Recent Advances / Controversies In Clinical Endocrinology

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Disclosures

- Competitive research grants
  - Pfizer
  - Novo Nordisk
- Speaker honoraria
  - Ipsen
  - Novo Nordisk
  - Novartis
- Pituitary advisory board
  - Novartis
- Pituitary educational meeting steering committee
  - Ipsen

Presentation Aims

- Highlight important clinical studies published since January 2015 in five areas of endocrinology
- Place results in historical, clinical and geographical context
- Cover a range of endocrine topics

Presentation Outline

1. Empaglifozin and cardiovascular disease in patients with type 2 diabetes
2. Diagnostic testing for thyroid nodules
3. New Zealand adult growth hormone replacement program
4. Oestrogen and cardiovascular disease in women
5. Testosterone and cardiovascular disease in men

Cardiovascular Outcome Trials Post 2008

Agent	Patients	Median duration (years)	Primary outcome	Hazard ratio (95% CI)
Saxagliptin[1]	16,492	2.1	3 point MACE	1.00 (0.89-1.12)
Alogliptin[2]	5,380	1.5	3 point MACE	0.96 (≤1.16)
Sitagliptin[3]	14,671	3.0	4 point MACE	0.98 (0.88-1.09)
Lixisenatide[4]	6,068	2.1	4 point MACE	1.02 (0.89-1.17)

[1] Scirica et al. N Engl J Med 2013;369:1317-26; [2] White et al. N Engl J Med 2013;369:1327-35;
[3] Green et al. N Eng J Med 2015;373:232-42; [4] Pfeffer et al. N Engl J Med 2015;373:2247-57

Holy grail: Improve glycaemic control and reduce cardiovascular disease

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

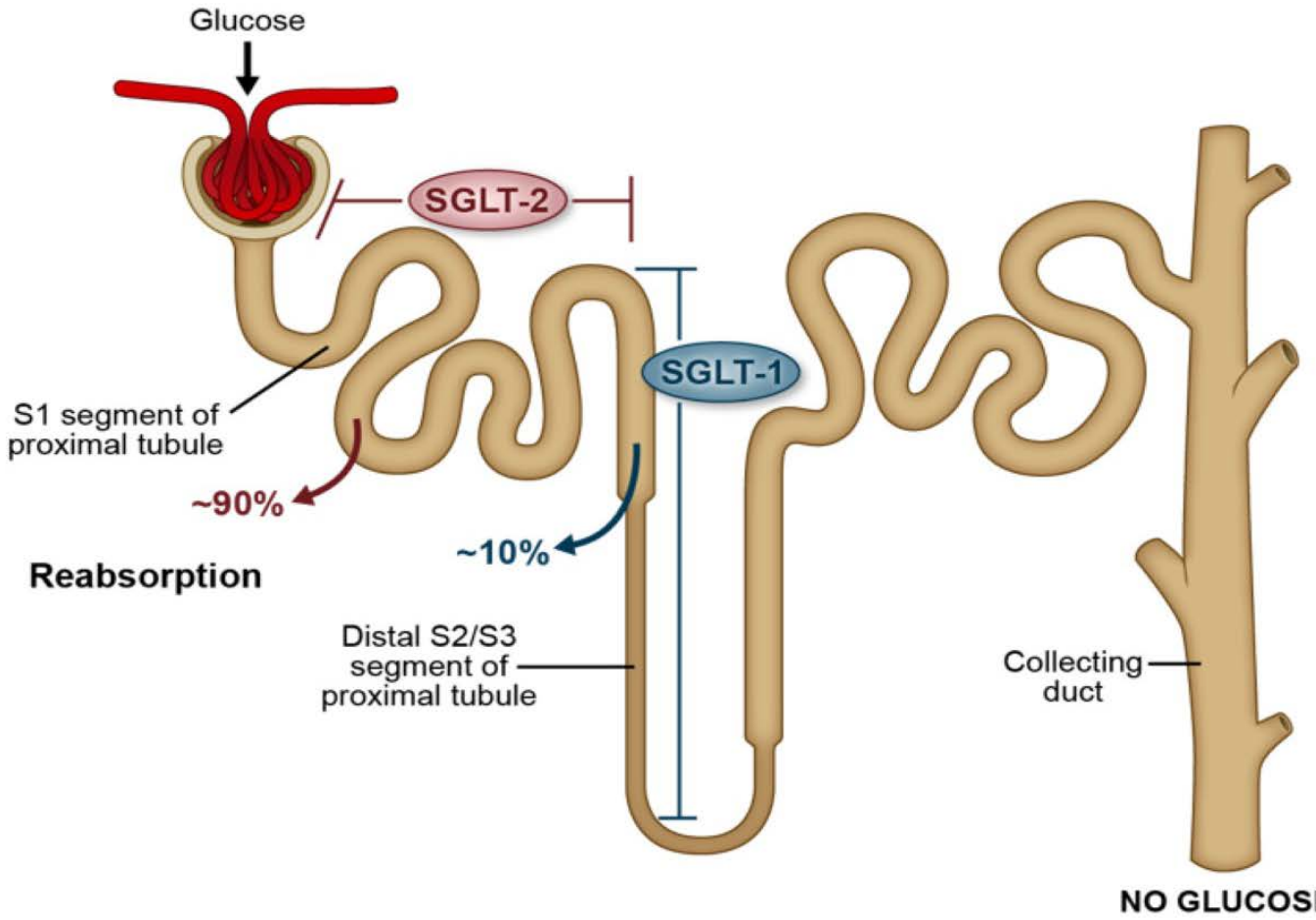
The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the

Zinman et al. N Eng J Med 2015;373:2117-28

Empaglifozin: A SGLT2 Inhibitor



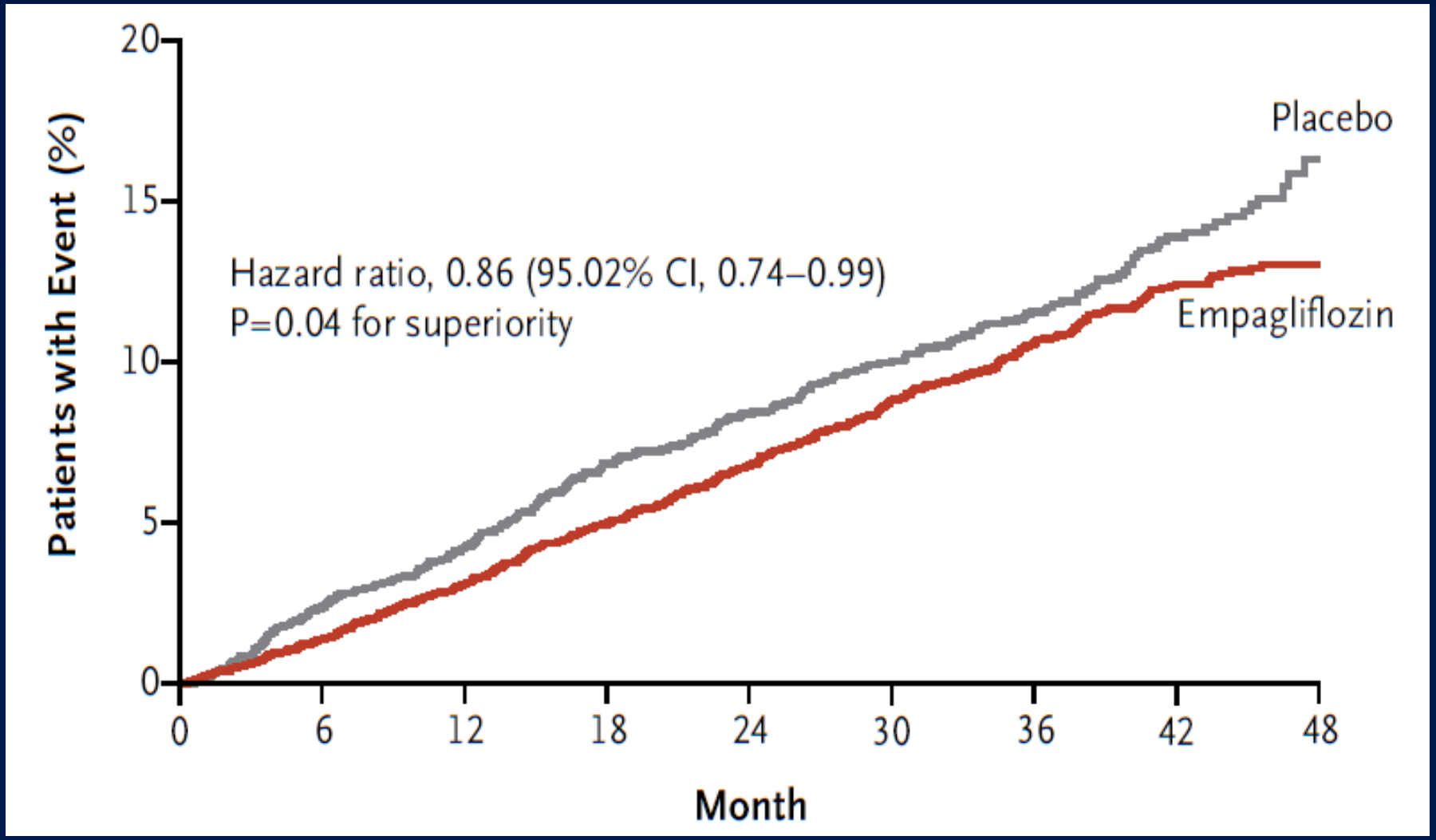
Wright EM, et al. *J Intern Med*. 2007;261:32-43[2]; Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[3]; Wright EM. *Am J Physiol Renal Physiol*. 2001;280:F10-F18.[4]

