Trick or Treat, 2016

Dov Gandell MDCM, FRCPC

October 28, 2016

UNIVERSITY OF TORONTO

Sunnybrook HEALTH SCIENCES CENTRE

Final assessment: trick or treat

- **Treat**
  - a positive result that is valid and may influence practice
- **Trick**
  - a negative result that does not terminate that area of investigation
  - a positive result with validity concerns

Methods: article selection

- Canvassed Geriatricians from across the province
  - Dr. Gary Naglie, Dr. Camilla Wong, Dr. Rajin Mehta
- Scanned table of contents and read major journals/reviews
- Reviewed articles presented at the Geriatric Medicine Journal Club
- Favoured randomized controlled trials


WORLD PREMIERE
STRICTLY LIMITED ENGAGEMENT
PRIOR TO BROADWAY
Sections
News · World
High hopes new
'game changer' a
incurable Alzhein
An experimental antibody treatment signific
proteins in the brains of Alzheimer's patient
nature
TARGETING AMYLOID
Antibody aducanumab reduces Alzheimer's
disease-associated amyloid in human brain
DNA MEMORIES
CHEATING HAPPENS
SPHERES OF INFLUENCE
's drug a 'game-
Top stories
Early voting promising for Clinton
Engagement pic became a wake-up call
TIME
An Alzheimer's Drug Shows Serious Promise
HEALTH BRAIN
An Alzheimer's D
Alice Park @aliceparkny | Aug. 31, 2016
Experts are excited about a drug that, at high doses, seems to chip away at Alzheimer's damage in the brain
Treating Alzheimer's likely won't ever be an easy or simple thing. Researchers think that managing the disease will require a combination of treatments, possibly tailored to each person. But in a paper published Wednesday in the journal Nature, scientists from a biotech company report the most encouraging
Trade in your device and get up to $300 towards a new HTC 10.
Learn more
Bell
Tom Cruise Sends Dakota Fanning Shoes Every Year For Her Birthday
94-Year-Old Man Retiring As Pennsylvania City Fire Chief After 63-Year Tenure
Amy Schumer and Goldie Hawn's Recreated Beyoncé 'Formation'
theguardian
browse all sections
s that new
efit early-
condition in patients at

ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

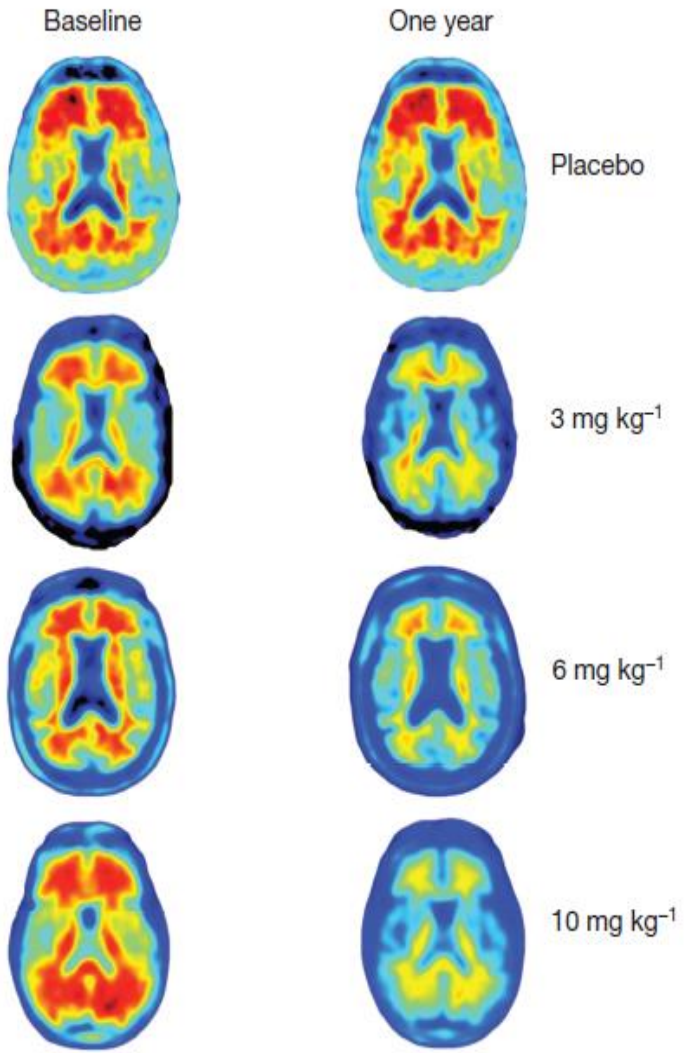
Nature 2016;537:50-58

- Phase 1 randomised controlled trial (RCT)
- Number (N) = 165
- Prodromal or mild Alzheimer's dementia
  - MMSE 24

