Question 17

Which one of the following would be a relative contraindication to the use of raloxifene (a selective oestrogen receptor modulator) in a peri-menopausal woman?

A. Severe hot flushes
B. Hypertension
C. Family history of breast cancer
D. Hypercholesterolaemia
E. Osteoporosis

Answer:
Selective oestrogen receptor modulators (SERMS)
- Competitive inhibitor of oestrogen binding to the oestrogen receptor (ER)
- Mixed agonist and antagonist action dependant on target tissue
- Bind to ER -> conformational changes depending on target tissue -> variable interaction with different cofactors (either activators/ repressors) -> ↑ or ↓ transcriptional activity

- Examples are tamoxifen (Tamosin, Nolvadex) and raloxifene (Evista)
- Main difference in tamoxifen and raloxifene is their effect on the uterus (tamoxifen -> endometrial proliferation -> ↑ uterine cancer risk)

Raloxifene
- Indicated for treatment and prevention of osteoporosis in post-menopausal women
- Only PBS approved as the sole post-menopausal anti-resorptive agent in established osteoporosis in patients with fracture with minimal trauma/ as continuing treatment (year of x-ray/MRI must be included in application)
- ↑ BMD with raloxifene < bisphophonates < bisphophonates + raloxifene
- ↑ BMD with raloxifene < oestrogen (HRT)

- Positive effects on bone and lipid metabolism (↑ total cholesterol by 5-6% and LDL by 8-10% but no effect on TAG and HDL -> unclear if translates to cardioprotection)
- Negative effects on breast and endometrium
- Reasonable alternative to tamoxifen for breast cancer chemo-prevention in post-menopausal women at high breast cancer risk
- No alleviation of post-menopausal symptoms eg hot flushes, urinary incontinence, vaginal symptoms
- Does not accumulate in target tissues -> ongoing treatment needed for benefit

- Skeletal effects (↓ bone resorption and urinary calcium losses)
  1) Treatment of osteoporosis (daily dose 60mg orally)
  - Large randomised, placebo-controlled, double blind trial of 7705 post-menopausal women for 3 years (median age 67 years, t score ≤ -2.5)
  - All received concomitant calcium and vitamin D supplements
  - ↓ incidence of vertebral fractures by 55% (whether or not they had a previous fracture)
  - Does not ↓ incidence hip fractures
  - ↑ BMD of spine and hip by 2-3%
  - ↑ BMD of total body and radius by 1-2%

  2) Prevention of osteoporosis
  - 3 large trials recruiting post-menopausal women with z scores between -2.0 and -2.5
  - Also randomised, placebo controlled and supplemented with calcium
  - ↑ BMD in spine and hip up to 2.4%
  - ↑ BMD in total body up to 4%
  - Inconsistent effect on forearm/radius BMD
- **Contraindications**
  - Pregnancy (foetal malformations in rats)
  - Lactation (growth suppression in puppies)
  - Male
  - **History of venous thrombo-embolic events**

- **Adverse effects**
  - Commonest cause for discontinuation: **hot flushes** (most commonly reported in 1st 6 months, no difference thereafter)
  - Other side effects: peripheral oedema, leg cramps
  - **Small ↑ in stroke mortality** (no ↑ incidence/ overall mortality)
  - ↑ venous thrombo-embolic events (RR 2.3)
  - Worsening of TAG profile in those with pre-existent hypertriglyceridaemia
  - ↑ plasma levels in hepatic insufficiency (not recommended)

**Osteoporosis**
- ↓ bone mass/ bone density + deterioration of bone architecture -→ ↑ fracture risk
- **WHO criteria**: **T score < -2.5** (bone density less than 2.5 standard deviations from young healthy adults of same race and sex)
- **Z score refers to age-matched** individuals (no treatment based on this)
- T scores between -1.0 and -2.5 defined as **osteopenia** -→ ↑ risk of developing osteoporosis

- Fractures of **distal radius** ↑ frequency before age 50, plateaus age 60, modest age-related ↑ thereafter
- Incidence of **hip fractures doubles every 5 years after age 70** (? Tend to fall on hip rather than outstretched hand)
- **Greatest frequency of vertebral fractures**
- Risk of DVT +/- PE greatest amongst hip fracture group (20-50%) and high mortality rate (5-20%) in the year after surgery
- Other fractures closely related to osteoporosis: pelvis and proximal humerus

**Tests:**
- Blood: FBE/ TSH/ serum calcium/ serum 1,25(OH)2D +/- PTH +/- ALP
- Urine: 24 hour urinary calcium
- DEXA scan
- Bone biopsy (rare nowadays)

**Management:**
1) Non-pharmacological: Diet/ Weight bearing exercise/ Smoking cessation

2) **Pharmacological:**
   - Bisphosphonates
   - Hormonal therapy – SERMs, oestrogen only, oestrogen-progestin therapy
   - PTH (intermittent pulse therapy, also effective in men)
   - Calcitonin (nasal spray, tachyphylaxis, less ↑ BMD compared to other therapy, only 1st line for pain management in acute osteoporotic fracture)
   - Combination therapy
   - Others: calcitriol, phyto-oestrogens, thiazides, fluoride, tibolone (synthetic steroid)
   - Watch this space: strontium, denosumab (TNF), androgens, growth hormone/ IGF, statins