NOACs and antiplatelets- The review of the not-so new

Adam Livori-
Cardiology Pharmacist, Ballarat Health Services

Ballarat Health Services

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How NOACs work

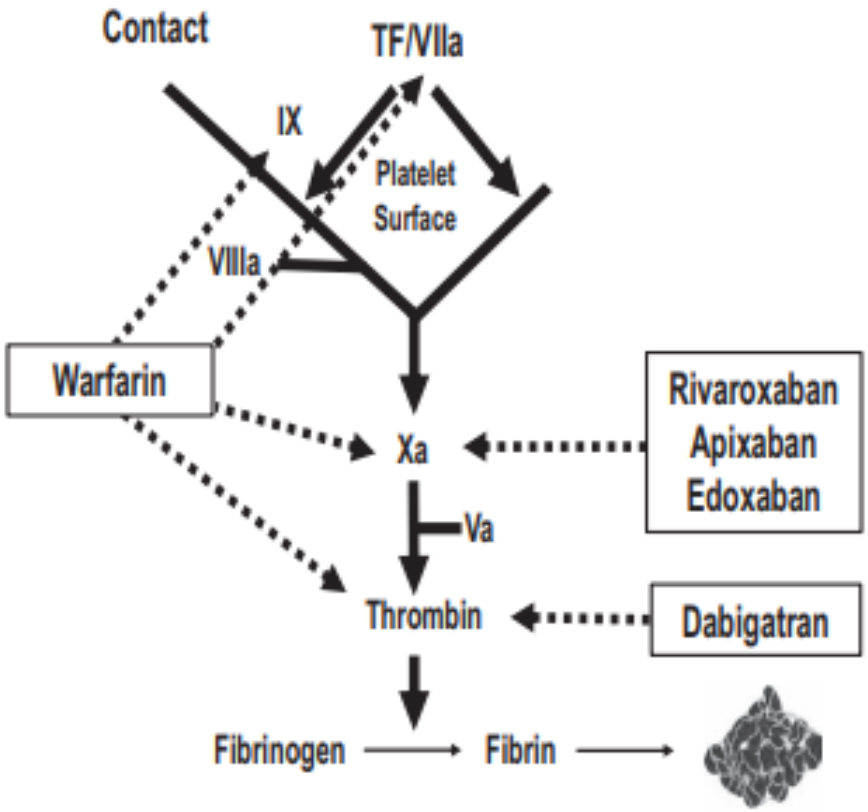

Figure. Sites of action of warfarin and the non-vitamin K oral anticoagulants. TF indicates tissue factor.

What NOACs are used for

- Non-valvular AF
- VTE Treatment and secondary prevention
- VTE prophylaxis in hip or knee replacement

- That is all as far as Australian practice is concerned

What warfarin is used for

- Non-valvular AF
- VTE Treatment and secondary prevention
- VTE prophylaxis
- Prevention of thromboembolism in prosthetic heart valves
- Prevention and treatment of mural thrombus

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What warfarin is used for

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Why use NOACs

- Each NOAC has had at least one major study to support its safety and efficacy when compared to warfarin
  - RE-LY, ROCKET, ARISTOTLE
- Lots of robust data (more than 70,000 patients across the main NOACs)
- Compared with warfarin, NOACs as a class are non-inferior in stroke and embolism prevention and ~10% reduction in all cause mortality
- Rates of major bleeding similar or lower, with less intracranial bleeding

Limitations of NOACs

- Lack of easily accessible monitoring
  - Is this really an issue?
- Apixaban and rivaroxaban do not have “antidotes”
- Not as forgiving when considering missed doses
  - Importance of continuing therapy
- Low and high body weights and dosing

NOAC side effects

SIDE EFFECT	APIXABAN	RIVAROXABAN	DABIGATRAN	WARFARIN
Intracranial hemorrhage	0.33%	0.8%	0.3%	0.8/ 0.7/ 0.74
Gastrointestinal bleeding	0.76%	3.2%	1.51%	0.86/0.9/1.02
Major/clinically relevany bleed	4.07%	5.6%	3.11%	6.01/3.4/3.4
Increased LFTs	<1%	2%	1.9%	N/A
Nausea	3%	Not reported	Not reported	Not reported
Gastritis/abdominal pain	Not reported	3%	11.8%	Not defined
Dizziness/CNS effects	Not reported	2%	8.1%	Not defined