Empa-Reg Trial: Methods

- Subjects (n=7,028)
  - Type 2 diabetes
  - GFR > 30 ml per minute per 1.73 m^2 body surface area
  - Established cardiovascular disease
- Study design: Randomized-controlled trial (1:1:1)
  - Empaglifozin 10 mg od
  - Empaglifozin 25 mg od
  - Placebo

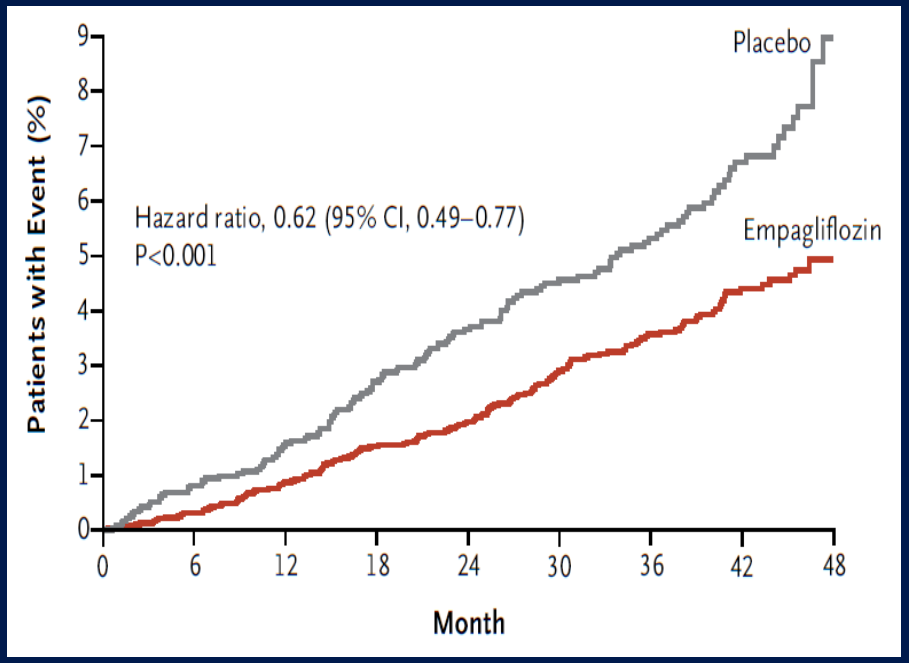
  Combined for statistical analysis
- Primary outcome: Death from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke
- Median duration of follow-up: 3.2 years

Primary Outcome: 3 point MACE

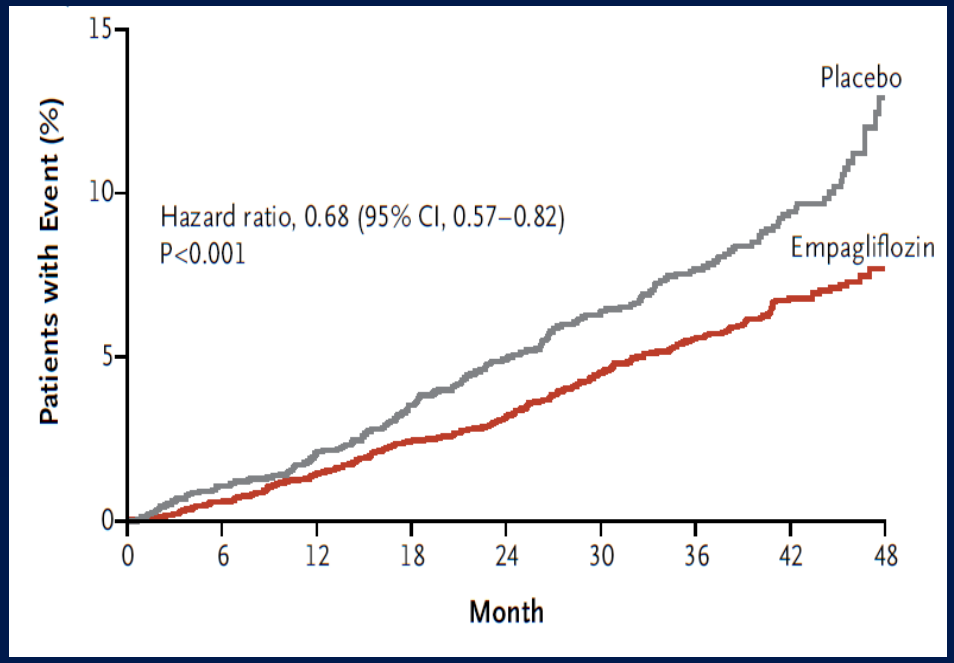


Mortality

Cardiovascular



All Cause



Number needed to treat for 3 years
to prevent one death = 39

Other Effects

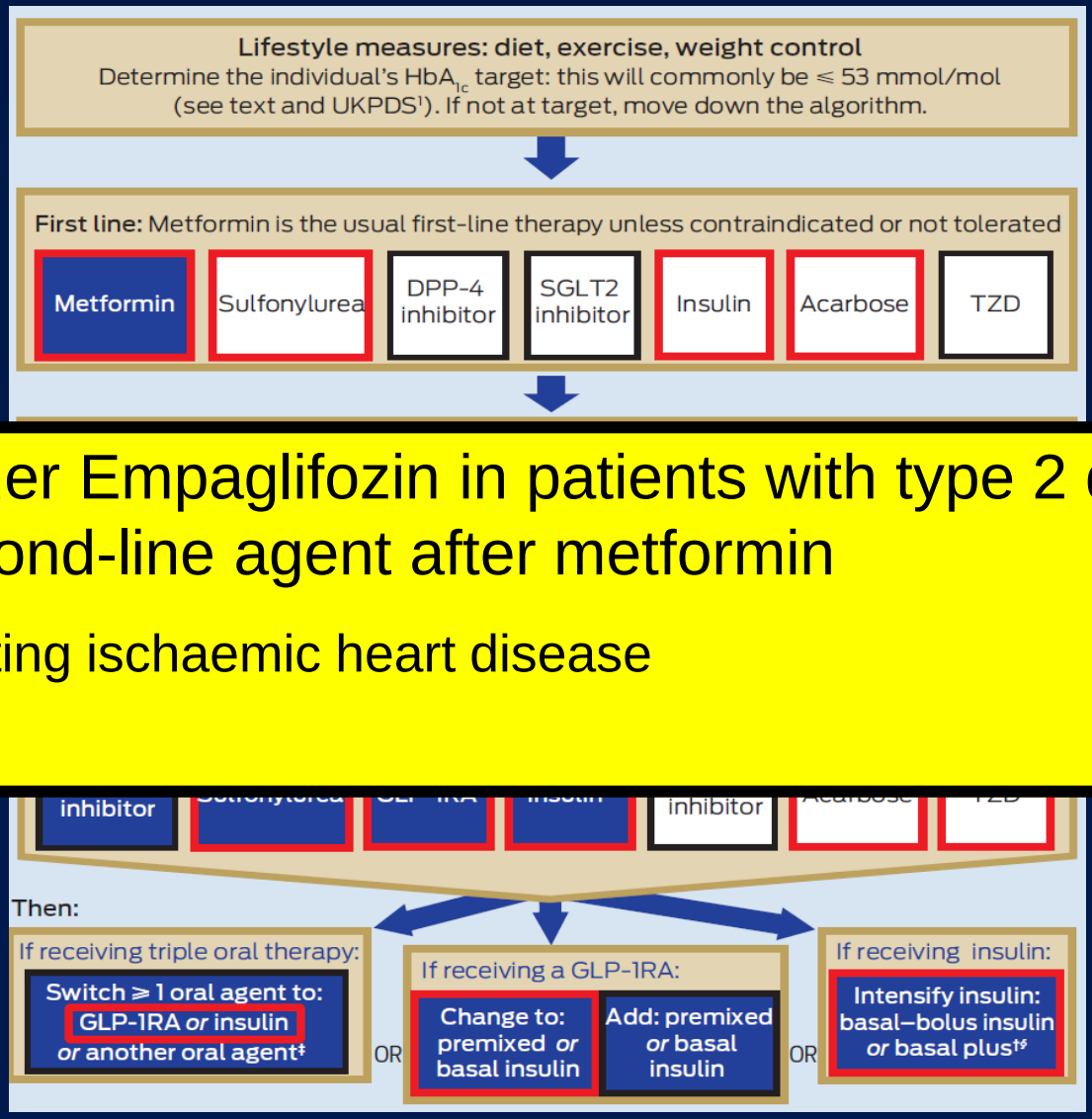
Benefit

- Reduced heart failure
- Increased HDL cholesterol
- Reduced weight
- Reduced uric acid
- Reduced blood pressure

Neutral / Adverse

- No effect on stroke
- Increased LDL cholesterol
- Increased genital infections
- (Euglycaemic ketoacidosis)

Clinical Application



- Consider Empaglifozin in patients with type 2 diabetes as second-line agent after metformin
  - Co-existing ischaemic heart disease
  - Men

Gunton et al. MJA 2014;201:650-3

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force
on Thyroid Nodules and Differentiated Thyroid Cancer

Diagnosis → Surgery and I131 → Surveillance for recurrence → Kinase inhibitors

Background: Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. Since the American Thyroid Association's (ATA's) guidelines for the management of these disorders were revised in 2009, significant scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer.

