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Endocrine hypertension- molecules and genes

Marie Freel
Senior Lecturer in Endocrinology
ABCD Spring Meeting
2nd May 2014

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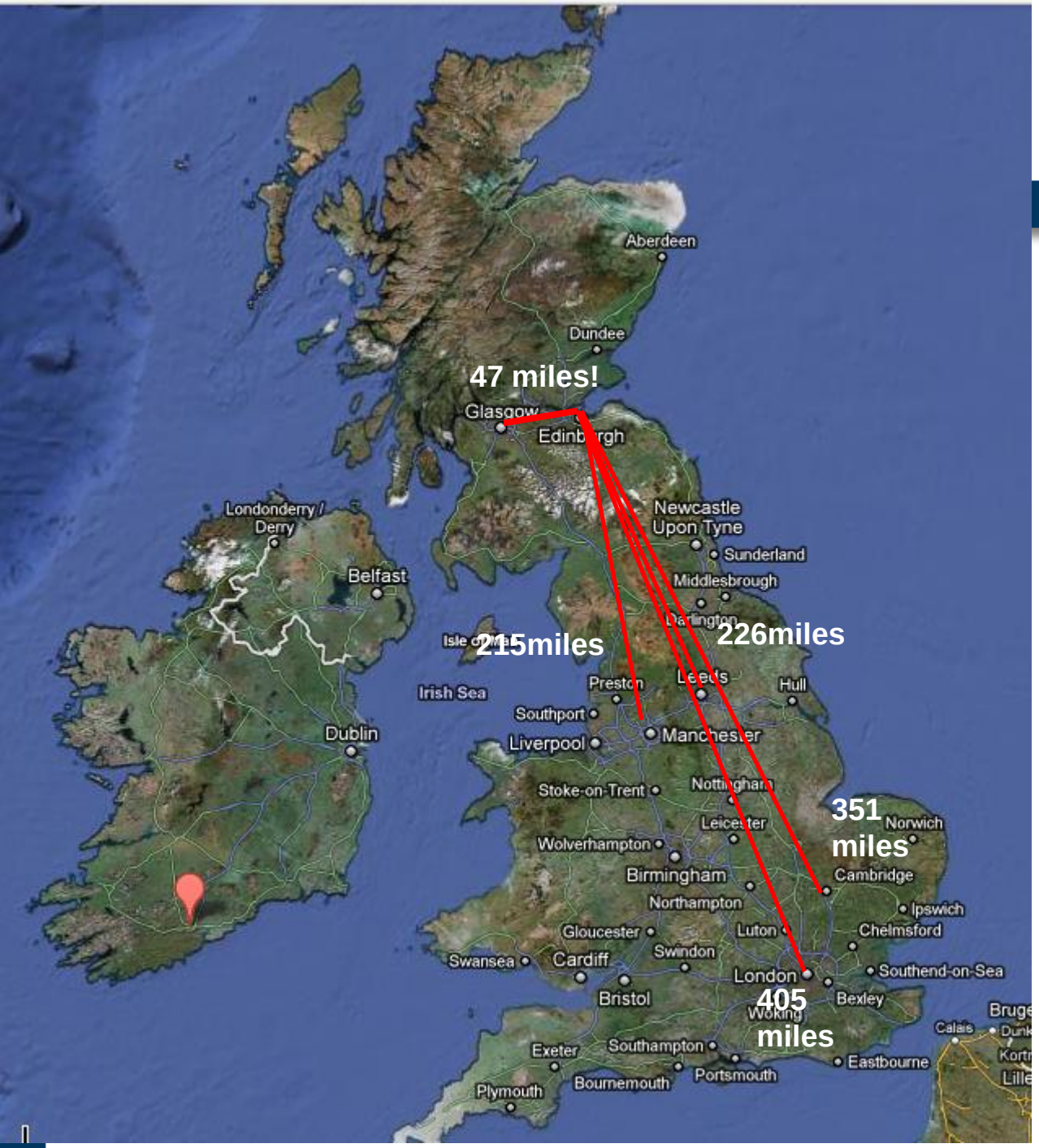

"An expert is someone who is more than 50 miles from home, has no responsibility for implementing the advice he gives and shows slides."
Edwin Meese III

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Plan

- Mineralocorticoid hypertension
- ‘Myths’ surrounding Primary Aldosteronism (PA)
- New developments in genetic aspects of PA

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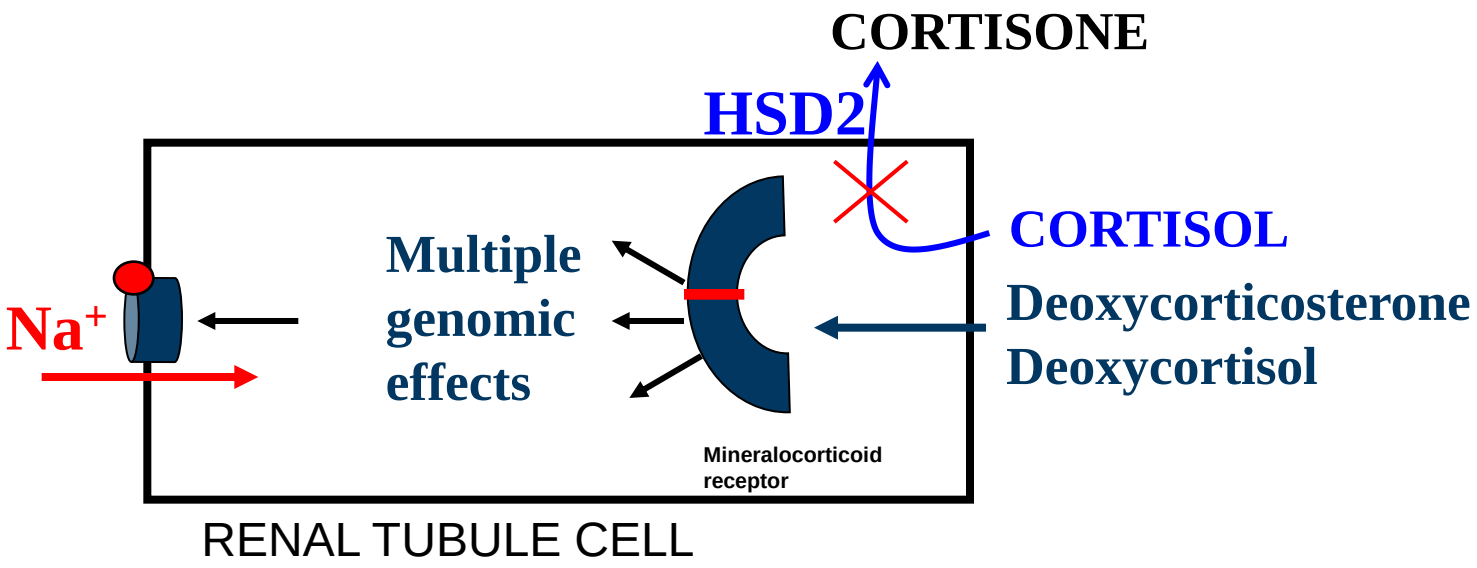
Mineralocorticoid actions



Post-receptor

Liddle's syndrome

Abnormal receptor

Progesterone induced hypertension

Abnormal ligand

Cortisol (syndrome of apparent mineralocorticoid excess-SAME)

Mineralocorticoid precursors (congenital adrenal hyperplasia -CAH)

Normal ligand

Primary Aldosteronism

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Just another case of hypertension…….?

