Pharmacology Review and Update 2016

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Disclosures

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Type 2 Diabetes: Review and Update of Pathogenesis and Pharmacotherapy
Objectives

• Discuss the etiology and pathophysiology of Type 2 diabetes and targets for pharmacological intervention

• Explain the basic and clinical pharmacology of the various classes of medications used to improve glycemic control in Type 2 diabetics.

• Recognize common side effects and the potential for serious, potentially life-threatening adverse effects that may occur with treatment with various antidiabetic medications
Diabetes Complications

**Microvascular**
- Nephropathy
- Neuropathy
- Retinopathy
- Possibly dementia

**Macrovascular**
- Cardiovascular disease
- Cerebrovascular disease
Insulin Resistance

Not an issue of loss of insulin receptors

Loss of coupling of insulin-receptor complex to intracellular signalling pathways
Normal Glucose Uptake in Peripheral Tissues – GLUT 4 transporter
Insulin Resistance & GLUT 4 transporter

Adipokines / FFAs
Inflammatory mediators
... Glucotoxicity
... Lipotoxicity

Insulin Receptor

Glucose
hyperglycemia

Muscle
Adipose
Normal Insulin Action in Liver

- GLUT2 is bi-directional depending on concentration gradient
- Insulin promotes cellular utilization of glucose
- Concentration gradient is inward
Insulin Resistance in Liver

- No signal to turn on cellular glucose utilization or storage
- Shift in biochemical pathways to glucose production
- Concentration gradient outward
Normal Beta Cell Function

- Inward flow (only) of glucose through GLUT2
- Initiates series of steps leading to membrane depolarization and insulin release
- Well coupled to glucose concentration in serum
Events leading to Beta Cell Dysfunction and Death
Natural history of type 2 diabetes

- Pre-diabetes (IFG, IGT)
- Diabetes Diagnosis
- Postprandial Glucose
- Fasting Glucose
- Insulin resistance
- Insulin level
- B-cell function
- Incretin effect
Targets of Medications

- Sulfonylureas
- Meglitinides
- GLP-1 agonists
- Gliptins
- Thiazolidinediones
- Metformin
- alpha-glucosidase inhibitors
- SGLT2 inhibitors
Medications

Biguanides
Sulfonylureas
Meglitinides
Thiazolidinediones
GLP-1 receptor agonists
DPP-4 inhibitors
SGLT-2 inhibitors
alpha-glucosidase inhibitors
colesevelam
dopamine-2 agonists
amylin mimetics
Metformin Effects in Liver

• Decreases normal energy by interfering with mitochondria
• Increases activity of back up pathway to restore energy
• AMP Kinase pathway flips cell to utilizing glucose / turns off gluconeogenesis
Metformin Effects in Muscle

- AMP-Kinase pathway also turns on
- Instrumental in shuttling GLUT4 to membrane surface
- Upregulates Adiponectin in adipose tissue – decreases inflammation – also increases glucose uptake for use in making triglycerides (decreases FFAs)
Metformin

Can reduce A1c 1 – 1.5%

**Advantages:**
- Low risk of hypoglycemia
- Not linked to weight gain
- Good effect on LDL cholesterol
- Good effect on triglycerides
- No interactions
- Useful in fixed-dose combinations
- Low cost
Metformin

Disadvantages:

Higher risk of GI side effects (nausea and diarrhea)

Risk of lactic acidosis

Cannot be used in moderate to severe CKD - caution in CHF

May affect vitamin B12 levels
TZDs (pioglitazone)

Agonists of PPAR gamma receptors

Decrease circulating FFAs

Increase glucose/lipid utilization within peripheral tissues.

Enhance glucose uptake (w insulin)

Suppress hepatic glucose production
Thiazolidinediones

Advantages

Low risk of hypoglycemia
Slight increase in HDLs
May decrease triglycerides
Convenient dosing
Generally well tolerated
Thiazolidinediones

Disadvantages

- Higher risk of heart failure
- Weight gain (5 to 10 pounds)
- Fluid retention, edema
- Bone fractures in females
- Increase in “bad” (LDL) cholesterol
- Slower onset of action
- Increased risk of bladder cancer
Sulfonylureas
Glipizide - Glyburide - Glimepiride

Sulfonylurea

ATP-gated Potassium Channel

Glut 2

PO₄

Krebs
ADP

ATP

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Ca²⁺

Insulin
Sulfonylureas

Advantages

- Powerful / Long acting
- A1C ~ 1.5%
- Benefits on both FG and PPG
- Inexpensive
Sulfonylureas

Disadvantages

- Hypoglycemia
- Weight gain
- May not work in 10% of patients
- May stop working over time
- P450 Drug Interactions
- Potential for hypersensitivity (low)
Sulfonylureas

CYP2C9

Cotrimoxazole
Metronidazole
Fluconazole
others
Meglitinides
repaglinide - nateglinide

Rapid onset – short half-life

Taken pre-prandially
from 1 - 30 minutes prior to meal

PPG > FG reduction

A1C ~ 0.5 - 1%
Meglinitidines

Disadvantages

Potential for weight gain
Frequent dosing
More expensive than sulfonylureas
Potential for hypoglycemia
(< sulfonylureas)
Cytochrome P450 interactions
Repaglinide Interactions

ethythromycin, clarithromycin, verapamil, azole antifungals, ritonivir, gemfibrazol, trimethoprim, metronidazole, fluconazole . . . others
Incretins

Gastric Inhibitory Peptide GIP
Glucagon-like Peptide-1 (GLP-1)
GLP-1

- Glucose-dependent insulin secretion
- Stimulates insulin biosynthesis
- Stimulates islet neogenesis / proliferation
- Increases Beta cell mass
  (decreases apoptosis)
- Inhibits glucagon secretion
- Slows gastric emptying
- Suppresses appetite (central effect)
GLP-1 secretion appears normal in diabetics.

GLP-1 actions appear diminished in diabetics.
Exenatide

Affinity and intrinsic activity at GLP-1 receptors

Poor substrate for DPP-4
## Available GLP-1 agonists

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>~A1C Decrease</th>
<th>Dosing Frequency</th>
<th>Reconstitution required</th>
<th>~Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide <em>(Byetta)</em></td>
<td>1 %</td>
<td>Twice DAILY</td>
<td>No</td>
<td>4 lbs</td>
</tr>
<tr>
<td>liraglutide <em>(Victoza)</em></td>
<td>1.5 %</td>
<td>Once DAILY</td>
<td>No</td>
<td>6 lbs</td>
</tr>
<tr>
<td>exenatide ER <em>(Bydureon)</em></td>
<td>1.5 %</td>
<td>Once WEEKLY</td>
<td>Yes</td>
<td>6 lbs</td>
</tr>
<tr>
<td>albiglutide <em>(Tanzeum)</em></td>
<td>1 %</td>
<td>Once WEEKLY</td>
<td>Yes</td>
<td>2 lbs</td>
</tr>
<tr>
<td>dulaglutide <em>(Trulicity)</em></td>
<td>1.5 %</td>
<td>Once WEEKLY</td>
<td>No</td>
<td>6 lbs</td>
</tr>
</tbody>
</table>
GLP-1 Agonists

Advantages

- Lower A1c 1 – 1.5%
- Significantly improve PPG levels
- Low incidence of hypoglycemia
- No weight gain / may cause weight loss

Direct benefits to other organs beyond benefit of glycemic control
GLP-1 Agonists

Disadvantages

- Injection only
- Expensive!!
- Nausea, vomiting common
- Potential for profound hypoglycemia
  (with insulin or oral secretagogue)
- Possibility of Pancreatitis (rare)
- Possibility of Thyroid C-cell tumors
  (boxed-warning)
Gliptins

sitagliptin - saxagliptin
linagliptin - alogliptin
Gliptins

Advantages

Orally available
No weight gain
Little risk of hypoglycemia
Few drug interactions
Generally well tolerated
Available in combinations
with metformin and pioglitazone
Gliptins
Disadvantages

Dizziness, headache, nasopharyngitis
Expensive
Weaker than most - A1C reductions ~0.7%
Patients with renal insufficiency require dosage adjustments (except Linagliptin)
Pancreatitis (necrotizing, hemorrhagic)
Increased risk of heart failure
SGLT2 Inhibitors

- canagliflozin
- dapagliflozin
- empagliflozin

Gluconeogenesis
Reuptake/elimination
SGLT2 inhibitors
SGLT2 Inhibitors

Advantages

- Lower both fasting and post-prandial
- Do not produce hypoglycemia
- Can lower SBP (3 to 5 mm Hg)
- Weight loss
SGLT2 Inhibitors
Disadvantages

- Vaginal yeast infection (7 – 10%)
- Balantitis (~ 5%)
- Urinary tract infections
- Increased risk of hypotension
- Increased risk of renal impairment
- Slight elevation in LDL cholesterol
- Expensive
SGLT2 Inhibitors and Diabetic ketoacidosis (DKA)

- FDA reports ≥ 20 cases in 2014 requiring ER or hospitalization
- Relatively rapid onset after SGLT2 treatment initiation
- Only half of cases associated with recognizable DKA-precipitating factor
SGLT2 Inhibitors and Diabetic ketoacidosis (DKA)

Early Symptoms:
- thirst
- frequent urination
- sweet, fruity breath
- confusion
- nausea
- stomach pain, vomiting
- difficulty breathing
SGLT2 Inhibitors and Diabetic ketoacidosis (DKA)

Patients should continue to take their other diabetes meds at usual doses and frequency with SGLT2 inhibitors . . .

