Creating Clear Messaging from Complex Clinical Topics

4th International Conference on Academic Detailing
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FACILITATORS
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PURPOSE
To work through the development process for a complex academic detailing topic example which will include creating clear messages and preparing academic detailers on delivering the messages.

LEARNING OBJECTIVES
- Review what makes an academic detailing topic complex.
- Provide an opportunity to craft clear messages on a complex topic.
- Practice tailoring messages to specific healthcare providers (i.e. specialists, primary care prescribers, pharmacists).
- Review ways to support academic detailers and enhance learning for upskilling on a complex topic

AGENDA
1. Introduction (20 minutes)
    a. Introduction to workshop / what makes a topic complex
    b. Introduction to the RxFiles example:
        - DAPT for Cerebrovascular Indications

2. How to craft clear messaging for complex topics (Lynette/Brenda, small group work) 30 minutes

3. Participants will select between one of the two group activities:
    a. Tailoring messages to multiple healthcare providers (Lynette, small group work) 30 minutes

    b. Academic Detailing Upskilling & Adult Learning on Complex Topics (Brenda, small group work) 30 minutes

4. Wrap-up

Complex Topics

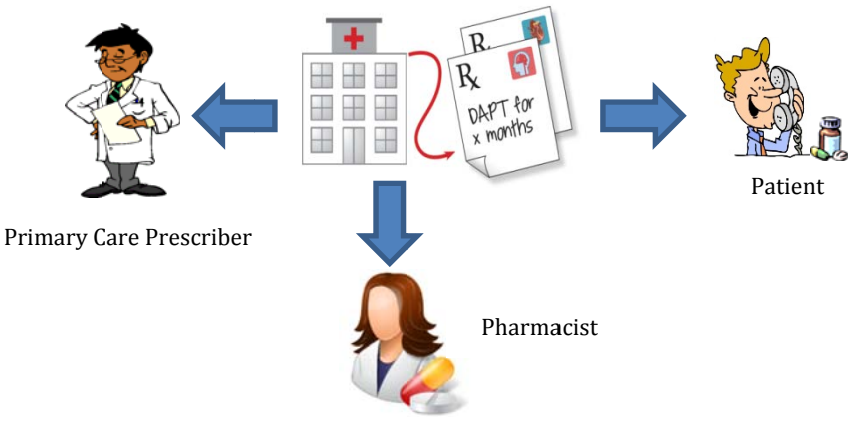
What makes a topic complex: examples

- Identified gaps in practice.
- Ambiguity in usual standard of care.
- System issues that can affect patient care.
- Issues related to the evidence
    - Lack of evidence / poor quality of evidence
    - Old guidelines that haven't incorporated new evidence
    - Conflicting evidence
    - Evidence not implemented / translated into practice
    - Numerous new medications (e.g. COPD)
- Relevance to target audience.
  Lack of interest in a particular topic
    - Lack of awareness of the relevance to their practice.
- Different environmental factors / program approaches.
- Local initiatives that compete with key messages (e.g. DOAC).

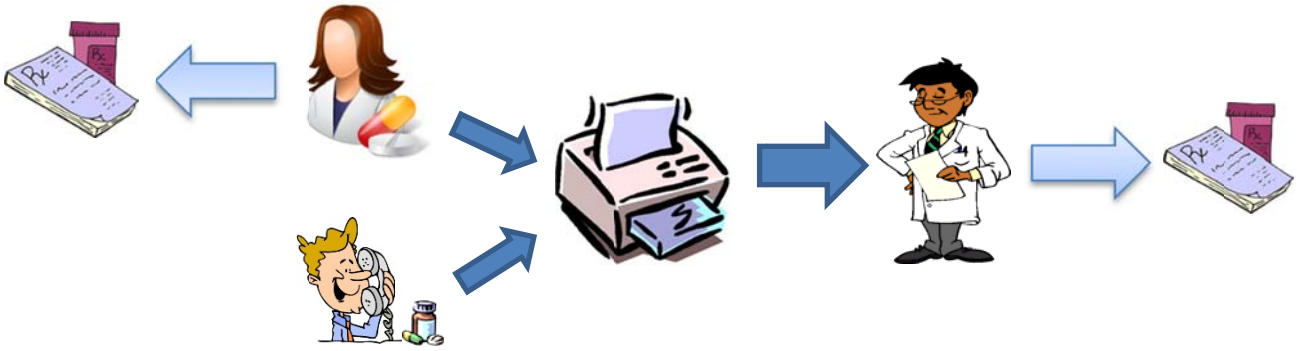
Your own notes on what makes a topic complex:

SYSTEM ISSUES WHICH CREATE GAPS in CARE for DUAL ANTIPLATELET & TRIPLE THERAPY

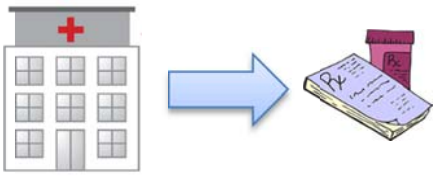
1. Patients are discharged from hospital after a stroke (or heart attack) with a prescription for dual antiplatelet or triple therapy. Ideally, information on the indication, intended duration & instructions for step-down are provided to the primary care prescriber, pharmacist & patient. However, the information may be delayed, not sent or not clear.



