An overlooked cause of hypertensive emergency

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Clinical Presentation

- Middle aged female patient presented to ED by acute compressing chest pain radiating to the back of more than 30 minutes duration and was associated with rapid palpitation
- Soon after presentation she developed acute pulmonary edema with sudden onset of extreme breathlessness, anxiety and feelings of drowning
- She had similar attacks of chest pain and dyspnea for the last 5 days before presentation but of shorter duration and less severity.

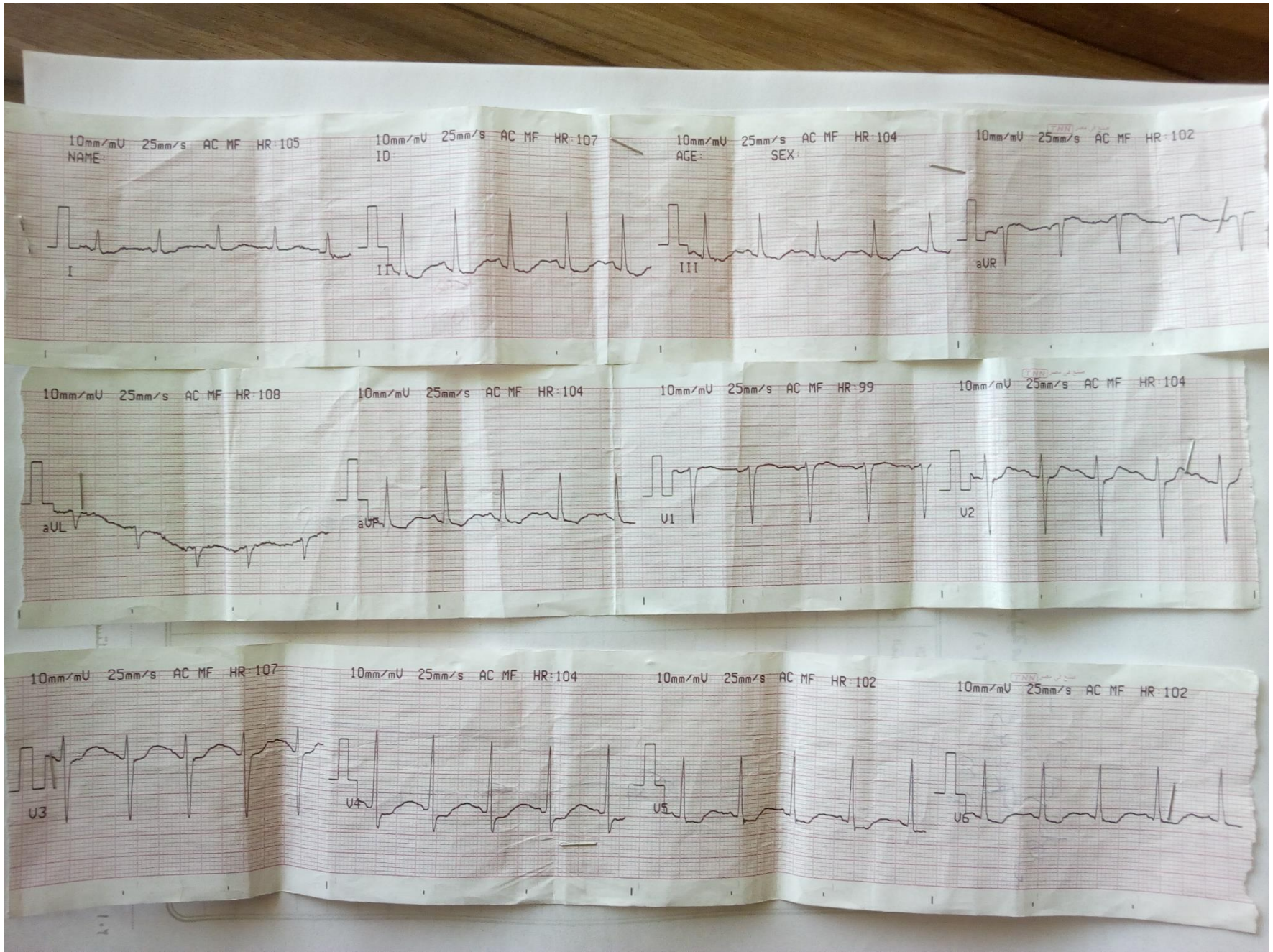
Clinical Background

- 51 years old female patient married with 4 offspring
- Menopause for 4 years
- Hypertensive for 5 years controlled on Indapamide
- Not diabetic nor smoker
- Chronic headache with regular use of simple analgesic
- History of breast cancer 3 years ago managed by right sided mastectomy and radiotherapy, the last session was 1 year ago
- Family history of premature CAD of her mother at the age of 60