Unless otherwise told to do differently by the HCP managing their condition
Psychopharmacology Update (and review)
Objectives

• Explain the most current hypothesis regarding the cause of depression, newer therapeutic targets, older and newer drugs being investigated for antidepressant action.
• Review second generation antipsychotics with regards to approved uses and basic and clinical pharmacology
• Understand the pathophysiology of ADHD and the rationale for use of stimulant medications
• Discuss treatment options, best medications and durations of treatment for anxiety
Amino Acid Neurotransmitters

Glutamate
Excitatory in the CNS

GABA
Inhibitory in the CNS
Antidepressants

Depression is a state of low mood aversion to activity that can affect a person's thoughts, behaviour, and physical well-being. Depressed people may feel sad, anxious, hopeless, helpless, worthless, irritable, or restless.
Types of Depression

- Reactive / situational depression
- Endogenous
  - Unipolar
  - Bipolar
- Psychotic
- Postpartum
- Drug-induced
50 Years of Theories as to what causes Depression

• **Monoamine hypothesis (1960s-1970s)**
  – Depression due to decreased availability of monoaminergic neurotransmitters (NE, DA, 5HT)
  – Antidepressants boost monoamine levels

• **Monoaminergic receptor hypothesis (1980s)**
  – Depression due to abnormalites in monoamine receptors
  – Chronic antidepressants alter sensitization state of receptors
50 Years of Theories as to what causes Depression

- **Hypothesis of signaling adaptation (1990s)**
  - Chronic antidepressants induce adaptive changes in post-receptor signaling cascades, and in gene expression

- **Hypothesis of neuroplasticity (2000s)**
  - Chronic antidepressant use changes neuroplasticity, cellular resilience, and synaptic plasticity - neurotrophic hypothesis of depression.
Hippocampal Pyramidal Neuron
Up to 30,000 excitatory connections
- Glutamate -
Up to 2,000 inhibitory connections
- GABA -
Most Recent Theory

- MRI shows volume of hippocampus decreased in patients with depression and PTSD
- Atrophy in the hippocampus most significant neuroanatomical findings in depressed patients
- Reduction in hippocampal volume directly related to the length of illness.

Additionally, atrophy of prefrontal cortex and amygdala - regions that control cognition, mood, and anxiety - has also been reported in patients with depression or bipolar disorder.
Most Recent Theory

- Glucocorticoids (Stress) cause neuronal atrophy and retraction of dendritic processes in hippocampus (very high levels of GC receptors) and down regulate BDNF - which influences neuronal survival, differentiation and synaptic strength.

Continuous electrical activity *required* to maintain synaptic connections with other neurons (use-it-or-lose-it arrangement), this downshift is part of the shrinking of connections.
Most Recent Theory

• Stress also decreases the proliferation of newborn granule cells in the dentate gyrus
  – The hippocampus is one of two brain regions where neurogenesis continues to occur
• Enriched environment, exercise and learning increase neurogenesis, while aging, stress and exposure to drugs of abuse decrease neurogenesis
• LTP and LTD
Brain-Derived Neurotrophic Factor (BDNF)

- Supports survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses
- Highly active in hippocampus, cerebral cortex, basal forebrain—areas vital to learning, memory, higher thinking
  - Important for long-term memory
- Also secreted by contracting skeletal muscle – plays role in muscle repair, regeneration, differentiation.
Glutamate and Depression

From:
Dopamine and Glutamate in Psychiatric Disorders [Hardcover] Werner Schmidt and Maarten E. A. Reith (EDs) Humana Press; 2005 (p218)
The “chemical imbalance” and possible symptoms

- **↓ Dopamine**
  - Anhedonia
  - Poor motivation

- **↓ Norepinephrine**
  - Anergy
  - Psychomotor retardation

- **↓ Serotonin**
  - Apathy
  - Dysthymia
  - Incessant Ideation
Treatment Options

Antidepressants

- SSRIs
- SNRIs
- DRIs
- TCAs
- 5HT-2 Antagonists
- Mixed mechanisms
- MAOIs

Supplements
- ECT
- Psychotherapy
vilazodone (Viibryd)

- Unique Antidepressant
- Dual Mechanism
- serotonin reuptake inhibitor
  - About similar in action and potency to SSRIs
- 5-HT1A receptor partial agonist
  - Similar to Buspirone
vilazodone

• Eight week clinical trials
  – After 8 weeks, significantly higher response rate than placebo.
  – Considered to be well tolerated and reported adverse effects ranged from mild to moderate in intensity
    • Side effects included diarrhea, nausea, and somnolence
    • More likely to occur than with standard SSRI
vilazadone

- **Place in therapy**
- No data showing that it is better than any other antidepressant for either anxiety or depression.
- Caution in interpreting sexual side effect data
  - Did not control for pre-treatment sexual dysfunction in both placebo and treatment groups
  - Need to look at it in patients who don't *already* have the sexual dysfunction to begin with.
  - FDA has standards for antidepressant makers to claim their products do not cause sexual dysfunction
  - According to FDA, clinical data on this for vilazadone has officially barred touting vilazadone as a low sexual side effect antidepressant.
levomilnacipran (Fetzima)

- Active enantiomer (levo) of milnacipran
- Not approved for the management of fibromyalgia
- Most noradrenergically active of the SNRI class of antidepressant drugs – almost selective for NE (NSRI vs SNRI)
- Dose response opposite of venlafaxime - greater noradrenergic selectivity at low doses and increasing effect on serotoninergic neurotransmission with upward dose escalation.
• **Common SEs**
  – Irritability, erectile dysfunction (dose-related), constipation, tachycardia, urinary hesitation (dose-related), palpitations, vomiting
• **Interactions**
  – Strong CYP3A4 inhibitors: Do not exceed 80 mg/day
  – Serotonin Syndrome with other serotonin meds
• **Caution**
  – Renal impairment – dose adjustment
• **Warnings**
  – Black Box re: antidepressants and suicide risk
Place in Therapy?

- May be advantageous among subsets of depressed patients, i.e., those with prominent fatigue, anergia, more pronounced functional impairments (low NE), or treatment-emergent sexual dysfunction (from 5HT).
- May be useful for patients not responding to, or intolerant of, SSRIs.
vortioxetine (Brintellix)

- Inhibition of serotonin (5-HT) reuptake
  - Also an agonist at 5-HT$_{1A}$ receptors, partial agonist at 5-HT$_{1B}$ receptors and antagonist at 5-HT$_3$, 5-HT$_{1D}$ and 5-HT$_7$ receptors
  - Considered first and only compound with this combination of pharmacodynamic activity.
  - Contribution of each of the above to the antidepressant effect not been established.

- Six clinical studies conducted for FDA’s approval
- Shows some improvement by 2 weeks but probably not clinically relevant
vortioxetine

- Most common side effects:
  - nausea, constipation, vomiting, headache
- Some sexual dysfunction (> placebo)
- Little or no weight gain
- Long half-life (~ 66 hrs)
- CYP2D6 metabolism
  - Caution with strong inhibitors (fluoxetine, paroxetine, bupropion) or strong inducers (rifampin)
  - Be aware for Poor 2D6 Metabolizers
- Like all other serotonergic drugs
  - additive risk for Serotonin syndrome
Place in Therapy?

- Tolerability is comparable with other serotonergic antidepressants
- Efficacy no better than other current agents
- May be a useful alternative to serotonergic antidepressants for some patients who are partial responders or nonresponders
- $$$
- Caution: possible name confusion vs Brillinta (ticagrelor)
Factors to Consider in Choosing an Antidepressant Medication

- **Safety, tolerability, cost**
- Ease of administration
  - Daily number of doses
  - Titration schedule
- Patient preference
- Nature of prior response to medication
- Co-occurring psychiatric or general medical conditions
  - anticipated side effects
  - potential drug interactions
- Half-life (concern for discontinuation syndrome)
### Characterizing “real world” Treatment Outcomes

<table>
<thead>
<tr>
<th>STATE</th>
<th>OBJECTIVE CRITERION</th>
<th>CLINICAL STATUS</th>
<th>PREVALENCE (in studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>≥75% reduction in Ham-D</td>
<td>No residual psychopathology</td>
<td>~ 40%</td>
</tr>
<tr>
<td>Response</td>
<td>50-74% decrease in HAM-D</td>
<td>Substantially improved, but with residual sxs</td>
<td>~ 25%</td>
</tr>
<tr>
<td>Partial response</td>
<td>25%-49% decrease in HAM-D</td>
<td>Mild-moderate improvement</td>
<td>~ 10%</td>
</tr>
<tr>
<td>Non response</td>
<td>&lt; 25% decrease in HAM-D</td>
<td>No clinically meaningful response</td>
<td>~ 25%</td>
</tr>
</tbody>
</table>
Considerations for poor response to antidepressants

- Incorrect primary diagnosis
- 2\textdegree{} to meds (iatrogenic)
  - beta-blockers, sedatives, corticosteroids, etc
- 2\textdegree{} to comorbidity
  - Comorbid psychiatric disorders
    - Personality disorders, Anxiety, Substance abuse
    - Prior emotional / sexual abuse
  - Comorbid non-psych disorders
    - CVD, Chronic pain, Parkinson’s, brain neoplasms, vitamin deficiencies, hypothyroidism, alcoholism.
- Underestimating severity / chronicity of depression
Considerations for TRD?

- **Patient factors**
  - Compliance
  - Unusual pharmacokinetics
    - e.g., CYP2D6 UEMs

- **Provider factors**
  - Dose too low
  - Dose too high
    - side effects
  - Inadequate length of treatment
Pharmacological Options
After Failure of First Antidepressant

**Switching** - Change to different antidepressant

- Same class
  - Better tolerability? – ie., paroxetine $\Rightarrow$ sertraline
  - Subtle differences between SSRIs
- Different class
  - Remission rates higher for patients not responding to SSRI switched to non-SSRI vs another SSRI
  - After two negative SSRI trials- preferable to choose agent that affects different neurotransmitter
Pharmacological Options
After Failure of First Antidepressant

Augmentation

• Add 2\textsuperscript{nd} Antidepressant
  – Rational combinations
  – eg., SSRI + NE or DA enhancers
    • Bupropion, $2^0$ TCA (nortriptyline), buspirone
    • Use caution with SSRIs + TCAs
    • Use caution with combining CYP2D6 drugs
• Add a non-antidepressant
Antidepressant Augmentation

Adding Buspirone or Bupropion to SSRI

– Buspirone – 5HT1A agonist
– Bupropion – NE / DA reuptake inhibitor

• Buspirone augmentation (of citalopram) = bupropion in STAR*D
• Both strategies helped improve ~50% of patients, with remission rates of ~30% for both treatments.
• Mean doses/day:
  – bupropion=267mg; buspirone=41mg
  – Bupropion better tolerated
• Both may help with SSRI- sexual dysfunction
Antidepressant Augmentation

