Adverse Effects of Antihypertensive Drugs (and How to Deal with Them)

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11 MAR 22

Presenter Disclosure Information

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DISCLOSURE INFORMATION:

Dr. Elliott has received research funding, honoraria, and/or travel expenses from essentially **every** pharmaceutical company that makes, markets, or distributes antihypertensive drugs in the United States. A former full-time employee of **RUSH** Medical College, he was prohibited from (and still does not) own individual stocks or financial instruments related to healthcare.

Affidavit of Originality

- The following material is based exclusively on the speaker's own opinion, knowledge and expertise.
- There is no organization, company, or entity that has exercised any control or influence over the content of this presentation, nor has any other person or organization had any part in drafting, scripting or designing its content.
- The information presented is based on the principles of "Evidence-Based Medicine," and is intended to avoid promotion of any specific commercial interest, product, or company.

“Off-Label Use” Disclaimer

WARNING!

During this discussion, attempts will be made to avoid discussion of “off-label” or investigational uses of medicines or devices not yet approved by the US FDA, but very few antihypertensive medicines or devices have been specifically approved to reduce the risk of cardiovascular or renal disease, or to reduce the incidence or severity of adverse effects.

DISCLAIMER:

The audience member should interpret each example and every statement in the context of the “local standard of care” regarding medical practice, and judge each allegation regarding drug therapy within the standards approved by the most current product information for each marketed agent, as reflected in the most recent FDA-approved package insert. The speaker assumes no liability for any erroneous interpretation of the information contained herein, stated or implied.

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Educational Objectives

- At the end of this 50-minute session, the **awake** audience member should be able to:
  1) Name three (3) common and one (1) rare adverse effect of each of the six (6) major classes of antihypertensive medications.
  2) Name one (1) adverse effect of each of the six (6) major classes of antihypertensive medications that should prompt consideration of discontinuing the medication.
  3) Name one (1) adverse effect of each of the six (6) major classes of antihypertensive medications that responds to an appropriate change in the medication regimen, but continuation of the class of medication.

Hypertension & Public Health

- **#1 Chronic condition for which Americans see a healthcare provider** (each year since 1989)
- **#1 or #2** Risk Factor for **Coronary Heart Disease**
  - **#1** cause of death in USA each year since 1917
- **#1** Population-attributable Risk Factor for **Stroke**
  - **#5** cause of death in USA in 2013-4 (#4: 2009-12; #3: 1958-2008)
  - **#1** cause of long-term disability since 1928
- **#1** Risk Factor for **Heart Failure**
  - **#1** cause of hospitalization: Medicare beneficiaries
- **#1 or #2** Risk Factor for **End-Stage Renal Disease**
  - **#1** in Medicare expenditures per patient, 2019
- **#3** Risk Factor for **Peripheral Vascular Disease**
  - **#2** cause of loss of lower limbs since 2013
- **#1** Risk Factor for **(Vascular) Dementia**
  - #7 cause of death, 2020; **#2** cause of NHP now

Circulation. 2022;**145**:e1-e152; epub 22 JAN 22; doi: 10.1161/CIR.000000000105

Avoidable Deaths & Medical Costs Due to Suboptimal Medical Care, 2010

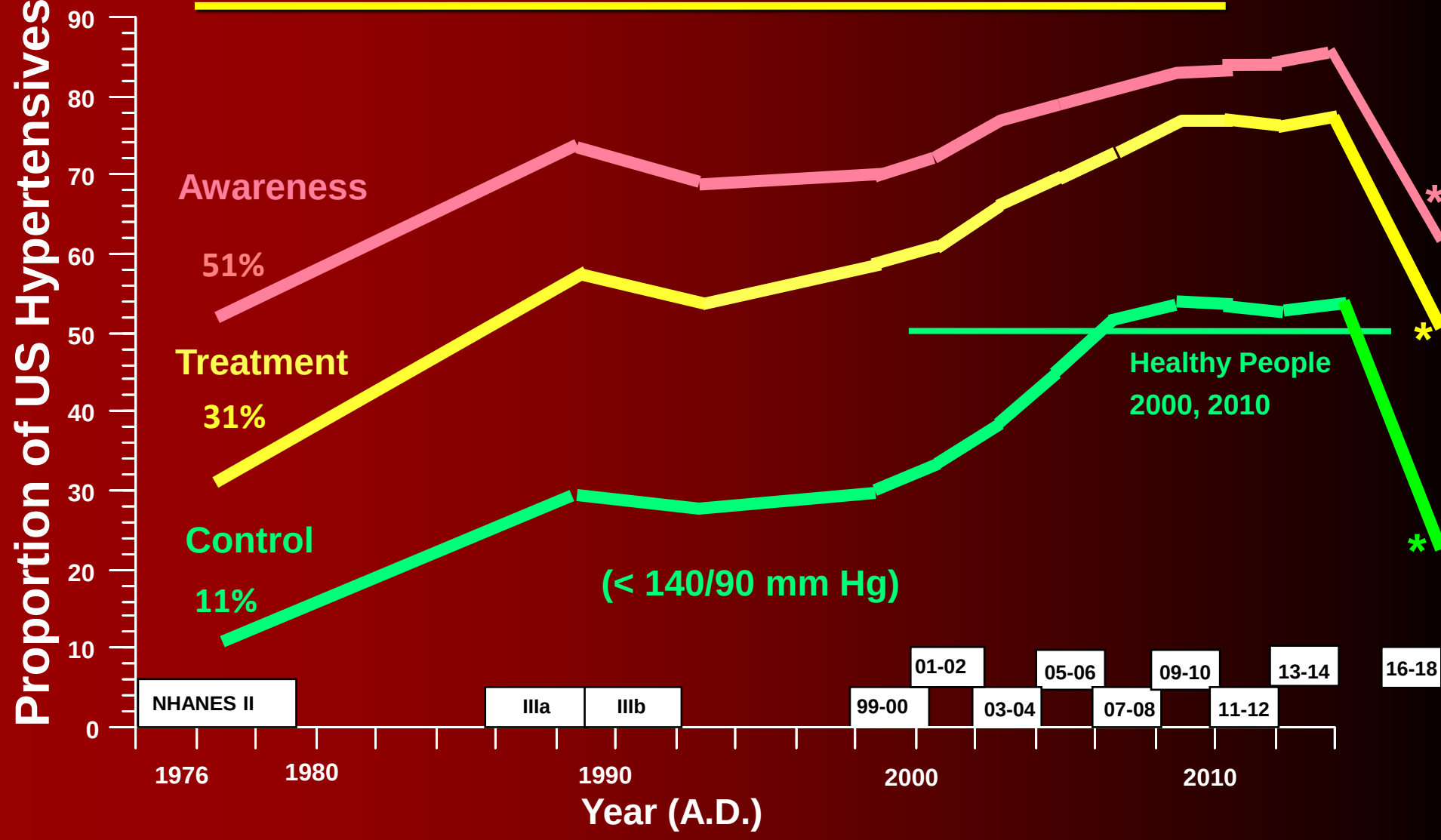
Measure	Avoidable Deaths	Avoidable Costs/yr*
Controlling high BP	28,000	$1,925,000,000
Cholesterol mgmt	5,700	$2,395,000,000
Smoking cessation	9,000	$748,000,000
Controlling A1c	7,500	$925,000,000
Colon Ca screening	7,000	Costs money!
Prenatal care	1,300	Not available
Breast Ca screening	1,200	$222,000,000
Beta-blocker post MI	900	$8,500,000
Cervical Ca screening	700	Not available

*Calculated for the US population as a whole, including sick days and lost productivity, when applicable.

