Rheumatologic Considerations in the Geriatric Patient

Richard A. Pascucci, Philadelphia College of Osteopathic Medicine
RHEUMATOLOGIC CONSIDERATIONS IN THE GERIATRIC PATIENT

Richard A. Pascucci, DO, FACOI
Vice Dean for Clinical Education
Professor of Medicine
TYPICAL PRESENTATIONS OF RA

1. Insidious polyarthritis
2. Chronic polyarthritis (deforming)
3. Acute migratory polyarthritis
4. Palindromic rheumatism
5. JRA-Still's Variant
6. Monarticular RA
7. Robust reaction type
8. Rheumatoid nodulosis
9. Elderly Onset

CLINICAL CHARACTERISTICS OF ELDERLY ONSET RA (EORA)

Onset after age 60
Acute onset common
F:M Ratio<3:1
Increased incidence of systemic symptoms
Predilection for large joints

EORA COMPARED TO YORA

Increased Incidence
Shoulder & Hip Synovitis
Acute Onset
PMR-like presentation
Elevated ESR

Decreased Incidence
Small Joint disease
Extra-articular disease
Nodules
Seropositivity
REVISED CRITERIA FOR RA (ACR 1987)

- Morning Stiffness
- Swelling of ≥ 3 joints
- Swelling of wrist, MCP, or PIP joints
- Symmetrical joint swelling
- Hand x-ray changes
- Subcutaneous nodules
- Positive Rheumatoid factor

DIFFERENTIAL DIAGNOSIS OF RA

- CTD
- SBE
- Thyroid
- HPO
- Infection
- Osteoarthritis
- Seronegative Spondylitis
- Gout (Tophi)
- PMR (Elderly)
- Rheumatic Fever
- Fibromyalgia
Anti-Cyclic Citrullinated Peptide Ab (Anti-CCP)
- Detected by Elisa technique
- As sensitive as (47-80%) but more specific (97%) than IgM rheumatoid factor
- Marker of erosive disease
- Undifferentiated CTD-may predict RA
- Detected in “Healthy” population years before clinical RA
- Found in 40% “Seronegative RA”

RHEUMATOID ARTHRITIS
- Treat aggressively, EARLY!
- The most significant damage to the joints occurs in the initial 1-2 years of disease.
CURRENT MANAGEMENT OF RA

RITUXIMAB
ABATACEPT

SINGLE AGENT:
SSZ/HCQ/TNF
LEF-GOLD (?)

COMB-TX:
1) MTX & SSZ
2) TRIPLE TX
3) MTX & TNF

MTX

NSAID

ADJUNCTIVE STEROIDS (ORAL OR IA)

CURRENT MANAGEMENT OF RA

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MTX

NSAID

ADJUNCTIVE STEROIDS (ORAL OR IA)

Additional TNF Inhibitors

A) Certolizumab Pegol (Cimzia)
   - Prohibited ± addition of PEG to reduce immunogenicity and
     immunogenicity
   - Dosing: 400 mg sub-q initially, week 2 & week 4
     continued dose depends on response

B) Golimumab (Simponi)
   50 mg sub-q every 4 weeks

Interleukin – 6 Inhibitor (IL-6)

Tocilizumab (ACTEMRA) —
   - IL-6 Receptor Inhibitor indicated for RA after at least one (1)
     TNF Inhibitor has failed

   - Dosing 8mg kg IV, increased to 8mg kg based on clinical
     response (linear extension, IV dose q 4 weeks)

   - Side Effects: Infections, headache, HTN, ↑ LFTs,
     Anaphylaxis, ↓ WBC or Platelets
Systemic Corticosteroids

Advantages
- Control of symptoms
- May facilitate disease control by DMARDs
- Control of life-threatening emergencies

Disadvantages
- No effect on disease progression
- Hypercorticism

Source: Hardin and Longenecker, 1992
A 63-year-old female presents to the office with the complaint of difficulty getting out of a chair. She also has vague symptoms such as fatigue and lack of energy in association with morning stiffness and aching in the proximal portions of her arms and legs. Lab data reveals a mild anemia, normal biochemistry profile, and a Westergren sedimentation rate of 75 mm/hr. PE is unremarkable.

