Arthritis and Diabetes Pharmacotherapy

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Rheumatoid Arthritis

- Distinctly different than osteoarthritis
- Affects 1% of the American population
  - 5.0% in women > 65 yrs:
  - Female to male ratio is 3:1
  - Peak age of onset is between 20 and 50 years
- > 9 million medical visits annually:
  - National cost of RA > $8.5 billion
- 60% disability rate
- Increase risk of premature death primarily due to cardiovascular (CV) disease

Natural Course of Disease

Stage I:
Presentation of unknown antigen to the T cell; No symptoms

Stage II:
Initiation and perpetuation of the inflammatory response; T- and B-cell proliferation, cytokine release; No symptoms

Stage III:
Soluble mediators of inflammation and neutrophil infiltration into synovial fluid, synovial proliferation; Symptoms - joint pain/swelling, and morning stiffness

Stage IV:
Radiographs show only juxta-articular osteoporosis; Symptoms - as in stage III

Stage V:
Erosion of bone, distortion of the articular architecture; Radiographs reveal erosions and joint space narrowing; Symptoms – joint pain/swelling/instability

Goals of Therapy

- Ultimate goal is a complete remission
  - defined as the absence of:
    - (1) symptoms of active inflammatory joint pain,
    - (2) Morning stiffness,
    - (3) Fatigue,
    - (4) Synovitis on joint examination,
    - (5) Progressive radiographic damage,
    - (6) Elevated ESR or C-reactive protein

- Short of a complete remission:
  - control disease activity; pain relief; maintaining function essential for activities of daily living; maximizing QOL; and slowing the rate of joint destruction
Clinical Case

- Betty is 50-year-old woman who was just diagnosed with RA in 8 of her hand joints and in 8 feet joints. Her current pain is 4 out of 10 despite self-treatment with OTC naproxen 220 mg BID for the past 3 months, but her pain has not significantly improved.
- Her past medical history is significant for hypertension (treated with lisinopril 20 mg daily) and dyslipidemia (treated with dietary modifications).
- All of her recent laboratory tests are normal.

Polling Question…

- Which of the following recommendations is the most important for the chronic treatment of Betty’s RA?
  - Increase Naproxen to 500 mg BID
  - Add Prednisone 10 mg daily
  - Add Methotrexate 15 mg weekly
Pharmacotherapy for Rheumatoid Arthritis

- Disease modifying anti-rheumatic drugs (DMARDs)
  - Non-Biologic agents
  - Biologic agents
    - TNF-alpha blockers
    - Other biologic agents
- Corticosteroids
- Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- Essential treatment for patients with RA
- All patients are candidates for DMARD therapy
- Benefit:
  - Capable of reducing/preventing joint damage, preserve joint integrity/function
- Limitations:
  - may not prevent damage despite apparent control;
  - efficacy may not last long-term;
  - many agents have toxicities that require monitoring

Arthritis Rheum 2002;46:328-346
2008 ACR Guidelines

Determination of non-Biologic and Biologic DMARD treatment

Three parameters are needed:
- Duration of Disease
- Assessment of Disease Activity
- Determination of Prognostic Factors

ACR Guidelines

- Determination of non-Biologic DMARD treatment:
  - A: < 6 month duration

Arthritis Rheum 2008;59(6):762-84
ACR Guidelines

- Determination of non-Biologic DMARD treatment:
  - B: 6-24 month duration

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Disease Activity

Low
-----
Features of Poor Prognosis

MTX+SSZ+HCQ
LEF
MTX
SSZ

With
Without

High

Moderate or High

Features of Poor Prognosis

MTX+HCQ
LEF
MTX
SSZ

With
Without

Arthritis Rheum 2008;59(6):762-84
```

ACR Guidelines

- Determination of non-Biologic DMARD treatment:
  - C: >24 month duration

```
Disease Activity

Low or Moderate
-----
Features of Poor Prognosis

MTX+LEF
MTX+SSZ+HCQ
LEF
MTX
SSZ

With
Without

High

Features of Poor Prognosis

MTX+HCQ
LEF
MTX
SSZ

With
Without

Arthritis Rheum 2008;59(6):762-84
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## Non-Biologic DMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time to benefit</th>
<th>Usual Dose</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine [HCQ] (Plaquenil)</td>
<td>2-6 mo</td>
<td>200 mg BID</td>
<td>• Disease duration ≤ 24 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Low disease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No poor prognostic factors</td>
</tr>
<tr>
<td>Minocycline [MIN]</td>
<td>Up to 6 mo</td>
<td>100 mg BID</td>
<td>• Any disease duration All disease activity levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No poor prognostic factors</td>
</tr>
<tr>
<td>Sulfasalazine [SSZ]</td>
<td>1-3 mo</td>
<td>1,000 mg BID-TID</td>
<td>• Any disease duration All disease activity levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No poor prognostic factors</td>
</tr>
<tr>
<td>Methotrexate [MTX] (Rheumatrex, Trexall)</td>
<td>1-2 mo</td>
<td>7.5 to 20 mg Q week (may go to 25 mg/week)</td>
<td>• Any disease duration All disease activity levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Irrespective of poor prognostic factors</td>
</tr>
<tr>
<td>Leflunomide [LEF] (Arava)</td>
<td>1-3 mo</td>
<td>100 mg daily x 3 days, then 10-20 mg daily</td>
<td>• Any disease duration All disease activity levels</td>
</tr>
</tbody>
</table>

