A PRACTICAL REVIEW OF THE NOVEL ORAL ANTICOAGULANTS

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LEARNING OBJECTIVES

AS A RESULT OF THIS PRESENTATION, THE AUDIENCE WILL BE ABLE TO

1. DISCUSS THE KEY DIFFERENCES BETWEEN WARFARIN AND THE NON-VITAMIN K ORAL ANTICOAGULANTS

2. IDENTIFY PATIENT CHARACTERISTICS THAT WOULD DIFFERENTIATE WHICH ANTICOAGULANT WOULD BE PREFERRED

3. ADDRESS COMMON MISCONCEPTIONS BY PATIENTS AND HEALTHCARE PROVIDERS ABOUT THE APPROPRIATE ROLE OF THE NON-VITAMIN K ORAL ANTICOAGULANTS.
THE NAME GAME

• NOAC
  • NOVEL ORAL ANTICOAGULANT
  • NON-VITAMIN K ORAL ANTICOAGULANT
• TSOAC
  • TARGET SPECIFIC ORAL ANTICOAGULANT
• DOAC
  • DIRECT ORAL ANTICOAGULANT


CURRENT FDA INDICATIONS

<table>
<thead>
<tr>
<th></th>
<th>VTE prevention</th>
<th>VTE treatment</th>
<th>Non-Valvular AF</th>
<th>Mechanical heart valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>√ (hip + knee)</td>
<td>√</td>
<td>√</td>
<td>0</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>√ (hip)</td>
<td>√</td>
<td>√</td>
<td>0</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>0</td>
<td>√</td>
<td>√</td>
<td>0</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>√ (hip + knee)</td>
<td>√</td>
<td>√</td>
<td>0</td>
</tr>
<tr>
<td>Warfarin (Coumadin® or Jantoven)</td>
<td>√ (hip + knee)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

HOW DO THEY WORK?

- **WARFARIN**
  - INHIBITS VITAMIN K EPOXIDE REDUCTASE
  - FACTORS VII, IX, X, II
- **DABIGATRAN**
  - DIRECTLY INHIBITS Factor IIa
- **RIVAROXABAN, APIXABAN, EDOXABAN**
  - DIRECTLY INHIBITS Factor XA

WHY ARE THE NOACS SO APPEALING

• WARFARIN IS HIGH MAINTENANCE
  • VITAMIN K
  • NARROW THERAPEUTIC INDEX
  • MANY DRUG INTERACTIONS
  • DELAYED PHARMACODYNAMICS ONSET

• NOAC ARE MORE PREDICTABLE
  • NOT IMPACTED BY DIETARY VITAMIN K
  • MORE CONSISTENT PHARMACOKINETICS
  • FEWER DRUG INTERACTIONS
  • RELATIVELY QUICK ONSET OF ACTION
  • NOT ALL REQUIRE HEPARIN ADMINISTRATION PRIOR TO USE FOR VTE*
SO WHAT IS THE CATCH?

- MISCONCEPTIONS
  - PATIENTS AND PROVIDERS
- COST
- PATIENT SELECTION

COMMON PATIENT AND PROVIDER MISCONCEPTIONS

- ASSUMED SIMILARITY TO WARFARIN
- ASSUMED SIMILARITY TO LOW MOLECULAR WEIGHT HEPARINS
- MECHANICAL HEART VALVES
- BLEEDING IS MORE OF A PROBLEM WITH THE NOACS
- NOACS HAVE NO DRUG INTERACTIONS
- MANUFACTURER COPAY CARDS WILL OFFSET THE HIGHER COST
ISN’T IT JUST LIKE WARFARIN WITHOUT THE TESTING?

- IMPACT OF NON-ADHERENCE
- LABORATORY MONITORING
- PRE-SURGICAL INTERRUPTION

IMPACT OF A MISSED DOSE

WARFARIN

NOAC
CAN'T I JUST CHECK AN INR TO MAKE SURE MY NOAC IS WORKING?