Methods: The specific clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on

Haugen et al. Thyroid 2016;26:1-133

RACP Evolve Program

- Endocrine Society of Australia surveyed its members: Number one recommendation

"Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland"

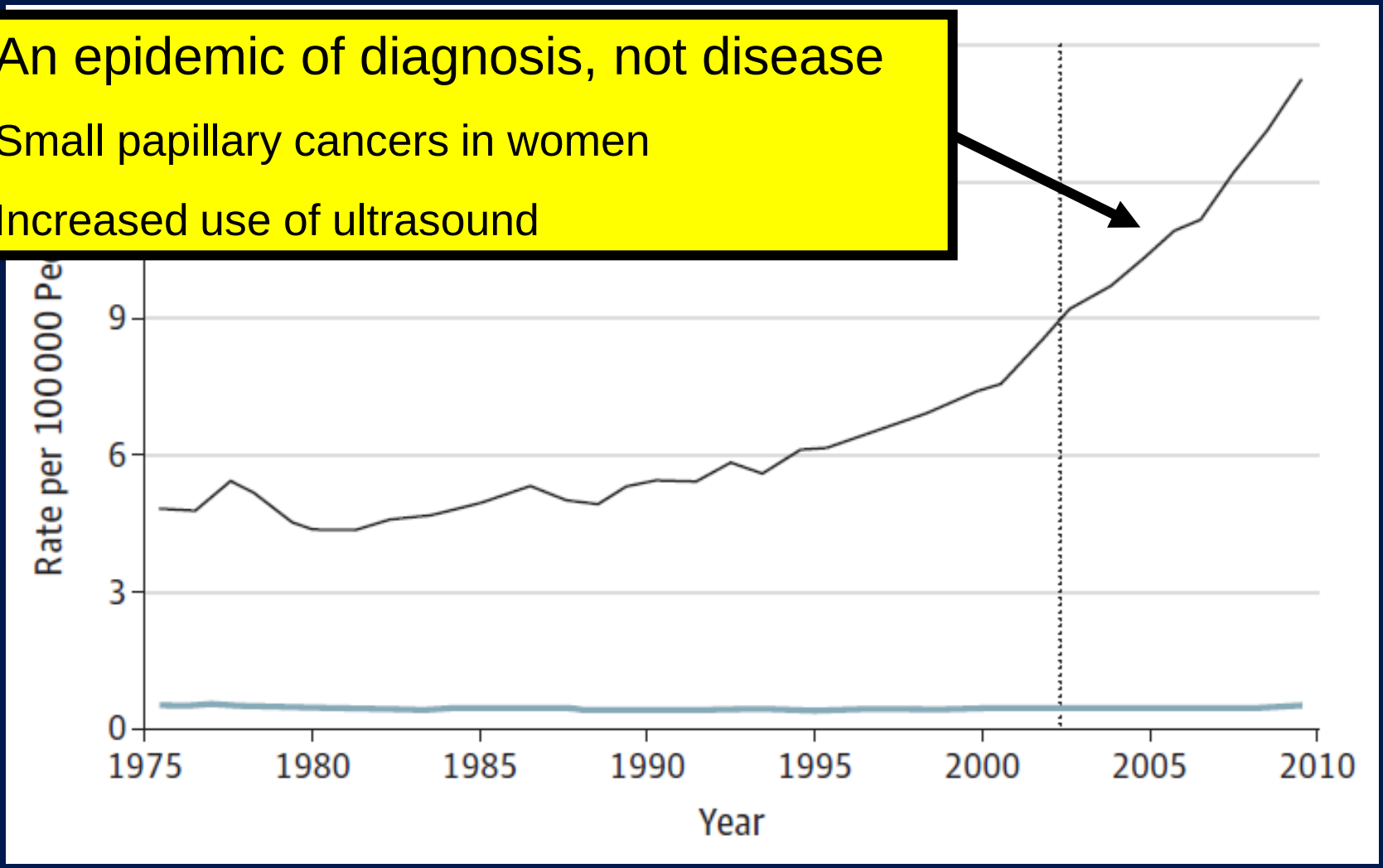
Thyroid Epidemiology

- Thyroid nodules present at ultrasound or autopsy in ~50% of older subjects
- 7-15% thyroid nodules are malignant
- >90% of thyroid cancers are well differentiated with an extremely good prognosis

Haugen et al. Thyroid 2016;26:1-133

Thyroid Cancer Epidemiology

- An epidemic of diagnosis, not disease
  - Small papillary cancers in women
  - Increased use of ultrasound

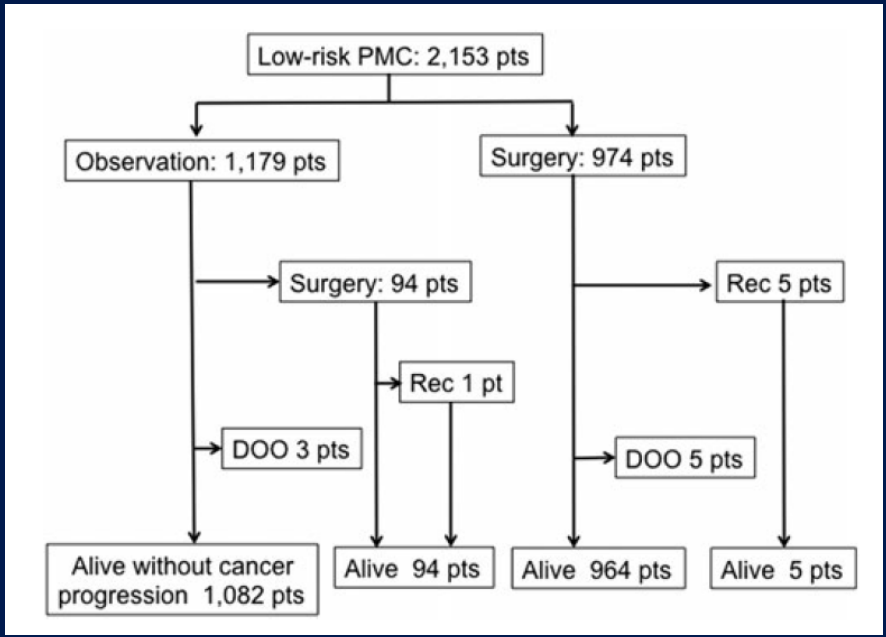


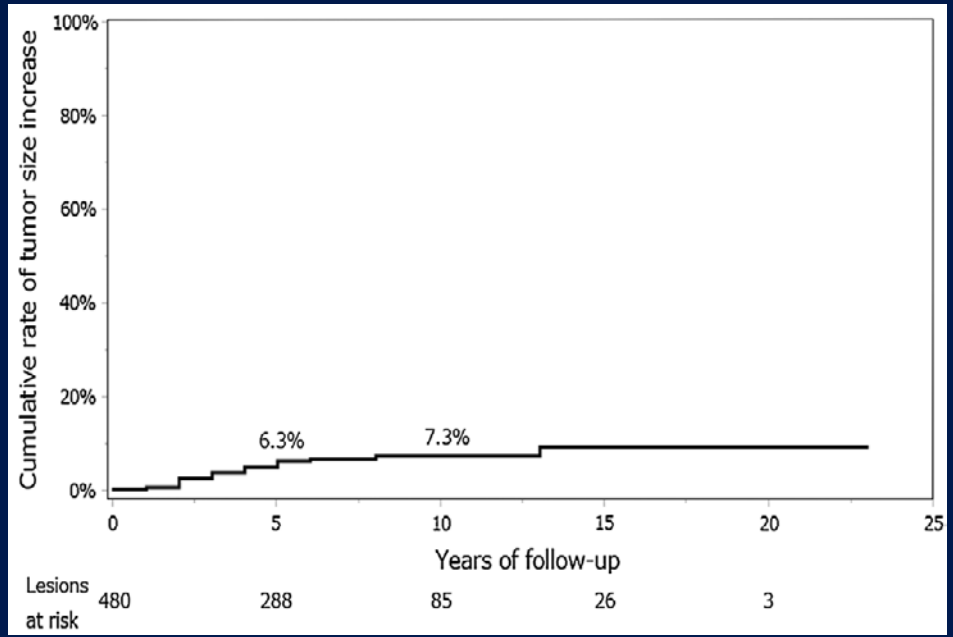
Davies and Welch. JAMA Otolaryngol Head Neck Surg 2014;140:317-22

Observation Of Papillary Thyroid Microcarcinoma (<1 cm)

Median follow-up 47 months[1]
- 1,179 patients observed
- No disease-specific mortality

Mean follow-up 6.8 years[2]
- 480 cancers observed
- 6% increased in size





[1]Oda et al. Thyroid 2016;26:150-5; [2]Fukuoka et al. World J Surg 2016;40:529-37

