Stroke Case Studies

Dr Stuti Joshi
Neurology Advanced Trainee
Telestroke fellow
Case 1

- 64 year old female with dysphasia and right arm weakness 3 hours prior
- CT head: dense M1 sign. No established ischaemia
- No contraindication to tPA

Next best therapy?

1. IV tPA
2. IV tPA + thrombectomy
3. Thrombectomy alone
4. Rectal aspirin
Case 1

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2. IV tPA + thrombectomy
3. Thrombectomy alone
4. Rectal aspirin
Is tPA dead?
Should patients eligible for mechanical thrombectomy still receive IV tPA?

- Yes!

- All the trials gave tPA to all eligible patients

- No thrombectomy trials to date which compare tPA and thrombectomy vs thrombectomy alone

- Even though tPA achieved pre-endovascular recanalization in <10% of trial patients sometimes there are extended delays obtaining endovascular therapy

- sometimes the endovascular procedure fails due to poor access etc

- tPA may help with small distal emboli +/-soften clot
<table>
<thead>
<tr>
<th></th>
<th>MR CLEAN</th>
<th>EXTEND – IA</th>
<th>ESCAPE</th>
<th>SWIFT PRIME</th>
<th>REVASCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>Upto 6 hours (500 pts)</td>
<td>Upto 8 hours (70 pts)</td>
<td>Upto 12 hours (316 pts)</td>
<td>Upto 6 hours (196 pts)</td>
<td>Upto 8 hours (206 pts)</td>
</tr>
<tr>
<td>Pt selection 1: Prerequisites for Occlusion sites</td>
<td>ICA, M1, M2, A1, A2</td>
<td>ICA, M1 or M2</td>
<td>ICA, M1, M2, A1, A2</td>
<td>ICA, M1</td>
<td>ICA, M1</td>
</tr>
<tr>
<td>Patient selection II</td>
<td>CTB &amp; CTA</td>
<td>CT, CTA, CTP ‘Dual Target’ - Exclusion - &gt;70ml infarct vol</td>
<td>Multiphase CTA-exclusion -large infarct core &amp; poor collaterals</td>
<td>CTB &amp; CTA - Large infarct core excluded</td>
<td>CTB &amp; CTA</td>
</tr>
<tr>
<td>OR - mRS 0-2 at 90 days</td>
<td>2.16</td>
<td>2.0</td>
<td>1.8</td>
<td>1.70</td>
<td>2.71</td>
</tr>
<tr>
<td>Intervention</td>
<td>Std care (IV tPA) Vs Std care + IA therapy (mainly mechanical thrombectomy with stent retriever)</td>
<td>Std care (IV tPA) Vs Std care + Mechanical thrombectomy with Solitaire FR</td>
<td>Std care Vs Std care + Mechanical thrombectomy with Solitaire FR 4</td>
<td>Std Care Vs Std care + Mechanical thrombectomy (Solitaire FR)</td>
<td>Std Care Vs Std care + Mechanical thrombectomy (Solitaire FR)</td>
</tr>
<tr>
<td>NNT MRS &lt; 2</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>6.5</td>
</tr>
<tr>
<td>Time to reperfusion</td>
<td>Time to stroke onset to groin puncture – 260 mins</td>
<td>210 mins</td>
<td>185 mins</td>
<td>224 mins</td>
<td>269 mins</td>
</tr>
<tr>
<td>% IV tPA (Rx vs Control)</td>
<td>87 vs 91%</td>
<td>100 vs 100%</td>
<td>73 vs 79%</td>
<td>100 vs 100%</td>
<td>68 vs 78%</td>
</tr>
</tbody>
</table>
- **Time = Brain**
  The typical patient loses 1.9 million neurons each minute in which stroke is untreated

- **NNT for tPA:**
  - Within 90 minutes: NNT ~4.5
  - 1.5-3 hour window: NNT ~9
  - 3-4.5 hour window: NNT ~14.1

- NNT increases by 1 for every 20 min of delay
When is tPA not enough?
Rates of recanalization following tPA based on location of occlusion

