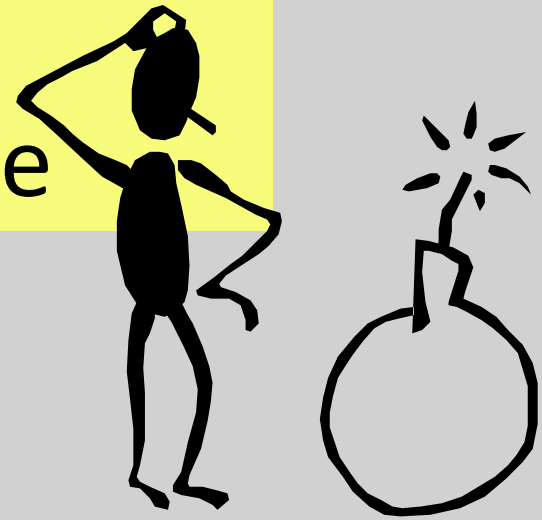
- Iperplasia surrenalica congenita
- Tumori producenti DOC
- Sindrome di Cushing
- Deficit 11-ß-OHSDH
- Mutazioni attivanti MR
- Sindrome di Liddle

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- L'Iperaldosteronismo primitivo è più comune di quanto si pensasse

5-10% degli ipertesi
20% dei pazienti con ipertensione resistente



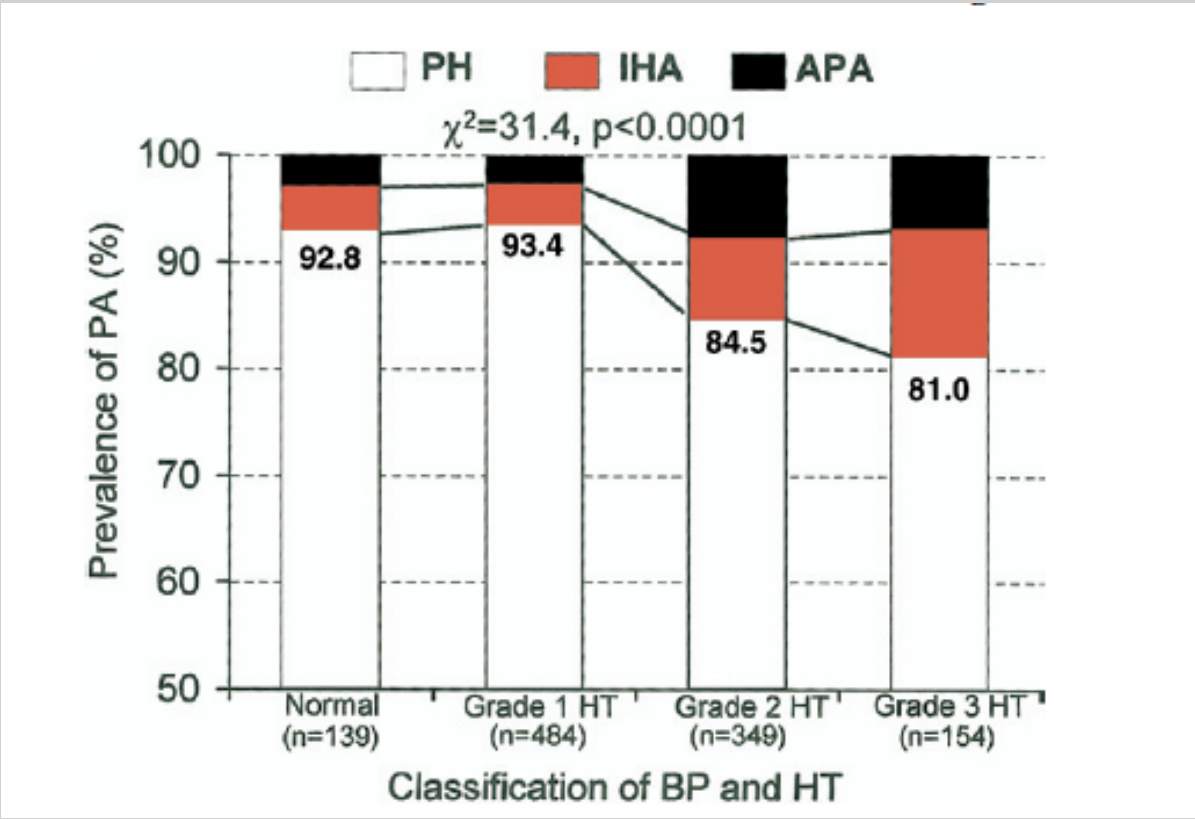
ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

Rossi *et al.*
Diagnosis of Hyperaldosteronism

JACC Vol. 48, No. 11, 2006
December 5, 2006:2293–300

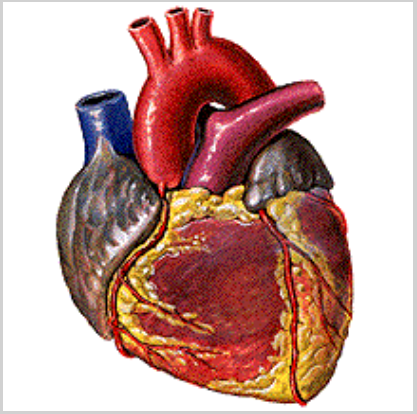


ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- L'eccesso di aldosterone comporta danno a livello cardiovascolare e renale

….non solo per effetto degli aumentati valori pressori, ma soprattutto per l'azione diretta dell'aldosterone su cuore, vasi e reni



ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Excess Aldosterone Is Associated With Alterations of Myocardial Texture in Primary Aldosteronism

Rossi et al

Hypertension. 2002;40:23-27

Renal Damage in Primary Aldosteronism
Results of the PAPY Study

Rossi et al

Hypertension. 2006;48:232-238

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Mineralocorticoids

Long-Term Cardiac Effects of Adrenalectomy or Mineralocorticoid Antagonists in Patients With Primary Aldosteronism