Thyroid Ultrasound: Assess Cancer Risk

Cancer suspicion

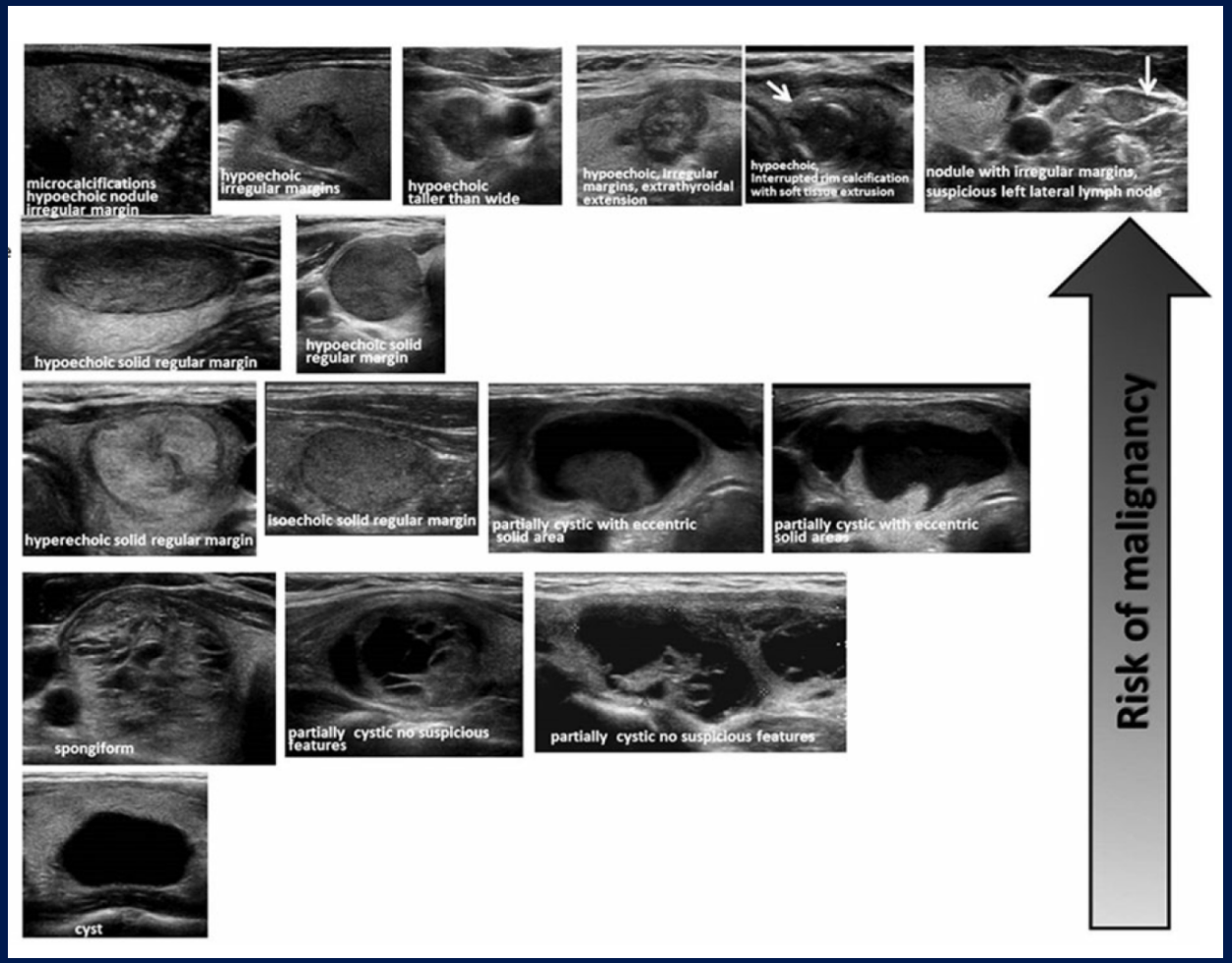
High >70-90%

Intermediate 10-20%

Low <5-10%

Very low <3%

Benign <1%



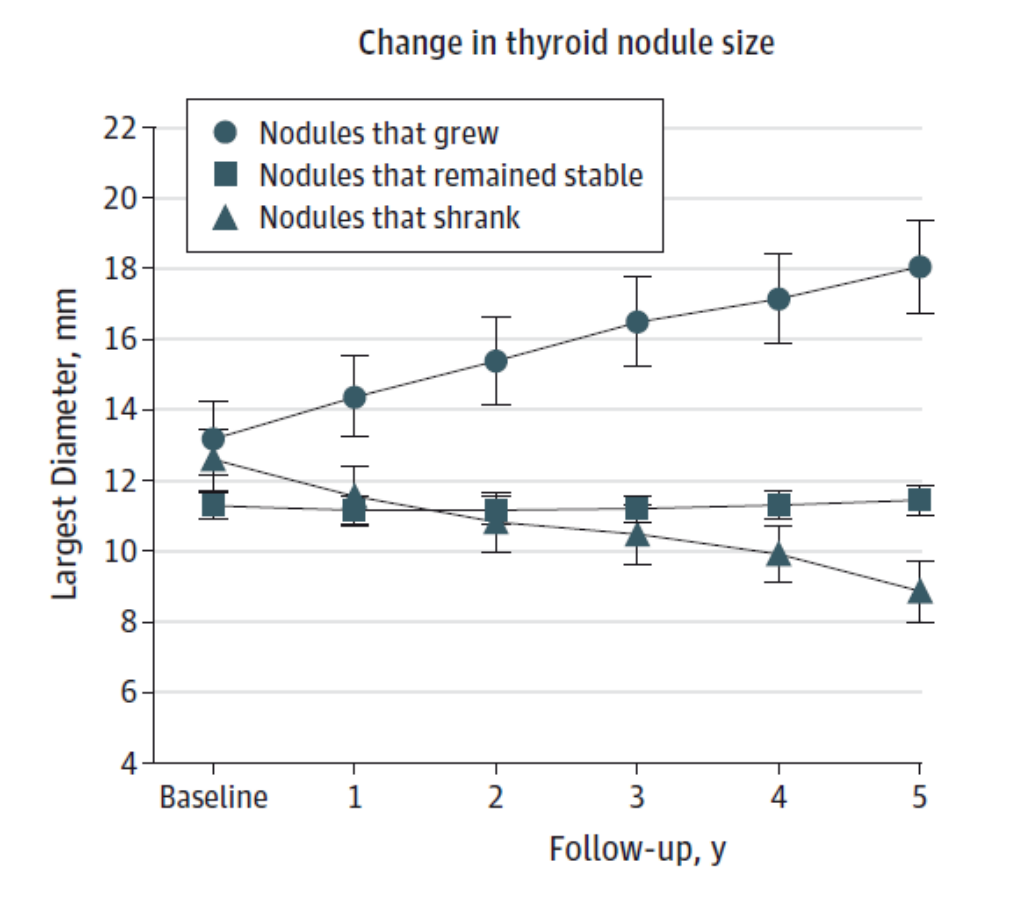
Haugen et al. Thyroid 2016;26:1-133

American Thyroid Association Guidelines

- Indications for thyroid ultrasound
  - Nodular goitre
  - Abnormality detected on other imaging modality
- Indications for fine needle aspirate stratified based on size and sonographic malignancy risk
  - <1 cm: Not indicated regardless of sonographic features
  - >1 cm: High or intermediate risk
  - >1.5 cm: Low risk
  - >2 cm: Very low risk

Haugen et al. Thyroid 2016;26:1-133

“Benign” Thyroid Nodules



11% (n=174)

76% (n=1188)

13% (n=205)

Thyroid cancer diagnosed in 0.3%

Durante et al. JAMA 2015;313:926-35

Clinical Application

- The medical profession needs to employ a safe but cost-effective approach to diagnostic testing for thyroid cancer
- Most thyroid nodules are benign
- Most thyroid cancers have a good prognosis
- We need to better identify the small number of patients with a poor prognosis
- There is a low risk of false negative in patients with benign cytology

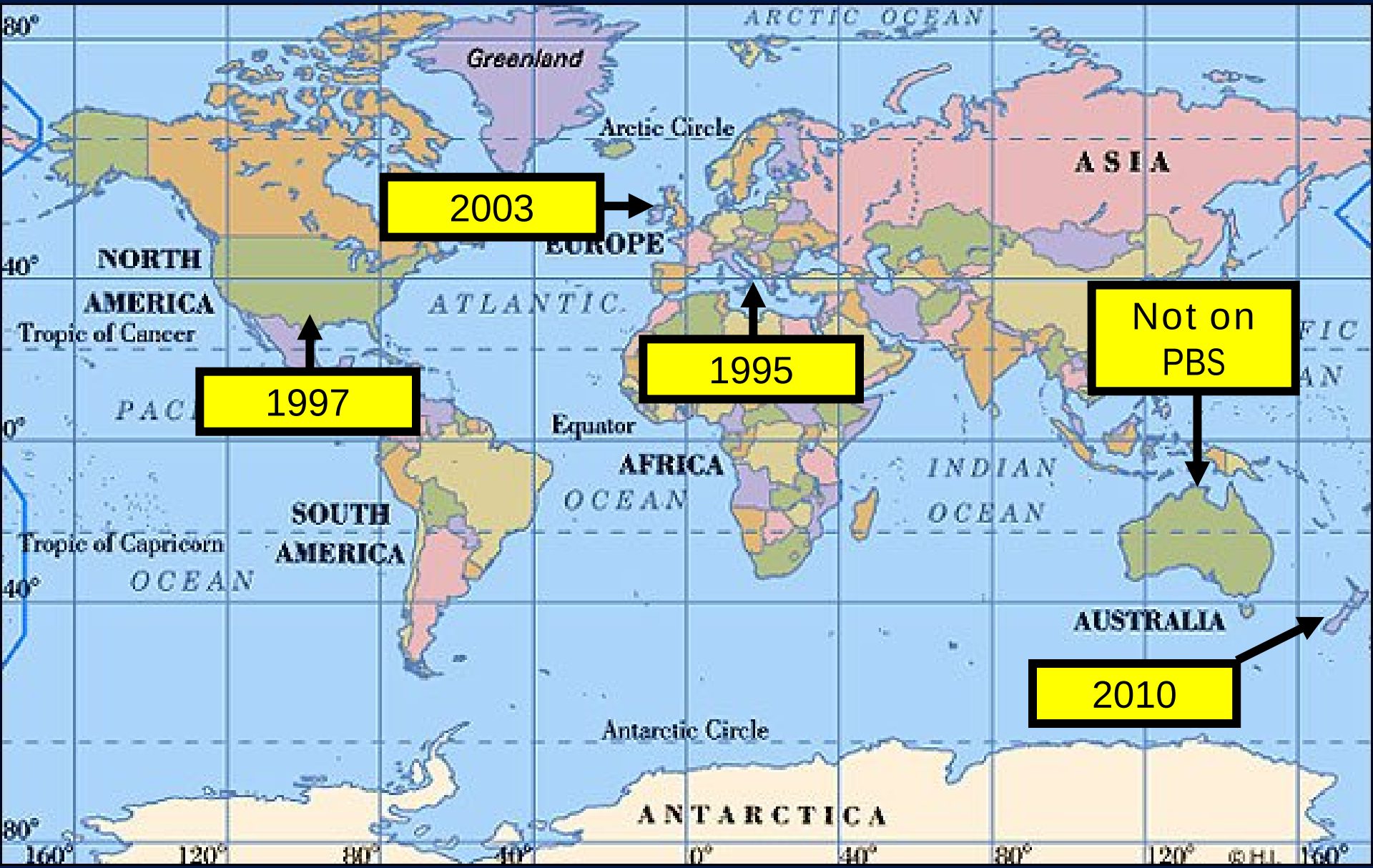
Pituitary Hormone Replacement In Australia