- 38 y female
- 6 years of hypertension, well controlled on ramipril
- But now BP difficult to control (162/95 mm/Hg) despite addition of amlodipine
- UE: Na 136, K 4.1 Chl 95 Ur 4.2 Cr 68
- Plasma aldosterone (supine) 395 pmol/L (100-400), plasma renin activity (PRC) 1.2 µIU/ml (5-44.9)
  - Aldosterone to renin ratio (ARR) **329**

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The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
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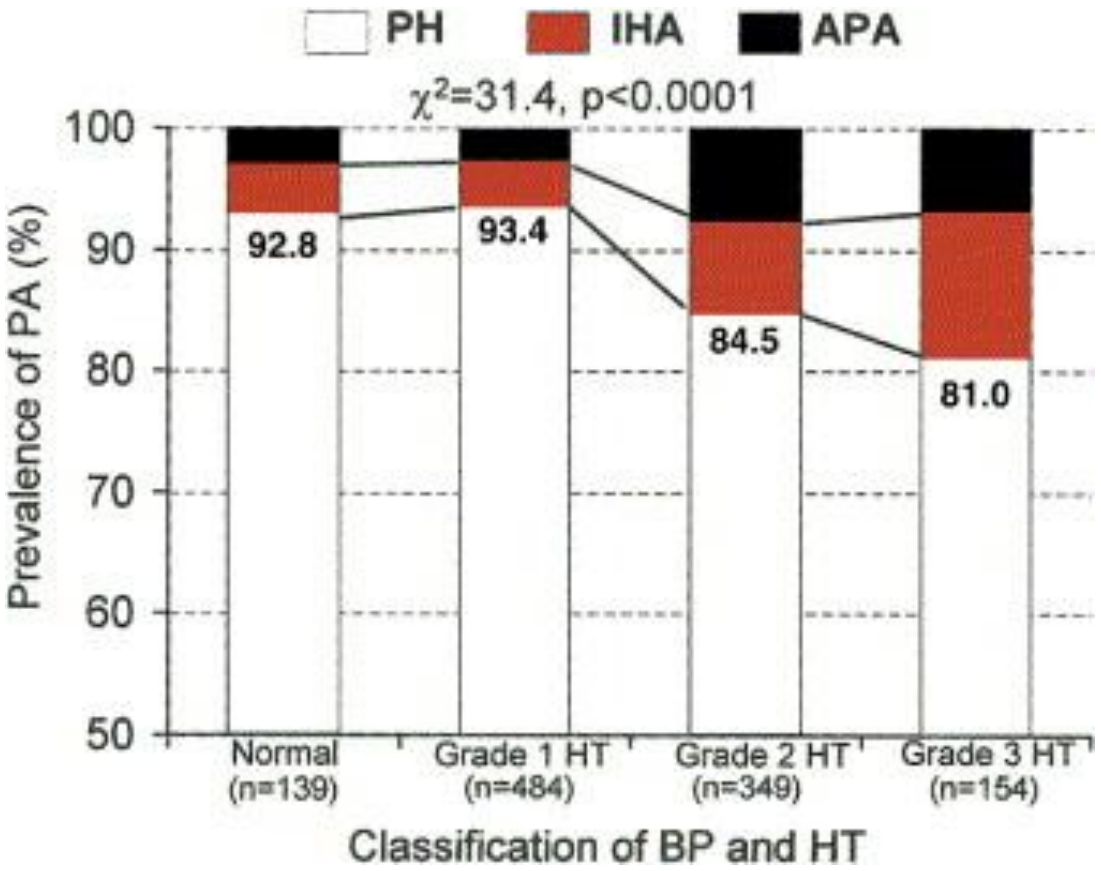
Prevalence of Primary Aldosteronism



Rossi et al. J Am Coll Cardiol 2006

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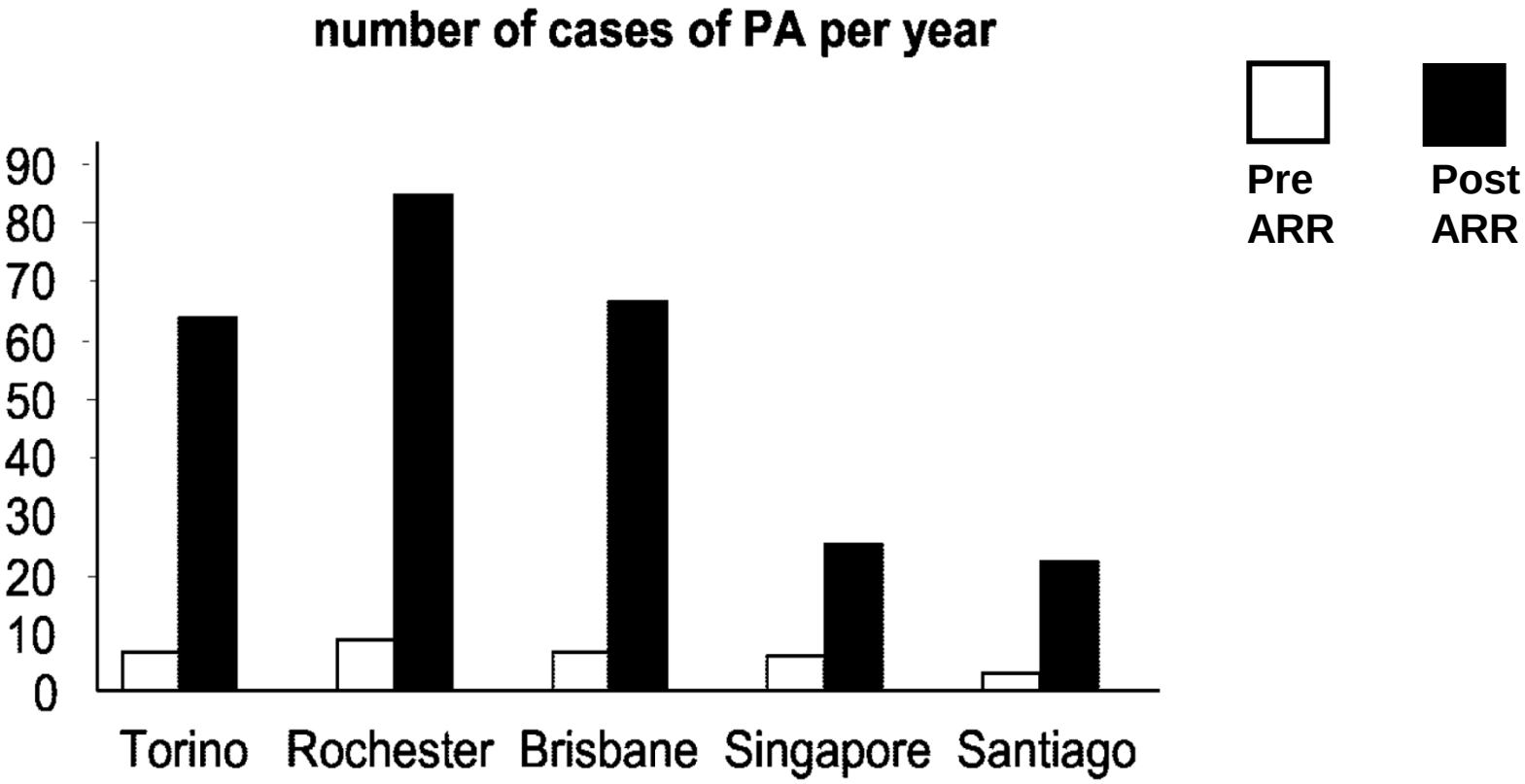
Five Continents study: change in PA detection rate