National Committee for Quality Assurance. State of Health Care Quality. 2010, Figure 10. Available on the Internet at: http://www.ncqa.org/Portals/0/Newsroom/SOHC/SOHC_10.pdf, accessed 02 JUL 16.


CDC
National Health and Nutrition
Examination Surve
monitoring the nation's health
PNWU
FACULTY
& STAFF
PARKING

Hypertension Awareness, Treatment, & Control: USA—1976 to 2018



NHANES, National Health and Nutrition Examination Survey; AHA Heart & Stroke Statistics, 2022

Challenges in Controlling BP

- Long-term adherence to lifestyle modifications (low-sodium diet, exercise…)
- Long-term adherence to drug therapy
  - Cost of drug therapy
  - Adverse effects of drug therapy
  - Depression and other mental health issues
- Healthcare plan formulary changes
- Provider and patient “inertia”
- Inaccurate BP measurements
- Different goal BPs in different guidelines (?)

1° Adherence to Drug Therapy

- 15,961 Patients in a primary care network of 131 physicians in Québec, Canada had 37,506 incident prescriptions monitored in a prospective cohort study.
- **31.3%** of the prescriptions were **never** filled.
- Drugs in the upper quartile of **price** were least likely to be filled (OR 1.11, 95% CI: 1.07-1.17).
- Odds of filling the prescription were higher for older patients, antiinfectives, **no** out-of-pocket copayments, and greater proportion of visits with the same prescriber.

Ann Intern Med. 2014;**160**:441-50.

1° Non-Adherence in Québec

Ann Intern Med. 2014;**160**:441-50.

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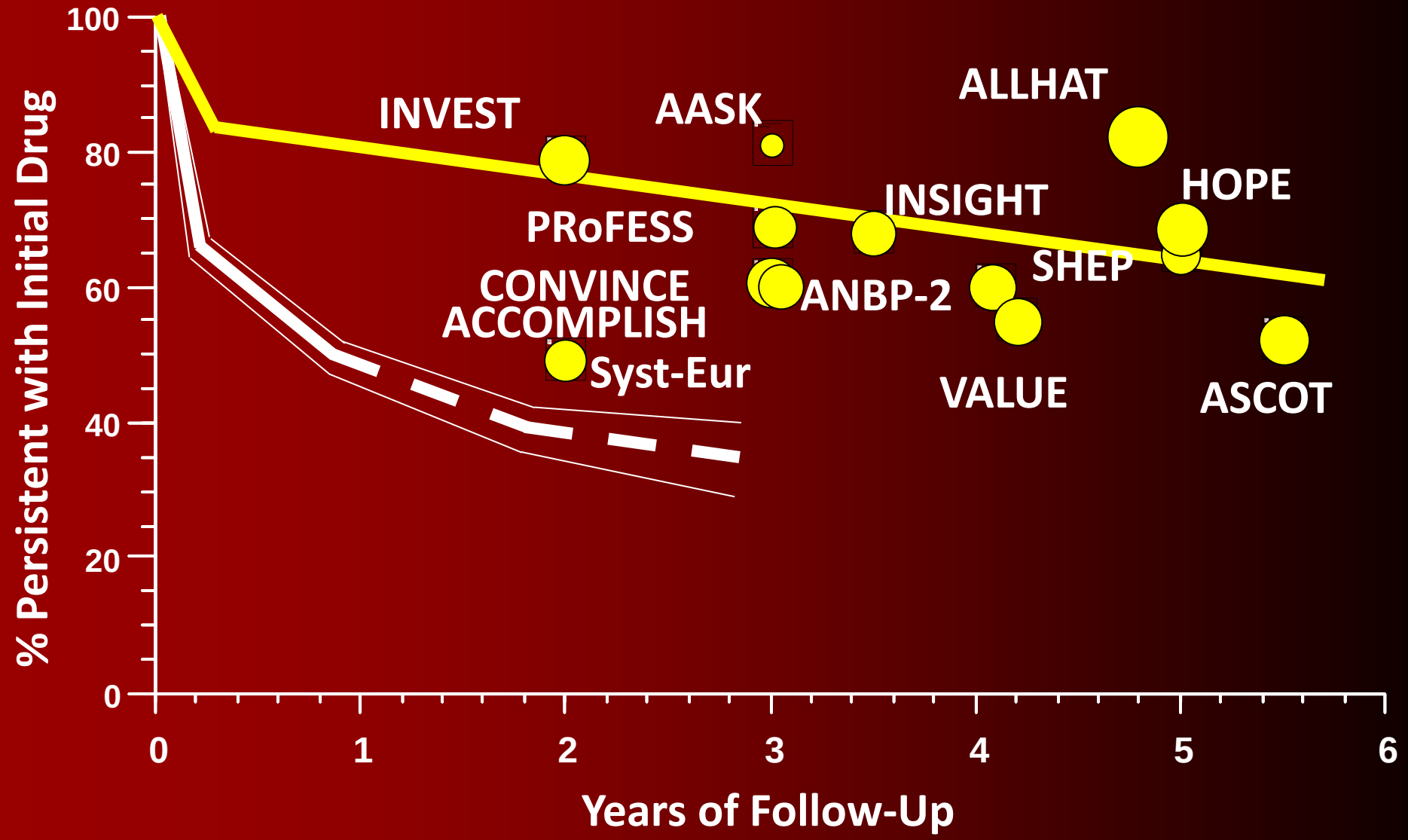
EBM & Real-World BP Control

- JNC 8 and some other hypertension guidelines rely solely on data from RCTs.
- RCTs are rarely done with generic drugs, which constitute 90% of prescriptions today.
- RCTs have inherent biases, including free medications and medical care, required re-challenge if drug is stopped, reimbursed travel costs, and few physician encounters.
- Long-term adherence data are quite different for RCTs and observational studies.