ANTICOAGULANT RECOMMENDATIONS WITH PROCEDURES: GENERAL PRINCIPLES

- BRIDGING WITH LMWH
  - IS NOT GENERALLY NECESSARY DUE TO THE QUICK ONSET/OFFSET OF NOACS.
  - ONLY IN HIGH THROMBOTIC RISK WARFARIN PATIENTS
- MINOR PROCEDURES – INTERRUPTION MAY NOT BE NEEDED FOR ANY ANTICOAGULANT
  - MINOR DERMATOLOGICAL PROCEDURES, CATARACT PROCEDURES, AND DENTAL CLEANINGS/FILLINGS
- MAJOR PROCEDURES – INTERRUPTION ALWAYS REQUIRED
  - ANY MAJOR SURGERY WITH EXTENSIVE TISSUE INJURY SUCH AS CANCER SURGERIES, MAJOR ORTHOPEDIC SURGERIES, AND RECONSTRUCTIVE PLASTIC SURGERIES; UROLOGIC OR GASTROINTESTINAL SURGERIES SUCH AS BOWEL RESECTION, NEPHRECTOMY, KIDNEY BIOPSY, AND PROSTATE RESECTION; ANY CARDIAC, INTRACRANIAL, OR SPINAL SURGERY; OR ANY OTHER MAJOR OPERATION (PROCEDURE DURATION >45 MINUTES) OR SURGERY IN A HIGHLY VASCULAR ORGAN (KIDNEY, LIVER, SPLEEN, ETC.)

ANTICOAGULANT COMPARISON: PRE-SURGICAL INTERRUPTION

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;2 days</td>
<td>&gt;3 days</td>
<td>&gt;2 days</td>
</tr>
<tr>
<td>&gt;50</td>
<td>&gt;2 days</td>
<td>&gt;3 days</td>
<td>&gt;2 days</td>
</tr>
<tr>
<td>30-50</td>
<td>&gt;3 days</td>
<td>&gt;4-5 days</td>
<td>&gt;3 days</td>
</tr>
<tr>
<td>15-30</td>
<td>Not indicated</td>
<td>&gt;3 days</td>
<td>&gt;4 days</td>
</tr>
<tr>
<td>&lt;15</td>
<td>no indication for use</td>
<td></td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

ANTICOAGULANT RECOMMENDATIONS WITH PROCEDURES: CLINICAL PITFALLS

• STANDARD PROTOCOLS IN SOME SURGEON OFFICES
  • MANY HAVE NOT BEEN UPDATED FOR NOAC
  • MANY HAVE “ONE SIZE FITS ALL” APPROACH

• COMMON SURGEON FEAR CENTERS ON ABILITY TO REVERSE NOAC
  • DABIGATRAN REVERSAL – IDARUCIZUMAB (PRAXBIND®)
  • XA INHIBITOR REVERSAL – ANDEXANET (STILL IN CLINICAL TRIALS)

• BEWARE OF PROCEDURES INVOLVING SPINAL COLUMN (PAIN MANAGEMENT)
  • LEAN TOWARD “HIGH RISK” RECOMMENDATIONS FOR INTERRUPTIONS

CAN I USE { NOAC } INSTEAD OF ENOXAPARIN FOR BRIDGING?

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SPLITTING HAIRS?

<table>
<thead>
<tr>
<th></th>
<th>NOAC</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life</td>
<td>9-17 hours</td>
<td>4-7 hours</td>
</tr>
<tr>
<td>Onset of action</td>
<td>1-3 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>Overlap with warfarin</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOACS AND VALVULAR HEART DISEASE

- RE-ALIGN STUDY
  - DABIGATRAN VERSUS WARFARIN IN PATIENTS WITH AORTIC OR MITRAL VALVE REPLACEMENTS
  - 12 WEEK PHASE 2 DOSE FINDING STUDY
  - STUDY TERMINATED EARLY DUE TO EXCESS STROKE AND BLEEDING WITH DABIGATRAN
    - ENROLLED 252 RATHER THAN INITIAL TARGET OF 405
    - STROKE (9 VS 0 PATIENTS)
    - PERICARDIAL BLEEDING (4 VS 2)
    - 32% OF ALL DABIGATRAN PATIENTS REQUIRED DOSE ADJUSTMENT OR DISCONTINUATION
NOACS AND VALVULAR HEART DISEASE

