Hypertension

Terry McCormack
Declaration of interests

- Research Grants – Amgen, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, NIHR, Servier
- Advisory Boards and Speaker Fees – Alere, Astellas, AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Lundbeck, MSD, Roche, Sunovian
- NONE RELATED TO HYPERTENSION
- Member NICE Hypertension GDG and TEG
- Secretary British Hypertension Society
- Medtronic Advisory Board over 2 years ago
Did You Know, Number One?

• In many parts of the World doctors start people with proven moderate hypertension on **two drugs** from the very start, usually as a single tablet

• Where is the **proof** for this concept?
Proportion of patients with previously uncontrolled hypertension who achieve target blood pressure through participation in the BHS’s prevention and treatment of hypertension with algorithm based therapy (PATHWAY) trials

Pathway 1
Combination v Monotherapy for Initial Treatment of Hypertension

Pathway 2
Resistant Hypertension: placebo-controlled crossover

Pathway 3
Thiazide vs K⁺-sparing diuretic v Combo
PATHWAY 1
Losartan & HCTZ - Reports Autumn 2014+

- Monotherapy
  - Losartan & HCTZ

- Combination Rx
  - Losartan & Hydrochlorothiazide
  - Losartan & Cozaar-comp

- Combo Rx
  - CC 100/12.5
  - CC 100/25
Study hypothesis

- Lowering BP using drugs triggers adaptive responses
- If triggered early in treatment, they impair further attempts to achieve target BP
- Therefore significant patients become resistant to Rx
Did You Know, Number Two?

- Renal Denervation as a treatment option in hypertension is on hold
The Sympathetic NS Influences
Metabolic Homeostasis

- Secretion of adrenaline & noradrenaline from adrenal glands
- Dilates pupils
- Inhibits salivation
- Relaxes bronchi
- Accelerates heart
- Inhibits digestive activity
- Stimulates glucose release by liver
- Secretion of adrenaline & noradrenaline from adrenal glands
- Relaxes bladder
- Contracts rectum

Cervical
Thoracic
Lumbar
Renal Injury Induces Activation of Sensory Efferent Signals

- Smooth muscle migration
- Vasoconstriction
- Atherosclerosis

- Renal ischemia
- ↓ Stroke volume
- ↑ Adenosine

- Hypertrophy
- Arrhythmias
- Ischemia
- Heart failure

- ↑ Renin release
- Systemic sympathetic gain
- ↑ Na+ retention
- Hypervolemia
- Wall stiffness
- ↓ Decreased RBF
- ↑ Proteinuria
- ↓ BNP resistance

BNP = brain natriuretic peptide; CNS = central nervous system; RBF = renal blood flow.
The Renal Denervation Procedure

- 4-6 focal treatments are delivered
  - 120 seconds per RF treatment
  - ≥5 mm between locations
  - Stable, unique locations
  - Circumferential coverage

- The catheter is pulled, rotated, and new location and prior treatment site are assessed

RF= radiofrequency
Data on file. Medtronic, Inc.
SYMPPLICITY HTN-1: Significant, Sustained BP Reduction to 3 Years

Change in Blood Pressure (mm Hg)

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>-10</td>
<td>-22</td>
</tr>
<tr>
<td>1 Year</td>
<td>-14</td>
<td>-27</td>
</tr>
<tr>
<td>2 Years</td>
<td>-14</td>
<td>-29</td>
</tr>
<tr>
<td>3 Years</td>
<td>-14</td>
<td>-32</td>
</tr>
</tbody>
</table>

$P < 0.01$ for $\Delta$ from baseline for all time points.
Data is reported only on the patients available at each time point.

Expanded results presented at the European Society of Cardiology Annual Meeting, 2013.
SYMPPLICITY HTN-2: BP Reductions Sustained to 3 Years

Sustained Reductions in the Pooled (RDN and Crossover) Group*

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>-28</td>
<td>-10</td>
</tr>
<tr>
<td>12 Months</td>
<td>-26</td>
<td>-10</td>
</tr>
<tr>
<td>18 Months</td>
<td>-31</td>
<td>-12</td>
</tr>
<tr>
<td>24 Months</td>
<td>-30</td>
<td>-11</td>
</tr>
<tr>
<td>30 Months</td>
<td>-34</td>
<td>-13</td>
</tr>
<tr>
<td>36 Months</td>
<td>-33</td>
<td>-14</td>
</tr>
</tbody>
</table>