Physical Examination

- BP 190/100
- Pulse: 110/min regular equal on both sides
- Respiratory rate : 30/min Sa02: 90% on room air
- Elevated jagular venous pressure up to angle of the mandible
- Bilateral coarse crepitations up to apical zones associated with expiratory wheezes
- Lower limb: warm with intact pulsations with no edema
- Cardiac auscultation: Accentuated S1 & S2 with no additional sounds or murmurs

ECG on admission



Medical stabilization at the CCU

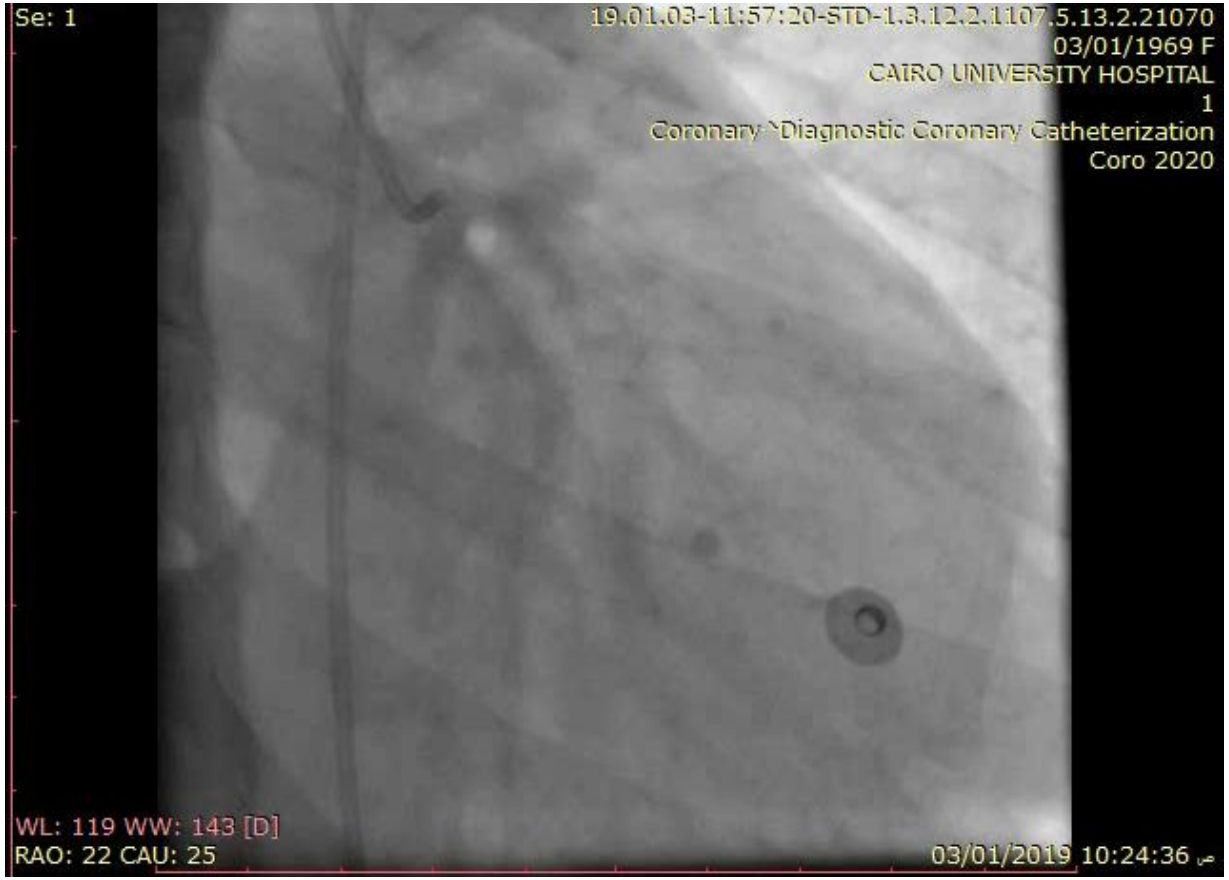
- Oxygen therapy using CPAP
- Furosemide IV 120mg on three divided boluses
- Nitroglycerine(IV infusion) titrated guided by BP and symptoms
- Acetyl salicylic acid 300 mg loading then 75mg daily
- Clopidogrel 300 mg loading then 75mg daily
- Enoxaparin 1 mg kg S.C/12 h
- Atorvastatin 40 mg daily
- Pantoprazole 40 mg IV
- Bisoprolol 2.5mg tab (after relieve of pulmonary congestion)