*Arthritis Rheum 2002:46:328-346*

## Methotrexate (MTX)
- Preferred first line DMARD, the “gold standard”:
  - ↓ signs/symptoms and structural damage; improves physical functioning
- CV disease mortality is lower in RA patients with methotrexate treatment
- GI intolerance is minimized by:
  - Splitting the weekly oral dose q 12 hours x 3
  - Supplemental folic acid 1 mg daily
  - Subcutaneous dosing instead of oral dosing
- Ethanol increases hepatotoxicity risk
- Routine laboratory monitoring is essential
Clinical Case, cont…

- After 3 years of methotrexate therapy, Betty’s pain is overall well controlled with 20 mg once weekly. Her other RA medications are folic acid, prednisone 10 mg daily, and ibuprofen 800 mg TID prn.
- All of her regularly monitored blood tests (CBC, LFTs, serum chemistries) are normal.
- She has routine X-rays of her hands. They show increased erosion of her affected joints compared to a year prior.

Polling Question…

- Which of the following is the most appropriate change to Betty’s regimen?
  - Increase methotrexate to 30 mg weekly
  - Add adalimumab
  - No change; re-evaluate in 6 months
Biologic DMARDs in RA

- Significant innovations in therapy
  - ↓ signs/symptoms and ↓ bone erosion
- For moderate/severely active RA in those who have failed ≥1 DMARD(s)
- Generally in combination with another DMARDs, but never another biologic
- Typical annual cost is $10,000 to $30,000 (methotrexate is ~$1500)
- Approximate time to benefit is 1 to 3 weeks

ACR Guidelines

- Determination of Biologic DMARD treatment :
  - A: < 6 month duration
ACR Guidelines

- Determination of Biologic DMARD treatment:
  - **B**: ≥ 6 month duration but failed MTX
  - **C**: ≥ 6 mo. duration but failed MTX combination therapy or other non-biologics
Role of Cytokines in RA

Up-regulated cytokines in RA

TNF-α

IL-1

Endogenous IL_1 receptor antagonist

Immune Cells in joints

Inflammation in synovial fluid

Cartilage degradation

Bone resorption

Bone EROSION

TNF-alpha Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Role</th>
<th>Adult RA Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Soluble recombinant human TNF-α receptor protein that binds/neutralizes TNF-α</td>
<td>Moderate/severely active RA</td>
<td>50 mg SQ QW</td>
<td>Potential sepsis, injection site reaction, rash, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Monoclonal (murine) antibody to TNF-α</td>
<td>For patients with an inadequate response to MTX as add-on therapy</td>
<td>5 mg/kg IV at 0, 2, 6 wks then q 8 wks; requires 2-hr administration at infusion center</td>
<td>Potential sepsis, infusion reactions, antibody development, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>Monoclonal (human) antibody to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>40 mg SQ QOW (QW if not on MTX)</td>
<td>Potential sepsis, injection site reaction, antibody development, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimiza)</td>
<td>Pegylated monoclonal antibody (does not have Fc region) to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>400 mg SQ at 0, 2 and 4 wks, then 200 mg q 2 wks or 400 mg q 4 wks</td>
<td>Potential sepsis, injection site reaction, antibody development, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Monoclonal (human) antibody to TNF-α (both soluble and transmembrane active)</td>
<td>Moderate/severely active RA in combination with MTX</td>
<td>50 mg SQ q month</td>
<td>Potential sepsis, injection site reaction, antibody development, worsening or new onset heart failure</td>
</tr>
</tbody>
</table>
Etanercept (Enbrel)

*Soluble recombinant human TNF-α receptor protein that binds and neutralizes TNF*

- Approved for moderate/severely active RA:
  - Can be used with or without methotrexate
  - Also approved in juvenile RA, ankylosing spondylitis, psoriasis, psoriatic arthritis
- Dosing: 50 mg SQ QW
- Adverse effects: Potential sepsis, injection site reaction, rash, worsening or new onset heart failure

### Biologic DMARDs: TNF-alpha Blockers

- **Chimeric monoclonal antibody**
  - infliximab
- **Human monoclonal antibody**
  - adalimumab
- **Human recombinant receptor/Fc fusion protein**
  - etanercept
- **PEGylated Humanized Fab fragment**
  - certolizumab pegol

*Weir et al. Therapy 2006;3(4):535-545*
Nomenclature of Monoclonal Antibodies

- Infix preceding “…mab” denotes the source
  - “a”  rat
  - “e”  hamster
  - “i”  primate
  - “o”  mouse
  - “u”  human
  - “xi” chimeric, 66% human
  - “zu” humanized, 95% human
- Infix preceding the source indicates the target
  - Ci(r) cardiovascular
  - Kin(n) interleukin
  - Li(m) immune
  - O(s) bone
  - Vi(r) viral

Infliximab (Remicade)

*Monoclonal (murine) antibody to TNF-α*

- Approved for active RA
  - Only for use in combination with methotrexate
  - Also approved in ankylosing spondylitis, Crohn disease, psoriasis, psoriatic arthritis, ulcerative colitis
- Dosing: 3 mg/kg IV at 0, 2, 6 wks then q 8 wks; 2-hr administration
- Adverse effects: Potential sepsis, infusion reactions, antibody development, worsening or new onset heart failure
- Contraindicated in moderate/severe heart failure, active infection, known murine allergy
Adalimumab (Humira)

