Evaluation of Studies That Made Waves: How Big Are They?

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Speaker has no conflicts of interest to disclose

Objectives

- Describe the findings of the study that assessed venlafaxine and estradiol for vasomotor symptoms in menopausal women.
- Compare the efficacy and safety of the addition of canagliflozin versus sitagliptin in patients with type 2 diabetes inadequately controlled on a regimen of metformin and a sulfonylurea.
- Identify how dalbavancin may affect the approach to treating skin infections given the findings of the DISCOVER-1 and DISCOVER-2 trials.
- Explain differences between superiority and noninferiority trials.

Outline

- Pertinent background
- Study objective
- Methods
- Results
- Critique/clinical implications

LOW-DOSE ESTRADIOL AND VENLAFAXINE FOR VASOMOTOR SYMPTOMS

JAMA Intern Med. 2014;174(7):1058-1066.

Menopause

- Menopausal transition involves changing levels of estradiol, progesterone, and FSH
  - Median age in U.S. is 51 years
- Vasomotor symptoms (VMS)
  - Hot flushes/flashes – sudden, extreme heat in face, chest neck
    - 87% of women who report these experience them daily
    - 33% experience them up to 10x daily
  - Night sweats

Obstet Gynecol. 2014;123(1):202.

Vasomotor symptoms (VMS)

- Pathophysiology
  - Hormone level changes
  - Thermoregulatory mechanism changes
  - Serotonergic, noradrenergic, opioid, adrenal, autonomic systems
- Risk factors
  - Affects African American women the most and Asian women the least
    - Diets?
    - Perceptions?
  - Common in obesity
- Limited evidence that VMS predictive of adverse health outcomes

Obstet Gynecol. 2014;123(1):202.

Medications for VMS

- Hormonal
  - Estrogen alone or combined with progestin
    - Standard, low, ultra-low dose
- Nonhormonal
  - Paroxetine (recently FDA-approved)
  - Clonidine
  - Gabapentin

Obstet Gynecol. 2014;123(1):202.

Concerns with Use of Hormonal Therapy

- Combined (estrogen and progestin)
  - CHD
  - Stroke
  - Breast cancer
  - Thromboembolic events
- Estrogen only
  - Thromboembolic events
- Contraindications to use
  - Breast/endometrial cancer
  - Thromboembolic disease
  - Dementia

JAMA. 2002;288:321–333.

Venlafaxine

- Serotonin-norepinephrine reuptake inhibitor (SNRI)
- Doses of 37.5 mg to 150 mg daily po have been studied for hot flashes
  - Reduction of up to >50% in hot flash activity
- Although limited direct comparisons of SNRIs and SSRIs with HRT, generally considered less effective

Obstet Gynecol. 2005;105(1):161-166.
Lancet. 2000;356(9247):2059-2063.

Estradiol and Venlafaxine for VMS

- Study objective
  - To determine efficacy and safety of estrogen therapy (ET) and venlafaxine (V) compared to placebo in reducing # of VMS reported
- Methods
  - Multicenter, 3-arm, randomized, double-blind, placebo-controlled 8-week trial performed in the U.S. in 2012

Estradiol and Venlafaxine for VMS

Inclusion

- Healthy women ages 50 to 62 years
- Menopausal transition, postmenopausal, or met FSH and estradiol lab requirements
- ≥14 VMS per week

Exclusion

- Suicide attempt in past 3 years
- Diagnosis of bipolar disorder or psychosis
- Major depressive episode or drug or EtOH use in past year
- Hormone therapy (recent or current)
- Selective estrogen receptor modulators or aromatase inhibitors
- History of uncontrolled hypertensive, CV, thrombotic, or endometrial disease
- Pre-breast cancer conditions
- Breast or gynecologic cancer
- Unstable medical illness