Mulatero *et al*, *JCEM*, 2004, 89, 1045

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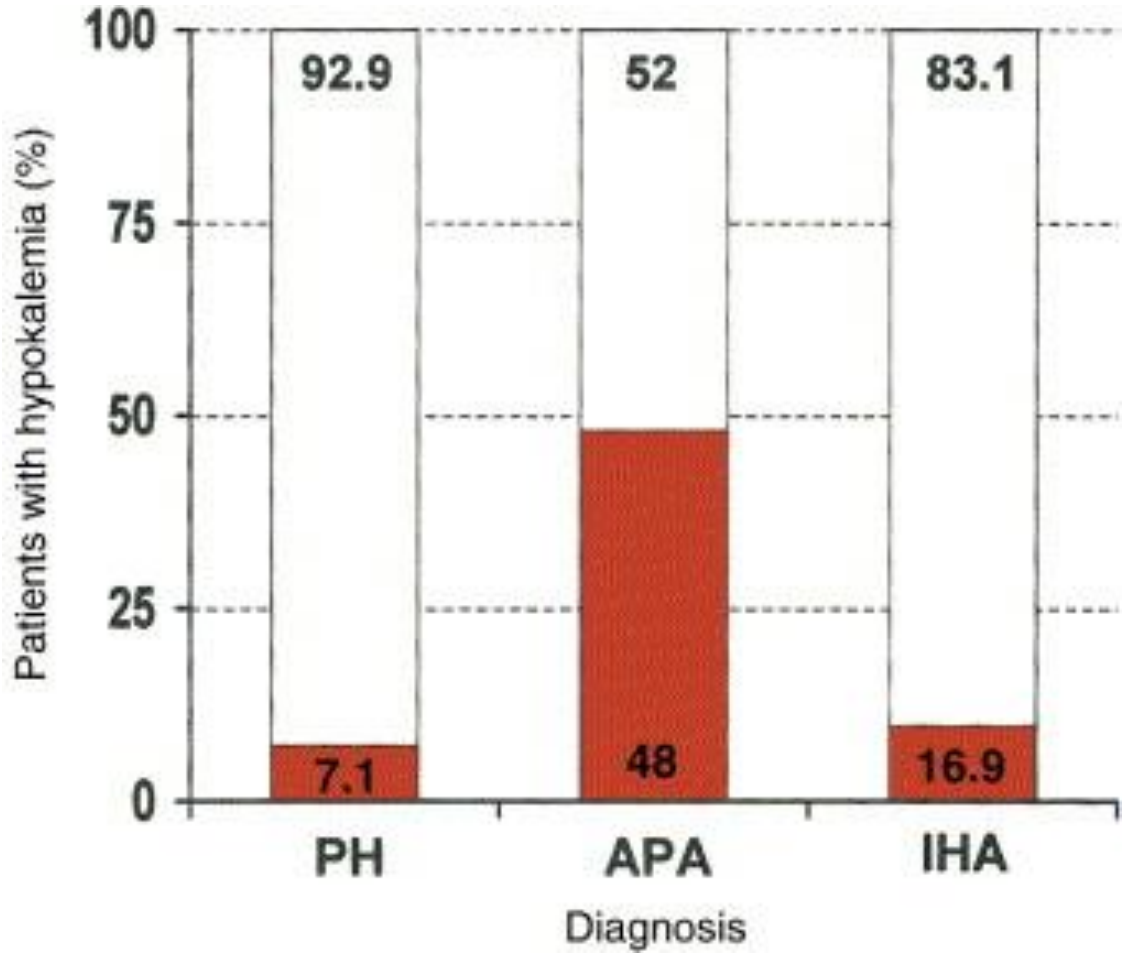
Hypokalaemia and Primary Aldosteronism



Rossi et al. J Am Coll Cardiol 2006

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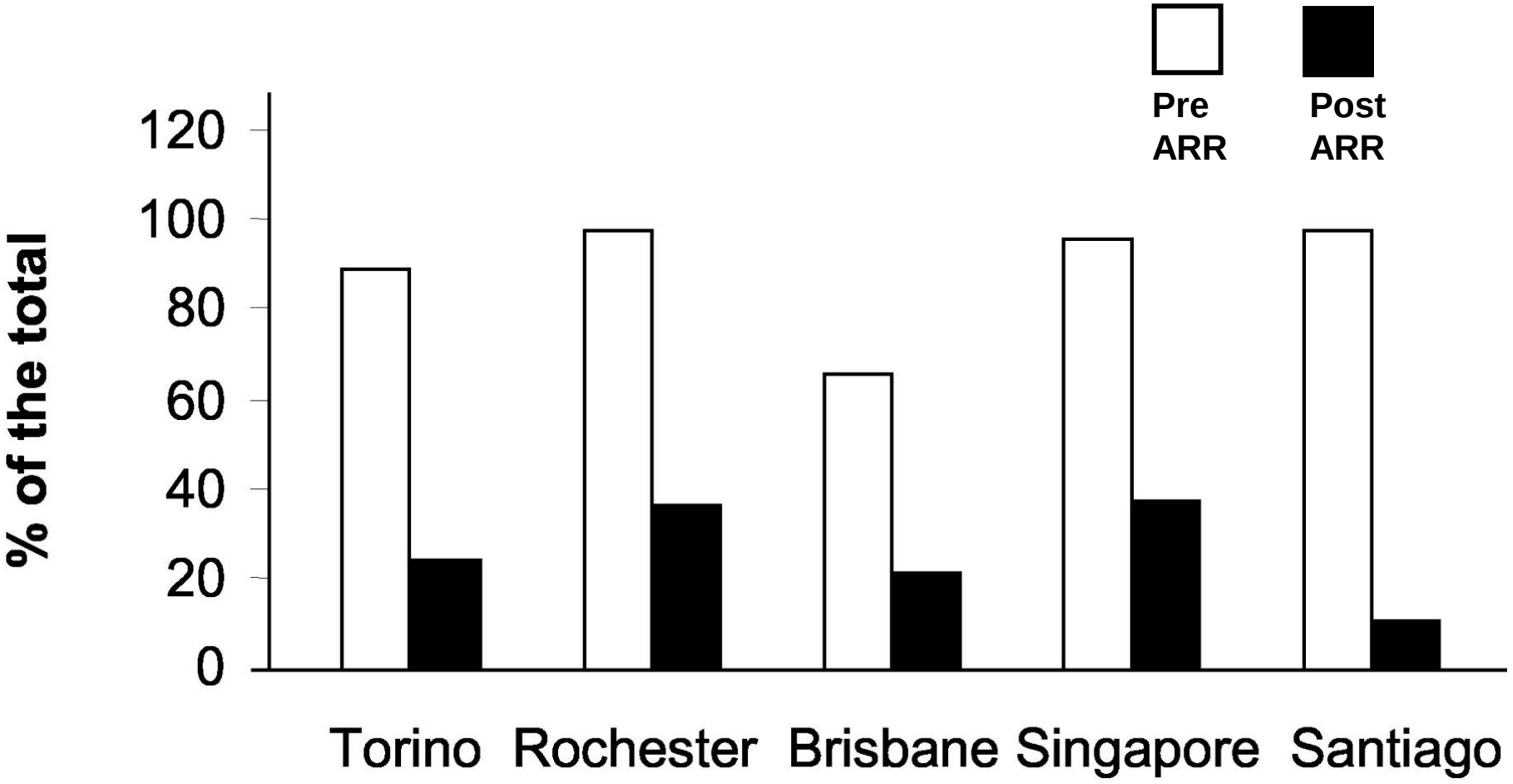
Frequency of hypokalaemia in PA



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PA or not PA?

- High ARR mainly due to low renin
- How does this differ from low-renin essential hypertension?
    - Subset of hypertensives with low PRA but normal aldosterone
    - Sodium sensitive, diuretic responsive
    - More common in elderly and black populations

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Spectrum of relative aldosterone excess

Bilateral Adrenal Hyperplasia

LREH

Essential Hypertension

Sodium intake

Genetic predisposition

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Does aldosterone need to be high in PA?

