Two medications I would actively stop in elderly patients

Dr Luc Radermacher

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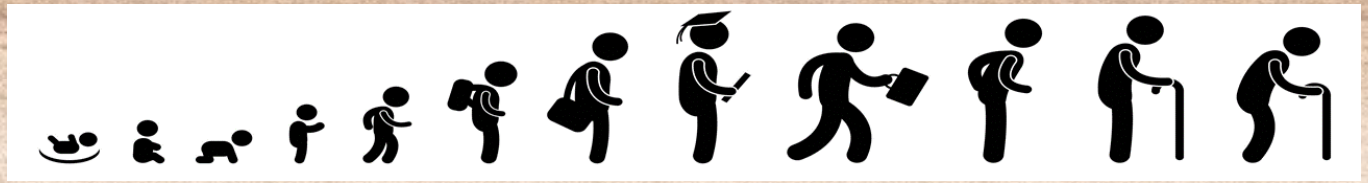
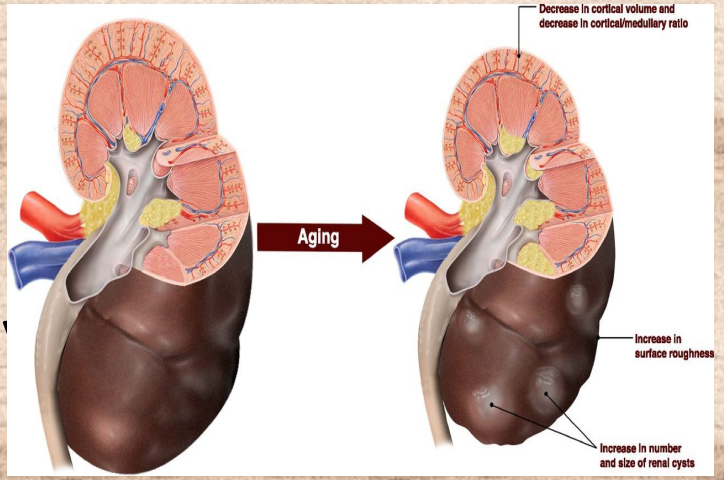
Aging



A chronic multi-organ failure:



- **Brain:** dementia, Parkinson, ...
- **Heart:** heart failure
- **Kidneys : renal insufficienc**
- **Lungs :** COPD – emphysema
- **Liver :** hepatocellular insufficiency - cirrhosis
- **Bones and joints :** oteoporosis and arthrosis
- **Sensory organs :** blindness, deafness, ...
- **Immune system :** fatal infections, cancers, ...
- **Skin :** wrinkles, lentigo, warts, hair loss, ...
- **Hormonal system :** hypothyroidism, diabetes, ...

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Natural aging of the kidneys

- **GFR Decline from age 35** :
  0.4 - 2.6 ml/min/year or 5 - 10% per decade

- **Causes :** Apoptosis / Regeneration => cell atrophy

⇒**Glomerular, tubular and vascular atrophy**

⇒**Glomerulosclerosis and ↓ tubular fct.**

⇒**Gradual loss of nephrons.**

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Prevalence of CKD with age

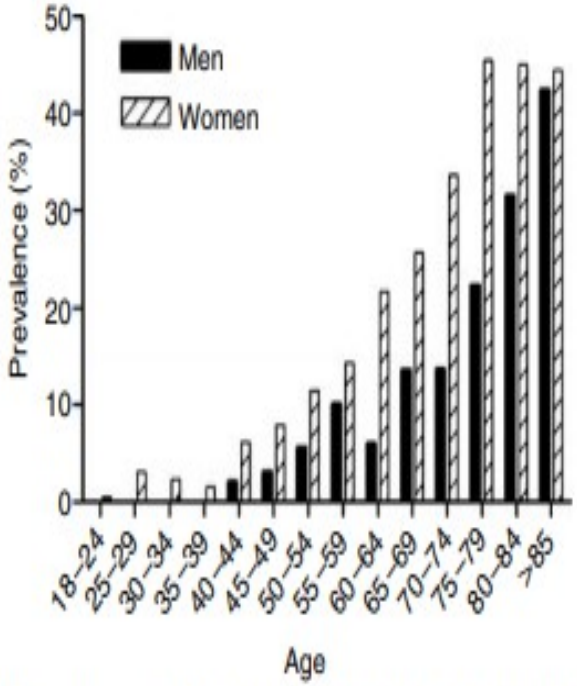

Figure 3 | Prevalence of CKD stages 3-5 (GFR < 60 ml/min/1.73 m^2) according to age in the non-diseased Caucasian Nijmegen Biomedical Study population. Black bars represent men and open bars women.