Estradiol and Venlafaxine for VMS

- Interventions (2:2:3)
  - 17β-estradiol (n=97): 0.5 mg/day x 8 weeks
    - Followed by medroxyprogesterone acetate (10 mg/day) x 14 days
  - Venlafaxine XR (n=96): 37.5 mg/day x 1 week, then 75 mg/day x 7 weeks
    - Followed by taper to 37.5 mg/day x 14 days
  - Placebo (n=146)

Estradiol and Venlafaxine for VMS

- Data collection
  - 3 site visits and 2 telephone assessments
  - Questionnaires at baseline and at 8 weeks
  - Diaries: VMS and vaginal bleeding recorded twice daily

Estradiol and Venlafaxine for VMS

- Primary outcome
  - VMS frequency (before weeks 4 and 8 assessments)
    - 1 (mild)
    - 2 (moderate)
    - 3 (severe)
- Secondary outcomes
  - VMS severity, bother, perceived VMS interference
- Adverse events

Estradiol and Venlafaxine for VMS

- Statistics
  - Intent-to-treat analysis
  - 2-sided α of 0.025
  - 90% power to detect a 0.52-SD unit difference between placebo and interventions for primary outcome
  - Wald statistics from linear regression

Baseline Characteristics

- No differences between groups in baseline characteristics
- Mean age 55 years
- 60% white, 34% African American
- 2/3 had BMI <30
- 75% postmenopausal

Baseline Characteristics

Insomnia	
None	31%
Subthreshold score	39%
Moderate insomnia	23%
Severe	4%

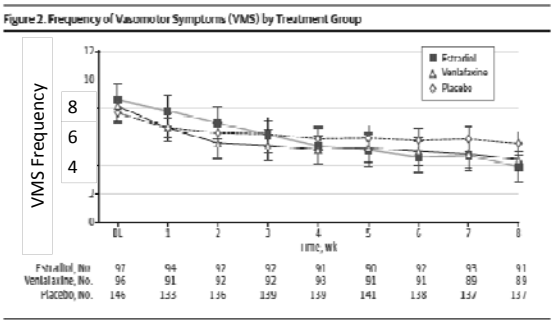
Sleep Quality	
Good	20%
Moderate	30%
Poor	45%

Depressive Symptoms	
None	73%
Mild	19%
Moderate	8%

Anxiety Symptoms	
None	78%
Mild	15%
Moderate	7%

Results – Primary Outcome

Daily Vasomotor Symptom Frequency Mean Differences from Placebo at Week 4 and 8		
	Estradiol (n=97) Mean Difference (95% CI)	**Venlafaxine (n=96)** Mean Difference (95% CI)
Baseline	0.9 (-0.5 to 2.2)	0.5 (-0.8 to 1.8)
Week 4 – baseline	-1.2 (-2.2 to -0.2)	-1.4 (-2.3 to -0.4)
Week 8 – baseline	-2.3 (-3.4 to -1.3)	-1.8 (-2.7 to -0.8)
P-value (vs. placebo)	<0.001	0.005



JAMA Intern Med. 2014;174(7):1058-1066.

Results – Secondary Outcomes

Daily Vasomotor Symptom Severity, Bother, and Interference Mean Differences from Placebo at Week 8

	Estradiol (n=97) Mean Difference (95% CI)	**Venlafaxine (n=96)** Mean Difference (95% CI)	P-value
Severity			
Week 8 – baseline	-0.3 (-0.4 to -0.1)	-0.2 (-0.3 to 0.0)	E vs. PBO: 0.02 V vs. PBO: 0.02
Bother			
Week 8 – baseline	-0.3 (-0.5 to -0.1)	-0.2 (-0.3 to 0.0)	E vs. PBO: 0.01 V vs. PBO: 0.07
Interference			
Week 8 – baseline	-9.3 (-15.3 to -3.4)	-6.4 (-12.7 to -0.1)	E vs. PBO: <0.001 V vs. PBO: 0.03