Cristiana Catena, GianLuca Colussi, Roberta Lapenna, Elisa Nadalini, Alessandra Chiuch, Pasquale Gianfagna, Leonardo A. Sechi

J Hypertension 2007, 50: 911-918

Rapid Reversal of Left Ventricular Hypertrophy and Intracardiac Volume Overload in Patients With Resistant Hypertension and Hyperaldosteronism
A Prospective Clinical Study

K Gaddam, C Corros, E Pimenta, M Ahmed, T Denney, I Aban, S Inusah, H Gupta, SG Lloyd, S Oparil, A Husain, LJ Dell'Italia, DA Calhoun

J Hypertension 2010, 55: 1137

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Long term renal outcomes in patients with primary hyperaldosteronism

LA Sechi, M Novello, R Lapenna, S Baroselli, E Nadalini, GL Colussi, C Catena

JAMA. 2006 Jun 14;295(22):2638-45

Dosiamolo per prevenire…

Bari,
7-10 novembre 2013

Le linee guida dell'Endocrine Society raccomandano di estendere lo screening per iperaldosteronismo negli ipertesi per ottimizzare il management dei pazienti che possono beneficiare di una terapia specifica

ALDOSTERONE: pitfalls

Bari,
7-10 novembre 2013

Abbiamo visto le difficoltà connesse al dosaggio dell'aldosterone in laboratorio:

Come può il clinico aiutare a rendere il dosaggio dell'aldosterone più attendibile e interpretabile?

- c
- Sospensione dei farmaci (può richiedere tempo e mettere a rischio il paziente).
- Tests per renina e aldosterone ancora poco standardizzati

ALDOSTERONE

Bari,
7-10 novembre 2013

- Pazienti da sottoporre a screening?
- Quale test di screening?
- Importanza dei test di conferma?

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- Pazienti da sottoporre a screening
- Quale test di screening?
- Importanza dei test di conferma?

Pazienti da sottoporre a screening

Bari,
7-10 novembre 2013

Paziente maschio, 15 anni

Ipertensione arteriosa di 2-3°.

Ionemia nella norma.

Dosereste l'aldosterone?

Anche la renina?

Pazienti da sottoporre a screening

Bari,
7-10 novembre 2013

Paziente maschio, 54 annni

Ipertensione arteriosa di 2° farmacologicamente

ben controllata.

Ipopotassiemia.

Dosereste l'aldosterone?

Anche la renina?

Pazienti da sottoporre a screening

Bari,
7-10 novembre 2013

Paziente femmina, 40 anni

Ipertensione arteriosa di 1°.

Incidentaloma surrenale di 1.5 cm.

Dosereste l'aldosterone?
Anche la renina?

Quali pazienti sottoporre a screening?

Bari,
7-10 novembre 2013

- Ipertensione Grado 3 di Prima Diagnosi (>180/110)
- Ipertensione Resistente (ipert con + 3 farmaci a piena dose)
- Ipertensione + Ipopotassiemia (spontanea o indotta da basse dosi di diuretico)
- Incidentaloma in Iperteso
- Tutti gli Ipertesi Grado 2 e 3 (?)

Mulatero P Trends Endocrinol Metab **2006**

Iperaldosteronismo primitivo nei gruppi ad alta prevalenza

Bari,
7-10 novembre 2013

Ipertensione lieve (PAS 140-160, PAD 80-100 mmHg)	2%
Ipertensione moderata (PAS 160-180, 100-110 mmHg)	8%
Ipertensione severa (PAS >180, PAD >110 mmHg)	13%
Ipertensione resistente (>140/90 mmHg con tre farmaci)	17-23%
Ipertensione con incidentaloma surrenalico	2 (1-10)%

Funder J, *J Clin Endocr Metab*, 2008

Quali pazienti sottoporre a screening?

Bari,
7-10 novembre 2013

SPECIAL FEATURE

Clinical Practice Guideline

Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Carlos Fardella, Celso E. Gomez-Sanchez, Franco Mantero, Michael Stowasser, William F. Young Jr., and Victor M. Montori*

Prince Henry's Institute of Medical Research (J.W.F.), Clayton VIC 3168, Australia; University of Virginia Health System (R.M.C.), Charlottesville, Virginia 22908; Facultad de Medicina Pontificia Universidad Católica de Chile (C.F.), Santiago 1365, Chile; G.V. (Sonny) Montgomery VA Medical Center (C.E.G.-S.), Jackson, Mississippi 39216; University of Padova (F.M.), 35100 Padua, Italy; University of Queensland (M.S.), Brisbane QLD 4000, Australia; and Mayo Clinic (W.F.Y., V.M.M.), Rochester, Minnesota 55902

Objective: Our objective was to develop clinical practice guidelines for the diagnosis and treatment of patients with primary aldosteronism.

Participants: The Task Force comprised a chair, selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society, six additional experts, one methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Evidence: Systematic reviews of available evidence were used to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria to describe both the quality of evidence and the strength of recommendations. We used "recommend" for strong recommendations and "suggest" for weak recommendations.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during one group meeting, several conference calls, and multiple e-mail communications. The drafts prepared by the task force with the help of a medical writer were reviewed successively by The Endocrine Society's CGS, Clinical Affairs Core Committee (CACC), and Council. The version approved by the CGS and CACC was placed on The Endocrine Society's Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: We recommend case detection of primary aldosteronism be sought in higher risk groups of hypertensive patients and those with hypokalemia by determining the aldosterone-renin ratio under standard conditions and that the condition be confirmed/excluded by one of four commonly used confirmatory tests. We recommend that all patients with primary aldosteronism undergo adrenal computed tomography as the initial study in subtype testing and to exclude adrenocortical carcinoma. We recommend the presence of a unilateral form of primary aldosteronism should be established/excluded by bilateral adrenal venous sampling by an experienced radiologist and, where present, optimally treated by laparoscopic adrenalectomy. We recommend that patients with bilateral adrenal hyperplasia, or those unsuitable for surgery, optimally be treated medically by mineralocorticoid receptor antagonists. (*J Clin Endocrinol Metab* 93: 3266–3281, 2008)