**CLINICAL FEATURES OF PMR (SYMPTOMS AND SIGNS)**

- Pain
- Disability
- Stiffness
- Tenderness
- Fatigue
- Limitation of motion - areas of involved
- Depression
- Arthritis
- Carpal Tunnel Syndrome

**CHARACTERISTICS OF POLYMALGIA RHEUMATICA**

- Older patient
- Normal physical examination
- Aching and stiffness
DEFINITION OF PMR
1. Pain in neck, shoulders, and pelvic girdle for at least one month. Morning stiffness and gelling without muscle atrophy or weakness.
2. Age ≥ 50 years old
3. ESR ≥ 50 mm/hr
4. Relief of symptoms within 4 days with as low as 10-15 mg Prednisone per day

DIFFERENTIAL DIAGNOSIS OF PMR
- RA and other CTD
- Viral Myalgias
- Polymyositis
- Multiple Myeloma
- Osteoarthritis
- Fibromyalgia
- Occult CA
- Occult Infection

LAB IN PMR
- Anemia
- ESR (≥ 50 mm/hr)
- RA (-)
- ANA (-)
- Muscle Enzymes – Normal
- EMG – Normal
- Liver Profile
PMR – THERAPY

A) NSAIDS – trial warranted?
   - will not prevent vascular complications

B) Corticosteroids - *Drug of choice (low dose)
   If sx free x 6-12 months, may D/C steroids
   50% may relapse
   ? Add MTX (steroid sparing)
   conflicting reports

Prognosis
? Assoc. with ↑ CV mortality

MANAGEMENT OF PMR

ASA or NSAID's
Corticosteroids
   - Dosage
   - Duration

Biopsy
   - Indications

Education
** N.B. 1 – Sudden Blindness 7 Years After Dx.
N.B. 2 – PMR May Evolve into RA
GCA – THERAPY

Corticosteroids 0.7-1.0mg/kg/day
- maintain x one monthly before tapering

* Addition of 81mg ASA
  May prevent occlusive disease

* Add Imuran/CTX/MTX?
  Steroid sparing
### RHEUMATIC DISEASES: ASSOCIATED CRYSTALS

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<thead>
<tr>
<th>Crystal</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Monosodium urate monohydrate</td>
<td>Gout</td>
</tr>
<tr>
<td>Calcium pyrophosphate dihydrate</td>
<td>Pseudogout</td>
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<tr>
<td>Dicalcium phosphate dihydrate</td>
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<tr>
<td>Apatite</td>
<td>Osteoarthritis?</td>
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<tr>
<td>Adrenal corticosteroid esters</td>
<td>Tendon, muscle, and/or synovial calcification</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Intracapsular postinjection flare</td>
</tr>
<tr>
<td></td>
<td>None (chronic effusion)</td>
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</table>
Patient Demographics of Osteoarthritis

• Affects more than 22 million Americans
• About 80% of patients show x-ray evidence of osteoarthritis by age 55
• Peak incidence reported in patients over age 65
• Women affected approximately twice as often as men

SYMPTOMS OF OSTEOARTHRITIS

• Pain
  - Localized to characteristic joints
  - Aggravated by activity
• Stiffness
  - Generally less than 15 minutes duration
  - With inactivity
• Onset gradual and additive
• Acute and intermittent flares

CLINICAL FEATURES OF OSTEOARTHRITIS

Age: > age 40 (usually)
Morning Stiffness: Usually insignificant
Joint Distribution: DIP, PIP, First CMC, Knee, Hip, First MTP, Spine
Insidious Onset
Rare Systemic Manifestation
Osteophytes and Eburnation
JOINTS USUALLY SPARED IN OSTEOARTHRITIS

MCPs
WRISTS
SHOULDERS
ELBOWS
ANKLES

DIFFERENTIAL DIAGNOSIS OF OSTEOARTHRITIS

RA – ESR, DISTRIBUTION, SYSTEMIC, ETC.
Other DIP Diseases – Psoriatic, Reiter’s
CPPD – Distribution, Flares, Crystals, etc.
Localized Joint Disorders (Early) –
Aseptic necrosis, PVS
Infections, etc.

