Antiplatelet Therapies and the New Medicine Service

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Contents

• Adherence – why is it such an issue?
• Disease process
• Indications for antiplatelet therapies
• Mechanisms of action
• Importance of dual antiplatelet therapy
  – Clopidogrel, prasugrel, ticagrelor
• Take home messages
  – NMS – intervention interview schedule
Why is adherence such a big problem in cardiovascular disease management.....?
An estimated 50% of medicines for chronic conditions are not taken as prescribed

There are many reasons why people don’t get the most out of medicines

<table>
<thead>
<tr>
<th>Barriers to optimal use of medicines</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional</td>
<td>Inappropriate prescribing, Mistakes in dispensing or administration</td>
</tr>
<tr>
<td>Practical</td>
<td>Forgetfulness, Inability to open containers</td>
</tr>
<tr>
<td>Information</td>
<td>Instructions not understood, Poor understanding of condition/treatment</td>
</tr>
<tr>
<td>Lifestyle choices</td>
<td>Unpleasant side effects, Inconvenience, No perceived benefit</td>
</tr>
<tr>
<td>Beliefs about medicine</td>
<td>Unnatural, Addictive, Poisonous, Diminishing efficacy</td>
</tr>
</tbody>
</table>

Non-Intentional

Intentional
Patients’ beliefs biggest factor in decision

Beliefs about necessity of prescribed treatment

Concerns about dependence & long term effects

I don't want to be dependent on drugs

I don't like taking medicines

I feel fine – is it really that serious?

It's too late for me – I've done too much damage already

This medicine doesn't make me feel any better

These tablets make me feel worse

I don't want to be labelled

Many believe benefits outweighed by harms

Source: MORI/Medicines Partnership survey of 2019 adults, 2003. 9% of adults surveyed gave no response to this question.

New Medicine Service - Interview Schedule

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you had the chance to start taking your new medicine yet?</td>
</tr>
<tr>
<td>2. How are you getting on with it?</td>
</tr>
<tr>
<td>3. Are you having any problems with your new medicine, or concerns about</td>
</tr>
<tr>
<td>taking it?</td>
</tr>
<tr>
<td>4. Do you think it is working? (Prompt: is this different from what you were</td>
</tr>
<tr>
<td>expecting?)</td>
</tr>
<tr>
<td>5. Do you think you are getting any side effects or unexpected effects?</td>
</tr>
<tr>
<td>6. People often miss taking doses of their medicines, for a wide range of</td>
</tr>
<tr>
<td>reasons. Have you missed any doses of your new medicine, or changed when you</td>
</tr>
<tr>
<td>take it? (Prompt: when did you last miss a dose?)</td>
</tr>
<tr>
<td>7. Do you have anything else you would like to know about your new medicine</td>
</tr>
<tr>
<td>or is there anything you would like me to go over again?</td>
</tr>
</tbody>
</table>
Coronary Heart Disease

- Stenoses in coronary arteries reduce blood and oxygen supply to the myocardium resulting in ischaemic damage.

Common Underlying Atherothrombotic Disease Process

- MI, myocardial infarction; PAD, peripheral arterial disease; CV, cardiovascular.
Platelet Adhesion and Activation

Normal platelets in flowing blood

Platelets adhering to damaged endothelium and undergoing activation

Aggregation of platelets into a thrombus

Activated and Inactivated Platelets

Indications

• Primary prevention
  – Prevent an event, e.g. ischaemic stroke or MI, in a patient who has not had any previous events or diagnosis of CVD

• Secondary events
  – Prevent recurrent CV events
Indications for Oral antiplatelets

• Primary prevention?
• Stable coronary heart disease (ie stable angina)
  – Aspirin 75mg od long term
• MI or UA (12 months) or elective PCI (1-12 months)
  – Dual antiplatelet (aspirin with ADP inhibitor)
• Ischaemic stroke or PAD
  – Clopidogrel 75mg od long term
• TIA
  – Dipyridamole MR 200mg bd and aspirin 75mg od

Primary Prevention

• Aspirin– 75mg once daily
• Risks of bleeding verses benefit
Data from a real-world patient population

This latest analysis included administrative data from individuals in the Italian National Health Service identified as new users of low-dose aspirin (81 mg) from 2003 to 2009. From the initial cohort of 241,844 individuals taking aspirin, 186,425 were selected using propensity-score matching and compared with an equal number of individuals not currently taking low-dose aspirin. During a median follow-up of 5.7 years, there were 1.6 million person-years of observation.

Overall, there were 6507 first episodes of major bleeding requiring hospitalization, including 4487 gastrointestinal bleeds and 2414 intracranial hemorrhages. For individuals currently taking aspirin, the rate of total hemorrhagic events per 1000 person-years was 5.55, whereas the rate was 3.60 per 1000 person-years in those not taking aspirin. The incidence rate ratio (IRR) for total hemorrhagic events, gastrointestinal bleeding, and intracranial hemorrhage all showed an increased risk of bleeding among the aspirin-treated patients (IRR 1.55, 1.55, and 1.54 per 1000 person-years, respectively).