Antipsychotics

- May reduce anxiety, agitation, psychotic symptoms
- May ↑ mood
- FDA Approved as adjunct
  - **Aripiprazole** (2 – 5 mg/d)
    » Increase DA activity
    » Also partial agonist at 5 HT1A receptors
  - **Quetiapine** (150-300 mg/day)
    » Active metabolite of quetiapine inhibits the activity of NE reuptake pumps
Other Augmentation Possibilities

• **Folic Acid Deficiency?**
  – Several epidemiologic studies over the years have shown a relationship between low serum and/or red blood cell folate and depression and other neuropsychiatric conditions
  – Folate deficiency → Depression?
  – Depression → Folate deficiency?
Folate and Neurotransmitters

NMDA receptor agonist

Serotonin

5-HTP

Tryptophan

L-DOPA

Tyrosine

Dopamine

Norepinephrine

Enhanced synaptic connectivity

Neuroplasticity

Stress Depression

Antidepressant

BDNF

Glutamate

NMDA

Coriand

PKA

pCREB

PAO

ROS

Glucose uptake

ROS

GSK-3

ATF

BAD

Bcl-2

RSK-2

Enhanced synaptic connectivity
Other Augmentation Possibilities

• Folic Acid Deficiency?
• Mounting evidence suggest that while folic acid alone does not have antidepressant actions, it may increase antidepressant efficacy.
  – But which folate product?
  – Folate must be converted to methylfolate for use as cofactor in monoamine neurotransmitter synthesis

  – Folate vs methylfolate supplementation?
Folate and Depression

• Options:
  – OTC folic acid supplements (at least 500 mcg/day) might be worth a trial before going to augmenting drugs such as antipsychotics, buspirone, thyroid, lithium, etc.
  – Methylfolate products (ie., Deplin) may be an option if folic acid is not effective.
  – No definitive evidence it works better – just hypothetically
  – Much more expensive than simple folic acid
Ketamine

- NMDA (glutamate) receptor antagonist
- Studied more than a decade ago for Depression
- Improves mood within hours in treatment resistant depressed patients.
- Review by Duman & Aghajanian (2012) in “Science” calls this “…perhaps the most important discovery in half a century.”
- About a 60 - 70% response rate in a matter of hours.
- Typically response lasts for 3 – 7 days, up to a couple of weeks
Ketamine

- Single IV infusion
- Rapid benefit (< 24 hours)
- Antidepressant effects independent of its transient psychoactive effects \(t_{1/2} = 2 - 3\) hrs
- Generally well tolerated
  - Associated with dissociative symptoms, hallucinations
- Also recently shown to be beneficial by nasal inhalation
Ketamine

Experimental Studies* Suggest Ketamine to Be Rapid, Effective Treatment for Refractory Depression, Suicidality

RESPONSE RATE AT 1 DAY COMPARED TO >8 WEEKS WITH CURRENT RXs IN REFRACTORY POPULATIONS

- % Response
  - Ketamine: 53%, 71%
  - Placebo: 6%

RAPID DECREASES IN HIGH SUICIDAL IDEATION WITH SINGLE DOSE KETAMINE

Scale for Suicidal Ideation (SSI)

- Baseline SSI
- High SSI (≥4)
- Low SSI (≤3)

* Proof of concept studies from academic sources.
Nitrous Oxide

- Similar action as ketamine on glutamate NMDA receptors
- 50-60 minute treatment (similar to dental dosing - 50%NO / 50% O2)
- Small study (2014) showed treatment response in 20% of the [TRD pts] and remission in 15%
- Benefit sustained for at least 24 hours and in some patients for 1 week
- NO differs from ketamine in lacking use-dependence and is not a trapping open channel blocker (+ no psychotic SEs).
In the pipeline - GLYX 13

- Agent with more selective action than ketamine
  - Partial agonist at glycine site on NMDA receptor
- Has relatively rapid antidepressant effect (24 – 48 hr) without significant dissociative symptoms.
- Must be administered as an infusion
- Antidepressant effect lasts up to 1 week
- Fast tracked by FDA in March 2014
- Currently in Phase 2b clinical trials
In the pipeline - NRX-1074

- Second-generation follow-on to GLYX
- Similar to GLYX-13, but is orally active and significantly more potent.
- Drug is in Phase 2 clinical development for the treatment of major depressive disorder (MDD).
Antipsychotics

Major clinical uses
- Acute psychosis
- Schizophrenia
- Psychotic depression
- Bipolar disorder
- Adolescents: agitation, conduct disorder
- Elderly: dementia with agitation, delirium
Antipsychotics

1st Generation

Low Potency
Thorazine
Mellaril

High Potency
Haldol
Stellazine

2nd Generation

Atypicals
Clozaril
Risperdal
Zyprexa
Seroquel
Geodon
Abilify
Others

Florid Symptoms = Dopamine Blockade
Dopamine Pathways

Nigrostriatal Pathways

Mesolimbic Pathway

Mesocortical Pathways

Tuberoinfundibular
2nd Generation Antipsychotics

Haloperidol

Risperdal

Seroquel

Zyprexa

clozapine
Ziprasidone (Geodon)

- Schizophrenia and acute treatment of mania and mixed states associated with bipolar disorder
- Approved dose range considered low by many
- SEs: sedation, insomnia, orthostasis
  - may cause EPS
- Weight neutral
- May prolong QT-interval - caution
  - initial cardiac concerns appear insignificant for most
- Availability
  - oral capsules and IM (for acute agitation)
- Must be taken with fat-containing meal/snack
Aripiprazole (Abilify)

- Atypical antipsychotic drug known as 'dopamine system stabilizer' (DSS)
- Partial dopamine agonist - distinct mechanism of action - also antagonizes serotonin (5HT2A)
- Can be either activating or sedating
  - SE - nausea most common, dose related akathesia
- Overall efficacy in schizophrenia appears similar to haloperidol & risperidone
- Approved as adjunct to antidepressants for depression
Aripiprazole

- Metabolized by the Cytochrome P450 isoenzymes 3A4 and 2D6
- Some somnolence, orthostatic hypotension
- **Akathisia**, headache, somnolence or weakness, nausea, vomiting, constipation, light-headedness
- No weight gain
- Oral, ODTs, solution for injection
iloperidone (Fanapt)

- Treatment of adults with schizophrenia
- Dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia and weight gain
- Weight gain
- Associated with only modest elevations of prolactin and a low incidence of extrapyramidal symptoms
asenapine (Saphris)

• Approved for the treatment of both schizophrenia and acute mania or mixed episodes in bipolar I disorder.
• First drug to receive initial approval for both indications simultaneously.
• Combination of antagonist activity at D2 and 5-HT2A receptors.
• Available in 5 or 10 mg sublingual tablets.
lurasidone (Latuda)

• Tenth approved SGA
• Approved for the treatment of schizophrenia
  – pending review and approval for bipolar disorder
• Long half-life (18 hrs)
  – Once daily dosing with no titration
• No weight gain, increase in lipids or glucose, no increase prolactin, no QTC prolongation
• Akathisia in 22% of study patients
• Metabolized by CYP3A4
Brexpiprazole (Rexulti)

- FDA-approved indications
- Adjunctive therapy for the treatment of major depressive disorder
  - Recommended dose: 2 mg/day
  - Maximum dose: 3 mg/day
- Treatment of schizophrenia
  - Recommended dose: 2-4 mg/day
  - Maximum dose: 4 mg/day
Brexpiprazole (Rexulti)

• Partial agonist:
  – D2 receptor
  – D3 receptor
  – 5HT1A receptor

• Antagonist
  – 5-HT receptors: 5HT2A
  – 5HT2B
  – 5HT7

• Antagonist at alpha receptors:
  – Alpha-1A, 1B, 1D, 2C

Brexpiprazole has a clinical and pharmacological profile very similar to aripiprazole.
Brexpiprazole (Rexulti)

• Drug interactions

• Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors
  • Strong CYP2D6 or CYP3A4 inhibitors
    – Administer half of usual dose
  • Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors
    – Administer a quarter of usual dose
  • Known CYP2D6 Poor Metabolizers taking strong/moderate CYP3A4 inhibitors
    – Administer a quarter of usual dose
Brexpiprazole (Rexulti)

- **Patients Taking CYP3A4 Inducers**
- **Strong CYP3A4 inducers**
  - Double the usual dose and further adjust based on clinical response
- Brexpiprazole may be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine)
• Adverse reactions
• Adverse effects occurring in ≥5% of patients taking brexpiprazole and more frequently than in those taking placebo in at least 1 clinical trial included:
  – akathisia, weight gain, headache, and somnolence. Mean weight gain over 6 weeks was 1.0-1.3 kg greater with brexpiprazole 2 mg/day than with placebo.
Cariprazine (Vraylar)

- FDA-approved indications
- Treatment of schizophrenia
  - Starting dose: 1.5 mg/day
  - Recommended dose: 1.5 mg to 6 mg/day
- Acute treatment of manic or mixed episodes associated with bipolar disorder
  - Starting dose: 1.5 mg/day
  - Recommended dose: 3 mg – 6 mg/day
Cariprazine (Vraylar)

- **Partial agonist at:**
  - D2 receptors
  - D3 receptors
  - 5-HT1A receptors

- **Antagonist at:**
  - 5-HT2B receptors
  - 5-HT2A receptors

- **Antagonist at (moderate to low affinity):**
  - H1 receptors
  - 5-HT2C receptors

It has been suggested that 5-HT1A and 5-HT2B receptor effects could improve negative symptoms via activation of DA neurotransmission in frontocortical regions. To date, no conclusive data from RCTs support this.
Cariprazine (Vraylar)

• Drug interactions
• Metabolized by CYP3A4
  – Strong CYP3A4 inhibitors: reduce dosage by half
  – CYP3A4 inducers: do not recommend use with cariprazine
Cariprazine (Vraylar)

• Adverse reactions
  – Schizophrenia trials:
    • extrapyramidal symptoms and akathisia
  – Bipolar mania trials:
    • extrapyramidal symptoms, akathisia, dyspepsia, somnolence, restlessness
Weight Gain from SGAs

- Typically emerges early
- Associated with adherence issues
- Often reversible
- May become precursor for Metabolic Syndrome
  - Especially: Diabetes, Hyperlipidemia
- Clozapine = Olanzepine > Riperidone = Quitiapine >> Aripiprazole = Ziprasidone
Incidence of > 7% Increase in Body Weight in Short term Trials
Shift in Risk Perception of Antipsychotics

Past Areas of Concern
- Tardive Dyskinesia
- Sedation
- Weight Gain
- Insulin Resistance
- Hyperlipidemia
- CHD
- Prolactin

Current Medical Realities
- Diabetes
- TD
- Weight Gain
- Prolactin
- Hyperlipidemia
- Insulin Resistance
- Coronary Heart Disease
- Sedation
#### Clinical Considerations When using SGAs

<table>
<thead>
<tr>
<th>Inquiry</th>
<th>Measure</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history:</td>
<td>Height</td>
<td>Fasting Glucose</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Weight</td>
<td>Fasting Lipids</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Waist circumference</td>
<td></td>
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<tr>
<td>CHD (MI or Stroke)</td>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
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</tr>
</tbody>
</table>
ADHD and STIMULANTS
**Frontal Cortex**
- Reinforcement
- Response Consistency
- Inhibition of impulses

**Prefrontal Cortex**
*Executive Function*
- Working Memory
- Selective attention
- Organization
- Hierarchical Thinking

**Brain Stem**
- Sensory input
- Brain arousal
Pathophysiology

MRI studies in ADHD have found:

Decreases in total cerebral volume, smaller anterior regions in the corpus callosum, left-side prefrontal cortex, particularly the posterior-inferior lobules.