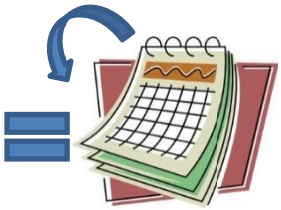
2. Once the initial prescription is complete, the pharmacist may generate a prescription refill request (to the specialist or primary care prescriber) without realizing the intended duration of therapy is done. Patients may also generate a refill request using the automated prescription refill function through the pharmacy's phone tree. The primary care prescriber may re-new the prescription, without realizing the intended duration of therapy is complete. Pharmacists may also use their prescriptive authority to temporarily extend therapy.



3. The patient may be admitted to hospital for another indication (i.e. not a repeat event) while on the intended duration of therapy, & may receive an extension of therapy when discharged from hospital.



4. A concern specifically with dual antiplatelet therapy after a stroke is that therapy may be stepped down to clopidogrel alone (i.e. stop the ASPIRIN). However, ASPIRIN is easily accessible as an over-the-counter product, and may be perceived as safe to continue by patients.



The above systems issues do not occur in all patients, but can result in an inadvertent extension of therapy.

HOW TO CREATE CLEAR MESSAGING FOR COMPLEX TOPICS

Interactive activity: small group work (30 minutes)

Participants will work in small groups to create short, clear, balanced statements on dual antiplatelet therapy for ischemic stokes/transient ischemic attacks. Consider the evidence (benefit and harm), guideline recommendations, the role of single versus dual antiplatelets, duration of dual antiplatelet therapy (if used) and step down therapy. Groups may also incorporate graphics as a way to communicate messages.

Consider the following:

Should dual antiplatelet therapy be used after a non-cardioembolic ischemic stroke?

e.g. Dual antiplatelet therapy may be used in some patients post-stroke, but single antiplatelet agents are preferred.

If used, how *long* should dual antiplatelet therapy be prescribed for?

What is the *benefit* of using dual antiplatelet therapy after a stroke?

What is the *harm* of using dual antiplatelet therapy after a stroke?

Other considerations:

diastolic blood pressure targets consistently lower than 80 mmHg (Evidence Level B).

iii. **In patients with nondiabetic chronic kidney disease**, blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke to attain a blood pressure consistently lower than 140/90 mmHg (Evidence Level C).

iv. For recommendations on specific agents and sequence of agents for the secondary prevention of ischemic stroke, refer to the Canadian Hypertension Education Program treatment guidelines (14).

v. Randomized controlled trials have not defined the optimal time to initiate blood pressure–lowering therapy after stroke or TIA. Blood pressure–lowering treatment should be initiated or modified before discharge from hospital (Evidence Level B).

vi. Patients who are not started on hypertensive therapy in acute care should have arrangements made for follow-up with primary care for ongoing evaluation and management (Evidence Level C).

vii. For children, blood pressure should be targeted below the 95 percentile for age, height and gender (Evidence Level B).

Section 4: Lipid management

4.0 Patients who have had an ischemic stroke or TIA should have their serum lipid levels assessed and aggressively managed (Evidence level A).

4.1 Lipid assessment

i. Fasting lipid levels [total cholesterol, total triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol] should be measured on all patients presenting with stroke or TIA (Evidence Level B).

4.2 Lipid management

i. Patients with ischemic stroke or TIA should be managed with aggressive therapeutic lifestyle changes to lower lipid levels, including dietary modification, as part of a comprehensive approach to lower risk of first or recurrent stroke (Evidence Level B).

ii. A statin should be prescribed as *secondary prevention* to most patients who have had an ischemic stroke or TIA in order to achieve an LDL cholesterol of less than 2·0 mmol/l, or a 50% reduction in LDL cholesterol from baseline (Evidence Level B) (15).

iii. Statin therapy is not indicated for prevention of intracerebral hemorrhage (Evidence Level B).

Section 5: Diabetes and stroke

5.0 Patients with diabetes who have had an ischemic stroke or TIA should have their diabetes assessed and optimally managed (Evidence level A).

5.1 Diabetes assessment

i. Patients with ischemic stroke or TIA should be *screened for diabetes* with a fasting plasma glucose, glycated hemoglobin (A1C) or 75 g oral glucose tolerance test soon after admission to hospital (Evidence Level C) (16).

ii. For *patients with diabetes* and either ischemic stroke or TIA, glycated hemoglobin (A1C) should be measured as part of a comprehensive stroke assessment (Evidence Level B).

