Newer Anti-Anginal Agents and Anticoagulants

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Clinical Assistant Professor, Tulane University School of Medicine
Burden of Chronic Angina in the U.S.

- 9.1 million American adults have chronic angina
- 500,000 new cases diagnosed per year
- Approx. 50% of pts presenting with MI at the hospital have preceding angina

The Cost of Chronic Angina

Direct Costs 2004 Estimates: $1.9 – $8.9 Billion (US)*

- Emergency Department: 12.1%
- Hospitalization: 16.3%
- Prescription Drugs: 15.1%
- Home Health: 6.2%
- Nursing Home: 12.0%
- Outpatient: 38.3%

*Direct costs for angina $1.9 billion when it is the first-listed diagnosis and $8.9 billion when it is listed in any position

Angina Symptoms Predict Total Mortality in Patients with CAD

Prospective study with 8900 VA patients with CAD, greater physical limitations due to angina had higher mortality rates:

COURAGE: Treatment Effect on Primary Outcome

All-Cause Mortality, MI

Optimal Medical Therapy (OMT)

PCI + OMT

Survival free of primary outcome

No. at risk
Medical therapy
PC1

0 1 2 3 4 5 6 7

0 0.5 0.6 0.7 0.8 0.9 1.0

Years

HR 1.05* (0.87-1.27) P = 0.62

* Unadjusted

Angina Symptoms Persist in Many Patients Despite Revascularization

Continued angina and antianginal medication use 12 months after revascularization for angina (n=1205)

- Stenting group
- Surgery group

<table>
<thead>
<tr>
<th></th>
<th>Stenting group</th>
<th>Surgery group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued angina</td>
<td>21%*</td>
<td>11%</td>
</tr>
<tr>
<td>Continued antianginal medication</td>
<td>79%*</td>
<td>59%</td>
</tr>
<tr>
<td>Continued angina and/or antianginal medication</td>
<td>81%*</td>
<td>62%</td>
</tr>
</tbody>
</table>

*p < 0.001

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Studies in patients with stable CAD</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridine CCBs</td>
<td>CAMELOT</td>
<td>No impact on mortality or MI in CAMELOT ACTION: no reduction in CV events</td>
</tr>
<tr>
<td></td>
<td>ACTION</td>
<td></td>
</tr>
<tr>
<td>Nicorandil</td>
<td>IONA</td>
<td>Primary endpoint reduced, but no impact on mortality or non fatal MI</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Meta regression analysis</td>
<td>Evidence only in post-MI and CHF</td>
</tr>
<tr>
<td></td>
<td>CIBIS-II</td>
<td></td>
</tr>
<tr>
<td>Others (nitrates, diltiazem, verapamil)</td>
<td>-</td>
<td>No prognostic data in stable CAD patients</td>
</tr>
</tbody>
</table>
Despite β-blockers, many CAD patients have a heart rate >70 bpm

Mean resting HR at initial assessment in the overall patient population (n = 3 674) and in patients with β-blockers (n= 2 005) from The Euro Heart Survey

Resting HR and Beta-blocker Tx

- With BB: 62%
- Without BB: 38%

Heart rate (bpm)

- With BB: 69 ± 8
- Without BB: 73 ± 8

p < 0.001

## New Antianginal Drugs

<table>
<thead>
<tr>
<th>Pathophysiologic Target</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivabradine</strong></td>
<td></td>
</tr>
<tr>
<td>Old (HR)</td>
<td>New ($I_f$ inhibition)</td>
</tr>
<tr>
<td><strong>Ranolazine</strong></td>
<td></td>
</tr>
<tr>
<td>“New” (Ca overload)</td>
<td>New (late $I_{Na}$ inhibition)</td>
</tr>
</tbody>
</table>
RANOLAZINE: Late Na current Inhibitor

Ischemic Heart Disease

Ischemia/
\[ \downarrow C_2 \text{ & ATP} \]

\[ \downarrow \text{LV function} \]

\[ \downarrow \text{Micro-circulation} \]

\[ \uparrow \text{LVEDP/} \]
\[ \uparrow \text{LV wall tension} \]

Ranolazine

\[ \text{late } I_{Na} \]

\[ \uparrow \text{Na}^+ \]

\[ \uparrow \text{Ca}^{2+} \]

NCX

\[ \uparrow \text{Myofilament activation} \]

Angina Pectoris
RANOLAZINE: Key Clinical Trials

• CARISA
  - N = 823
  - Ranolazine Vs Placebo + Standard therapy for Chronic Angina