PET scans show reduced perfusion to the bilateral frontal areas, the caudate nuclei, and the basal ganglia.
Neurotransmitters

• NE is critical to reasoning, learning, problem solving, priority setting, organizational thought

• NE functions in maintaining arousal, regulating excitability related to danger, contributes to memory storage and retrieval

• DA is involved in motor control, and interacts with NE in the frontal lobe to maintain attention
Pathophysiology

Some studies suggest a defect in the dopamine receptor **D4 (DRD4)** receptor

DRD4 receptor uses DA and NE to modulate attention to and responses to an environment.

Some studies report an **overexpression** of dopamine transporter-1 (**DAT1**).

Other studies suggest a decrease in available DA transporters – secondary to decreased production or release of DA.
Pathophysiology

Normal Transmission

Dopamine Transporter (DAT-1)

Presynaptic Neuron

Postsynaptic Neuron

Dopamine Receptors

Signal!
Pathophysiology

Overexpression of Dopamine Transporter DAT-1

ADHD

Presynaptic Neuron

Postsynaptic Neuron

Dopamine Receptors

Noise
Pathophysiology

Smaller Size + Less perfusion + Decreased NE / DA

Lack of connectivity of key brain regions that modulate attention, stimulus processing, and impulsivity

Also

Reward and Motivation
Stimulant Medications

Methylphenidate (MPH)
(eg. Ritalin, Concerta, Metadate, others)

Amphetamine
(eg. Dexedrine, Adderall)

Although producing slightly different cellular and molecular effects, the final outcome for each drug class - an increase in monoamine activity - is quite similar.
History of Stimulant Formulations

1937 - IR $d,l$-amphetamine
1940 - IR $d$-amphetamine
1950 - IR methylphenidate
1970 - IR pemoline
1980 - SR methylphenidate
2000 - Concerta
2001 - Metadate CD, Focalin, Adderall XR,
2002 - Ritalin LA
2006 - Daytrana (patch)
2007 – Vyvanse

2016

**Methylphenidate**
- Aptensio XR
  - 1st 12-hour sprinkle cap
- QuilliChew ER
  - 1st 8-hour chewable tab

**Amphetamine**
Adzenys XR-ODT
- new once-daily ER forms - orally disintegrating tab
*Dyanavel XR*
- first suspension
Mechanism of Action
Amphetamine Derivatives

Amphetamine
Mechanism of Action
Methylphenidate Derivatives

Methylphenidate affects DA > NE.
Mechanism of Action
Methylphenidate Derivatives

Overexpression of Dopamine Transporter
DAT-1

Presynaptic Neuron

Postsynaptic Neuron

ADHD

Dopamine Receptors

Postsynaptic Neuron
Clinical Pros and Cons of “Stimulants”

Considered 1st Line Treatments for ADHD (without comorbidities)

Advantages:

- safest of the medications (when used as directed)
- lowest “adverse” effects
- most robust short term effect (~ 85% benefit)
- wide therapeutic window in dosing schedules
- Many different options for formulations
Clinical Pros and Cons of “Stimulants”

Disadvantages:

• All Schedule II drugs
• Abuse potential
• Diversion - Selling or giving to others
Stimulant Side Effects

- Anxiety, Insomnia
  - dose/formulation related
- Anorexia, weight loss
  - amphetamine/sustained release worse
- Sympathomimetic effects
  - headaches, elevated BP / HR
- Rebound (end of dose phenomenon)
  Irritability, hyperactivity, impulsivity > untreated symptoms
  Dinner / Homework time 5-9 p.m.
  Increases family stress
  May require short acting stimulant after school hours
Interactions

Primarily Pharmacodynamic –
Additive effects with other stimulant-like medications:
- Insomnia
- Arrhythmias, tachycardia
- Irritability
- Nervousness
- Seizures

B-agonists, OTC decongestants, dietary supplements or lifestyle interactions possible
Stimulant Formulations

Short-Acting – Immediate Release Formulations

*Ritalin, Metadate, Focalin, Dexadrine, Adderall*

- Good for flexible dosing options
- Achieve faster peak levels
- Achieve higher peak levels
  - may be better for some patients
- Capable of very low dose titrations
  - may be better for very young children
- Rapid on - rapid off: avoid “feeling on” all day
- Useful as boosters
Stimulant Formulations

Extended-Release Formulations

Concerta, Adderall XR, Focalin-XR, Metadate CD, Ritalin-LA

• Generally Favored
• Easier, for parents and patients
• No need for in-school dosing
• Stability of effect for most of day
• Improved treatment adherence
• Less abuse/misuse potential
• Better profile for pts at risk for substance abuse
Choosing: Methylphenidate or Amphetamine?

- Patient and/or clinician factors
  - Family history (ie, positive or negative response)
  - Patient preference/bias
  - Clinician preference/bias
  - Clinical relevance of the type of encapsulation or delivery
    - Sprinkles for food (able with Adderall XR; not with Concerta)
    - Patch (Daytrana) only with methylphenidate

- Cost / Insurance Factors
“Drug Holidays”

Periodic discontinuation of medication in order to:
1. Assess the patient's requirements
2. Decrease tolerance
3. Limit suppression of linear growth and weight

Not mandatory
Some patients may not need a holiday
In some cases Holiday may be counterproductive
What about Comorbidities?

When stimulants may not be best initial choice:

- **Tic Disorders**
  - Alternatives
    - Atomoxetine
    - Stimulant, with $\alpha_2$-agonist or SGA

- **Anxiety Disorders**
  - Atomoxetine
  - Stimulant, with SSRI for anxiety
What about Comorbidities?

When stimulants may not be best initial choice:

- **Substance Abuse Disorders**
  - Atomoxetine
  - Methylphenidate Patch
  - Vyvanse

- **Depression, mania, aggression**
  - Treat more severe morbidity first
    - Depression, aggression
Primary Anxiety Disorder Types

- Generalized Anxiety Disorder
- Panic Disorder
- Obsessive Compulsive Disorder
- Post-Traumatic Stress Disorder
- Social Phobia
Anxiety

• Placebo response rate with GAD is about 40%
• Because of long term nature of disorder, treatment plan must be carefully thought out
• Drug treatment of GAD is sometimes seen as a 6 to 12 months treatment, some evidence indicates that treatment should be long term, perhaps life long
• About 25% of patients relapse in the first month after the discontinuation of therapy and 60 to 80% relapse over the course of next year
Different types have different etiologies

- Autonomic imbalance / hyperarousal state locus ceruleus
- Dorsal & medial raphe nuclei (Serotonin imbalance)
- Chronic hyperventilation & CO$_2$ receptor hypersensitivity
- Hypersensitive to stress
- Decreased GABAergic function

Amygdala / orbitofrontal cortex
Dorsal raphe nuclei
Locus Ceruleus
Benzodiazepines - Anxiolytics

- chlordiazepoxide (Librium®)
- diazepam (Valium®)
- clonazepam (Klonopin®)
- clorazepate (Tranxene®)
- lorazepam (Ativan®)
- oxazepam (Serax®)
- alprazolam (Xanax®)
Benzodiazepines

**Advantages**
- Effective, mainly in somatic symptoms
- Fast onset of action
- Reproducible response

**Disadvantages**
- Less effective for psychic symptoms
- Dependence issues with long-term use
- Withdrawal symptoms and rebound anxiety
- Cognitive and psychomotor impairment
- Drug-drug interactions (CYP 3A4)
Benzodiazepines
Mechanism of Action

- Bind to the benzodiazepine site on GABA$_A$ receptors
- GABA is the major inhibitory neurotransmitter in the CNS
- Benzodiazepines relieve anxiety through enhancement of the inhibitory activity of GABA
- Most appropriate for use during the first 2 - 3 weeks of antidepressant use- then discontinued as the antidepressant begins working.
- Controlled Substance (C-IV)
Specific Sites and Actions

Amygdala, orbitofrontal cortex & insula
  - Alleviation of anxiety, agitation and fear
Spinal cord, cerebellum & brain stem
  - Muscle relaxation (also anxiolytic)
Cerebellum and hippocampus
  - Antiepileptic action
Cerebral cortex and hippocampus
  - Mental confusion and amnesia
Ventral tegmentum and nucleus accumbens
  - Rewarding behavioral effects (depend/abuse)
### Benzodiazepines Pharmacokinetic Differences

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Onset</th>
<th>Elimination half-life (hrs)</th>
<th>Active metabolite</th>
<th>Approx. Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5 - 2</td>
<td>9 - 20</td>
<td>No</td>
<td>0.5 (tid)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1 – 1.5</td>
<td>20 - 100</td>
<td>Yes [36 – 200 hrs]</td>
<td>2–10 (bid-qid)</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>1.5 - 4</td>
<td>5 - 30</td>
<td>Yes [36 – 200 hrs]</td>
<td>5 – 10 (tid – qid)</td>
</tr>
<tr>
<td>Clonazepam**</td>
<td>1 - 4</td>
<td>6 - 18</td>
<td>No</td>
<td>0.25 -0.5 (bid)</td>
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<tr>
<td>Lorazepam</td>
<td>1 – 1.5</td>
<td>10 - 20</td>
<td>No</td>
<td>1 – 3 (bid – tid)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>3 - 4</td>
<td>4 – 15</td>
<td>No</td>
<td>10 – 20 (tid – qid)</td>
</tr>
</tbody>
</table>

*
Buspirone

• Partial agonism or mixed agonism/antagonism at 5-HT type 1A receptors -
  – High concentration in dorsal raphe and hippocampus
  – Inhibits the firing rate of 5-HT-containing neurons in the dorsal raphe
  – Increases firing in the locus ceruleus
  – May explain why benzos cause drowsiness while buspirone does not.