Kidney Int. Wetzels JSL et al. Sep.2007

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The chronic elderly

Multiple health concerns & complaints

Multiple preventive and curative therapeutic needs

Toxic iatrogenic loop

Polypharmacy

Increased side effects and toxicity

Drugs Interactions

PK modifications related to CKD and HF

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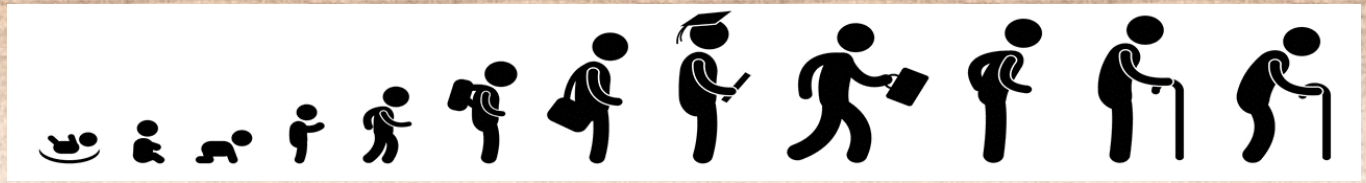
The chronic elderly



Customised and rationalized treatments:

- Identify preventive and curative priorities and progressively favour comfort care. Constantly weigh the risk/benefit ratio.
- Prescription support tools (STOPP & START list, EURO-FORTA list)
- Identify and neutralize the toxic iatrogenic loops
- Prefer drugs with a wide therapeutic window and low renal elimination (see www.renadaptor.org)

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The acute elderly

- Background:
  - Falls
  - Infections (gastroenteritis) and sepsis
  - Vascular injuries
  - ….etc….
- Direct consequences => Acute treatments/medications => Beware of AE, increase in indirect consequences and toxic loops
- Indirect consequences :
  - Neuro-cognitive decompensation => Alleviate / stop "neurotropic" medications
  - Stress cardiac decompensation => Reinforce tonicardiac treatment
  - Stress endocrine decompensation (Diabetes, adrenal, thyroid,...) => Reinforce replacement therapies
  - ARF => IV rehydration, discontinuing some medications, RRT
  - Acute MOF => Death

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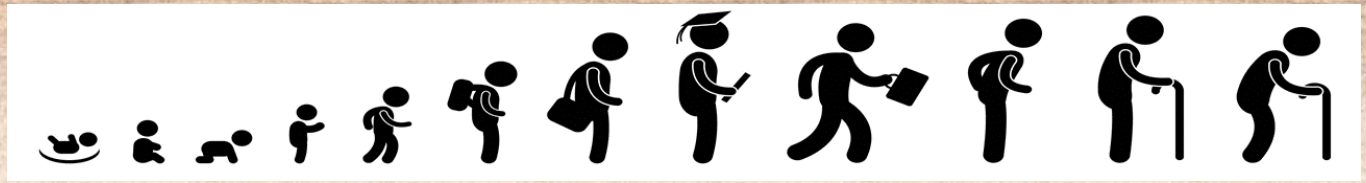
The chronic elderly



2 medications to stop

- Aspirin in primary prevention
- Statins in primary prevention

Medication to be discussed (risk/benefit ratio) especially if CKD

- Anticoagulants in AF (Beware of fallers)
- Antihypertensive drugs (Beware of orthostatic hypotension)
- Oral antidiabetics (Beware of hypoglycemia: sulfonylureas)
- Hypophosphoremics (Beware of digestive disorders, diarrhea, constipation, malnutrition)

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The chronic elderly

Discontinuation of aspirin in primary prevention:

Ineffective and increased bleeding risk

The NEW ENGLAND JOURNAL of MEDICINE

October 18, 2018

ORIGINAL ARTICLES

ASPREE Investigator Group

Effect of Aspirin on Disability-free Survival in the Healthy Elderly

J.J. McNeil and Others

In a trial comparing 100 mg of aspirin with placebo in nearly 20,000 community-dwelling persons 70 years of age or older in Australia and the United States, aspirin use had no effect on the rate of survival free from dementia or physical disability.

