Will They Have an Impact? A Closer Look at Recent Noteworthy Trials

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The speaker has no conflicts to disclose in relation to this program.

Objectives

- Describe the methods and key findings of the papers presented.
- Explain how the AMPLIFY-EXT trial may affect venous thromboembolism (VTE) prevention strategies.
- Compare and contrast 5 days and 14 days of prednisone in acute exacerbation of chronic obstructive pulmonary disease (COPD).
- Identify patients who may be at risk for development of VTE with glucocorticoid use.
- Summarize the findings and implications for practice of the trial that compared treatment strategies in patients with rheumatoid arthritis who failed methotrexate therapy.

Outline

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

Noteworthy Trial #1

APIXABAN FOR EXTENDED TREATMENT OF VENOUS THROMBOEMBOLISM

Apixaban

- Factor Xa inhibitor
- FDA-approved to reduce risk for stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Dose-adjusted for age, body weight, renal function

Prevention of Recurrent VTE

- Unprovoked at higher risk for recurrence than provoked
- Unprovoked VTE
  - Anticoagulation for 3 months
  - Evaluate risk/benefit ratio after 3 months
    - Risk of recurrence
    - Inconvenience
    - Risk of bleeding
    - Compliance issues

CHEST. 2012;141(2_suppl):e419S-e494S.

VTE: Extended Anticoagulation Studies

	Intervention	Control	Primary Outcome (recurrent VTE)	Safety
RE-MEDY	Dabigatran 150 mg bid	Warfarin: INR 2 to 3	Dabigatran noninferior to warfarin	Lower bleed risk with dabigatran than warfarin, but higher rates of MI
RE-SONATE	Dabigatran 150 mg bid	Placebo	Dabigatran superior to placebo	Higher bleed risk with dabigatran than placebo
WARFASA/ASPIRE	Aspirin 100 mg daily	Placebo	Aspirin superior to placebo	No difference in AEs
EINSTEIN-EXT	Rivaroxaban 20 mg daily	Placebo	Rivaroxaban superior to placebo	Higher bleed risk with rivaroxaban than placebo

N Engl J Med. 2013;368(8):709. *Expert Rev Cardiovasc Ther.* 2011;9(7):841. *N Engl J Med.* 2012;366(21):1959. *N Engl J Med.* 2012;367(21):1979.

AMPLIFY-EXT

- Study objective
  - To assess the benefit of 2 doses of apixaban for prevention of recurrent VTE after completion of 6 to 12 months of anticoagulation therapy
- Methods
  - Randomized, placebo-controlled, double blind, 12-month study
  - Stratified based on initial event (DVT or PE) and participation in AMPLIFY trial

AMPLIFY-EXT

Inclusion

- ≥18 years of age
- Symptomatic DVT or PE
- 6 to 12 months of anticoagulation OR AMPLIFY

Exclusion

- Symptomatic recurrence during prior anticoagulation
- Clinical equipoise
- Contraindication to anticoagulant therapy
- Hg <9 mg/dL
- Plt <100,000/mm^3
- SCr >2.5 mg/dL or CrCl <25 mL/min
- Liver enzymes >2x ULN

AMPLIFY-EXT

- Interventions
  - Apixaban 2.5 mg once daily (n=840)
  - Apixaban 5 mg once daily (n=813)
  - Placebo once daily (n=829)
- Follow-up
  - Clinic or phone monthly for 1 year + 30 d after

AMPLIFY-EXT

- Primary endpoint
  - Composite of recurrent VTE or death from any cause
- Secondary endpoints
  - Composite of recurrent VTE or VTE-related death
- Safety
  - Major bleeding (primary safety)
  - Major or clinically relevant nonmajor bleeding

AMPLIFY-EXT

- Superiority study for both apixaban doses compared to placebo
- 810 patients in each group for 90% power
- Two-sided alpha of 0.05
- Efficacy analyses
  - Data from ITT population
  - Lost to follow-up = had a primary outcome
    - Not for secondary analysis though

AMPLIFY-EXT

- Demographics
  - No significant differences between groups
  - Mean age: 56 years
  - Approximately 58% male
  - 1/3 participated in AMPLIFY
  - Approximately 70% had CrCl >80 mL/min
  - Co-morbid conditions
    - 27% were obese
    - 11% had diabetes
    - 30% had hypercholesterolemia
    - 40% had hypertension
    - 19% smoked