<table>
<thead>
<tr>
<th>Site of occlusion</th>
<th>Success at 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid terminus</td>
<td>5%</td>
</tr>
<tr>
<td>MCA M1</td>
<td>30%</td>
</tr>
<tr>
<td>MCA M2</td>
<td>42%</td>
</tr>
<tr>
<td>Basilar</td>
<td>11%</td>
</tr>
<tr>
<td>Overall</td>
<td>30%</td>
</tr>
</tbody>
</table>

Stroke. 2010 Oct;41(10):2254-8
Case 2

- 65 year old female with hypertension and hyperlipidaemia, severe left sided weakness, NIHSS 10.
- Inconsistent use of anti-hypertensive but does take aspirin daily.
- BP 216/108, platelets 260, INR 1.1

What is the next best step in management:

1. GTN infusion
2. Tranexamic acid
3. Platelet transfusion
4. Recombinant Factor VII
Platelet Transfusion in Cerebral Haemorrhage (PATCH) trial

- Randomized 190 pts within 6 hrs of ICH onset to standard of care or standard + platelet transfusion
  - Antiplatelet therapy for at least 7 days prior
  - GCS ≥ 8, mRS 0-1

- Results: **Odds of death or dependence at 3 months higher in platelet transfusion grp** (adjust OR 2.05, p=0.0114)
  - No difference in ICH growth
  - More serious adverse events during hospital stay in platelet transfusion grp

“Platelet transfusion is inferior to standard care for ICH and cannot be recommended for this indication in clinical practice”

Blood Pressure Management & ICH

- Elevated BP is very common in acute ICH
  - variety of factors: stress, pain, increased ICP, & premorbid HTN

- High SBP associated w greater haematoma expansion, neurological deterioration, death & dependency after ICH

- Previously hesitant to lower BP too dramatically because of concern for possible ischaemic penumbra in ICH
INTERACT 2 trial: Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

- Randomized 2839 pts w ICH in previous 6 hrs to BP lowering
  - Intensive (SBP <140 w/in 1 hr) vs Standard (SBP <180)
  - 1° outcome of death or disability (mRS 3-6) at 3 mo

- Results: Intensive lowering of BP did not result in lower rate of death or disability than standard

- 2° outcome: Ordinal analysis of mRS scores showed improved functional outcomes w intensive tx
  - No significant difference in mortality btw grps
  - No significant difference in hematoma volume at 24 hrs
  - No significant difference in serious adverse outcomes

Anderson et al NEJM 2013
ATACH-2 trial: Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

- Randomized 1000 pts w ICH to BP lowering w nicardipine within 4.5 hrs of sx onset
  - Intensive (SBP 110-139) vs Standard (140-179)
  - 1° outcome of death or disability (mRS score 4-6) at 3 mos

- Results: Intensive BP tx did not result in lower rate of death or disability than standard

- No difference in haematoma expansion btw grps

- Higher rate of adverse renal events w/in 7 days of tx in intensive group (9% vs. 4%, p=0.002)

- Higher % of serious adverse events w/in 3 mos in intensive grp (26% vs. 20%, p=0.05)

Qureshi et al. NEJM 2016
Recommendations:

11 Acute blood pressure lowering therapy

Weak recommendation AGAINST

Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 [116])

Research evidence  Key info  Rationale  References

Weak recommendation

Benefits outweigh harms for the majority, but not for everyone. The majority of patients would likely want this option. Learn more

In patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below). (Tsivgoulis et al. 2014 [119]; Qureshi et al. 2016 [117])
Case 3:

- 66 yo female with left sided weakness
- Background of hypertension and T2DM
- Medications: Metformin
- Admitted to stroke unit
Investigations

- CTA: No significant stenosis
- TTE: Normal
- 24 hr Holter: No AF
- Lipids: Normal
- Thrombophilia/ Vasculitis screen: Normal
How do you classify this stroke?
Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O’Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Figure 1: Distribution of ischaemic stroke subtypes in North American and European studies
The distribution in Asian and African populations differs from that in North American and European populations.
Cryptogenic Vs ESUS