Medical Management of OA
Non-Pharmacologic Therapy

• Patient Education – self-help, social support
• Weight loss
• Physical Therapy
  - ROM
  - Strengthening
  - Assistive Devices
• Occupational Therapy
• Aquatic Exercise Therapy
• Aerobics
Pharmacologic Therapy
• Analgesics – e.g. oral (acetaminophen) or Topical
• NSAID’s
• Opioid Analgesics (e.g. Propoxyphene, codeine)
Experimental Therapies
PHARMACOLOGIC THERAPY FOR PATIENTS WITH OA

ORAL
- Acetaminophen
- COX-2 Specific Inhibitor ??
- Nonselective NSAID plus Misoprostol or PPI
- Other Pure Analgesics
  - Tramadol
  - Opioids
- Intraarticular
  - Steroids
  - Hyaluronan
- Topical
  - Capsaicin
  - Methylsalicylate

*Choice of Agent(s) should be individualized


Glucosamine Sulfate-Chondroitin Sulfate

- Repair and Maintenance of Cartilage
- Several short-term controlled human studies show modest decrease OA symptoms
- May have Remittive Effect

Hyaluronic Acid Treatment “Viscosupplementation”

Supplement Abnormal hyaluronic Acid
- Injected into knee joint for 3-5 consecutive weeks
- Equally as effective as Acetaminophen (pain relief) or Naprosyn
- No proof of altered joint Biology
- FDA Approved – side effects include local irritation or severe allergy (rare)
Future Directions in OA Therapy

- MMP inhibitors
- NO inhibitors
- COX-2 specific inhibitors
- Disease-modifying interventions

LATE-ONSET SLE
Occurrence after age 50
F>M
Frequent Misdiagnosis
Conservative Therapy

LATE-ONSET SLE CLINICAL MANIFESTATIONS
Arthritis
Rash
Constitutional Sx.
Pleuritis/Pericarditis
Nephritis
Hematologic
LATE-ONSET SLE
LESS COMMON CLINICAL FEATURES

Lymphadenopathy
Raynaud’s Phenomenon
Neuropsychiatric Disease
Alopecia

DRUG – INDUCED SLE

1. Criteria
2. Female:Male Ratio
3. Black vs. White
4. Systems Spared
5. Serum Antibody
6. Clinical Symptoms
7. Predisposition –
   (a) HLA – type
   (b) Slow Acetylator
**Lupus-like Syndrome: Drugs Implicated in Induction**

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<tr>
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<td>Methysergide</td>
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**Lupus-like Syndrome: Drugs Implicated in Induction (continued)**

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POMA 107th Annual Clinical Assembly  
April 29 – May 2, 2015
Prevention  Treatment

- Alendronate  Yes  Yes
- Risedronate  Yes  Yes
- Calcitonin  No  Yes
- Conjugated Estrogens  Yes  No
-Raloxifene  Yes  Yes
-PTH  No  Yes

Treatment of Postmenopausal Osteoporosis

FDA-Approved Indications

- Approved November 2002
- Anabolic Agent

Indications:
1. Post-Menopausal ¥ High Risk for fx
   - Previous fx
   -Signif. Low Bone mass
   -Intolerant or unresponsive to other Tx.
2. ¥ Primary or hypogonadal osteoporosis

CI
- Paget's
- Pregnancy
- Osteomalacia

ESRD
METS
Stone Disease

TEIPARATIDE TX. FOR OSTEOPOROSIS

-Approved November 2002
- Anabolic Agent

Indications:
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   -Previous fx
   -Signif. Low Bone mass
   -Intolerant or unresponsive to other Tx.
2. ¥Primary or hypogonadal osteoporosis

CI
- Paget's
- Pregnancy
- Osteomalacia

ESRD
METS
Stone Disease
TERIPARATIDE TX. FOR OSTEOPOROSIS CONT.