• WHY DIDN'T DABIGATRAN WORK?
  • THROMBIN GENERATION
    • ATRIAL FIBRILLATION – TRIGGERED BY STASIS
    • MECHANICAL HEART VALVE – TRIGGERED BY RELEASE OF TISSUE FACTOR

BLEEDING RISK: WARFARIN VS NOAC

• GI BLEED
  • DABIGATRAN HAD 28-41% HIGHER RISK THAN WARFARIN
  • COMPOSITE OF ALL NOAC SHOWED NO STATISTICAL DIFFERENCE COMPARED TO WARFARIN

• INTRACRANIAL HEMORRHAGE
  • STUDIES FAVORED NOAC OVER WARFARIN (~ 54% RELATIVE REDUCTION)

• TOTAL BLEEDING
  • STUDIES TRENDED TOWARD NOAC BETTER THAN WARFARIN
### NOAC DRUG INTERACTIONS

- **P-GLYCOPROTEIN**
  - DABIGATRAN
  - EDOXABAN
  - APIXABAN
  - RIVAROXABAN

- **STRONG INHIBITORS WILL INCREASE SERUM DRUG LEVELS BY LIMITING RE-SECRETION TO GUT**

- **CYP 3A4**
  - RIVAROXABAN
  - EDOXABAN (MINOR)
  - APIXABAN (MINOR)

- **STRONG INHIBITORS WILL INCREASE DRUG LEVELS**

- **STRONG INDUCERS WILL DECREASE DRUG LEVELS**

### ANTICOAGULANT COMPARISON: DRUG INTERACTIONS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>No adjustment</td>
<td>Precaution</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Precaution</td>
<td>Precaution</td>
<td>Precaution</td>
<td>Avoid</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Avoid</td>
<td>Precaution</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Safe</td>
</tr>
<tr>
<td>NSAID/ ASA</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
</tr>
<tr>
<td>Clopidogrel – antiplatelets</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
<td>Caution</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Unknown</td>
<td>Caution</td>
<td>Caution</td>
<td>Unknown</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Avoid</td>
<td>Caution</td>
<td>Caution</td>
<td>Avoid</td>
</tr>
<tr>
<td>Heparin/ ticagrelor</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

ECONOMICS OF NOACS

- From 2010-2013 NOAC medications accounted for
  - 62% of new anticoagulation prescriptions
  - 98% of total anticoagulant drug cost
- 1st 6 months of therapy for a patient
  - NOAC $900 per patient greater cost than Warfarin (Insurer + Patient cost)
- Many insurances have at least one NOAC at tier 3 copay (preferred brand)
- May have impact on rate to reach coverage gap in Medicare patients

WHAT ABOUT COPAY ASSISTANCE CARDS

- Eligibility
  - Any patient with government funded insurance is ineligible for recurrent copay assistance programs (i.e. split bill)
  - If not processed through any insurance, patients may be eligible on short term RX
    - 30 day free trial
- Word of caution
  - If patient fills RX with 30 day trial – be sure a plan is in place for subsequent refills
    - If refills too expensive, patient likely to discontinue the anticoagulant
COST-EFFECTIVENESS OF NOAC

- FEW CLINICAL TRIALS ASSESSING COST EFFECTIVENESS VERSUS WARFARIN AT HEALTH CARE SYSTEM LEVEL
  - USING EVENT RATES FROM CLINICAL TRIALS (RE-LY, ROCKET-AF, ARISTOTLE) ONE ANALYSIS PROJECTED:
    - AGE >75: APIXABAN AND RIVAROXABAN MORE COST EFFECTIVE THAN WARFARIN, BUT DABIGATRAN LESS COST EFFECTIVE
    - AGE <75: ALL 3 NOAC MORE COST EFFECTIVE THAN WARFARIN
    - LIMITATION: REAL WORLD DATA VERSUS CONTROLLED TRIAL DATA
  - FUTURE RESULTS OF THESE TRIALS MAY CHANGE INSURERS WILLINGNESS TO COVER NOAC

Deitelzweig, et al. Medical costs in the US of clinical events associated with oral anticoagulant (OAC) use compared to warfarin among non-valvular atrial fibrillation patients ≥75 and <75 years of age, based on the ARISTOTLE, RE-LY, and ROCKET-AF trials. J Med Econ. 2013 Sep;16(9):1163-8.

