Imaging Biomarkers: utilisation for the purposes of registration

EMEA-EFPIA Workshop on Biomarkers
15 December 2006
Vascular Imaging Technologies

- Carotid Ultrasound-IMT
- IVUS-PAV
- QCA-% stenosis
Evidence to establish surrogacy

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>QCA</th>
<th>CIMT</th>
<th>IVUS</th>
</tr>
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<td><strong>Biological Plausibility</strong></td>
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Quantitative Coronary Angiography (QCA)

First accepted imaging surrogate of clinical efficacy

- Set the standard for the field when placebo control groups were still acceptable
- Measures lumen diameter (mm) or percent stenosis
QCA progression and clinical events

Imaging measurements and clinical events with cholesterol lowering therapies

- QCA meta-analyses (Rossouw)

![Graph showing odds ratio of progression and clinical event](image)

Rossouw J E. Am J Cardiol. 1995;76:86C-92C.
QCA Limitations

Limitations

- QCA can only measure “luminal atherosclerosis” (i.e., advanced disease that impinges the lumen)
- Most events occur in non-stenotic vessels

Digital QCA loses spatial resolution
  - Not sufficient resolution for active control studies

Smith. Circulation. 1996;93:2205-2211 (data from four studies)
Vascular Ultrasound

**Advantages**

- Coronary and carotid ultrasound permit direct visualisation of vascular disease
- Detects latent disease not visible to angiography

De Franco AC, Nissen SE, Am J Cardiol 2001;88:7M-20M
Carotid Ultrasound

Measures of intima-media thickness
Evidence that Carotid IMT Predicts Clinical Disease

- Epidemiological Data
  - Rotterdam Study
  - CLAS (Cholesterol Lowering Atherosclerosis Study) post-treatment long-term outcomes follow-up
  - CHS (Cardiovascular Health Study)

<table>
<thead>
<tr>
<th>Study</th>
<th>∆ in CIMT</th>
<th>risk of MI</th>
<th>risk of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam</td>
<td>0.163 mm SD</td>
<td>1.43 (OR)</td>
<td>1.41 (OR)</td>
</tr>
<tr>
<td>CLAS</td>
<td>0.03 mm/yr</td>
<td>2.2 (RR)</td>
<td></td>
</tr>
<tr>
<td>CHS</td>
<td>0.2 mm SD</td>
<td>1.46 (OR)</td>
<td>1.43 (OR)</td>
</tr>
</tbody>
</table>

Cardiovascular Health Study: Baseline CIMT Predictive of Stroke and MI

- 4,476 subject without CHD at baseline
- Median follow-up 6.2 yrs
- RR of stroke or MI for highest vs. lowest CIMT quintile was 3.87

Evidence that changes in CIMT Predict Clinical Disease: Lipid intervention studies: meta-analysis

Clinical trials involving HMG-CoA reductase inhibitors that reported both Carotid IMT and Cardiovascular Event Outcomes

<table>
<thead>
<tr>
<th>Clinical Trial (N*)</th>
<th>Statin</th>
<th>Relative Impact on IMT Progression of Primary Outcome (mm/yr): Mean [95% CI] (Reported p-Value)</th>
<th>Relative Impact on Reported Cardiovascular Endpoints: Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS(^{25}) (N=919)</td>
<td>Lovastatin</td>
<td>-0.015 [-0.023, -0.007] (p=0.001)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>KAPS(^{26}) (N=447)</td>
<td>Pravastatin</td>
<td>-0.014 [-0.022, -0.006] (p=0.005)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>PLAC-II(^{47}) (N=151)</td>
<td>Pravastatin</td>
<td>-0.009 [-0.031, 0.013] (p=0.44)</td>
<td>Clinical Coronary Events</td>
</tr>
<tr>
<td>CAIUS(^{48}) (N=305)</td>
<td>Pravastatin</td>
<td>-0.014 [-0.021, -0.005] (p=0.0007)</td>
<td>CVD Death, MI</td>
</tr>
<tr>
<td>REGRESS(^{28}) (N=255)</td>
<td>Pravastatin</td>
<td>-0.030 [-0.056, -0.004] (p=0.002)</td>
<td>Clinical Events</td>
</tr>
<tr>
<td>BCAPS(^{49}) (N=793)</td>
<td>Fluvastatin</td>
<td>-0.008 [-0.013, -0.003] (p=0.002)</td>
<td>CVD Death, MI, Stroke</td>
</tr>
<tr>
<td>FAST(^{50}) (N=164)</td>
<td>Pravastatin</td>
<td>Significant Benefit (p &lt;0.001)</td>
<td>CVD Death, MI</td>
</tr>
<tr>
<td><strong>Pooled Estimate</strong></td>
<td></td>
<td>-0.012 [-0.016, -0.007]**</td>
<td></td>
</tr>
</tbody>
</table>