Results - Safety

- Newly emergent AEs reported
  - Estradiol: 56%; venlafaxine: 69%; placebo: 62%
- Most frequent
  - Estradiol: insomnia; venlafaxine and placebo: fatigue
- Blood pressure (SBP/DBP) mean changes
  - ET: -6/-0.9
  - V: +0.5/+2.1
  - P: -5.6/-1.4

Results – Compliance and Satisfaction

- 94% took ≥80% of dispensed pills
- 94% completed diaries
- Satisfaction
  - ET: 70.3%
  - V: 51.1%
  - P: 38.4%

Estradiol and Venlafaxine for VMS

Strengths

- Design (RCT with blinding)
- 2 interventions, including gold standard, assessed in 1 trial
- Compared to commonly used dosing of estradiol
- Appropriate outcomes
- Free from manufacturer bias

Limitations

- While outcomes appropriate, still subjective
- No breakdown of hot flashes and night sweats
- Short study duration
- Relatively small sample size
- Did not directly compare interventions

Take-Home and Considerations

- First RCT to assess low-dose estrogen and venlafaxine simultaneously
- VMS reduced by approximately
  - 48% with V
  - 53% with ET
- Both improved VMS severity
- ET improved bother but V did not
- V would not help with vaginal symptoms of menopause but ET would
- Further evidence to support use of SNRIs for VMS

Venlafaxine did NOT significantly decrease which VMS measure compared to placebo?

A. Frequency
B. Severity
C. Bother
D. Interference

ADJUNCTIVE CANAGLIFLOZIN VS. SITAGLIPTIN FOR TYPE 2 DIABETES

Diabetes Care. 2013;36(9):2508-2515.

Background

- Type 2 diabetes often requires combination therapy to meet glycemic targets
- ADA and EASD recommend agents with different mechanisms of action if using 3 agents
- Add-on options
  - Sulfonylurea
  - DPP4 inhibitors
  - GLP-1 receptor agonists
  - TZDs
  - Insulin

Diabetes Care. 2014;37(1):S14-S80.
Diabetes Care. 2012;35:1364–1379.

Canagliflozin

- Inhibitor of sodium glucose transporter (SGLT2) in proximal renal tubules
  - Increases urinary glucose excretion
- Dose: 100 mg – 300 mg po once daily before morning meal
- Contraindicated if eGFR <30 mL/min/1.73 m^2
- Monotherapy: lowers A1C by approximately 0.77% to 1.03%

Sitagliptin

- GLP-1 agonist; inhibits breakdown of incretin hormones
- Dose: 100 mg orally once daily
  - Lower dose may be used in combination with sulfonylurea or insulin
  - Adjusted based on renal function
    - CrCl 30 to 50 mL/min: 50 mg po once daily
    - CrCl <30 mL/min: 25 mg po once daily
- Monotherapy: decreases A1C by approximately 0.6% to 1.05%

CANTATA-D2

- Study objective
  - To determine the safety and efficacy of canagliflozin 300 mg vs. sitagliptin 100 mg as add-on to metformin and a sulfonylurea in patients with poorly-controlled type 2 diabetes
- Methods
  - Randomized, double blind, active-controlled 52-week trial in 140 centers in 17 countries
  - 2-wk single-blind run-in phase
  - 52-wk treatment phase
  - 4-wk follow-up phase

CANTATA-D2

Inclusion

- ≥18 years of age taking stable dose of metformin and sulfonylurea
- **IF** on max or near-max doses of metformin and sulfonylurea **AND** A1C ≥7.0% and ≤10.5%, then entered single-blind 2-wk phase

Exclusion

- FPG ≥300 mg/dL
- History of type 1 diabetes
- CVD
- Uncontrolled HTN
- Treatment with any other antihyperglycemic agent within 12 wks
- SCr ≥1.4 for men; ≥1.3 for women

CANTATA-D2

- Interventions (1:1)
  - Canagliflozin 300 mg once daily (n=378)
  - Sitagliptin 100 mg once daily (n=378)
- Randomization
  - Permuted block
  - Stratified
    - A1C ≥9%
    - Whether they underwent a FS-MMT