5.2 Diabetes management

i. Glycemic targets must be individualized; however, therapy in most patients with type 1 or type 2 diabetes and stroke or TIA should be treated to achieve a glycated hemoglobin (A1C) level ≤7·0% to reduce the risk of microvascular complications (Evidence Level A) and, in individuals with type 1 diabetes, macrovascular complications (Evidence Level C).

ii. To achieve an A1C ≤7·0%, patients with type 1 or type 2 diabetes should aim for a fasting plasma glucose or preprandial plasma glucose target of 4·0 to 7·0 mmol/l (Evidence Level B).

iii. The two-hour postprandial plasma glucose target is 5·0 to 10·0 mmol/l (Evidence Level B). If A1C targets cannot be achieved with a postprandial target of 5·0 to 10·0 mmol/l, further postprandial blood glucose lowering, to 5·0 to 8·0 mmol/l, can be considered (Evidence Level C).

iv. Adults with diabetes and ischemic stroke are at high risk of further vascular events and should also be treated with a statin to achieve a low-density lipoprotein cholesterol ≤2·0 mmol/l (Evidence Level A).

v. Unless contraindicated, low-dose acetylsalicylic acid (ASA) therapy (80 to 325 mg/day) is recommended in all patients with diabetes with evidence of stroke or cardiovascular disease (Evidence Level A).

Section 6: Antiplatelet therapy in ischemic stroke and TIA

6.0 All patients with ischemic stroke or TIA should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation (Evidence Level A).

i. Acetylsalicylic acid (80 mg to 325 mg), combined ASA (25 mg) and extended-release dipyridamole (200 mg), or clopidogrel (75 mg) are all appropriate options, and selection should depend on the clinical circumstances (Evidence Level A).

ii. Short-term concurrent use of ASA and clopidogrel (up to 90 days) has not shown an increased risk of bleeding (Evidence Level A); however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternate indication (e.g. drug-eluting stent requiring dual antiplatelet therapy), due to an increased risk of bleeding and mortality (Evidence Level A).

iii. The combination of ASA (81 mg) and clopidogrel 75 mg is still of uncertain benefit in the Canadian setting for early prevention of recurrent stroke when used within 90 days, and should not be routinely used in all patients (Evidence Level C). *Although the CHANCE clinical trial has demonstrated the efficacy of 21 days ASA and clopidogrel therapy in a Chinese population, the generalization of these findings to the Canadian population and North America standards of care remains*

unclear. These findings will be further investigated in the POINT trial.

iv. At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent (Evidence Level C). In all cases of recurrent stroke while on antiplatelet therapy, all other vascular risk factors should be reassessed and aggressively managed. *Refer to Prevention of Stroke section 2 on Lifestyle and Risk Factor Management for additional recommendations.*

v. In children with stroke the usual maintenance dosage of ASA is 1 to 5 mg/kg per day for the prevention of recurrent stroke (Evidence Level B). The usual maximum dose is 81 mg/day.

vi. The evidence for clopidogrel use in children is sparse at this time. Clopidogrel may be considered an alternative for adolescents at a dose of 1 mg/kg/day up to a maximum of 75 mg/day. Younger children may have higher anti-platelet effects of clopidogrel, and the suggested doses should be considered within the range of 0·2–0·5 mg/kg/day (Evidence Level C).

Refer to Prevention of Stroke section 7 on Stroke and Atrial Fibrillation for additional recommendations on anticoagulant therapy.

Section 7: Anticoagulation for individuals with stroke and atrial fibrillation

7.1 Detection of Atrial Fibrillation

i. All patients with suspected TIA or ischemic stroke should undergo a 12-lead ECG to assess baseline cardiac rhythm and identify atrial fibrillation or flutter, and to provide information regarding evidence of structural heart disease (i.e. previous myocardial infarction, left ventricular hypertrophy) (Evidence Level C).

ii. In cases where the ECG or initial cardiac rhythm monitoring (e.g. 24 or 48 h ECG monitoring) does not show atrial fibrillation but a cardioembolic mechanism is suspected, prolonged ECG monitoring is recommended in selected patients for detection of paroxysmal atrial fibrillation (Evidence Level B) (17).

7.2 Prevention of recurrent stroke in patients with nonvalvular atrial fibrillation

i. Patients with TIA or ischemic stroke *and* atrial fibrillation should receive oral anticoagulation (Evidence Level A).

a. In most patients, direct oral anticoagulants (DOAC) such as apixaban, dabigatran, rivaroxaban, or edoxaban (when available in Canada), should be prescribed in preference over warfarin (Evidence Level B).

b. When selecting oral anticoagulants, patient-specific criteria should be considered (Evidence level C). *Refer to table 7 for additional information on anticoagulant medications, available at* www.strokebestpractices.ca.

ii. The time to start oral anticoagulation following TIA or ischemic stroke is unclear and therapy should be started as soon as it is thought to be safe for the patient (Evidence Level C).

iii. For patients with acute ischemic stroke and atrial fibrillation, routine use of bridging with heparin is not recommended (Evidence Level B). Physicians should use antiplatelet agents until the patient is anticoagulated (Evidence Level C). *Refer to Prevention of Stroke section 6 on Antiplatelet Therapy for Ischemic Stroke and TIA for additional recommendations on antithrombotic therapy.*