“The bleeding rate was five times higher than the bleeding rate expected based on the results of previously published randomized clinical trials,” said Nicolucci. “Even among patients not taking aspirin, the risk of bleeding was much higher than observed in randomized clinical trials. Furthermore, the risk is much higher in elderly individuals. So, when we have to balance the risk and benefits of aspirin, we have to remember that the baseline risk of bleeding can be very high in some subgroups of patients.”
Aspirin

- Primary prevention (in doubt)
  - Risks outweigh benefits
- Stable angina - 75mg once daily
- As part of dual antiplatelet therapy

- Irreversibly inhibits the synthesis of TxA₂ by inhibition of COX pathway

TXA, thromboxane;
Clopidogrel is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease or
- for people who have had a myocardial infarction only if aspirin is contraindicated or not tolerated.

Modified-release dipyridamole in combination with aspirin is recommended as an option to prevent occlusive vascular events:

- for people who have had a transient ischaemic attack or
- for people who have had an ischaemic stroke only if clopidogrel is contraindicated or not tolerated.

Modified-release dipyridamole alone is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke only if aspirin and clopidogrel are contraindicated or not tolerated or

5.5.1A For patients with ischaemic stroke or TIA in sinus rhythm, clopidogrel should be the standard antithrombotic treatment:
> clopidogrel should be used at a dose of 75 mg daily.
Coronary Heart Disease (1)

- Stenoses in coronary arteries reduce blood and oxygen supply to the myocardium resulting in ischaemic damage.

Radiographic image of angioplasty procedure
ADP antagonists

- Clopidogrel & Prasugrel
  - Thienopyridines
  - Effects last for lifetime of platelet
  - Once daily
  - Pro-drugs
- Ticagrelor
  - Cyclo-pentyl-triazolo-pyrimidine (CPTP)
  - Reversible
  - Twice daily
Biotransformation and Mode of Action of Clopidogrel, Prasugrel and Ticagrelor

Activated Platelet

Clopidogrel
Prasugrel
Ticagrelor

Gp IIb/IIIa fibrinogen receptor

ADP

Activation

Concerns regarding dual antiplatelet therapy e.g. aspirin and clopidogrel

- **Cautions**
  - Patients at risk of increased bleeding
    - Trauma, surgery etc
  - Discontinue before 7 days before elective surgery if appr

- **Contra-indications**
  - Active bleeding, breast feeding

- **Side effects**
  - Dyspepsia, abdo pain, diarrhoea
  - Bleeding episodes – epistaxis, bruising
  - Less commonly; N & V, gastritis….
Difficulties with clopidogrel

• Persistence with therapy
• Clopidogrel resistance:
  – Non-responders - ‘clopidogrel failures’
  • Poor compliance, inadequate dose, poor absorption genetic polymorphisms, drug interactions
• Slow onset of action
• Adverse effects
  – Rashes – but not every rash is due to clopidogrel!
  – Bleeds – do we look for them post discharge?
Prasugrel Is Effective for Clopidogrel Non-Responders

IPA at 24 hours (%)

Response to Clopidogrel 300 mg
Response to Prasugrel 60 mg

Prasugrel vs Clopidogrel

- More potent
- More rapid in onset
- More consistent inhibition of platelet aggregation (IPA)
- Less frequent poor IPA response
- More efficient generation of its active metabolite

IPA – inhibition of platelet aggregation


TRITON – TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA \downarrow

Double-blind

N=13,000

PRASUGREL
CLOPIDOGREL

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Re-ischemia
CV death, MI, UTVR

CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; MI=Myocardial Infarction; TIMI=Thrombolysis In Myocardial Infarction

TRITON-TIMI 38: Rates of Key Study End Points (All ACS)

CV Death, MI, Stroke

Non-CABG TIMI Major Bleeds

Prasugrel
Clopidogrel

HR 0.81
(0.73-0.90)
P<0.001
ARR=2.2
NNT=46

TRITON-TIMI 38: Diabetic Subgroup Analysis (n=3,146)

CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT=Number Needed to Treat; TIMI=Thrombolysis In Myocardial Infarction

Adapted from Antman EM et al. American Heart Association Scientific Sessions; 2007, Nov 4-7; Orlando, FL

Evolution of Antiplatelet Therapy in ACS

ASA

- 22%

ASA + Clopidogrel

- 20%

ASA + Prasugrel

- 19%

Reduction in ischemic Events

Increase in Major Bleeds

Placebo

+ 60%

APTC

+ 38%

CURE

+ 32%

TRITON-TIMI 38

Higher IPA

Single Antiplatelet Rx

Dual Antiplatelet Rx

Higher IPA
Prasugrel – an advantage!