Reference: ARISTOTLE, ROCKET-AF, RE-LY trials

Falls vs. Stroke

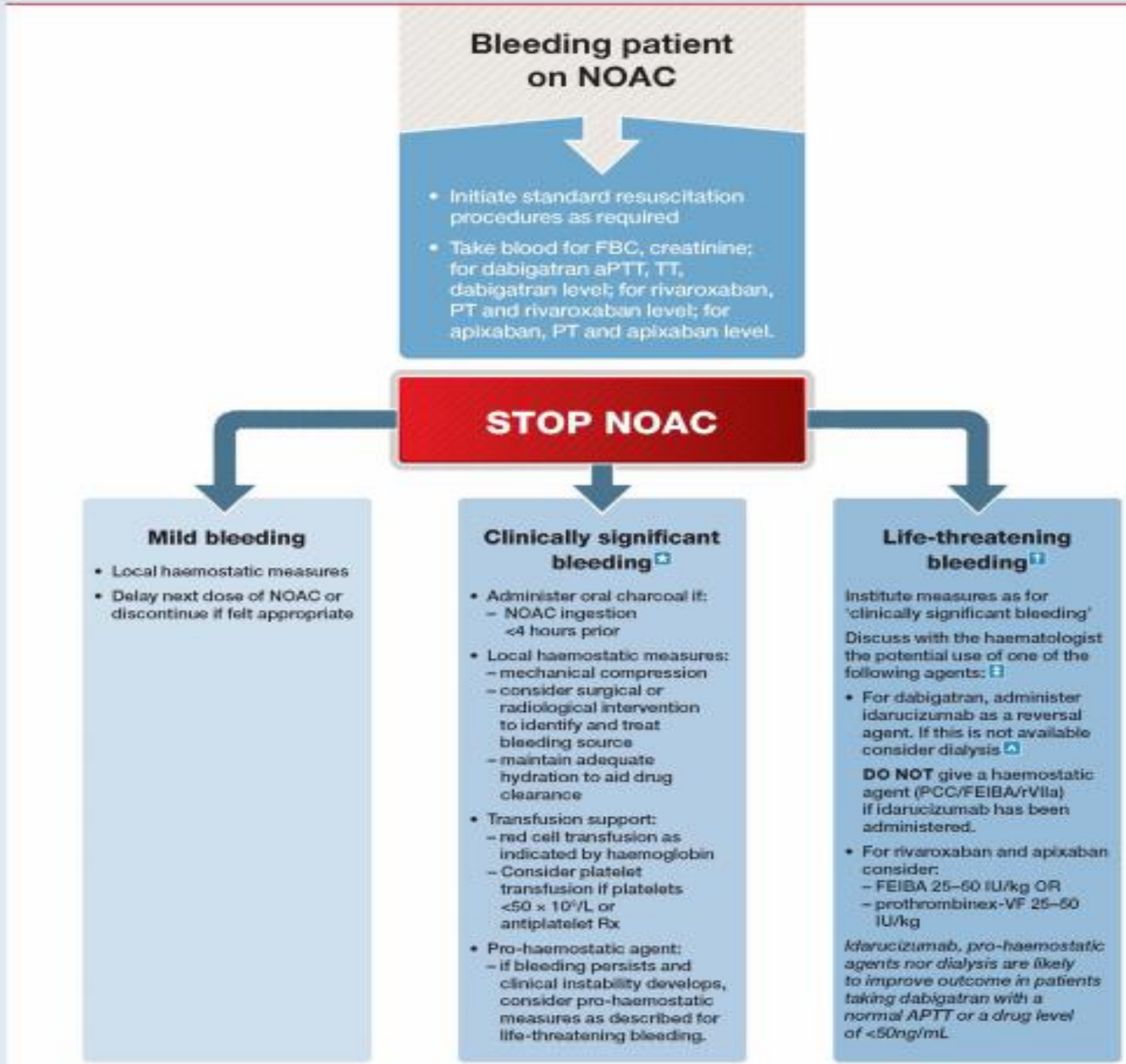
- CSANZ Guidelines for management of atrial fibrillation 2018:
  - Currently a risk/benefit recommendation
  - Modelling states 300 falls a year required to offset risk of no anticoagulation
  - Risk of bleeding increases less than risk of stroke as patients age
- Falls are considered a modifiable risk factor in HAS-BLED score calculation

Managing bleeding

- Almost all bleeding risk calculators share similar aspects as CHADS-VAA
  - Therefore higher risk of stroke is often attributable to an increased risk of bleeding as well i.e. hypertension
- Bleeding risk scores should not be used to avoid anticoagulation, but to make clinicians aware of greater attention required to modifiable risk factors