Labs

Troponin I	**Weak positive**		**CKMB**	**20 (25)**
Hb	13		CK total	68(26)
TLC	8.5		Na	135
PLT	251		K	3.2
Urea	28		Ca	8
Creat.	0.64		Mg	1.8
ALT	17		Cholesterol	142
AST	20		TGs	126
INR	1		LDL	92
Albumin	3.9		HDL	25

Provisional diagnosis

- Hypertensive emergency complicated by high risk NSEACS and acute pulmonary edema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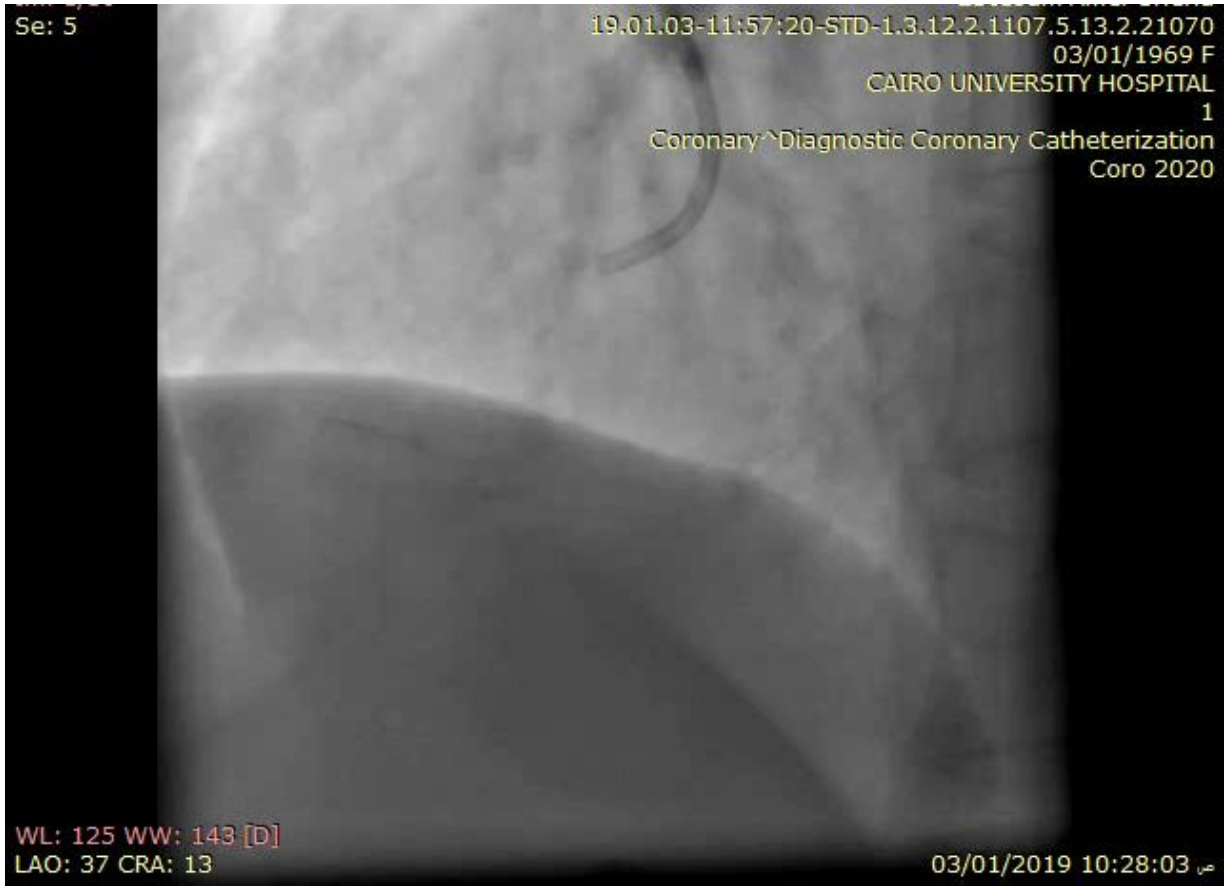
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On Proper Reviewing The Patient's History