7.3 Enhancing anticoagulation therapy and minimizing bleeding complications

i. Medication adherence is important for patients on *all* oral anticoagulants. For patients with atrial fibrillation that are taking warfarin, careful dosing and consistent international normalized ratio monitoring is recommended to minimize adverse events; warfarin efficacy is dependent on maintaining therapeutic international normalized ratio control, and declines significantly when the international normalized ratio falls below 2·0 (Evidence Level A).

ii. For patients prescribed apixaban, dabigatran, rivaroxaban, or edoxaban (when available in Canada), renal function should be routinely monitored, and measured at least once annually or when there is a change in health status (Evidence Level C). Dose adjustments may be required based on changes in renal function if detected.

iii. Concomitant antiplatelet therapy with oral anticoagulation is not recommended in patients with atrial fibrillation unless there is a specific medical indication (Evidence Level B).

Section 8: Management of extracranial carotid disease and intracranial atherosclerosis

8.1 Symptomatic carotid stenosis

Patients with TIA or nondisabling stroke and ipsilateral 50% to 99% internal carotid artery stenosis should have an evaluation by an individual with stroke expertise and selected patients should be offered carotid endarterectomy *as soon as possible* (Evidence Level B).

i. Carotid stenosis should be measured by CTA alone or two concordant noninvasive imaging modalities such as MRA and carotid ultrasound or digital subtraction angiography (DSA) [Evidence Level C].

ii. Individuals with mild stroke or TIA should have carotid endarterectomy performed within 48 h of symptom onset (NASCET Trial, NNT = 3) (18), and within 14 days for patients who are not clinically stable within the first 48 h (Evidence Level B).

a. Carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of less than 6% (Evidence Level A).

iii. Carotid stenting may be considered for patients who are not operative candidates for technical, anatomic or medical reasons (Evidence Level A).

a. Interventionalists should have expertise in carotid procedures and an expected risk of peri-procedural morbidity and mortality rate of less than 5%.

iv. Carotid endarterectomy is more appropriate than carotid stenting for patients over age 70 who are otherwise fit for surgery because stenting carries a higher peri-procedural risk of stroke and death (Evidence Level A).

SUMMARY OF DUAL ANTIPLATELET THERAPY FOR SECONDARY NON-CARDIOEMBOLIC ISCHEMIC STROKE/TIA PREVENTION TRIALS

The studies below were all randomized, double-blind, placebo-controlled multisite intention-to-treat trials with concealed allocation & blinded adjucation.

	POPULATION / DESIGN	INTERVENTION	BENEFIT/HARM
DAPT vs ASA	**CHANCE: C**lopidogrel in **H**igh-risk patients with **A**cute **N**on-disabling **C**erebrovascular **E**vents (NEJM 2013)		
	- 5170 patients enrolled **within 24 hours** of a minor ischemic stroke (72%) or TIA (28%) - 1% were on ASA within 90 days of study enrolment - Conducted in **China** (stroke rate in China is 5x higher than in the United States)	- **Days 1 to 21:** DAPT (ASA 75mg + clopidogrel 75mg po daily*) vs ASA - **Days 22 to 90:** clopidogrel vs ASA *loading dose given on Day 1	**DAPT for 21 days, followed by clopidogrel up to 90 days, compared to ASA alone:** - Reduced the risk of **recurrent stroke** (primary endpoint) ▪ Need to treat 29 people with DAPT for 21 days to *prevent* 1 additional stroke (NNT=29) - No difference in **all-cause mortality** or **major bleeding** between the treatment groups.
	SPS3: Secondary **P**revention of **S**mall **S**ubcortical **S**trokes (NEJM 2012)		
	- 3020 patients with recent (**2 weeks to 180 days, mean 62 days**) minor ischemic stroke (97%) or TIA (3%) - 28% on ASA at time of stroke - International: 65% North America - Antiplatelet component of the trial was **stopped early** due to lack of efficacy & increased harm	- DAPT (ASA 325mg + clopidogrel 75mg po daily) vs ASA alone for a **mean of 3.4 years**	**DAPT for 3.4 years, compared to ASA alone:** - Did not reduce the risk of **recurrent stroke** (primary endpoint) - Increased the risk of harm: ▪ Need to treat 44 people with DAPT for 3.4 years to *cause* 1 additional **death** (all-cause mortality) (NNH=44) ▪ need to treat 32 people with DAPT for 3.4 years to *cause* 1 additional **major bleed** (NNH=32)
DAPT vs Clopidogrel	**MATCH: M**anagement of **AT**herothrombosis with **C**lopidogrel in **H**igh-risk patients (Lancet 2004)		
	- 7,599 patients with recent (**within 3 months**, **mean 26 days**) minor ischemic stroke (79%) or TIA (21%) plus one or more additional vascular risk factors (previous ischemic stroke, heart attack, angina, diabetes or symptomatic peripheral artery disease within the previous 3 years) - 80% on ASA & 25% on clopidogrel prior to randomization - International: 28 countries	- DAPT (ASA 75mg + clopidogrel 75mg po daily) vs clopidogrel alone x **18 months**	**DAPT for 18 months, compared to clopidogrel alone:** - Did not reduce the risk of **major vascular events** = ischemic stroke, heart attack, vascular death, or rehospitalization for acute ischemia (primary endpoint composite) - Increased the risk of harm: ▪ need to treat 50 people with DAPT for 18 months *cause* 1 additional **life-threatening bleed** (NNH=50)