2008

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- ❑ Ipertensione in stadio 2 (>160-179/100-109 mmHg), stadio 3 (>180/110 mmHg) secondo il Joint National Commission

- ❑ Ipertensione resistente alla terapia

- ❑ Ipertensione associata a ipokaliemia

- ❑ Ipertensione associata a ipokaliemia indotta da diuretici

- ❑ Ipertensione associata all'evidenza di incidentaloma surrenalico

  1 ⊕⊕◯◯

- ❑ Storia familiare di ipertensione precoce o incidente cerebrovascolare in età giovanile (<40 aa)

  1 ⊕◯◯◯

Prevalence of primary hyperaldosteronism in mild to moderate hypertension without hypokalaemia

JS Williams[1], GH Williams[1], A Raji[1], X Jeunemaitre[2], NJ Brown[3], PN Hopkins[4] and PR Conlin[1,5]

Table 2 Characteristics of hypertensive patients according to ARR screen

	Positive screen N = *26*	*Negative screen* N = *321*	P-*value*
Age, years	49.6 ± 1.2	48.5 ± 0.4	0.51
Aldo/PRA ratio	64.8 ± 6.0	14.8 ± 0.8	<0.01
Urine values			
Creatinine, mg/24 h	1442 ± 71	1449 ± 27	0.94
Na, mmol/24 h	255 ± 10	220 ± 4	0.01
K, mmol/24 h	74 ± 4	70 ± 1	0.36

Prevalence of PA in population with ***mild/moderate hypertension*** : 3.2%

Journal of Human Hypertension (2006) 20, 129–136

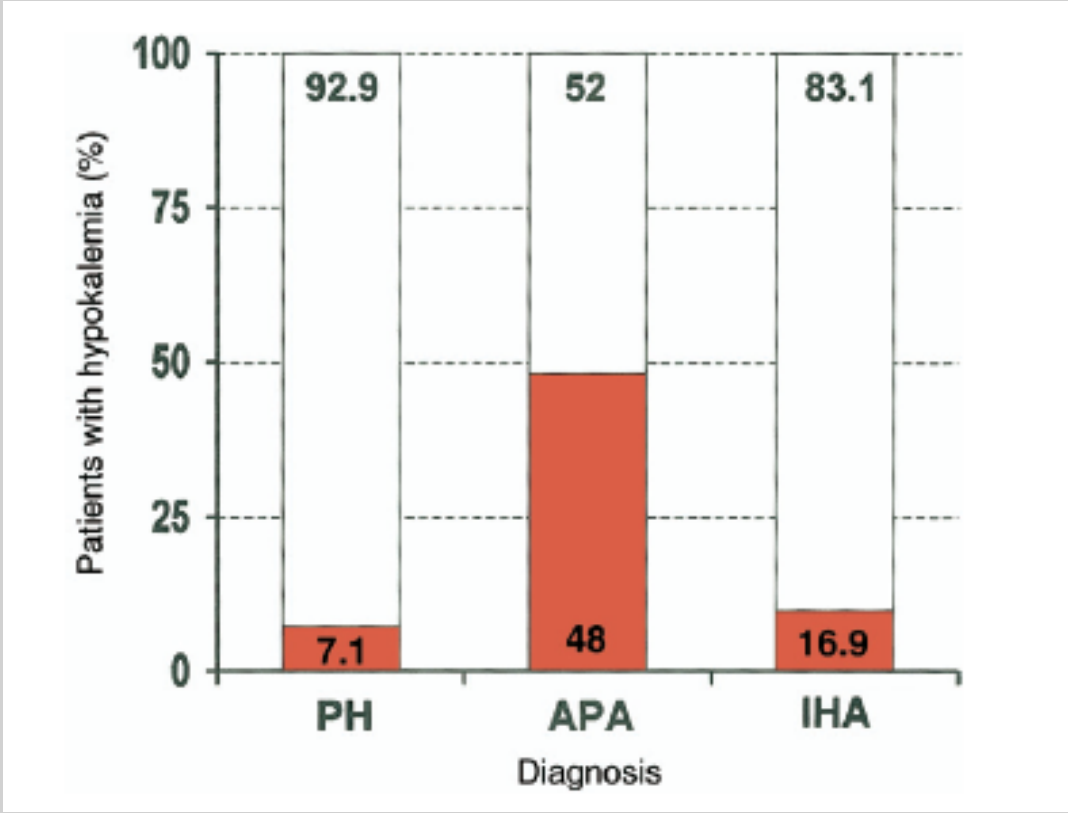
ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

Rossi *et al.*
Diagnosis of Hyperaldosteronism

JACC Vol. 48, No. 11, 2006
December 5, 2006:2293–300



ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Clinical Endocrinology (2008) 69, 20–28 doi: 10.1111/j.136

ORIGINAL ARTICLE

Clinical and biochemical characteristics of normotensive patients with primary aldosteronism: a comparison with hypertensive cases

Virginie Médeau*, François Moreau†, Ludovic Trinquart‡, Maud Clemessy§, Jean-Louis Wémeau¶, Marie Christine Vantyghem¶, Pierre-François Plouin* and Yves Reznik†

Evidence of primary hyperaldosteronism in a predominantly female cohort of normotensive individuals: a very hight odds ratio for progression in arterial hypertension

A Markou et al.

JCEM. 2013 **Apr;98(4):1409-16**

Quali pazienti sottoporre a screening?

Bari,
7-10 novembre 2013

Curr Hypertens Rep
DOI 10.1007/s11906-010-0134-2

Prevalence and Diagnosis of Primary Aldosteronism

Gian Paolo Rossi

Table 2 Conditions that should trigger the search for primary aldosteronism in a hypertensive patient

- Hypokalemia (spontaneous or diuretic-induced)
- Resistant hypertension; grade 2 or 3 hypertension
- Early-onset (juvenile) hypertension and/or stroke (<50 years)
- First-degree relatives of patients with primary aldosteronism
- Incidentally discovered, apparently nonfunctioning adrenal mass ("incidentaloma")
- Evidence of organ damage (left ventricular hypertrophy, diastolic dysfunction, AV block, carotid atherosclerosis, microalbuminuria, endothelial dysfunction), particularly if disproportionate for the severity of hypertension
- Obstructive sleep apnea syndrome
- Overweight/obesity

ALDOSTERONE: pitfalls

Bari,
7-10 novembre 2013

Alcuni Autori premono per estendere lo screening a tutti gli ipertesi considerando che:

-Più a lungo è misconosciuta la diagnosi più il paziente svilupperà danni irreversibili da ipertensione ed eccesso di aldosterone e minore sarà la risposta a terapia medica o chirurgica.

