Diabetes Professional Care 2019

Cardiovascular Disease Prevention – the MDT Panel

The ABC of CVD Prevention
Declaration of Conflict of Interests

Dr Jim Moore FRCP Edin
GP and GPwSI in Cardiology, Cheltenham

President Elect Primary Care Cardiovascular Society
NICE Guideline Committee member - Chronic Heart Failure 2018
National Heart Failure Audit Steering group
Chair of the GLOS CCG Circulatory Clinical Programme Group

In the last year Honoraria received from AstraZeneca, Bayer and Novartis for various activities including attending and participating in educational events and advisory boards
Primary Care Cardiovascular Society

www.pccsuk.org
How to register for Membership

**Annual Subscription**
GPs £40
Pharmacists, GP Registrars and Nurses £20

**How to Register**
To register for membership please follow this link
http://pccs.lcwmmed.co.uk

Or call 01444 414264
Or email registrations@LCWmed.co.uk
New website
The ABC of CVD Prevention
The deadly quartet

- Type 2 diabetes
- Hypertension
- Obesity
- Dyslipidemia

Insulin resistance leads to:

- Early cardiovascular disease/endothelial dysfunction
  - Macrovascular
  - Microvascular

Atrial Fibrillation
Current detection and management of Atrial fibrillation (AF)

Now

79% Detection 84% Management

2029

85% 90%
The **REAL** Importance of AF

- Most important preventable cause of stroke
- Emboli from the LA appendage
There is a national programme across England to tackle the issue of AF-related strokes

There is a national programme across England to tackle the issue of AF-related strokes\(^1\)

**DETECT**

**FIND MORE**
Awareness campaigns, educate and encourage people to check their pulse rhythm\(^2\)

**PROTECT**

**TREAT MORE**
Ensure that all suitable patients with AF receive appropriate treatment\(^2\)

**PERFECT**

**TREAT BETTER**
Ensure optimal treatment in all patients\(^2\)

---

Maximise routine opportunities for case finding to improve AF detection rates

OPPORTUNISTIC pulse checking
Closes the DIAGNOSIS GAP

UNDIAGNOSED → DIAGNOSED

Suspected paroxysmal AF undetected by 12L ECG

Event recorder (AliveCor FDA approved)
AF screening in chronic disease management / health promotion

✓ Hypertension
✓ Heart failure
✓ CHD
✓ Stroke
✓ Diabetes
✓ CKD
✓ Weight management
✓ NHS Health Check

> 90% target population coverage
There is a national programme across England to tackle the issue of AF-related strokes

What are the perceived barriers to anticoagulation?
Physician’s judgement is a major factor in withholding anticoagulation

Why physicians withhold VKAs in patients at risk of stroke (CHADS$_2$ score ≥2)*

<table>
<thead>
<tr>
<th>Main reason anticoagulant not used</th>
<th>Eligible patients n=2302 [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol misuse</td>
<td>11 (0.5)</td>
</tr>
<tr>
<td>Already taking antiplatelet drugs for other medical condition</td>
<td>117 (5.1)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>165 (7.2)</td>
</tr>
<tr>
<td>Previous bleeding event</td>
<td>55 (2.4)</td>
</tr>
<tr>
<td>Taking medication contraindicated or cautioned for use with VKA</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>239 (10.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>587 (25.5)</td>
</tr>
<tr>
<td>Physician’s choice</td>
<td>1112 (48.3)</td>
</tr>
</tbody>
</table>

*Physicians’ clinical judgment of stroke risk appears to incorporate factors not included in CHADS2 and CHA2DS2-VASc. Kakkar AK et al. PLoS One 2013;8:e63479
Physician’s judgement is a major factor in withholding anticoagulation

Why physicians withhold VKAs in patients at risk of stroke (CHADS$_2$ score $\geq$2)*

<table>
<thead>
<tr>
<th>Main reason anticoagulant not used</th>
<th>Eligible patients n=2302 [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s choice</td>
<td>1112 (48.3)</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>170 (7.4)</td>
</tr>
<tr>
<td>Concern over patient compliance</td>
<td>121 (5.3)</td>
</tr>
<tr>
<td>Guideline recommendation</td>
<td>32 (1.4)</td>
</tr>
<tr>
<td>Fall risk</td>
<td>150 (6.5)</td>
</tr>
<tr>
<td>Low risk of stroke</td>
<td>95 (4.1)</td>
</tr>
<tr>
<td>Other</td>
<td>544 (23.6)</td>
</tr>
</tbody>
</table>