4-Year Persistence: BP Pills

JAMA. 2002;**288**:2981; *Clin Ther*. 2001;**23**:1999

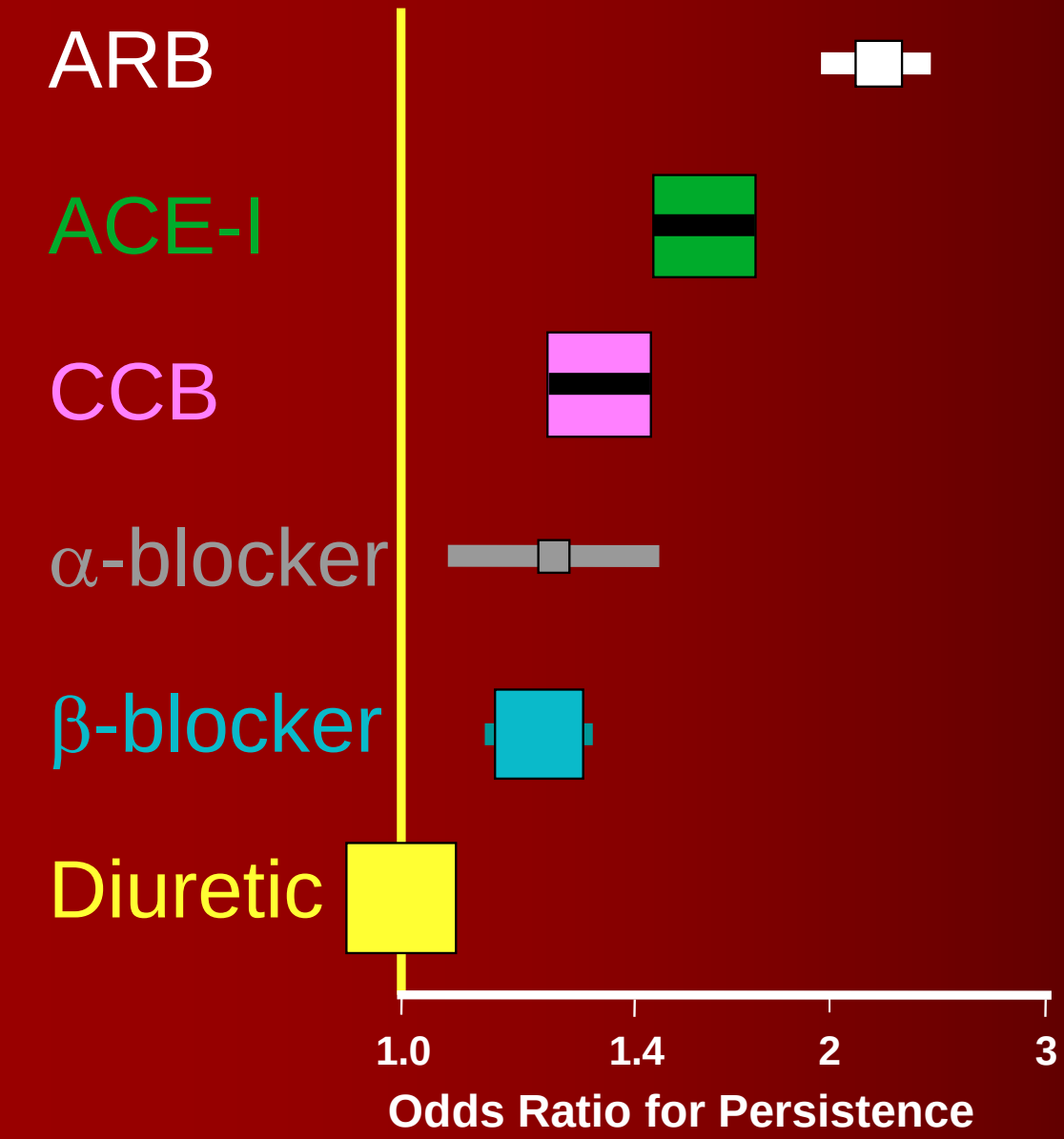
Long-Term Persistence: BP Drugs



Worldwide 1-Year Persistence

J Clin Hypertens (Greenwich). 2008;**10 (Suppl. A)**:A113-A114

Network Meta-analysis: Persistence



2.26 (2.05-2.50) p<0.0001

1.67 (1.54-1.82) p<0.0001

1.40 (1.29-1.52) p<0.0001

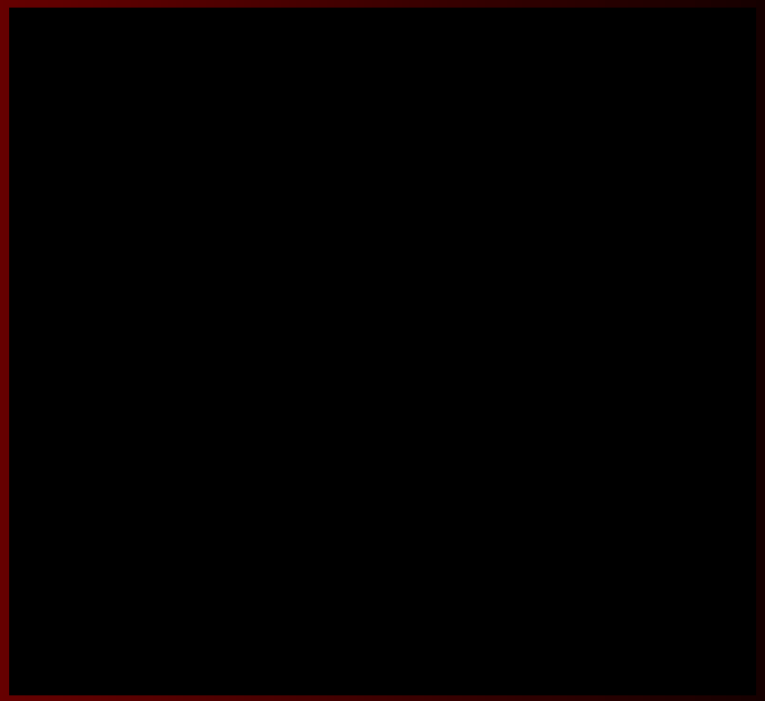
1.29 (1.07-1.55) p=0.008

1.27 (1.16-1.38) p<0.0001

Referent

Incoherence = 0.000007

J Clin Hypertens. 2008;**10 (Suppl. A)**:A113-4



Side Effects & Persistence

Health Technol Assess. 2003;**7**:1-94*; J Clin Hypertens.* 2008;**10 (Suppl. A)**:A113-A114

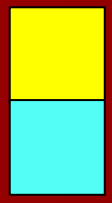
Classification: Adverse Effects

- **"Objective" adverse effects**
  - Listed in official product information
  - Externally validated in placebo-controlled trials
  - *Caveat*: "The rule of 10"
- **"Subjective" adverse effects**
  - Not listed in official, FDA-approved, product information
  - New, rare, or "odd" adverse effects
    - "Hair hurts, teeth itch…"