*Monoclonal (human) antibody to TNF-α*

- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Can be used with or without another DMARD
  - Also approved in ankylosing spondylitis, Crohn disease, psoriasis, psoriatic arthritis
- Dosing: 40 mg SQ QOW (QW if monotherapy)
- Adverse effects: Potential sepsis, injection site reaction, antibody development, worsening or new onset heart failure

Certolizumab pegol (Cimzia)

*Pegylated monoclonal antibody (does not have Fc region) to TNF-α*

- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Can be used with or without another DMARD
  - Also approved in Crohn disease
- Dosing: 400 mg SQ at 0, 2, 4 wks, then 200 mg q 2 wks or 400 mg q 4 wks
- Adverse effects: Potential sepsis, injection site reaction, worsening or new onset heart failure
Golimumab (Simponi)

Monoclonal (human) antibody to TNF-\(\alpha\) (both soluble and transmembrane active)

- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Only for use in combination with methotrexate
  - Also approved in ankylosing spondylitis, psoriatic arthritis
- Dosing: 50 mg SQ once monthly
- Adverse effects: Potential sepsis, injection site reaction, worsening or new onset heart failure

Other Biologic DMARDs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Role</th>
<th>Adult RA Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra (Kineret)</td>
<td>Recombinant human interleukin-1 receptor antagonist</td>
<td>Moderate/severely active RA</td>
<td>100 mg SQ daily</td>
<td>Potential sepsis, injection site reaction, rash</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>Inhibits T-cell activation and decreases cytokine production</td>
<td>Moderate/severely active RA after an inadequate response to ≥1 DMARD(s), such as MTX or TNF antagonists.</td>
<td>500-1000 mg IV; second dose in 2-4 wks then q 4 wks; requires 30-min administration, or 125 mg SQ within 1 day, then once weekly</td>
<td>Potential sepsis, infusion reactions</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Monoclonal antibody that depletes CD20 B-cells</td>
<td>Moderate/severely active RA in combination with MTX after an inadequate response to ≥1 TNF antagonists</td>
<td>1000 mg IV 2 doses separated by 2 wks, may repeat course q16-24 wks; methylprednisolone 100 mg IV 30 min prior to reduce infusion reactions</td>
<td>Severe infusion reactions, mucocutaneous reactions, hepatitis B reactivation, cardiac arrhythmias, progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>Interleukin-6 receptor inhibitor</td>
<td>Moderate/severely active RA after an inadequate response to ≥1 TNF antagonists.</td>
<td>4 mg/kg IV q 4 wk; may increase to 8 mg/kg if needed.</td>
<td>Neutropenia, thrombocytopenia, dyslipidemia, hepatotoxicity</td>
</tr>
</tbody>
</table>
Anakinra (Kineret)

*Recombinant human IL-1 receptor antagonist*

- Approved for moderate/severe active RA in patients who have failed one or more DMARDs
  - Can be used with or without another DMARD
- Dosing: 100 mg SQ daily
- Adverse effects: Potential sepsis, injection site reaction, rash
- Contraindicated if known hypersensitivity to *e.coli* derived proteins

Abatacept (Orencia)

*Decreases production of several cytokines (TNF-α, IL-2, interferon-γ) by inhibiting T-cell activation*

- Approved for moderate/severe active RA after an inadequate response to ≥1 DMARD(s), such as methotrexate or TNF antagonists
  - Monotherapy or in combination with another DMARD
- Dosing: 500-1000 mg IV, then:
  - second IV dose in 2-4 wks then q 4 wks, or
  - 125 mg SQ within 1 day then once weekly
- Adverse effects: potential sepsis, infusion reactions
**Rituximab (Rituxan)**

*Monoclonal antibody that depletes CD20 B-cells*

- Approved for moderate/severe active RA after an inadequate response to ≥1 TNF antagonists
  - Must be used in combination with methotrexate
  - Also approved for certain cancers (lymphoma, leukemia)
- Dosing: 1000 mg IV 2 doses separated by 2 wks, may repeat course q16-24 wks; methylprednisolone 100 mg IV 30 min prior to reduce infusion reactions
- Adverse effects: severe infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hepatitis B reactivation, cardiac arrhythmias, progressive multifocal leukoencephalopathy

**Tocilizumab (Actemra)**

*Monoclonal antibody that inhibits the interleukin-6 receptor*

- Approved for moderate/severe active RA after an inadequate response to ≥1 TNF antagonists
  - Also approved for certain lymphomas and leukemias
- Dosing: 4 mg/kg IV q 4 wk; may increase to 8 mg/kg if needed
- Adverse effects: Neutropenia, thrombocytopenia, dyslipidemia, hepatotoxicity
Post-Marking Information Regarding Biologic Agents

- Infections and/or sepsis:
  - Temporarily stop if infection develops
  - Use with caution in immunosuppressed patients
- Can activate tuberculosis (TB):
  - PPD skin test prior to therapy
  - If positive, treat latent TB infection first
- Heart Failure with TNF-α blockers

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**Additional Information for Healthcare Professionals**