• ERICA
  - N = 565
  - Ranolazine Vs Placebo + Amlodipine for Chronic Angina

• MERLIN TIMI-36
  - N = 6560
  - Non-STE ACS pts
  - Ranolazine Vs Placebo + Standard Care
ERICA / CARISA Efficacy Summary

- Ranolazine is an effective antianginal therapy in combination with β-blockers, amlodipine and nitrates
  - Increases ETT exercise duration, time to angina and ST depression
  - Decreases rate of angina attacks
  - Decreases NTG consumption

- Provides significant antianginal efficacy on top of maximum approved doses of amlodipine
- Antianginal and anti-ischemic effects do not depend on changes in BP or HR

MERLIN: Components of Primary Endpoint

**CV Death or MI (%*)**
- Placebo 10.5%
- Ranolazine 10.4%

**Recurrent Ischemia (%*)**
- Placebo 16.1% (N=3,281)
- Ranolazine 13.9% (N=3,279)

HR 0.99 (95% CI 0.85 to 1.15) P = 0.87
HR 0.87 (95% CI 0.76 to 0.99) P = 0.030

*KM Cumulative Incidence at 12 months

IVABRADINE

• Prototype of a new class of drugs, the \( I_f \) Inhibitors

• A new concept for a drug providing anatomical (sinus node cell) and functional (\( I_f \) channel) selectivity
The $I_f$ Current...

- $f = \text{funny}$
- Described in 1979 by Brown, Di Francesco, and Noble
- Present only in the sinus node and retina
- Important for pacemaker depolarization a.k.a. heart rate
- Mixed ion channel, conducts $\text{Na}^+$ and $\text{K}^+$
- Controlled by sympathetic and parasympathetic systems
Sinus node

Sinus node channels

Ca channel
T-type

Ca channel
L-type

K channel

f-channel

Sinus node action potential and currents

mV
0
500 ms

pA
-50

I_f

I_K

I_CaL

I_CaT

I_NaCa

Robinson RB, DiFrancesco D. Fundamental and Clinical Cardiology; NY; Marcel Decker; 2001:151-170.
Ivabradine, contrary to b-blockers, maintains cardiac contractility.
Effects of Ivabradine on HR

HR decrease (at rest) versus other HR lowering agents

Diltiazem*

- 180-240 mg bid\(^1\)
- 200 & 300 mg od\(^2\)

- \(n=208\)
- \(n=182\)

Ivabradine**

- 5 mg bid
- 7.5 mg bid

- \(n=595\)
- \(n=300\)

Atenolol**

- 50 mg od
- 100 mg od

- \(n=286\)

Expected clinical benefits from pure HR reduction

• Stable Angina / Ischemia

• CAD and LV dysfunction

• CHF
Ivabradine Vs beta-blockers

Increase in exercise capacity per 1 beat of heart rate reduction (after 4-month treatment)

Changes in TED (Total Exercise Duration, sec)

X 2

atenolol 100 mg

Ivabradine 7.5 mg

**Ivabradine reduces heart rate in patients already receiving β-blockers**

889 stable angina patients, 20 countries

- **Ivabradine 5 mg bid**
  - Baseline: 67 bpm
  - M2: 66 bpm
  - M4: 66 bpm

- **Ivabradine + atenolol**
  - Baseline: 60 bpm (-7 bpm)
  - M2: 58 bpm (-9 bpm)

Ivabradine 7.5 mg bid (90% of pts) or 5 mg bid (10%)

Ivabradine increases all ETT parameters in patients already receiving BBs further.

889 stable angina patients, 20 countries

- **Ivabradine + atenolol**
- **Placebo + atenolol**

*Evaluated at trough of drug activity*

NOVEL ORAL ANTICOAGULANTS
Why New Anticoagulants?

LIMITATION
- Slow onset and offset of action
- Genetic variation in metabolism
- Multiple food and drug interactions
- Narrow therapeutic window

CONSEQUENCE
- Overlap with parenteral agent; prolonged time to procedures
- Variable dose requirements; increased monitoring
- Frequent coagulation monitoring
- Frequent coagulation monitoring; increased propensity for adverse events

Bates SM et al Br J Haematol 2006;134: 3-19
Novel Anticoagulants

Oral

- TTP889
- Apixaban
- Edoxaban
- Rivaroxaban
- Tecarfarin
- ATI-5923 (VKA)

Parenteral

- TF/VIIa
- NAPc2F
- XI
- IXa
- Vlla
- Va

- Dabigatran

- Fibrinogen
- Fibrin

- DX-9065a
- Otamixaban (IV)