CANTATA-D2

- Primary outcome
  - Change in A1C from baseline through week 52
- Secondary outcomes
  - Change from baseline in
    - FPG
    - SBP
    - Body weight
    - Triglycerides
    - HDL cholesterol
  - Proportion of pts reaching A1C <7% and <6.5%
  - β-cell function

CANTATA-D2

- Hypothesis: Canagliflozin noninferior to sitagliptin in reducing A1C
- Statistics
  - NI margin of 0.3% for upper limit of 2-sided 95% CI
    - If NI met, superiority tested
  - Analyses on mITT, also PP
  - Power of 90%
  - 2-sided significance level of 5%
  - ANCOVA
  - Least squares mean difference

Quick break for trial design!

Noninferiority

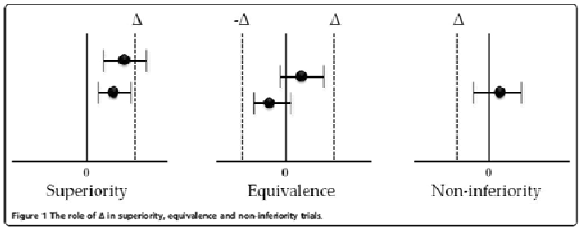


Figure 1 The role of Δ in superiority, equivalence and non-inferiority trials.

Trials. 2011;12:106.

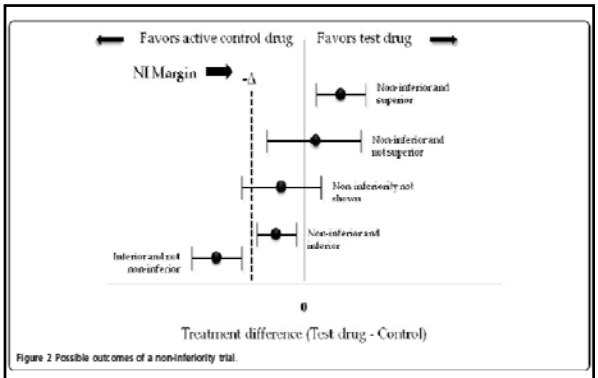


Figure 2 Possible outcomes of a non-inferiority trial.

Trials. 2011;12:106.

Back to CANTATA –D2…

Baseline Characteristics

- Mean age 57 years
- 56% male
- Race
  - 64% white
  - 11.7% black or African American
- Ethnicity
  - 21.1% Hispanic or Latino
- BMI: 31.6
- A1C: 8.1%
- FPG: 167
- Duration of diabetes: 9.6 years

Background Sulfonylurea Treatment

	SITA 100 mg (n = 378)	CANA 300 mg (n = 377)	Total (N = 755)
Sulfonylurea at baseline, n (%)			
Glipizide	40 (11)	47 (12)	87 (12)
Glipizide extended release	18 (5)	16 (4)	34 (5)
Glyburide/glibenclamide	133 (35)	128 (34)	261 (35)
Glimepiride	106 (28)	121 (32)	227 (30)
Gliclazide	30 (8)	26 (7)	56 (7)
Gliclazide modified release	50 (13)	37 (10)	87 (12)
Glyburide micronized	0	2 (1)	2 (<1)
Tolazamide	1 (<1)	0	1 (<1)

Diabetes Care. 2013;36(9):2508-2515.