- Patients treated with TNFα blockers are at increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens.
- The bacterial pathogens *Legionella* and *Listeria* have been added to the Boxed Warning for the entire class of TNFα blockers.
- The risks and the benefits of TNFα blockers should be considered prior to initiating therapy in patients with chronic or recurrent infection and patients with underlying conditions that may predispose them to infection.
- Patients greater than 65 years old and patients taking concomitant immunosuppressants may be at greater risk of infection.
- Prior to initiating TNFα blockers and periodically during treatment, patients should be evaluated for active tuberculosis and tested for latent infection.
- Patients should be monitored for signs and symptoms of serious infections while taking TNFα blockers.
- Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Healthcare professionals should encourage patients to read the Medication Guide that accompanies their prescription for a TNFα blocker.

http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm#sa
Polling Question…

- Betty experiences an acute exacerbation of her RA, which is associated with 7/10 pain and acute inflammation in all of her affected joints. Which of the following regimens is most appropriate therapy?
  - Prednisone
  - High-dose Ibuprofen therapy
  - Oxycodone/Acetaminophen

Corticosteroids in RA

- **“Burst” Therapy:**
  - For acute exacerbations
- **Maintenance therapy:**
  - For active disease despite NSAIDs and after trial(s) of DMARDs
  - Joint damage may progress despite apparent control of symptoms
- **Bridging agent:**
  - For immediate symptom control after starting a new DMARD

Arthritis Rheum 2002;46:328-346
NSAIDs in RA

- For symptomatic pain management of RA, but not the sole treatment of RA
- Analgesic/anti-inflammatory effects; will not prevent joint destruction
- Best used prn (not regularly scheduled) to minimize risk of toxicity
- Major adverse reactions with chronic use:
  - Gastric bleeding, nephrotoxicity, increased risk of CV events
- Dosing:
  - Moderate to high doses for anti-inflammatory effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBOXYLIC ACIDS</td>
<td>Acetylated Salicylic Acid</td>
<td>Aspirin (Plain, Enteric Coated, Buffered)</td>
</tr>
<tr>
<td></td>
<td>Non-acetylated Salicylic Acid Derivatives</td>
<td>Na Salicylate / Mg Salicylate, Choline Salicylate (Arthropan®), Choline Mg Trisalicylate (Trilisate®), Salsalate (Disalcid®), Diflunisal (Dolobid®)</td>
</tr>
<tr>
<td></td>
<td>Carbo and Heterocyclic Acetic Acids</td>
<td>Diclofenac (Voltaren®, Cataflam®), Etodolac (Lodine®), Indomethacin (Indocin®), Sulindac (Clinoril®), Tolmetin (Tolectin®), Ketorolac (Toradol®)</td>
</tr>
<tr>
<td></td>
<td>Propionic Acids</td>
<td>Fenoprofen (Nalfon®), Flurbiprofen (Ansaid®), Ibufrofen (Motrin®, Rufen®, Nuprin®, Advil®), Ketoprofen (Orudis®), Naproxen (Naprosyn®, Alave®, Anaprox®, Oxaprozin (Daypro®)</td>
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<tr>
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<td>Antranilic Acids</td>
<td>Meclomenamate (Meclomen®), Mefenamic acid (Ponstel®)</td>
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<tr>
<td>ENOLIC ACIDS</td>
<td>Oxicams</td>
<td>Piroxicam (Feldene®), Meloxicam (Mobic®)</td>
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<tr>
<td>NON-ACIDIC</td>
<td>-</td>
<td>Nabumetone (Relafen®)</td>
</tr>
<tr>
<td>COX-2 Selective</td>
<td>-</td>
<td>Celecoxib (Celebrex®), Rofecoxib (Vioxx®), Valdecoxib (Bextra®)</td>
</tr>
</tbody>
</table>
NSAID-Associated Adverse Events

- Morbidity/mortality estimates:
  - Up to 25% of chronic NSAID users will develop ulcer disease
  - 2 to 4% will experience bleed or perforate (serious complications)
  - >100,000 hospitalizations/year for NSAID-associated complications
  - 7,000 to 10,000 deaths annually are directly related to NSAID use

Risks for NSAID Gastropathy

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk (1 to 2 risk factors)</th>
<th>Low Risk</th>
</tr>
</thead>
</table>
| • History of previously complicated ulcer, especially recent
  • Multiple (>2) risk factors | • Age >65 yrs
  • High-dose NSAID therapy
  • Previous history of uncomplicated ulcer
  • Concurrent use of aspirin (including low-dose), corticosteroids or anticoagulants | • No risk factors |

Celecoxib Long-term Arthritis Safety Study (CLASS)

- 8059 patients with arthritis, randomized, double-blind to
  - Celecoxib 400 mg BID
  - Ibuprofen 800 mg TID or diclofenac 75 mg BID
- 4573 received treatment for 6 mo.

CLASS: Subgroup Analyses

Patients on low-dose aspirin
- Primary Endpoint (p=0.92)
- Secondary Endpoint (p=0.49)

Patients not on low-dose aspirin
- Primary Endpoint (p=0.04)
- Secondary Endpoint (p=0.02)

Reflective Question…

Which long term toxicities related to NSAID therapy should pharmacists include when discussing chronic NSAID therapy with patients?