*Physicians’ clinical judgment of stroke risk appears to incorporate factors not included in CHADS2 and CHA2DS2-VASc. Kakkar AK et al. PLoS One 2013;8:e63479
### CHA2DS2-VASc Score and Stroke Risk?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke/ TIA or systemic embolism</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Congestive heart failure*</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

Add points together

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Stroke rate events/100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>23.64</td>
</tr>
<tr>
<td>8</td>
<td>22.38</td>
</tr>
<tr>
<td>7</td>
<td>21.50</td>
</tr>
<tr>
<td>6</td>
<td>19.74</td>
</tr>
<tr>
<td>5</td>
<td>15.26</td>
</tr>
<tr>
<td>4</td>
<td>9.27</td>
</tr>
<tr>
<td>3</td>
<td>5.92</td>
</tr>
<tr>
<td>2</td>
<td>3.71</td>
</tr>
<tr>
<td>1</td>
<td>2.01</td>
</tr>
<tr>
<td>0</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*Or moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%).

TIA, transient ischaemic attack

The risk of ischaemic stroke ‘without’ OAC exceeds the risk of intracranial bleeding ‘with’ OAC*

Relation between risk scores and annual event rates of ischaemic stroke and ICH in relation to use of oral anticoagulation in 159,013 Swedish AF patients followed up for 1.5±1.1 years (2005–2008)

*Except those with a very low risk of stroke
Who should be anticoagulated? (ESC 2016)

Mechanical heart valves or moderate or severe mitral stenosis

No

Estimate stroke risk based on number of CHA2DS2-VASc risk factors

0\textsuperscript{a}

No antplatelet or anticoagulant treatment (IIbB)

1

OAC should be considered (IIaB)

≥2

Oral anticoagulation indicated
Assess for contra-indications
Correct reversible bleeding risk factors

LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)

NOAC (IA)\textsuperscript{b}

VKA (IA)\textsuperscript{c}

\textsuperscript{a} Includes women without other stroke risk factors

\textsuperscript{b} IIaB for women with only one additional stroke risk factor

\textsuperscript{c} IIB for patients with mechanical heart valves or mitral stenosis

Adapted from The ESC. 2016 ESC Guidelines for the management of atrial fibrillation. Available at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management. Accessed February 2019
NOACs showed a favourable benefit-risk profile versus warfarin

- Meta-analysis of Phase III trials for stroke/SE prevention in non-valvular AF patients on NOACs vs warfarin

19%* reduction in stroke/SE
52%* reduction in ICH
14%† reduction in major bleeding
25%# increase in GI bleeding vs warfarin

NOAC events vs warfarin events
911 vs 1107
204 vs 425
1541 vs 1802
751 vs 591

The relative efficacy and safety profile of NOACs was consistent across a wide spectrum of non-valvular AF patients

Note: 42,411 participants received a new oral anticoagulant and 29,272 participants received warfarin

*P<0.0001; †P=0.06; # P=0.04
There is a national programme across England to tackle the issue of AF-related strokes\(^1\)

### DETECT

**FIND MORE**

Awareness campaigns, educate and encourage people to check their pulse rhythm\(^2\)

### PROTECT

**TREAT MORE**

Ensure that all suitable patients with AF receive appropriate treatment\(^2\)

### PERFECT

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Ensure optimal treatment in all patients\(^2\)

---

Warfarin and its challenging therapeutic window


Requires dose adjustment and regular monitoring

**Intracranial bleed**

**Therapeutic range**

**International normalized ratio (INR)**

- **Ischaemic stroke**
- **Intracranial bleed**
Time in therapeutic range matters

Proportion of patients without a stroke over time stratified by time spent within therapeutic range (INR 2.0–3.0), N=37,907 patients with AF

*The non-warfarin group comprised AF patients not treated with antithrombotic therapy, defined as study patients with no record ever of INR measurements or prescribing of warfarin, aspirin or clopidogrel, or dipyridamole. Warfarin group: study patients with at least one INR measurement in medical history.