1499-1508 FREE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil and Others

In older persons without known cardiovascular disease, the use of low-dose aspirin resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo.

1509-1518 FREE

Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

J.J. McNeil and Others

After a median follow-up of 4.7 years, there were 1.6 more deaths per 1000 person-years among healthy older adults who were randomly assigned to receive aspirin than among those who received placebo. Cancer-related death accounted for much of the excess mortality.

1519-1528 FREE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group

A multicenter, randomized trial involving participants with diabetes and no evident cardiovascular disease at trial entry showed that aspirin led to a lower risk of serious vascular events than placebo but also caused a higher risk of major bleeding.

1529-1539 FREE

Figure 1. Cumulative Incidence of Cardiovascular Disease.

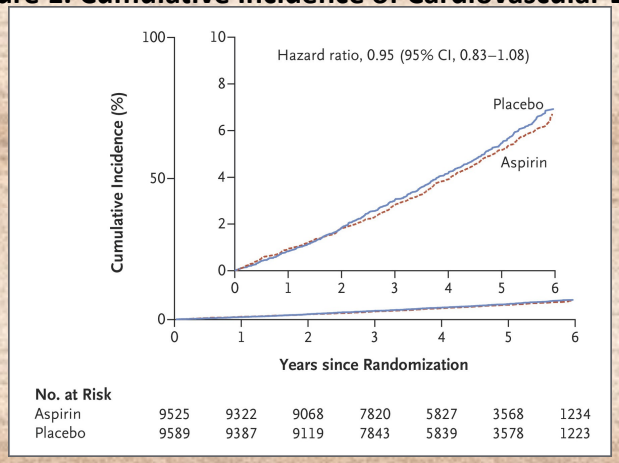
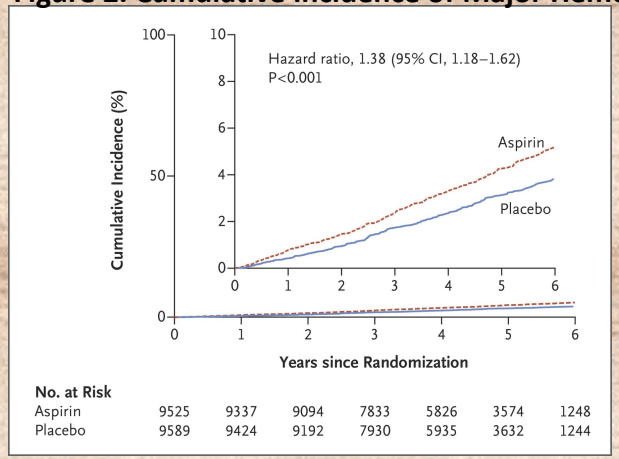


Figure 2. Cumulative Incidence of Major Hemorrhage.



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The chronic elderly

Discontinuation of aspirin in primary prevention:

Ineffective on CKD progression

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES 40 YEARS

NATIONAL KIDNEY FOUNDATION®

CORRESPONDENCE | ARTICLES IN PRESS

Effect of Aspirin on CKD Progression in Older Adults: Secondary Analysis From the ASPREE Randomized Clinical Trial

Kevan R. Polkinghorne, MBChB MClinEpi FRACP PhD • James B. Wetmore, MD MS • Le Thi Phuong Thao, PhD • ... Raj C. Shah, MD • John J. McNeil, MBBS MSc PhD FRACP FAFPHM • Anne M. Murray, MD MSc • Show all authors

Published: April 13, 2022 • DOI: https://doi.org/10.1053/j.ajkd.2022.02.019

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The chronic elderly

Discontinuation of statins in primary prevention (> 75 y)