- ESUS is a subtype of cryptogenic stroke
  - Inadequate/ inappropriate diagnostic workups
  - multiple etiologies factors for stroke – unclear which was causative
  - Contribution from an unknown etiology
Definition of ESUS

- Stroke detected by CT or MRI that is not lacunar
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia
- No major-risk cardioembolic source of embolism*
- No other specific cause of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug misuse etc)

*Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis.
Panel 1: Causes of embolic strokes of undetermined source

Minor-risk potential cardioembolic sources*

Mitral valve
- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

Aortic valve
- Aortic valve stenosis
- Calcific aortic valve

Non-atrial fibrillation atrial dysrhythmias and stasis
- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

Atrial structural abnormalities
- Atrial septal aneurysm
- Chiari network

Left ventricle
- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction
- Endomyocardial fibrosis

Covert paroxysmal atrial fibrillation

Cancer-associated
- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

Arteriogenic emboli
- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

Paradoxical embolism
- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula
What additional investigations would you arrange?
Cryptogenic Stroke 
and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., 
Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., 
Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., 
Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., 
Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., 
and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*
441 Patients with cryptogenic stroke with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring underwent randomization into either long-term monitoring with an insertable cardiac monitor (ICM) versus conventional follow-up (control) for detecting atrial fibrillation.

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM group versus 1.4% of patients in the control.

By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group versus 2.0% of patients in the control group.
B Detection of Atrial Fibrillation by 12 Months

Hazard ratio, 7.3 (95% CI, 2.6–20.8)
P<0.001 by log-rank test

No. at Risk
Control 220 200 197 194 184 184 167
ICM 221 198 194 191 186 182 173

Months since Randomization

C Detection of Atrial Fibrillation by 36 Months

Hazard ratio, 8.8 (95% CI, 3.5–22.2)
P<0.001 by log-rank test

No. at Risk
Control 220 194 167 114 72 36 7
ICM 221 191 173 102 57 29 8

Months since Randomization
Prolonged Cardiac Monitoring
If prolonged monitoring is normal, what is the treatment of ESUS?
- Compared treatment of 7213 ESUS stroke patients with Aspirin 100mg vs Rivaroxaban 15mg

- Trial terminated early at median of 11 months because of
  - A lack of benefit with regard to stroke risk (4.7% stroke in both arms)
  - Bleeding associated with rivaroxaban (1.8% vs 0.7% in Aspirin).

- Conclusion: Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding
A Kaplan–Meier Curves for Time to Event in the Primary Efficacy Outcome

Hazard ratio, 1.07 (95% CI, 0.87–1.33)

Numbers of patients with primary efficacy outcome:
- Rivaroxaban: 100
- Aspirin: 100

Proportion with primary efficacy outcome

Days of follow-up

B Kaplan–Meier Curves for Time to Major Bleeding Event

Hazard ratio, 2.72 (95% CI, 1.68–4.39)

Numbers of patients with major bleeding event:
- Rivaroxaban: 20
- Aspirin: 20

Proportion with major bleeding event

Days of follow-up
If Prolonged monitoring showed AF how do you treat?

1. Determine if non-valvular or valvular AF
   - Valvular: Mechanical heart valve or mod- severe mitral stenosis
   - If you have MR/ AS/ bioprosthetic valve you can still use a DOAC

2. Other indications for warfarin:
   - If creatinine clearance < 25ml/min
   - LV thrombus
   - Other causes of VTE e.g. malignancy
   - Stable long term control
   - Drug interactions: pheynytin, carbamazepin, HAART, azole antifungals

