Cardiac Controversies:
Acute Coronary Syndromes, Heart Failure & more
2006 Annual Meeting
Hospital Medicine 2006: Setting the Standard
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University of Chicago

Outcomes in Stable and Unstable Coronary Disease

6-month Mortality for Acute Coronary Syndromes

Granger CB et al. J Am Coll Cardiol. 1998;31:79A.
Unstable Angina – Low Risk

- No prior angina; no ongoing angina
- Little or no prior use of anti-ischemic regimen
- Normal or unchanged ECG
- No cardiac enzymes detected
- Younger age

Yeghiazarians et al. NEJM 2000;342:101

Unstable Angina – Intermediate Risk

- New-onset or accelerated angina
- Angina at rest or ongoing angina (> 20 minutes)
- No ST-segment deviation
- No cardiac enzymes detected

Yeghiazarians et al. NEJM 2000;342:101

Unstable Angina – High Risk

- Angina at rest or prolonged angina; ongoing angina
- Angina after myocardial infarction
- Prior use of intensive anti-ischemic regimen
- Older age
- Dynamic ST-segment deviation
- Cardiac enzyme detected
- Hemodynamic instability

Yeghiazarians et al. NEJM 2000;342:101
Unstable Angina/NSTEMI: Risk Assessment

<table>
<thead>
<tr>
<th>No. of Risk Factors</th>
<th>Rate of Composite Endpoint, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
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<td>4</td>
<td>20</td>
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<tr>
<td>5</td>
<td>25</td>
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<td>6 or 7</td>
<td>30</td>
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<tr>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
</tr>
</tbody>
</table>

TIMI Risk Score:
- Age > 65
- 3 or more risk factors
- 50% coronary stenosis
- ST deviation
- Severe angina >2/24hrs
- Aspirin use last 7 d
- Elevated cardiac markers

Composite Endpoint = all cause mortality, myocardial infarction severe recurrent ischemia prompting urgent revascularization

Unstable Angina – Antianginal Therapy

- Beta-blockers
  - Decrease myocardial oxygen demand
  - 13% reduction in risk of Myocardial Infarction
- Nitrates
  - Intravenous nitroglycerine first-line therapy
  - Tolerance may develop in first 24 hours
  - Does not reduce mortality or MI rate
- Calcium Channel Blockers
  - Diltiazem and verapamil may give survival advantage and reduced rate of MI in patients with normal EF only
  - Reserved for patients in whom beta-blockers contraindicated or symptoms despite aggressive therapy

Thrombus Formation in Acute Coronary Syndromes

- Fibrin
- Red cells
- Platelets
- Plaque rupture
Unstable Angina/NQMI -
Antithrombotic therapy

- Immediate aspirin
- Thienopyridine if aspirin not used
- Clopidogrel preferred over ticlopidine
- Heparin (IV unfractionated; LMW) with antiplatelet agents listed above
- Eptifibatide or tirofiban for continued ischemia despite ASA + heparin, for high-risk pts, and for planned PCI
- Abciximab for 12-24 h if PCI planned within 24 hours

Treatment of Acute Coronary Syndromes
Sites of anti-thrombotic drug action

<table>
<thead>
<tr>
<th>Tissue factor</th>
<th>Aspirin</th>
<th>Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor Xa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin</td>
<td>adenosine diphosphate (ADP)</td>
<td></td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TICLOPIDINE</td>
<td>clopidogrel</td>
<td></td>
</tr>
<tr>
<td>PLATELET AGGREGATION</td>
<td>GPIIIa inhibitors</td>
<td></td>
</tr>
<tr>
<td>BIVALIRUDIN</td>
<td>hirudin</td>
<td></td>
</tr>
<tr>
<td>ARGATROBAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPARIN</td>
<td>unfractionated</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABICOXIMAB</td>
<td></td>
<td></td>
</tr>
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</table>