$P < 0.01$ at all time points

*Crossover patients only had 30 months post-procedure data.
SYMPPLICITY HTN-3: Severe Drug-Resistant HTN
Office SBP ≥160 mm Hg

- 2:1 randomization, blinded and controlled
- **Sham** procedure in control patients that included renal angiogram
- 535 subjects randomized out of 1441 enrolled (63% screen failure rate)
- 2-week screening process, including maximum tolerated doses of antihypertensives

2 weeks

**Screening Visit 1**
- Office SBP ≥160 mm Hg
- Full doses ≥3 meds
- No med changes in past 2 weeks
- No planned med changes for 6 mo

**Screening Visit 2**
- Office SBP ≥160 mm Hg
- 24-h ABPM SBP ≥135 mm Hg
- Documented med adherence

**Sham Procedure**
- Renal angiogram; Eligible subjects randomized

**Renal Denervation**

2 weeks

1 mo 3 mo

Home BP & HTN med confirmation

6 mo

Primary endpoint

12-60 mo

1 mo 3 mo

1 mo

- Patients, BP assessors, and study personnel all blinded to treatment status
- No changes in medications for 6 M
Patient Disposition

1441 subjects assessed for eligibility

Excluded:
- 880 not eligible for randomization
- 26 eligible but not randomized because randomization cap was reached

535 subjects randomized

364 subjects randomly allocated to renal denervation  2:1  171 subjects randomly allocated to sham control

- 2 subjects died
- 1 subject withdrew
- 11 missed 6-month visit

350 (96.2%) subjects with 6 month follow-up

169 (98.8%) subjects with 6 month follow-up
Primary Efficacy Endpoint
Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin

-2.39 (-6.89, 2.12), $P = 0.255$ (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint
Secondary Efficacy Endpoint
Ambulatory Systolic Blood Pressure at 6 Months, 2 mm Superiority Margin

-1.96 (-4.97, 1.06), $P = 0.979$ (ITT analysis with 2 mm Hg superiority margin)

- Did not meet secondary efficacy endpoint
Guidelines/Consensus Statements on Renal Denervation are Available

United Kingdom¹

ESH²

The Joint UK Societies current perspective:
Data from the trial will be reported at a forthcoming international meeting and in peer reviewed journals. To make a proper evaluation of the implications of this trial for renal denervation we need to thoroughly review the results of Symplicity HTN3 and not rush to hasty conclusions. While we await the data from Symplicity HTN3, we recommend a temporary moratorium on renal denervation procedures for all cases as part of routine care in the NHS and private practice in the UK.

ESH=European Society of Hypertension.
Bipolar Energy Delivery
A localized, more precise treatment approach.
Did You Know, Number Three?

• The Government is keen on apps
• 2018 target for open records
Patient self-management

- Encourage home monitoring
  TASMINH2
- Many apps available
- 9700 health apps at March 2013
- >1.7 billion mobile health users by 2018
iMonitors

- Withings wireless £109
- iHealth wireless £60
- Qardioarm £95
- Bioimpedance will be the future
• **Urine Spot Testing** is a potential breakthrough in the management of resistant hypertension
High rates of non-adherence to antihypertensive treatment in patients from a specialist cardiovascular centre

The results of high-performance liquid chromatography-tandem mass spectrometry urine analysis

Drug Resistant Hypertension

- Multiple consultations
- Multiple investigations
- Multiple-drug regimens
- Renal Denervation
- ROX procedure

• NHS → ££££££££££
Directly Observed Therapy Service

- Specialist Nurse evaluation
- Time-consuming
- Expensive
- Risks of 1st time administration of multiple-drug therapy

→ Alternative needed
Spot Urine Analysis by Mass Spectrometry

- Simple
- Reproducible
- Relatively Cheap: £30/analysis
- In-house design by a Leicester Chemical Pathologist
Indication for urine Adherence Test
208 Sequential Patients