Managing bleeding

Modifiable bleeding risk factors	Comment
Hypertension (SBP >160)	Blood pressure control reduces the potential risk of bleeding
Labile INR (TTR <60%)	Consider changing to a NOAC
Concomitant medications including antiplatelet agents and NSAIDs	Minimise duration of double or triple therapy in patients with coronary disease and AF
Excess alcohol (>8 drinks per week)	
Potentially modifiable bleeding risk factors	Correct these factors where possible
Anaemia	
Impaired renal function	Monitor, especially in situations when renal function may be affected
Impaired liver function	
Frailty and falls	Walking aids, footwear, aged care home review
Non-modifiable bleeding risk factors	
Advanced age	Stroke risk outweighs bleeding risk
History of major bleeding	
Previous stroke	Risk of recurrent stroke outweighs risk of bleeding
Dialysis-dependent kidney disease	The role of anticoagulation (warfarin only indicated) in this population is controversial
Cirrhotic liver disease	Contraindication to NOACs (these patients are excluded from trials); consider advice from hepatologist
Malignancy	Individualise decisions about anticoagulation based on risk and benefit


Bleeding patient on NOAC
• Initiate standard resuscitation procedures as required
• Take blood for FBC, creatinine; for dabigatran aPTT, TT, dabigatran level; for rivaroxaban, PT and rivaroxaban level; for apixaban, PT and apixaban level.
STOP NOAC
Mild bleeding
• Local haemostatic measures
• Delay next dose of NOAC or discontinue if felt appropriate
Clinically significant bleeding
• Administer oral charcoal if:
– NOAC ingestion <4 hours prior
• Local haemostatic measures:
– mechanical compression
– consider surgical or radiological intervention to identify and treat bleeding source
– maintain adequate hydration to aid drug clearance
• Transfusion support:
– red cell transfusion as indicated by haemoglobin
– Consider platelet transfusion if platelets <50 × 10⁹/L or antiplatelet Rx
• Pro-haemostatic agent:
– if bleeding persists and clinical instability develops, consider pro-haemostatic measures as described for life-threatening bleeding.
Life-threatening bleeding
Institute measures as for 'clinically significant bleeding'
Discuss with the haematologist the potential use of one of the following agents:
• For dabigatran, administer idarucizumab as a reversal agent. If this is not available consider dialysis
DO NOT give a haemostatic agent (PCC/FEIBA/rVIIa) if idarucizumab has been administered.
• For rivaroxaban and apixaban consider:
– FEIBA 25–60 IU/kg OR
– prothrombinex-VF 25–60 IU/kg
Idarucizumab, pro-haemostatic agents nor dialysis are likely to improve outcome in patients taking dabigatran with a normal APTT or a drug level of <50ng/mL

Reversal strategies

Drug	Strategies
Warfarin	Vitamin K (note onset can take up to 4 hours) Consider prothrombin complex concentrates
Dabigatran	Idarucizumab Dabigatran 60% dialyzable Activated charcoal if taken within 4 hours
Apixaban	Not dialyzable Andexanet not available in Australia Consider prothrombin complex concentrates or FEIBA Activated charcoal if taken within 6 hours
Rivaroxaban	Not dialyzable Andexanet not available in Australia Consider prothrombin complex concentrates or FEIBA Activated charcoal if taken within 6 hours