- Semuloparin

## PK/PD of 5 Novel Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (thrombin)</th>
<th>Apixaban (Xa)</th>
<th>Rivaroxaban (Xa)</th>
<th>Edoxaban (Xa)</th>
<th>Betrixaban (PRT054021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>Hrs to Cmax</td>
<td>2</td>
<td>1-3</td>
<td>2-4</td>
<td>1-2</td>
<td>NR</td>
</tr>
<tr>
<td>CYP Metabolism</td>
<td>None</td>
<td>15%</td>
<td>32%</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Half-Life</td>
<td>12-14h</td>
<td>8-15h</td>
<td>9-13h</td>
<td>8-10h</td>
<td>19-20h</td>
</tr>
<tr>
<td>Renal Elimination</td>
<td>80%</td>
<td>33%</td>
<td>33%</td>
<td>35%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; NR = not reported

**References**

- Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
How do we determine stroke risk?

- **CHADS2** (Gage, et al.: JAMA 2001)
  - Congestive heart failure - 1pt
  - Hypertension - 1pt
  - Age > 75 - 1 pt
  - Diabetes - 1pt
  - Stroke or TIA - 2 pts

- 0 points – **low risk** (1.2-3.0 strokes per 100 patient years)
- 1-2 points – **moderate risk** (2.8-4.0 strokes per 100 patient years)
- ≥ 3 points – **high risk** (5.9-18.2 strokes per 100 patient years)
Table 2—The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA$_2$DS$_2$-VASc

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Age ≥ 75 y</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Stroke/TIA/TE</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Age 65-74 y</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex category (ie female gender)</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
CHADS$_2$ vs. CHA$_2$DS$_2$-VASc

- CHADS$_2$ score 0: 1.4% events
- CHA$_2$DS$_2$-VASc 0: 0 events

- CHA$_2$DS$_2$-VASc score 1: 0.6% events
- CHA$_2$DS$_2$-VASc score 2: 1.6% events

Recommended approach: anticoagulation when Isch stroke risk > 0.9%/year
The problem with Warfarin??
Warfarin

- Effective
- Reversible
- Inexpensive
- Slow onset of action
- Regular monitoring
- Food interaction
- Medication interaction
- Difficult titration-regular dose adjustments
Dabigatran versus Warfarin in Patients with Atrial Fibrillation


ABSTRACT

BACKGROUND
Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS
In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John’s National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica. Rosario. Argentina (R.D.): Ladv
RE-LY

AF + ≥ 1 additional risk factor:

N = 18,113
951 centers in 44 countries

Warfarin, dose adjusted (INR: 2.0–3.0) n = 6022
Dabigatran 110 mg, 2x/d n = 6015
Dabigatran 150 mg, 2x/d n = 6076

Primary outcome: stroke/SE

Risk factors:
• Stroke or TIA
• LVEF < 40%
• HF ≥ NYHA class II
• Age ≥ 75 years
• Age ≥ 65 years + either DM, CAD or hypertension

Dabigatran 110 mg is not FDA approved for this indication; for informational purposes only.

*Noninferiority; †Superiority.

### Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/Systemic Embolism</td>
<td>1.11</td>
<td>1.69</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01</td>
<td>1.57</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.92</td>
<td>1.20</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.10</td>
<td>0.38</td>
</tr>
<tr>
<td>MI</td>
<td>0.74</td>
<td>0.53</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>3.64</td>
<td>4.13</td>
</tr>
</tbody>
</table>

### Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>3.11</td>
<td>3.36</td>
</tr>
<tr>
<td>ICH</td>
<td>0.30</td>
<td>0.74</td>
</tr>
<tr>
<td>Major GI Bleeding</td>
<td>1.51</td>
<td>1.02</td>
</tr>
</tbody>
</table>
# Table 2  Recommendation for emerging antithrombotic agents

<table>
<thead>
<tr>
<th>2011 Focused update recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td></td>
</tr>
<tr>
<td>1. Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance &lt;15 mL/min) or advanced liver disease (impaired baseline clotting function).³ (Level of Evidence: B)</td>
<td>New recommendation</td>
</tr>
</tbody>
</table>
Rivaroxaban
ROCKET AF: Design

AF + risk for future stroke (history of stroke/TIA/SE) or ≥ 2 additional risk factors

Risk factors:
- CHF or LVEF ≤ 35%
- Hypertension
- Age ≥ 75 years
- DM

N = 14,264
1178 centers in 45 countries

Oral rivaroxaban 20 mg + placebo*
Warfarin* + placebo

*Titrated by INR/sham INR to INR: 2.5 (range: 2.0-3.0).