ASA = acetylsalicyclic acid (aspirin), **DAPT** = dual antiplatelet therapy (clopidogrel + aspirin), **NNH** = number needed to harm, **NNT** = number needed to treat, **TIA** = transient ischemic attack (mini stroke)

Patient cost for clopidogrel is ~$26/month. In Saskatchewan, provincial drug coverage is only available for patients who have failed ASA, or are allergic or intolerance to ASA.

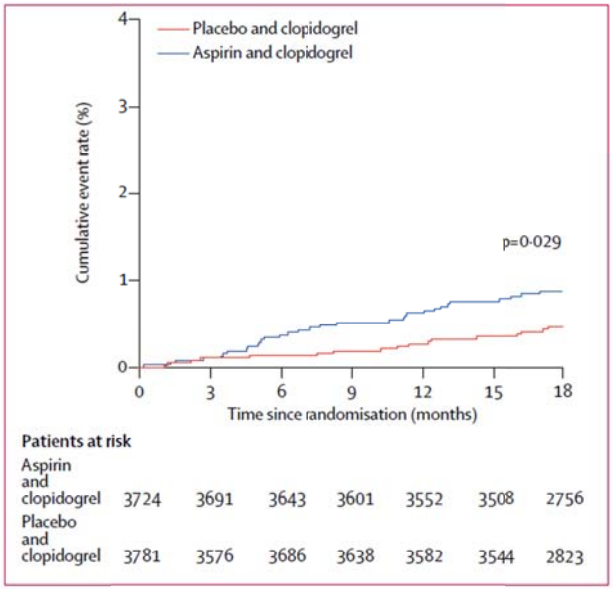


Figure 4: Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage

Above Figure from the MATCH trial; data used by the Canadian stroke prevention guidelines to caution against DAPT greater than 90 days.

TAILORING MESSAGES FOR SPECIALISTS, PRIMARY CARE PRESCRIBERS & PHARMACISTS

Interactive activity: small group work (30 minutes)

Participants will work in small groups to create messages for one of the three targeted healthcare providers (i.e. specialists, primary care prescribers, pharmacists). Type of healthcare provider will be assigned to the groups by the facilitators. Participants are to reflect on the system issues shared in the Introduction (refer to handout) and the below key messages.

Key messages for dual antiplatelet after ischemic stroke or transient ischemic attack:

1. Know & assist in the implementation of the intended duration of dual antiplatelet therapy prescribed by the initiating specialist.

2. Emphasize the importance of the treatment duration to patients (i.e. avoid over & under treating), and identify & address causes of non-compliance.

For example, a message we had for pharmacists was to add the intended duration of therapy to the prescription label.

Academic Detailer Training & Adult Learning on Complex Topic

Interactive activity: small group work (30 minutes)

Objective:

- To review ways to support academic detailers and enhance learning for upskilling on a complex topic.

Question:

Your upskilling day is set for 2 months from today. Discuss in general terms how this current topic which is a particularly complex topic might influence how you plan the upskilling of the detailers.

Factors that might influence	Comments

ACTIVITY:

In planning for your team's upskilling day on a complex topic what special factors might you consider in planning the agenda, the types of activities that you might have the detailer participate in?

Consider what you might have the detailer do

1. PRIOR to the upskilling day
2. DURING the upskilling day
3. AFTER the upskilling day

Detailer Upskilling on Complex Topic		
Prior to Upskilling Day	**During Upskilling Day**	**After Upskilling Day**

Sample Tools from RxFiles:
*see next pages for samples of tools developed with the Dual Antiplatelet (DAPT) topic to assist in the upskilling on this complex topic. See sample of a homework assignment for our detailers prior to an upskilling day on our COPD topic. These are just a few samples of ways to assist the detailer in their mastery of a topic.

DUAL ANTIPLATELET & TRIPLE THERAPY ACADEMIC DETAILING UPSKILLING DAY
Use of Games to Engage Academic Detailers
RxFiles Academic Detailing Program

Background

When taking on complex topics academic detailers need to have appropriate time to undertake self-directed learning. Upskill training provides opportunity for detailers to come together and further work through areas of controversy, uncertainty, issues that require group discussion, or solidification of knowledge.

Using games in learning is intended to make education more fun and engaging without undermining its credibility. Gamification can boost inquiring to learn more, and can stimulate further discussions and learning.