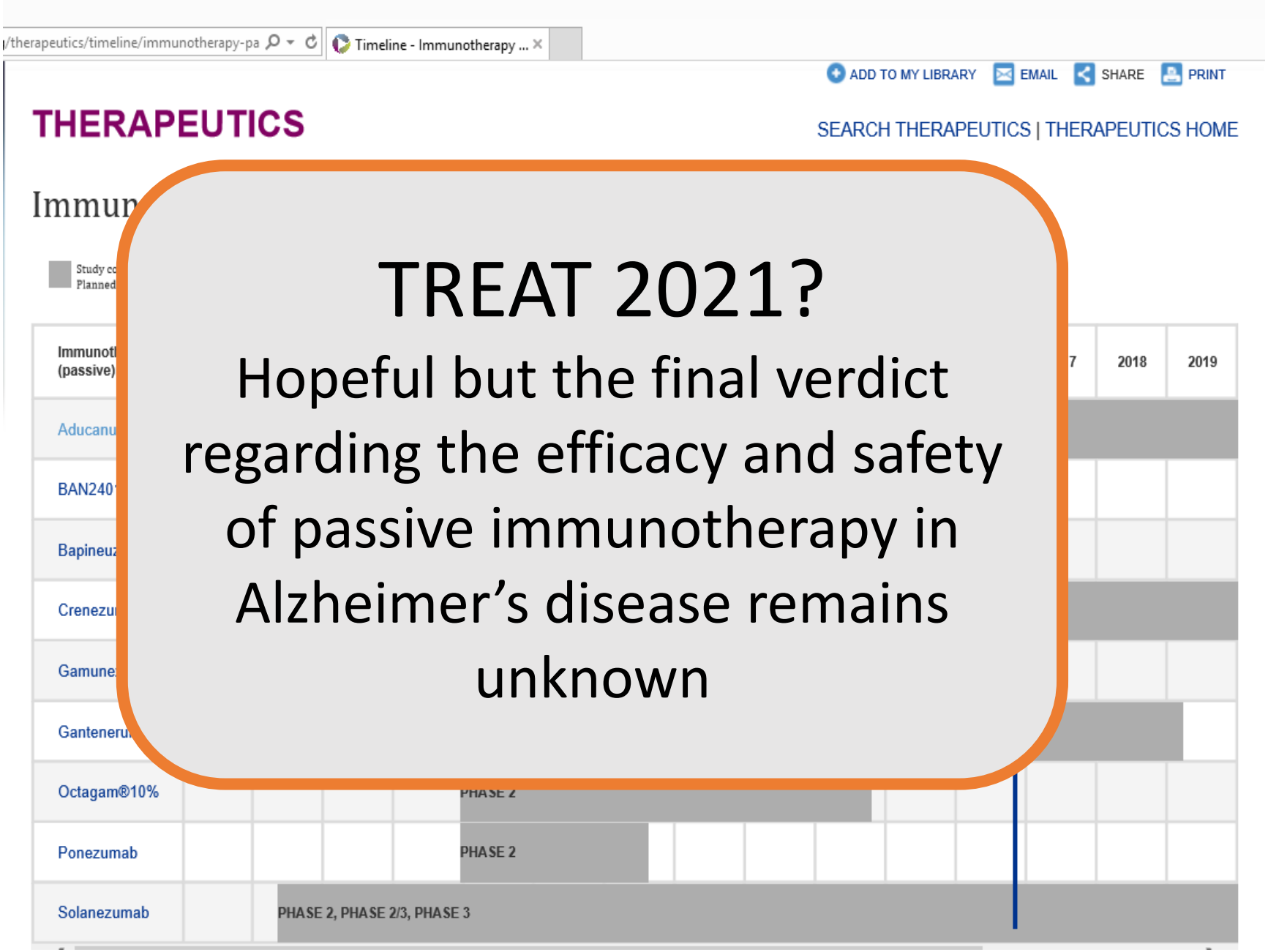
- **Intervention**
  - Monthly aducanumab 1, 3, 6, 10 mg/Kg for 1 year versus placebo

- **Primary outcome**
  - Reduction in brain A_{β} plaques, positron emission tomography (PET)

Nature 2016;537:50-58



Nature 2016;537:50-58



https://dian-tu.wustl.edu/en/home/

http://www.alzforum.org/

Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial

Xian Su, Zhao-Ting Meng, Xin-Hai Wu, Fan Cui, Hong-Liang Li, Dong-Xin Wang, Xi Zhu, Sai-Nan Zhu, Mervyn Maze, Daqing Ma

Published online August 15, 2016. http://dx.doi.org//10.1016/s0140-6726(16)30580-3

- Randomized, double-blind, placebo-controlled

- **Intervention**
  - Dexmedetomidine 0.1 μg/kg per h from ICU admission on day of surgery until 0800h on post-operative day 1 versus placebo (intravenous normal saline)