Subject Disposition

- mITT: N=755
- PP: N=464 (61%)
- Discontinuation
  - Sitagliptin (44.4%)
  - Canagliflozin (32.6%)
  - 22% met glycemic withdrawal criteria
    - 88% after week 26
      - FPG >200 mg/dL and A1C >8.0%

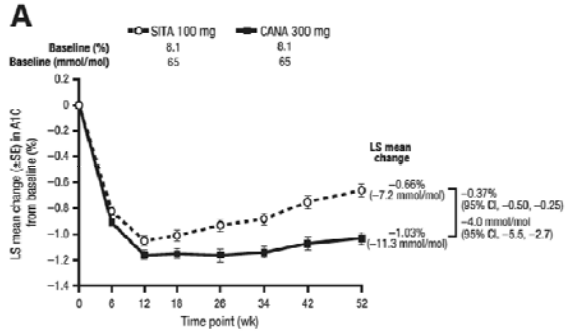
Results – Primary Outcome

	A1C Lowering (Least squares mean change)		
	CANA 300 mg (n=377)	SITA 100 mg (n=378)	LS Mean Difference
mITT	-1.03%	-0.66%	-0.37% (95% CI, -0.50 to -0.25)
PP	-1.15%	-0.94%	-0.21% (95% CI, -0.34 to -0.08)

Since the upper limit is also <0, what can we also conclude?

Superiority!

Results - Primary Outcome



Diabetes Care. 2013;36(9):2508-2515.

Results – Secondary Outcomes

	Least Squares Mean Change	
	CANA 300 mg	SITA 100 mg
SBP*	-5.1 ± 0.7	0.9 ± 0.7
TG	5.7 ± 5.2	2.4 ± 5.1
HDL	7.6 ± 0.9	0.6 ± 0.9
LDL	11.7 ± 1.8	5.2 ± 1.8
Body weight*	-2.5%	0.3%
FPG*	-5.9	-29.9
A1C Proportion who met goal of		
<7%	47.6%	35.3%
<6.5%	22.5%	18.9%

Results - Safety

	CANA 300 mg	SITA 100 mg
Any AE	76.7%	77.5%
AEs leading to discontinuation	5.3%	2.9%
Hypoglycemia	43.2%	40.7%
Genital mycotic infection		
Male	9.2%	0.5%
Female	15.3%	4.3%

Balanitis, balanitis candida, balanoposthitis, genital candidiasis/fungal infection

Vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis

Conclusions

- Canagliflozin noninferior and superior to sitagliptin for A1C reduction in type 2 diabetes when added on to metformin and a sulfonylurea
  - Canagliflozin may provide better sustained decrease in A1C
- Canagliflozin results in greater reduction in
  - FPG
  - Weight
  - SBP
- Canagliflozin increases LDL
- Genital mycotic infections are greatest safety concern with this drug

CANTATA-D2

Strengths

- Study design
- Study duration
- Wide range of A1Cs at baseline

Limitations

- No lifestyle modification component
- Withdrawal rather than rescue therapy for hypoglycemic episodes
- ITT protocol used for NI analysis
- Not generalizable to add-on for other combinations with metformin

Which of the following parameters did NOT significantly decrease with canigliflozin compared to sitagliptin?

A. SBP
B. Body weight
C. FPG
D. LDL

If a treatment is noninferior to a standard of care, it is the same as being inferior to the standard of care.

A. True
B. False

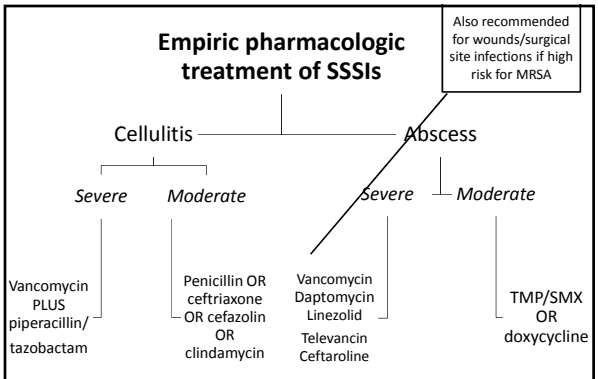
ONCE-WEEKLY DALBAVANCIN VS. CONVENTIONAL THERAPY FOR SKIN INFECTION

N Engl J Med. 2014;370(23):2169-2179.