AMPLIFY-EXT

EFFICACY RESULTS					Relative Risk (95% CI)		
		Apixaban 2.5 mg (N=840)	Apixaban 5 mg (N=813)	Placebo (N=829)	Apixaban 2.5 mg vs. Placebo	Apixaban 5 mg vs. Placebo	Apixaban 2.5 mg vs. Apixaban 5 mg
Primary Efficacy Outcome	Recurrent VTE or death from any cause	3.8%	4.2%	11.6%	0.33 (0.25 to 0.53) **NNT=13**	0.36 (0.25-0.53) **NNT=14**	NA
Secondary Efficacy Outcome	Recurrent VTE or VTE-related death	1.7%	1.7%	8.8%	0.19 (0.11-0.33)	0.20 (0.11-0.34)	0.97 (0.46-2.02)

AMPLIFY-EXT

SAFETY RESULTS					Relative Risk (95% CI)		
		Apixaban 2.5 mg (N=840)	Apixaban 5 mg (N=813)	Placebo (N=829)	Apixaban 2.5 mg vs. Placebo	Apixaban 5 mg vs. Placebo	Apixaban 2.5 mg vs. Apixaban 5 mg
Primary Safety Outcome	Major bleeding	0.2%	0.1%	0.5%	0.49 (0.09-2.64)	0.25 (0.03-2.24)	1.93 (0.18-21.25)
Secondary Safety Outcome	Clinically relevant nonmajor bleeding	3.0%	4.2%	2.3%	1.29 (0.72-2.33)	1.82 (1.05-3.18) **NNH=53**	0.71 (0.43-1.18)

AMPLIFY-EXT

- Arterial events
  - Small # in each group – no difference
- Subgroup analyses
  - Mostly consistent with overall treatment effect except
    - Age ≥75 yrs: only the 5 mg dose effective
    - Questionable efficacy with severe to moderate renal impairment (both doses)
    - Questionable efficacy when weight ≤60 kg (both doses)

AMPLIFY-EXT

- Both apixaban doses superior to placebo for the primary outcome
- Relevant non-major bleeding increased with the 5 mg dose
- No difference in efficacy between 2 doses
  - Could use low-dose for extended treatment of VTE?

AMPLIFY-EXT

Strengths

- Well-designed
- Conservative estimations for primary outcome
- Equipoise of included population

Limitations

- Small # of patients >75 years of age and weight <60 kg
- Not compared to active control
  - RE-MEDY trial only one thus far
- No well-defined antidote

Which type of bleeding was significantly increased with the apixaban 2.5 mg dose compared to placebo?

1. Major
2. Clinically relevant nonmajor
3. Composite of major or clinically relevant nonmajor
4. None of the above

Noteworthy Trial #2

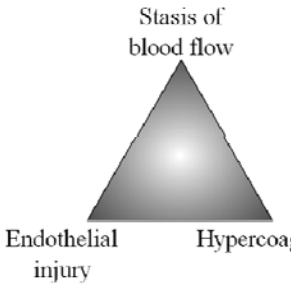
USE OF GLUCOCORTICOIDS AND RISK OF VENOUS THROMBOEMBOLISM

Glucocorticoids

- Background
  - Widely prescribed
    - Allergies, asthma, COPD
    - Autoimmune diseases
    - Neoplastic disorders
- Previous studies
  - Increased VTE risk with use in specific populations (surgical, multiple myeloma, IBD, SLE, etc)
  - One study found 3-fold increased VTE risk in general population with use of oral glucocorticoids compared to nonusers

Arch Intern Med. 2007;167(9):935

Venous Thromboembolism



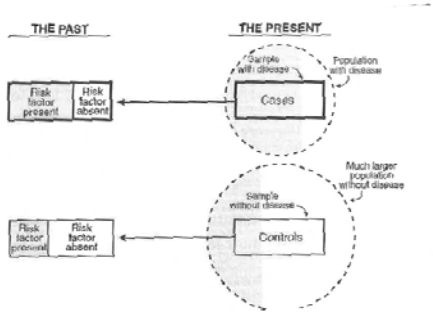
Glucocorticoids?

