General Medicine Update - Ambulatory

Steve Hillson
Hennepin County Medical Center
University of Minnesota
Fall 2016

Framing it Up

- Ambulatory-focused articles
  - Relevant to GIM
  - Plausibly practice changing
  - Culled from all original research published in
    - NEJM, AIM, JAMA, BMJ, Lancet
    - Plus selected other sources
    - October 2015 through September 2016

My Own Take

- I will offer what I see as important
- I am not a domain expert
- You should read these for yourself
  - Consider your experience, your patients
  - Perhaps consult with domain experts you trust

George Washington

Few men
have virtue to withstand
the highest bidder.

Audience Response

- For my hypertensive patients I:
  A. Aim for a blood pressure of 140/90 or less
  B. Aim for a systolic BP of 135-140
  C. Aim for a systolic BP of 120 or less
  D. Have different targets depending on risks such as Age, Diabetes, etc
  E. Do something else

Blood Pressure Targets

- Two Articles from the Systolic Blood Pressure Intervention Trial (SPRINT)
  - A Randomized Trial of Intensive versus Standard Blood-Pressure Control
    - The SPRINT research group
    - NEJM 11/26/15
  - Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged 75+ years.
    - Williamson et al
    - JAMA 6/28/16
- Sponsored by the NIH

Blood Pressure Targets

- Study Questions
  - Is a target BP of 120 superior to target BP of 140 (actually 135-139) in a high-risk, non-diabetic group?
  - And specifically in an older group?
- Background
  - Target SBP < 140 remains the general standard for treatment
  - Benefit has only been proven for SBP target of 150
  - Observational studies suggest lower is better.
  - Trials of tighter control in diabetes and stroke have not shown benefit
  - Lower blood pressure comes at a price

Design – Unblinded RCT

- 9300 patients throughout US
  - Age at least 50, SBP 130-180
  - No cerebrovascular disease or Diabetes
  - Increased risk: 1 or more of
    - CV disease, GFR 20-60, Framingham 15%+, age 75+
- Received
  - Increased medication as needed to achieve SBP <120, OR
  - BP titrated to 135-139
    - Medication reduced if SBP < 130 once or 135 twice
- Followed 5 years (planned) for MI, ACS, CVA, CHF, CV Death.
  - Expected reduction from 2.2% to 1.75% per year.
  - Stopped after about 3 years