3. Otherwise, select a DOAC as first line. But which one?
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Peak plasma levels</strong></td>
<td>1-2hrs</td>
<td>2-4hrs</td>
<td>3-4hrs</td>
</tr>
<tr>
<td><strong>Stroke incidence: Warfarin vs NOAC %/year</strong></td>
<td>RE-LY trial N=18,113 Warf: 1.69% Dab 110mg: 1.53% Dab 150mg: 1.11%</td>
<td>ROCKET - AF trial N=14,264 Warfarin: 2.2% Rivaroxaban: 1.7%</td>
<td>ARISTOTLE trial N= 18,201 Warfarin: 1.6% Apixaban: 1.27%</td>
</tr>
<tr>
<td><strong>Safety: Major bleeding warfarin vs NOAC %/year</strong></td>
<td>Warfarin: 3.36% Dab 110mg: 2.71% Dab 150mg: 3.11%</td>
<td>Warfarin: 3.4% Rivaroxaban: 3.6%</td>
<td>Warfarin: 3.09% Apixaban: 2.13%</td>
</tr>
<tr>
<td><strong>GI bleeding %/year</strong></td>
<td>Warfarin: 1.02% Dab 110mg: 1.12% Dab 150mg: 1.51%</td>
<td>Warfarin: 2.2% Rivaroxaban: 3.2%</td>
<td>Warfarin: 0.86% Apixaban: 0.76%</td>
</tr>
<tr>
<td><strong>ICH %/year</strong></td>
<td>Warfarin: 0.38% Dab 110mg: 0.12% Dab 150mg: 0.10%</td>
<td>Warfarin: 0.7% Rivaroxaban: 0.5%</td>
<td>Warfarin: 0.80% Apixaban: 0.33%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>P-gp inhibitors/ inducers</td>
<td>P-gp/CYP 3A4 inhibitors/ inducers</td>
<td>P-gp/CYP 3A4 inhibitors/ inducers</td>
</tr>
<tr>
<td><strong>Reversal agents</strong></td>
<td>Idaricizumab, haemodialysis removes ~65% of active drug</td>
<td>Andexanet in trials (recombinant modified human factor Xa decoy protein)</td>
<td>Andexanet in trials (recombinant modified human factor Xa decoy protein)</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Half life with normal renal function</strong></td>
<td>12-18 hrs</td>
<td>5-13 hrs</td>
<td>12-15 hrs</td>
</tr>
</tbody>
</table>
Selecting a DOAC based on patient characteristics:

- Recurrent ischaemic events, low bleeding risk: Dabigatran 150mg BD
- Mod – severe renal impairment: Rivaroxaban or apixaban (2.5mg BD) (or warfarin)
- High risk of bleeding (HAS BLED score 3 or higher): Apixaban, Dabigatran 110mg BD
- High risk of GI bleeding: Apixaban or dabigatran 110mg BD
- Compliance: Rivaroxaban (or warfarin)
- Apixaban Dose reduction: Age 80 years or older, Weight 60kg or less, Serum creatinine 133 mmol/L

Case 3:

- 51 year old male with expressive dysphasia
- PMH: None. No regular medications. Non smoker
- TTE: EF 55%, PFO with right to left shunt on bubble study
- CTA: No significant intra or extranial stenosis
- 24 hr Holter: No AF
How would you manage this patient?

1. Standard treatment
2. Standard treatment + PFO closure
3. Anticoagulation

What are the current guidelines for PFO management?
**RoPE score:** Is the PFO incidental or pathogenic?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
</tr>
<tr>
<td>No history of Stroke or TIA</td>
<td>1</td>
</tr>
<tr>
<td>Non smoker</td>
<td>1</td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
</tr>
<tr>
<td>RoPE score</td>
<td>No. of patients</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td>0-3</td>
<td>613</td>
</tr>
<tr>
<td>4</td>
<td>511</td>
</tr>
<tr>
<td>5</td>
<td>516</td>
</tr>
<tr>
<td>6</td>
<td>482</td>
</tr>
<tr>
<td>7</td>
<td>434</td>
</tr>
<tr>
<td>8</td>
<td>287</td>
</tr>
<tr>
<td>9-10</td>
<td>180</td>
</tr>
</tbody>
</table>
Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D.,
Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc.,
Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settgren, M.D., Ph.D.,
Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D.,
David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D.,
for the Gore REDUCE Clinical Study Investigators∗

No. at Risk
PFO closure group 238 238 232 200
Antiplatelet-only group 235 229 223 198