- Increase in factors VII, VIII, XI
- Increase in plasminogen activator inhibitor-1
- Von Willebrand factor?
- Fibrinogen?

J Thromb Haemost. 2010;8(11):2483.

Glucocorticoids and VTE

- Study objective
  - To examine the association between glucocorticoid use, including different routes and dosages, and VTE
- Methods
  - Population-based case-control study in Denmark



Hulley SB et al. *Designing Clinical Research*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

Glucocorticoids and VTE

- Study cohort
  - Danish National Registry of Patients between 2005 and 2011
  - Danish National Database of Reimbursed Prescriptions

Inclusion	Exclusion
First-time and recurrent diagnosis of DVT or PE (inpatient and outpatient)	PE diagnosis in outpatient but no VTE diagnosis as inpatient within the following month
	Emergency department visit diagnoses

Glucocorticoids and VTE

- Controls
  - 10 controls for every 1 case
    - Matched by age, sex, and risk
  - Glucocorticoid use
    - Systemic, inhaled, and intestinal-acting
- VTE risk factors
  - Comorbidities identified prior to index date

Glucocorticoids Identified

Systemic	Inhaled	Acting on the intestines
Betamethasone	Beclomethasone	Prednisolone
Methylprednisolone	Budesonide	Hydrocortisone
Prednisolone	Flunisolide	Budesonide
Triamcinolone	Fluticasone	Local steroids for hemorrhoids
Hydrocortisone	Mometasone	
Prednisone		

VTE Risk Factors and Confounders

VTE risk factors/comorbidities

- CV disease
- COPD/asthma
- Diabetes
- Liver disease
- Obesity
- Osteoporosis
- Renal failure
- Autoimmune disease

Other confounders

- Within 3 months of index event
  - Infection or antibiotic treatment
  - Cancer
  - Inpatient admission

Glucocorticoids and VTE

- Analysis
  - Logistic regression and multiple logistic regression to estimate odds ratios (ORs)
    - Route: systemic (and individual systemic), inhaled, and intestinal
    - Dose: 7 dosing categories for systemic route
    - Exposure:
      - Present (within 90 days)
        - » New
        - » Continuing
      - Recent (90 to 365 days)
      - Former (>365 days)
  - Subgroup analyses
    - Based on risk factors/confounders

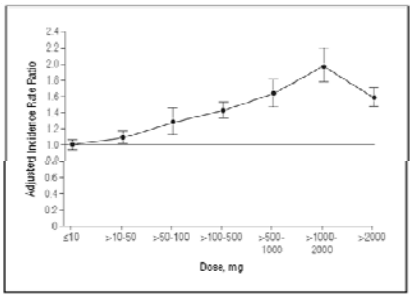
Glucocorticoids and VTE

- Results: descriptive data
  - 38,765 VTE cases; 387,650 controls
  - Cases
    - 58% had unprovoked VTE
    - 61% had DVT
    - 39% had PE
    - Median age 67 years
    - 54% women
  - Covariates more prevalent among cases than controls
    - Exception: statins and hormone therapy

VTE Associated with Use of Glucocorticoids by Route and Exposure

		Incidence Rate Ratio (95% CI)	
		Unadjusted	Adjusted
Systemic glucocorticoid use	Present	4.09 (3.91-4.29)	2.31 (2.18-2.45)
	Recent	1.71 (1.61-1.82)	1.18 (1.10-1.26)
	Former	1.15 (1.10-1.21)	0.94 (0.90-0.99)
Inhaled glucocorticoid use	Present	1.38 (1.25-1.51)	1.03 (0.93-1.15)
	Recent	1.38 (1.24-1.55)	1.06 (0.94-1.20)
	Former	1.28 (1.19-1.39)	0.99 (0.91-1.08)
Intestinal glucocorticoid use (present)	Present	3.08 (2.39-3.98)	1.90 (1.40-2.58)
	Recent	1.52 (1.10-2.09)	1.01 (0.71-1.45)
	Former	1.26 (1.02-1.56)	0.89 (0.70-1.13)