- N = 700

- **Primary Outcome**
  - Incident delirium (Confusion Assessment Method - CAM) in the first 7 post-operative days

Published online August 15, 2016. http://dx.doi.org//10.1016/s0140-6726(16)30580-3

- **Inclusion**
  - ≥ 65
  - Elective, non-cardiac surgery
  - General anesthesia
  - Not demented

- **Average participant**
  - 68% intra-abdominal surgery
  - 72% malignant
  - 2.5hrs surgery

Published online August 15, 2016. http://dx.doi.org//10.1016/s0140-6726(16)30580-3

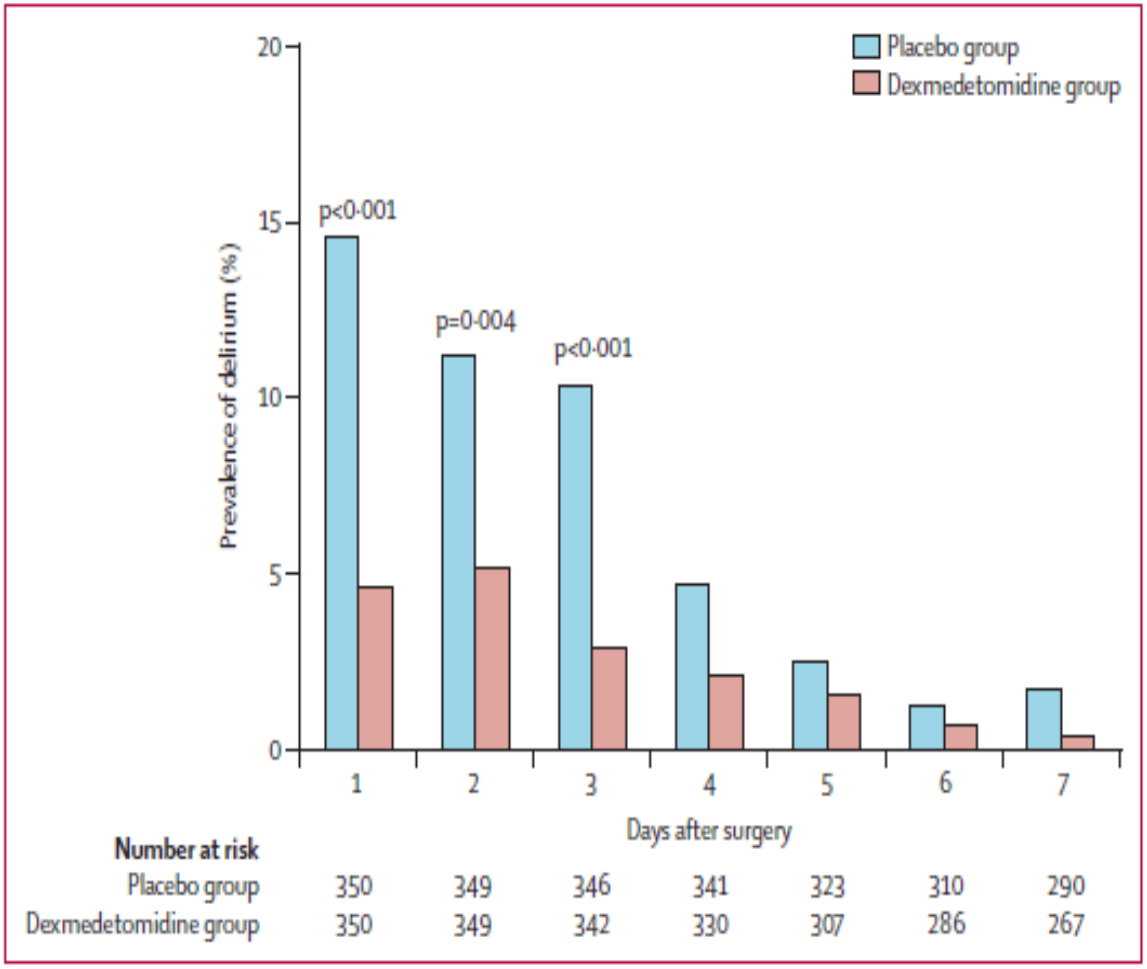


***Figure 2*: Daily prevalence of postoperative delirium**

Sample sizes differ from the first to seventh day because some patients were discharged from hospital or died during this period.