PATIENT #1

- MR. CLEAN HAS BEEN TAKING WARFARIN TO PREVENT A STROKE RELATED TO ATRIAL FIBRILLATION FOR THE PAST SEVERAL YEARS AND HE IS REALLY INTERESTED IN SWITCHING TO A NOAC BUT WANTS YOUR OPINION.
  - WHAT INFORMATION DO YOU WANT TO FIND OUT FROM MR. CLEAN BEFORE GIVING A RECOMMENDATION?
**IMPACT OF RENAL FUNCTION ON SELECTION**

<table>
<thead>
<tr>
<th>NOAC RENAL DOSING (AF)</th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
<th>APIXABAN</th>
<th>RIVAROXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>150MG BID</td>
<td>C/I IF CLCR &gt;95</td>
<td>C/I IF CLCR &lt;15</td>
<td>5MG BID</td>
<td>20MG DAILY</td>
</tr>
<tr>
<td>75MG BID IF CLCR 15-30</td>
<td>60MG DAILY IF CLCR 50-95</td>
<td>2.5MG BID IF 2 OF THE FOLLOWING PRESENT:</td>
<td>15MG DAILY IF CLCR 15-50</td>
<td>15MG DAILY</td>
</tr>
<tr>
<td>C/I IF CLCR &lt;15</td>
<td>30MG DAILY IF CLCR 15-50</td>
<td>WT ≤ 60 KG</td>
<td>C/I IF CLCR &lt; 15</td>
<td>C/I IF CLCR &lt; 15</td>
</tr>
</tbody>
</table>

**All Creatine Clearance in ml/min using Cockroft-Gault formula**
IMPACT OF ADHERENCE FACTORS

- WITH FOOD
  - RIVAROXABAN

- SPECIALIZED PACKAGING
  - DABIGATRAN

- NUMBER OF DOSES PER DAY

- ONCE DAILY
  - RIVAROXABAN
  - EDOXABAN

- TWICE DAILY
  - DABIGATRAN
  - APIXABAN

OTHER ITEMS TO CONSIDER

- DOSING CONSIDERATIONS
  - AGE
    - APIXABAN
  - WEIGHT
    - APIXABAN
  - DRUG INTERACTIONS

- GENERAL PATIENT CARE
  - CONCURRENT ANTIPLATELET THERAPY
  - POTENTIAL DECREASED PATIENT- PROVIDER CONTACT BY ELIMINATING INR MONITORING VISITS
  - ONCOLOGY OR THROMBOPHILIA PATIENTS
SUMMARY OF PATIENT COUNSELING POINTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>With food</th>
<th>Can crush</th>
<th>Missed dose</th>
<th>Dose per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>+/-</td>
<td>Y</td>
<td>Take ASAP in same day</td>
<td>2</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>+/-</td>
<td>N</td>
<td>Take ASAP with at least 6 hr between doses</td>
<td>2</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>+/-</td>
<td>N</td>
<td>Take ASAP in same day</td>
<td>1</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Take with food</td>
<td>Y</td>
<td>Take ASAP in same day</td>
<td>1 (2 if in 1st 21 days of VTE)</td>
</tr>
<tr>
<td>Warfarin (Coumadin® or Jantoven)</td>
<td>+/-</td>
<td>Y</td>
<td>Take if before midnight same day *may call provider</td>
<td>1</td>
</tr>
</tbody>
</table>

TRANSITION OF WARFARIN TO NOAC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start when INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>≤ 2.5</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>&lt; 3.0</td>
</tr>
</tbody>
</table>
PATIENT #2

• MRS BUTTERSWORTH WAS DIAGNOSED WITH A DEEP VEIN THROMBOSIS BY HER PRIMARY CARE PHYSICIAN TODAY. SHE DOES NOT HAVE THE DEXTERITY TO GIVE HERSELF INJECTIONS (I.E. ENOXAPARIN) AND HAS NO LOCAL FAMILY MEMBERS THAT CAN ASSIST. WHICH ORAL ANTICOAGULANTS ARE STILL AN OPTION?