- Lo screening prima di iniziare la terapia permette di evitare l'effetto dei farmaci sull'interpretazione dell'ARR

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- Pazienti da sottoporre a screening
- Quale test di screening
- Importanza dei test di conferma?

Quale test di screening?

Bari,
7-10 novembre 2013

A Screening Test to Identify Aldosterone-Producing Adenoma by Measuring Plasma Renin Activity. Results in Hypertensive Patients

K Hiramatsu, T Yamada, Y Yukimura, I Komiya, K Ichikawa, M Ishihara, H Nagata, T Izumiyama

Arch Intern Med 1981, 141:1589-1593

ARR = aldosterone / PRA

Rappresenta il migliore test di screening. La sua applicazione ha aumentato drasticamente il numero di casi diagnosticati

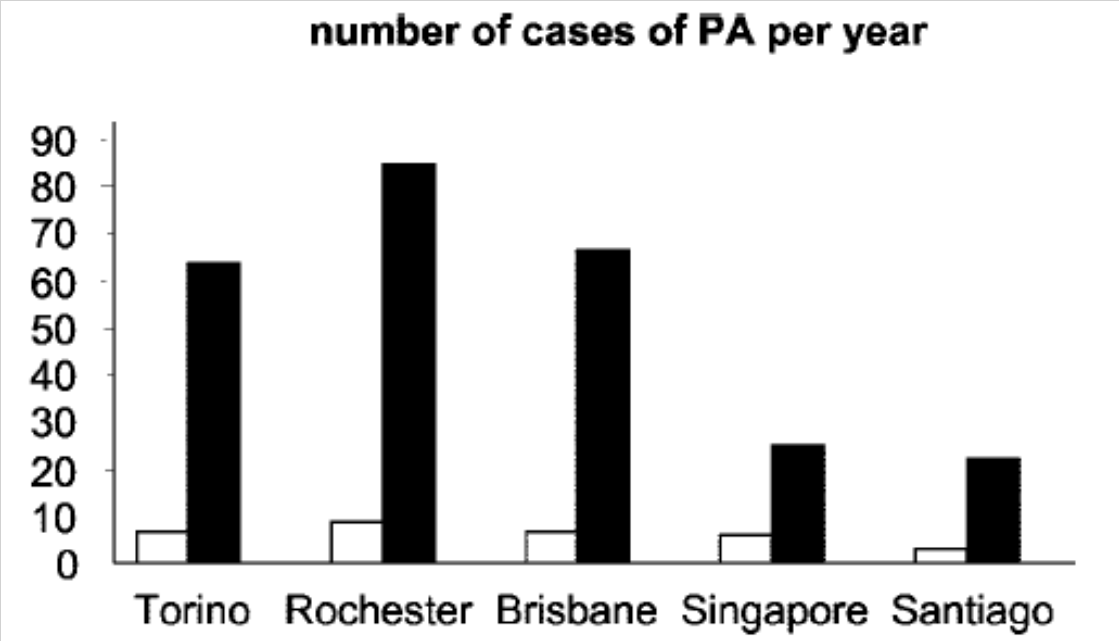
ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Increased Diagnosis of Primary Aldosteronism, Including Surgically Correctable Forms, in Centers from Five Continents

Mulatero *et al.*

J Clin Endocrinol Metab, March 2004, 89(3):1045–1050



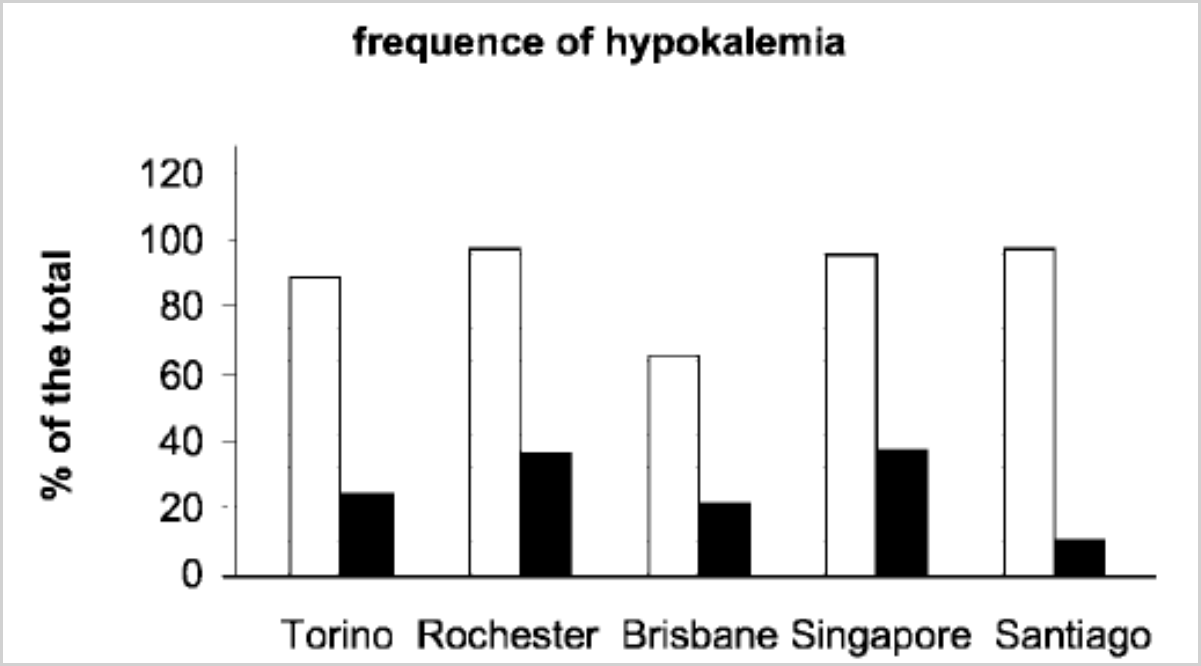
ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Increased Diagnosis of Primary Aldosteronism, Including Surgically Correctable Forms, in Centers from Five Continents