Published online August 15, 2016. http://dx.doi.org//10.1016/s0140-6726(16)30580-3

- **Results**
  - Dexmedetomidine 9% (32/350) versus placebo 23% (79/350)
- **Adv**
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- **We**
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  - Ra
  - Cost-benefit analysis
  - Result requires duplication

TRICK

Based on this trial, dexmedetomidine should not be used routinely for post-operative delirium prophylaxis

Published online August 15, 2016. http://dx.doi.org//10.1016/s0140-6726(16)30580-3

Partial and No Recovery from Delirium in Older Hospitalized Adults: Frequency and Baseline Risk Factors

Martin G. Cole, MD,[*†‡] *Robert Bailey, MD,*[‡§] *Michael Bonnycastle, MD,*[‡¶] *Jane McCusker, MD, DrPH,*[†**] *Shek Fung, MD,*[‡§] *Antonio Ciampi, PhD,*[†**] *Eric Belzile, MSc,*[†] *and Chun Bai, MMath*[†]

J Am Geriatr Soc 2015;63:2340-2348

- Prospective cohort study

- **Objective**
  - Determine the frequency and baseline risk factors for partial and no recovery from delirium in hospitalized adults
- N = 265

- **Outcomes**
  - Recovery from delirium at 1 and 3 months follow-up
  - Recovery classified as full, partial, no-recovery

J Am Geriatr Soc 2015;63:2340-2348

- **Inclusion**
  - ≥ 65
  - Admitted to medical or surgical ward

- **Average participant**
  - 60% > 85 years old
  - 76% female
  - 50% institutionalized
  - 80% medical inpatients
  - MMSE 14

J Am Geriatr Soc 2015;63:2340-2348

Demented	Full recovery	Partial recovery	No recovery
1 month follow-up	6.3	11.3	74.6
3 month follow-up	7.9	15.1	57.6

NOT Demented	Full recovery	Partial recovery	No recovery
1 month follow-up	14.3	17	50.9
3 month follow-up	19.2	20.2	31.7

J Am Geriatr Soc 2015;63:2340-2348

- **Results**
  - Baseline risk factors for delirium persistence
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- **Stre**
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- **We**
  - C
  - Big discrepancy between eligible (2200) versus enrolled (278) patients

TREAT

Data is helpful to enhance understanding, communication, and advocacy

J Am Geriatr Soc 2015;63:2340-2348

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2016 VOL. 375 NO. 11

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C. Vanden Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S.A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, and T.C. Heineman, for the ZOE-70 Study Group*

N Engl J Med 2016;375:1019-1032

- Multicenter, placebo controlled, randomized controlled trial
- N = 13 900
- **Intervention**
  - 2 doses herpes zoster subunit vaccine (HZ/su) glycoprotein E and the ASO1B adjuvant system intramuscularly two months apart or placebo
- 3.7 years
- **Primary outcomes**
  - Incident herpes zoster
  - Post-herpetic neuralgia

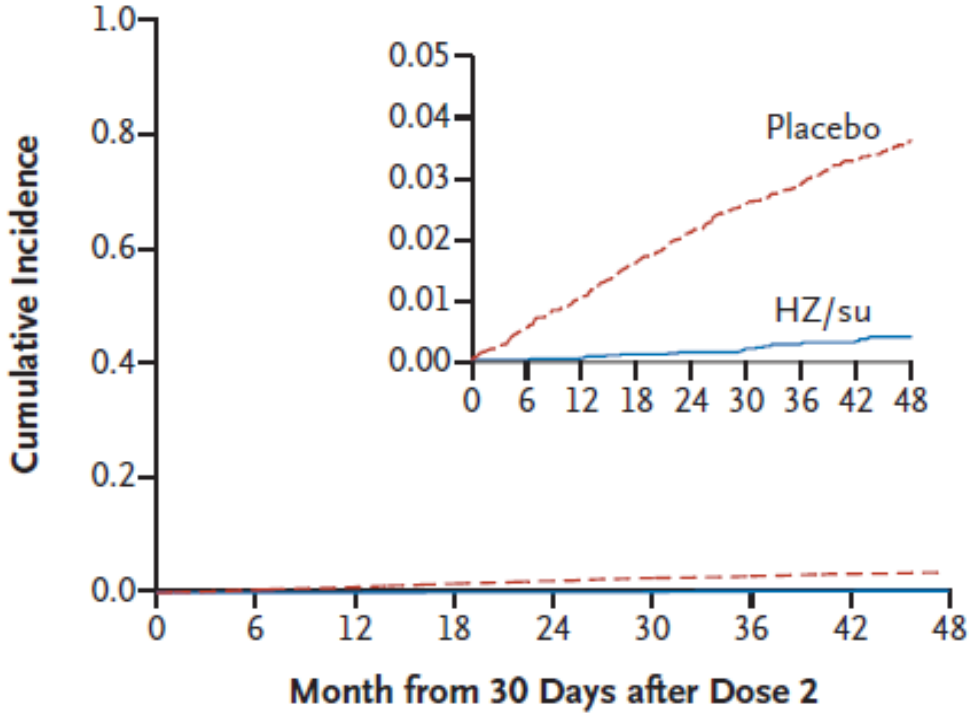
N Engl J Med 2016;375:1019-1032

- **Inclusion**
  - ≥ 70 years old
  - No history of zoster
  - No history of zoster immunization
  - No history of immunosuppression