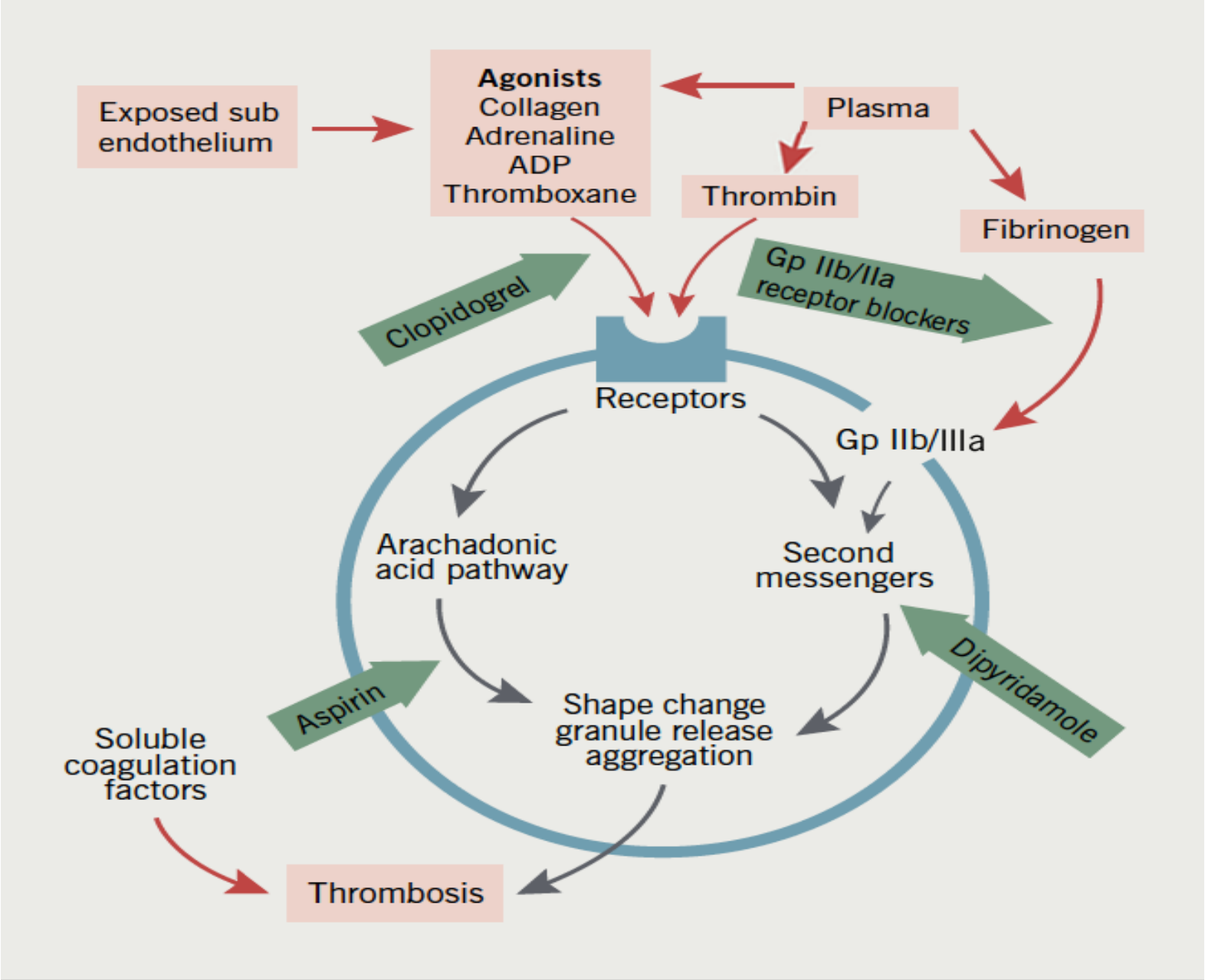
Reversal agents

- Idarucizumab – humanized specific monoclonal antibody fragment that binds dabigatran with high affinity.
- Two 2.5g doses administered intravenously
- Only binds dabigatran, does not reverse the action of dabigatran
- Based on consensus and data from RE-VERSE AD, recommencement of anticoagulation should happen within 7 days

Reversal agents

- Andexanet alfa – recombinant modified factora Xa protein and acts as a decoy and binds to rivaroxaban and apixaban, neutralizing their effects
- Approved by FDA in May 2018 for reversal of anticoagulation by apixaban or rivaroxaban
- ANNEXA-4, open label phase 3/4 trial currently running, due to complete in 2022

Antiplatelets-different kettle of fish!



Key: ADP = adenosine diphosphate; gp = glycoprotein. Reproduced from Blann AD *et al.*

NOACs and antiplatelets

- Complicated and controversial topic!
- Current recommendations are to use aspirin and clopidogrel is anticoagulation is indicated
- Apixaban not currently recommended for use with antiplatelets until results of AUGUSTUS trial published
- Lack of powered trials regarding other antiplatelets

Side effects- Antiplatelets

- All anti-platelets carry with them bleeding risks
- From the major trials, prasugrel and ticagrelor have shown greater benefit in reducing MI and nonfatal stroke
- Both prasugrel and ticagrelor carry higher bleeding risks, but you need to know your patient!
- Ticagrelor known for also causing dyspnea (~14%)
  - Effects typically wear off within 2 days after ceasing
  - Can also cause ventricular pauses within the first few weeks, no clinical risks determined to be related to this

Case Study: Mr Link

- 68 year old male
- PMHx
  - Permanent AF (rate controlled)
  - Osteoarthritis
  - Gout
  - Hypertension
  - T2DM
- Recent NSTEMI
  - Referred to cardiac rehab program
  - So far attended first 2 weeks without any concerns
  - Complaining of pain in stomach

Case Study: Mr Link

- Current medications
  - Metformin 500mg bd
  - Metoprolol 50mg bd
  - Dabigatran 150mg bd
  - Allopurinol 100mg mane
  - Amlodipine 5mg nocte
  - Ibuprofen 400mg tds prn
- Next steps?