Primary outcome: stroke/SE

ROCKET – AF: Primary Efficacy Outcome

- **Rivaroxaban:** Event Rate 1.71
- **Warfarin:** Event Rate 2.16

Cumulative Event Rate (%)

- **HR (95% CI):** 0.79 (0.66, 0.96)
- **P-value noninferiority:** <.001


Efficacy Outcomes
- Stroke/Systemic Embolism
- Stroke
- Ischemic Stroke
- Hemorrhagic Stroke
- Myocardial Infarction
- All-Cause Mortality

Safety Outcomes
- ICH
- Major Bleeding
- Major GI Bleeding
- Major + CRNM Bleeding

Mean CHADS₂ score = 3.5

Rivaroxaban better
Warfarin better

Hazard Ratio

3.15% vs 2.16%, P<0.001
Apixaban
ARISTOTLE Trial Design

AF + ≥ 1 additional risk factor:

N = 18,206
1000 centers in 40 countries

Risk factors:
- Age ≥ 75 years
- Prior stroke, TIA, SE
- CHF or LVEF ≤ 40%
- DM
- Hypertension

Apixaban 2.5-5 mg BID + placebo*

Warfarin* (target INR: 2-3) + placebo

Primary outcome: stroke/SE

* Adjusted by INR/sham INR at encrypted point-of-care testing device.

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Apixaban (n = 9120) Event Rate (%/Year)</th>
<th>Warfarin (n = 9081) Event Rate (%/Year)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>1.27</td>
<td>1.60</td>
<td>0.79 (0.66-0.95)</td>
<td>.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.19</td>
<td>1.51</td>
<td>0.79 (0.65-0.95)</td>
<td>.01</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>0.09</td>
<td>0.10</td>
<td>0.87 (0.44-1.75)</td>
<td>.70</td>
</tr>
</tbody>
</table>

## ARISTOTLE: Efficacy and Bleeding Outcomes

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Event Rate</th>
<th>HR 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban n = 9120</td>
<td>Warfarin n = 9081</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.52</td>
<td>3.94</td>
<td>0.89 (0.80-0.998)</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>2.13</td>
<td>3.09</td>
<td>0.69 (0.60-0.80)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.33</td>
<td>0.80</td>
<td>0.42 (0.30-0.58)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>18.1</td>
<td>25.8</td>
<td>0.71 (0.68-0.75)</td>
</tr>
</tbody>
</table>

EDOXABAN
Warfarin (INR 2.0–3.0)

High-dose Edoxaban 60* mg QD

Low-dose Edoxaban 30* mg QD

21,105 PATIENTS
AF on electrical recording within last 12 m
CHADS\textsubscript{2} ≥2

RANDOMIZATION
1:1:1 randomization is stratified by CHADS\textsubscript{2} score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

1\textsuperscript{o} Efficacy EP = Stroke or SEE
2\textsuperscript{o} Efficacy EP = Stroke or SEE or CV mortality
1\textsuperscript{o} Safety EP = Major Bleeding (ISTH criteria)

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

CI = confidence interval; CrCl = creatinine clearance; ISTH = International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE = systemic embolic event

Compared to well-managed warfarin (TTR 68.4%) once-daily edoxaban:

- Non-inferior for stroke/SEE (both regimens)
  - High dose ↓stroke/SEE on Rx (trend ITT)
- Both regimens significantly reduced:
  - Major bleeding (20%/53%) - ICH (53%/70%)
  - Hem. stroke (46%/67%) - CV death (14%/15%)
- Superior net clinical outcomes

No excess in stroke or bleeding during transition → oral anticoagulant at end of trial
## Dosing Schedules

### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt; 30 cc/min: 150 mg, BID</td>
</tr>
<tr>
<td>75mg, 150mg</td>
<td>CrCl 15 to 30 cc/min: 75 mg, BID</td>
</tr>
<tr>
<td></td>
<td>Avoid &lt; 15 cc/min</td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl &gt; 15 cc/min: 5 mg, BID</td>
</tr>
<tr>
<td>2.5mg, 5mg</td>
<td>Any 2 (&gt; 80 yrs, &lt; 60 kg, SCr &gt; 1.5mg/dL: 2.5 mg, BID)</td>
</tr>
<tr>
<td></td>
<td>Avoid &lt; 15 cc/min</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt; 50 cc/min: 20 mg, Qday</td>
</tr>
<tr>
<td>10mg, 15mg, 20mg</td>
<td>CrCl 15-50 cc/min: 15 mg, Qday</td>
</tr>
<tr>
<td></td>
<td>Avoid CrCl &lt; 15 cc/min</td>
</tr>
</tbody>
</table>