- **Average participant**
  - 75 years old
  - 55% female
  - 75% Caucasian
  - 75% Europe, Asia, Australia

N Engl J Med 2016;375:1019-1032

A **Modified Vaccinated Cohort in ZOE-70**



No. at Risk									
HZ/su	6541	6469	6379	6285	6137	6055	5898	5760	2692
Placebo	6622	6516	6372	6249	6076	5946	5776	5628	2589

Cumulative No. of Cases									
HZ/su	0	0	2	6	8	12	17	19	23
Placebo	0	34	68	104	136	165	184	208	221

N Engl J Med 2016;375:1019-1032

- **Results**
  - Herpes zoster 89.8% (84.2 – 93.7, p<0.001)
    - 23 cases in HZ/su versus 223 placebo (0.9 versus 9.2 per 1000-
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  - Tw ose or altered schedule
  - Another option for immunocompromised patients

TREAT

New option with possible improved efficacy

N Engl J Med 2016;375:1019-1032

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

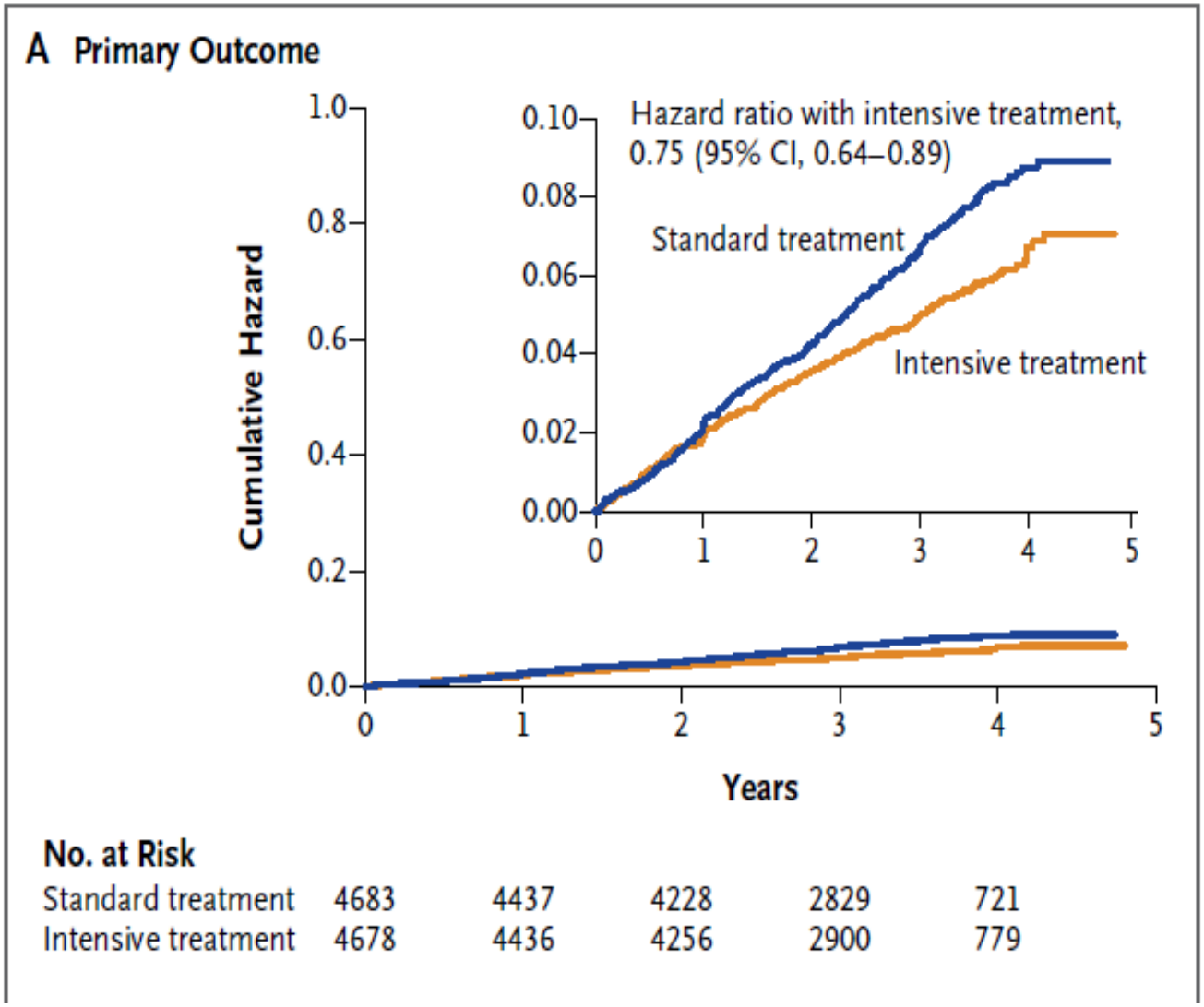
ABSTRACT

- Double-blind, randomized controlled trial
- N = 9361
- **Intervention**
  - Intensive treatment (systolic blood pressure SBP < 120 mm Hg versus standard treatment SBP < 140 mm Hg)
- 3.2 years
- **Primary outcome**
  - Myocardial infarct, acute coronary syndrome, heart failure, stroke, or death from cardiovascular causes