How is this different if you patient has a history of CV disease?
FDA NSAID Medication Guide

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

CV Risk with NSAID Therapy

- Meta-analysis of 31 trials, 116,429 patients with more than 115,000 patient years
  - Non-selective NSAIDs (ibuprofen, naproxen, diclofenac), COX-2 selective (rofecoxib, celecoxib, lumericoxib, etoricoxib) NSAIDs and placebo
  - Increased CV risk with all NSAIDs studied, but naproxen seemed least harmful.
- Overall relative risk is small; however, risk/benefit considerations in patients with CV risk is very important and required medication guides address these risk

BMJ 2011;342:c7086
Harmful Effects of NSAIDs among Patients with Hypertension and Coronary Artery Disease

- Post hoc analysis of the INVEST trial in 882 chronic NSAID users versus 21,694 non-chronic NSAID users
- Results after a mean of 2.7 years
  - More CV events in chronic NSAID users:
    - 4.4 vs. 3.7 events/100 pt-yrs
    - HR=1.47 (1.19-1.82) (p=0.0003)
  - Higher CV death risk in chronic NSAID users
    - HR 2.26 (1.70-3.01) (p<0.0001)


Duration of Treatment with NSAIDs and Impact on Risk of Death and Recurrent MI

- Cohort study in 83,677 patients with a history or prior MI in Denmark
  - 42.3% received NSAIDs some time after MI
  - 35,257 experienced death and/or recurrent MI
    - NSAID treatment associated with an increased death/recurrent MI soon after starting NSAID and throughout treatment
      - At 0 to 7 days HR=1.45 (1.29-1.62)
      - At > 90 days HR=1.55 (1.46-1.64)
      - Highest risk, diclofenac; Lowest risk, naproxen

Circulation. 2011;123:2226-2235.)
Guidelines for Prevention of NSAID-Related Ulcer Complications
American College of Gastroenterology Practice Guidelines

<table>
<thead>
<tr>
<th>Gastrointestinal Risk</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV Risk</td>
<td>NSAID alone</td>
<td>NSAID + PPI or misoprostol</td>
<td>Use alternative therapy if possible, or COX-2 selective NSAID + PPI or misoprostol</td>
</tr>
<tr>
<td>High CV Risk</td>
<td>Naproxen + PPI or misoprostol</td>
<td>Avoid NSAID or COX-2 selective NSAID</td>
<td></td>
</tr>
<tr>
<td>(Low-Dose Aspirin Required)</td>
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<td></td>
</tr>
</tbody>
</table>

Clinical Case, cont…

- Many years later, Betty’s RA is now treated with methotrexate 15 orally mg weekly, folic acid 5 mg once a week (separated from her methotrexate), adalimumab 40 mg SC every other week, prednisone 5 mg daily.
- Her past medical history still includes hypertension and dyslipidemia, but she had an MI last year.
- Her other medications are alendronate 70 mg weekly, calcium/vitamin D, lisinopril 40 mg daily, metoprolol 50 mg daily, aspirin 81 mg daily.
Polling Question…

- Which of the following is the most appropriate recommendation to reduce Betty’s CV risk?
  - Add simvastatin
  - Discontinue methotrexate
  - Increase the prednisone dose

Cardiovascular Risk in RA

Expert Recommendations:
- RA may be an independent CV risk factor, persistent inflammation is an additional risk factor;
- In patients requiring glucocorticoid therapy, use of the minimal effective dose to minimize CV risk;
- Methotrexate may protect against CV mortality;
- TNF-α antagonists are contraindicated in patients with RA and severe heart failure;
- Achieve recommended LDL-cholesterol goals;
- Consider statin therapy when needed;
- When aspirin is used, concomitant NSAID therapy may decrease antiplatelet effects and increase GI side effects

Rheumatoid Arthritis Conclusions


Cardiometabolic Risk
Global Diabetes/CVD Risk

- Insulin Resistance Syndrome
  - Lipids
  - BP
  - Glucose

- Overweight/Obesity
- Genetics
- Age
- Genetics

- Abnormal Lipid Metabolism
  - LDL-C
  - ApoB
  - HDL-C
  - Triglycerides

- Smoking, Physical Inactivity, Unhealthy Eating
- Hypertension
- Inflammation, Hypercoagulation

- Age, Race, Gender, Family History

Millions of Cases of Diabetes

Diagnosed and Undiagnosed Diabetes in the US


Criteria for Diagnosis of Diabetes
ADA 2012

1. A1C value $\geq$ 6.5%* (NEW in 2010)
2. FPG $\geq$ 126 mg/dL (Fasting is defined as no caloric intake for at least 8 hours)*
3. A 2-hour plasma glucose $\geq$ 200mg/dL during an 75-g oral glucose tolerance test (OGTT)*
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose concentration of $\geq$ 200mg/dL

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.


Reflective Question…

How strictly do you control A1C values in patients with diabetes?
ACCORD vs. ADVANCE: Compare and Contrast each study

- Glycemic targets in both groups
  - ACCORD - <6% vs. 7-7.9%
  - ADVANCE - <6.5% vs. “standard”

- Glycemic values achieved in both groups
  - ACCORD - 6.4% vs. 7.5%
  - ADVANCE - 6.5% vs. 7.3%

- Effects on complications and death
  - ACCORD - increased death, no change in CV events
  - ADVANCE - less complications, no change in death
Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE & VA Diabetes Trials

ADA/ACC Foundation/AHA

- A1C targets to reduce complications:
  - Microvascular: <7% is proven
  - Macrovascular: <7% is reasonable

- Individual A1C targets:
  - More stringent than <7% has small incremental benefits
  - Less stringent than <7% may be appropriate for some*

  * Patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions or those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.