- 51 years old female patient married with 4 offspring
- Menopause for 4 years
- Hypertensive for 5 years controlled on Indapamide
- Not diabetic nor smoker
- Chronic headache with regular use of analgesic
- History of breast cancer 3 years ago managed by right sided mastectomy and radiotherapy, the last session was 1 year ago
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- On reviewing the clinical history, the patient was diagnosed to have migraine 10 years ago with infrequent use of NSAIDS to relieve the acute headache.

- But for the last two weeks before presentation the severity and frequency of the migraine became worse and she used to take Migrainil (Ergotamine Tartarate) daily.

- Migraine is a common primary headache disorder, it affects nearly 15% of the population or about one billion people worldwide, and it is most common in women and has a strong genetic component. Approximately 90% of all patients have their first attack before the age of 50 years.

- Migraine is a complex neurobiological disorder. The core features of migraine are headache, which is usually throbbing and often unilateral, moderate to severe pain, aggravated by routine physical activity, and associated with nausea and/ or vomiting, photosensitivity and phonosensetivity, lasting minimally for 4 hours up to 72 hours

- Migraine has been long regarded as a vascular disorder because of the throbbing nature of the pain. However Up to one-third of patients do not have throbbing pain. Also modern imaging has demonstrated that vascular changes are not linked to pain and diameter changes are not linked with treatment.

- Nowadays the neurovascular theory is emerging, According to this theory, migraine is primarily a neurogenic process with secondary changes in cerebral perfusion.

- Cortical Spreading Depolarization (CSD) is a well-defined wave of neuronal excitation in the cortical gray matter that spreads from its site of origin at the rate of 2-6 mm/min. This cellular depolarization causes the primary cortical phenomenon or aura phase; in turn, it activates trigeminal fibers, causing the headache phase

- Dural perivascular nerve activity results in release of substances such as substance P, neurokinin A, calcitonin gene-related peptide, and nitric oxide, which interact with the blood vessel wall to produce dilation, protein extravasation, and sterile inflammation

Pharmacological Treatment of Migraine Headache

Acute/abortive medications

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Selective serotonin receptor (5-hydroxytryptamine–1, or 5-HT1) agonists (triptans)
- Serotonin 5-HT1F agonists (ditans) (eg, Lasmiditan) with no vasoactive effect
- Ergot alkaloids (eg, ergotamine, dihydroergotamine [DHE])
- Antiemetics (metoclopramide)
- Oral Calcitonin gene-related peptide (CGRP) receptor antagonists (ie, rimegepant, ubrogepant)

Preventive/prophylactic medications

- Antiepileptic drugs (Na valproate/ Topiramate)
- Beta blockers (propranolol)
- Tricyclic antidepressants
- Calcium channel blockers
- Selective serotonin reuptake inhibitors (SSRIs)
- NSAIDs
- Serotonin antagonists
- Botulinum toxin revention of acetylcholine from presynaptic membrane
- Monoclonal antibodies against CGRP (Erenumab, fremanezumab, galcanezumab)

- Ergotamine has been used in clinical practice for the acute treatment of migraine for over 50 years due to its vasoconstrictor properties. Ergotamine acts as an agonist at α-adrenoceptors, 5-HT (particularly 5-HT1B/1D) and dopamine D2 receptors.

- In humans, Ergotamine can constrict several isolated blood vessels, including the pulmonary, cerebral, temporal and coronary arteries. The drug seems to be more active on large arteries (conducting vessels) than on arterioles (resistance vessels) causing moderate elevation of arterial blood pressure in therapeutic doses.

- Most formulations of Ergotamine are not very useful due to an inappropriate amount of ergotamine or compounding with other drugs, such as caffeine, chlorcyclizine or meprobamate

- In essence, ergotamine, from a medical perspective, is the drug of choice in a limited number of migraine sufferers who have infrequent or long duration headaches and are likely to comply with dosing restrictions.