Mulatero *et al.*

J Clin Endocrinol Metab, March 2004, 89(3):1045–1050



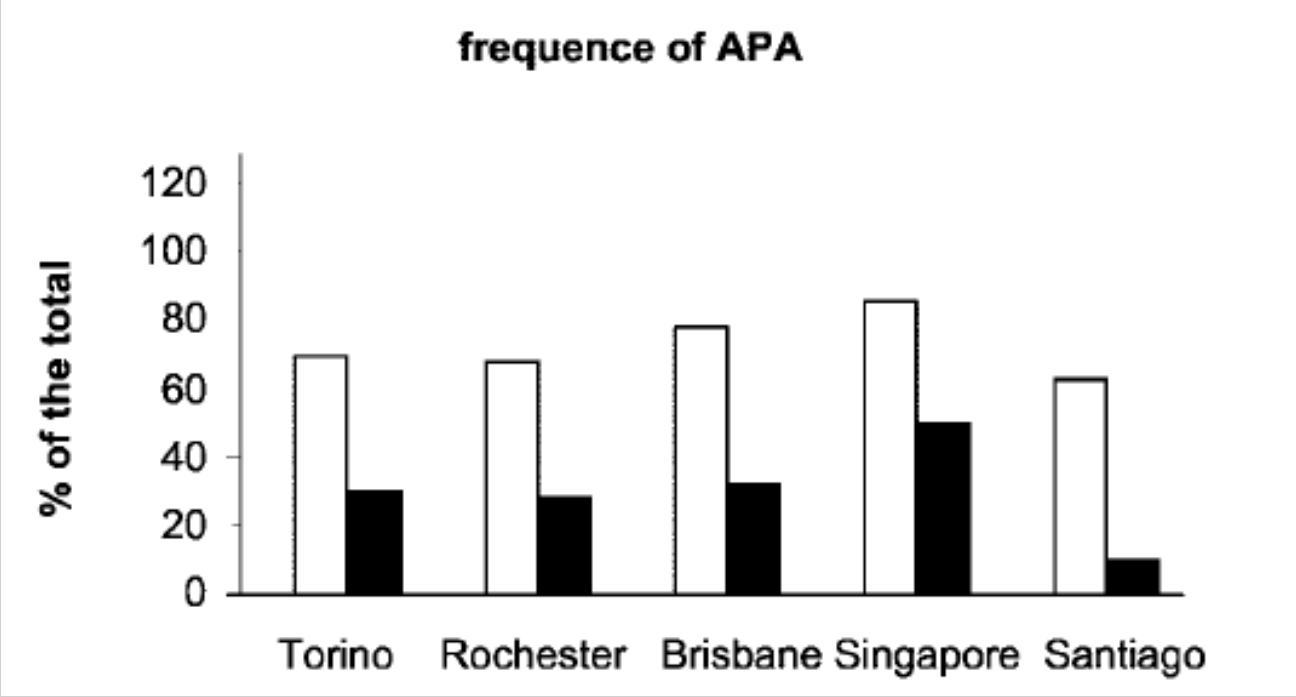
ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Increased Diagnosis of Primary Aldosteronism, Including Surgically Correctable Forms, in Centers from Five Continents

Mulatero *et al.*

J Clin Endocrinol Metab, March 2004, 89(3):1045–1050



ARR: pitfalls

Bari,
7-10 novembre 2013

- Variabili pre-analitiche

(età, sesso, postura, ipokaliemia, introito di sale, farmaci in corso, modallità di raccolta del campione, orario del prelievo)

- Quale cut off?

ARR: pitfalls

Bari,
7-10 novembre 2013

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
Beta-adrenergic blockers	↓	↓↓	↑ (FP)
Central alpha-2 agonists (e.g., clonidine, alpha-methyldopa	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
K^+-wasting diuretics	→↑	↑↑	↓ (FN)
K^+-sparing diuretics	↑	↑↑	↓ (FN)
ACE inhibitors	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
Ca^{2+} blockers (DHPs)	→↓	↑	↓ (FN)
Renin inhibitors	↓	↓↑*	↑ (FP)* ↓ (FN)*

ARR: pitfalls

Bari,
7-10 novembre 2013

Sospendere la terapia anti-ipertensiva?

Schirpenbach, Nature 2007	Sospendere almeno spironolattone e β-bloccanti. Meno importante sospendere ACEI e Ca-antagonisti.
PAPY	Terapia permessa: α-bloccanti e Ca-antagonisti.

Consensus **ESH 2013**

“…è necessario sospendere **beta bloccanti** e ovviamente **diuretici risparmiatori di potassio**”.