Results – Dose



Results – highest VTE risk for systemic category

- Prednisolone (new)
  - Unadjusted: IRR, 8.97 (95% CI, 8.17-9.86)
  - Adjusted: IRR, 3.53 (95% CI, 3.15-3.95)
- Prednisone (new)
  - Unadjusted: IRR, 10.28 (95% CI, 7.67-13.78)
  - Adjusted: IRR, 5.40 (95% CI, 3.82-7.63)

Results Cont'd

- Greater risks for PE than DVT, especially with systemic glucocorticoids
- "New" users had a greater risk than "continuous" users
  - New users 3-fold increased risk (systemic)
    - 11 extra VTE cases/1000 new users annually
- Likely won't change practice
  - Focus on patient education

Glucocorticoids and VTE

Strengths

- Large sample size
- Controls matched by age, gender, and risk
- Different routes and dosages assessed
- Attempted to mitigate effects of confounders

Limitations

- Data subject to inaccuracy
  - Missing data (ER admits)
  - Coding errors
- Confounders
- Observational
  - Cannot establish cause and effect
- No info on
  - Dexamethasone
  - Adherence
- Danish population only

According to the study findings, which of the following may be associated with the greatest risk for VTE development?

1. Rx for prednisone burst filled 100 days ago
2. Rx for inhaled fluticasone filled 100 days ago
3. Rx for prednisone 40 mg/day x 7 days filled 45 days ago
4. Rx for hydrocortisone rectal suppository filled 30 days ago

Noteworthy Trial #3

SHORT-TERM VS. CONVENTIONAL GLUCOCORTICOID THERAPY IN ACUTE EXACERBATIONS OF COPD

COPD Acute Exacerbations

- COPD exacerbations result in >800,000 hospitalizations annually in the US
- Treatment (pharmacologic)
  - Short-acting bronchodilators
  - Systemic corticosteroids:
    - Evidence A
      - Shortens recovery time
      - Improves FEV_1 and PaO_2
      - Reduces relapse, length of hospital stay
    - Evidence D
      - 30-40 mg prednisolone/day x 10-14 days
  - Antibiotics
    - Controversial

http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf

Glucocorticoids for Exacerbations

- Benefits
  - Symptom relief
  - Accelerate lung function recovery
  - Prevent relapse
- Adverse effects
  - Hyperglycemia
  - Weight gain
  - Insomnia
  - Long-term use of corticosteroids risk factor for mortality in patients with COPD
- No difference in outcomes for short duration vs. long duration glucocorticoid treatment

Chest. 2003;124(2):459-467.
Cochrane Database Syst Rev. 2011;(10):CD006897.

REDUCE

- Study Objective
  - To investigate whether 5 days of systemic glucocorticoid treatment of COPD exacerbation is noninferior to 14 days of treatment
- Methods
  - Multicenter, randomized, double-blind, placebo-controlled noninferiority trial from 2006 to 2011 in Switzerland; 180 days follow-up

JAMA. 2013;309(21):2223.

REDUCE

- Interventions
  - Short-term treatment: 5 days of systemic glucocorticoids (n=156)
  - Conventional treatment: 14 days of systemic glucocorticoids (n=155)
  - 40 mg prednisone-equivalent for both arms
- All received
  - Broad-spectrum antibiotic x 7 days
  - Nebulized, short-acting bronchodilator prn
  - Inhaled glucocorticoids twice daily
  - Inhaled beta-2 agonist twice daily
  - Tiotropium 18 μg once daily
- Additional glucocorticoids at discretion of physician

REDUCE

Inclusion

- COPD exacerbation; any of the following 2:
  - Change in baseline dyspnea, cough, or sputum quality or purulence
- Age >40 years
- Smoking history of 20 pack-years or more

Exclusion

- History of asthma
- FEV_1:FVC >70%
- Pneumonia
- Expected survival <6 mo.