Cough Incidence with Enalapril

Am J Med. 2010;**123**:1016-30

Incidence of Cough with ACE-I



RCTs
PDR

Placebo-Adjusted Cough Incidence (%)

Am J Med. 2010;**123**:1016-30

"-pril"

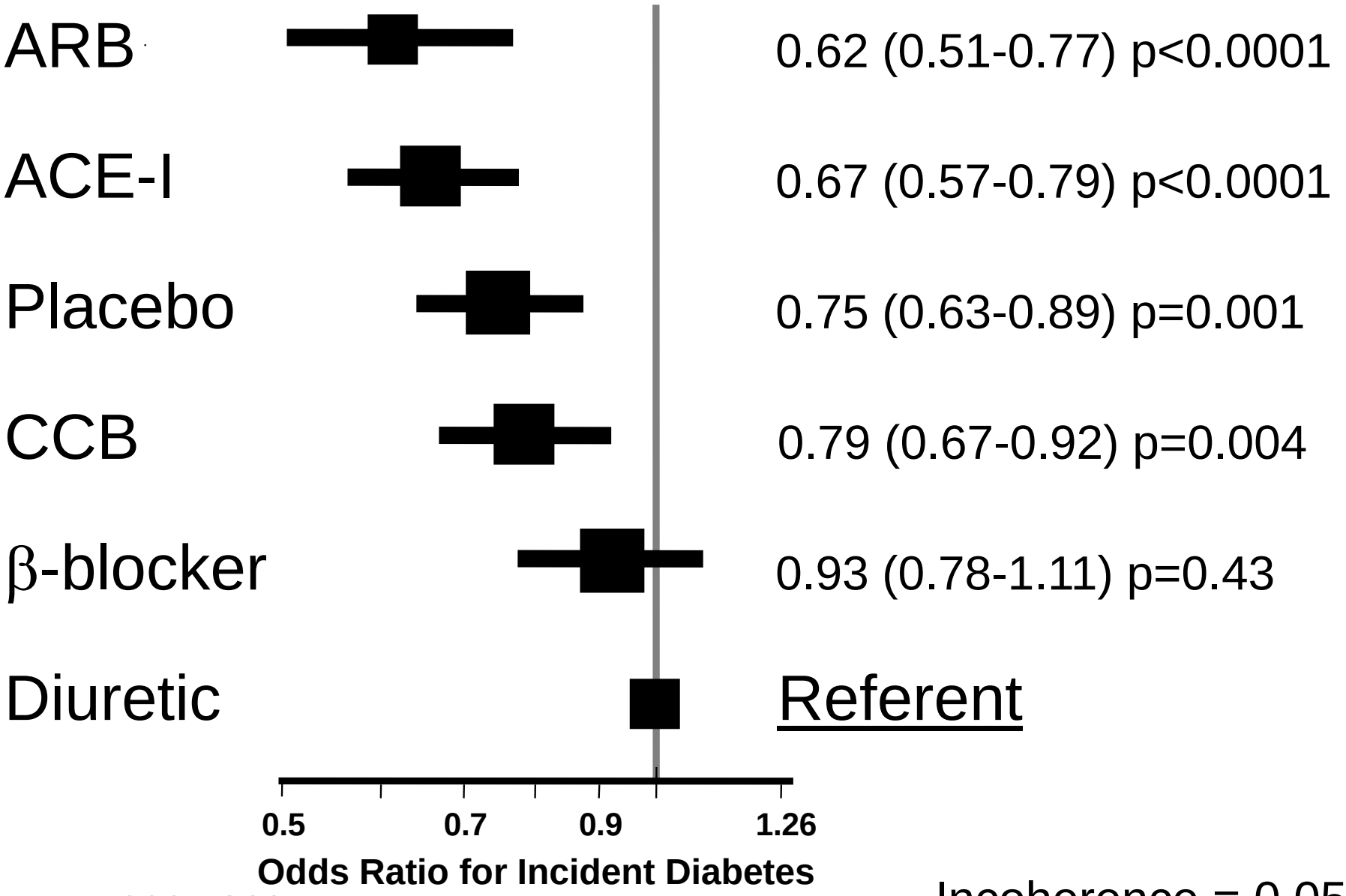
Major Classes of Antihypertensive Agents

- Diuretics
- Beta-blockers
- Alpha-1 blockers
- Alpha-2 Adrenergic Agonists?
- Calcium Antagonists
- Angiotensin Converting-Enzyme Inhibitors
- Angiotensin II Receptor Blockers
- (Direct) Renin Inhibitor(s)

Diuretics: Adverse Effects

- **Dose-dependent**:
  - Hypotension (esp. orthostatic), volume depletion, polyuria
  - Hypokalemia, hypomagnesemia, **hyponatremia**
- **Metabolic Adverse Effects:**
  - Hyperglycemia (and increased risk of incident diabetes)
  - Hypercholesterolemia
  - Hyperuricemia
  - **The clinical importance of these is very controversial!**
- **Erectile dysfunction**
  - May be more common with thiazides than with other commonly-used antihypertensive drugs