- ACTH deficiency: Hydrocortisone
- TSH deficiency: Thyroxine
- Gonadotrophin deficiency: Oestrogen or testosterone
- Growth hormone deficiency: Not replaced
  - Approved by Therapeutic Goods Administration
  - Not on Pharmaceutical Benefit Scheme
  - $50 per mg ($15-50 per day)

Growth Hormone Deficiency

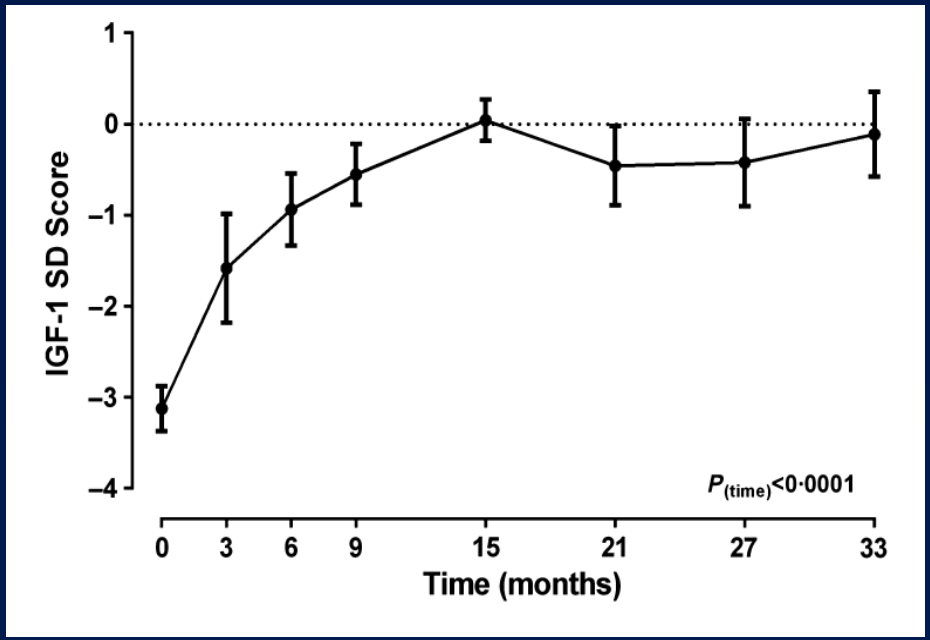
	Associations	GH Treatment
Body composition	Adverse effect	Benefit
Physical function	Adverse effect	Benefit
Surrogates for CV disease	Adverse effect	Benefit
Quality of life	Adverse effect	↔ / ↑
Mortality	Increased	?

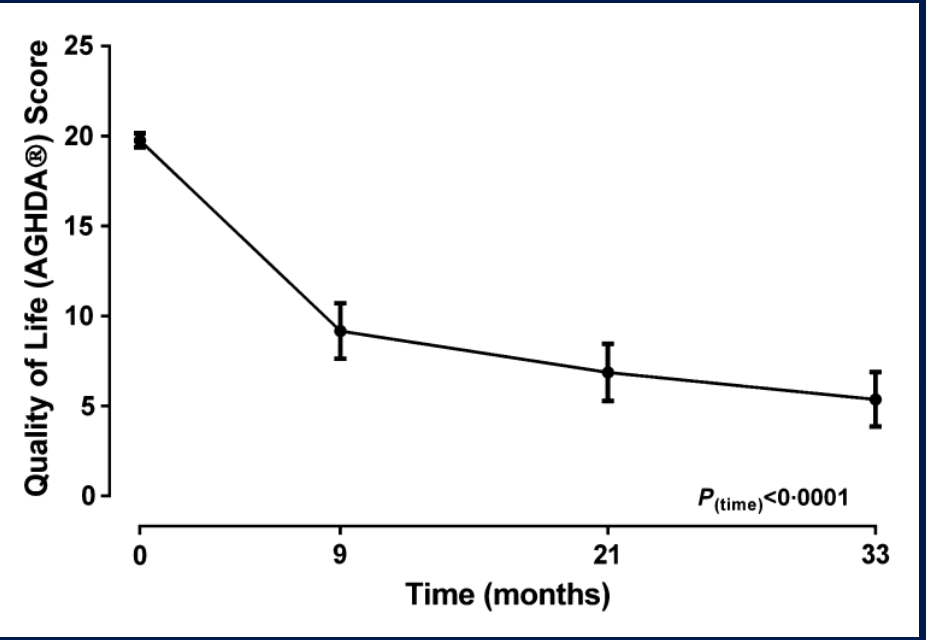
Adult GH Replacement



New Zealand Adult Growth Hormone Replacement Program

- 191 patients with severe GH deficiency, reduced quality of life
- Mean GH dose 0.39 mg / day for women, 0.31 mg / day for men





Holdaway et al. Clin Endocrinol 2015;83:85-90

New Zealand Adult Growth Hormone Replacement Program

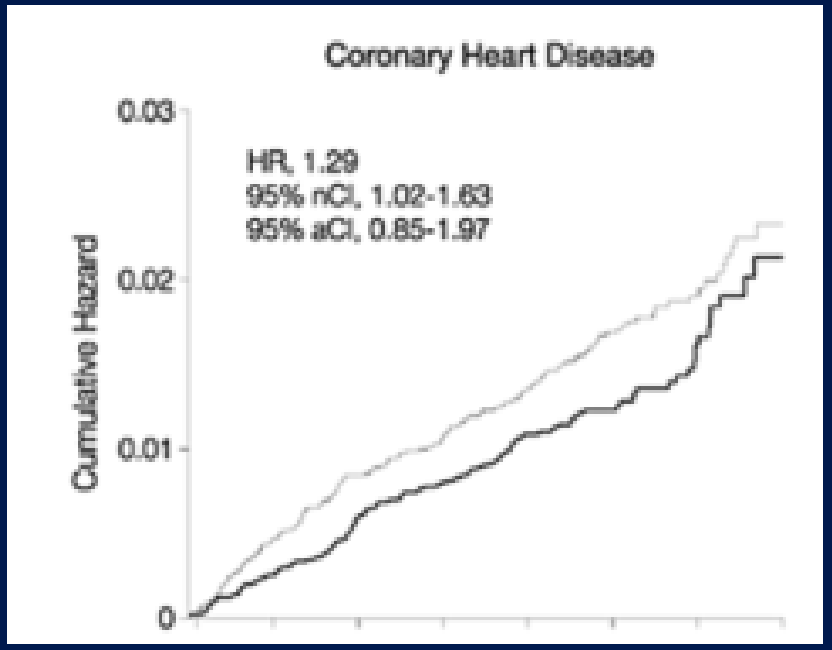
- Limitations of this data
  - Observational
  - Not placebo controlled
- Relatively small numbers of patients
- Relatively low growth hormone doses

Good model for Australia to consider

Oestrogen And Cardiovascular Disease Women's Health Initiative Studies

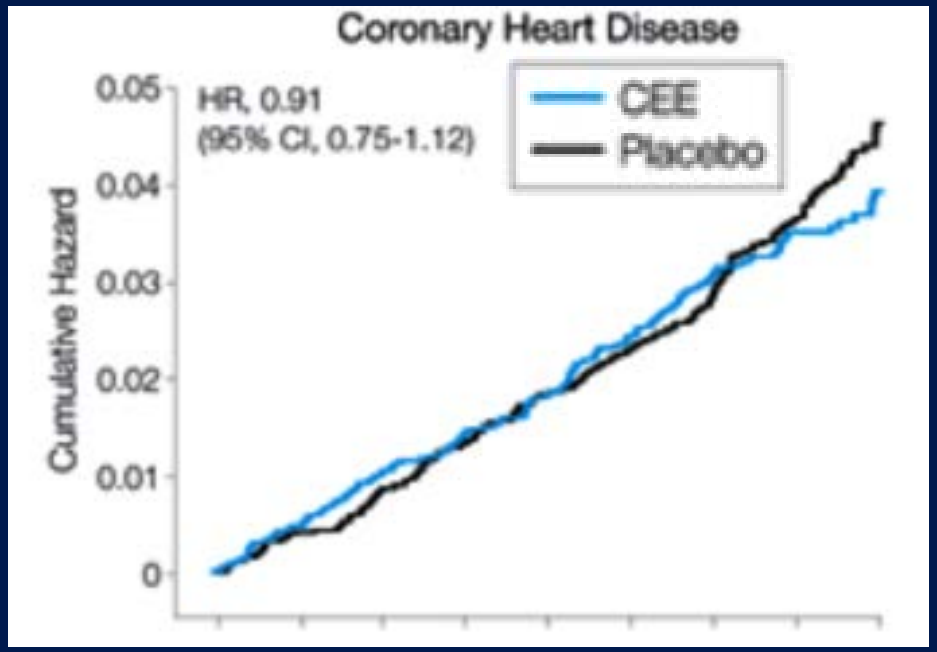
Oestrogen plus progesterone[1]