Benefit of Aspirin in Unstable Angina

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Duration of FU</th>
<th>Death/MI Rate</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. (VA)</td>
<td>1983</td>
<td>1266</td>
<td>12 wks</td>
<td>10.1%</td>
<td>5.0%, 51%</td>
</tr>
<tr>
<td>Cairns et al. (Can)</td>
<td>1985</td>
<td>555</td>
<td>18 mo</td>
<td>17.0%</td>
<td>8.6%, 51%</td>
</tr>
<tr>
<td>Theroux et al.</td>
<td>1988</td>
<td>239</td>
<td>6 d</td>
<td>11.9%</td>
<td>3.3%, 71%</td>
</tr>
<tr>
<td>RISC</td>
<td>1990</td>
<td>796</td>
<td>3 mo</td>
<td>17.1%</td>
<td>6.5%, 63%</td>
</tr>
</tbody>
</table>

P<0.01 for each trial.

**Unstable Angina – Aspirin Recommendations**

- Bolus dose of 160-324 mg to rapidly inhibit thromboxane A2 generation by platelets
- Maintenance dose 80-160 mg/day
- Low dose aspirin as effective as high doses with fewer side effects
- Avoid when:
  - Hypersensitivity
  - Active Bleeding
  - Severe Bleeding Risk

**Platelet Activation**

**Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)**

- N=12,562
- Primary End Point: MI/Stroke/CV Death
- * In combination with standard therapy, ASA dose 75-325 mg/d
ACC/AHA Unstable Angina Guidelines Update 2002

- ASA should be administered as soon as possible after presentation
- Clopidogrel for patients unable to take ASA (hypersensitivity, GI intolerance)
- Hospitalized patients, non-interventional approach or PCI planned in patient not at risk for bleeding: clopidogrel should be added to ASA as soon as possible and continued for at least 1 month (evidence level A) and up to 9 months (evidence level B)

Addition of Heparin to Aspirin in Unstable Angina

<table>
<thead>
<tr>
<th>Source</th>
<th>Favor Heparin Plus Aspirin</th>
<th>Favor Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theron et al, 1998^10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSC Group, 1990^7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen et al, 1990^11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen et al, 1994^12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holdrith et al, 1994^13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gurfinkel et al, 1995^14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary Relative Risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk of MI or Death during randomized treatment: 0.67 (0.44-1.02) (33% reduction in risk)

Problems with Unfractionated Heparin

- Many Patients not in Therapeutic Range
- Stimulation of Platelet Aggregation
- Clinical Rebound after Infusion is Discontinued
- Heparin Induced Thrombocytopenia (HIT)
Trials of low molecular weight heparin vs. unfractionated heparin
Death, MI, recurrent ischemia ± urgent revascularization

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Patients (n)</th>
<th>Placebo</th>
<th>Odds ratio + 95% CI</th>
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<tbody>
<tr>
<td>PTCA Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EPILOG</td>
<td>Eptifibatide</td>
<td>2762</td>
<td>10.1%</td>
<td>7.1%</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Eptifibatide</td>
<td>4015</td>
<td>10.1%</td>
<td>7.1%</td>
</tr>
<tr>
<td>EPIC</td>
<td>Eptifibatide</td>
<td>4015</td>
<td>9.9%</td>
<td>6.6%</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>Tirofiban</td>
<td>2158</td>
<td>9.0%</td>
<td>6.9%</td>
</tr>
<tr>
<td>RESTORE</td>
<td>Tirofiban</td>
<td>2158</td>
<td>9.0%</td>
<td>6.9%</td>
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<tr>
<td>ERGONIST</td>
<td>Tirofiban</td>
<td>2158</td>
<td>10.0%</td>
<td>6.2%</td>
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<tr>
<td>UA/NSMU Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRISM</td>
<td>Tirofiban</td>
<td>3231</td>
<td>7.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>PRISM PLUS</td>
<td>Tirofiban</td>
<td>1570</td>
<td>11.1%</td>
<td>8.7%</td>
</tr>
<tr>
<td>PARAGON</td>
<td>Lamifiban</td>
<td>2382</td>
<td>11.5%</td>
<td>11.5%</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Eptifibatide</td>
<td>16,544</td>
<td>10.2%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>32,735</td>
<td>11.1%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Death/nonfatal MI at 30 days in platelet GP IIb/IIIa trials