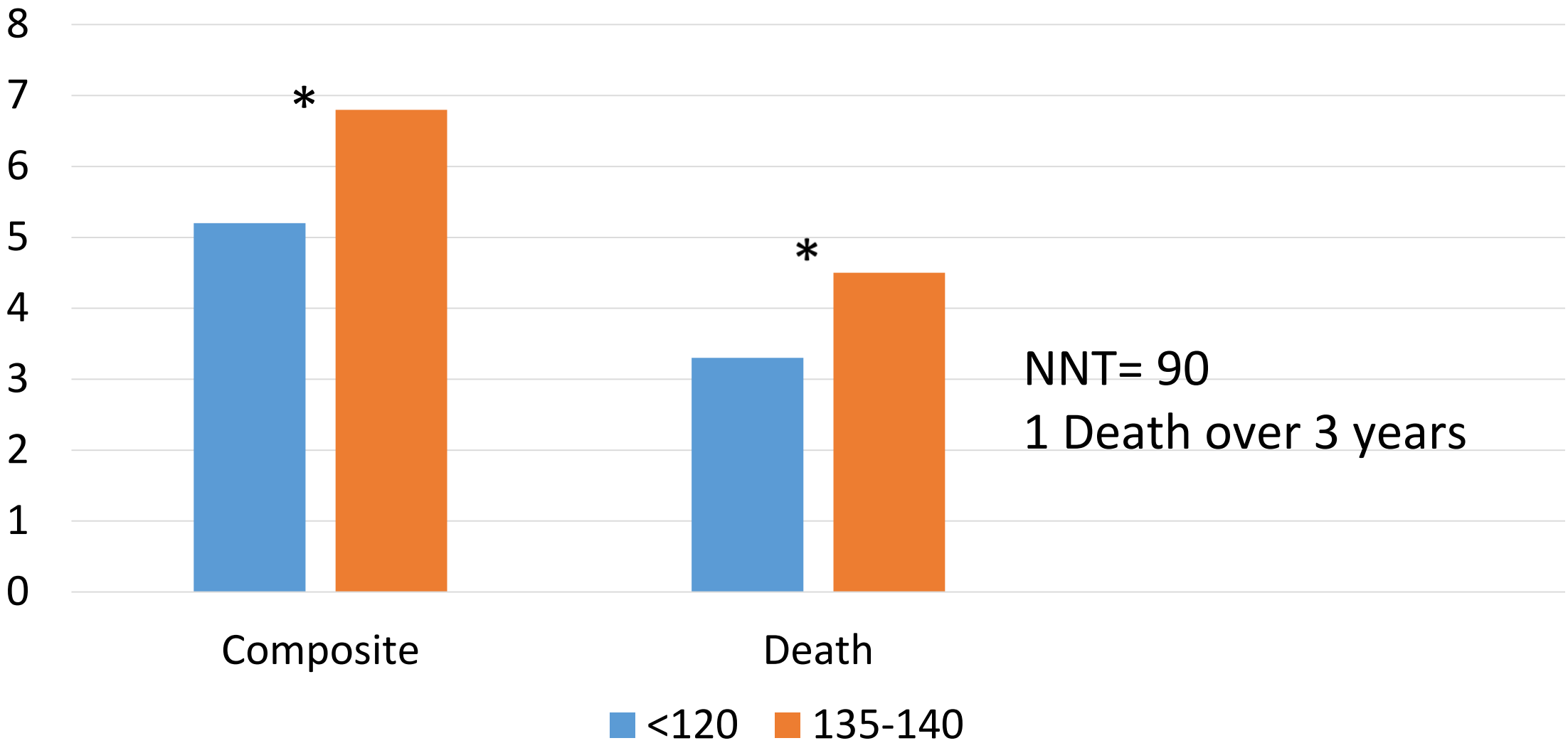
Results – Baseline

	<120	135-140
Age	68	68
Female	36%	35%
Black	31%	32%
Framingham Risk 15%+	61%	61%
CKD	28%	28%
Statin	42%	45%

Results – Process

	<120	135-140
Achieved Blood Pressure	121	136
Number of Medications	2.8	1.8

Results – Outcomes



Cautions

- Intensive treatment group had more syncope, AKI, etc
- Open label
  - Potential for other differences in care
- Lack of statin treatment
- Controls were not really “Usual Care”
  - Aggressive down-titration of medications
- Does not apply to those with Diabetes or cerebrovascular disease