- Consider effects of medication
- What is high?
- Normal aldosterone (<416 pmol/L) in several studies:
  - 27/74 patients with definite PA on biochemical testing
  - 16/37 patients in another study
  - 4/21 with unilateral aldosterone excess proven on adrenal vein sampling (AVS)

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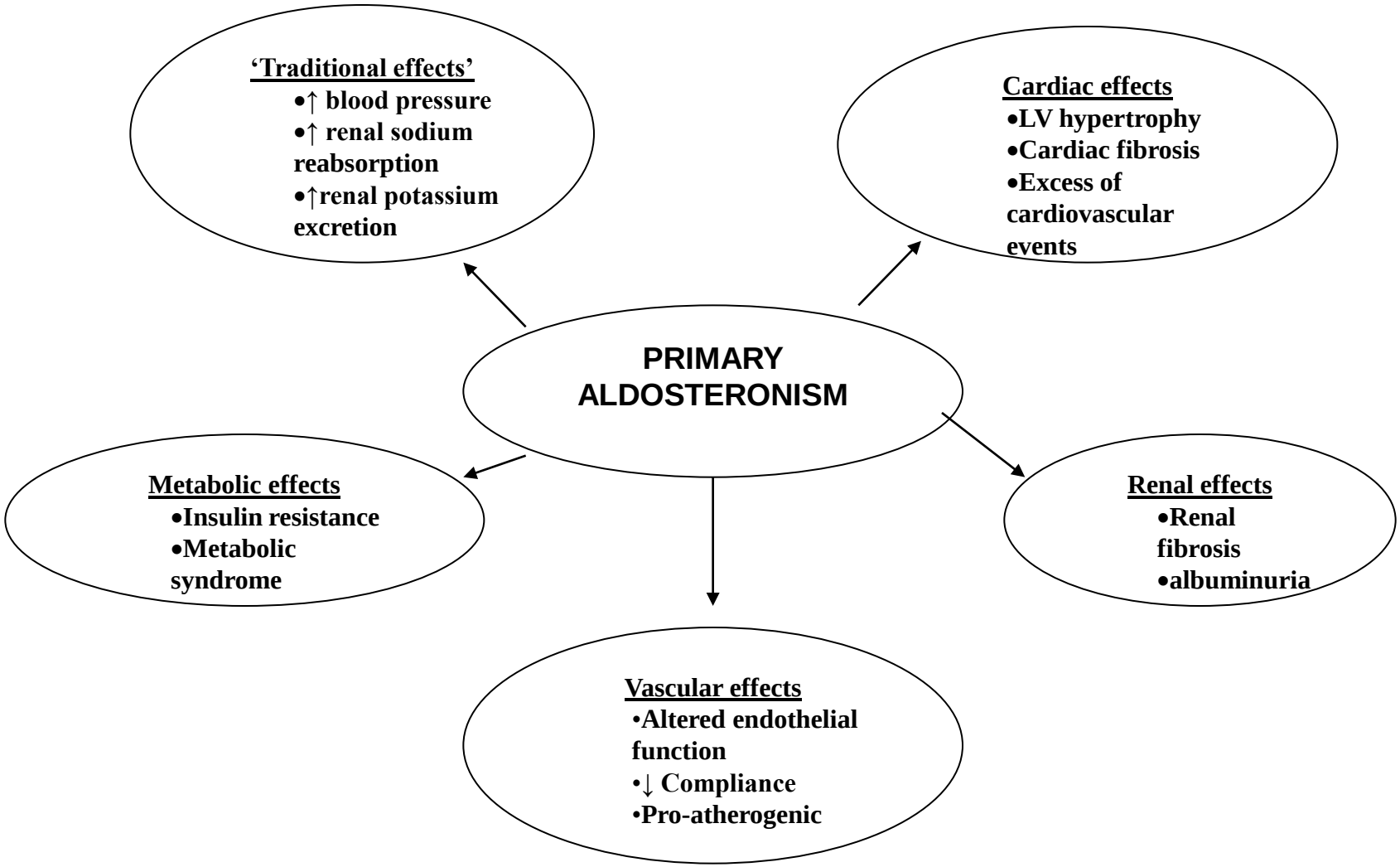
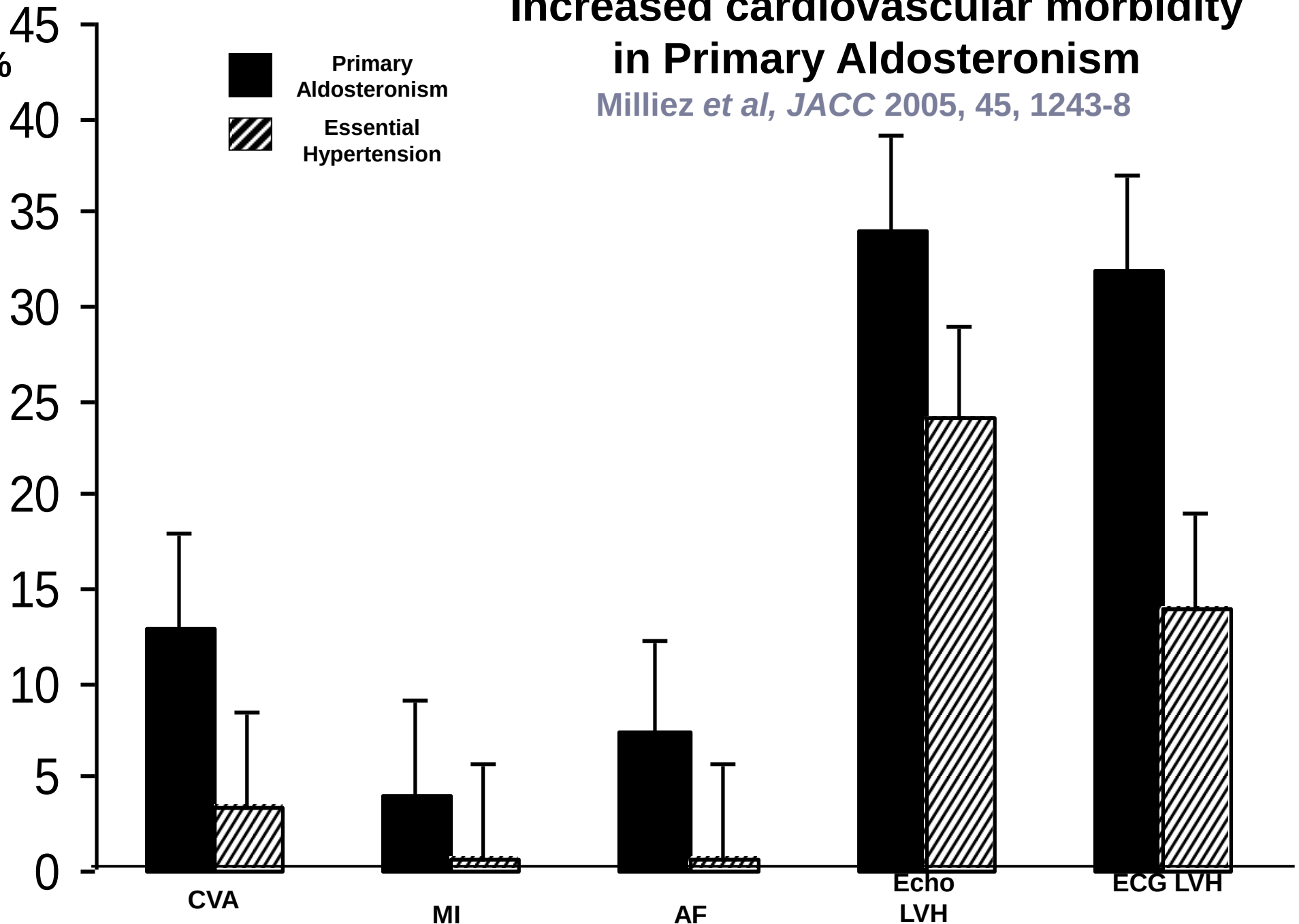
Multiple end organ effects of aldosterone excess