• Also binds to dopamine (DA2) receptors
  – Acts as agonist and an antagonist
Buspirone

- Dosing 7.5mg BID titrate every 2-3 days by 5mg/d to max of 60mg/d
- Target dose 30mg/d (15mg BID)
- Side Effects:
  - nausea, dizziness, headache, insomnia, agitation
- No potential for abuse, physical dependence or withdrawal symptoms
- Delayed onset of action (2-3 weeks)
- Not appropriate for PRN dosing
SSRIs, Effexor in Anxiety

All studied in various types of anxiety
GAD, SAD, PD, PTSD, OCD
SSRIs are first-line therapy for many anxiety disorders due to:

• Broad spectrum activity in mood / anxiety disorders.

• Relatively favorable side effect profile

• Better tolerated than older classes of antidepressants

• Generally higher doses require

• Slow titration = long time to benefit
Belsomra (suvorexant) is the first approved drug of its class—orexin receptor antagonists. It is available in 5, 10, 15, and 20 milligrams, and should be dosed once per night within 30 minutes of bedtime. Three clinical trials showed decreased sleep latency and increased sleep maintenance (compared to placebo). The most common side effects are next-day drowsiness and driving issues. Belsomra is cleared by CYP3A4 and is not recommended with strong CYP3A4 inhibitors or liver impairment. Belsomra is schedule IV and has the same boxed warning as all other sleeping pills, re: complex behaviors including sleep-walking, driving, talking, and eating.
Alternatives To Benzos & Schedule IV Hypnotics

- Antihistamines (Diphenhydramine, Hydroxyzine, etc…)
- Antidepressants
  - Trazodone (Desyrel®)
  - TCA’s (Amitriptyline, Doxepin, etc…)
  - Mirtazapine (Remeron®)
- Melatonin
- Rozerem (melatonin receptor agonist)
- Herbals
Cardiovascular Pharmacology Update
Objectives

• Evaluate the role for newly approved medications in the management of heart failure and/or ischemic heart disease

• Compare and contrast the basic and clinical pharmacology of the novel oral anticoagulant drugs (NOACs)

• Discuss recent findings from the SPRINT Trials regarding lower than currently published blood pressure targets and the implications for treating hypertension in patients.
Heart Failure Statistics

• Nearly 5 million Americans are currently living with congestive heart failure (CHF).
• Approximately 550,000 new cases are diagnosed in the U.S. each year.
• The incidence of CHF is equally frequent in men and women, and African-Americans are 1.5 times more likely to develop heart failure than Caucasians.
• Heart failure is responsible for 11 million physician visits each year, and more hospitalizations than all forms of cancer combined.
Heart Failure Statistics

- CHF is the first-listed diagnosis in 875,000 hospitalizations, and the most common diagnosis in hospital patients age 65 years and older.
- In that age group, 20% of all hospitalizations have a primary or secondary diagnosis of HF.
- More than half of those who develop CHF die within 5 years of diagnosis.
- Deaths from heart failure have decreased on average by 12 percent per decade for women and men over the past fifty years.
Risk Factors for Heart Failure

- Coronary artery disease
- Hypertension (LVH)
- Valvular heart disease
- Diabetes
- Congenital heart defects
- Alcoholism
- Infection (viral)
- Other:
  - Obesity
  - Age
  - Smoking
  - High or low hematocrit level
  - Obstructive Sleep Apnea
General Causes of HF

1. Ischemic heart disease
   - Coronary artery disease / myocardial infarction
2. Valvular disease
3. Hypertension
4. Non-ischemic dilated Cardiomyopathy
   - Idiopathic
   - Myocarditis / pericarditis
   - Arrhythmias
   - Thyroid disease
   - Pregnancy
   - Toxins (alcohol, chemotherapy)
5. Hypertrophic cardiomyopathy
6. Restrictive cardiomyopathy
   1. Amyloid
   2. Sarcoidosis
   3. hemochromatosis
Goals of Therapy

1. Identify and Treat the Underlying Cause
   Cardiac cath if necessary
2. Eliminate the acute precipitant
3. Manage HF symptoms
4. Slow progression of LV disease
5. Improve long-term survival
Treatment of Systolic Heart Failure

• Correction of systemic factors
  – Thyroid dysfunction
  – Infections
  – Uncontrolled diabetes
  – Hypertension

• Lifestyle modification
  – Lower salt intake
  – Alcohol cessation
  – Medication compliance

• Maximize medications
  – Discontinue drugs that may contribute to heart failure (NSAIDS, antiarrhythmics, calcium channel blockers)
Rational for Medications

- Improve Symptoms
  - Diuretics
  - Digoxin

- Improve Survival
  - Beta blockers
  - ACE-inhibitors
  - Aldosterone blockers
  - Angiotensin receptor blockers (ARB’s)
  - Newer agents
Evidence-based, guideline-directed medical therapy.
## Recommendations for Treatment of **Stage B HF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; infarction; and N/A, not available.

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# Recommendations for Pharmacological Therapy for Management of Stage C HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B&lt;sup&gt;27,91&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIB</td>
<td>B&lt;sup&gt;589&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LOE, Level of Evidence.

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Recommendations for Pharmacological Therapy for Management of Stage C HFrEF

- **Diuretics:**
  - Recommended in patients with HFpEF with fluid retention

- **ACE Inhibitors:**
  - Recommended for all patients with HFpEF

- **ARBs:**
  - Recommended in patients with HFpEF who are ACE inhibitor intolerant
  - Recommended as alternatives to ACE inhibitors as first-line therapy in HFpEF
  - Addition of an ARB may be considered in persistently symptomatic patients with HFpEF on GDMT
  - Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful

- **Beta blockers:**
  - Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients

- **Aldosterone receptor antagonists:**
  - Recommended in patients with NYHA class II–IV who have LVEF ≤35%
  - Recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM
  - Inappropriate use of aldosterone receptor antagonists may be harmful

Recommendations for Pharmacological Therapy for Management of Stage C HFrEF

Hydralazine and isosorbide dinitrate
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HFrEF on GDMT
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs

Digoxin
Digoxin can be beneficial in patients with HFrEF

Anticoagulation
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*
The selection of an anticoagulant agent should be individualized
Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke*
Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source

## Recommendations for Pharmacological Therapy for Management of Stage C HFrEF

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>Statins are not beneficial as adjunctive therapy when prescribed solely for HF</td>
</tr>
<tr>
<td><strong>Omega-3 fatty acids</strong></td>
<td>Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HFrEF patients</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td>Nutritional supplements as treatment for HF are not recommended in HFrEF</td>
</tr>
<tr>
<td></td>
<td>Hormonal therapies other than to correct deficiencies are not recommended in HFrEF</td>
</tr>
<tr>
<td></td>
<td>Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
</tr>
<tr>
<td></td>
<td>Long-term use of infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>Calcium channel-blocking drugs are not recommended as routine treatment in HFrEF</td>
</tr>
</tbody>
</table>

Drugs to avoid in HF

- NSAIDS
- Corticosteroids
- All class I agents and the class III agents sotalol, dronedarone, and ibutilide are contraindicated in HF
- Thiazolidinediones (pioglitizone) should be avoided in patients with class III or IV HF
- Metformin should also be avoided in patients with class III/IV HF or frequent exacerbations with cardio-renal syndrome due to a risk of lactic acidosis
- Non-dihydropyridine CCBs, e.g. verapamil and diltiazem, are contraindicated in patients with systolic HF due to their negative inotropic effect and neurohormonal activation resulting in worsening of HF
The New Kids on the Block

Entresto - (sacubitril/valsartan)
Corlanor - ivabradine
Funny Stuff

- Funny current ($I_f$) is highly expressed in spontaneously active cardiac regions, such as the SA and AV nodes and the Purkinje fibers of conduction tissue.
- $I_f$ is controlled by intracellular cAMP and is thus activated and inhibited by β-adrenergic and muscarinic M2 receptor stimulation, respectively, it represents a basic physiological mechanism mediating autonomic regulation of heart rate.
Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study

Effect of ivabradine on outcomes in patients with chronic heart failure and HR ≥75 bpm
Aim

To assess the effect of ivabradine on outcomes in heart failure patients on recommended background therapies with heart rates ≥75 bpm in the SHIFT trial
Baseline background treatment

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine n=2052</th>
<th>Placebo n=2098</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers, %</strong></td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>At least half target dose</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>At target dose</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td><strong>ACE inhibitors/ARBs, %</strong></td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>Diuretics (excludes AAs), %</strong></td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td><strong>Aldosterone antagonists, %</strong></td>
<td>63</td>
<td>61</td>
</tr>
</tbody>
</table>
Effect of ivabradine on primary outcome

CV death or hospitalization for HF

Hazard ratio = 0.76

P < 0.0001

Effect of ivabradine on cardiovascular death

Hazard ratio = 0.83

Placebo

Ivabradine

Patients with cardiovascular death (%) vs. Time (months)


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Effect of ivabradine on hospital admission for worsening heart failure

Hazard ratio = 0.70

$P < 0.0001$

Effect of ivabradine on outcomes according to HR achieved at 28 days

Patients with primary composite end point (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75 bpm</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>70 to &lt;75 bpm</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>65 to &lt;70 bpm</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>60 to &lt;65 bpm</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>&lt;60 bpm</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

www.shift-study.com

Effect of ivabradine on outcomes according to magnitude of HR reduction

Patients with primary composite end point (%)