ARR: pitfalls

Bari,
7-10 novembre 2013

Potassium status			
Hypokalemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑ (FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓ (FN)
Sodium loaded	↓	↓↓	↑ (FP)
Advancing age	↓	↓↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑↑	↓ (FN)
Renovascular HT	↑	↑↑	↓ (FN)
Malignant HT	↑	↑↑	↓ (FN)

The ovarian cycle as a factor of variability in the laboratory screening for primary aldosteronism in women

	7th day	*14th day*	*21st day*	*28th day*	*Friedman's test*	*Significant multiple comparisons (Bonferroni-adjusted Wilcoxon test)*
PRA (ng ml^{-1} h^{-1})	0.23 (0.20–0.37)	0.40 (0.20–0.50)	0.35 (0.20–0.63)	0.31 (0.20–0.45)	0.004	7th vs 21st (=0.012) 7th vs 28th (=0.036)
ALDO (ng 100 ml^{-1})	11.2 (7.9–18.5)	15.7 (10.0–22.3)	17.8 (14.9–26.7)	16.2 (11.1–23.8)	0.004	7th vs 21st (=0.001)
ARR	42.5 (28.1–60.8)	45.0 (26.8–66.2)	50.2 (31.4–82.4)	50.0 (36.5–64.6)	NS	—
K (mEq l^{-1})	3.7 (3.6–4.1)	3.8 (3.5–4.0)	4.0 (3.7–4.3)	3.8 (3.7–4.0)	NS	—
SBP (mm Hg)	147 ± 17	143 ± 18	142 ± 14	140 ± 17	NS	—
DBP (mm Hg)	90 ± 10	85 ± 11	88 ± 6	82 ± 11	NS	—

	7th day	*14th day*	*21st day*	*28th day*	*χ^2 test*	*Significant multiple comparisons (Bonferroni-adjusted χ^2 test)*
Total number of women	26	25	25	21		
Parameters						
Cutoffs:						
ALDO						
>18 ng 100 ml^{-1}	6	10	11	9	NS	
>15 ng 100 ml^{-1}	8	15	19	12	0.012	7th vs 21st (=0.018)
>12 ng 100 ml^{-1}	12	18	21	15	0.030	
PRA						
<0.65 ng ml^{-1} h^{-1}	24	22	19	19	NS	
<0.5 ng ml^{-1} h^{-1}	23	19	18	17	NS	
<0.3 ng ml^{-1} h^{-1}	17	10	10	10	NS	
ARR						
>40	15	14	15	15	NS	
>35	17	18	17	17	NS	
>30	19	18	20	20	NS	
>30 with PRA <0.5 → =0.5	7	12	16	12	0.049	
>30 and ALDO >15 ng 100 ml^{-1}	7	12	17	10	0.034	7th vs 21st (=0.047)

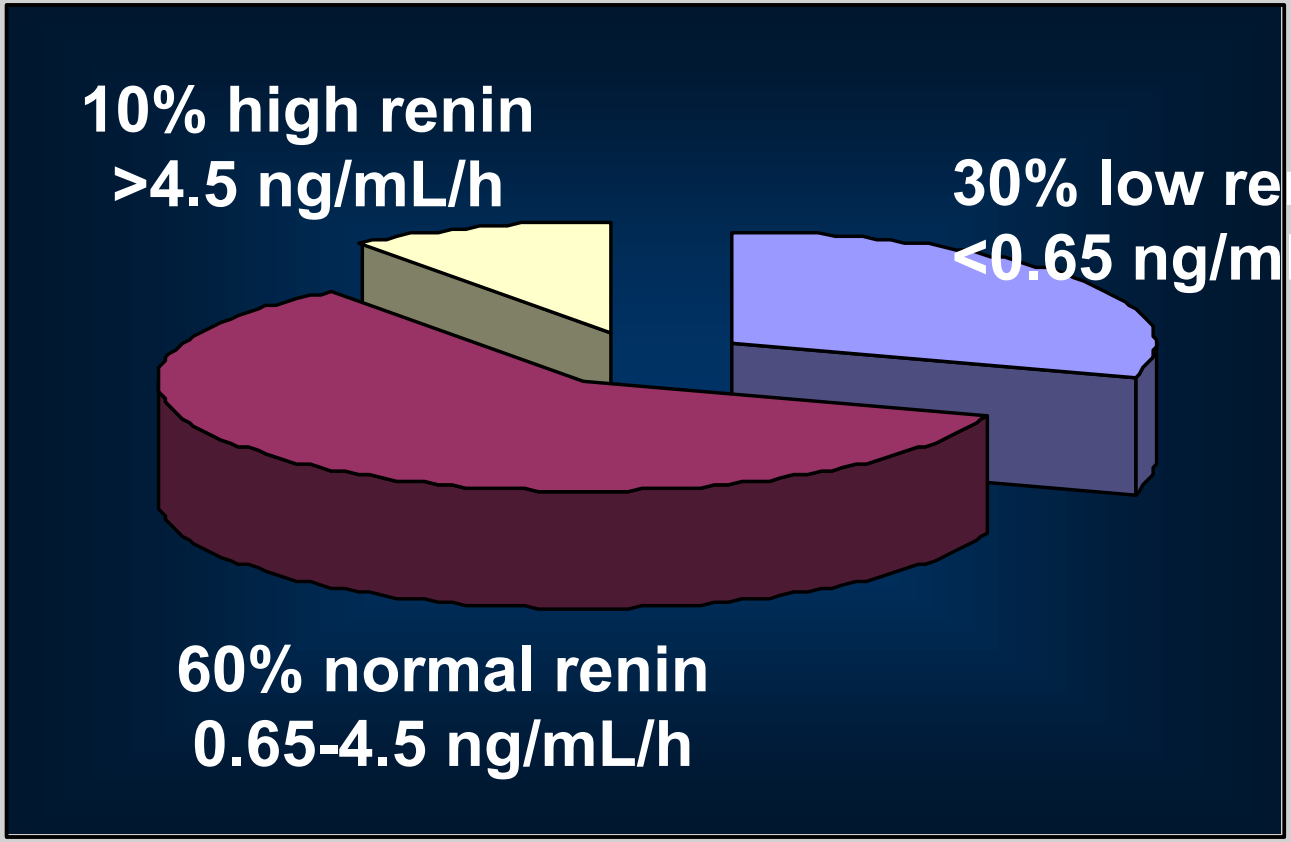
Fommei E. Journal of Human Hypertension 2009

Ipertensione Secondaria a Bassa Renina

Bari,
7-10 novembre 2013

- Iperaldosteronismo Primitivo
  - Sporadico
  - Familiare (GRA o FH-I, FH-II, FH-III)
- Pseudoipoaldosteronismo tipo II (sindrome di Gordon)
- Sindrome da eccesso apparente di mineralcorticoidi (AME)
  - Familiare
  - Acquisita (liquirizia, pompelmo)
- Sindrome di Liddle
- Mutazione attivante il recettore mineralocorticoideo
- Iperplasia surrenalica congenita
  - Deficit di 11beta-idrossilasi
  - Deficit di 17alfa-idrossilasi
- Resistenza ai glucocorticoidi

PRA values in the Hypertensive Population



Sealey J, Trends Endocrinol Metab 2005

Quale cut off?