Increased cardiovascular morbidity in Primary Aldosteronism

Milliez *et al, JACC* 2005, 45, 1243-8



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Aldosterone and cardiovascular complications

Table 3. Published Series on Primary Aldosteronism and Cardiovascular Complications

	Number of patients		Blood Pressure		
Published Series	Cases	Controls	Cases	Controls	Conclusions
Takeda et al[25]	224 patients with surgically proven APA	224 sex- and age-matched patients with EH	170±26/94±15	179±25/106±17	Myocardial infarction (1.8% vs 4.0%) Heart failure (3.6% vs 4.0%)
Milliez et al[4]	124 patients with PA	465 patients with EH of similar age, sex, and BP	176±23/107±14	174±20/106±14	Myocardial infarction (4.0% vs 0.6%; OR, 6.5) Atrial fibrillation (7.3% vs 0.6%; OR, 12.1)
Catena et al[27]	54 patients with PA	323 patients with EH of similar age, sex, BMI, severity, and duration of HTN	167±16/103±9	166±18/103±8	Cardiovascular events more frequent in PA patients (35% vs 11%; OR, 4.61; $P<0.001$) Sustained arrhythmia (15% vs 3%; OR, 4.93) Cerebrovascular events (11% vs 3%; OR, 4.36) Coronary heart disease (20% vs 8%; OR, 2.80)
Current study	459 patients with PA	1290 patients with EH matched for age, sex, and BP	151±24/88±13	150±22/87±13	Myocardial infarction (4.4% vs 1.7%; OR, 2.8) Atrial fibrillation (3.9% vs 1.1%; OR, 4.3) Coronary artery disease (5.7% vs 2.8%; OR, 2.2) Heart failure (4.1% vs 1.2%; OR, 3.5)

Savard et al Hypertension 2013

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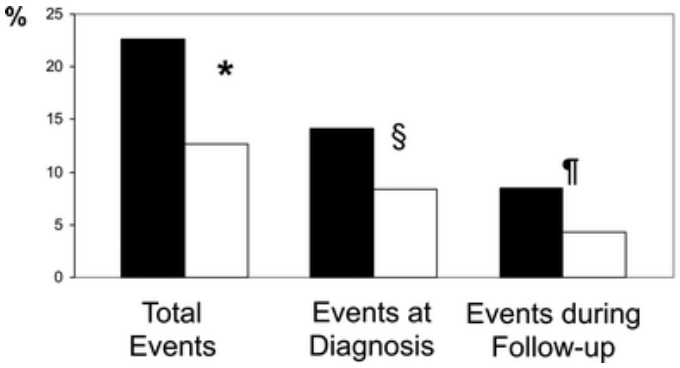
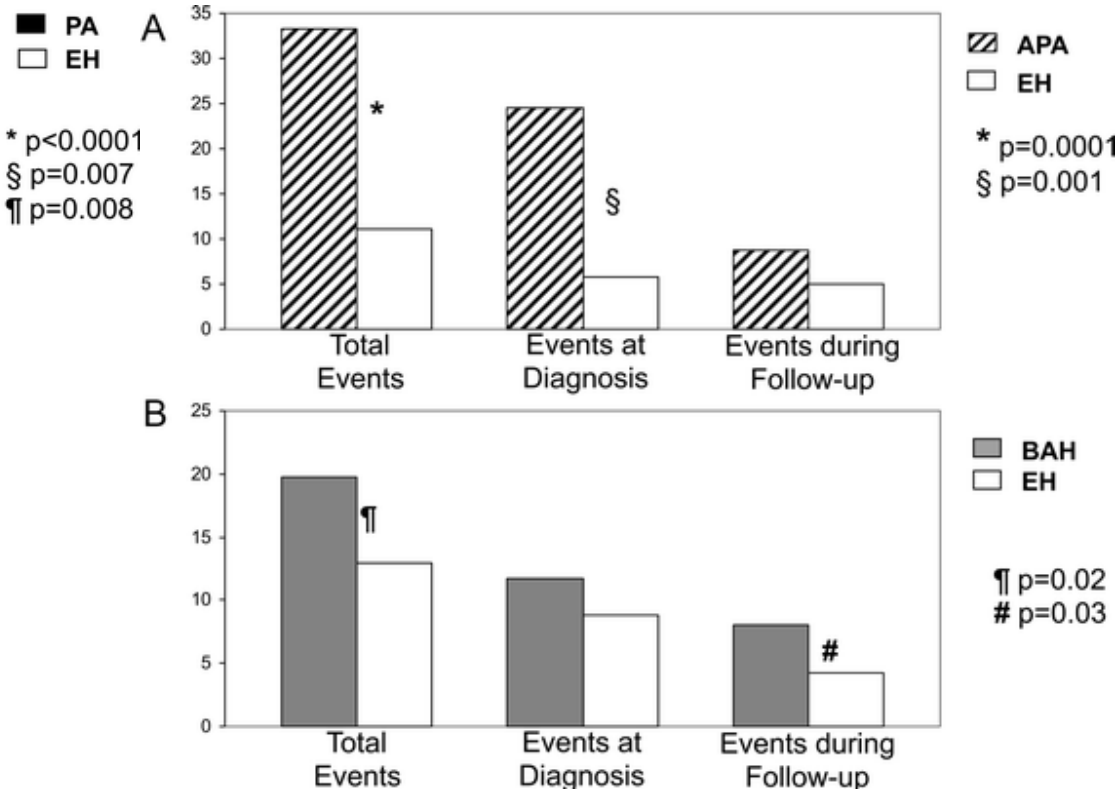
PA and cardio/cerebrovascular events