Ivabradine Side Effect

CV:
- Bradycardia (6% to 10%)
- Hypertension (9%)
- Atrial fibrillation (5% to 8%)
- Heart block
- Sinoatrial arrest

Central nervous system:
- Phosphene (3%)

• Interactions
  - Cleared via CYP3A4 – avoid with moderate to strong inhibitors and inducers
Conclusions

- In HF in sinus rhythm with HR ≥75 bpm heart rate reduction with ivabradine improves outcomes, including all-cause death and cardiovascular death reduces
- Ivabradine-associated risk reductions are related to both HR achieved and magnitude of HR reduction
- Patients achieving <60 bpm or with >10 bpm reduction have the best prognosis
A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF
One Enzyme — Neprilysin — Degrades Many Endogenous Vasoactive Peptides

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites

Neprilysin inhibition

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention
Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

- Increased activity or response to maladaptive mechanisms
- Decreased activity or response to adaptive mechanisms

Evolution and progression of heart failure
Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

- Increased activity or response to maladaptive mechanisms
- Decreased activity or response to adaptive mechanisms

Evolution and progression of heart failure

Angiotensin receptor blocker + Inhibition of nephrilysin
Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

LCZ696 400 mg daily ↔ Enalapril 20 mg daily
PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% ➔ 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

(all comparisons are versus enalapril 20 mg daily, not versus placebo)
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

**Enalapril**
(n=4212)

**LCZ696**
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Days After Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>LCZ696</td>
<td>4187</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Cardiovascular Death

HR = 0.80 (0.71-0.89)  
P = 0.00004  
Number need to treat = 32

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>4187</th>
<th>4056</th>
<th>3891</th>
<th>3282</th>
<th>2478</th>
<th>1716</th>
<th>1005</th>
<th>280</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>4212</td>
<td>4051</td>
<td>3860</td>
<td>3231</td>
<td>2410</td>
<td>1726</td>
<td>994</td>
<td>279</td>
<td></td>
</tr>
</tbody>
</table>
PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.0000002</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>
PARADIGM-HF: All-Cause Mortality

HR = 0.84 (0.76-0.93)
P<0.0001

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>4056</td>
<td>4051</td>
</tr>
<tr>
<td>360</td>
<td>3891</td>
<td>3860</td>
</tr>
<tr>
<td>540</td>
<td>3282</td>
<td>3231</td>
</tr>
<tr>
<td>720</td>
<td>2478</td>
<td>2410</td>
</tr>
<tr>
<td>900</td>
<td>1716</td>
<td>1726</td>
</tr>
<tr>
<td>1260</td>
<td>1005</td>
<td>994</td>
</tr>
<tr>
<td></td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril in . . .**

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril . . .**

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Pharmacological management of patients with newly discovered AF

Pharmacologic management of the patient with newly discovered AF

Paroxysmal
- No therapy needed unless significant symptoms (e.g., hypotension, HF, angina pectoris)
  - Anticoagulation as needed

Persistent
- Accept permanent AF
  - Anticoagulation and rate control as needed
- Rate control and anticoagulation as needed
  - Consider antiarrhythmic drug therapy
    - Cardioversion
    - Long-term antiarrhythmic drug therapy as necessary

# Evolution of Anticoagulation

<table>
<thead>
<tr>
<th>1930s</th>
<th>1950s</th>
<th>1980s</th>
<th>1990s</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td><strong>Warfarin</strong></td>
<td><strong>LMWH</strong></td>
<td><strong>Xa Inhibitors</strong></td>
<td><strong>DTI / Xa</strong></td>
</tr>
<tr>
<td>Parenteral</td>
<td>Oral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td>Narrow TI</td>
<td>Narrow TI</td>
<td>HIT</td>
<td>Must transition</td>
<td>Predictable</td>
</tr>
<tr>
<td>Unpredictable</td>
<td>Unpredictable</td>
<td>HIT</td>
<td>to warfarin</td>
<td>Some drug interactions</td>
</tr>
<tr>
<td>Req Monitoring</td>
<td>Req Monitoring</td>
<td>Antidote</td>
<td>Direct Thrombin</td>
<td>No monitoring</td>
</tr>
<tr>
<td>HIT</td>
<td>Drug interactions</td>
<td>(Vit K)</td>
<td>Inhibitors</td>
<td>No antidote</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>Diet Interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidote (protamine)</td>
<td>Lifestyle Interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antidote (Vit K)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The ‘Ideal’ Anticoagulant

- Oral, preferably once daily
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Low propensity for food and drug interactions
- Fixed doses (one size fits all)
- Wide therapeutic window
- Easy to use with no need for monitoring
- Quick, effective and safe antidote
The Newer Oral Anticoagulants

- Direct Thrombin Inhibitors:
  - Dabigitran

- Factor Xa inhibitors:
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Do they meet the IDEAL criteria?
Atrial Fibrillation and the need for effective anticoagulation

• Estimated 2.3 – 2.7 million Americans suffer from non-valvular atrial fibrillation.
  – Projected to increase to 6 – 12 million by 2050
• Median age for patients with atrial fibrillation is 66.8 years for men and 74.6 years for women.
• Stroke & heart failure are two most common complications.
• In addition to the five times greater risk of stroke compared with people without the condition, strokes for those affected are twice as likely to be fatal or seriously disabling.
Intracranial Bleeding
Hemorrhagic stroke

The delicate balancing act with using anticoagulants for treating Atrial Fibrillation
dabigatran (Pradaxa)

- Oral Direct Thrombin Inhibitor
- Reversible
- Prodrug, converted to dabigatran
  - Binds clot-bound and free thrombin with high affinity and specificity
- Twice daily dosing
- More predictable pharmacology than warfarin
- No requirement for monitoring
dabigatran

Currently Indicated for:

Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (RELY)

• 150 mg dose, as compared with warfarin, associated with lower rates of stroke (ischemic and hemorrhagic) and systemic embolism but similar rates of major hemorrhage.

DVT and pulmonary embolism

• 150 mg twice daily (after 5 to 10 days of parenteral anticoagulation)
dabigatran – PK considerations

Absorption
- Requires acidic pH for optimal absorption
- Capsules contain a tartaric acid core
- Possible explanation for ↑ dyspepsia and GI bleeding

Half-life: 12–17 hours = BID dosing
- 14-17 hours (Elderly)
- 15 – 18 hours (Mild-to-moderate renal impairment)
≥28 hours (Severe renal impairment)

Hepatic impairment
- No dosage adjustment required

Renal impairment
- Clcr 15-30 mL/min : 75 mg twice daily
- Clcr <15 mL/min: not recommendation
dabigatran - Drug Interactions

• No cytochrome P450 issues
• Substrate for P-glycoprotein efflux transporter
  – P-gp inducers or inhibitors may alter dabigatran bioavailability
    • **Inducers** rifampin
    • **Inhibitors** quinidine, ketoconazole, verapamil, amiodarone, clarithromycin
• PPIs may decrease bioavailability
Is dabigatran
The ‘Ideal’ Anticoagulant

- Oral (although b.i.d)
- Rapid onset and offset
- Predictable PK and PD
- Easy to use with no need for monitoring
- Low propensity for drug (food, lifestyle) interactions
- Fixed doses (one size fits all)

Good tolerability ??? GI issues

- Effective & safe antidote Yes? (but short $t_{1/2}$ and dialyzable)
- Renal status for dosing is critical
- Increased risk of MIs (appears to be DTI class effect)
- Contraindicated in Pts w Mechanical Prosthetic Valves
rivaroxaban (Xarelto)

- First oral direct factor Xa inhibitor
- Once daily dosing - dose not affected by age, gender or weight
- More predictable pharmacology than warfarin
- No requirement for monitoring
- No specific antidote if hemorrhage occurs
- Greater risk of stroke upon DC rivaroxaban in AF patients (black boxed warning)
rivaroxaban

Currently indicated for

• Prevention of stroke & systemic embolism in pts with nonvalvular atrial fibrillation
  – Non-inferior to warfarin
  – Major & non-major bleeding = warfarin
  – Intracranial hemorrhage < warfarin
  – Fatal bleeding < warfarin

• DVT prophylaxis after knee or hip surgery
  – Reduced composite of symptomatic VTE and all-cause mortality compared to enoxaparin
  – Major bleeding events = LMWH
rivaroxaban

Currently indicated for

Deep vein thrombosis / pulmonary embolism

- Acute, systematic, proximal DVT w/o pulm embolism (PE)
  - Daily b.i.d. similar efficacy and safety to standard therapy

• Acute symptomatic PE with or without DVT:
  - Non-inferiority to LMWH/VKA for efficacy
  - Similar findings for principal safety outcome
  - Superiority for reducing major bleeding
rivaroxaban - PK Considerations

• Absorption: Rapid and complete
• Protein binding: ~92% to 95% (primarily to albumin)
• Half-life: Terminal: 5-9 hours; Elderly: 11-13 hours
• Hepatic Impairment
  – Metabolized (30%) via hepatic via CYP3A4/5*
  – Moderate-to-severe hepatic impairment and patients with any hepatic disease associated with coagulopathy: Avoid use
• Renal Impairment (depends on indication)
  – $Cl_{cr} > 50$ mL/minute: No dosage adjustment necessary.
  – $Cl_{cr} 15-50$ mL/minute: 15 mg once daily with the evening meal
  – $Cl_{cr} < 15$ mL/minute: Avoid use.
Drug interactions - rivaroxaban

- **CYP3A4 substrate**
  - **Inhibitors:** Increase risk of bleeds
    - Emycin, clarithromycin,azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - **Inducers:** Decrease efficacy (↑ clot risk)
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort
Is rivaroxaban
The ‘Ideal’ Anticoagulant

✓ Oral, preferably once daily YES
✓ Rapid onset and offset
✓ Predictable PK and PD
✓ Good tolerability
✓ Fixed doses (one size fits all)
✓ Easy to use with no need for monitoring

Low propensity for drug (etc) interactions (CYP3A4)
Renal impairment dose adjustments
Effective & safe antidote (short $t_{1/2}$ potential benefit)
**apixaban (Eliquis)**

- Second approved oral direct factor Xa inhibitor
- Twice daily dosing
- More predictable pharmacology than warfarin
- No requirement for monitoring
- Cleared through CYP3A4
- Less renal adjustment issues compared to dabigatran & rivaroxaban
- No specific antidote if hemorrhage occurs
apixaban

Currently indicated for

Prevention of stroke or systemic embolism in patients with atrial fibrillation
  – Apixaban superior to warfarin in preventing stroke or systemic embolism
  – Associated with less bleeding than warfarin
  – Associated with lower all cause mortality vs warfarin

DVT & PE

Postoperative thromboprophylaxis (orthopedic surgery)
Drug interactions - apixaban

- CYP3A4 substrate
  - Inhibitors: Increase risk of bleeds
    - Emycin, clarithromycin, azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - Inducers: Decrease efficacy (↑ clot risk)
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort
Is apixaban
The ‘Ideal’ Anticoagulant

✓ Oral (although b.i.d)
✓ Rapid onset and offset
✓ Predictable PK and PD
✓ Good tolerability
✓ Fixed doses (one size fits all)
✓ Easy to use with no need for monitoring

Low propensity for drug (etc) interactions (CYP3A4)
Wide therapeutic window
Effective & safe antidote (short $t_{1/2}$ potential benefit)
Edoxaban (Savaysa)

- 3rd Oral Factor Xa inhibitor (4th NOAC)
- Once-daily dosing
- Approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Also to treat DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.
Edoxaban (Savaysa) Clinical Trials

• Atrial Fib
  – Higher dose (60 mg)* similar to warfarin (non-inferior) for the reduction in the risk of stroke with significantly less major bleeding compared to warfarin.