Bari,
7-10 novembre 2013

Schirpenbach, Nature 2007	ARR (cut-offs 200-500)
Mulatero, Trend in E.M. 2005	ARR + Aldo>150 pg/ml
Giacchetti, J Hypertens 2006	ARR>400
PAPY 2006	ARR>400 Captopril: ARR>300
Kaplan, J Hypertens 2004	Elevato aldosterone plasmatico o urinario in supplemento orale di Na

Cut off

Bari,
7-10 novembre 2013

TEST POSITIVO

ARR = aldosterone / PRA

> valore ***laboratorio***

Verona
ARR >32-35

- **aldosterone** **smo probabile**
- **aldosterone 9–15 ng/dl iperaldosteronismo molto raro**
- **aldosterone < 9 ng/dl iperaldosteronismo improbabile**

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

- Pazienti da sottoporre a screening
- Quale test di screening
- Importanza dei test di conferma

ALDOSTERONE: certezze

Bari,
7-10 novembre 2013

Primary Aldosteronism Guidelines

2.1 **Instead of proceeding directly to subtype classification, we recommend that patients with a positive aldosterone-renin ratio (ARR) measurement undergo testing, by any of four confirmatory tests, to definitively confirm or exclude the diagnosis (Figure 1). (1⊕⊕OO)**

Confirmatory Tests in the Diagnosis of Primary Aldosteronism

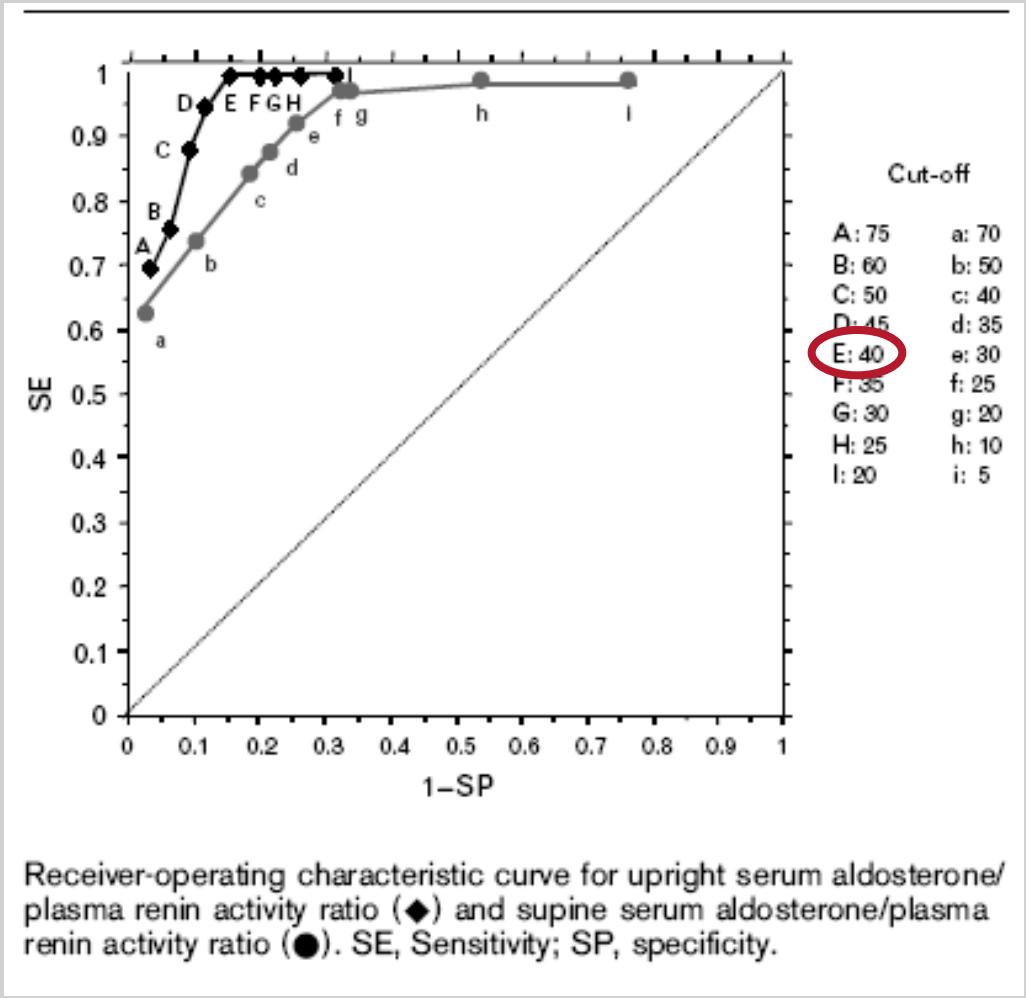
P. Mulatero[1], S. Monticone[1], C. Bertello[1], G. Mengozzi[2], D. Tizzani[1], A. Iannaccone[1], F. Veglio[1]

Horm Metab Res 2010; 42: 406–410

Analysis of screening and confirmatory tests in the diagnosis of primary aldosteronism: need for a standardized protocol

Gilberta Giacchetti[a], Vanessa Ronconi[a], Giulio Lucarelli[a], Marco Boscaro[a] and Franco Mantero[b]

J Hypertension 2006, 24: 737-745



Receiver-operating characteristic curve for upright serum aldosterone/plasma renin activity ratio (◆) and supine serum aldosterone/plasma renin activity ratio (●). SE, Sensitivity; SP, specificity.