*Arms used in meta-analysis; ** Excludes FAST.
## Change in CIMT in Blood Pressure Lowering Trials: meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Baseline IMT (µm)</th>
<th>Change/y (µm)</th>
<th>Difference (µm/y, 95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migdalis</td>
<td>20:20</td>
<td>680:701</td>
<td>103:30</td>
<td></td>
</tr>
<tr>
<td>PART2</td>
<td>309:308</td>
<td>790:800</td>
<td>5:8</td>
<td></td>
</tr>
<tr>
<td>SECURE 2.5 mg</td>
<td>227:232</td>
<td>1146:1148</td>
<td>22:18</td>
<td></td>
</tr>
<tr>
<td>SECURE 10 mg</td>
<td>227:234</td>
<td>1146:1160</td>
<td>22:14</td>
<td></td>
</tr>
<tr>
<td>Hosomi</td>
<td>50:48</td>
<td>700:700</td>
<td>20:10</td>
<td></td>
</tr>
<tr>
<td>PREVEND</td>
<td>323:319</td>
<td>770:770</td>
<td>11:8</td>
<td></td>
</tr>
<tr>
<td>All ACEIs</td>
<td>929:1161</td>
<td></td>
<td></td>
<td>−6 (−12 to 0.4)</td>
</tr>
<tr>
<td>All BBs</td>
<td>434:428</td>
<td>897:894</td>
<td>12: −12</td>
<td>−10 (−33 to 13)</td>
</tr>
<tr>
<td>PREVENT</td>
<td>186:191</td>
<td>1258:1259</td>
<td>11: −4</td>
<td>−7 (−12 to −2)</td>
</tr>
<tr>
<td>All trials</td>
<td>1549:1780</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wang et al. *Stroke* 2006;37:1933-40
CIMT as surrogate for CV events: Summary Of LDL and BP Trials

- IMT change produces parallel estimates of risk and benefit. Changes in events are deductible from observed changes in the surrogate

<table>
<thead>
<tr>
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<th>CIMT effect (mm/yr)</th>
<th>CV event effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin RCTs</td>
<td>-0.012 [-0.016, -0.007]</td>
<td>0.48 [0.30, 0.78]*</td>
</tr>
<tr>
<td>BP RCTs</td>
<td>-0.007 [-0.012, -0.002]</td>
<td>0.71 [0.55, 0.92]**</td>
</tr>
</tbody>
</table>

** Wang et al. *Stroke* 2006;37:1933-40

RCT = randomized control trial
# Atherosclerosis Imaging: QCA and IMT

Current cardiovascular imaging supported USA and/or CAN Labeling

<table>
<thead>
<tr>
<th>Compound</th>
<th>Imaging type: endpoints</th>
<th>Supporting Studies</th>
<th>Imaging Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin (Mevacor®, 1995)</td>
<td>QCA: MLD, % stenosis CIMT</td>
<td>QCA: CCAIT, MARS, FATS CIMT: ACAPS</td>
<td>slow progression of CAD</td>
</tr>
<tr>
<td>Pravastatin (Pravachol®, 1996)</td>
<td>QCA: MLD CIMT</td>
<td>QCA: PLAC I; REGRESS CIMT: PLAC II, REGRESS, KAPS</td>
<td>slow progression of CAD</td>
</tr>
<tr>
<td>Simvastatin (Zocor®, 1996)</td>
<td>QCA: MLD</td>
<td>QCA: MAAS</td>
<td>slow progression of coronary atherosclerosis; reduce new lesions and total occlusions (Canada)</td>
</tr>
<tr>
<td>Fluvastatin (Lescol®, 1997)</td>
<td>QCA: MLD</td>
<td>QCA: LCAS</td>
<td>slow progression of CAD</td>
</tr>
<tr>
<td>Niacin (Niaspan®, 1997) + resin</td>
<td>QCA: global change score, % stenosis</td>
<td>QCA: CLAS, FATS</td>
<td>slow progression or promote regression of CAD</td>
</tr>
</tbody>
</table>

Coronary Ultrasound: Evidence that IVUS Predicts Clinical Disease

Epidemiological Data

- CHD patients (Von Birgelen et al)
  - Correlation with change in left main coronary artery atheroma cross sectional area (CSA) with
    - Risk factors
    - Risk scores
    - Clinical events

Coronary Ultrasound: Evidence that IVUS Predicts Clinical Disease

Plaque & Media Changes / Year (%)

- Total Cholesterol ≥204 mg/dl (n=31) vs Total Cholesterol <204 mg/dl (n=25)
  - Total Cholesterol: 16.6 ± 19.5 vs 6.1 ± 16.5
  - p <0.05

- LDL-Cholesterol ≥125 mg/dl (n=28) vs LDL-Cholesterol <125 mg/dl (n=28)
  - LDL-Cholesterol: 19.8 ± 19.1 vs 3.8 ± 15.2
  - p <0.001