- Therefore, for most migraine sufferers requiring a specific anti-migraine treatment, a triptan is generally a better option from both an efficacy and side-effect perspective being more selective serotonin receptor agonist, with high affinity for 5-HT1B and 5-HT1D receptors

Cardiovascular risk of Migraine Headache

- Increased levels of C-reactive protein
- Increased levels of interleukins
- Increased levels of TNF-alpha and adhesion molecules (systemic inflammation markers)
- Oxidative stress and endothelial dysfunction
- High homocysteine level
- Hypercoagulability and platelet aggregation
- High blood pressure
- Hypercholesterolemia
- Impaired insulin sensitivity
- Increased body weight
- Medications

  - Liberal use of NSAIDS

  - Use of migraine specific VC (Triptans & Ergot) in susceptible patients

Cumulative Incidence of Cardiovascular Events in Migraine and General Population Comparison Cohorts

Migraine and risk of cardiovascular diseases: Danish population based matched cohort study

Kasper Adelborg,[1] Szimonetta Komjáthiné Szépligeti,[1] Louise Holland-Bill,[1] Vera Ehrenstein,[1] Erzsébet Horváth-Puhó,[1] Victor W Henderson,[1,2,3] Henrik Toft Sørensen[1,2]

BMJ 2018; 360 doi: https://doi.org/10.1136/bmj.k96 (Published 31 January 2018)