Gallagher AM et al. Thromb Haemost 2011;106:968–977

Poor INR control increases the risk of stroke in real-world practice
Dose adjustments are required in the presence of renal impairment

**Rivaroxaban**
- Patient has risk factor for stroke
  - Estimate CrCl
    - <15 mL/min
    - 15-49 mL/min*
    - ≥50 mL/min
    - Not recommended
  - 15 mg OD
  - 20 mg OD

*Rivaroxaban to be used with caution in patients with CrCl 15–29 mL/min

**Dabigatran**
- Patient has risk factor for stroke
  - Estimate CrCl
    - <30 mL/min
    - 30–50 mL/min
    - >50 mL/min
      - See Footnote
      - Age ≥80 y or taking verapamil
      - 75–80 y or with any of the issues listed in Footnote*
      - ≥80 y or taking verapamil
      - 75–80 y or with any of the issues listed in Footnote*
    - Contra-indicated
    - 110 mg BID
    - 150 mg BID
    - 110 mg BID
    - 110 mg BID
    - 110 mg BID
    - 110 mg BID
    - 150 mg BID
    - 150 mg BID

*Dabigatran dose of 110 mg or 150 mg BID, based on individual assessment of thromboembolic and bleeding risk in patients with gastritis, esophagitis or gastroesophageal reflux, or increased bleeding risk

1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

**Apixaban**
- Patient has risk factor for stroke
  - Estimate CrCl
    - <15 mL/min
    - 15–29 mL/min
    - ≥30 mL/min
      - Check age
      - ≥80 years
      - ≤60 kg
      - ≥133 μmol/L
      - If ≥2 features
      - If ≤1 feature
    - Not recommended
    - 2.5 mg BID
    - 2.5 mg BID
    - 5 mg BID

**Edoxaban**
- Patient has risk factor for stroke
  - Estimate CrCl
    - <15 mL/min
    - 15–29 mL/min
    - ≥30 mL/min
      - Check serum creatinine
      - ≥80 years
      - ≤60 kg
      - ≥133 μmol/L
      - If ≥2 features
      - If ≤1 feature
    - Not recommended
    - 30 mg OD
    - ≤60Kg
    - Potent P-gp Inhibitors*
      - 60 mg OD
      - 30 mg OD
      - 30 mg OD
      - 30 mg OD

*Potent P-gp inhibitors include dronedarone, erythromycin, ciclosporin and ketoconazole
Dose adjustments are based on severity of renal impairment, so...

<table>
<thead>
<tr>
<th>Category</th>
<th>eGFR (mL/min/1.73m²)</th>
<th>CrCl (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥90</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Mild</td>
<td>60–89</td>
<td>50–80</td>
</tr>
<tr>
<td>Moderate</td>
<td>30–59</td>
<td>30–50</td>
</tr>
<tr>
<td>Severe</td>
<td>15–29</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

85-year-old woman who weighs 92 kg with serum creatinine 132 has an:
- eGFR 32
- Estimated CrCl 40

85-year-old woman who weighs 55 kg with a serum creatinine 132 has an:
- eGFR 32
- Estimated CrCl 24

Potential under-dosing in AF is associated with higher risk of stroke/systemic embolism

A retrospective claims database analysis of 13,392 patients without renal indication for dose reduction*

No head-to-head clinical trials have been performed between NOACs to evaluate this data

Inappropriate dosing is not recommended. Please refer to relevant NOAC SmPC for appropriate dosing regimen for stroke prevention in patients with NVAF

NVAF: non valvular atrial fibrillation; SE: systemic embolism. *Excluded: apixaban, serum creatinine ≥1.5 mg/dl; dabigatran, eGFR <30 ml/min/1.73 m2; rivaroxaban, eGFR <50 ml/min/1.73 m2. Propensity score matching used to account for differences in baseline characteristics between patients receiving reduced and standard doses. Yao X et al. J Am Coll Cardiol 2017;69:2779–90

HR (95% CI) 0.92 (0.30–2.87) (p=0.89)
HR (95% CI) 1.09 (0.63–1.87) (p=0.76)
HR (95% CI) 0.71 (0.24–2.09) (p=0.54)
HR (95% CI) 0.91 (0.45–1.85) (p=0.80)
HR (95% CI) 1.29 (0.48–3.42) (p=0.61)
The question is not who we should anticoagulate.

Few patients have a CHA$_2$DS$_2$-VASc=0.

Therefore...

The question is not who we should anticoagulate.

Few patients are ineligible for an OAC.

Therefore...

The question is who we should not anticoagulate.
"B"

Blood Pressure
Hypertension – what’s new?