Skin and Skin Structure Infections (SSSIs)

- Annually in the US
  - 15 million infections
  - 870,000 hospital admissions
- Acute SSSI
  - A bacterial infection of the skin with a lesion size area ≥75 cm^2 characterized by redness, edema, and/or induration
    - Cellulitis – diffuse, spreading areas of redness
    - Wound – purulent drainage
    - Abscess – collection of pus within the dermis

BMC Infect Dis. 2013;13:252.
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf



Clin Infect Dis. 2014;59(2):e10-e52

Standard of Care Downfalls

- Vancomycin
  - Toxicity/narrow therapeutic window
  - Resistance
  - IV/frequent administration
  - Intolerances

Dalbavancin

- Semisynthetic lipoglycopeptide antibiotic for gram positive infections
  - *Staphylococcus aureus* (MRSA and MSSA)
  - *Streptococcus* sp.
- Dose: 1000 mg IV x 1, then 500 mg IV one wk later
  - CrCl <30 mL/min: 750 mg IV x 1, then 375 mg one wk later

Dalvance [package insert]

Dalbavancin

- Activity correlates with AUC:MIC
- $t_{1/2}$ of 2 weeks
- 93% protein binding

Dalvance [package insert]

Dalbavancin History

- Development in the late '90s
- 2004: NDA filed
- 2007: Approval letter from FDA but required more data before marketing approval
  - Marketing app withdrawn to conduct more studies
- FDA-approved May 2014 for acute SSSI
  - Expedited review
- First Qualified Infectious Disease Product (QIDP) drug
  - Marketing exclusivity

http://www.drugdevelopment-technology.com/projects/dalvabancin/

Dalbavancin History

- Phase 2 trial for CR-BSI
  - Dalbavancin had higher success than vancomycin at treating BSIs
- Phase 2 trial for SSSI
  - Similar success rates compared to variety of abx
- Phase 3 trial for SSSI
  - Dalbavancin NI to linezolid

Clin Infect Dis. 2005;40(3):374-380.
Clin Infect Dis. 2003;37(10):1298-1303.
Clin Infect Dis. 2005;41(10):1407-1415.

DISCOVER 1&2

- Study objective
  - To test the efficacy of dalbavancin for skin infection as measured by new endpoint (absence of fever and stabilization in size of infected area) and assess association with historical standard of investigator-assessed response to treatment
- Methods
  - **2** double-blind, double-dummy, international, multicenter, 10 to 14 days, randomized trials

DISCOVER 1&2

Inclusion

- Acute bacterial SSSI
  - Cellulitis
  - Major abscess
  - Wound
- ≥75 cm^2 erythema
- Required ≥3 days IV abx
- ≥1 sign of systemic infection
- ≥2 local signs

Exclusion

- Abx within 14 days

DISCOVER 1&2

- Interventions
  - Dalbavancin 1 g IV x 1, then 500 mg 1 wk later + placebo
    - (n=659 pooled)
  - Vancomycin 1 g (or 15 mg/kg body weight) IV q 12 h for ≥3 d, then possible switch to linezolid 600 mg q 12 h for total of 10-14 days of treatment
    - (n=653 pooled)
  - Could be inpatient/outpatient
- Randomization
  - 1:1
  - Blocks of 4
  - Stratified by infection type and +/- fever

DISCOVER 1&2

- Primary outcome (ITT population)
  - Successful outcome at 48 to 72 h of therapy
    - Cessation of spread of erythema

    AND
    - Temperature ≤37.6 C x 3
- Secondary outcomes (PP population)
  - Clinical status at EOT
    - Investigator assessment
    - Programmatic assessment
- Safety (safety population)

DISCOVER 1&2

- Statistics
  - Pooled analysis: weighted difference in success rates
  - 2-sided alpha of 0.05
  - NI margin of 10% (lower limit of 95% CI)
  - 556 patients for 90% power
  - ITT