PRIOR TO UPSKILLING

- A crossword puzzle was created & disseminated to team members to help them with terminology related to the topics (e.g. definite versus probable stent thrombosis)

UPSKILLING DAY - GAME SHOW THEME

We wanted training day to be fun, interactive & informative. We wanted to give everyone the opportunity to participate in the games, but we also did not want to cause any stress by putting team members "on the spot". As such, we built in "life-lines" into each game.

JEOPARDY

- Questions were based on the reading package materials disseminated in advance
- PowerPoint game template used
- Categories were as follows:
  - **CATEGORY 1: Strength in Numbers**
    - questions were based on the DAPT post coronary stent meta-analyses
  - **CATEGORY 2: Time after Time**
    - questions were based landmark studies / guideline recommendations on step-down therapy (i.e. what to do when DAPT or TT is complete)
  - **CATEGORY 3: You Stay Classy, RxFiles (a la Ron Burgundy)**
    - questions were based on oral anticoagulant & antiplatelet medication classes (i.e. the role and evidence to support use in DAPT or TT)
  - **CATEGORY 4: (in)Famous Trials (involving drugs, not criminals)**
    - questions focused on the landmark trials (i.e. interventions and durations)
  - **CATEGORY 5: Safety First**
    - questions were based on safety concerns related to DAPT & TT (e.g. bleeding, stent thrombosis, etc)
  - **CATEGORY 6:** Real or Rubbish (can you spot the sham study)
    - this category served as the "life-line"
    - participants had to guess if a study was real or rubbish based on the study title (e.g. "Earlobe crease shapes and cardiovascular events"… which is surprisingly a real study)
  - **FINAL JEOPARDY**

FAMILY FEUD

- Questions included lists that were included in our newsletter or relevant to the topic
- "Studies say…" or "Experts say…"
- Answers were in alphabetical order (versus based on survey results)
- Life-line: could consult with team
- PowerPoint game show template used
- Examples of included questions:
    - **When should you consider gastroprotection with a PPI for a patient on DAPT**
    - **When may you consider switching from one P2Y12 inhibitor to another**
    - **What are some strategies for reducing the risk of bleeding with triple therapy**
    - **When would you consider DAPT <12 months post coronary stent**
    - **What indications for oral anticoagulation appropriate for triple therapy**

WIN, LOSE or DRAW

- Focused on the stent thrombosis / bleeding risk factors that are included in the DAPT Score (i.e. should DAPT be continued beyond 12 months after coronary stent insertion)
- Instead of having detailers memorize the list of risk factors, we thought having their team members attempt to draw the risk factors would be a fun & easier way to remember the list
- Team members were assigned their risk factor a few weeks prior to upskilling day, so they had a chance to brainstorm how best to draw their clue. They were not told how each of their clues related (i.e. DAPT Score risk factors). Once all risk factors were identified, team members had to guess the linkage, i.e. DAPT Score risk factors.
- Life-line: if teams did not correctly guess the clue within 1 minute, the drawer could use words & numbers to help represent the clue.
- Flip charts & markers were used

HOLLYWOOD SQUARES

- Statements were based on controversial statements or expert opinions found in the reading package
- The Squares were filled with various celebrities, and each team member was assigned to represent one celebrity
- Life-line: the assigned celebrity status (i.e. celebrities often use their status to speak on various topics, yet may have incomplete or misinformation)
- PowerPoint game show template was used

PRICE IS RIGHT

- Patient cases were presented, and participants had to select from 3 courses of action (i.e. Door #1, Door #2, and Door #3)
- Life-line: participants only had to raise their hands to indicate their selection, and discussion afterwards was open to all

CELEBRITY APPRENTICE

- Academic detailers were split into teams. Everyone reassured that no one would be fired. :)
- Their assignment was to:
    1) refine draft key messages, brainstorm ideas for an infographic & practice detailing
    2) "pitch" their ideas to the whole group on key message revisions & an infographic, as well share comments on practice detailing

SUMMARY OF CANADIAN, AMERICAN & EUROPEAN GUIDELINE RECOMMENDATIONS FOR DAPT POST-ACS with PCI

Ideally, DAPT is continued for 12 months after PCI.

Table 3: DAPT post-ACS (NSTEACS or STEMI) with PCI

- The below guidelines grouped NSTEACS and STEMI recommendations together under "ACS" as both fall under the spectrum of ACS. However, since the majority of the guidelines still report recommendations separately, these recommendations are listed here but also summarized under Table 2 & 3.