Risks: ↑ Osteosarcoma in Rats
(Use only for 2 years)
Side effects: Dizziness & Leg Cramps
Baseline lab: Ca++ Alk. Phos.
    Po4 = 25-OH Vit D.
Creatinine
Dose: 20 ug Sub = Q daily
Cost: AWP = $7592/year

COMBINATION THERAPY

A) "The Effects of Parathyroid Hormone and Alendronate alone or in combination in postmenopausal osteoporosis"
Black DM, Greenspan SC, Ensrud KE, ET AL.
NEJM - September 25, 2003
Conclusion: No Evidence of synergistic effect

B) Raloxifene + PTH
Combination Better Than PTH alone.
Deal, C.- Presented at ACR (October 2004)

DENOSUMAB

* Anti-Resorptive agent
  - Inhibits RANKL

Trial Compared Denosumab to Alendronate (open case)
(412 pm females with low bone mass)
Denosumab
60 mg sub Q every 6 months
Results (24 months)

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<tr>
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<th>Denosumab</th>
<th>Alendronate</th>
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<tr>
<td>BMD HIP</td>
<td>↑ 5%</td>
<td>↑ 3.5%</td>
</tr>
<tr>
<td>BMD L. SPINE</td>
<td>↑ 7%</td>
<td>↑ 6%</td>
</tr>
<tr>
<td>BMD Radius</td>
<td>↑ 1.75%</td>
<td>↑ 0.5%</td>
</tr>
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</table>
- **RANKL** –
  Receptor Activator of nuclear factor KAPPA B Ligand
  - Mediates resorptive phase of bone remodeling
  - Blocking the binding of RANK to its ligand inhibits the Osteoclast

**BISPHOSPHONATE-ASSOCIATED AVN OF JAW (ONJ)**

**CLINICAL PRESENTATION**
- Predominantly maxilla but also occurs in mandible
  - Woman ≥ 65 years
  - Painful area
  - Periapical jaw x-ray
  - CT or MRI scan
  - Bone scans

**Risk Factors**
- Onconnective tissue disorders
- History of smoking
- History of alcoholism
- Pathologic fractures
- Other medical conditions (HIV/AIDS, cancer)

**Mechanism**
- Secondary to local exposure of the bone to bisphosphonates
**Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur**

D.M. Black MP, Kelly, KH Connell, L. Polermo et al

*New 362: 19. 1761-1771 May 15, 2010*

*Secondary Analysis of 3 large, randomized Bisphosphonate Trials:

1. FIT (Fracture Intervention Trial)
2. FLEX (FRT Long-Term Extension)
3. HORIZON (Health Outcome and Reduced Incidence with Zoledronic Acid once yearly) Pubertal Fracture Trial (PFT).

Results: Review of 264 records for hip or femur fractures among 14,105 in those trials.

12 Fractures in 10 patients occurred in subtrochanteric or diaphyseal femur (2.3 per 10,000 patient years).

**Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur (cont')**

*Relative Hazard: 1.03 in FIT
1.33 in FLEX
1.50 in HORIZON-PFT

Conclusions: 1) Occurrence of atypical fracture was rare, even among patients TX for 10 years
2) No significant increase in risk (but study underpowered for definitive conclusions)

*Not Significant*
Editorial

Intracranial fractures usually occur from fall from standing and are associated with osteoporosis. They may have atypical configuration may have bone density loss associated with typical presentation, featuring headache, vomiting, and altered mental status.

- Osteoporotic fractures are characterized by a thin, transverse, or wedge-shaped bone.
- They are often associated with multiple fractures and may be difficult to diagnose.
- Biological markers of bone turnover may be useful in predicting the risk of future fractures.

In summary, identifying and treating osteoporosis is crucial to prevent fractures and improve patient outcomes.
“The Effects of Strontium Ranelate on the Risk of Vertebral fracture in women with post menopausal osteoporosis”

*NEJM 350:5, 459-468, Jan-29, 2004*

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**STRONTIUM RANELATE**

“Re-Launched” as a new compound

**Mode of Action**
- Stimulates Bone Formation
- Decreases Bone Resorption
- May Suppress PTH
- No Mineralization Defects

**Dosage:** 2 Grams/Day

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**VERTEBROPLASTY**

Utilizes cement injection into bone for stabilization of compression fracture(s)