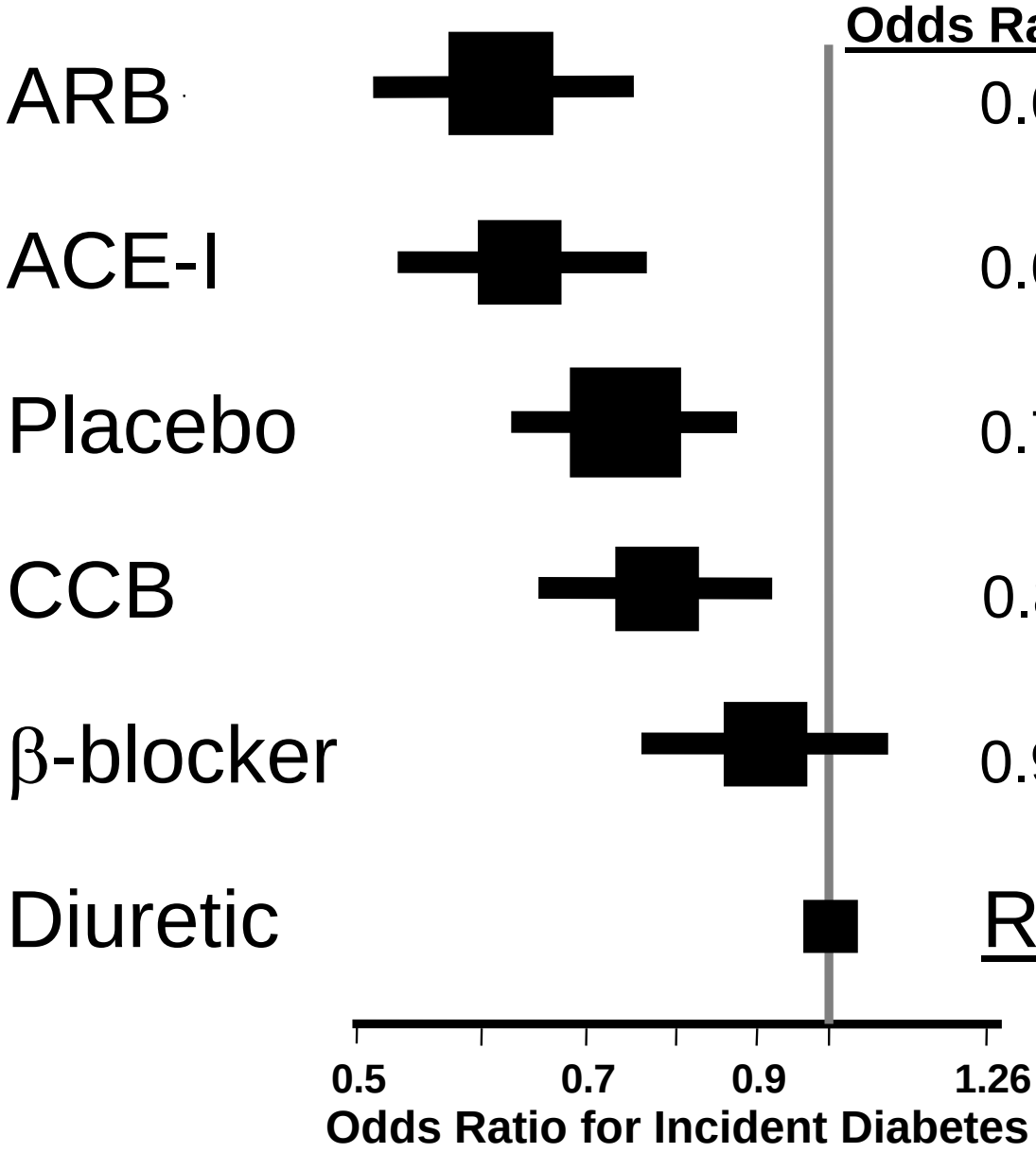
Network Meta-analysis: New DM



Lancet. 2007;**369**:1515

Incoherence = 0.054

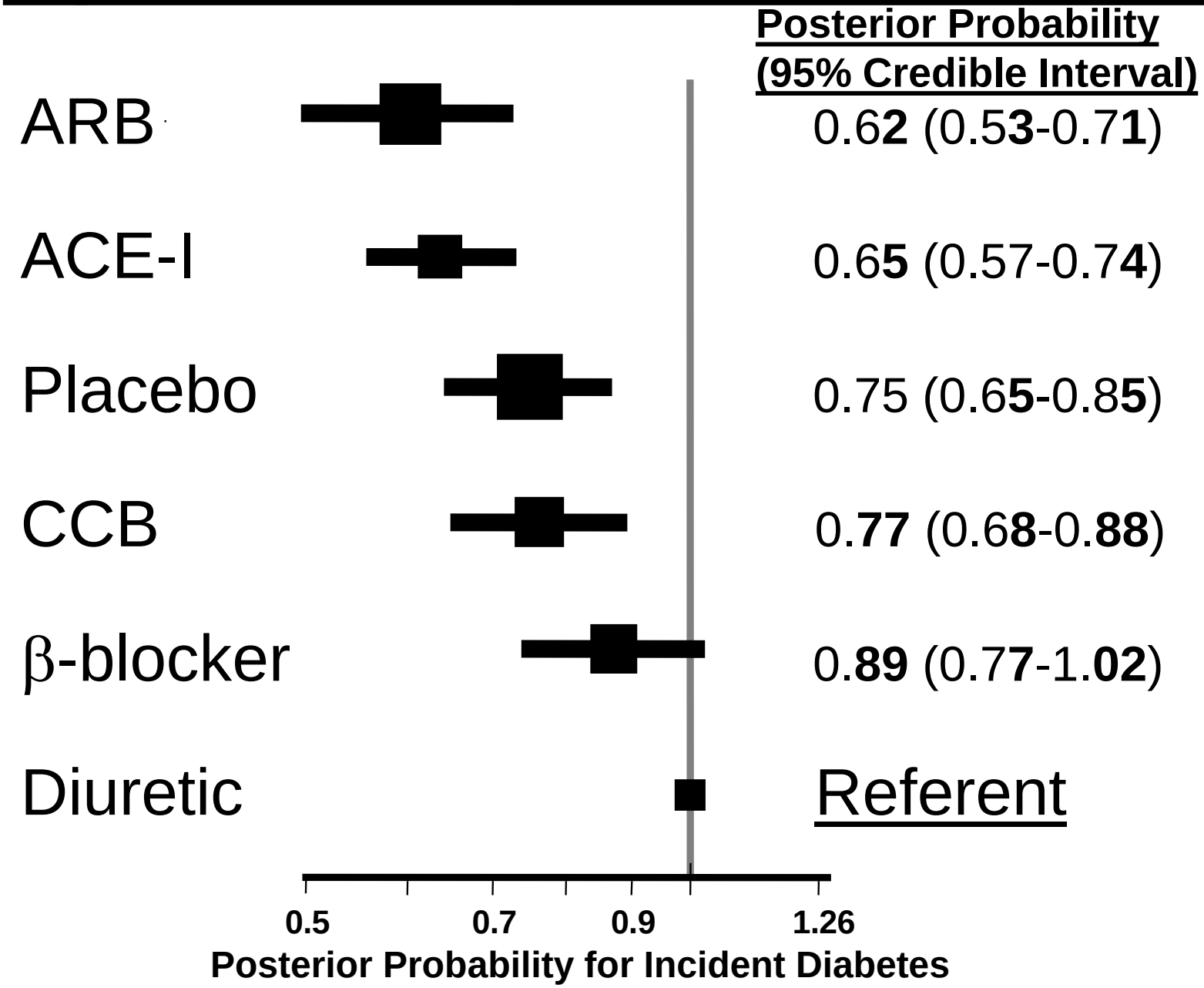
Updated Network Meta-Analysis



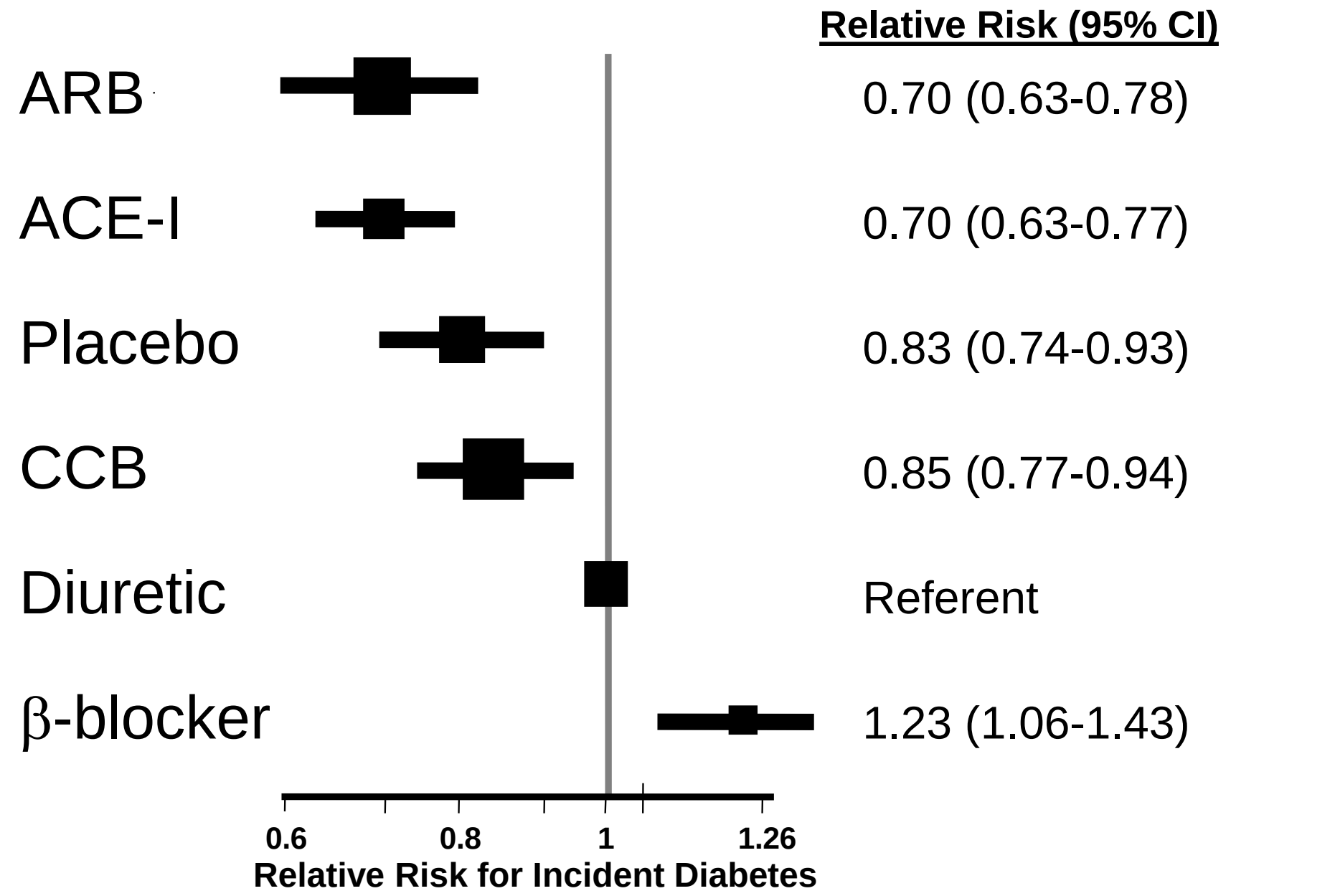