Cohen, et al. NEJM 1997;337:1457-52
GP IIb/IIIa Inhibitors in Patients with UA/NSTEMI treated with PCI
Death and MI – 30 Days

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Pts</th>
<th>Placebo</th>
<th>GP IIb/IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>321</td>
<td>10.9</td>
<td>9.8</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1285</td>
<td>11.0</td>
<td>10.2</td>
</tr>
<tr>
<td>EPILOG</td>
<td>1328</td>
<td>10.6</td>
<td>10.0</td>
</tr>
<tr>
<td>PRISM</td>
<td>335</td>
<td>8.9</td>
<td>8.3</td>
</tr>
<tr>
<td>RESTORE</td>
<td>2139</td>
<td>10.3</td>
<td>10.2</td>
</tr>
<tr>
<td>IMPACT II</td>
<td>1103</td>
<td>11.2</td>
<td>11.5</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>1228</td>
<td>10.6</td>
<td>10.5</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>943</td>
<td>12.4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Relative Reduction & Absolute Reduction

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>GP IIb/IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>8.1%</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>6.5%</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>4.3%</td>
<td>2.9%</td>
</tr>
<tr>
<td></td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td></td>
<td>2.1%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>


GP IIb/IIIa Inhibitor During Medical Management and After PCI: CAPTURE, PURSUIT, PRISM-PLUS

Medical Rx

Control

GP IIb/IIIa inhibitor

Post PCI


Recommendations for antithrombotic therapy

<table>
<thead>
<tr>
<th>Definite ACS with invasive strategy or high risk</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>SQ LMWH or IV heparin</th>
<th>IV platelet IIb/IIIa antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely/definite ACS</td>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>SQ LMWH or IV heparin</td>
<td></td>
</tr>
<tr>
<td>Possible ACS</td>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Incidence of Failure of Medical Therapy (UA/NQMI)

TIMI IIIb Trial
Conservative therapy - failure of medical Tx leading to invasive therapy

Factors: ST depression, h/o angina, older age, FH CHD, use of aspirin or heparin

TACTICS-TIMI 18: Background

- Treatment strategies:
  - Invasive: routine early cath and revasc
  - Conservative: stress test → if + then cath
- Prior trials - mixed results
- Current era - improved medical Rx and PCI: use of GP IIb/IIIa inhibitors, stents
- 1st Hypothesis: Invasive strategy will be superior

TACTICS: Percutaneous Coronary Intervention in Acute Coronary Syndromes

Primary Endpoint
Death, MI, Rehosp for ACS at 6 Months

Cannon et al, NEJM 2001; 344:1879
Early Invasive Strategy

- Recurrent angina at rest/low level activity despite therapy
- Elevated cardiac enzymes (troponins)
- New ST-segment depression
- Recurrent angina with CHF, EF<0.40, low BP
- Positive stress test
- Sustained VT
- PCI < 6 mos, prior CABG

Patients with Acute MI Who Have Multiple Complex Coronary Plaques on the Initial Angiogram Have a Higher Incidence of Recurrent Events Over Subsequent 12 Months

Outcome after MI in pts with multiple complex plaques vs single complex plaque

Goldstein et al. NEJM 2000;343:915
Multiple Complex Plaques

Circumflex Occlusion  LAD ulcerated plaque

Lipid Lowering after an Acute Coronary Syndrome

Retrospective, nonrandomized comparison of 2141 pts taking and 6374 pts not taking a lipid lowering drug after a non-ST elevation ACS in the PURSUIT Trial