Circulation 2009;119:351-357.

A1C: Goals Should be Individualized

**Reasonable A1C goal < 7%**
- Shown to reduce microvascular complications of diabetes
- If implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease

**More Stringent A1C goal <6.5%**
For selected individuals, if achieved without significant hypoglycemia:
- short duration of diabetes,
- long life expectancy,
- no significant CVD

**Less Stringent A1C goal <8%**
May be appropriate for patients:
- history of severe hypoglycemia
- limited life expectancy
- advanced complications
- extensive comorbid conditions

Goal Fasting Plasma Glucose (FPG): 70-130 mg/dL
Goal Post Prandial Glucose (PPG): <130 mg/dL

Composition of A1C


A1C Ranges

Contribution, %

ADA/EASD Algorithm for Type 2 DM

Tier 1: Well-validated core therapies

Diagnosis: Lifestyle + Metformin

Step 1

Lifestyle + Metformin + Basal Insulin

Step 2

Lifestyle + Metformin + Sulfonylurea

Lifestyle + Metformin + Intensive Insulin

Step 3

Tier 2: Less well validated core therapies

Lifestyle + Metformin + Pioglitazone

Lifestyle + Metformin + GLP-1 agonist

Lifestyle + Metformin + Pioglitazone + Sulfonylurea

Lifestyle + Metformin + Basal Insulin

**A1C 6.5 – 7.5%**
- **Monotherapy**
  - MET + GLP-1 or DPP4
  - TZD or GLP-1 or DPP4
- **Dual Therapy**
  - MET + GLP-1 or DPP4 or TZD or SU or Glinide
- **Triple Therapy**
  - MET + GLP-1 or DPP4 or TZD or SU or Glinide

**A1C 7.6 – 9.0%**
- **Dual Therapy**
  - MET + GLP-1 or DPP4 or TZD or SU or Glinide
- **Triple Therapy**
  - MET + GLP-1 or DPP4 or TZD or SU or Glinide

**A1C > 9.0%**
- **Drug Naive**
  - Under Treatment
  - Symptoms
  - No Symptoms

**Diabetes Drugs**

**Oral Agents**
- Biguanide
- Sulfonylurea (including meglitinides or secretagogues)
- Thiazolidinedione (TZD)
- DPP-4 inhibitors
- Alpha-glucosidase inhibitors
- Bromocriptine

**Injectable Agents**
- Insulin
  - Basal insulin
  - Prandial insulin
- GLP-1 agonists (incretin mimetics)
- Amynomimetic
Polling Question…

- Which of the following drugs for type 2 diabetes targets primarily lowering fasting blood glucose?

- Glyburide
- Metformin
- Stiagliptin
## Personalized Choices of Common Diabetes Medications

<table>
<thead>
<tr>
<th>Blood Glucose Targets</th>
<th>Key Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Hypoglycemia rare, weight neutral</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Hypoglycemia rare</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Most effective</td>
</tr>
<tr>
<td>Post-Prandial Blood Glucose</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Rapid acting</td>
</tr>
<tr>
<td>Glucosidase Inhibitors</td>
<td>Hypoglycemia rare</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Hypoglycemia rare, weight loss</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Hypoglycemia rare, weight neutral</td>
</tr>
<tr>
<td>Prandial Insulin</td>
<td>Most effective</td>
</tr>
</tbody>
</table>

### Comparison of Diabetes Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction</th>
<th>Severe Hypoglycemia</th>
<th>Weight Change</th>
<th>Daily Dosing Frequency</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>No</td>
<td>Neutral</td>
<td>1-2</td>
<td>Oral</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.4</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>Oral</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2</td>
<td>SC</td>
</tr>
<tr>
<td>Sulfonyleureas</td>
<td>1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2</td>
<td>Oral</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>0.5-1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td>Oral</td>
</tr>
<tr>
<td>Glucosidase Inhibitors</td>
<td>0.5-1.0</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>Oral</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.6-0.8</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>Oral</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>0.5-1.5</td>
<td>No</td>
<td>Loss</td>
<td>1-2</td>
<td>SC</td>
</tr>
<tr>
<td>Prandial Insulin</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>2-4</td>
<td>SC</td>
</tr>
</tbody>
</table>
ADA 2012 Standards of Care

- Meta-analyses suggest that overall, each new class of noninsulin agents added to initial therapy lowers A1C 0.9-1.1%
- New guidance for individualization of use of medication classes and combinations in patients with type 2 diabetes to be published in early 2012
- Less prescriptive than prior algorithms and will discuss all available medications

Metformin

- The only available biguanide
- First-line: Initiate at diagnosis unless contraindicated
- Generally well tolerated except GI side effects
- UKPDS trial demonstrated long term benefits

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>Relative Risk Reduction (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1997</td>
</tr>
<tr>
<td>Any Diabetes Related Endpoint</td>
<td>32% (0.0023)</td>
</tr>
<tr>
<td>Microvascular Disease</td>
<td>29% (0.19)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>39% (0.01)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>36% (0.011)</td>
</tr>
</tbody>
</table>