No. at Risk
PFO closure group 441 422 417 398 278 182 102
Antiplatelet-only group 223 202 194 173 116 78 30

Hazard ratio for recurrent stroke, 0.23 (95% CI, 0.09–0.62)
P=0.002 by log-rank test
<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>RESPECT: Extended f/u</strong></th>
<th><strong>CLOSE</strong></th>
<th><strong>REDUCE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Cryptogenic Stroke (included small/deep strokes)</td>
<td>- EMBOLIC stroke (Excluded deep lacunar stroke)</td>
<td>- Embolic appearing cryptogenic stroke</td>
</tr>
<tr>
<td></td>
<td>- PFO</td>
<td>- High risk PFO (ASA or large shunt)</td>
<td>- PFO</td>
</tr>
<tr>
<td></td>
<td>- Age 19-60</td>
<td>- Age 16-60</td>
<td>- Age &lt; 60</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>980</td>
<td>473</td>
<td>664</td>
</tr>
<tr>
<td><strong>Device vs medical</strong></td>
<td>Amplatzer vs medical Mx (antiplatelet/anticoagulation)</td>
<td>Any approved device (Amplatzer in &gt; 51%) vs aspirin vs anticoagulation</td>
<td>Gore Helex septal occluder/ cardioform septal occluder vs antiplatelet therapy 2:1</td>
</tr>
<tr>
<td><strong>Follow up</strong></td>
<td>5.9 years</td>
<td>5.3 years</td>
<td>3.2 yrs</td>
</tr>
<tr>
<td><strong>Actual event rates:</strong></td>
<td>Closure: 18 (1.8%) Antiplatelet: 28 (3.3%) Hazard Ratio for recurrent stroke: 0.55 (loss of 27% in medical arm to fu)</td>
<td>Closure: 0 Antiplatelet: 14 (2%) Anticoag: 3 (0.6%) Hazard Ratio 0.03</td>
<td>Closure: 6 (1.4%) Antiplatelet: 12 (5.4%) Hazard ratio: 0.23</td>
</tr>
<tr>
<td><strong>New AF:</strong></td>
<td>0.6% in both arms</td>
<td>6.6% vs 0.4%</td>
<td>4.9% vs 0.6%</td>
</tr>
</tbody>
</table>
Methodological concerns:

- Open label end-point
- High loss to follow up and cross-over
- Low event rates
- Duration not long enough to demonstrate sustained benefits
2018 Meta-analyses:

- 2892 subjects and follow-up ranging from 3.2 to 5.9 years, PFO closure reduced the absolute risk of recurrent stroke by 3.2 percent (95% CI 1.4-5.0)

- A second meta-analyses found that PFO closure reduced the absolute risk of stroke or TIA by 2.9 percent (95% CI 1.2-5.4)

- The number needed to treat (NNT) with PFO device closure to prevent one recurrent stroke was approximately 31.

- ARR of stroke - 0.66% per year and ~3% at 5 years
  - For select patients

- New AF or flutter occurred at a rate of 3.7%
15 Patent foramen ovale management

Strong recommendation

Patients with ischaemic stroke or TIA and PFO should receive optimal medical therapy including antiplatelet therapy or anticoagulation if indicated. (Homma et al 2002 [178])

Weak recommendation AGAINST

Routine endovascular closure of patent foramen ovale is not recommended. Endovascular closure may be reasonable in highly selected young ischaemic stroke patients after thorough exclusion of other stroke aetiologies. (Kent et al 2016 [179])
For patients considering PFO closure:

- Complete thorough evaluation:
  - CTA/ MRA
  - TOE to identify degree of shunting and atrial septal aneurysm
  - Embolic appearing stroke on imaging
  - Under 60y, no other vascular risk factors
  - Thrombophilia testing
  - Prolonged cardiac monitoring to exclude occult A. Fib

- Benefit is uncertain in patients who require life-long anticoagulation (thrombophilia/ A Fib/ valve/ unprovoked DVT)
  - PFO closure not recommended in these pts for now

- Shared decision making between patient, cardiologist, neurologist
Questions