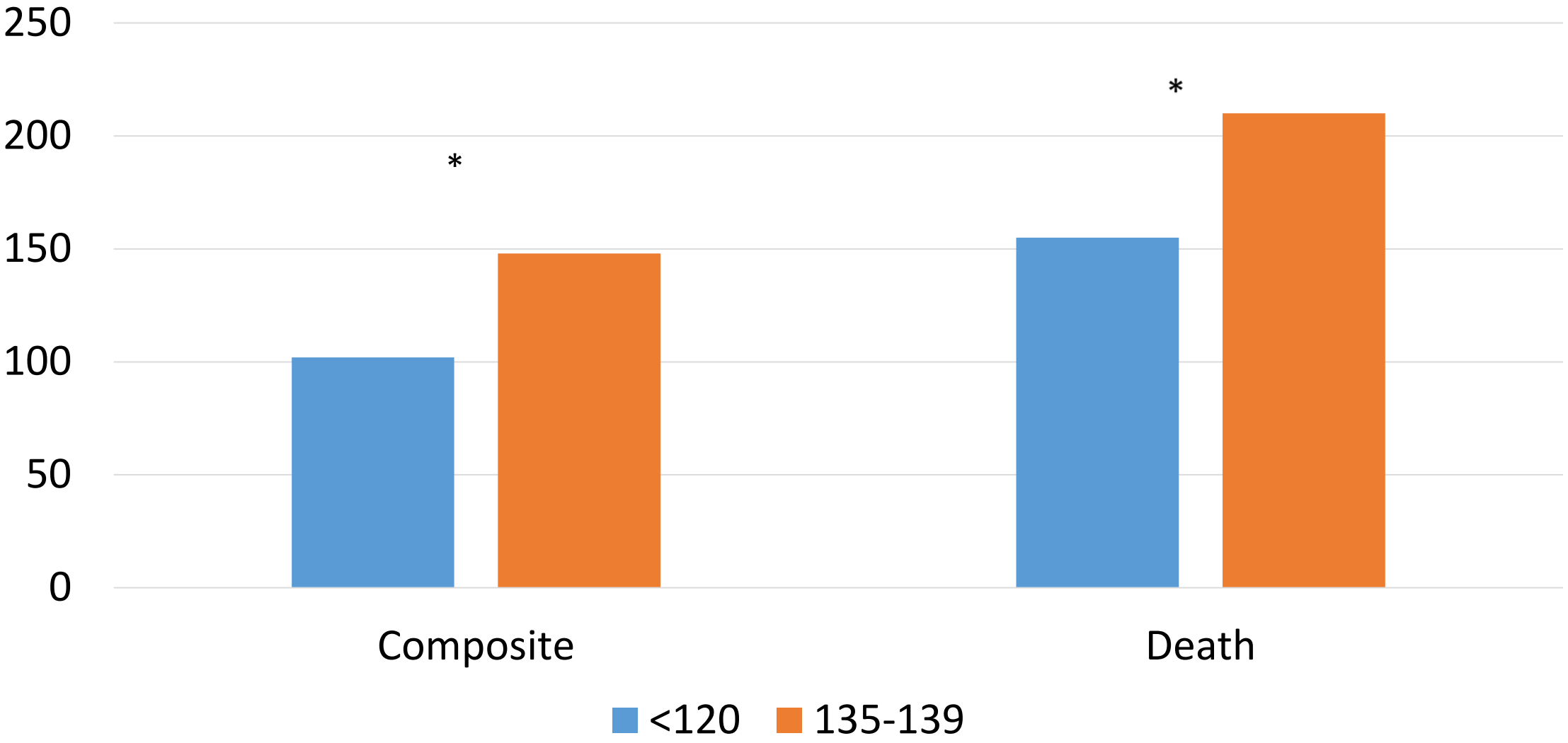
Conclusions

- SBP of 120 is a very aggressive goal
  - Accompanied by important, predictable side effects
- Substantial survival benefit
  - But likely over-stated in comparison to true usual care
- Serious concern about achieving 120 in non-research context
  - I struggle to get to 140
- I am not adopting this broadly
  - I see it as close to a toss-up
  - But see below…

The Senior SPRINT

- A sub-study of SPRINT
- Analyzed just the 2600 subjects age 75+
  - About 1/3 “frail” but not in residential care

Results – Outcomes



NNT’s Over 3 years

- For Death
  - Older – 41
  - Younger – 160 (est)
- For Vascular Composite
  - Older - 27
  - Younger – 110 (est)

Conclusions

- A target SBP of 120 is superior to a target of 135-139 in this setting
- The benefit accrues mostly to older patients
- I am beginning to offer this to my older patients
- I am concerned about
  - Whether it is better than true “usual care”
  - “Creep” to excluded patients
    - Especially lower risk, and those with DM or Stroke
  - Side effects and other penalties

James Madison

If Tyranny and Oppression
come to this land,
it will be in the guise
of fighting a foreign enemy.

Audience Response

When dealing with a healthy patient with a skin abscess, I:

A. Drain it
B. Drain it, pack it
C. Drain it, pack it, and usually prescribe an antibiotic
D. Something else

TMP/Sulfa for Skin Abscess

- Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess
  - DA Talan et al
  - NEJM 3/3/16
  - Supported by the NIH

Skin Abscess

- Study Question
  - Does TMP/Sulfa improve cure rates for drained skin abscesses?
- Background
  - I&D is generally regarded as curative for uncomplicated skin abscess
  - IDSA recommends antibiotic only for special cases
    - SIRS, immunosuppression, etc.
  - Practicing clinicians often prescribe antibiotics anyway