Questionable effectiveness in terms of morbi-mortality

Increases the risk of AE and toxic cycles

THE LANCET

ARTICLES | VOLUME 393, ISSUE 10170, P407-415, FEBRUARY 02, 2019

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

Cholesterol Treatment Trialists' Collaboration † • Show footnotes

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The chronic elderly

Stopping statins for people > 75 years old

THE LANCET

ARTICLES | VOLUME 393, ISSUE 10170, P407-415, FEBRUARY 02, 2019

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
Participants without vascular disease			
≤55 years	290 (0·8)	408 (1·2)	0·68 (0·56–0·83)
>55 to ≤60 years	350 (1·0)	415 (1·2)	0·81 (0·67–0·99)
>60 to ≤65 years	416 (1·1)	545 (1·5)	0·73 (0·61–0·87)
>65 to ≤70 years	374 (1·2)	581 (1·8)	0·61 (0·51–0·73)
>70 to ≤75 years	400 (2·1)	462 (2·4)	0·84 (0·70–1·01)
>75 years	295 (2·7)	308 (2·8)	0·92 (0·73–1·16)
Total	**2125 (1·3)**	**2719 (1·6)**	**0·75 (0·71–0·80)**
Trend test χ^2_1=3·85 (p=0·05)			
Participants with vascular disease			
≤55 years	1927 (4·0)	2370 (5·1)	0·77 (0·71–0·83)
>55 to ≤60 years	1391 (4·2)	1692 (5·2)	0·80 (0·73–0·88)
>60 to ≤65 years	1822 (4·4)	2178 (5·3)	0·81 (0·75–0·88)
>65 to ≤70 years	1889 (4·3)	2286 (5·5)	0·79 (0·73–0·86)
>70 to ≤75 years	1593 (4·8)	1877 (5·8)	0·80 (0·73–0·88)
>75 years	756 (6·0)	845 (6·8)	0·85 (0·73–0·98)
Total	**9378 (4·4)**	**11248 (5·4)**	**0·80 (0·77–0·82)**
Trend test χ^2_1=1·42 (p=0·2)			

99% CI ◇ 95% CI

0·5 0·75 1 1·5

Statin or more intensive better | Control or less intensive better

Figure 4: **Effects on major vascular events per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation and by previous vascular disease**

Data from participants with missing baseline data included in the totals. RR=rate ratio.

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
≤75 years			
Heart failure trials	304 (3·0)	308 (3·1)	0·96 (0·79–1·16)
Dialysis trials	432 (7·9)	459 (8·5)	0·93 (0·78–1·11)
Other trials	9716 (2·9)	12 047 (3·6)	0·77 (0·74–0·80)
Subtotal	**10 452 (2·9)**	**12 814 (3·7)**	**0·78 (0·76–0·80)**
Heterogeneity test χ^2_1=14·51 (p=0·0001)			
>75 years			
Heart failure trials	175 (4·8)	189 (5·1)	0·95 (0·75–1·22)
Dialysis trials	74 (12·8)	71 (11·4)	1·10 (0·71–1·71)
Other trials	802 (4·1)	893 (4·7)	0·82 (0·70–0·95)
Subtotal	**1051 (4·5)**	**1153 (5·0)**	**0·87 (0·79–0·96)**
Heterogeneity test χ^2_1=3·37 (p=0·07)			
All participants			
Heart failure trials	479 (3·5)	497 (3·6)	0·95 (0·82–1·11)
Dialysis trials	506 (8·3)	530 (8·8)	0·95 (0·81–1·12)
Other trials	10 518 (2·9)	12 940 (3·7)	0·77 (0·75–0·80)
Total	**11 503 (3·0)**	**13 967 (3·7)**	**0·79 (0·77–0·81)**
Heterogeneity test χ^2_1=21·01 (p<0·0001)			

99% CI ◇ 95% CI

0·5 0·75 1 1·5

Statin or more intensive better | Control or less intensive better

Figure 2: **Effects on major vascular events per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation and particular trial populations**

Data from participants with missing baseline data included in the totals. RR=rate ratio.

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The chronic elderly

Statins in dialysis patients

Is serum phosphate associated with statin efficacy in dialysis patients?

CJASN
Clinical Journal of the American Society of Nephrology

Methods and Cohorts

The AURORA Study

2776 patients on dialysis

Randomized to high intensity statin or placebo

MACE
Primary endpoint

Post Hoc Analysis

- Phosphate trajectories
- Mixed model for LDL changes with interaction between time and Phosphate trajectory, for placebo and treatment
- Time-dependent Cox model

Validation

The 4D Study

1255 patients < 2y dialysis w/ T2DM

Results

LDL change over time was the same for both Phosphate trajectories, regardless of treatment arm

Statin was only protective against MACE and All Cause Death at Phos <5mg/dL

Protective effect of statin in low phosphate group not observed in 4D trial

Conclusion Statins have lower efficacy in dialysis patients in the presence of hyperphosphatemia.

Ziad A. Massy, Thomas Merkling, Sandra Wagner, et al. ***Association of Serum Phosphate with Efficacy of Statin Therapy in Hemodialysis Patients.*** CJASN doi: 10.2215/CJN.12620921. **Visual Abstract by Anna Gaddy, MD**

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The acute elderly

Medications to be discontinue to reduce the risk of ARF

- RAAS inhibitors (ACEi, ARBs)
- Diuretics
- SGLT2 inhibitors ?