Incoherence = 0.0627

J Clin Hypertens (Greenwich., 2011;**12 (Suppl. 1)**:A20.

Updated Bayesian Meta-Analysis

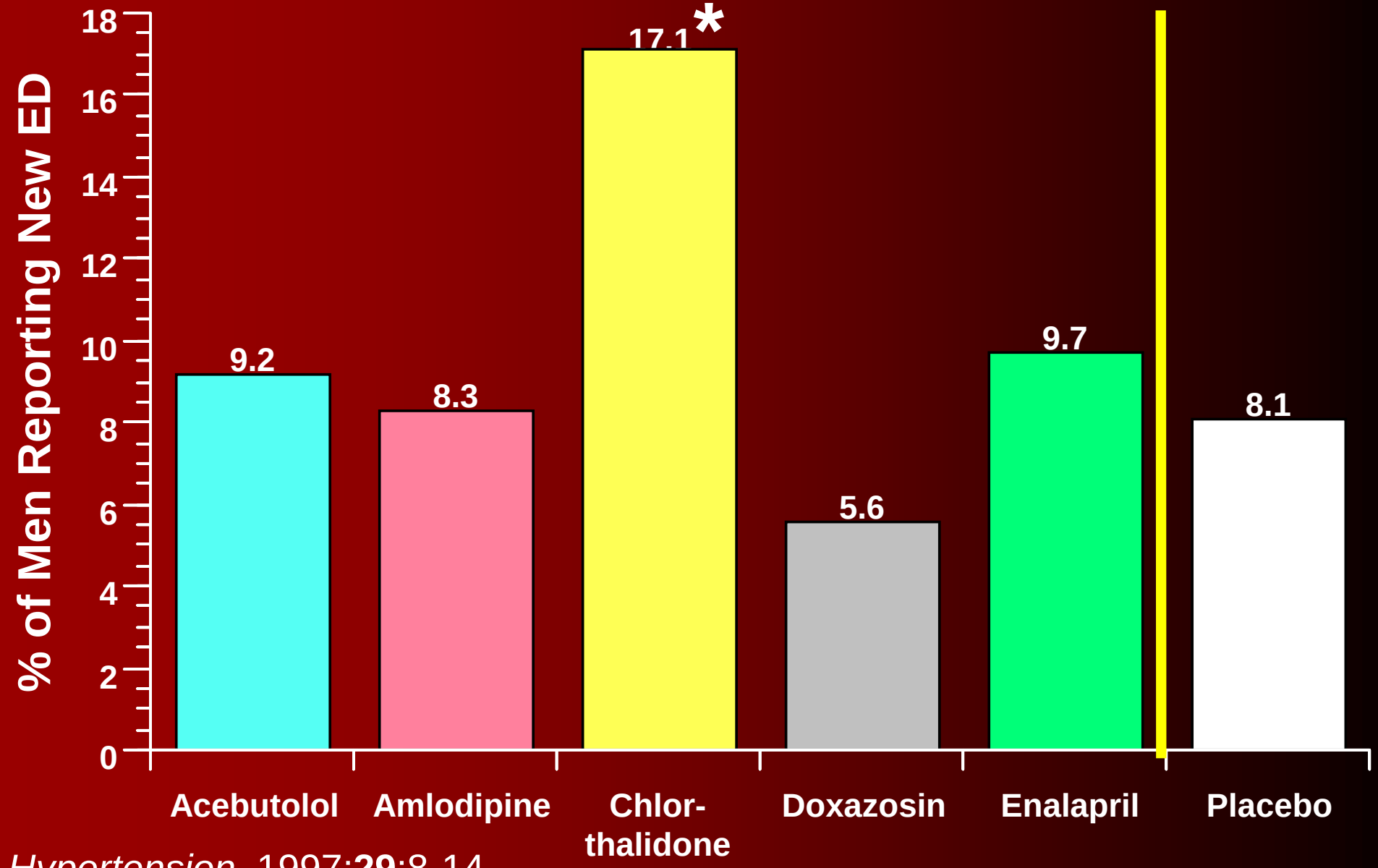


Patient-Level Data Meta-Analysis



Lancet. 2021;**398**:1803-10.