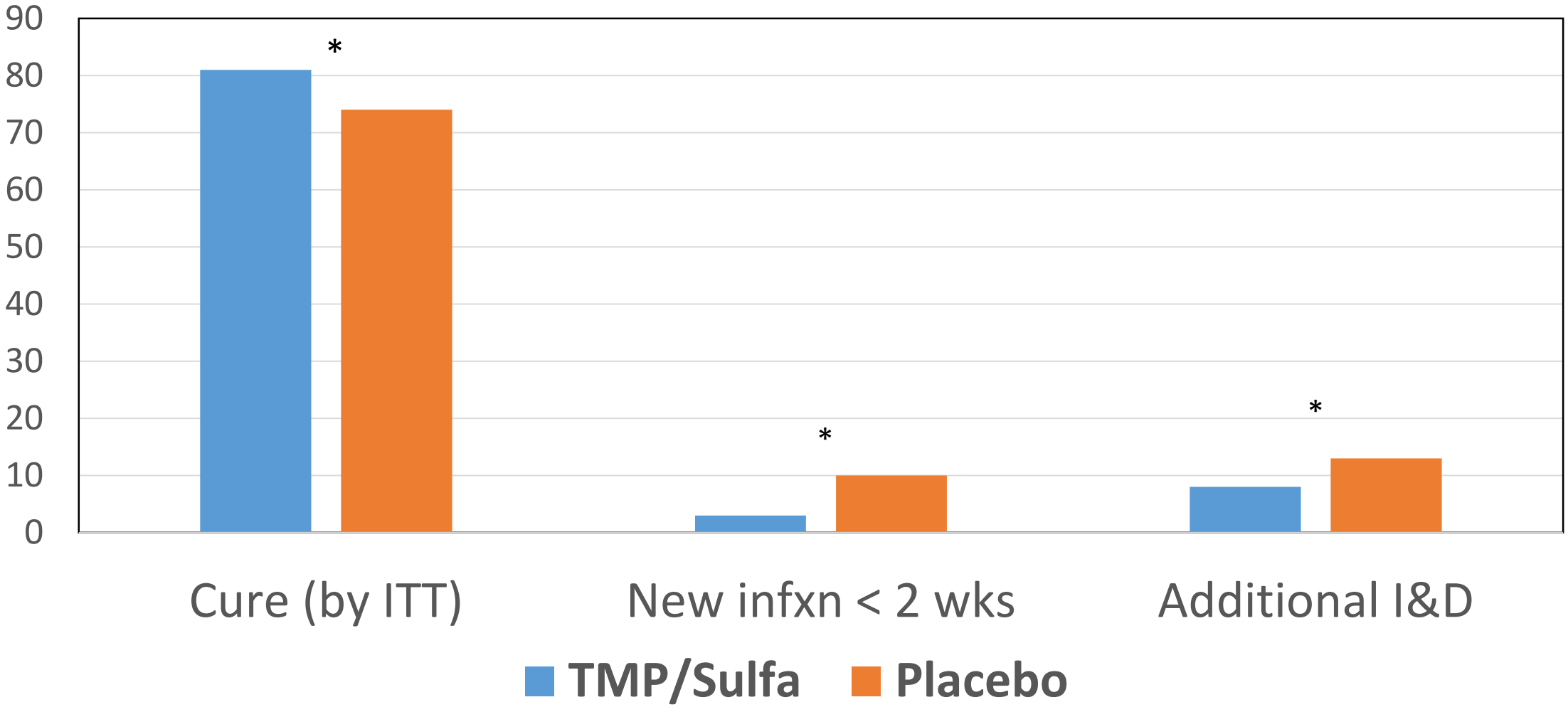
Design – Blinded RCT

- 1250 US patients with skin abscess
  - Age 12+
  - Purulent abscess at least 2 cm
  - Planned outpatient care
- Received I&D plus
  - TMP/Sulfa, **4 Single Strength bid** for 7 days OR
  - Placebo
- Followed for clinical cure at 7-14 days
- Sought improvement from 90% to 97.5% cure

Results – Baseline Characteristics

	TMP/Sulfa	Placebo
Age	35	35
Female	41	42
Diabetes	11	11
MRSA	47	43

Results – Outcomes



Cautions

- Those who failed follow-up were deemed treatment failure
  - I suspect they were cured
  - Would have made TMP/Sulfa look even better if presumed cured
- Somewhat small study
  - Will miss rare but serious side effect difference
    - E.g., Stevens-Johnson syndrome

Conclusions

- TMP-Sulfa improves cure and recurrent skin abscess compared to drainage alone
  - NNT around 12
- Antibiotic stewardship and potential side effects are serious balancing concerns
- Is this permission?
  - Less guilt when I use it
  - Perhaps will aim it at less robust patients
    - (Evidence-free medicine)

George HW Bush

It's no exaggeration
to say that the undecideds
could go one way
or another.