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The acute elderly

Transient discontinuation of ACEI/ARBs: reducing the risk of ARF

CJASN
Clinical Journal of the American Society of Nephrology

2022 Mar;17(3):423-425.

Renin-Angiotensin-Aldosterone System Inhibitors and the Risk of AKI in COVID-19 Compared with Influenza

Bethany C. Birkelo, Sharidan K. Parr, Amy M. Perkins, Robert A. Greevy, Juan Pablo Arroyo, Adriana M. Hung, Andrew J. Vincz, Shailja C. Shah, Tarun Kapoor, Michael E. Matheny and Edward D. Siew

CJASN March 2022, 17 (3) 423-425; DOI: https://doi.org/10.2215/CJN.11190821

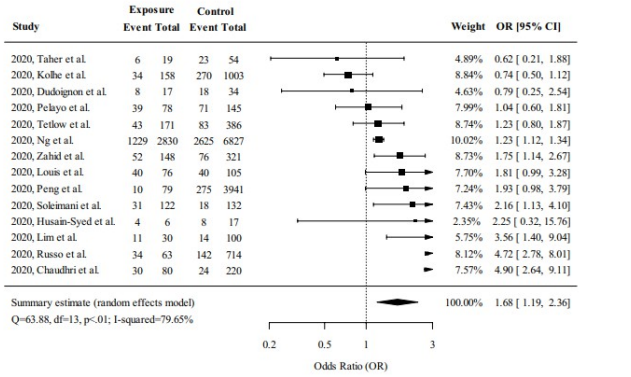


Figure 2. Meta-analysis of odds ratios for incident AKI in hospitalized COVID-19 patients based on exposure to RAAS inhibitors. Higher odds ratio indicates a higher risk of AKI in the RAAS blockade exposure group. *AKI* acute kidney injury, *RAAS* renin–angiotensin–aldosterone system, *OR* odds ratio, *CI* confidence interval.

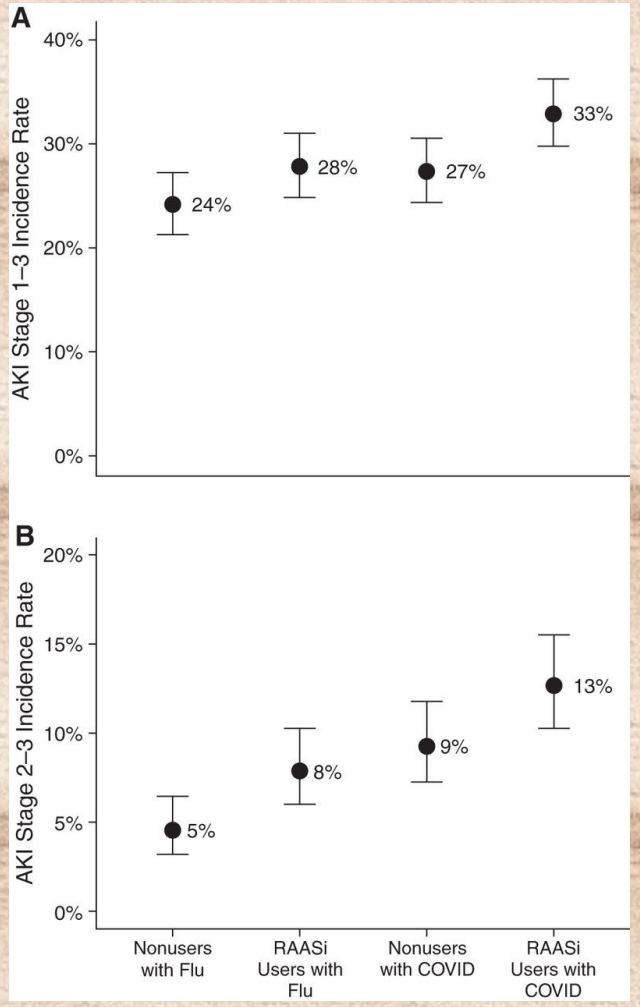
scientific reports

2021 Jun 30;11(1):13588.

OPEN

Increased risk of acute kidney injury in coronavirus disease patients with renin–angiote nsin–aldosterone-system blockade use: a systematic review and meta-analysis