N Engl J Med 2015;373:2103-2116

- **Inclusion**
  - ≥ 50 years old
  - SBP between 130 and 180 mm Hg
  - Increased risk of cardiovascular disease
  - Excluded: diabetes or prior stroke
- **Average participant**
  - 68 years old
  - Caucasian
  - 140/78
  - 1.8 anti-hypertensive medications

N Engl J Med 2015;373:2103-2116



N Engl J Med 2015;373:2103-2116

- **Results**
  - 1.65%/yr versus 2.19%/yr. HR 0.75 (95 CI 0.64 – 0.89, p<0
- **Adv**
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  - Long term renal and cognitive outcomes unknown
  - Frailty

TREAT

Reaffirms systolic blood pressure as a spectrum of risk. Selected older adults may benefit from a target below 150mmHg

N Engl J Med 2015;373:2103-2116

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2016 VOL. 374 NO. 7

Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*

N Engl J Med 2016;374:611-624

- Randomized, placebo-controlled, double-blind
- N = 790

- **Interventions**
  - Testosterone 5 g gel daily or placebo gel for 1 year

- **Primary outcome**
  - Sexual function – Psychosexual Daily Questionnaire (PDQ – 4)
  - Physical function – distance on 6 min walk test > 50 meters
  - Vitality – Functional Assessment in Chronic Therapy – Fatigue (FACIT – fatigue) score

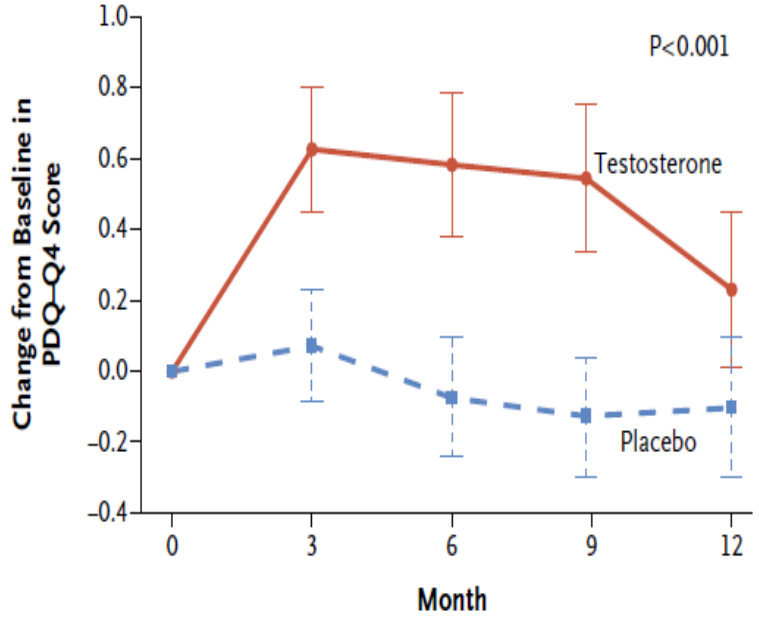
N Engl J Med 2016;374:611-624

- **Inclusion**
  - ≥ 65 years old
  - Serum total testosterone average < 275ng/dL
    - (300ng/dL – 800ng/dL)

- **Average participant**
  - 72 years old
  - Married, caucasian
  - Hypertension
  - Body mass index (BMI) 31, Obstructive sleep apnea
  - Folstein Mini Mental Status Exam 28