DISCOVER 1&2

- Baseline characteristics
  - Mean age 49 years
  - 58% male
  - 1/3 from US/Canada
  - 2/3 from Europe, South Africa, Asia
  - 13% with diabetes
  - 15% history of recent or current IV drug use
  - 25% received outpatient treatment

DISCOVER 1&2

- Infection type
  - 53% cellulitis
  - 25% major abscess
  - 20% wound infection
- 85% temperature ≥38 C
- 40% white count >12,000/mm^3
- 50% met SIRS criteria

DISCOVER 1&2

	Dalbavancin	Vancomycin-Linezolid	Absolute Difference (95% CI)
Primary endpoint			
Pooled data	79.7%	79.8%	-0.1 (-4.5 to 4.2)
Sensitivity analysis			
Pooled data	88.6%	88.1%	0.6 (-2.9 to 4.1)
Secondary endpoints			
Clinical status (pooled)	90.7%	92.1%	-1.5 (-4.8 to 1.9)
Sensitivity analysis	93.5%	94.9%	-1.4 (-4.2 to 1.4)
Investigator's assessment of outcome	96.0%	96.7%	-0.7 (-3.0 to 1.5)

Based on the pooled results of DISCOVER 1 &2, dalbavancin can be considered _____ and _____ in relation to vancomycin-linezolid for the primary outcome?

A. Inferior and not noninferior
B. Noninferior and superior
C. Noninferior and inferior
D. Noninferior and not superior

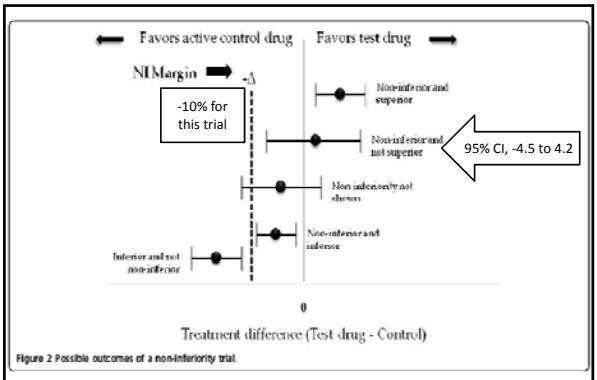


Figure 2 Possible outcomes of a non-inferiority trial.

Microbiological Outcomes

Investigator-assessed clinical response at EOT according to baseline pathogen		
	Dalbavancin (N=652)	Vanomycin-Linezolid (N=651)
Staphylococcus aureus	97.9%	96.6%
Methicillin-resistant *S. aureus*	97.3%	98.0%
Streptococcus pyogenes	100.0%	92.3%

- Of those with pathogens isolated at baseline, only 24%
- Overall, only approx. 12%

Safety Outcomes

- Nausea, diarrhea, and pruritis most common in both groups
  - Diarrhea, pruritis more common in vancomycin-linezolid group
- Similar rate of overall AEs and serious AEs
- 7 deaths in vancomycin-linezolid group compared to 1 death in dalbavancin group (P=0.03)

Conclusions

- Dalbavancin once weekly noninferior to vancomycin-linezolid for SSSIs
  - Type of infection did not affect efficacy
- Results similar with FDA recommended endpoint and traditional endpoint

DISCOVER 1&2

Strengths

- Strong design (RCT)
- Objective primary outcome
- Compared treatment success measured objectively and subjectively

Limitations

- Standard of care arm
  - Vancomycin → linezolid??
- Necessity of blinding?
- Limited amount of MRSA data
- ITT population used for statistical analysis of NI
- Differences in definitions of SSSIs with guidelines

Dalbavancin

Advantages

- Well-tolerated
- TDM not needed
- Minimal drug-drug interactions
- Dosing schedule
- Treatment on outpatient basis

Disadvantages

- Cost
- Safety not fully elucidated
- Adherence with 2nd dose?
- Limited data

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