• DVT / PE
  – 3.2 percent of participants had a symptomatic recurrent VTE compared to 3.5 percent of those taking warfarin.

* Patients receive 30 mg once daily if they meet one or more of the following criteria: CrCL 30 to 50 mL/min, body weight ≤ 60 kg, or concomitant use of specific P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole).
Edoxaban (Savaysa)

- **Boxed Warning:** Do not administer to nonvalvular atrial fibrillation (NVAF) patients with CrCl >95 mL/minute.
  - In clinical trials, these patients had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin.

- **Other Renal adjustments:**
  - CrCl 15 to 50 mL/minute: 30 mg once daily
  - CrCl <15 mL/minute: Use is not recommended
## Summary of Clinical Trial Results (vs warfarin) in AF Stroke Prevention

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET - AF)</th>
<th>Apixaban (ARISTOTLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Superior 5 strokes/1000 per year</td>
<td>Non-inferior</td>
<td>Superior 3 strokes/1000 per year</td>
</tr>
<tr>
<td><strong>Hemorrhagic Stroke</strong></td>
<td>74% reduction</td>
<td>40% reduction</td>
<td>50% reduction</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Similar to warfarin</td>
<td>Similar to Warfarin</td>
<td><strong>30% reduction</strong></td>
</tr>
<tr>
<td><strong>Ischemic Strokes</strong></td>
<td><strong>Reduction</strong></td>
<td>Similar to warfarin</td>
<td>Similar to warfarin</td>
</tr>
<tr>
<td><strong>All cause Mortality</strong></td>
<td>No difference</td>
<td>No difference</td>
<td><strong>11% Reduction</strong></td>
</tr>
</tbody>
</table>
Comparing them all

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half-life</td>
<td>12-17 h</td>
<td>12 h</td>
<td>9-11 h</td>
<td>5-9 h (young)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11-13 h (elderly)</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~6.5%</td>
<td>~50%</td>
<td>~62%</td>
<td>~66% (w/o food)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>~100% (with food)</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clearance: non-renal/renal of absorbed dose if normal renal function</td>
<td>20%/80%</td>
<td>73%/27%</td>
<td>50%/50%</td>
<td>65%/35%</td>
</tr>
<tr>
<td>Liver metabolism: CYP450</td>
<td>No</td>
<td>Yes (CYP3A4/5, CYP1A2, 2C8, 2C9, 2C19, 2J2)</td>
<td>Yes (CYP3A4/5)</td>
<td>Yes (CYP3A4, CYP2J2, and CYP-independent mechanisms)</td>
</tr>
<tr>
<td>Absorption with food</td>
<td>No effect</td>
<td>No effect</td>
<td>6%-22% more</td>
<td>+39%</td>
</tr>
<tr>
<td>Intake with food?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No official recommendation yet</td>
</tr>
<tr>
<td>NOACs, novel oral anticoagulants</td>
<td></td>
<td></td>
<td></td>
<td>Mandatory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warfarin [Once daily]</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 - 72 hours</td>
</tr>
<tr>
<td>Peak Effect: 5 - 7 days</td>
</tr>
<tr>
<td>~100%</td>
</tr>
<tr>
<td>20-60; Mean: 40</td>
</tr>
<tr>
<td>92% (inactive metabolites)</td>
</tr>
<tr>
<td>Inhibitors of CYP3A4, 1A2, 2C9/19</td>
</tr>
<tr>
<td>PT/INR quantitative</td>
</tr>
<tr>
<td>$20 – 30 generic</td>
</tr>
<tr>
<td>$40 – 80 Coumadin</td>
</tr>
</tbody>
</table>


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0099276
Apples-to-Oranges
Problems with comparing new drugs

• Differences between the trial designs
  – RE-LY open label / ROCKET & ARISTOTLE blinded

• Patient Populations
  – Dabigatran - Mean age 82, mean CHADS$_2$ score 2.1
    • (31% having a score of 0 or 1)
  – Rivaroxaban Mean age 73, mean CHADS$_2$ score 3.5
  – Apixaban Median age 70, mean CHADS$_2$ score 2.1

• Warfarin comparators – Time in therapeutic range (INR)
  – RE-LY (dabigatran) 64%, ROCKET (rivaroxaban) 57.8%,
    ARISTOTLE (apixaban) 62%
Risk vs Benefit for Individual Patient

- “Use of either apixaban or low-dose edoxaban is appealing in patients at high risk of bleeding - they show the best bleeding profile and are not associated with a higher rate of GI bleeding compared with warfarin“
- "Low-dose edoxaban showed higher rates of ischemic stroke than warfarin, whereas apixaban showed a trend to lower rates of ischemic stroke”

Risk vs Benefit for Individual Patient

• "Rivaroxaban and higher-dose edoxaban have the advantage of once-daily dosing but appear to be associated with a higher rate of GI bleeding than warfarin."

• Dabigatran 150 mg twice daily was the only regimen that showed significant superiority over warfarin in preventing nonhemorrhagic stroke.

QD vs BID dosing

- Peak to trough ratios high in QD dosing
- Seems reasonable to reduce trough-to-peak ratios as much as possible to allow for the best risk-benefit balance regarding the prevention of thromboembolic and bleeding events throughout the time interval of 24 hours.
- Patients will be at increased risk for stroke when one or more NOAC doses are missed. This is especially valid when drugs with a short half-life (12 hours or less) are dosed QD.
- Based on pharmacokinetic evaluations, missing a dose translates to ~2 hours at risk in a BID dosing regimen and ~10 hours at risk for QD dosing.
**QD vs BID dosing**

- Hypothesis seems to be supported by the final results of the phase 3 trials with NOACs, as follows:
  - BID dosing regimens provided superior efficacy in the prevention of stroke and systemic embolism, with a very good or even superior safety profile compared with well-controlled warfarin.
  - QD dosing of rivaroxaban or edoxaban showed non-inferior efficacy and a similar or superior safety profile compared with warfarin treatment


Indirect comparison of BID vs QD with the CEs and results from respective NOACs.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0099276
Converting to a NOAC from Warfain

• **Dabigatran**
  – Discontinue warfarin and initiate dabigatran when INR < 2.0

• **Rivaroxaban**
  – Discontinue warfarin and initiate rivaroxaban as soon as INR falls to < 3.0

• **Apixaban**
  – Discontinue warfarin and initiate apixaban when INR is < 2.0
What about surgery?

• Risk of bleeding weighed against urgency of procedure

• Dabigatran
  – Discontinue 24 – 48 hours ($Cl_{cr} \geq 50$ mL/minute) or 3-5 days ($Cl_{cr} < 50$ mL/minute) before invasive or surgical procedures

• Rivaroxaban
  – Discontinue at least 24 hours prior to procedure

• Apixaban
  – Discontinue at least 24 hrs prior to procedures with low risk of bleeding: At least 48 hours moderate-to-high risk

• Edoxaban
  – Discontinue edoxaban at least 24 hours prior to elective surgery or invasive procedures
Monitoring

• Not routine / not for dosage adjustment
• Dabigatran
  – Bleeding risk can be assessed by ecarin clotting time (ECT)
  – aPTT **may** provide approximation of anticoagulant activity
• Rivaroxaban and Apixaban
  – Prothrombin time (PT), INR, and aPTT are prolonged
  – PT may be used to detect presence of Factor Xa inhibitors (qualitative only)
  – Anti-FXa assay may be helpful in guiding clinical decisions
    • plasma concentrations exhibit linear relationship with anti-FXa activity
Antidotes

• Prothrombin complex concentrate (PCC) (theoretical)
  – Usefulness in clinical settings not yet established

• Fresh frozen plasma
  – Short-term reversal, short half-life of 3-5 hours

• Dabigatran
  – Maintain adequate diuresis (60% dialyzable 2 – 3 hrs
  – Praxbind® (idarucizumab) approved 10/2015

• Factor Xa inhibitors
  – Andexanet alfa (Phase 3)
  – Decoy protein (looks like Xa – but not functional)
Praxbind

• Healthy volunteers - immediate reduction in plasma Pradaxa lasting for a period of at least 24 hours.
• Most common SE in healthy controls – headache
• In “bleeding” patients on Pradaxa - most common side effects were hypokalemic, confusion, constipation, fever and pneumonia.
• FDA warns that reversing the effect of Pradaxa exposes patients to the risk of blood clots and stroke from their underlying disease (such as AF)
• Labeling on Praxbind packaging recommends patients resume their anticoagulant therapy as soon as medically appropriate, as determined by their health care provider.
Summary: Benefits of New Agents

- All new agents associated with lower rates of intracranial hemorrhage (ICH) vs warfarin
- Predictable PD/PK
- No monitoring necessary
- No diet / lifestyle interactions
- No genetic polymorphism
Summary: Limitations of New Agents

- No monitoring
  - Unable to titrate dose
  - Treatment failure vs. poor compliance (no INR)
- Short $t_{1/2}$
  - Poor compliance may affect efficacy more than vitamin K antagonists (eg., warfarin)
- All four have boxed warning - Greater risk of stroke upon DC in AF patients
  - Need to bridge to warfarin or parenteral anticoagulant
  - *See supplemental document on “new oral anticoagulant conversion recommendations”
Summary: Limitations of New Agents

- Renal / hepatic dose adjustments likely required
  - Elderly
  - Renal disease / Hepatic disease
  - Use with CYP3A inhibitors / Pgp inhibitors
- High Cost
- Primary care providers lack experience with their use
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND
The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS
We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

Sprint Trial – Reconsidering Goals in HTN

Systolic Blood Pressure Intervention Trial    NEJM November 26, 2015; 373:2103
Sprint Trial –
Reconsidering Goals in HTN

• SPRINT focused on an especially high-risk population of adults with hypertension who were aged 50 years or older and had an average Framingham risk score of 20%.