**Patient Selection**
- (1) Severe Back pain < 12 months
  - (Refractory to analgesics)
- (2) Vertebral body compression fracture(s)
  - (Pain elicited with palpation at specific level(s))
- (3) MRI/Bone scan-no other explanation
  - *Osteoporotic or pathologic Fx treated*
**Osteoporosis Therapy Options Postmenopausal Women**

<table>
<thead>
<tr>
<th>During Hot Flushes</th>
<th>After Fracture</th>
<th>Bisphosphonates</th>
<th>Teriparatide</th>
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<tr>
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**Age Staging**

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<thead>
<tr>
<th>Stage</th>
<th>Risk/Status</th>
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<tr>
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<table>
<thead>
<tr>
<th>Higher</th>
<th>Lower</th>
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<tbody>
<tr>
<td>Score</td>
<td>-25</td>
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* Increasing risk of fracture with age

**Cyclooxygenase Isoenzymes**

- **Physiologic Stimulus**
  - Platelets
  - Endothelium
  - Stomach
  - Kidney

- **Inflammatory Stimulus**
  - Macrophages
  - Leukocytes
  - Fibroblasts
  - Endothelial cells

**COX-1**
- Constitutive
  - TXA₂, PGI₂, PGE₂

**COX-2**
- Inducible
  - PGJ₂, PGE₂

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

- Largest class of pharmaceutical agents used worldwide
- Common in the pharmacologic therapy of arthritis
- Effective in relieving pain, inflammation, and stiffness in arthritis patients
- Enhance function and quality of life in arthritis patients
- Good safety profile when prescribed and monitored appropriately
Utilization of NSAIDs

2000 -
- 111, 490, 000 Rx for NSAIDs in US
- $5 Billion Cost
- $2 Billion OTC NSAIDs
- 34% age ≥ 65 use on daily basis

Today -
- 17, 000, 000 Americans utilize on daily basis
- $10 Billion Market Worldwide
- Marketed directly to consumers

Use of NSAIDs

- Osteoarthritis
- Rheumatoid Arthritis
- Other arthritic conditions
- Pain syndromes
  - Musculoskeletal pain syndrome
  - Soft tissue pain syndrome

Mechanism of Action of Traditional NSAIDs and COXIBs

- COX-1 "Nonselective"
- COX-2 "Inhibitor"
- Arachidonic acid
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Prostaglandins
- Thromboxane A2
- Platelet function and hemostasis
- Protection of gastric mucosa
- Mediate pain, inflammation, and fever
TOXIC EFFECTS OF NSAIDs

- GI disorders (dyspepsia, PUD, occult blood)
- CNS
- Toxicity
- Rash
- Hypersensitivity Reactions (ASA Allergy)
- Hepatotoxicity
- Nephrotoxicity (edema, K+ ARF, papillary necrosis, interstitial nephritis)

PROTECTIVE EFFECTS OF CHRONIC NSAID USE ON COGNITIVE DECLINE IN OLDER PERSONS

- Interview Study of 7671 Patients (personal-3 and Telephone-4)
- Utilize SPMSQ (Short, Portable Mental Status Questionnaire)
- Chronic NSAID Usage (3 years at 2 Interviews)
- Role of Amyloid (?) in Alzheimer's

SUMMARY: BENEFITS OF COX-2 SPECIFIC INHIBITION

- COX-2 Specificity
  - Inflammation and pain reduced, similar to non-selective NSAIDs
- COX-1 sparing
  - GI toxicity reduced, in contrast to non-selective NSAIDs
  - Lack of effect on platelets

[References]
- Schneeweiss et al. 1999;25:332E Coagul Proteins

POMA 107th Annual Clinical Assembly
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Cox-2 Cardiovascular Effects Hypothesis

Inhibition of vascular PGI₂ (Prostacyclin) synthesis
And
Lack of Effect on Platelet Thromboxane Synthesis
↓ Imbalance
↓ Prothrombotic State
↓ Increased Thromboembolic CV Events

COXIBs/NSAIDs (Traditional or Non-Selective) Questions to be Answered

CV
- Role of Coxibs and CV/Thrombotic Events
- Effect of NSAID + ASA on MI Prevention
- Do Non-Selective NSAIDs cause MI? (Traditional)