Polling Question…

- A 65 year old woman with type 2 diabetes is treated with metformin 1000 mg twice daily. Her A1C is 6.8%. However, his serum creatinine has risen to 1.7 mg/dL (was 1.0 mg/dL 2 years ago), and his CrCl is 40 mL/min. What would you do?
  - Replace metformin with another agent
  - Decrease the metformin dose by 50%
  - Keep metformin unchanged

Metformin Contraindications

1. Renal disease or dysfunction
   - SCr ≥1.4 mg/dL women, ≥1.5 mg/dL men
   - Abnormal creatinine clearance
2. Known hypersensitivity
3. Acute or chronic metabolic acidosis
4. Temporary d/c in patients receiving IV iodinated contrast materials

- Black Box Warning: Lactic Acidosis (very rare)

### Proposed recommendations for use of metformin based on eGFR

<table>
<thead>
<tr>
<th>eGFR (mL/min per 1.73 m²)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>• No renal contraindication to metformin</td>
</tr>
<tr>
<td></td>
<td>• Monitor renal function annually</td>
</tr>
<tr>
<td>&lt; 60 and ≥ 45</td>
<td>• Continue use</td>
</tr>
<tr>
<td></td>
<td>• Increase monitoring of renal function (every 3-6 months)</td>
</tr>
<tr>
<td>&lt; 45 and ≥ 30</td>
<td>• Prescribe metformin with caution</td>
</tr>
<tr>
<td></td>
<td>• Use lower dose (e.g., 50% or half maximum dose)</td>
</tr>
<tr>
<td></td>
<td>• Closely monitor renal function (every 3 months)</td>
</tr>
<tr>
<td></td>
<td>• Do not start new patients on metformin</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>• Stop metformin</td>
</tr>
</tbody>
</table>

- Additional caution is recommended in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

*Diabetes Care* 2011; 34:1431-1437.

### Thiazolidinedione: 2011 FDA Labeling Changes

**Rosiglitazone**
- Possible increased risk of myocardial infarction
- Risk evaluation and mitigation strategy (REMS)
- Restricted access and distribution

**Pioglitazone**
- Use for more than one year may be associated with bladder cancer
- Do not use in patients with active bladder cancer
- Use with caution in patients with prior bladder cancer; but, benefits should be weighed against the unknown risks of cancer recurrence

- Incidence rate and HR of bladder cancer with pioglitazone use:

<table>
<thead>
<tr>
<th></th>
<th>Median Bladder Cancer Incidence Rate (per 100,000 person-yrs.)</th>
<th>Fully Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Users</td>
<td>68.8 (61.7-73.6)</td>
<td>Ref</td>
</tr>
<tr>
<td>Ever Users</td>
<td>81.5 (64.7-98.4)</td>
<td>1.2 (0.9-1.5)</td>
</tr>
<tr>
<td>Duration of Therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>48.4 (29.0-67.8)</td>
<td>0.8 (0.6-1.3)</td>
</tr>
<tr>
<td>12-24 months</td>
<td>86.7 (52.0-121.4)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>&gt;=24 months</td>
<td>102.8 (71.7-133.8)</td>
<td>1.4 (1.03-2.0)</td>
</tr>
</tbody>
</table>

Diabetes Care 2011;34:916-922.

Incretin Hormones

- GI hormones that cause and increase in the amount of insulin released from beta cells after eating
  - GLP-1 (glucagon-like peptide-1)
    - Increases insulin release
    - Suppresses glucagon
  - GIP (glucose-dependent insulinotropic polypeptide)
    - Increases insulin release
The Incretin Effect in Type 2 Diabetes

Control Subjects
(n=8)

Patients With Type 2 Diabetes
(n=14)

The incretin effect is diminished in type 2 diabetes.

Role of Incretins in Glucose Homeostasis

Ingestion of food

Pancreas

Glucose-dependent

Insulin from beta cells
(GLP-1 and GIP)

Beta cells

Alpha cells

Glucose dependent

Glucagon from alpha cells
(GLP-1)

Blood glucose

+ Glucose uptake by muscles

+ Glucose production by liver

GLP-1 Agonists (Incretin Mimetics)

**Exenatide (Byetta)**
- Dosed SC twice daily 30-60 min before meals
- Do not take after meals or if skipping meal
- Approved for use with metformin, sulfonylurea, or TZD
- Approved for use with insulin glargine, +/- metformin, and/or TZD
- May provide better post-prandial glucose lowering

**Liraglutide (Victoza)**
- Dosed SC once daily regardless of meal
- May provide better fasting coverage and lower A1C
- Approved for use with metformin, sulfonylurea, or TZD
  - Not monotherapy
  - Not with insulin
- Black-box warning for thyroid c-cell tumors in rodents

GLP-1 Agonists: Considerations

- **Warnings:**
  - CrCl < 30 mL/min
  - Gastroparesis
  - History of pancreatitis
  - Hypoglycemia
- Dose titration needed
- Both available in dosing pen formulations
DPP-4 Inhibitors

- Three oral agents are available
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Linagliptin (Tradjenta)
- Approved for use as monotherapy or in combination with metformin or TZD
- Target post-prandial glucose lowering
- Well tolerated, but brand-name only