Mulatero JCEM 2013

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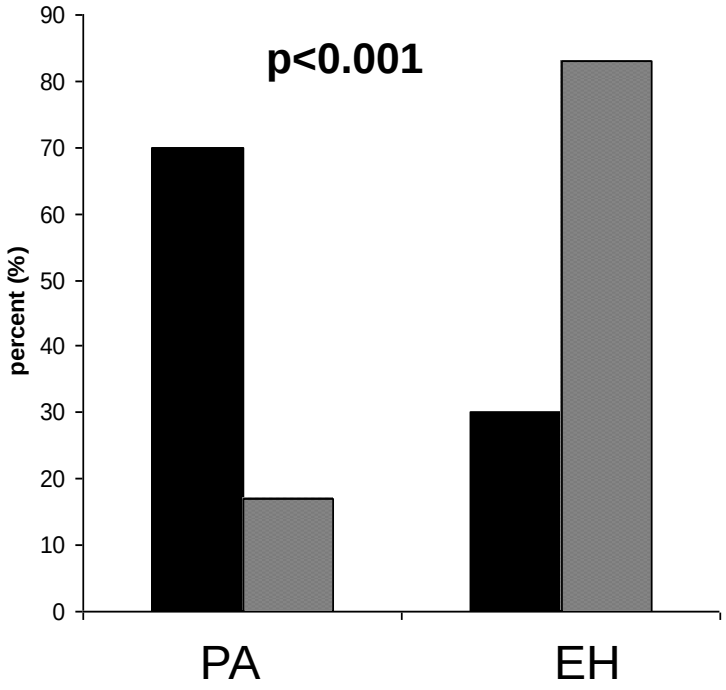
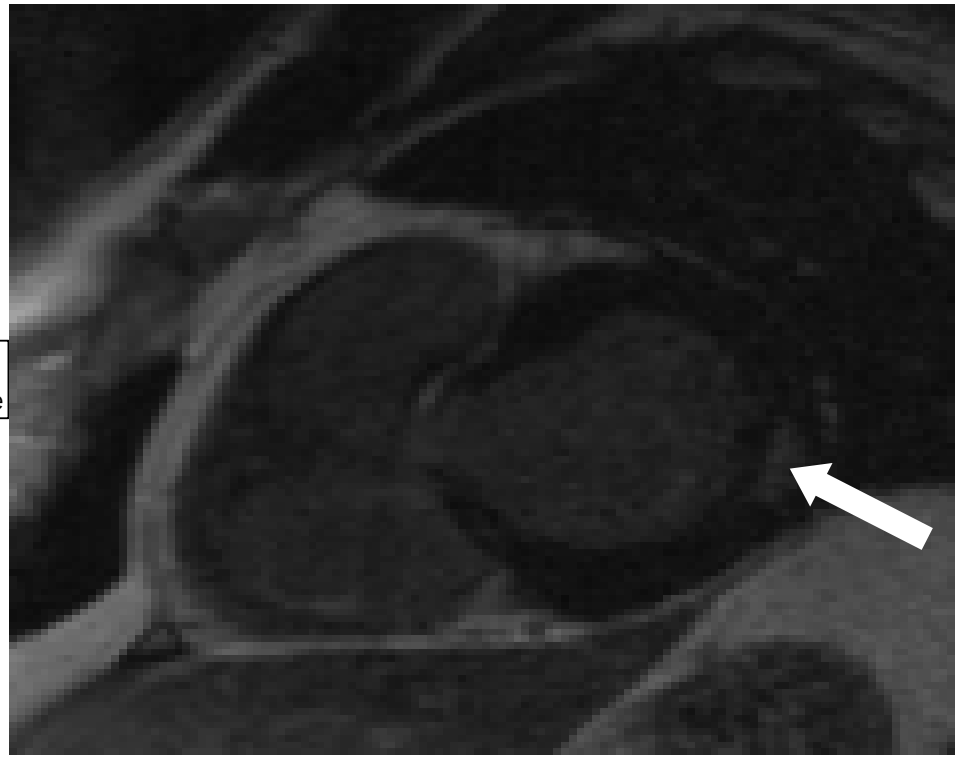
Myocardial fibrosis more common in PA versus EH patients





Freel et al. Circ CV Imaging 2013

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Genetic aspects of aldosterone excess

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Inherited aldosterone excess syndromes

- Familial hyperaldosteronism type I
  - Glucocorticoid remediable aldosteronism (GRA)
- Familial hyperaldosteronism type II
- Familial hyperaldosteronism type III

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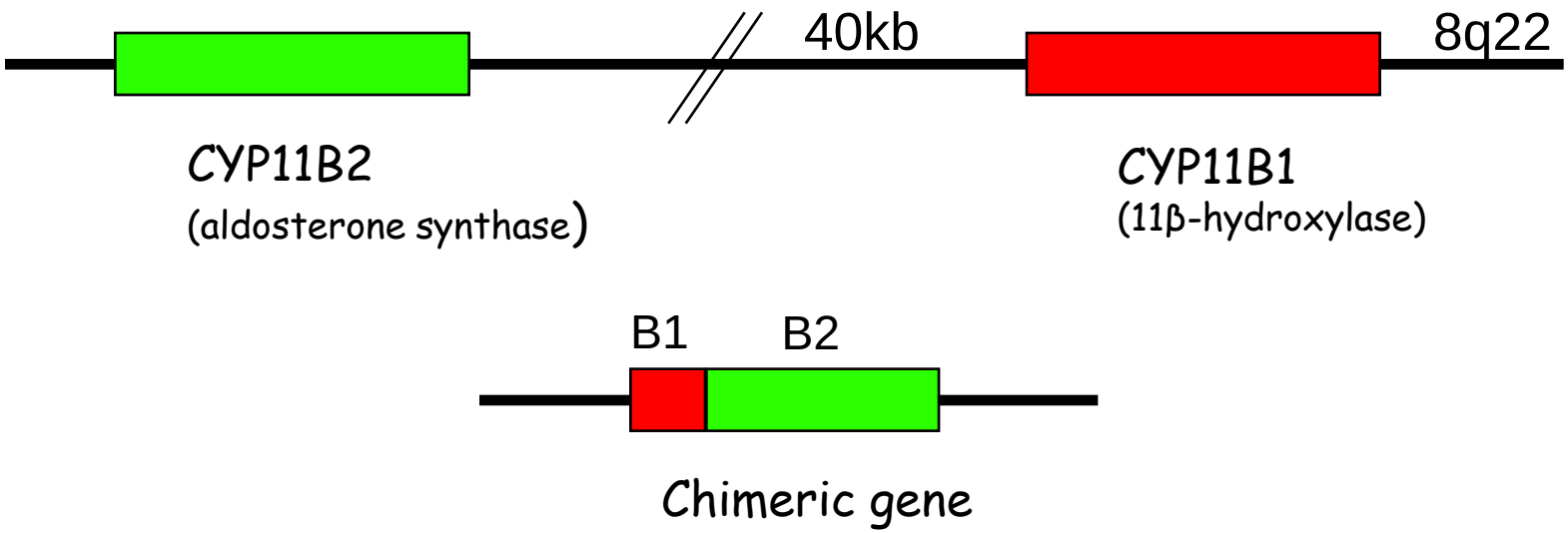
Glucocorticoid remediable aldosteronism (FH I)



- ACTH dependent aldosterone excess
- Autosomal dominant
- Severe hypertension in early life; hypokalaemia worsened by thiazide
- PCR to diagnose
- Treat with MR blockade or small dose of glucocorticoid

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Familial hyperaldosteronism type II

- Family history of PA, either APA or bilateral hyperplasia
  - Need 2 or more affected first-degree relatives
- Indistinguishable from non-familial PA
- Probably autosomal dominant
- Genetic basis unclear
  - Linkage has identified area on chromosome 7p22

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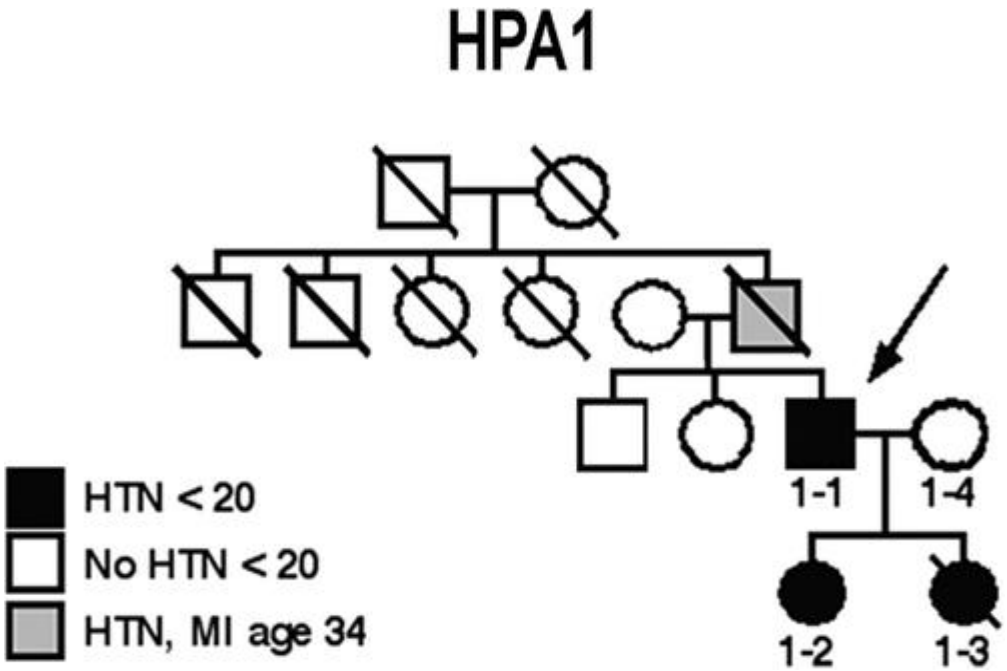
Familial hyperaldosteronism type III