MIRACL Trial – UA/NQWMI

Time to first occurrence of:
- Death (any cause)
- Non-fatal MI
- Resuscitated cardiac arrest
- Worsening angina with new objective evidence of ischemia requiring urgent rehospitalization

Relative risk = 0.84
P=0.048

TIMI 22: Study Design

Double-blind, randomized trial in 4,162 patients with Acute Coronary Syndrome <10 days and Total Cholesterol < 240 mg/dL

Primary Endpoint: Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

ASA + Standard Medical Therapy

Pravastatin 40 mg

Atorvastatin 80 mg

Gatifloxacin

Placebo

Duration: Mean 2 year follow-up (1001 events)

TIMI 22 RESULTS: All-Cause Death or Major CV Events in All Randomized Subjects

% with Event

Pravastatin 40mg

537/2063 (26.3%)

Atorvastatin 80mg

464/2099 (22.4%)

16% RRR at 2 years

(p = 0.005)

Months of Follow-up
TIMI 22: Reductions in Major Clinical Endpoints by Treatment Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Atorva 80</th>
<th>Prav 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 80 mg</td>
<td>28.3%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>28.3%</td>
<td>20.4%</td>
</tr>
<tr>
<td>CHD Death</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Non-CHD Death</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>MI</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Revasc &gt; 30 d</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>UA Req Hosp</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Stroke</td>
<td>25.6%</td>
<td>20.4%</td>
</tr>
</tbody>
</table>

NCEP Report: Implications of Recent Clinical Trials

- An LDL-C goal of < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
- If LDL-C is > 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
- If baseline LDL-C is < 100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.

Circ 2004;110:227

Severity of Coronary Artery Stenosis Before Acute MI

Smith, Circ 1996;93:2205
Coronary Artery Response to Infusion of Acetylcholine

![Graph showing coronary artery response to Acetylcholine infusion.](image)

Diseased Coronary Artery Response to Acetylcholine

![Graph showing diseased coronary artery response to Acetylcholine infusion.](image)

Severe Endothelial Dysfunction Associated With Increased CV Risk in Patients With Mild CAD

![Bar chart showing cardiac events in different groups.](image)

*CBF = coronary blood flow response to acetylcholine.
Mean follow-up: 3.5 months.
**Prevalence of Heart Failure Increases with Age**


**Heart Failure Pathophysiology**

ANP=atrial natriuretic peptide, AVP=plasma arginine vasopressin, BNP=endogenous B-type natriuretic peptide, LV=left ventricular, RAAS=renin-angiotensin-aldosterone system, SNS=sympathetic nervous system.
Hemodynamic Profile Assessment

<table>
<thead>
<tr>
<th>Congestion at Rest</th>
<th>Low Perfusion at Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Warm &amp; Dry</td>
</tr>
<tr>
<td>Yes</td>
<td>Warm &amp; Wet</td>
</tr>
<tr>
<td>No</td>
<td>Cold &amp; Dry</td>
</tr>
<tr>
<td>Yes</td>
<td>Cold &amp; Wet</td>
</tr>
</tbody>
</table>

Signs/symptoms of congestion
- Orthopnea/PND
- JVD
- Ascites
- Edema
- Rales

Possible evidence of low perfusion
- Narrow pulse pressure
- Sleepy/obtunded
- Cool extremities
- Hypotension with ACE inhibitor
- Renal dysfunction (one cause)


Patient Selection and Treatment

<table>
<thead>
<tr>
<th>Congestion at Rest</th>
<th>Low Perfusion at Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Warm &amp; Dry</td>
</tr>
<tr>
<td>Yes</td>
<td>Warm &amp; Wet</td>
</tr>
<tr>
<td>No</td>
<td>Cold &amp; Dry</td>
</tr>
<tr>
<td>Yes</td>
<td>Cold &amp; Wet</td>
</tr>
</tbody>
</table>