HISTORY OF CV EVENTS WITH COXIBs

- VIGOR Trial - Rambautre, et al. 2000 - Disappearance of data after 8 weeks of therapy
- CLASS Trial - Silverstein et al. 2000 - No statistically significant
- APPROVE Trial - Glauser F. Prevention on Vascular events in non-acute patients
- Disappearance after 15 months (Twice as frequent in some patients)
- led to withdrawal of rofecoxib Sept. 2004

COX-2 PROVEN TO BE DOMINANT SOURCE OF PGI₂ (PROSTACURIN)

- Vasodilation
- Inhibits Platelet Aggregation
- Prevents Proliferation of vascular smooth muscle cells (in Vitro)

Fitzgerald, GA: NEJM 351:17 (October 17, 2004)

COXIBs/NSAIDs & HEART DISEASE

A) Blood Pressure
B) Fluid Retention
C) Oxidative Modification of Biologic Lipids (possible) leading to atherosclerosis
D) Exacerbation of CHF (esp. with Renal Fx.)


Cox-2 Cardiovascular Effect

HYPOTHESIS

Inhibition of vascular PGI₂ (Prostacyclin) synthesis
And
Lack of Effect on Platelet Thromboxane Synthesis
↓ Imbalance
↓ Prothrombotic State
↓ Increased Thromboembolic CV Events
Is CV Disease a COX-2 Class Effect?

- Events more likely with higher dosage and longer duration of therapy.
- Inconclusive evidence of class effect.

**Recommendation:** Utilize a Risk/Benefit analysis of each patient.

N.B. Patient with Inflammatory disease at higher risk for MI

Inhibition of Clinical Benefits of Aspirin on First Myocardial Infarction by NSAIDs


**Findings:**
- ASA 325 mg q ovar day vs. 1st MI by 44%
- NSAID use for 1-5 days or > 60 days (p < 0.05)

**Conclusions:**
- Possible that differences in inhibition of ASA’s effect on platelets may lead to differences in clinical outcomes (not yet proven).

- Discontinue & Redo results had no effect.

**Recommendation:** Take ASA at least 2 hours prior to the NSAID.

Long Term Use of NSAIDs and the Risk of Myocardial Infarction in the General Population

- Garcia Rodriguez, JA and Gonzalez-Pinto, A. BMJ Medicine 2009; 3:17

- nested case control analysis of 1078 cases of acute MI and 2790 controls (DFR 1:3:1:1)
- NSAIDs use (ibuprofen, diclofenac, Naprosyn) for > 1 year did not + risk for MI
- NSAIDs use for > 1 year: + risk for nonfatal MI
- Discontinuation reached statistical significance for small risk
- While aspirin may have reduced risk, ibuprofen revealed unacceptable risk in statistical signif.
- The use of ASA countered the risk for MI.
RISK OF MI WITH PROLONGED USE OF TRADITIONAL NSAIDs

- Numerous trials with variable results
- ASA appears to obviate risk with NSAIDs
- Interaction between Ibuprofen (and others) and ASA not substantiated
- NSAIDs alone do not appear to offer Cardioprotection

Summary & Recommendations:
1) Take ASA 2 hours prior to NSAID
2) Must take ASA + NSAID if the risk for CAD

Recommendations (Considerations) for the use of NSAID/Cox-2 in 2006

- Careful consideration to the patient need (indication) for an NSAID or COX-2 (Avoid with CAD
- Prefer NSAID/COX-2 in those with the lowest cardiovascular (CV) and/or GI risk if possible (instruct patient in direction for Decision Making)
- Consider alternative therapies (chondroitin, injections, topical) if the risk is determined to be too great.
- Utilize the lowest effective dose for the shortest period of time.
- Bone therapy, Monitor patients for signs of developing toxicity.

Andrew K. Boxes in International Journal of Advances in Rheum, Vol. 2 No. 4, 2008
MONITORING NSAID THERAPY

Initially: CBC, UA, K, SGOT, Creatinine
Q 1-3 Months

Stable: Same Lab Q 3-12 months

From: Guidelines for Reviewers of Rheumatic Disease Care ACR (CORC)