DPP-4 Inhibitors: Dosing

- **Sitagliptin (Januvia)**
  - CrCl ≥ 50 mL/min: 100 mg daily
  - CrCl 30-50 mL/min: 50 mg daily
  - CrCl < 30 mL/min: 25 mg daily
- **Saxagliptin (Onglyza)**
  - CrCl ≥ 50 mL/min: 2.5-5 mg daily
  - CrCl < 50 mL/min: 2.5 mg daily
- **Linagliptin (Tradjenta)**
  - 5 mg daily, no dose adjustment for CrCl
Comparison of Insulin

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak (hr.)</th>
<th>Effective Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Acting:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lispro</td>
<td>5-15 min</td>
<td>0.5-1.5</td>
<td>2-3</td>
</tr>
<tr>
<td>Short Acting:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular</td>
<td>30 min</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>Intermediate Acting:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NPH or Lente</td>
<td>1-3 hr</td>
<td>6-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Long Acting:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ultralente</td>
<td>3-5 hr</td>
<td>8-14</td>
<td>18</td>
</tr>
<tr>
<td>- Glargine</td>
<td>1 hr</td>
<td>None</td>
<td>24-28</td>
</tr>
</tbody>
</table>

Reflective Question...

Which types of patients with type 2 diabetes do you consider treatment with basal insulin?
Basal Insulin Therapy

- Indicate for patients with:
  - A1C >7% on oral agents
  - A1C >11%
  - Fasting blood glucose > 250 mg/dL
  - Random blood glucose > 300 mg/dL
  - Ketonuria/ketonemia
  - Weight loss, polydipsia, polyuria

Basal Insulin Therapy: Initiation and Titration

- Use insulin glargine, detemir or NPH
- **Start**: 10-25 U daily
  (0.4-0.5 U/kg mean requirement)
- **Titrate**: FBG x 3 days, calculate mean FBG

3-0-3 Protocol:  

<table>
<thead>
<tr>
<th>Mean FBG</th>
<th>Insulin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 130</td>
<td>↑ 3 U</td>
</tr>
<tr>
<td>80-130</td>
<td>no change</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>↓ 3 U</td>
</tr>
</tbody>
</table>

Summary: ↑ by 3 U every 3 days until FBG <130 mg/dL
New Medications for Type 2 Diabetes

Any new diabetes medications must prove CV safety before FDA approved

- Colesevelam (Welchol): Bile acid sequestrant
- Bromocriptine (Cycloset): Dopamine agonist

- On the horizon:
  - Once weekly exenatide (Bydureon)
  - Dapagliflozin: inhibits SGLT2 cotransporter in the kidney resulting in glucose excretion
  - Others

---

**TABLE 1**

**SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS**

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

![Table Image]

* The abbreviations used here correspond to those used on the algorithm (Fig. 3).
** The term ‘glinide’ includes both repaglinide and nateglinide.
Polling Question…
In patients at high risk for developing type 2 diabetes, which of the following is effective in preventing progression to diabetes?

- Metformin
- Pioglitazone
- Intensive Lifestyle Modifications

American Diabetes Association: Standards of Medical Care in Diabetes

- Metformin for prevention of type 2 diabetes may be considered in those with:
  - Impaired glucose tolerance
  - Impaired fasting glucose, or
  - A1C 5.7-6.4%, especially if BMI > 35 kg/m², age > 60 years, and women with prior gestational diabetes

  – The Diabetes Prevention Program:
  - Metformin 850 mg BID reduced incidence of diabetes in high risk individuals (although not as well as intensive lifestyle modification)

N Engl J Med 2002;346:393-403
Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance (ACT NOW)

- Examined whether pioglitazone can reduce the risk of type 2 diabetes in adults with IGT
- Double-blind trial in 602 patients with IGT randomized to pioglitazone 30 to 45 mg daily or placebo for a median of 2.4 yrs
- Primary Outcome: Development of diabetes

ACT NOW: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pioglitazone (n=303)</th>
<th>Placebo (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.0</td>
<td>51.5</td>
</tr>
<tr>
<td>Men/Women (%)</td>
<td>58/42</td>
<td>58/42</td>
</tr>
<tr>
<td>Hispanic/White/Black/Other (#)</td>
<td>79/156/57/11</td>
<td>75/171/44/9</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>33.0</td>
<td>34.5</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>127/74</td>
<td>128/74</td>
</tr>
</tbody>
</table>

all comparisons, p=ns

Data displayed as mean values, unless otherwise specified
ACT NOW: Results

Time to Development of Diabetes

- Hazard ratio, 0.28 (95% CI, 0.16–0.49)
  - P<0.001

ACT NOW: Other Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone (n=303)</th>
<th>Placebo (n=299)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events</td>
<td>151</td>
<td>121</td>
<td>0.03</td>
</tr>
<tr>
<td>Edema</td>
<td>39 (12.9)</td>
<td>19 (6.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Weight Gain (&gt; 1 kg)</td>
<td>205</td>
<td>128</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Events</td>
<td>26</td>
<td>23</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Other significant improvements with pioglitazone:
  - Insulin sensitivity, carotid intima-media thickening, hepatic transaminases, diastolic BP, HDL-cholesterol, triglycerides
Diabetes Conclusions