PCWP normal
- CI normal (compensated)

PCWP elevated
- CI decreased

Inotropic Drugs
- Dobutamine
- Milrinone
- Calcium Sensitizers

Natriuretic Peptide
- Nesiritide
- Nitroprusside
- Nitroglycerin


Current Treatments for Acutely Decompensated Heart Failure

Diuretics: Reduce Fluid Volume
Vasodilators: Decrease Preload and Afterload
Inotropes: Augment Contractility
Natriuretic Peptide: Decrease Preload and Afterload; Reduce Fluid Volume
Intravenous Agents for Heart Failure

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CO</th>
<th>PCWP</th>
<th>BP</th>
<th>HR</th>
<th>Atrial Fibrillation</th>
<th>Shorter Onset</th>
<th>Longer Offset</th>
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<tbody>
<tr>
<td>Nitroprusside</td>
<td>+++</td>
<td>↔</td>
<td>↔</td>
<td>✏</td>
<td>***</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>+++</td>
<td>↔</td>
<td>→</td>
<td>▼</td>
<td>++</td>
<td>**</td>
<td>0</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>+++</td>
<td>↓</td>
<td>↑</td>
<td>▼</td>
<td>++</td>
<td>**</td>
<td>0</td>
</tr>
<tr>
<td>Milrinone</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>▼</td>
<td>++</td>
<td>**</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>▼</td>
<td>++</td>
<td>**</td>
<td>0</td>
</tr>
</tbody>
</table>

↑ increase; ↓ decrease; + effect (number of and qualitatively associated with degree of effect); 0 no effect.


Role of Inotropic Therapy in Patients with HF

- Routine use of inotropes as HF therapy is not indicated in either short- or long-term setting.
- Inotropes potentially appropriate as treatment for cardiogenic shock, diuretic/ACE inhibitor – refractory HF decompensations, or short-term bridge to definitive treatment, such as revascularization or cardiac transplant.
- Inotropes may be appropriate as palliative measure in patients with end-stage HF as part of hospice care.

Felker GM. Am Heart J. 2001;142:393.

Treatment Algorithm for ADHF

Volume Overloaded, Dyspnea, SBP >90 mm Hg

Initial Therapy

- IV Diuretics
- Oxygen
- Nesiritide

Compensation
- Optimize Oral Drug Regimen
- Optimize Patient Education
- Discharge Home

Inadequate Response

Refactory Therapy

- Hemodynamic Monitoring
- Increase Nesiritide Dose to max of 0.03 mcg/kg/min

Indications for Nesiritide

- Indicated for intravenous (IV) treatment of patients with ADHF who have dyspnea at rest or with minimal activity. In this population, nesiritide reduced pulmonary capillary wedge pressure (PCWP) and improved dyspnea.
- Nesiritide should not be used as primary therapy for patients with cardiogenic shock or in patients with systolic blood pressure (SBP) <90 mm Hg.
- Nesiritide is not recommended for patients for whom vasodilating agents are not appropriate and should be avoided in patients with low cardiac filling pressures.

The VMAC Study

**Vasodilation in the Management of Acute Congestive Heart Failure Trial**

- Patients presenting to the hospital with dyspnea at rest or with minimal activity (such as talking, eating, or bathing) due to acutely decompensated CHF that was severe enough to require hospitalization:
  - These decompensated CHF patients included patients with acute decompensation of chronic heart failure, gradual worsening of chronic heart failure, or with new onset of acutely decompensated CHF.
  - Patients could be receiving dobutamine or dopamine.


The VMAC Study Included “Real World” Acute Decompensated HF Patients

- Chronic NYHA Class III or IV: 84%
- Renal insufficiency: 21%
  - Defined as SCR ≥ 2.0 mg/dL
- Preserved systolic function (EF > 40%): 15%
- Acute coronary syndrome: 12%
- History of ventricular tachycardia: 13%
- Diabetes: 47%

VMAC was not powered to show an effect in these individual subgroups.