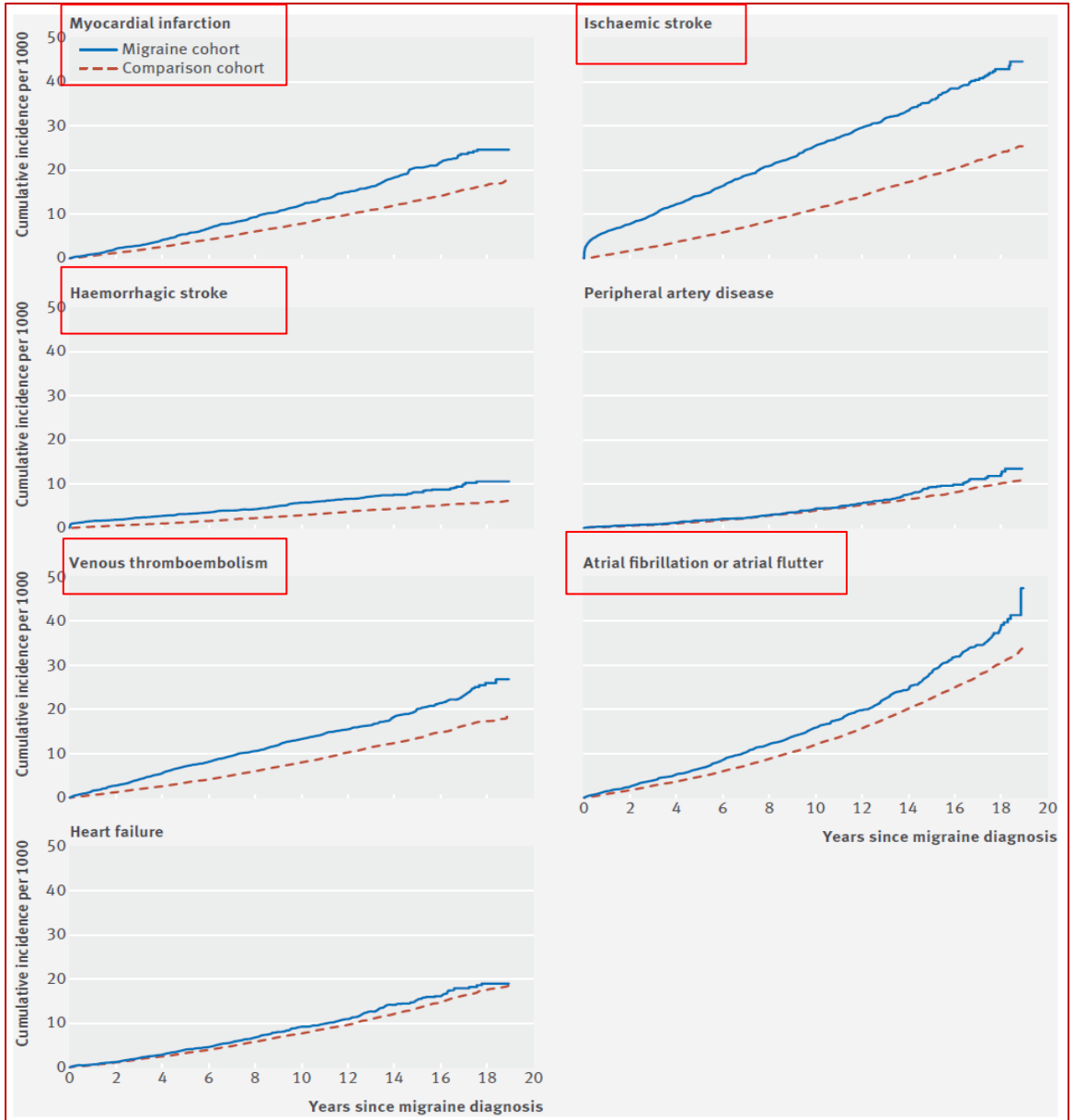
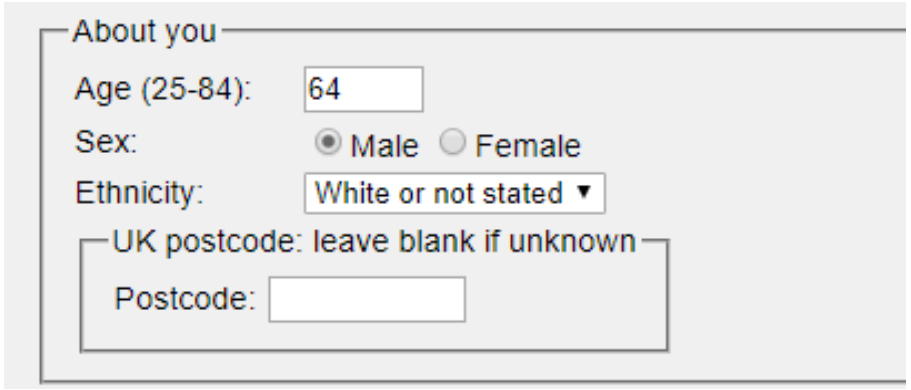
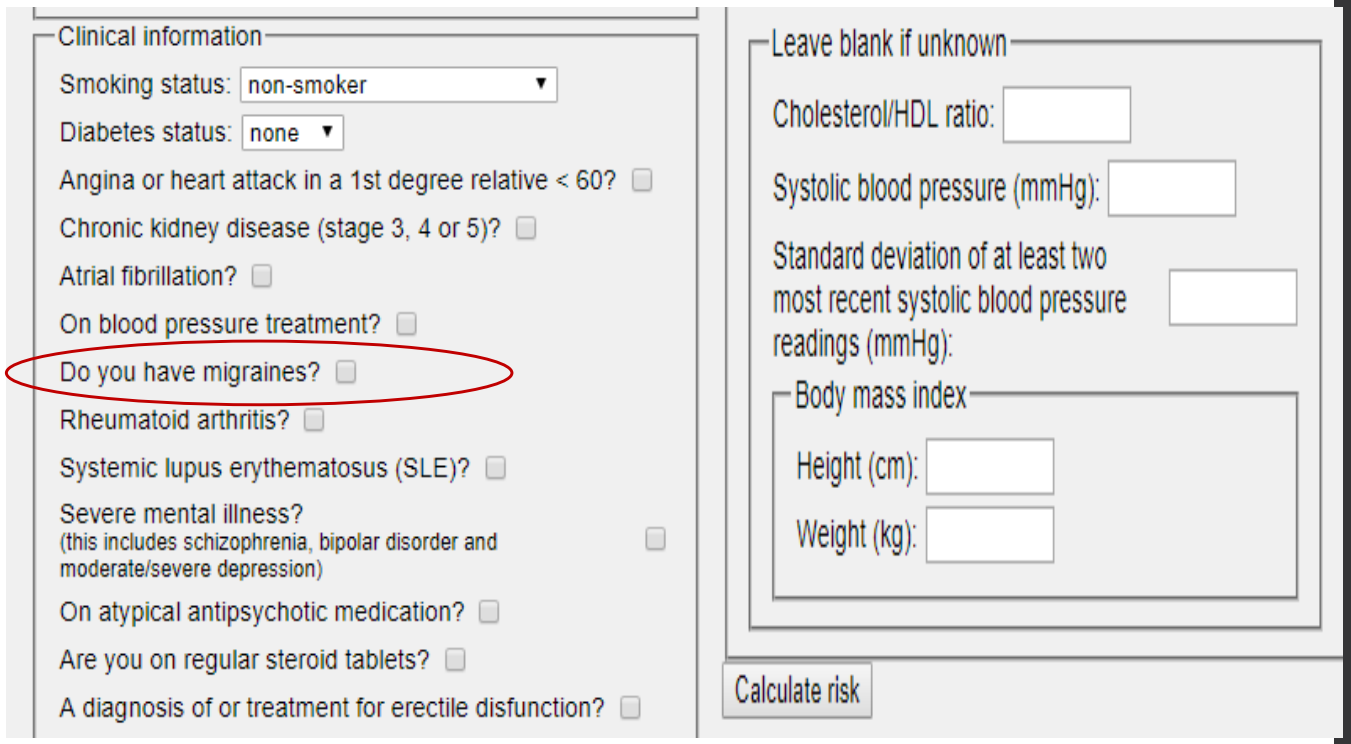