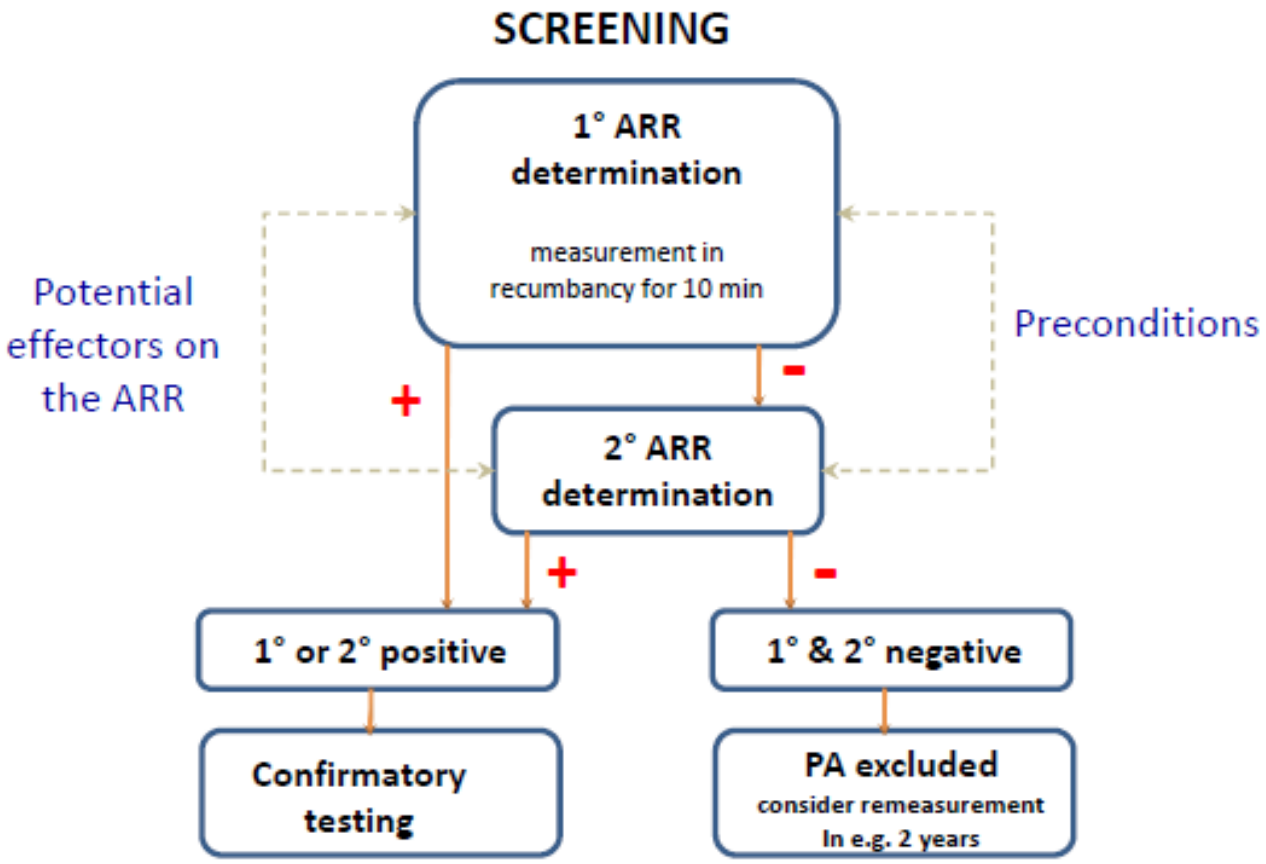
Review

Horm Metab Res 2010; 42(6): 382-391
DOI: 10.1055/s-0030-1248326

Aldosterone to Renin Ratio - A Reliable Screening Tool for Primary Aldosteronism?

A. Tomaschitz[1][*], S. Pilz[1][*]

[1] Department of Internal Medicine, Division of Endocrinology and Nuclear Medicine, Medical University of Graz, Graz, Austria



J. Clin. Endocrinol. Metab. 2004 89: 4221-4226

THE ENDOCRINE SOCIETY®

Aldosterone to Renin Ratio in a Primary Care Setting: The Bussolengo Study

OLIVIERO OLIVIERI, ALBERTO CIACCIARELLI, DENISE SIGNORELLI, FRANCESCA PIZZOLO, PATRIZIA GUARINI, CHIARA PAVAN, ANGELA CORGNATI, SALVATORE FALCONE, ROBERTO CORROCHER, ALESSIO MICCHI, CHIARA CRESSONI, AND GIANSTEFANO BLENGIO

Unit of Internal Medicine, Department of Clinical and Experimental Medicine (O.O., F.P., P.G., C.P., R.C.), and Institute of Clinical Chemistry (A.Co.), University of Verona, 37134 Verona, Italy; and General Practitioner (A.Ci., A.M., C.C.) and Service of Epidemiology, Bussolengo Health District (D.S., S.F., G.B.), 37012 Bussolengo, Italy

IN RECENT YEARS, growing evidence has consistently supported the view that arterial hypertension due to primary aldosteronism is much more frequent than was previously suspected

The final consideration stems from Lim's concept that an elevated AARR may serve as a guide for targeting drug therapy in hypertensive patients independently of the established diagnosis of aldosteronism (18, 19). Although this option was recommended for patients with resistant hypertension or those requiring more than two agents for BP control (17, 26), our results suggest that a much larger population could take advantage of such a therapeutic option.

Da: Clinical biochemistry discussion list
Inviato: lunedì 5 agosto 2013 13.43
A: ACB-CLIN-CHEM-GEN@JISCMAIL.AC.UK
Oggetto: Aldosterone assay requesting is likely to boom...

Mail Online health

Cheap cure for thousands with high blood pressure: Simple test could save thousands from life-threatening problems each year

- **At least 10% of the 16 million cases of high blood pressure are curable**
- **Cambridge University research suggests it can be detected using £15 test**
- **It would also greatly reduce the odds of heart attacks, strokes and other potentially fatal conditions**

By FIONA MACRAE

PUBLISHED: 17:38 GMT, 4 August 2013 | **UPDATED:** 06:38 GMT, 5 August 2013


Grazie per
l’attenzione