**VMAC - Primary Endpoint: PCWP through 3 Hours**

![Graph showing mean observed value and mean change in mmHg for Placebo, Nitroglycerin, and Nesiritide.](image)

- Placebo
- Nitroglycerin
- Nesiritide

* p < 0.05 versus placebo
* p < 0.05 versus NTG

**Adverse Events During Treatment with Standard Care Plus Either Nesiritide or IV Nitroglycerin**

<table>
<thead>
<tr>
<th>Most common adverse events through 24 hours at the recommended dose (VMAC trial)</th>
<th>Nesiritide n=273</th>
<th>IV nitroglycerin n=216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Asymptomatic hypotension</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Ventricular tachycardia (VT)</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>8%*</td>
<td>20%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1%*</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* p < 0.05, compared to nitroglycerin (Fisher Test)

Publications Committee for the VMAC Investigators, JAMA 2002;287:1531-1540.

**Nesiritide: Safety Information**

- **Renal Function**
  - In HF patients whose renal function may depend on RAAS activity, nesiritide administration may be associated with azotemia
  - Nesiritide is associated with a dose dependent increase in serum creatinine (SCr)
  - Higher doses of nesiritide increased the risk of hypotension
Effect of Nesiritide on Serum Creatinine: VMAC

<table>
<thead>
<tr>
<th>Patients with renal insufficiency (n=104)</th>
<th>All patients (n=489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide plus standard care</td>
<td>Nitroglycerin plus standard care</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Baseline Day 2 Day 5 Day 14 Day 30</td>
<td></td>
</tr>
</tbody>
</table>

Renal insufficiency defined as serum creatinine ≥ 2.0 mg/dL. Study drug discontinued following 24–48 hr of treatment in majority of patients in VMAC.


Relative Risk of SCR > 0.5 mg/dL by Nesiritide Initiation Dose

Relative Risk (95% Confidence Intervals)

Includes data from 5 studies: Mills et al. Efficacy, Comparative, PRECEDE NT, and VMAC (N = 1,222)


Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure (HF)</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage HF</td>
</tr>
</tbody>
</table>

Characteristics of Hypertension in African Americans

- Premature onset
- Increased severity
- Increased incidence of target-organ injury
  - Left ventricular hypertrophy (LHV)
  - Heart failure
  - Impaired renal function
- May need lower target BP (<130/80 versus <140/90 mm Hg for general population) to reduce heart/renal damage

Etiology of Heart Failure in African Americans

![Bar chart showing heart failure etiology in African Americans.]

ACC/AHA Guidelines for Patients at High Risk of HF: Hypertensive Patients

Suggested Therapy for Stage A/Hypertensive Patients:

- Control of systolic and diastolic hypertension in accordance with recommended guidelines
- Appropriate antihypertensive regimen frequently consists of several drugs used in combination
- Drugs that are useful for the treatment of both hypertension and HF are preferred (eg, diuretics, ACE inhibitors, β-blockers)
ACC/AHA Guidelines for Patients at High Risk of HF

- Patients at high risk for heart failure (eg, patients with HTN, CAD, DM, family history of cardiomyopathy)
  - Treat systolic and diastolic hypertension according to guidelines
    - An appropriate HTN regimen frequently consists of several drugs used in combination
    - When such a HTN regimen is devised, drugs that are useful for the treatment of both HTN and HF are preferred (eg, diuretics, ACE inhibitors, and β-blockers)
  - Encourage smoking cessation; treat lipid disorders; discourage alcohol intake

- Patients with heart failure
  - Treat with ACE inhibition* and β-blockade*
  - Diuretics and digitalis as required
  - Withdraw drugs known to adversely affect patient’s clinical status

*Unless contraindicated.

Utilization of Evidence-Based Therapies in Heart Failure

University Hospital Consortium HF Registry: 33 Centers, 1,239 patients, Year 2000.