Abraham Lincoln

Give me six hours
to chop down a tree
and I will spend the first four
sharpening the axe.

Audience Response

For my diabetic patients, my best chance to reduce early mortality is to use:

A. Insulin
B. Metformin
C. SGLT2 inhibitors
D. GLP-1 analogues
E. I don’t know anymore

Diabetes Treatment – Two Articles

- Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
  - B Zinman et al
  - NEJM 11/26/15
  - Re-Review*
- Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
  - SP Marso et al
  - July 28, 2016
- Both largely funded, designed, conducted, analyzed, written by the makers of the drugs

Diabetes Treatment

- Study Question
  - Is either Empagliflozin (SGLT2 inhibitor) or Liraglutide (GLP-1 analogue) better than other treatments for Type 2 diabetes?
  - Both studies designed as non-inferiority
- Background
  - Empagliflozin causes the kidneys to leak glucose
  - Liraglutide stimulates islet cells to release insulin
  - Both reduce A1C
  - Both thought to have potential important side effects
  - These studies were done to assess risk, not benefit

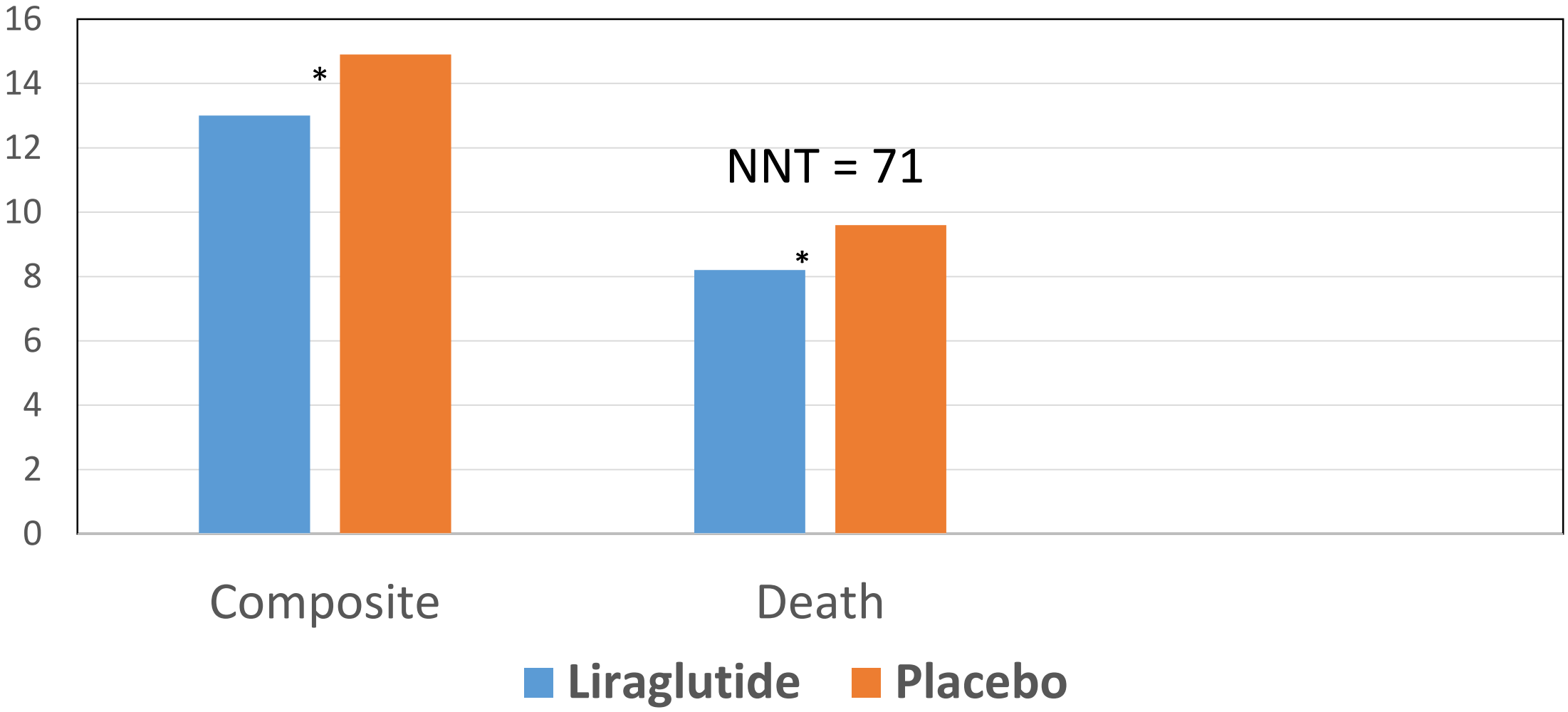
Design – Blinded RCT's

- 7000 patients (Empagliflozin) and 9300 patients (Liraglutide) worldwide with DM type 2
  - Liraglutide
    - A1C 7+, Age 50+ with CV disease or 60+ with risk
  - Empagliflozin
    - A1C 7-10, Age 18+ with CV disease
- Received
  - Active Drug
    - Empagliflozin 10 or 25 mg daily
    - Liraglutide 1.8 mg SC daily
  - Or Placebo
  - Also usual care
- Followed 3-4 years for CV death, MI, stroke
- Sought non-inferiority