Fig 1 | Cumulative incidence of cardiovascular events in migraine and general population comparison cohorts

QRISK®3-2018 risk calculator

The QRISK3 algorithm was recently developed and validated by UK national health service to predict 10 year risk of cardiovascular disease in men and women aged 25-84 years. For the first time, migraine was included in a cardiovascular risk stratification tool, highlighting the growing recognition of migraine as an important risk factor for CVD





Back to our case

- Migrainil had been stopped and neurological consultation was done for proper management of her headache and she was prescribed

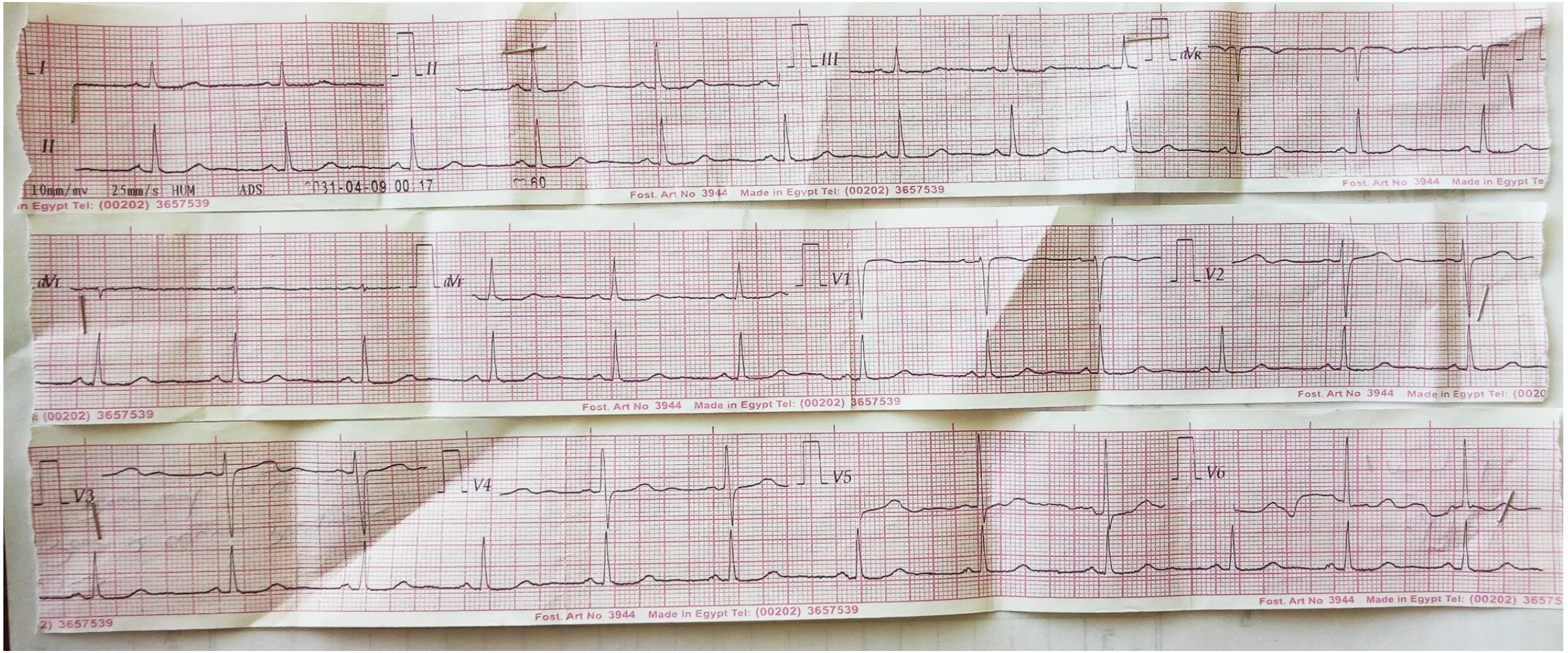
  - Depakine chrono (Na Valproate) tab 500mg twice daily