NEW REFERRALS 60%
N = 125

RENAAL
N = 17

FOLLOW-UPS 32%
N = 66

DENERVATION 8%

NEWLY REF. RENAL DENERVATION 1%

F/U RENAL DENERVATION 7%
## Results

**Drug Adherence by Indication for Urine Screen**

<table>
<thead>
<tr>
<th>Measure of Non-adherence</th>
<th>All</th>
<th>New Referrals</th>
<th>Follow-Ups</th>
<th>Renal Denerv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>208</td>
<td>125</td>
<td>66</td>
<td>17</td>
</tr>
<tr>
<td>Mean number of drugs screened</td>
<td>3.0</td>
<td>2.6</td>
<td>3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>[SD]</td>
<td>[1.5 ]</td>
<td>[1.4]</td>
<td>[1.5]</td>
<td>[1.5]</td>
</tr>
<tr>
<td>Mean number of drugs detected</td>
<td>2.3</td>
<td>2.0</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>[SD]</td>
<td>[1.5 ]</td>
<td>[1.3]</td>
<td>[1.5]</td>
<td>[1.8]</td>
</tr>
<tr>
<td>Complete non-adherence (n)</td>
<td>10.1%</td>
<td>8.8%</td>
<td>9.1%</td>
<td>23.5%</td>
</tr>
<tr>
<td></td>
<td>(21)</td>
<td>(11)</td>
<td>(6)</td>
<td>(4)</td>
</tr>
<tr>
<td>Partial non-adherence (n)</td>
<td>14.9%</td>
<td>9.6%</td>
<td>28.8%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(31)</td>
<td>(12)</td>
<td>(19)</td>
<td></td>
</tr>
<tr>
<td>Any non-adherence (n)</td>
<td>25.0%</td>
<td>18.4%</td>
<td>37.9%</td>
<td>23.5%</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td>(23)</td>
<td>(25)</td>
<td>(4)</td>
</tr>
</tbody>
</table>
## Results

### Association between BP and Non-Adherence

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Adherent</th>
<th>Non-Adherent</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic SBP(^1)</td>
<td>160.6 ± 24.0</td>
<td>170.4 ± 24.7</td>
<td>0.021</td>
</tr>
<tr>
<td>Clinic DBP(^1)</td>
<td>89.7 ± 14.4</td>
<td>99.5 ± 19.1</td>
<td>0.001</td>
</tr>
<tr>
<td>24-hour mean day-time SBP(^2)</td>
<td>152.4 ± 19.8</td>
<td>158.8 ± 21.1</td>
<td>0.181</td>
</tr>
<tr>
<td>24-hour mean day-time DBP(^2)</td>
<td>86.0 ± 13.1</td>
<td>93.7 ± 13.0</td>
<td>0.029</td>
</tr>
</tbody>
</table>

P-value* – level of statistical significance after adjustment for age, sex, ethnicity, and clinical category (new referrals, follow-up patients, referrals for renal denervation),

\(^1\)information available for 152 adherent and 52 non-adherent patients;

\(^2\)information available for 121 adherent and 26 non-adherent patients
Results

% Adherence by Number of Drugs Prescribed
All Patients [n]

1 drug [44]: 97.7
2 drugs [36]: 94.4
3 drugs [48]: 75
4 drugs [44]: 34.1
5 drugs [23]: 56.5
6 drugs [10]: 60
7 drugs [3]: 100

% adherence
% any non-adherence
Did You Know, Finally?

- Coincidences do occur
- The Press sometimes get things wrong
Gaddafi flees as regime collapses

By Richard Spencer
Middle East Correspondent and James Shipping in Kuwait City

The regime of Colonel Muammar Gaddafi in Libya was on the verge of collapse last night after opposition forces took Tripoli after months of siege and the defiant leader fled the capital.

Forces loyal to the 60-year-old dictator launched an early morning assault on the city and it was confirmed that he had fled to the western part of the country. The news came as the UK government said it planned to bring out British citizens. At least 100 Foreign Office staff are preparing to begin the evacuation today, and at least 300 other Britons are thought to be in the city.

William Hague, the Foreign Secretary, said the UK had sent urgent evacuation plans to the US and the European Union. The move would allow the UK to bring out its citizens by sea.

A suicide bomber attack in the Libyan capital, Tripoli, and that by the way, had left Gaddafi’s forces with the advantage. The city was a divided city, divided into two main parts.

Pro-Gaddafi forces received a second massacre in the southern town of Sebha, where they were ambushed and killed.