NOAC INITIATION IN DVT/PE

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Starting dose</th>
<th>Maintenance dose</th>
<th>Adjusted dose</th>
<th>Heparin induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>10mg BID for 1 week</td>
<td>5mg BID</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>----</td>
<td>150mg BID</td>
<td>Avoid use in Clcr &lt;30</td>
<td>Yes (5-10 days)</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>----</td>
<td>60mg daily</td>
<td>30mg daily (Wt &lt;60kg, Clcr 15-50)</td>
<td>Yes (5-10 days)</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>15mg BID for 3 weeks</td>
<td>20mg daily</td>
<td>Avoid use in Clcr &lt;30</td>
<td>No</td>
</tr>
<tr>
<td>Warfarin (Coumadin® or Jantoven)</td>
<td>5 or 10mg daily</td>
<td>Dose to INR 2.0-3.0</td>
<td>n/a</td>
<td>Yes (at least 5 days, pending INR ≥2.0)</td>
</tr>
</tbody>
</table>
PATIENT #2

• MRS BUTTERSWORTH RECEIVES APIXABAN 10MG TWICE DAILY FOR THE FIRST WEEK FOLLOWED BY 5MG TWICE DAILY THEREAFTER. HOWEVER, HER COPAY FOR THE MEDICATION IS NOW TOO EXPENSIVE FOR HER TO CONTINUE. HER PHYSICIAN WANTS TO TRANSITION HER TO WARFARIN, HOW WOULD YOU RECOMMEND THAT SHE SAFELY SWITCH?

TRANSITION OF NOAC TO WARFARIN

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Transition Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>Stop apixaban, start warfarin plus LMWH at time of next scheduled apixaban dose and bridge until INR ≥ 2.0</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>Overlap warfarin with dabigatran</td>
</tr>
<tr>
<td></td>
<td>Clcr ≥ 50 ml/min – overlap 3 days</td>
</tr>
<tr>
<td></td>
<td>Clcr 30-50 ml/min – overlap 2 days</td>
</tr>
<tr>
<td></td>
<td>Clcr 15-30 ml/min – overlap 1 days</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>60mg dose: ↓ to 30mg + overlap with warfarin</td>
</tr>
<tr>
<td></td>
<td>30mg dose: ↓ to 15mg + overlap with warfarin</td>
</tr>
<tr>
<td></td>
<td>Stop edoxaban when INR ≥ 2.0</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Stop rivaroxaban, start warfarin plus LMWH at time of next scheduled rivaroxaban dose and bridge until INR ≥ 2.0</td>
</tr>
</tbody>
</table>
UNANSWERED QUESTIONS
EVIDENCE-BASED PREFERRED NOAC?

• HOSPITALIZATION RATE
  • DABIGATRAN (HR 1.37, 95% CI 1.10-1.69) AND RIVAROXABAN (HR 1.57, 95% CI 1.30-1.90) WAS ASSOCIATED WITH INCREASED RATE OF ALL-CAUSE HOSPITALIZATION RELATIVE TO APIXABAN.
  • MEAN MONTHLY ALL-CAUSE COSTS WERE LOWER FOR PATIENTS ON APIXABAN COMPARED TO THOSE ON DABIGATRAN ($3,581 VS $4,236; P<0.0001) AND RIVAROXABAN ($3,581 VS $4,144; P<0.0001).

• VERSUS WARFARIN
  • 9% RELATIVE RISK REDUCTION IN MORTALITY IN COMPOSITE OF RE-LY, ROCKET-AF, AND ARISTOTLE
  • NONE OF THE INDIVIDUAL STUDIES WERE ABLE TO SHOW STATISTICAL SIGNIFICANCE ON ITS OWN


FOR MORE INFORMATION
(FOR PATIENTS AND HEALTHCARE PROVIDERS)

• CLOT CARE
  • NON-PROFIT ORGANIZATION
  • HTTP://WWW.CLOTCARE.COM/

• MICHIGAN ANTICOAGULATION QUALITY IMPROVEMENT INITIATIVE (MAQI²)
  • CONSORTIUM OF ANTICOAGULATION CLINICS AND EXPERTS
  • HTTP://WWW.ANTICOAGULATIONTOOLKIT.ORG/

• ANTICOAGULATION FORUM
  • GEARED TOWARD HEALTHCARE PROVIDERS ONLY
  • HTTP://ACFORUM.ORG
ANY QUESTIONS?