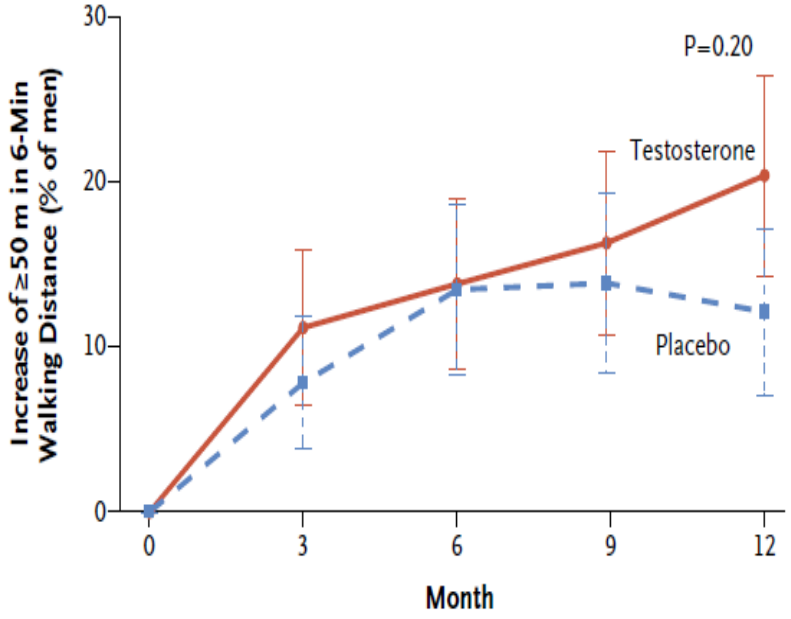
N Engl J Med 2016;374:611-624

A Sexual Activity



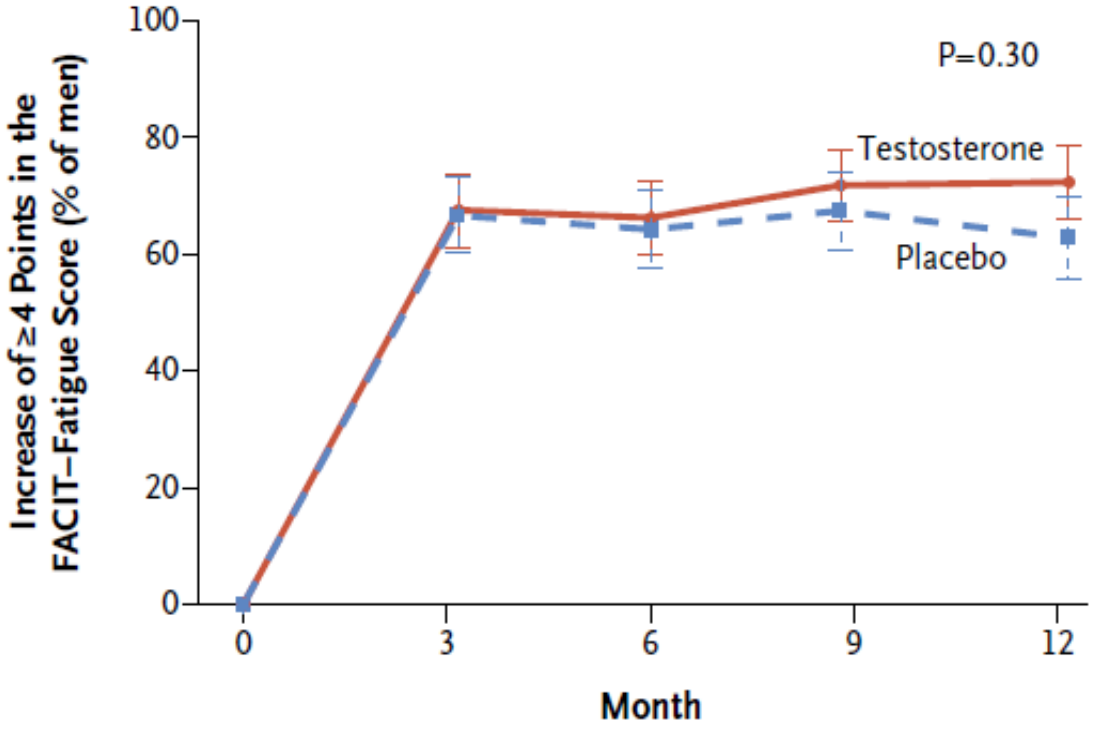
No. at Risk					
Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

B Walking Ability



No. at Risk					
Testosterone	193	179	174	172	172
Placebo	197	179	171	159	165

C Vitality



No. at Risk					
Testosterone	236	219	217	206	203
Placebo	238	207	196	188	191

- **Results**
  - Sexual function – PDQ-Q4 score 0.58, p<0.001
  - Exer… p=0.20
  - V… y –
- **Adv…**
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  - 1… one
  - …
- **Stre…**
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  - Gene…
  - Concern regarding adverse effects remain

TREAT

A well designed RCT providing more clarity that testosterone supplementation in older men is inappropriate

N Engl J Med 2016;374:611-624

CLINICAL INVESTIGATIONS

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

J Am Geriatr Soc 2015;63:2227-2246

- **Expert consensus guidelines – American Geriatrics Society (AGS)**
  - Explicit medication list of potentially inappropriate medications (PIM)
  - Update from 2012 iteration
  - 13 member interdisciplinary panel
  - Modified Delphi method