2016 ACC/AHA Guideline Focused Update on Duration of DAPT in CAD

Type of P2Y12 Inhibitor:

- In patients with ACS (NSTEACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use **ticagrelor** in preference to clopidogrel for maintenance P2Y12 inhibitor therapy. (IIa, B-R) PLATO
- In patients with ACS (NSTEACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose **prasugrel** over clopidogrel for maintenance P2Y12 inhibitor therapy. (IIa, B-R) TRITON
- **Prasugrel** should not be administered to patients with a prior history of stroke or TIA. (III, B-R) TRITON

Dose of ASA:

- In patients treated with DAPT, a daily ASA dose of 81mg (range, 75-100mg) is recommended. (I,B-NR)

Duration of DAPT in ACS with PCI:

- In patients with ACS (NSTEACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y12 inhibitor therapy (clopidogrel, prasugrel or ticagrelor) should be given for **at least 12 months**. (IB-R) DAPT, CREDO, PCI-CURE, CURE, PLATO, TRITON
- In patients with ACS (NSTEACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication & who are not a high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, OAC), continuation of DAPT (clopidogrel, prasugrel or ticagrelor) for **longer than 12 months may be reasonable**. (IIb,A) DAPT, REAL-LATE/ZEST-LATE, DES_LATE, PRODIGY, ARTIC-Interruption, ITALIC, CHARISMA, PEGASUS, TRITON, PLATO
- In patients with ACS treated with DAPT after **DES implantation** who develop a high risk of bleeding (e.g .treatment with OAC), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after **6 months may be reasonable**. (IIb,C-LD) SECURITY, EXCELLENT, RESET, OPTIMIZE, ISAR-SAFE, & meta-analyses

2012 CHEST Secondary Prevention of Cardiovascular Disease

For patients in the **1st year after** an **ACS (=NSTEAC + STEMI)** who have undergone PCI with stent:

- We recommend DAPT over single antiplatelet therapy (Grade 1B). Options:
  - **ticagrelor** 90mg BID + ASA PLATO

	Baseline risk (clopidogrel + ASA)	Risk difference (ticagrelor + ASA)
Vascular death	50/1000	10 fewer (95% CI -15 to -4)
MI	70/1000	11 fewer (95% CI -17 to -3)
Stroke	13/1000	NS
Major bleed	22/1000	6 more (95% CI 0 to +11)

- We suggest **ticagrelor** 90mg BID plus low-dose ASA over clopidogrel 75mg daily + low-dose ASA (Grade 2B). PLATO
  - **clopidogrel** 75mg daily + ASA CURE

	Baseline risk (ASA)	Risk difference (clopidogrel + ASA)
Vascular death	60/1000	NS
MI	70/1000	16 fewer (95% CI -23 to -8)
Stroke	20/1000	NS
Major bleed	30/1000	11 more (95% CI +4 to +20)

  - prasugrel 10mg daily + ASA TRITON-TIMI

	Baseline risk (clopidogrel + ASA)	Risk difference (prasugrel + ASA)
Vascular death	50/1000	NS
MI	70/1000	17 fewer (95% CI -23 to -10)
Stroke	13/1000	NS
Major bleed	22/1000	7 more (95% CI 0 to +15)

- **Prasugrel** results in no benefit or net harm in patients with a body weight <60kg, age >75 years, or previous stroke/TIA.
- **Beyond 1 year**, recommend long-term single antiplatelet therapy with ASA 75-100mg daily or clopidogrel 75mg daily over no antiplatelet therapy (IA). Suggest single over DAPT (2B).

DAPT: 12 vs 30 Months of Dual AntiPlatelet Therapy after Drug-Eluting Stents [1]

BOTTOM LINE

- In **DAPT**, a group of highly selected patients 56% excluded at randomization who received a drug-eluting stent (DES) 27% paclitaxel & dual antiplatelet therapy (DAPT, i.e. ASA + thienopyridine) beyond 1 year (30 months in total) had:
  - ↓ risk of stent thrombosis (NNT=100) and ↓ risk major adverse cardiovascular & cerebrovascular event (MACCE) (NNT=63) but ↑ risk of moderate-severe bleeding (NNH=112)
  - ↑ risk of all-cause mortality trend at 30 months, statistically significant at 33 months, NNH=200 (primarily driven by non-cardiovascular death)
- The ideal duration of DAPT therapy is still unknown. Extended DAPT therapy may be of most benefit in those who are at a very high risk of ischemic events & low risk of bleeding; however, high risk patients were excluded from **DAPT** (randomization phase).

BACKGROUND [1,2,3,4,5,6,7,8,9]