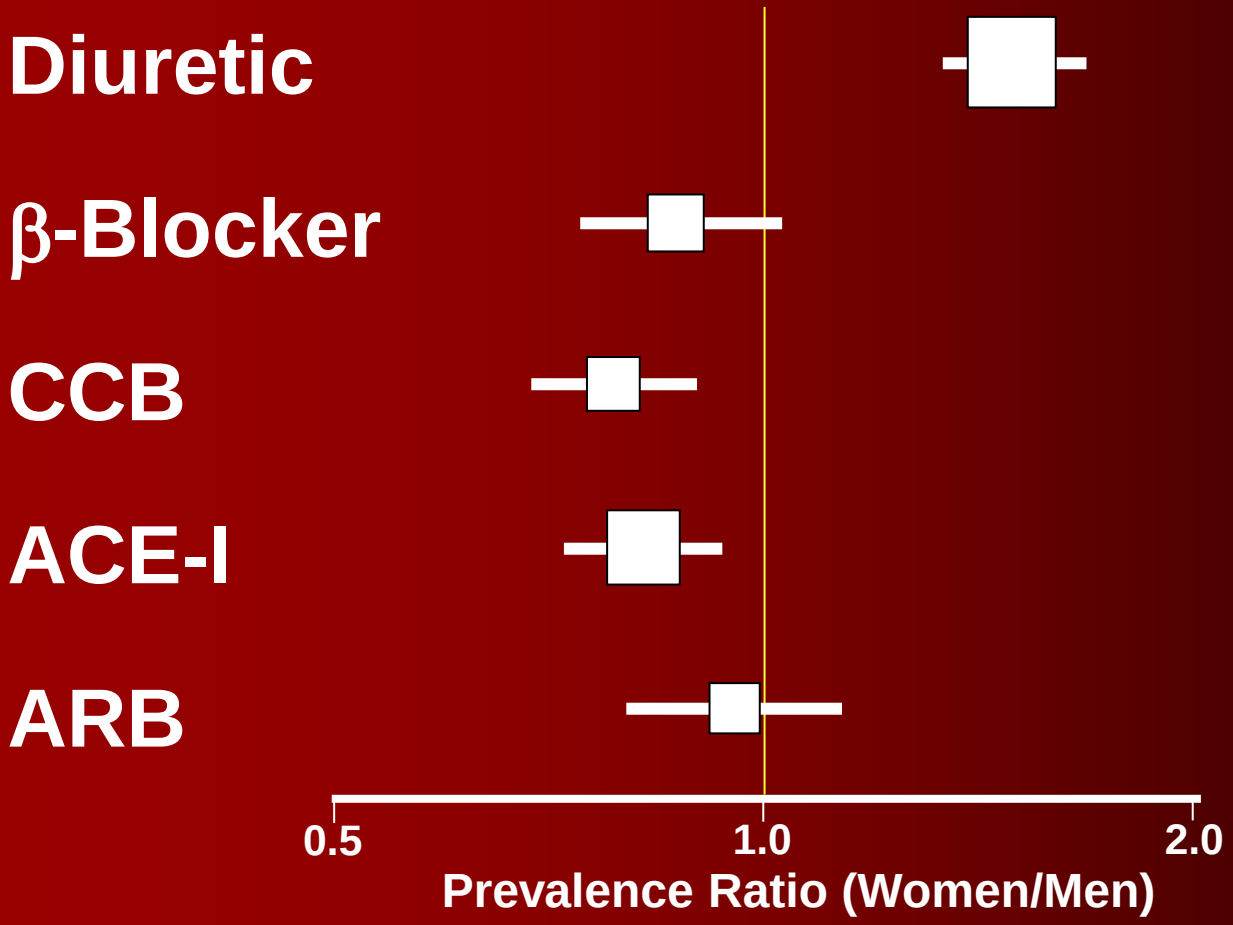
Erectile Dysfunction @ 2 Yrs: TOMHS



Hypertension, 1997;**29**:8-14

Gender Differences: Initial BP R_x

Pharmacy records of 3401 patients initiating antihypertensive drug therapy from 2003-2005 in a large Southeastern US managed care organization were analyzed.



Hypertension. 2009;**53**:617-623.

Adverse Effects of Thiazides

- **Acute gouty arthritis**
  - Occurred in 0.5% of men in HDFP
  - Often occurs within 3-5 days of starting thiazide (?)
  - Many preventive anti-gout medications are available
- **Hyperglycemia**
  - Occurs in 3-8% of patients in long-term clinical trials
  - Reversible??
  - In ALLHAT, “chemical diabetes” did not significantly increase CV risk (over a 2-year follow-up period?)
  - May take ~9 years to increase CV risk significantly.
- **Hypokalemia**
  - Dose-dependent, less common with today’s doses
  - Potassium supplements, more ACE-inhibitor or ARB?
- **Sexual dysfunction**
  - 17% in TOMHS men @ 2 years
  - Usually easily remedied with PDE-5 inhibitors ($?)

Hyponatremia from Thiazides

- **Incidence:**
  - 0.50%, 0.45% in two large Chicago clinics
  - 0.1%-0.5% across the literature
- **Severity & Persistence:**
  - Often 120-125 mEq/L; reversible on stopping drug
- **Risk factors:**
  - Older age
  - Women
  - CKD
  - Small BMI
- **Seldom effective:**
  - High-salt diet
  - Dose-reduction
  - Switch to loop diuretic

Electrolyte Blood Press. 2010;**8**:51-7

β-Blockers: Adverse Effects

- **Dose-dependent**:
  - Hypotension (esp. orthostatic), bradycardia, **heart failure**
  - **Heart block**, dizziness, palpitations (?)
  - **Bronchospasm**, cold extremities/claudication (β_2-effect)
- **"Central" Adverse Effects** (worse with lipid-soluble agents?)
  - Fatigue, depression, mental slowness, erectile dysfunction, vivid dreams, dry mouth (questionable per meta-analysis)
- **Metabolic Adverse Effects:**
  - Hyperglycemia (and increased risk of incident diabetes)
  - Hypertriglyceridemia/Hypo-HDL-cholesterolemia
  - **The clinical importance of these is controversial!**
- **Other**
  - Hypokalemia, GI upset, skin reactions (rash, Stevens-

Asthma from Beta-blockers?