Porn, my husband and me

By Simon Elson

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It is a much-heralded theme: the sexual revolution. And it’s not just the Western world that is in the grip of the movement.

In the US, for example, the number of women who have had sex with more than one partner in their lifetime has doubled in the past 20 years, according to recent research.

But in countries like China, where traditional values still hold sway, there is a growing acceptance of sexual freedom.

A new study has found that more than 40 per cent of people aged 18-29 in China now have multiple partners, compared to just 20 per cent in the 1990s.

This trend is particularly apparent among young couples, who are more likely to engage in casual relationships.

Millions with high blood pressure are misdiagnosed

By Edward Adams

In a landmark study published in the Lancet, researchers have found that millions of people with high blood pressure are being treated incorrectly.

The study, which was carried out in the UK, found that 30 per cent of people with high blood pressure were being prescribed medication that was not effective.

The researchers said that this could be putting patients at risk of heart disease and stroke.

The findings have led to calls for a review of current guidelines for the treatment of high blood pressure.

One in four people experiences a surge of pulse rate on entering a GPs’ room: it’s white coat syndrome

By John White

A new study has found that one in four people experiences a surge of pulse rate on entering a GPs’ room, a phenomenon known as white coat syndrome.

The research, which was carried out in the US, found that the effect was most common among older people and those with high blood pressure.

The findings have led to calls for GPs to be more sensitive to the potential effects of a patient’s anxiety.

The Blood Pressure Association has warned that doctors should be aware of the phenomenon and not assume that a surge in pulse rate is due to a medical condition.

The daily Telegraph

Newspaper of the Year

Irish Republic: £1.20
telegraph.co.uk
No 48,436
£1.00
Blood pressure drugs could do more harm than good

By Sarah Knapt
Science Correspondent

MILLIONS of elderly people taking high-blood pressure tablets, such as beta-blockers, may be doing themselves more harm than good. New research suggests that some recent studies have questioned whether the risks and side effects of medication are outweighing the benefits.

Hypertension drugs lower blood pressure but can lead to side-effects which include dizziness, excessive tiredness and blurred vision.

"Older patients and their doctors need to weigh the harms as well as the benefits in prescribing medications, particularly when the harms may be less as serious as the diseases we hope the medications prevent," says the lead author, Prof Mary Tinetti of Yale School of Medicine.

"Patients may find themselves in the tough position of either choosing to continue their blood pressure medication and risk side-effects that could lead to life-altering falls, or discontinuing their medications and risking heart attacks and strokes."

"Although we cannot exclude the possibility that factors other than the medications accounted for the increased risk of injury, these medications may be more harmful in some individuals than thought," she said. Researchers

Continued on Page 2

Troubled academy stripped of 10 schools

By Graeme Paton
Education Editor

ONE of England’s biggest academy chains is to be stripped of almost a third of its schools amid serious concerns over education standards. The Daily Telegraph has discovered.

E-ACT, a charity that sponsors 34 state-funded schools, is being forced to give up control of 10 to the Government after a series of investigations by Ofsted unearthed weaknesses.

It is believed the biggest wholesale withdrawal as claims that some groups running the schools have expanded too quickly. A number of chains have already been told that they cannot take on any more academies until concerns over standards have been addressed and E-ACT itself was at the centre of a critical report into financial mismanagement last year.

The latest announcement comes just weeks after David Laws, the Liberal Democrat schools minister, called for Ofsted to be given new powers to directly inspect academies without consent. By Graeme Paton

HAVE YOU SEEN THIS MAN?

By Christopher Hope
Senior Political Correspondent

HARRETT HARMAN was last night forced to deny supporting paedophilia after she admitted that a prominent child sex group was allowed to join a civil liberties organisation she helped to run in the Seventies.

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Ukraine’s ex-president

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Harman defends link to paedophile group

By Christopher Hope
Senior Political Correspondent

Miss Harman and Mr Dromey broke their week of silence following a series of newspaper articles alleging that they were “as^ologists for paedophilia” as officials at the National Council for Civil Liberties, known today as the campaign group Liberty. The Council controversially granted “affiliate” status to the Paedophile Information Exchange (PIE) in 1975, putting its founder Tom O’Cain on one of the council’s working groups. Miss Harman, for his part, led the movement to end the campaign group’s funding.
QUESTIONS?