- HDL-Cholesterol ≤46 mg/dl (n=28) vs HDL-Cholesterol >46 mg/dl (n=28)
  - HDL-Cholesterol: 21.2 ± 18.5 vs 2.4 ± 14.2
  - p <0.001

- Total-C/HDL-C-Ratio ≥4 (n=39) vs Total-C/HDL-C-Ratio <4 (n=17)
  - Total-C/HDL-C-Ratio: 15.3 ± 19.3 vs 3.7 ± 15.5
  - p <0.02

- Triglycerides ≥118 mg/dl (n=28) vs Triglycerides <118 mg/dl (n=28)
  - Triglycerides: 14.2 ± 22.4 vs 9.4 ± 14.6
  - p =0.4

- Systolic Blood Pressure ≥140 mmHg (n=34) vs Systolic Blood Pressure <140 mmHg (n=22)
  - Systolic Blood Pressure: 14.3 ± 18.4 vs 10.2 ± 19.3
  - p =0.4

- Age ≥59 Years (n=30) vs Age <59 Years (n=26)
  - Age: 13.2 ± 19.5 vs 10.6 ± 18.7
  - p =0.6

- Family History (n=10) vs No Family History (n=46)
  - Family History: 15.8 ± 23.9 vs 10.9 ± 17.8
  - p =0.6

- Diabetes Mellitus (n=10) vs No Diabetes Mellitus (n=46)
  - Diabetes Mellitus: 18.3 ± 15.2 vs 10.4 ± 19.5
  - p =0.2

- Smoker (n=16) vs No Smoker (n=40)
  - Smoker: 24.7 ± 17.5 vs 6.6 ± 17.0
  - p <0.002

Mean LDL Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials

Adapted from Nissen, S. E. et al. JAMA 2006;0:295.13.jpc60002-10.
Indirect Evidence that CIMT and IVUS Predict Clinical Events: Pravastatin/Atorvastatin Studies

**ARBITER (CIMT)**

- **Pravastatin**: Baseline, 6 Months, 12 Months
- **Atorvastatin**: Baseline, 6 Months, 12 Months

**REVERSAL (IVUS)**

- **Pravastatin 40 mg**: Significant atherosclerotic progression from baseline
- **Atorvastatin 80 mg**: No significant change from baseline; atherosclerotic progression was stopped

**PROVE-IT**

- **Death or Major Cardiovascular Event (%)**
  - 40 mg of Pravastatin
  - 80 mg of Atorvastatin

- **No. at Risk**
  - **Pravastatin**: 2063, 1688, 1536, 1423, 810, 138
  - **Atorvastatin**: 2099, 1736, 1591, 1485, 842, 133

- **P=0.005**
Combination therapies have the potential to reduce cardiovascular risk further than mono-therapy

Risk of Coronary Heart Disease and Lipid Levels

An example

Framingham Study; Am J Cardiol. 2000.
## Scientific objective

- Demonstrate the incremental benefit of novel therapy combined with LDL-C lowering therapy over standard of care alone in slowing the progression of atherosclerosis

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Atherosclerosis Imaging 2006
Questions

- Does the EMEA consider that carotid ultrasound now meets the criteria of ICH E9 for a surrogate variable, in consideration of the wealth of pathophysiologic, epidemiologic, and clinical trial data published since the guidance was issued? If not, why not?

- Does the EMEA concur that atherosclerosis is a systemic disorder and that IVUS measures of wall thickness represent a higher resolution image of IMT than that detected by carotid ultrasound? If not, why not?
What are the EMEA comments on the fact that vessel wall thickness is an integrated marker of cardiovascular risk and that IVUS, as an example does not attempt to assess vulnerable plaque, but as is the case with carotid IMT, is an assessment of the patient’s potential for future CV events?
Backup
Example of a Phase 3 Imaging Program

**Coronary IVUS Subject Population:**
- Angio. proven CAD (> 20% stenosis)
- Eligible for statin treatment

**Coronary IVUS**
- Core labs for central reading
- Multi-country, multi-center

**Carotid IMT Subject Populations:**
- Heterozygous FH
- Mixed hyperlipidemia, TG > 150
- Eligible for statin treatment

**B-mode US**
- Statin dose titration
  - Target: LDL-C to CV risk goal

**B-mode US / 6 months**
- Novo agent and statin

**Coronary IVUS**
- Statin alone*

- 24 months D-B/ randomized Tx
  - Same as statin dose at the end of the titration period.

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<table>
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<tr>
<th>Target population</th>
<th>technology</th>
<th>Number of subjects</th>
<th>Endpoint</th>
</tr>
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<tbody>
<tr>
<td>CHD</td>
<td>IVUS</td>
<td>~ 1000</td>
<td>Nominal Δ PAV</td>
</tr>
<tr>
<td>Mixed dyslipidemia</td>
<td>Carotid ultrasound</td>
<td>~ 800</td>
<td>Δ IMT (mm)/year</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td>Carotid ultrasound</td>
<td>~ 800</td>
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