Beverley Bostock RGN MSc QN
PCCS nurse board member
beverley.bostock@nhs.net
Hypertension in adults: diagnosis and treatment

Offer lifestyle advice and continue to offer it periodically

Clinic BP
- Under 140/90 mmHg: Check BP at least every 5 years and more often if close to 140/90 mmHg
- 140/90 to 179/119 mmHg: Offer ABPM (or HBPM if ABPM is declined or not tolerated), investigate for target organ damage, assess cardiovascular risk
- 180/120 mmHg or more: Refer for same-day specialist review if:
  - Retinal haemorrhage or papilloedema (accelerated hypertension) or
  - Life-threatening symptoms or
  - Suspected pheochromocytoma

ABPM or HBPM
- Under 135/85 mmHg: Check BP at least every 5 years and more often if clinic BP close to 140/90 mmHg. If evidence of target organ damage, consider alternative causes
- 135/85 to 149/94 mmHg (Stage 1): Discuss the person’s CVD risk and preferences for treatment, including no treatment. See NICE’s patient decision aid for hypertension. See next page for choice of drug, monitoring and BP targets.
  - Offer lifestyle advice and consider drug treatment
- 150/95 mmHg or more (Stage 2): Offer lifestyle advice and drug treatment
  - Age >40: Consider specialist evaluation of secondary causes and assessment of long-term benefits and risks of treatment

Use clinical judgement for people with frailty or multimorbidity

- Age >80 with clinic BP >150/90 mmHg:
  - Offer lifestyle advice and consider drug treatment
- Age >80 with target organ damage, CVD, renal disease, diabetes or 10-year CVD risk >10%:
  - Offer lifestyle advice and discuss starting drug treatment
- Age <60 with 10-year CVD risk <10%:
  - Offer lifestyle advice and consider drug treatment
- Age <40:
  - Consider specialist evaluation of secondary causes and assessment of long-term benefits and risks of treatment
Diagnosis

- If clinic BP $\geq 140/90$ – 179/119mm Hg check home readings
  - APBM – gold standard, using day time average
  - HBPM – if ABPM not available/unsuitable
  - BD readings for 4-7 days, losing day 1 before working out the average
Stages

◆ Stage 1
  ● Home: 135/85 – 149/94mm Hg

◆ Stage 2
  ● Home: >150/95mm Hg
Stage 1

- Treat if CVD risk >10%
- If evidence of CVD, renal problems, diabetes
- Consider treating under 60s anyway as lifetime risk may be underestimated
Stage 2

Treat
Treatment
The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to help lower blood pressure and prevent heart disease, stroke, diabetes and even some forms of cancer. It focuses on eating more fresh fruits and vegetables.

This is a guide to how much of each food group you should eat every day, based on eating 2,000 calories per day.
Choice of antihypertensive drug, monitoring treatment and BP targets

Hypertension with type 2 diabetes

Step 1
ACEI or ARB$^{2,3}$

Step 2
ACEI or ARB$^{2,3}$ + CCB or thiazide-like diuretic

Step 3
ACEI or ARB$^{2,3}$ + CCB + thiazide-like diuretic

Step 4
- Confirm resistant hypertension: confirm elevated BP with ABPM or HBPM, check for postural hypertension and discuss adherence
- Consider seeking expert advice or adding:
  - low-dose spironolactone if blood potassium level is ≤4.5 mmol/l
  - alpha-blocker or beta-blocker if blood potassium level is >4.5 mmol/l
- Seek expert advice if BP is uncontrolled on optimal tolerated doses of 4 drugs

Hypertension without type 2 diabetes

Step 1
CCB

Step 2
ACEI or ARB$^{2,3}$ + CCB

Step 3
ACEI or ARB$^{2,3}$ or thiazide-like diuretic

Monitoring treatment

Use clinic BP to monitor treatment.

Measure standing and sitting BP in people with:
- type 2 diabetes or
- symptoms of postural hypotension or
- aged 80 and over.

Advise people who want to self-monitor to use HBPM. Provide training and advice.

Consider ABPM or HBPM, in addition to clinic BP, for people with white-coat effect or masked hypertension.