- Incidence ~ 0.2% (old data!)
  - A population-based cohort study in Scotland showed 2.8% of asthmatics received a beta-blocker prescription, of whom about 1% required intensified oral steroids **each week**!
- Alternatives:
  - Beta-1 selective blocker?
    - Selectivity is not specificity!
    - *In vitro* selectivity is ~1:320 in the best case
    - Nadolol, timolol, propranolol probably the worst
  - In COPD, beta-blockers are probably OK.

Thorax. 2011;**66**:502-7; *Cleve Clin J Med*. 2010;**77**:498-9.

Adverse Effects of β-Blockers

- Cold hands/feet
  - Dose-dependent
  - More of a problem with non-selective agents (?)
  - Less of a problem with vasodilating β-blockers
- Erectile dysfunction
  - More of a problem with diuretics in young men
  - PDE-5 inhibitors are usually helpful, but $$
- Exercise intolerance
  - Vasodilating β-blockers, those with ISA?
- Hyperglycemia
  - Maybe takes > 9 years to increase CV risk?

J Hypertens. 2007;**25**:1311-7

“Impotence” in British MRC-1

% of Men Reporting New ED @ 2 Yr

Lancet. 1981;**2**:439-43

α_1-Blockers: Adverse Effects

- Orthostatic hypotension (occ. syncope with first dose, so give at h.s.), dizziness, falls, fractures, “stuffy nose”
- Tend to improve lipid profile, insulin resistance
- More heart failure when used as initial therapy (ALLHAT), so this is not done…
- Can improve symptoms in men with BPH/LUTS

Adverse Effects of α_1-Blockers

- Dizziness (19%-doxazosin vs. 9%-placebo)
  - More pronounced if given initially at full dose
  - Overlaps with orthostatic hypotension in ~10%
- Headache (14% vs. 16%)
  - May be related to nasal symptoms??
- Fatigue/Malaise (12% vs. 6%)
  - Pathophysiology uncertain, but same increment was seen in studies of patients with BPH
- Orthostatic hypotension (0.3% vs. 0%)
  - Increases risk of falls, fractures in the UK
- Priapism
  - Occurs "< 1 in several thousand," but permanent sequelae may result, thus: **WARNING in PI!**

α_2-Agonists: Adverse Effects

- **Sedation**
- **Dry mouth**
- **Lethargy**
- **Somnolence**
- Dizziness
- **Mental slowing**
- Erectile dysfunction (dose-dependent):
- **Rebound hypertension**
- Rash (with patch, less rebound hypertension)

CCBs: Adverse Effects

- **Gingival hyperplasia**
- Verapamil: constipation, bradycardia, AV block
- Diltiazem: dizziness, bradycardia, AV block
- Long-acting DHPs: edema, headache
- Short-acting DHPs: edema, headache, flushing, tachycardia, palpitations, fatigue, GI upset, etc.

Adverse Effects of DHP-CCBs

- Flushing (~5%), headache (7%), palpitations (2%)
  - All are dose-dependent
  - More of a problem with immediate-release preparations
- **Pedal edema**
  - Dose-dependent (e.g., amlodipine):
    - 2.5 mg: 1.8%, 5 mg: 3%, 10 mg: 10.8%
    - Worse with nifedipine?
  - Bigger issue in women
    - 14.6% vs. 5.8% in men
  - Seldom responds to increased diuretic
  - Can be reduced in incidence and severity with a co-prescribed ACE-inhibitor or ARB

Am J Med. 2011;**124**:128-35

Results: 10 mg/d Amlodipine

Summary Odds Ratio ± S.D.

Discontinuation of CCBs

- **Amlodipine**
  - Rare allergy, gynecomastia (with hospitalization) reported in updated PI
- **Shorter-acting sustained release-DHP-CCBs: similar**
  - Immediate release DHPs: tachycardia, flushing
- **Verapamil**
  - Constipation: dose-dependent: 8% in one Chicago clinic
- **Diltiazem**
  - Insufficient BP lowering (with low doses)
  - > 1° heart block (with high doses)

ACE-Inhibitor: Adverse Effects

- **Cough (0-44%):** ~40% less in whites than blacks or Asians, men, non-smokers
- **Angioedema** (~0.7%): ~3 x more in blacks
- Hyperkalemia (dose-dependent): worse with potassium supplements, high-K^+ foods, K^+-sparing diuretics
- Worsening of renal function (up to 25-30% increase in serum creatinine **expected**)
- Cholestatic jaundice (and rare fulminant hepatic necrosis if the drug is continued)

ARBs: Adverse Effects

- Hyperkalemia (dose-dependent): worse with potassium supplements, high-K^+ foods, K^+-sparing diuretics
- Worsening of renal function (up to 25-30% increase in serum creatinine **expected**)
- Diarrhea (~1-4%, ? mechanism)

Renin Inhibitor: Adverse Effects

- Hyperkalemia (dose-dependent): worse with potassium supplements, high-K^+ foods, K^+-sparing diuretics
- Worsening of renal function (up to 25-30% increase in serum creatinine **expected**)
- Diarrhea (~2.3%, ? mechanism)
- Gout (0.2%, ? mechanism)
- Kidney stones (0.2%, ? mechanism)

Summary: Discontinue if:

- Diuretic: persistent hyponatremia
- ACE-inhibitor: Angioedema, cough
  - **NOT** an innocuous increase in serum creatinine, which bodes well for the patient's future kidney function!
- Beta-blocker: Asthma?
- Calcium channel blocker: ?Allergy
  - Pedal edema: Add ACE-inhibitor or ARB?
- Angiotensin receptor blocker: Diarrhea?
  - **NOT** an innocuous increase in serum creatinine, which bodes well for the patient's future kidney function!
- Alpha-blocker: Priapism?

"Beneficial" Side-Effects?

- Thiazide diuretic for calcium stone formers
- Beta-blockers for familial tremor, stage fright
- CCB for women with Raynaud's phenomenon
- ACE-I for dihydropyridine-associated edema
- ARB or ACE-I for migraineurs
- Minoxidil for bald men, ?nail polish for women
- These are "off-label uses" for antihypertensive drugs!

Conclusions

- A good clinician is sensitive to patient reports of adverse effects, as they are very common.
- Antihypertensive drugs differ greatly regarding the objective incidence and types of adverse effects.
- Adverse effects correlate inversely with long-term adherence to therapy, and therefore impact BP control rates.
- Not all “side-effects” are “adverse effects;” sometimes beneficial side-effects can be used (off-label) for good!