UMPIRE trial
Use of a Multidrug Pill In Reducing cardiovascular Events

Simon Thom; UMPIRE Collaborative group

Cardiovascular combination pharmacotherapy summit,
Melbourne, 8 May 2014
Disclosure statement of financial interest

Within the past 2 years, I have had a financial arrangement with the healthcare related company listed below.

<table>
<thead>
<tr>
<th>Affiliation / financial relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant / research support</td>
<td>Dr Reddy’s Labs Ltd</td>
</tr>
</tbody>
</table>

Travel funds via my employing institution (Imperial College London) in relation to the UMPIRE trial.

Simon Thom
Primary objectives

- To test the hypothesis that a FDC-based strategy (a “polypill”) for delivery of preventive medications (aspirin, statin & 2 BP lowering drugs) compared with usual care might improve:
  - Adherence to indicated therapy
  - Systolic BP
  - LDL-cholesterol,

at the end of the study,
in people with (or at high risk of) CVD.
**PROBE design (c/o IMPACT & Kanyini-GAP)**

- Patients with established CVD; or at ≥ 15% 5-year risk (n = 2000, India & Europe)
  - Randomisation
    - Treatment strategy based on fixed dose combination
    - Continued “usual care”
  - 1 month, 6 month, 12 month, 18 month follow-up
  - 24 months or End of Study *

← inclusion

exclusion: contraindications or known intolerance of FDC components

* 12 months after last randomisation (range 12 – 24)
**Methods**

- Adherence: self-reported use of [antiplatelet, statin and ≥2 BP lowering drugs]
- BP: electronic Omron 705CP II + printer
- Cholesterol & blood tests: local laboratories

**Randomisation**

- FDC: usual care, 1 : 1 (web-based)
- Stratified by presence or absence of established CVD

**Trial sites**

- 28 in India
- 3 in Europe (Dublin, London, Utrecht)

**Recruitment**

- June 2010 – July 2011
## Study treatments

### Fixed dose combinations, x 2

<table>
<thead>
<tr>
<th>Version 1</th>
<th>Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin 75mg</td>
<td>aspirin 75mg</td>
</tr>
<tr>
<td>simvastatin 40mg</td>
<td>simvastatin 40mg</td>
</tr>
<tr>
<td>lisinopril 10mg</td>
<td>lisinopril 10mg</td>
</tr>
<tr>
<td>atenolol 50mg</td>
<td>hydrochlorothiazide 12.5mg</td>
</tr>
</tbody>
</table>

Physicians could add additional medications, stop the FDC & begin treatment with separate medications, or switch FDC version.

### Usual care

As per local clinical guidelines.

Participants in the FDC group were dispensed study FDC free of charge from their trial centre.

Participants in the usual care group acquired their medications subject to local payments or exemptions; 966 participants (48%) were exempt from medication charges.
Patients screened, 2138
Ineligible, 134
Randomised, 2004

FDC, 1002
Visits, 993
Visits, 977
Visits, 935
Visits, 524
Visits, 34

Usual care, 1002
Visits, 994
Visits, 993
Visits, 978
Visits, 925
Visits, 36

Baseline
Month 1
Month 6
Month 12
Month 18
Month 24

UMPIRE, Consort diagram

Visits, 955
Medication data, 945
BP, 927; LDL, 908

End of study
Visits, 952
Medication data, 947
BP, 913; LDL, 888

Median follow-up → 15 months
## Results

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>FDC (N = 1002)</th>
<th>Usual care (N = 1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.1 (10.4)</td>
<td>61.6 (10.8)</td>
</tr>
<tr>
<td>Male</td>
<td>81 %</td>
<td>82 %</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137.0 (21.3)</td>
<td>137.7 (21.1)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.3 (0.8)</td>
<td>2.4 (0.9)</td>
</tr>
</tbody>
</table>

### Medical history

- Established CVD: 88 %, 88 %
- Diabetes mellitus: 28 %, 28 %

### Current drug treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDC</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive treatment</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.6 %</td>
<td>6.6 %</td>
</tr>
<tr>
<td></td>
<td>1 BP drug</td>
<td>26.5 %</td>
</tr>
<tr>
<td></td>
<td>65.9 %</td>
<td>71.0 %</td>
</tr>
<tr>
<td>Statin</td>
<td>88.0 %</td>
<td>87.6 %</td>
</tr>
<tr>
<td>Anti-platelet drug</td>
<td>91.8 %</td>
<td>91.0 %</td>
</tr>
<tr>
<td>All indicated medications</td>
<td>59.7 %</td>
<td>63.4 %</td>
</tr>
</tbody>
</table>

Indicated medications = statin + anti-platelet + ≥2 anti-hypertensive drugs
## Effects on primary outcomes

- at end of study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FDC (N = 1002)</th>
<th>Usual care (N = 1002)</th>
<th>Treatment Effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (%)</td>
<td>86% (1%)</td>
<td>65% (2%)</td>
<td>1.33 (1.26; 1.41)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129.2 (0.5)</td>
<td>131.7 (0.5)</td>
<td>-2.6 (-4.0; -1.1)</td>
<td>0.0005</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.18 (0.02)</td>
<td>2.29 (0.02)</td>
<td>-0.11 (-0.17; -0.05)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