REDUCE

- Primary endpoint
  - Time to next COPD exacerbation during next 6 months
- Secondary endpoint
  - All-cause mortality
  - Change in FEV_1
  - Cumulative glucocorticoid dose
  - Glucocorticoid-associated adverse effects
    - Hyperglycemia
    - Hypertension
    - Infection

REDUCE

- Statistics
  - Clinically tolerable upper limit: 15% absolute difference in percentage of patients with re-exacerbation
    - Assumed 50% would experience exacerbation
      - 50%+15% = 65% could experience exacerbation in short-term group and still be NI to conventional group
    - Calculated to be upper limit of 1.515
  - Power of 85%
    - Requiring 150 patients in each study group
  - Intent to treat analysis

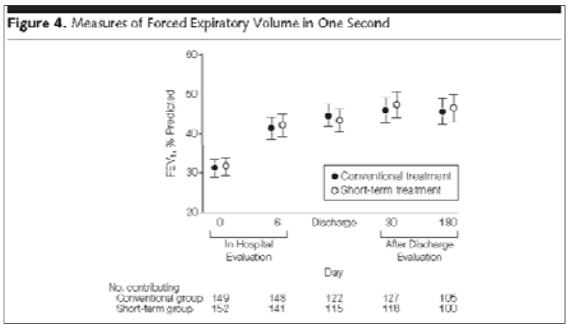
REDUCE

- Demographics
  - More women in conventional group than short-term group: 46.5% vs. 32.7%; P=0.02
  - Mean age 70 years
  - All were either current or former smokers
    - 45-50 pack years
  - Mean FEV_1 31% predicted
  - GOLD COPD grade
    - Over half were grade 4 (very severe)
  - Approximately 20% were taking systemic glucocorticoids prior to exacerbation

Primary endpoint	Conventional treatment (n=155)	Short-term treatment (n=156)	Hazard ratio (90% CI)	P-value (for noninferiority)
Reexacerbations (ITT)	36.8%	35.9%	0.95 (0.70-1.29)	0.006
Subgroups				
GOLD 1 and 2	33.3%	26.1%	0.73 (0.28-1.88)	0.10
GOLD 3	35.9%	33.3%	0.93 (0.52-1.67)	0.08
GOLD 4	39.7%	40.5%	0.99 (0.66-1.49)	0.04
Glucocorticoid pretreatment YES	46.4%	45.7%	0.93 (0.50-1.72)	0.09
Glucocorticoid pretreatment NO	35.8%	33.3%	0.88 (0.61-1.26)	0.006

Secondary endpoints	Conventional treatment (n=155)	Short-term treatment (n=156)	Comparison measure (95% CI)	P-value
Deaths during follow-up	8.4%	7.7%	HR, 0.93 (0.40-2.20)	0.87
Cumulative prednisone dose (mean)	793 mg	379 mg	Difference in means -414 (-521 to -307)	<0.001
Hyperglycemia	57.4%	56.9%	OR, 0.98 (0.58 to 1.66)	>0.99
Hypertension	17.8%	11.6%	OR, 0.61 (0.28 to 1.29)	0.22
Duration of hospital stay	9 (6 to 14)	8 (5 to 11)	HR, 1.25 (0.99 to 1.59)	0.04

REDUCE Results



Conclusion

- 5 day course of glucocorticoids for COPD exacerbation noninferior to 14 day course in regards to reexacerbation within 6 months
- Shorter course
  - Reduced glucocorticoid exposure
    - Reduced toxicity?
  - Slightly shorter hospitalization
- Reexacerbation rates still high overall
  - More than 1 in 3 within 6 months

REDUCE Trial

Strengths

- Strong design
- Appropriate endpoints
- Adequate length of follow-up

Limitations

- All sites in Switzerland
- Other treatments allowed may have resulted in "overtreatment" in some
  - Inconsistent with guidelines
- Some variables only measured during hospital stay
- External validity
  - Moderate to severe COPD
  - Smokers vs. nonsmokers

All of the following are true of the findings of the REDUCE trial EXCEPT:

1. 5-day glucocorticoid treatment was noninferior to 14-day and resulted in fewer glucocorticoid-related adverse effects.
2. 5-day glucocorticoid treatment was noninferior to 14-day and resulted in shorter length of hospital stay.
3. Patients received inhaled glucocorticoids twice daily and could receive open-label systemic glucocorticoid therapy if needed
4. All patients received a broad-spectrum antibiotic for 7 days

Noteworthy Trial #4

THERAPIES FOR ACTIVE RHEUMATOID ARTHRITIS AFTER METHOTREXATE FAILURE

Rheumatoid arthritis

- Better control of the disease
  - More aggressive treatment
    - Combination therapy (DMARDs, biologics)
  - More treatment options
    - Biologics
- Guidelines for treatment
  - When to start biologics?
    - Early RA
    - Established RA
  - Lack of definitive algorithms

J Intern Med. 2011;269(6):614.
Arthritis Care Res. 2012;64(5):625.