Results – Baseline, Liraglutide

	Liraglutide	Placebo
Age	64	64
ACE-I	52	50
Statin	73	71

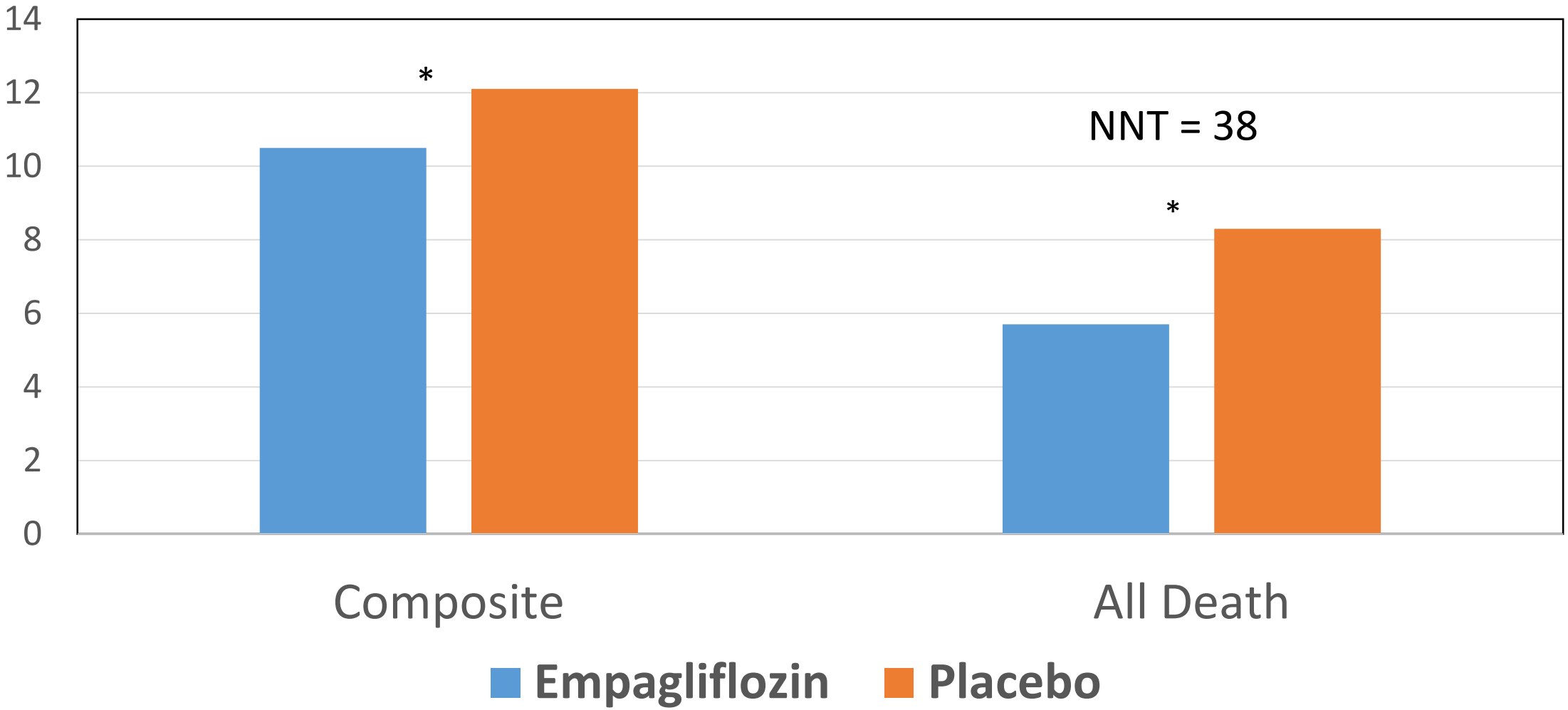
Results – Outcomes, Liraglutide



Results – Baseline, Empagliflozin

	Empagliflozin	Placebo
Age	63	63
ACE-I	81	80
Statin	78	76

Results – Outcomes, Empagliflozin



Cautions

- Liraglutide did not work in North America
  - Few African Americans or Hispanic Americans
- Not treated to US Standards
  - Underuse of statins, ACE-inhibitors, metformin
  - Especially given high baseline risk
- Unexpected effect
  - Not previously noted with other SGLT2 or GLP-1 drugs
  - Not previously noted with anything for DM-2
- Are these “too good to be true?”

Conclusions

- I still don’t entirely believe it
- But these two drugs have a better case for mortality benefit than anything else
  - Including metformin
- I will begin trying low-dose Empagliflozin
  - Type 2 patients with CV disease
    - Especially if intolerant to metformin
  - Not A1C driven
  - Not dose-dependent – will use 10 mg
  - EXPENSIVE
- Liraglutide an option but less convenient (injectable) and less persuasive
- I am prepared to be proven wrong on this

James Garfield

Things don't turn up
in this world
until somebody
turns them up.

Audience Response

My patients at risk for HIV are:

A. Asking me about PrEP
B. Teaching me about PrEP
C. Having trouble staying on their PrEP

Pre-Exposure Prophylaxis

- On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection
  - JM Molina et al
  - NEJM 12/3/2015
  - Supported by several public agencies and private foundations

Pre-Exposure Prophylaxis

- Study Question
  - Does on-demand PrEP reduce HIV transmission among men or transgender women who have anal receptive sex with men?
- Background
  - Daily anti-retroviral PrEP is effective HIV prevention
  - Adherence is important issue with daily PrEP
  - CDC guideline recommends daily PrEP as an option, but *against* intermittent PrEP