  - Tryptizole 10mg (Amitriptyline) one tab at bed time.

  - Propranolol 10 mg TDS instead of bisoprolol

- Patient was discharged with marked improvement of the frequency and severity of both angina pain and headache attacks with more than 9 months follow up since discharge.

Follow up ECG



Transthoracic Echocardiography

LVED	4.9	(3.5 – 5.7 cm)
LVES	2.9	(2.2 – 4.0 cm)
SWT	0.8	(0.7 – 1.1 cm)
PWT	0.8	(0.7 – 1.1 cm)
FS	40 %	(25 – 45 %)

LA	2.6	(1.9 – 4.0 cm)
Ao	2.4	(2.0 – 3.7 cm)
RV		(1.6 – 2.6 cm)
MVA		(2.0 – 4.0 cm^2)
EF	70 %	

Comment :

*Normal left ventricular internal dimensions, normal wall thickness with normal global contractility.
*No evidence of resting segmental wall motion abnormalities.
*Mitral valve: Normal leaflets' thickness and excursion. No mitral stenosis or incompetence.
*Doppler mitral inflow shows reversed E/A wave pattern denoting grade I diastolic dysfunction.
*Normal left atrial dimensions.
*Aortic valve: Trileaflet, normal leaflets' thickness and excursion. No aortic stenosis or incompetence.
*Normal right sided chambers dimensions and RV systolic function (TAPSE =1.9 cm). Normal right-sided valves leaflets' thickness and excursion. Mild tricuspid incompetence. No tricuspid stenosis. IVC not dilated. EPASP = 29 mmHg.
*No intracardiac masses or thrombi.
*No pericardial effusion.
*Intact septae.

Conclusion :

- Normal left ventricular interrnal dimensions with normal global contractility.
- Grade I diastolic dysfunction.

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Take Home Messages

- Most patients with elevated arterial blood pressure have essential hypertension or well known forms of 2ry HTN such renal disease, renal artery stenosis or common endocrine diseases (hyperaldosteronism or pheochromocytoma)
- Drug and chemical substances are frequently overlooked as 2ry cause of HTN. Therefore a comprehensive history including use of medications, over the counter agents and illegal substances should be elicited in every hypertensive individual particularly when a patient with well controlled hypertension is presented with acute blood pressure elevation
- In general drug induced BP increases are small and transient. However severe HTN involving encephalopathy, stroke and APE have also been reported particularly in patients with preexisting hypertension
- Identification and discontinuation of such substances may obviate the need for unnecessary, costly and potentially dangerous evaluations

- There is accumulating evidence linking migraine particularly with aura to increased risk for cardiovascular events. Calcitonin gene related peptide (CGRP) inhibitors is a novel therapeutic target that may reduce the burden of cardiovascular disease in high risk migraine patients.

- This case highlights the importance of careful history taking demonstrating the dangerous consequences of daily unrestricted use of Ergotamine Tartarate (Migrainil) which is potent vasoactive agent causing serious elevation of BP and myocardial ischemia in a susceptible patient with multiple comorbidities.

- 5-hydroxytryptamine–1 (5-HT1) agonists (triptans) are generally more effective in relieving acute migraine. Furthermore the safety of triptans is well established, and the risk of de novo coronary vasospasm from triptan use is exceedingly rare

THANK YOU