1 mmol/L = 38.67 mg/dl cholesterol
Adherence to indicated medications by treatment group

FDC
Usual Care

Indicated medications (%)

Baseline: 1002, 978, 935, 524, 34, 36
M24: 1002, 978, 935, 524, 34, 36

Numbers assessed
## Adherence by pre-specified subgroups

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Risk ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established CVD</td>
<td>1.29 (1.22, 1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 15% 5yr risk</td>
<td>1.93 (1.51, 2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reporting all 4 components at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.04 (1.01, 1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>3.35 (2.74, 4.09)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Continent
- Europe: 1.27 (1.18, 1.37)  
- India: 1.40 (1.30, 1.51)
## Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FDC (N = 1002)</th>
<th>Usual care (N = 1002)</th>
<th>Treatment Effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence at 12 months (%)</td>
<td>88% (1%)</td>
<td>65% (2%)</td>
<td>1.36 (1.29; 1.43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.8 (0.3)</td>
<td>75.2 (0.3)</td>
<td>-2.5 (-3.3; -1.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.06 (0.03)</td>
<td>4.12 (0.03)</td>
<td>-0.07 (-0.14; 0.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.14 (0.01)</td>
<td>1.13 (0.01)</td>
<td>0.01 (0.00; 0.03)</td>
<td>0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.61 (0.03)</td>
<td>1.57 (0.03)</td>
<td>0.04 (-0.03; 0.11)</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>94.6 (0.6)</td>
<td>91.9 (0.6)</td>
<td>2.7 (1.0; 4.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Quality of life (EQ5D; VAS)</td>
<td>76.1 (0.56)</td>
<td>73.7 (0.57)</td>
<td>2.43 (0.87; 3.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiovascular events (n)</td>
<td>50 (5%)</td>
<td>35 (3.5%)</td>
<td>1.45 (0.94; 2.24)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Cholesterol 1 mmol/L = 38.67 mg/dl; Triglyceride 1 mmol/L = 88.6 mg/dl; Creatinine I µmol/L = 0.0113 mg/dl.
Conclusions

- An FDC strategy including aspirin, statin & 2 BP lowering drugs improves adherence, BP & cholesterol in patients with established CVD & those at high risk.
- The effect, a 33% increase in adherence over a median interval of 15 months, was evident in a trial population with an unusually high reported use of indicated medication at the outset.
- The greatest effect, a 3-fold increase in adherence, was seen in those non-adherent at the outset.
- The effect on adherence was similar in those exempt or not exempt from medication charges (post hoc analysis).
Thanks for your attention

**Investigators**
- Michiel Bots (UMCU, Utrecht)
- Raghu Cidambi (Dr Reddy’s, Hyderabad)
- Jane Field (Imperial College London)
- Rick Grobbee (UMCU, Utrecht)
- Anushka Patel (George Inst. Hyderabad)
- Neil Poulter (Imperial College London)
- D. Prabhakaran (CCDC, Delhi)
- K. Srinath Reddy (PHFI, Delhi)
- Anthony Rodgers (George Inst. Sydney)
- Alice Stanton (RCSI, Dublin)
- Simon Thom (Imperial College London)

**Statisticians**
- Laurent Billot (George Inst. Sydney)
- Severine Bompoint (George Inst. Sydney)

**Links**
- [http://www.spacecollaboration.org](http://www.spacecollaboration.org)
- [http://www.ctri.in/Clinicaltrials/index.jsp](http://www.ctri.in/Clinicaltrials/index.jsp)
Systolic blood pressure by treatment group

Systolic BP (mm Hg)

Usual Care
FDC

Numbers assessed

Baseline 1002
Month 12 917
Month 18 479
Month 24 32

Usual Care
FDC

1002
892
475
31
LDL-cholesterol by treatment group

![Graph showing LDL-cholesterol levels over time for Usual Care and FDC treatment groups. Numbers assessed at baseline: 986/991, Month 12: 904/877, Month 18: 465/458, Month 24: 32/30.]
## Serious adverse events

<table>
<thead>
<tr>
<th>SAE category</th>
<th>FDC (N = 1002)</th>
<th>Usual care (N = 1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>154</td>
<td>142</td>
</tr>
<tr>
<td>Patients with at least one SAE</td>
<td>118 (11.8%)</td>
<td>102 (10.2%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>42 (4.2%)</td>
<td>27 (2.7%)</td>
</tr>
<tr>
<td>Infections &amp; infestations</td>
<td>16 (1.6%)</td>
<td>10 (1.0%)</td>
</tr>
<tr>
<td>Neoplasms benign &amp; malignant</td>
<td>13 (1.3%)</td>
<td>11 (1.1%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>11 (1.1%)</td>
<td>12 (1.2%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>9 (0.9%)</td>
<td>13 (1.3%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (1.0%)</td>
<td>11 (1.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (3.6%)</td>
<td>40 (4%)</td>
</tr>
</tbody>
</table>