Which methotrexate (MTX) combo is best?

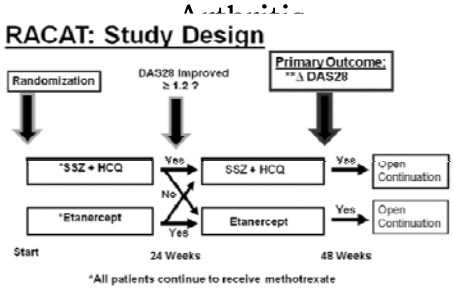
- Swefot (2009)
  - Sulfasalazine + hyroxychloroquine + MTX vs. infliximab + MTX
    - No difference at 6 months
    - Benefit with infliximab at 12 months
  - Not blinded
- TEAR (2012)
  - Various treatment strategies for early aggressive RA
  - Subgroup: no difference between etanercept + MTX and sulfasalazine + hyroxychloroquine +MTX

Lancet. 2009;374(9685):459.
Arthritis Rheum. 2012;64(9):2824-2835.

Therapies for Rheumatoid Arthritis

- Study objective
  - To compare the strategies of adding conventional DMARDs to MTX (triple therapy) with adding etanercept to MTX (etanercept-MTX) in patients with active RA despite MTX therapy
- Methods
  - Multicenter, randomized, double-blind, 48-week noninferiority trial

Therapies for Rheumatoid Arthritis



SSZ = sulfasalazine
HCQ = hydroxychloroquine
DAS28 = Disease Activity Score for 28-joint counts

Therapies for Rheumatoid Arthritis

- Dosing of study medications
  - MTX
    - Same dose as at time of enrollment
  - SSZ
    - 1 g daily x 6 weeks, then 2 g daily
    - Could reduce to 1 g daily if adverse effects
  - HCQ
    - 400 mg daily
  - Etanercept
    - 50 mg subcutaneous weekly

Therapies for Rheumatoid Arthritis

Inclusion

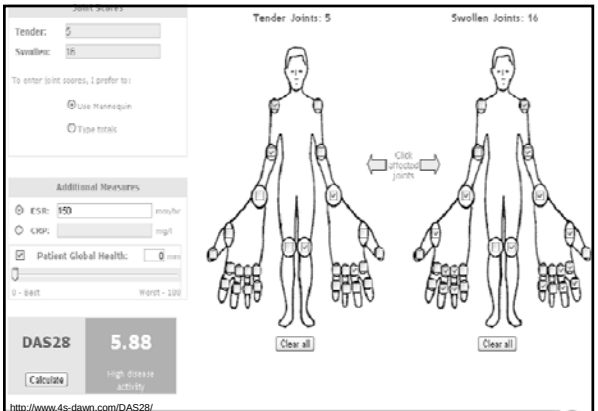
- ≥18 yrs of age with RA
- Receiving MTX 15 to 25 mg weekly for ≥12 wks
- DAS28 of 4.4 or higher
- Could be on stable doses of corticosteroids/NSAIDs

Exclusion

- Use of other DMARDs with MTX
- Prior treatment with TNF-a inhibitor for >5 wks
- Contraindications for TNF-a use
  - Infections
  - Live vaccines
  - Immunocompromised
  - Heart failure

Therapies for Rheumatoid Arthritis

- Primary outcome
  - Change in DAS28 at 48 weeks according to the initial regimen
  - DAS28
    - Scale of 2 to 10; higher = worse
    - # of swollen and tender joints (28 count)
    - Erythrocyte sedimentation rate
    - Visual-analogue scale of patient-reported disease activity
    - Decrease of 1.2 considered clinically meaningful