- Severe, refractory hypertension in childhood
- Massive bilateral adrenal hyperplasia
- Bilateral adrenalectomy curative
- Rare, AD
- Genetic basis recently described: KCNJ5 gene mutations

Geller et al. JCEM 2008

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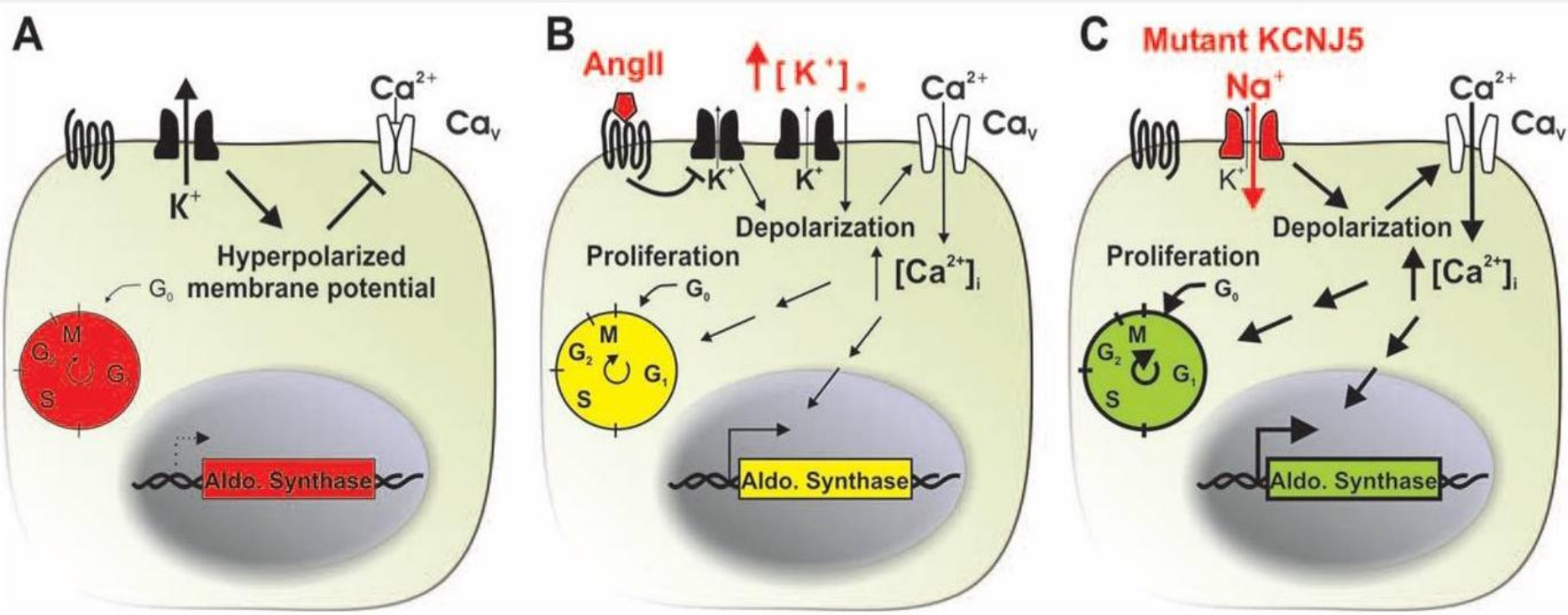
K channel mutations in FH III



Chio et al, Science, 2011, 331, 768-72

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KCNJ5 mutations summary

Author	Year	Number of APA	% somatic mutations	mutations
Choi et al	2011	22	41	G151R L168R
Boulkron et al	2012	380	35	G151R L168R
Akerstrom et al	2012	351	47	G151R L168R E145Q
Azizan et al	2012	73	41	G151R L168R Ile157del
Monticone et al	2012	47	38	G151R L168R
Mulatero et al	2012	46 (familial PA)	7	G151R L168R T158A

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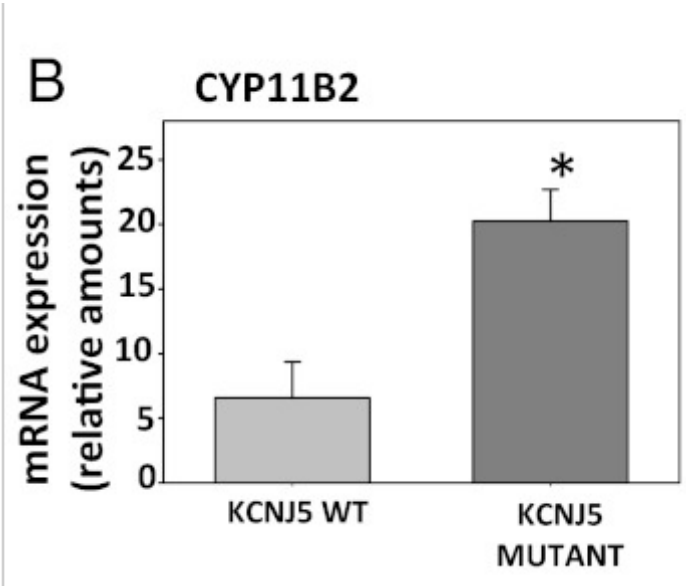
The genetics of APA

- Somatic mutations in KCNJ5 identified in aldosterone producing adenomas
- Mutant APA are larger and more common in women
- All cluster around selectivity filter of K+ channel pore
- Also evidence of ↑ CYP11B2 expression and aldosterone production



Monticone et al JCEM 2012

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Other somatic mutations in APA

- ATP1A1
  - α1 subunit of Na/K-ATPase
  - Prevalence of 5.2%
- ATP2B3
  - Plasma membrane Ca-ATPase
  - Prevalence of 1.6%
- CACNA1D
  - L-type Ca^{2+} channel
  - Prevalence of 11%

All lead to increased intracellular Ca^{2+}.

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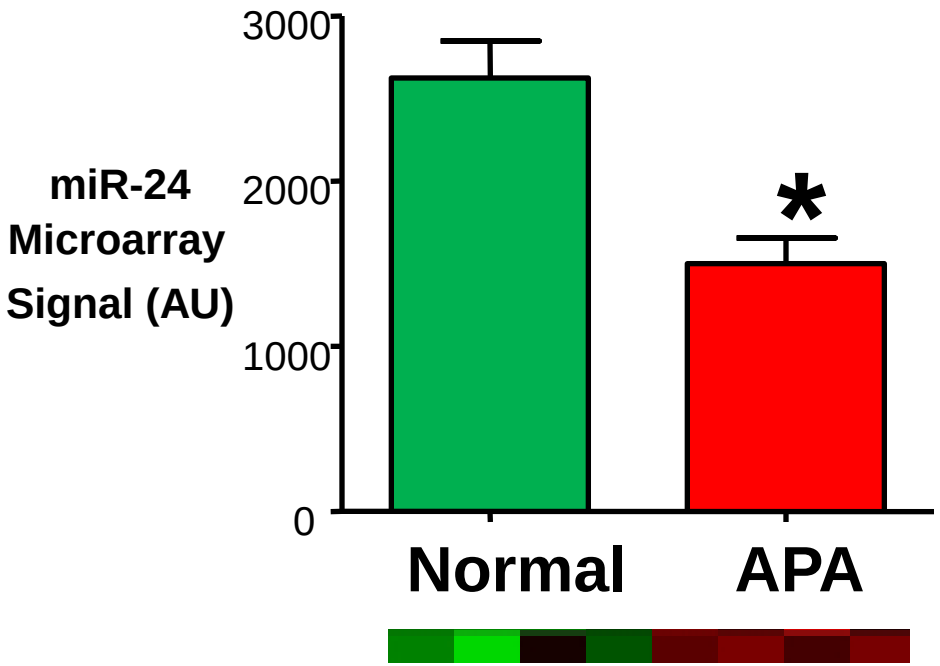
miRNA-24 in normal adrenals vs APA



N=4 normal adrenal
N=4 APAs

Robertson *et al*. Hypertension (2013);62(3):572-8.