• Patients with diabetes or a history of a stroke were not included.

• Study of 9361 participants who were randomized to either a lower, more intensive goal of less than 120 mm Hg systolic blood pressure (SBP) compared with a goal of less than 140 mm Hg systolic.
Who were the patients

- **Inclusion criteria:**
  - Patients > age 50
  - With high blood pressure
  - **Increased cardiovascular risk:** (At least one of the following)
    - actual blood vessel disease, chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] 20 to <60), Framingham risk greater than 15%, or age > 75.
  - They could be on medications (the majority were), but they didn't have to be.

- **Exclusion criteria:**
  - Patients with diabetes and prior stroke
  - Patients with 1-minute standing BP less than 110
Compliance with their antihypertensive medications, low-sodium diet, exercise and other CVD risk reduction therapy such as smoking cessation was regularly encouraged.
The graph shows the systolic blood pressure (mm Hg) over five years for two treatment groups: Standard treatment and Intensive treatment. The values are as follows:

- Standard treatment:
  - Year 0: 136/76
  - Year 5: 121/69

- Intensive treatment:
  - Year 0: 136/76 (same as Standard treatment)
  - Year 5: 121/69 (same as Standard treatment)

The table below provides the number of patients with data over the years for both treatment groups:

<table>
<thead>
<tr>
<th>Years</th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4683</td>
<td>4678</td>
</tr>
<tr>
<td>1</td>
<td>4345</td>
<td>4375</td>
</tr>
<tr>
<td>2</td>
<td>4222</td>
<td>4231</td>
</tr>
<tr>
<td>3</td>
<td>4092</td>
<td>4091</td>
</tr>
<tr>
<td>4</td>
<td>3997</td>
<td>4029</td>
</tr>
<tr>
<td>5</td>
<td>3904</td>
<td>3920</td>
</tr>
<tr>
<td></td>
<td>3115</td>
<td>3204</td>
</tr>
<tr>
<td></td>
<td>1974</td>
<td>2035</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>1048</td>
</tr>
<tr>
<td></td>
<td>274</td>
<td>286</td>
</tr>
</tbody>
</table>

The mean number of medications for each treatment group is also provided:

<table>
<thead>
<tr>
<th>Medications</th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Year 1</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Year 3</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Year 4</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Year 5</td>
<td>1.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

SPRINT   NEJM 11/26/15; 373:2103
The following special recommendations were also given:

1. Chlorthalidone at a dose of 12.5-25 mg/d was the thiazide-type diuretic of choice for the trial (it is more potent and longer-acting than hydrochlorothiazide).

2. Amlodipine was the CCB of choice for the trial.

3. ACE inhibitors (and likely other renin angiotensin system blockers) are less effective than other classes in lowering BP and in preventing CVD events in African American patients unless combined with a thiazide-type diuretic or calcium channel blocker.
The following special recommendations were also given:

4. A loop diuretic (e.g., furosemide) may be needed in persons with advanced chronic kidney disease (eGFR <30).

5. Any combination of ACE inhibitor, ARB, and renin inhibitor is discouraged.

6. Beta-adrenergic blockers are now considered to be less effective in preventing CVD events as primary treatment of hypertension but may be needed in persons with coronary artery disease.
Results

Primary end point:

- There were 243 (of 4678) primary outcome events in the intense-treatment arm vs 319 (of 4683) in the standard-treatment arm.
  - Over the 3.2 years of the trial, intense BP control prevented 76 events; the difference was 1.62% overall.
  - The number needed to treat (NNT) was 61. The percent same result was 98.4%.
Results

• Overall death: There were 155 deaths from any cause in the intense-treatment arm (of 4678) vs 210 in the standard-treatment arm (4683).
  – The difference was 1.2% or an NNT of 83. The percent same result was 98.8%.
• Death from CV causes: There were only 37 CV deaths in the intense treatment arm vs 65 in the standard arm.
  – The difference was 0.6% or an NNT of 167.
  – There were no significant differences in rates of stroke, MI, or ACS. Benefit in the primary outcome was driven most by heart-failure events and CV death.
Primary Outcome: MI, Acute Coronary Syndrome, Stroke, Heart Failure, CV Death

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

2.19%/yr

1.65%/yr

Absolute reduction in event rate = 0.54%/yr

NNT for 1 year = 185

Systolic Blood Pressure Intervention Trial    NEJM November 26, 2015
Death from Any Cause

Hazard ratio with intensive treatment, 0.73 (95% CI, 0.60–0.90)

Absolute reduction in rate of death = 0.37 %/yr
NNT for 1 year to prevent 1 death = 270

Systolic Blood Pressure Intervention Trial    NEJM November 26, 2015
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>243/4678 (5.2)</td>
<td>319/4683 (6.8)</td>
<td>0.75 (0.64–0.89)</td>
<td>0.36</td>
</tr>
<tr>
<td>Previous CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>135/3348 (4.0)</td>
<td>193/3367 (5.7)</td>
<td>0.70 (0.56–0.87)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108/1330 (8.1)</td>
<td>126/1316 (9.6)</td>
<td>0.82 (0.63–1.07)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>142/3361 (4.2)</td>
<td>175/3364 (5.2)</td>
<td>0.80 (0.64–1.00)</td>
<td></td>
</tr>
<tr>
<td>≥75 yr</td>
<td>101/1317 (7.7)</td>
<td>144/1319 (10.9)</td>
<td>0.67 (0.51–0.86)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Female</td>
<td>77/1684 (4.6)</td>
<td>89/1648 (5.4)</td>
<td>0.84 (0.62–1.14)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>166/2994 (5.5)</td>
<td>230/3035 (7.6)</td>
<td>0.72 (0.59–0.88)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Black</td>
<td>62/1454 (4.3)</td>
<td>85/1493 (5.7)</td>
<td>0.77 (0.55–1.06)</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>181/3224 (5.6)</td>
<td>234/3190 (7.3)</td>
<td>0.74 (0.61–0.90)</td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>No</td>
<td>149/3738 (4.0)</td>
<td>208/3746 (5.6)</td>
<td>0.71 (0.57–0.88)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94/940 (10.0)</td>
<td>111/937 (11.8)</td>
<td>0.83 (0.62–1.09)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>≤132 mm Hg</td>
<td>71/1583 (4.5)</td>
<td>98/1553 (6.3)</td>
<td>0.70 (0.51–0.95)</td>
<td></td>
</tr>
<tr>
<td>&gt;132 to &lt;145 mm Hg</td>
<td>77/1489 (5.2)</td>
<td>106/1549 (6.8)</td>
<td>0.77 (0.57–1.03)</td>
<td></td>
</tr>
<tr>
<td>≥145 mm Hg</td>
<td>95/1606 (5.9)</td>
<td>115/1581 (7.3)</td>
<td>0.83 (0.63–1.09)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Forest Plot of Primary Outcome According to Subgroups.
Results

• Adverse events overall: There were 1793 (38%) serious adverse events in the intensive group and 1736 (37.1%) in the standard group.
  – So, no difference overall.

• Adverse-events specifics:
  – Investigators reported more hypotension, syncope, electrolyte abnormalities, and acute kidney injury in the invasive group.
  – Falls with injury were not increased, and orthostatic hypotension was less frequent in the intensive arm(???)
### Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Treatment (N = 4678)</th>
<th>Standard Treatment (N = 4683)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of patients (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event*</td>
<td>1793 (38.3)</td>
<td>1736 (37.1)</td>
<td>1.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Conditions of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>110 (2.4)</td>
<td>66 (1.4)</td>
<td>1.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>107 (2.3)</td>
<td>80 (1.7)</td>
<td>1.33</td>
<td>0.05</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>87 (1.9)</td>
<td>73 (1.6)</td>
<td>1.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>144 (3.1)</td>
<td>107 (2.3)</td>
<td>1.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Injurious fall†</td>
<td>105 (2.2)</td>
<td>110 (2.3)</td>
<td>0.95</td>
<td>0.71</td>
</tr>
<tr>
<td>Acute kidney injury or acute renal failure‡</td>
<td>193 (4.1)</td>
<td>117 (2.5)</td>
<td>1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adverse laboratory measure§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium &lt;130 mmol/liter</td>
<td>180 (3.8)</td>
<td>100 (2.1)</td>
<td>1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium &gt;150 mmol/liter</td>
<td>6 (0.1)</td>
<td>0</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Serum potassium &lt;3.0 mmol/liter</td>
<td>114 (2.4)</td>
<td>74 (1.6)</td>
<td>1.50</td>
<td>0.006</td>
</tr>
<tr>
<td>Serum potassium &gt;5.5 mmol/liter</td>
<td>176 (3.8)</td>
<td>171 (3.7)</td>
<td>1.00</td>
<td>0.97</td>
</tr>
</tbody>
</table>

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Systolic Blood Pressure Intervention Trial  NEJM November 26, 2015; 373:2103
Clinical Relevance

• Role of patient selection:
  – Although there are millions of people with high blood pressure, the SPRINT trial had specific entry and exclusion criteria.
  – We must be careful extrapolating these results to patients. SPRINT-trial benefits apply to SPRINT-like patients.
  – Given that SPRINT included patients 50 years of age and older, the 2013 JNC 8 decision to relax blood-pressure goals in those 60 years and older to less than 150 mm Hg appears to be wrong.
Thank you for listening ~

Alan

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