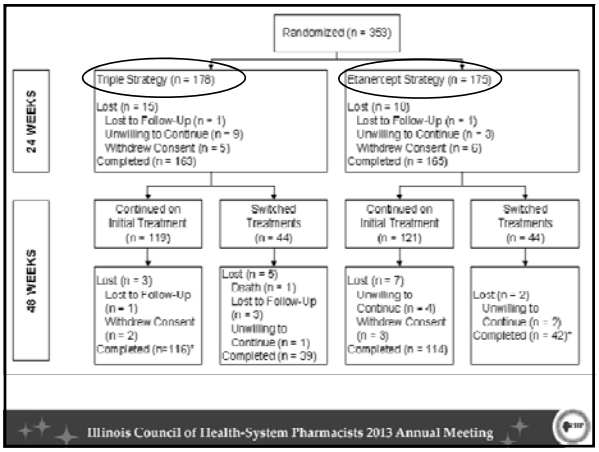
http://www.4s-dawn.com/DAS28/

Therapies for Rheumatoid Arthritis

- Secondary outcomes
  - Radiographic progression
  - Proportion of patients with DAS28 of ≤3.2
  - American College of Radiology 20, 50, and 70 responses

Statistics

- Triple therapy would be NI to etanercept-MTX therapy if:
  - Upper limit of 1-sided 95% CI for difference <0.6
- Power of 90% if 450 participants to detect a difference of 0.3
- 2 analyses
  - Adjustment for switching
  - No adjustment



Demographics

- No significant differences between groups
  - Withdrawal rates similar
- Mean baseline dose MTX = 19.6 mg/wk
- DAS28 of 5.8-5.9 (on scale of 2 to 10)
- 54% men
- Mean age 57 years
- 48% on oral glucocorticoids

Primary Outcome

Change in DAS28 score from baseline to 48 weeks

		Difference between groups	Upper limit of 95% one-sided CI	P-value for noninferiority
Accounting for switch	ITT	0.01	0.271	P<0.001
	PP	-0.17	0.116	
Not accounting for switch	ITT	0.165	0.407	P=0.002
	PP	0.042	0.305	

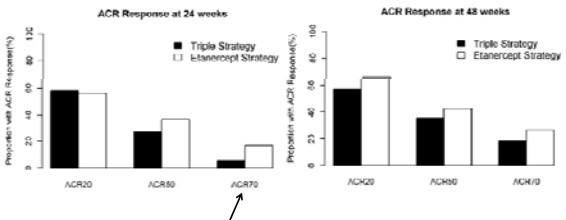
Switching

- Sig. improvement in both groups after 24 wks
- Equal frequency in both groups (27%)
- Sig. improvement in both groups after 48 wks
  - No difference between groups who switched for amount of improvement

Secondary Outcomes

- No difference between groups in radiographic progression (P=0.43)
  - Triple therapy: +0.54 Sharp score units
  - Etanercept-MTX: +0.29 Sharp score units
- No difference between groups in % with DAS28 ≤3.2 (P=0.16)
  - Triple therapy: 39% (no switch subset)
  - Etanercept-MTX: 48% (no switch subset)

Secondary Outcomes



Significantly more patients in etanercept group achieved ACR70 at 24 weeks, but this was not the case at 48 weeks

Safety

Table S4. Frequency of Serious Adverse Events (SAEs) by System, Organ, Class

	Triple Therapy (n=222)	Etanercept (n=219)
Total number of SAEs	33	39
Cardiac disorders	4	1
Gastrointestinal disorders	5	4
Infections and infestations	4	†2
Renal and urinary disorders	1	3
Respiratory, thoracic and mediastinal disorders	4	1
Surgical and medical procedures	3	5
Vascular disorders	3	4
Other (events occurring fewer than 3 times)	8	8

Conclusions

- First blinded trial to focus on biologic vs. oral DMARD strategy after MTX therapy
- Oral DMARD combo a cost-effective option after MTX failure?
- Trend toward favoring etanercept-MTX

Therapies for Rheumatoid Arthritis

Strengths

- Well designed, large trial
- Interim analysis for safety and efficacy
- Mandated switching
- Did not impute data

Limitations

- Target sample size not reached
- Lack of justification for noninferiority margin
- Cannot conclude noninferiority for secondary outcomes
- More men than in other trials
  - Better response to treatment than women?

Triple therapy was noninferior to etanercept–MTX therapy for the outcome of radiographic progression

1. True
2. False

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