Stopped in 2002 because of an increased risk of invasive breast cancer and a global index of risk / benefit



Oestrogen only[2]

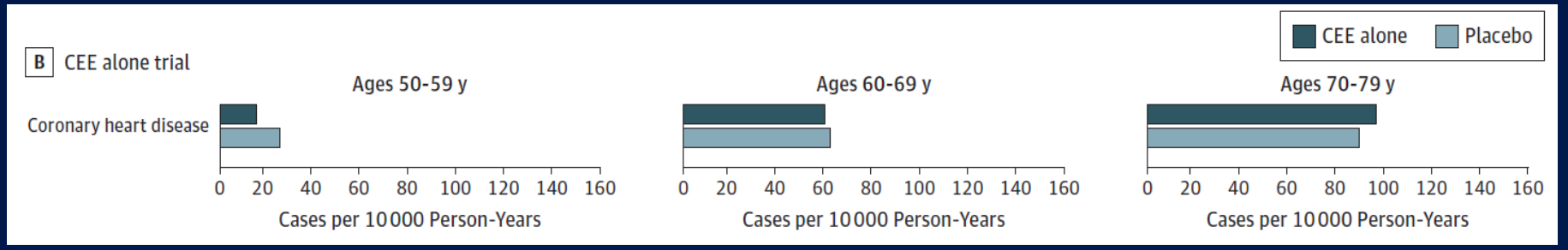
Stopped in 2004 because of an increased risk of stroke

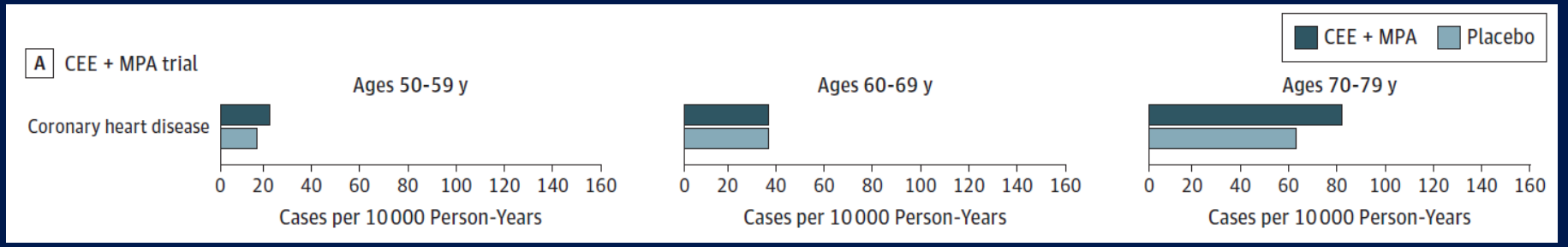


[1]Rossouw et al. JAMA 2002;288:321-33; [2]Anderson et al. JAMA 2004;291:1701-12

Subsequent Analysis Of WHI

- Timing hypothesis: Age of commencement of oestrogen alone influences cardiovascular risk

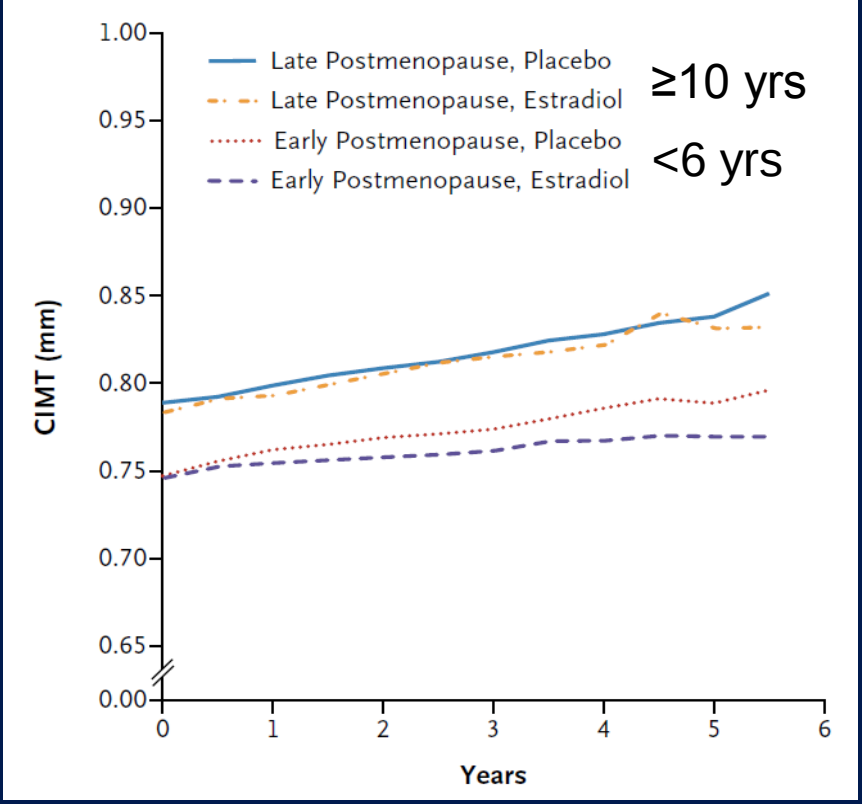




Manson et al. JAMA 2013;310:1353-68

Vascular Effects Of Oestradiol

- 643 post-menopausal women
- Sub-divided into early (< 6 years) or late (>10 years) post menopause
- Randomised to oral 17β oestradiol 1 mg/day (± 45 mg vaginal micronized progesterone gel) or placebo