- **Major changes**
  - Drugs for which renal adjustment is necessary
  - Drug-drug interactions
  - Some adjustments of recommendations and re-classifying previously listed medications

J Am Geriatr Soc 2015;63:2227-2246

Table 5. 2015 American Geriatrics Society Beers Criteria for Potentially Clinically Important Non-Anti-infective Drug–Drug Interactions That Should Be Avoided in Older Adults

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Antipsychotics	≥2 other CNS-active drugs	Increase risk of falls	Avoid total of ≥ 3 CNS-active drugs, minimize number of CNS active drugs	Moderate	Strong
Opioid receptor agonist analgesics	≥2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥3 CNS-active drugs[a]; minimize number of CNS drugs	High	Strong
Peripheral Alpha-1 blockers	Loop diuretics	Increased risk of Urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Theophylline	Cimetidine	Increased risk of Theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of Bleeding	Avoid when possible; monitor international normalized ratio closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of Bleeding	Avoid when possible; if used together, monitor for bleeding closely	High	Strong

J Am Geriatr Soc 2015;63:2227-2246

Table 6. 2015 American Geriatrics Society Beers Criteria for Non-Anti-Infective Medications That Should Be Avoided or Have Their Dosage Reduced with Varying Levels of Kidney Function in Older Adults

Medication Class and Medication	Creatinine Clearance, mL/min, at Which Action Required	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular or hemostasis					
Amiloride	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Increased risk of bleeding	Avoid	Moderate	Strong
Dabigatran	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Edoxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30 or >95		Avoid		
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30		Avoid		
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Central nervous system and analgesics					
Duloxetine	<30	Increased Gastrointestinal adverse effects (nausea, diarrhea)	Avoid	Moderate	Weak
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce dose Extended release: avoid	Low	Weak
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

- **Discussion**
  - C
  - H
  - L
  - C

treat

J Am Geriatr Soc 2015;63:2227-2246

PARLIAMENT *of* CANADA

First Session, Forty-second Parliament,
64-65 Elizabeth II, 2015-2016

STATUTES OF CANADA 2016

CHAPTER 3

An Act to amend the Criminal Code and to make related amendments to other Acts (medical assistance in dying)

ASSENTED TO

JUNE 17, 2016

BILL C-14

Première session, quarante-deuxième législature,
64-65 Elizabeth II, 2015-2016

LOIS DU CANADA (2016)

CHAPITRE 3

Loi modifiant le Code criminel et apportant des modifications connexes à d'autres lois (aide médicale à mourir)

SANCTIONNÉE

LE 17 JUIN 2016

PROJET DE LOI C-14

Bill C-14 – June 17, 2016

- Medical Assistance in Dying (MAiD)
  - Euthanasia / Physician assistance in dying
- Eligible for health services funded by a government in Canada
- 18 years old and **capable** of making health decisions
- Have a **grievous** and **irremediable** medical condition
- Have made a **voluntary** request
- Have given **informed consent**

- **Advance directives** and mature minors **excluded**

PAPER

Can physicians conceive of performing euthanasia in case of psychiatric disease, dementia or being tired of living?

Eva Elizabeth Bolt,[1] Marianne C Snijdewind,[2] Dick L Willems,[2] Agnes van der Heide,[3] Bregje D Onwuteaka-Philipsen[1]

J Med Ethics 2015;41:592-598

- Cross-sectional survey, Dutch physicians
- N = 2269 randomly selected
  - 400, specifically elder care physicians

- Can physicians conceive of granting a request for MAiD for people suffering from
  - Psychiatric disease
  - Dementia
  - Tired of living

- What physician characteristics are associated with conceiving of granting a request for MAiD in those circumstances?

J Med Ethics 2015;41:592-598

- Response rate 64%
- Con
  - C
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  - E
  - A
  - T
  - C nd MAID [illegible] amily practitioners or specialists
    - OR 0.41 (95 CI 0.26 – 0.67)

TRICK OR TREAT?

For you to decide

J Med Ethics 2015;41:592-598

Thank you!

Regarding blood pressure in older adults which one is true?

- A) Systolic blood pressure of 120 mmHg is the ideal target
- B) Diastolic blood pressure remains stable with age
- C) A systolic target below 150 mmHg may be appropriate for some patients
- D) The lower the better, so long as the patient is able to stand and produce urine

Which of the following is false?

- A) Aducanumab reduces brain amyloid plaque in Alzheimer's disease but has yet to demonstrate clinical outcomes
- B) Dexmedetomidine conclusively reduces the incidence of post-operative delirium in surgical patients admitted to the ICU
- C) Testosterone modestly improves sexual outcomes in older men with an unknown adverse effect profile
- D) Missing the second dose of the herpes zoster subunit vaccine may diminish its effectiveness

Can you conceive of granting a request for MAiD for an individual with dementia and an advanced directive?

- A) YES

- B) NO