- Superior to clopidogrel in ACS patients undergoing PCI
- Rapid onset of action – one step metabolism
- Reduced inter-patient variability – consistent antiplatelet effects

Guidance

Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary or
- stent thrombosis has occurred during clopidogrel treatment or
- the patient has diabetes mellitus.

People currently receiving prasugrel for treatment of acute coronary syndromes whose circumstances do not meet the criteria in 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
PLATO

ACS (STEMI or UA/NSTEMI)  ↓  ASA  N= 13,000

Double-blind

TICAGRELOR

CLOPIDOGREL

Median duration of therapy - 12 months

1º endpoint:  CV death, MI, Stroke
2º endpoints: CV death, MI, Stroke, Re-ischemia, CV death, MI, UTVR
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>Days after randomisation</td>
<td>6,743</td>
<td>6,743</td>
</tr>
<tr>
<td></td>
<td>8,628</td>
<td>8,521</td>
</tr>
<tr>
<td></td>
<td>8,219</td>
<td>8,124</td>
</tr>
<tr>
<td></td>
<td>6,743</td>
<td>6,463</td>
</tr>
<tr>
<td></td>
<td>5,161</td>
<td>5,096</td>
</tr>
<tr>
<td></td>
<td>4,147</td>
<td>4,047</td>
</tr>
<tr>
<td></td>
<td>3,721</td>
<td>3,596</td>
</tr>
<tr>
<td></td>
<td>3,391</td>
<td>3,271</td>
</tr>
<tr>
<td></td>
<td>3,061</td>
<td>2,941</td>
</tr>
<tr>
<td></td>
<td>2,731</td>
<td>2,611</td>
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<td></td>
<td>2,401</td>
<td>2,281</td>
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<tr>
<td></td>
<td>2,071</td>
<td>1,951</td>
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<tr>
<td></td>
<td>1,741</td>
<td>1,621</td>
</tr>
<tr>
<td></td>
<td>1,411</td>
<td>1,291</td>
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<tr>
<td></td>
<td>1,081</td>
<td>961</td>
</tr>
<tr>
<td></td>
<td>751</td>
<td>631</td>
</tr>
<tr>
<td></td>
<td>421</td>
<td>301</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92), p=0.0003

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Non-CABG and CABG-related major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO major bleeding</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Non-CABG TIMI major bleeding</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>CABG PLATO major bleeding</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>CABG TIMI major bleeding</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

p=0.026

K-M estimated rate (% per year)
**PLATO : Other Safety Events**

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=9,235)</th>
<th>Clopidogrel (n=9,186)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With discontinuation of study treatment</td>
<td>0.9</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p values were calculated using Fischer’s exact test


**Considerations with Ticagralor**

- Twice daily doing: impact on compliance?
- Short-acting: impact of non-compliance?
- Adverse effects in practice
  - Dyspnoea (14% vs 8% with clopidogrel)
Endothelial injury post stent implantation

Stent implantation causes arterial injury, which can initiate restenosis. The restenosis process includes inflammation, migration of smooth muscle cells, smooth muscle cell proliferation and extracellular matrix formation.
Stent thrombosis rates

According to select patient characteristics

- 29.0%
- 8.7%
- 5.5%
- 3.5%
- 3.2%
- 2.6%
- 1.3%

*Antiplatelet therapy discontinuation
Prior brachy Renal failure Bifurcations ULM Diabetes UA

*Premature discontinuation.

According to select patient characteristics

Premature discontinuation of anti-platelet therapy

"Premature discontinuation of antiplatelet therapy is the most important predictor of stent thrombosis after implantation"

Results:
- At 9 month follow-up, 29 patients had stent thrombosis (1.3%)
- Among the 29 patients, 13 died (case fatality rate 45%)

Common reasons for discontinuation include:
- 41% Surgical procedures
- 35% Intolerance to bleeding
- 24% Noncompliance

What does prescribing data tell us?

Long-term management of ACS patients is crucial

- Without appropriate long-term therapy, ACS patients are at early and long-term risk of further atherothrombotic events\(^1,2,3\)

- Around one third of patients with ACS discontinue 1 or more of their prescribed medicines within 3 months of hospital discharge\(^3\)
  - The majority occurs without provider involvement

- Patient education, better prescription drug coverage, and reminder strategies may encourage adherence 3 months after discharge from ACS admission\(^3\)

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Counselling

- Reduces the chance of unwanted blood clots forming which helps prevent heart attacks and strokes
- Take regularly – any time is ok – when would be easiest for you
- Like all medicines – unwanted side effects
  - Indigestion, heart burn, diarrhoea.
  - If unusual bleeding, such as dark or bloody stools, urine or unexplained bruising tell your doctors
- NSAIDs can’t be taken with antiplatelets
“Drugs don’t work in patients who don’t take them”

C. Everett Koop, MD

Coming soon.....

Anticoagulant Therapies and NMS

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