0.0100 vs 0.0088 mm/yr, p=0.29

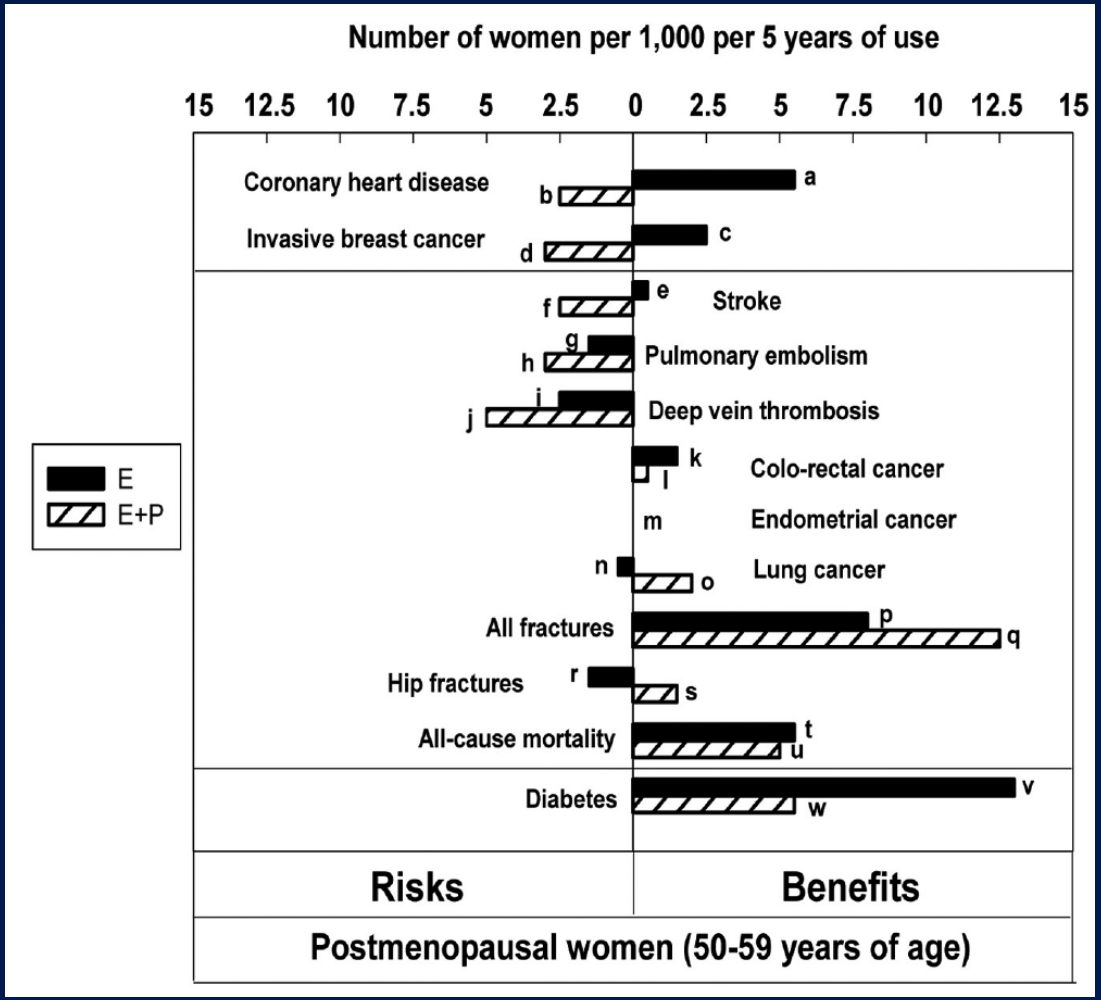
0.0044 vs 0.0078 mm/yr, p=0.008

Hodis et al. N Engl J Med 2016;374:1221-31

Clinical Application

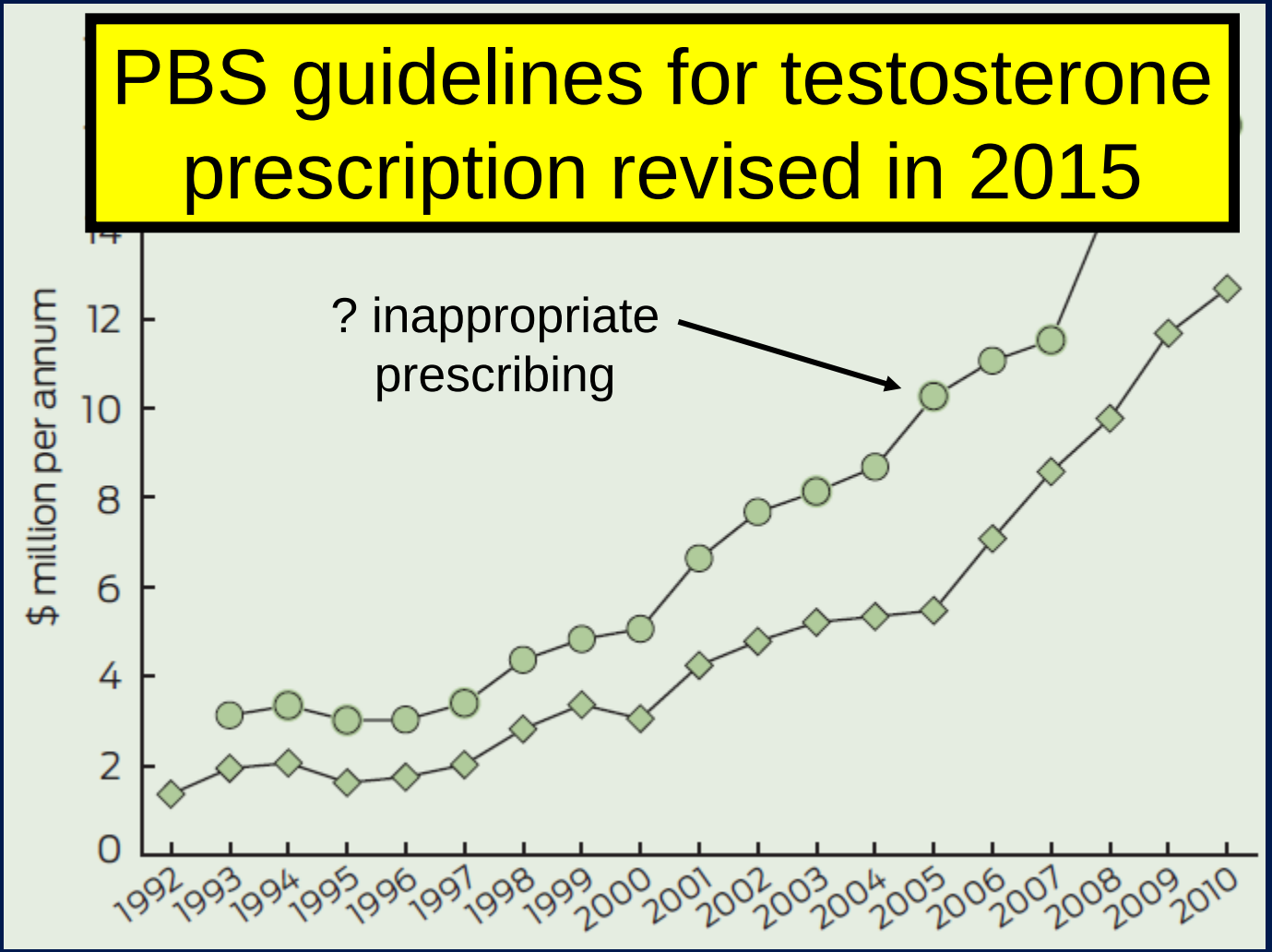
- Risk / benefit of oestrogen treatment is complex
  - Oestrogen formulation
  - Need for progesterone
  - Time relative to menopause
- Oestrogen should not be prescribed to early post-menopausal women to prevent cardiovascular disease
  - Secondary analyses and analyses of surrogate markers of cardiovascular disease
- Prescribing oestrogen for vasomotor symptoms in the early post-menopausal period probably does not increase cardiovascular risk

Endocrine Society Clinical Practice Guideline



Stuenkel et al. J Clin Endocrinol Metab 2015;100:3975-4011

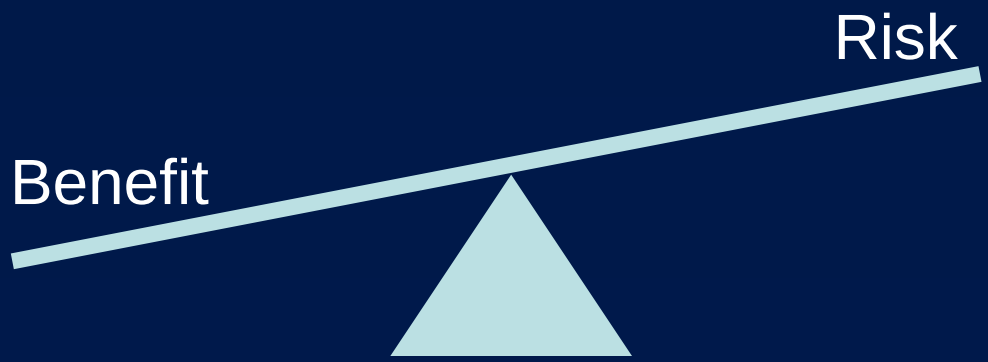
Testosterone Prescribing In Australia



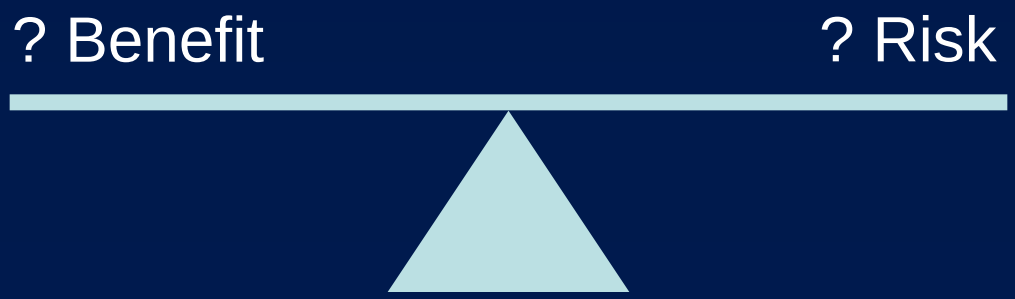
Handelsman. MJA 2012;196:642-5

Risk / Benefit Of Testosterone?