Sul A Lee[1,2], Robin Park[2], Ji Hyun Yang[2], In Kyung Min[3], Jung Tak Park[3], Seung Hyeok Han[3], Shin-Wook Kang[3] & Tae-Hyun Yoo[3]



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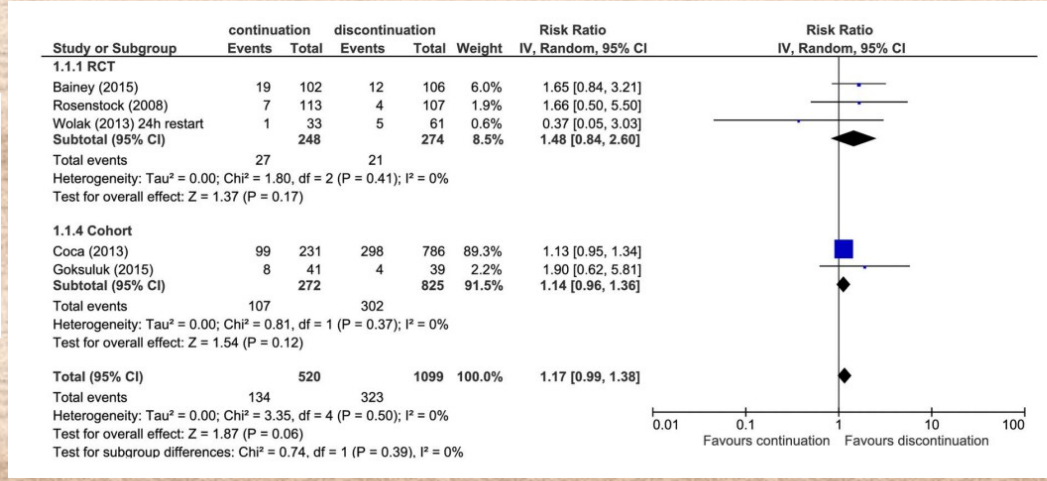
The acute elderly

Transient discontinuation of ACEI/ARBs: reducing the risk of ARF

Open Access Research

BMJ Open 2017 Apr

What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis



Study or Subgroup	continuation Events	Total	discontinuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 RCT						
Bainey (2015)	19	102	12	106	6.0%	1.65 [0.84, 3.21]
Rosenstock (2008)	7	113	4	107	1.9%	1.66 [0.50, 5.50]
Wolak (2013) 24h restart	1	33	5	61	0.6%	0.37 [0.05, 3.03]
Subtotal (95% CI)		**248**		**274**	**8.5%**	**1.48 [0.84, 2.60]**
Total events	27		21			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.1.4 Cohort						
Coca (2013)	99	231	298	786	89.3%	1.13 [0.95, 1.34]
Goksuluk (2015)	8	41	4	39	2.2%	1.90 [0.62, 5.81]
Subtotal (95% CI)		**272**		**825**	**91.5%**	**1.14 [0.96, 1.36]**
Total events	107		302			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Total (95% CI)		**520**		**1099**	**100.0%**	**1.17 [0.99, 1.38]**
Total events	134		323			
Heterogeneity: Tau² = 0.00; Chi² = 3.35, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%						

Risk Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours continuation Favours discontinuation

PHARMACOTHERAPY accp

2017 Oct

Original Research Article

Incidence of and Risk Factors for Severe Adverse Events in Elderly Patients Taking Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers after an Acute Myocardial Infarction

"We found a low incidence of ARF and hyperkalemia in elderly patients treated with ACEIs or ARBs after AMI hospitalization.
However, a high rate of treatment discontinuation might prevent a higher rate of occurrence of these events.
Long-term careful monitoring of severe adverse events and timely discontinuation of ACEIs or ARBs among elderly patients with advancing age and CKD after an AMI is warranted in clinical practice."

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Conclusions

- **In chronic stable situation :**
  - Stop aspirin in primary prevention
  - Stop statins in primary prevention in > 75y
  - Customised and rationalized treatment according to life expectancy
  - Take into account a very frequent latent CKD and adjust treatments accordingly (www.renadaptor.org)

- **In acute situation : preventing the ARF risk**
  - Stop transiently ACEi, ARBs, diuretics, … SGLT2i ? for an optimal risk/benefit ratio


Afin de guérir rapidement
Toujours bien prendre ses médoc !
MÉDOC
MÉDOC