BP targets

Reduce and maintain BP to the following targets:

Age <80 years:
- Clinic BP <140/90 mmHg
- ABPM/HBPM <135/85 mmHg

Age ≥80 years:
- Clinic BP <150/90 mmHg
- ABPM/HBPM <145/85 mmHg

Postural hypotension:
- Base target on standing BP

Frailty or multimorbidity:
- Use clinical judgement
In a nutshell

- Under 55 and/or diabetes?  ACEi or ARB
- 55+ or African-Caribbean?  CCB
- Step 2 – add the other one OR thiazide-like diuretic
- Before step 3 – check adherence to meds and lifestyle
- Step 3 means all three
"C"

Cholesterol
Current detection and management of
High Cholesterol and Familial Hypercholesterolaemia (FH)

High Cholesterol
Now 49% Detection 75% 2029 35% Management 45% 2029

Familial Hypercholesterolaemia (FH)
Now 5% Detection 2024 25%
Lipoproteins   HDL … LDL and non HDL

◆ High Density (Highly desirable) Lipoprotein or HDL
  - is inversely related to CHD risk….the higher the better!
  - average HDL value in the UK is 1.2 for men and 1.4 for women.
  - TC/HDL ratio greater predictive value for CHD than LDL.

◆ Low Density (Less desirable) Lipoprotein
  - is directly related to CHD risk….the lower the better

◆ Non-HDL cholesterol (Not desirable) ….TC minus HDL
  - is directly related to CHD risk….the lower the better
  - calculated by subtracting HDL from the total cholesterol
  - has a greater predictive value for CHD than LDL
  - is a surrogate for Apolipoprotein B
On-Treatment LDL and CHD Events in Statin Trials

Adapted from Rosenson RS. Expert Opin Emerg Drugs. 2004;9:269-279.
Non-adherence can lead to poor cholesterol management thereby increasing CV risk

2. NICE clinical guideline 67 for lipid modification. Available at: www.nice.org.uk Last accessed November 2014
Lipid profiles ........ the BIGGER picture

- Patient A - Tot Chol 5.5 : HDL 2.4, LDL 2.6, Non-HDL 3.1 , TG 1.9, TC/HDL 2.3

- Patient B - Tot Chol 5.5 : HDL 0.7, LDL 4.0, Non-HDL 3.8, TG 4.9, TC/HDL 7.8

- 95% confidence limits on a single cholesterol measurement are around ± 14% of the true value
Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181)

Published July 2014
Primary prevention
Identifying people for a full formal risk assessment

*Use a systematic strategy to identify those likely to be at high risk of CVD*

- estimate CVD risk and prioritise those with a 10 year CVD risk of 10% or more for a full formal risk assessment

- Review risk in over 40’s on an ongoing basis

*Do not use opportunistic assessment as the main strategy to identify CVD in unselected people*
Primary prevention

Offer atorvastatin 20mg to
- Up to age 84 years with 10% or greater risk of CVD over 10 years
- CKD
- Type 1 Diabetes
  - over 40 years old
  - for 10 years or not
  - concomitant nephropathy or CVD risk factors

Consider atorvastatin 20mg
- all adults with Type 1 Diabetes
- over 85 years old

GDG on…..”Why atorvastatin 20mg”
- QALY £4125
- “most clinically and cost effective option for Primary Prevention”
Lipid modification therapy

- Use evidence based therapies that reduce CVD morbidity and mortality
- Statins lower LDL
- If using statins then choose one of high intensity and low acquisition cost
Choose statin of high intensity and low acquisition cost

Reduction in low-density lipoprotein cholesterol

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>-</td>
<td>-</td>
<td>21%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>-</td>
</tr>
</tbody>
</table>

1. 20‒30%: low intensity
2. 31‒40%: medium intensity
3. Above 40%: high intensity
4. Note advice from the MHRA about the increased risk of myopathy associated with high-dose (80 mg) simvastatin (Drug Safety Update May 2010)

Choose statin of high intensity and low acquisition cost

Statin therapy – “the rule of 6”

Effect of Statin Therapy on LDL-C Levels: “The Rule of 6”

-6% -6% -6%

Statin 10 mg 20 mg 40 mg 80 mg

Three-step Titration

% Reduction in LDL Cholesterol
NICE Primary Prevention Decision Aid

Cardiovascular risk 10% over 10 years: no treatment

If 100 people at this level of risk take no statin, over 10 years on average:
- 90 people will not develop CHD or have a stroke (the green faces)
- 10 people will develop CHD or have a stroke (the red faces).