Established testicular or pituitary disease



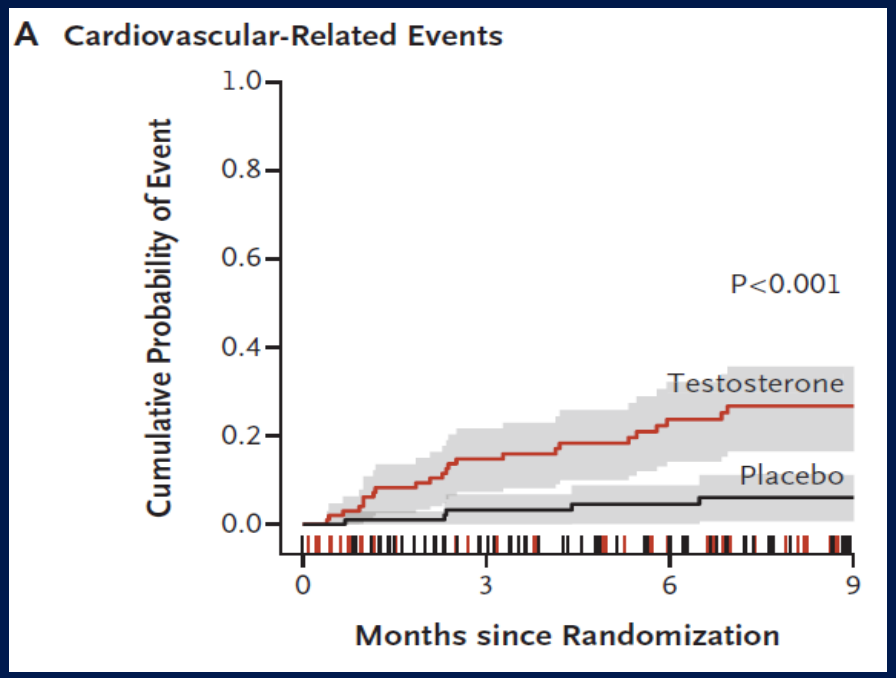
Other clinical scenarios e.g older men



Cardiovascular Effects Of Testosterone: Previous Data

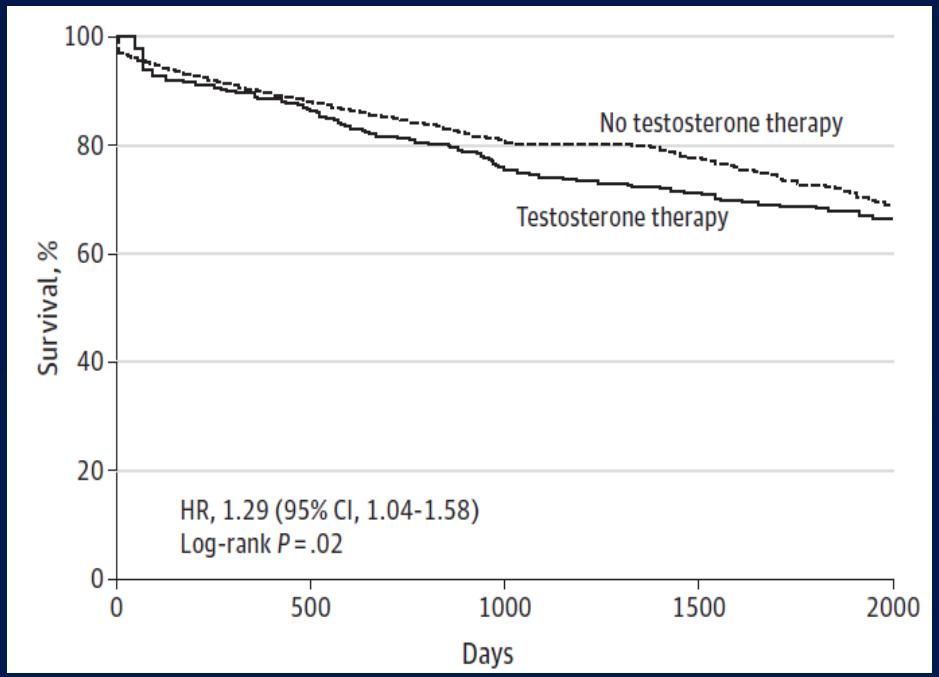
Randomized-controlled trial

- 209 men, mean age = 74 years
- Most men on 10 g testosterone gel



Cohort study

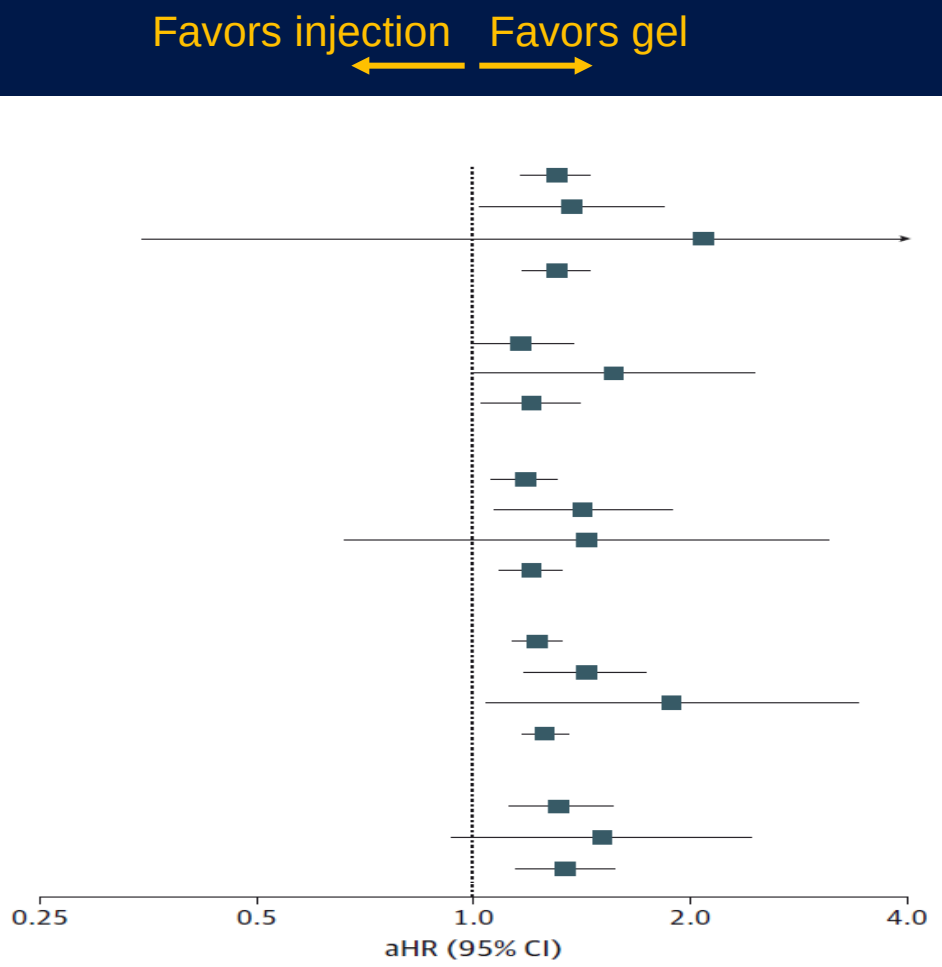
- Coronary angiogram, T <10.4 nmol/L
- Non-randomized



[1] Basaria et al. N Engl J Med 2010;363:109-22; [2] Vigen et al. JAMA 2013;310:1829-36

Cardiovascular Disease With Testosterone Injections Vs Gel

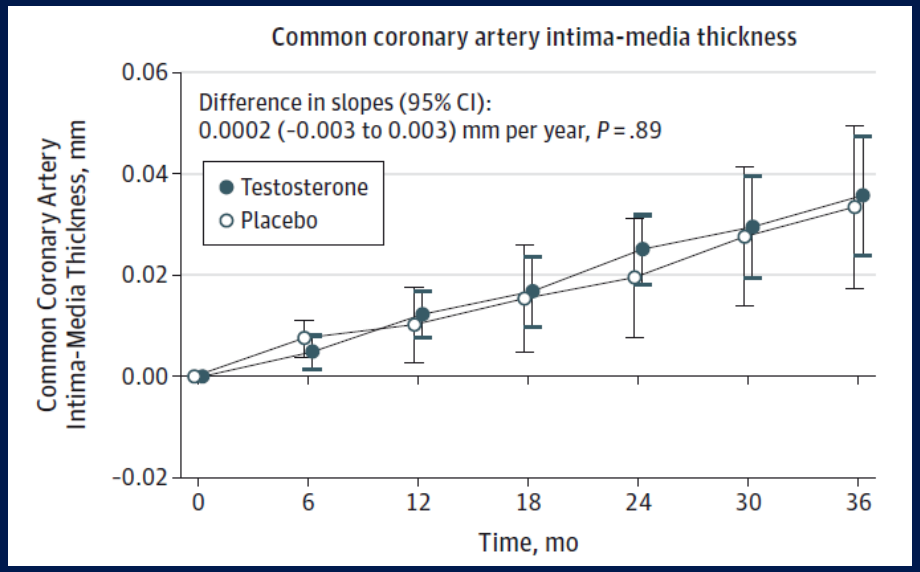
Outcome	Sample Size	aHR (95% CI)
Myocardial infarction		
MarketScan	479 199	1.30 (1.17-1.45)
Medicare	20 934	1.37 (1.02-1.83)
CPRD	5400	2.08 (0.35-12.60)
Pooled		1.30 (1.18-1.45)
Unstable angina		
MarketScan	479 199	1.17 (1.00-1.37)
Medicare	20 934	1.57 (1.01-2.45)
Pooled		1.21 (1.04-1.40)
Stroke		
MarketScan	479 236	1.18 (1.07-1.30)
Medicare	20 972	1.42 (1.08-1.88)
CPRD	5396	1.44 (0.67-3.10)
Pooled		1.21 (1.10-1.32)
Composite acute events		
MarketScan	478 175	1.23 (1.15-1.32)
Medicare	20 843	1.44 (1.19-1.73)
CPRD	5383	1.89 (1.05-3.40)
Pooled		1.26 (1.18-1.35)
Death		
Medicare	21 065	1.32 (1.13-1.55)
CPRD	5414	1.51 (0.94-2.42)
Pooled		1.34 (1.15-1.56)

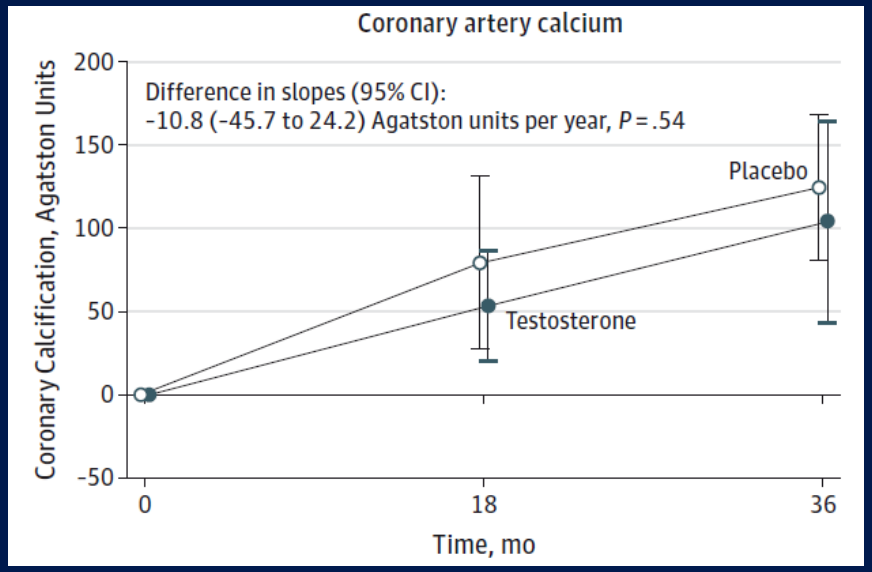


Layton et al. JAMA Intern Med 2015;175:1187-96

Transdermal Testosterone And Markers Of Cardiovascular Risk

- 308 men aged ≥ 60 years with testosterone 3.5-13.9 nmol/L
- Randomised to transdermal testosterone or placebo
- No significant difference in rate of change of carotid artery intima-media thickness or coronary artery calcium score





Basaria et al. JAMA 2015;314:570-81

Clinical Application

- Risk / benefit of testosterone therapy in older men is unknown and will only be answered by a long-term, sufficiently powered, randomized controlled trial
- Main known benefits of testosterone are symptomatic
- If you prescribe testosterone to older men consider using transdermal testosterone
- New PBS criteria for testosterone
  - Established pituitary or testicular disease
  - Morning testosterone <6 nmol/L

Summary

- Empaglifozin, a SGLT2 inhibitor, reduced mortality in patients with type 2 diabetes
- Small thyroid cancers have a good prognosis; this needs to be considered in investigation algorithms
- New Zealand adult growth hormone replacement program improved quality of life in participants
- Patient age may influence the atherogenic and consequently cardiovascular effects of oestrogen
- Effect of testosterone on cardiovascular risk in older men is not clearly established