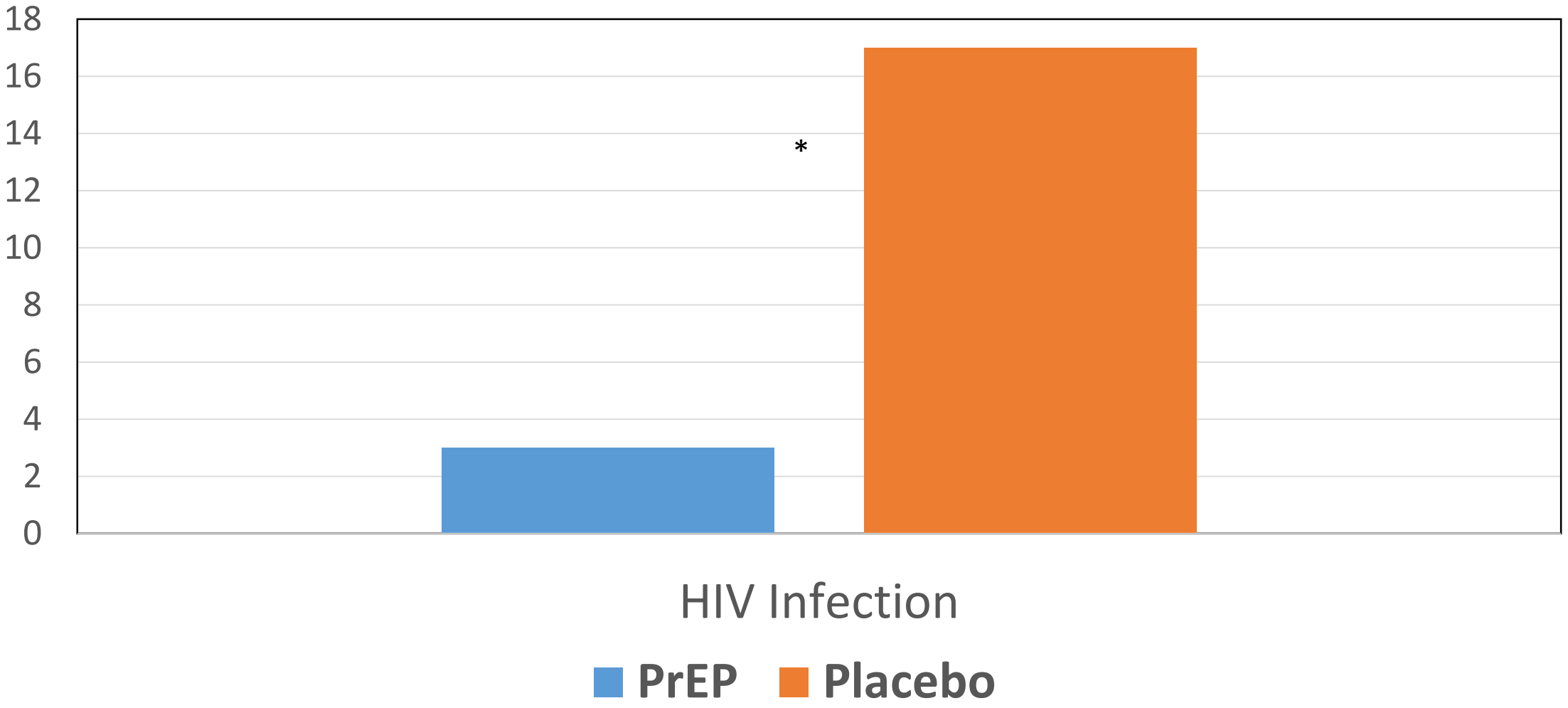
Design – Blinded RCT

- 414 MSM in France and Canada
  - HIV negative
  - 2+ unprotected anal sex partners in prior 6 months
- Received
  - Tonofovir 300/Emtricitabine 200 OR
  - Placebo
  - 2 tabs 2-24 hours pre-, plus 1 tab 24 and 48 hours post-exposure
- Followed 2 years for new HIV-1 infection
- Sought reduction from 3% per year to 1.5% per year
- Analyzed early due to positive pilot result from elsewhere

Results – Baseline Characteristics

	PrEP	Placebo
Age	35	34
Non-White	6	11
Median partners prior 2 months	8	8
Pills taken per month	15	15

Results – Outcomes



Additionally

- NNT 12 for a year
- Of the 3 new cases on PrEP
  - 1 converted before receiving medication
  - 2 never took any medication

Cautions

- Requires accurately anticipating exposure
- Adherence still an issue

Conclusions

- Daily PrEP is better researched
- I will offer this to HIV negative MSM who won’t use daily PrEP

William Howard Taft

No tendency is quite so strong
in human nature
as the desire to lay down
rules of conduct
for other people.

Woodrow Wilson

Golf is a game
in which one endeavors
to control a ball
with implements
ill adapted for the purpose.

Final Words

- I intend to
  - Offer an SBP target of 120 to my older hypertensives
  - Use TMP/Sulfa more comfortably in my skin abscess patients
  - Add low-dose empagliflozin in my high-risk diabetics
  - Offer on-demand PrEP to high risk men
- You will make your own decisions

Barack Obama

That's the good thing
about being president,
I can do
whatever I want.