Cardiovascular risk 10% over 10 years: taking atorvastatin

If all 100 people take atorvastatin for 10 years, over that time on average:
- 4 people will be saved from developing CHD or having a stroke (the yellow faces)
- 90 people will not develop CHD or have a stroke, but would not have done anyway (the green faces)
- 6 people will still develop CHD or have a stroke (the red faces).
Follow up & targets in Primary and Secondary prevention

- Measure TC, HDL and non-HDL at 3 months
- **Aim for a greater than 40% reduction in non-HDL cholesterol**
- Consider annual reviews for all patients thereafter

If not achieved non-HDL target
- optimise lifestyle measures (if not already achieved)
- Consider titrating dose of atorvastatin to 80mg where not already taking
- Consider combination therapy with ezetimibe

...still not achieved non-HDL target
- Consider alternative (higher potency) statin
- **Consider combination therapy with ezetimibe**

- **Discuss with patients (at medication review) on low/medium intensity statins the benefits/risks of high intensity statins**
The "NOCEBO effect"

<table>
<thead>
<tr>
<th>Muscle related</th>
<th>Blinded randomised phase (ASCOT-LLA)</th>
<th>Non-blinded non-randomised phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=5079)</td>
<td>Atorvastatin (n=5101)</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>283</td>
<td>298</td>
</tr>
<tr>
<td>AE rate (% per annum)</td>
<td>2:00%</td>
<td>2:03%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>1.03 (0.88-1.21)</td>
</tr>
<tr>
<td>p value</td>
<td>0.72</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Erectile dysfunction**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>302</th>
<th>272</th>
<th>99</th>
<th>88</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE rate (% per annum)</td>
<td>2:14%</td>
<td>186%</td>
<td>0:80%</td>
<td>0:68%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>0.88 (0.75-1.04)</td>
<td>1</td>
<td>0.89 (0.66-1.20)</td>
</tr>
<tr>
<td>p value</td>
<td>0.13</td>
<td>0.44</td>
<td>0.56%</td>
<td>0.56%</td>
</tr>
</tbody>
</table>

**Sleep disturbance**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>210</th>
<th>149</th>
<th>82</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE rate (% per annum)</td>
<td>1:46%</td>
<td>100%</td>
<td>0:66%</td>
<td>0:56%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>0.69 (0.56-0.85)</td>
<td>1</td>
<td>0.87 (0.63-1.20)</td>
</tr>
<tr>
<td>p value</td>
<td>0.005</td>
<td>0.40</td>
<td>0.56%</td>
<td>0.56%</td>
</tr>
</tbody>
</table>

**Cognitive impairment**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>32</th>
<th>31</th>
<th>36</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE rate (% per annum)</td>
<td>0:22%</td>
<td>0:20%</td>
<td>0:29%</td>
<td>0:17%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>0.94 (0.57-1.54)</td>
<td>1</td>
<td>0.59 (0.34-1.02)</td>
</tr>
<tr>
<td>p value</td>
<td>0.81</td>
<td>0.06</td>
<td>0.17%</td>
<td>0.17%</td>
</tr>
</tbody>
</table>

First event only in each phase reported; definite and probable AEs reported; number of patients with at least one event reported. AE=adverse event. HR=hazard ratio.

Table 2: Risk of adverse events of interest
Management of patients with possible statin related muscle symptoms

Exclude other causes of muscle symptoms and interactions

- **take TIME for patient**
  - 2-4 weeks break of statin

- Statin rechallenge
  - Symptoms re-occur:

  **Establish the highest tolerable statin dose**
  - Start with very low dose
  - Change statin, use potent statin
  - Consider alternate day dosing

  **Aim to achieve nHDL target**
  - Use combination therapy with Ezetimibe

  **PCSK9 inhibitors**

**No specific symptoms:**
- Continue statin

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EAS Consensus, EHJ 2015
PMID: 25694464
Laufs et al; Deutsches Arzteblatt 2015
Laufs, Scharnagi, Marz.
Curr Opinion Lipidos 2016
The statin-associated risk of developing diabetes is low in absolute terms when compared with the reduction in coronary events

- Results of a meta-analysis of 13 trials show that statins, as a class, slightly increase the risk of diabetes
- In pre-diabetic patients (FPG 5.6–6.9 mmol/L), rosuvastatin has been associated with an increased risk of diabetes
- Additional factors hypertension, ↑ Triglycerides, ↑BMI
- The risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment

NNH: number needed to harm – 1 additional case of diabetes for every 498 patients treated per year

NNT: number needed to treat – 155 patients treated with a statin to prevent 1 CV event per year

Figure adapted from Preiss D, et al. 2011

Thank you ...any questions?

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