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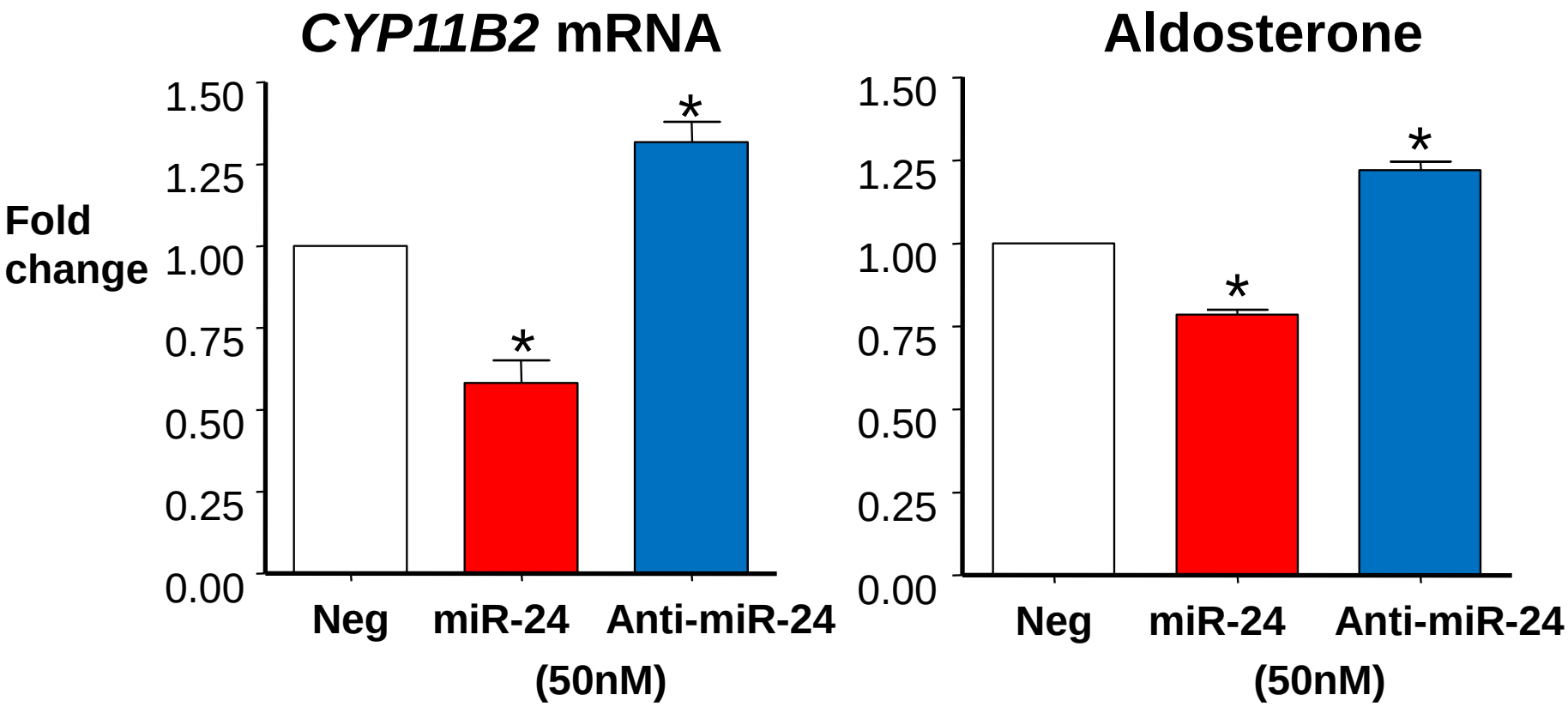
Role of micro RNA in modulation of aldosterone production

H295R cells



Decreased expression of miRNA-24 may contribute to increased aldosterone production in APA

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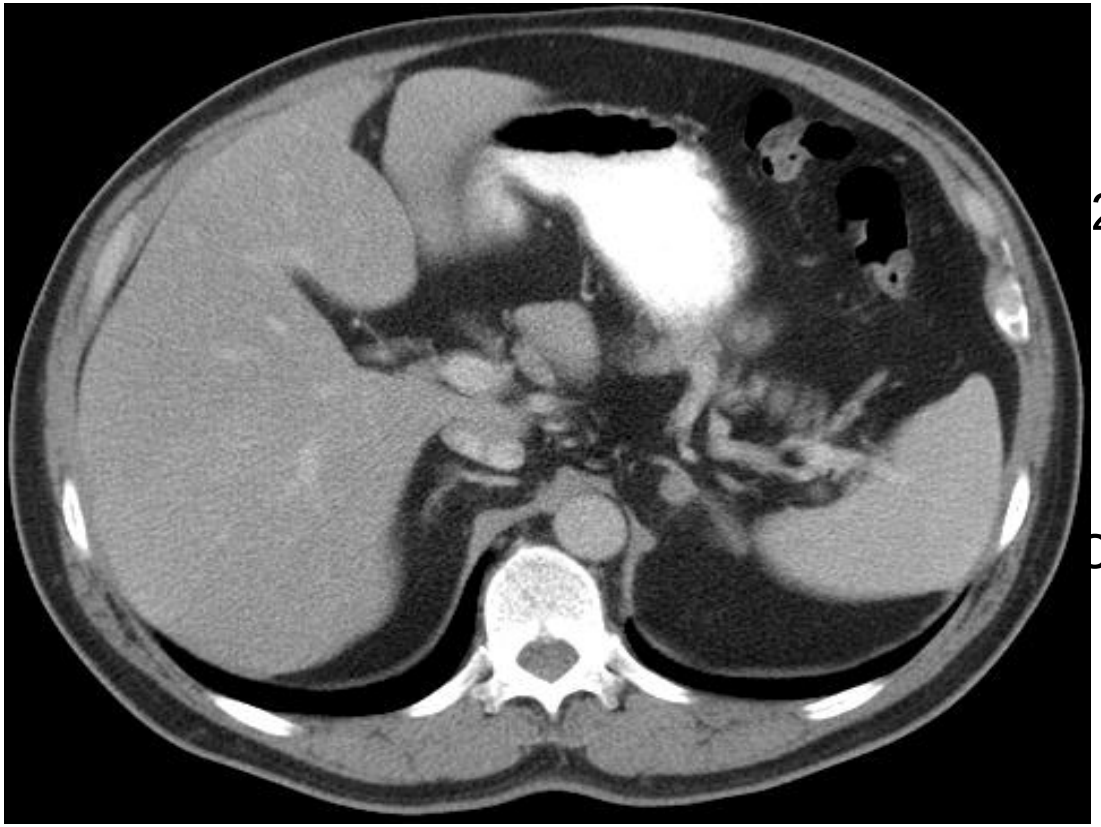
Not just another case of hypertension!



270

on no

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Summary

- Primary Aldosteronism found in 10% of ‘essential’ hypertension
  - Hypokalaemia in< 50%
  - Plasma aldosterone not necessarily elevated
- Aldosterone has deleterious effects independent of blood pressure
- Familial PA is rare
- Identification of common somatic mutations in APA provide novel therapeutic targets as well as insight into pathophysiology