- DAPT is recommended after bare-metal stent (BMS) & DES placement to ↓ the risk of stent thrombosis & MACCE.
- Compared to BMS, DES ↓ the risk of restenosis & the need for target vessel revascularization procedures; however, DES may ↑ the risk of stent thrombosis, depending on the type:
  - 1st generation DES (G_1DES; paclitaxel, sirolimus): ↑ risk of very late stent thrombosis (i.e. >1 year after PCI) compared to BMS.
  - Newer generation DES (e.g. everolimus, zotarolimus): similar rate of very late stent thrombosis as BMS.
- The **Canadian Cardiovascular Society 2012 Antiplatelet Guidelines** recommend DAPT x 12 months after a coronary stent has been inserted. The committee also suggests that DAPT may be continued beyond 12 months in patients who have a high risk of thrombosis & a low bleeding risk (conditional recommendation, low-quality evidence).[4]
- Several other clinical practice guidelines make similar statements with extended DAPT, which is based on observational studies that suggested DAPT beyond 1 year ↓ the risk of very late stent thrombosis with G_1DES.[5,6,7] The Food & Drug Administration (FDA) requested that a large randomized controlled trial be conducted to address this issue.
- Three randomized controlled trials have evaluated extended vs standard (12 months) DAPT – **DES-LATE**, **ARTIC-Interruption**, **DAPT**. All three studies excluded patients with a high thrombosis or bleed risk. Patients could only be randomized to extended DAPT if they were 'event-free' after 12 months of DAPT (i.e. no major adverse cardiac or cerebrovascular events, or major bleeding).
  - **ARTIC-Interruption** (2014, France):[8] n=1,259 patients with DES (~40% G_1DES), open-label DAPT x 12 months vs 18 to 30 months (90% clopidogrel, 10% prasugrel). Primary endpoint (death, MI, stent thrombosis, stroke or urgent revascularization): NS. Major bleeding (STEEPLE): NS; major & minor bleeding: ↑ risk with extended DAPT, NNH=100
  - **DES-LATE** (2014, Korea):[9] n=5,045 patients with DES (~64% G_1DES), open-label DAPT 12 months vs 36 months (100% clopidogrel). Primary endpoint (death from CV causes, MI, stroke): NS; stent thrombosis: NS. Major bleeding (TIMI): NS
- Of note, because very late stent thrombosis is rare (0.3% with G_1DES, 0.04% with newer generation DES), it is estimated that approximately 10,000 individuals would need to be recruited in order to evaluate extended DAPT for this outcome.

TRIAL BACKGROUND [1,2]

DESIGN: international 11 countries, multi-centre 452 sites, prospective, open-label followed by a randomized, double-blinded, placebo controlled trial. ITT & superiority for efficacy outcomes. Concealed allocation. Funding: 8 stent and pharmaceutical manufacturers, including the manufacturers of clopidogrel (Bristol Myers Squibb, Sanofi) and prasugrel (Eli Lilly), & the Harvard Clinical Research Institute. Enrolment period: August 2009 - July 2011.

INTERVENTION: DAPT (ASA + $P2Y_{12}$ receptor inhibitor) 12 months vs 30 months

- **Enrollment:** all participants received open-label DAPT x 12 months (months 0-12)
  - ASA 75-325mg daily x 6 months, then 75-162mg daily + clopidogrel 300-600mg x 1, then 75mg daily, **or** + prasugrel 60mg x 1, then 5-10mg daily (5mg daily if <60kg)
- **Randomization:** eligible patients were randomized to DAPT or placebo + ASA x 18 months (months 12-30)
- **Observational follow-up:** open-label ASA only x 3 months (months 30-33)
- Stent type, choice of thienopyridine, and dose of ASA was left to the discretion of the clinician overseeing care.

INCLUSION: Enrollment: age >18 years, undergoing PCI with DES or BMS stent (only DES data presented here)

- **Randomization:** "12 Month Clear" i.e. DAPT x 12 months, event free (i.e. no death, MI, stroke, repeat coronary revascularization, stent thrombosis, & moderate or severe GUSTO bleeding) and adherent to therapy (80-120% of doses during months 0-6 and without interruption of therapy >14 days during months 6-12)

EXCLUSION:

- **Enrollment:** stent diameter <2.25 or >4.0mm, pregnant women, planned surgery requiring discontinuation (>14 days) of antiplatelet therapy within 30 months post PCI, current medical condition with a life expectancy <3 years, on warfarin or similar anticoagulant, treated with both DES and BMS
- **Randomization:** switched thienopyridine type or dose within 6 months before randomization, PCI or cardiac surgery between 6 weeks post-index procedure and randomization, planned surgery requiring the discontinuation (>14 days) of antiplatelet therapy within 21 months after randomization

POPULATION at randomization: n=9961 of 22,866 who received a DES

- mean age ~62 years, ~75% ♂, 88% Caucasian, 89.5% from North America
- mean body weight 91.5kg (±19.5kg), BMI 30.5kg/m^2 (±5.8kg/m^2)
- 75% HTN 75.8% DAPT vs 74% placebo + ASA, p=0.03, 30.6% DM, ~25% smoker current or within past year, ~22% MI, ~3% stroke/TIA, ~5% HF, ~6% PAD
- ~30% prior PCI, ~11.5% prior CABG, ~51% had risk factor(s) for stent thrombosis e.g. STEMI, NSTEMI, renal failure, LVEF<30%, >2 vessels stented, etc
- **Indication for PCI:** ~38% stable angina, ~20% "other", ~17% unstable angina, 15.5% NSTEMI, ~10.5% STEMI
- **Type of thienopyridine:** ~65% clopidogrel, ~35% prasugrel; 22% were on a proton-pump inhibitor at randomization [3]
- **Type of DES:** ~47% everolimus, ~27% paclitaxel, ~13% zotarolimus, ~11% sirolimus & 2% >1 type
- Mean number: treated lesions 1.3, treated vessels 1, stents 1.5, stent length 27.5mm
- 53% stent diameter ≥3mm, 97% native coronary artery lesions (~40% left anterior descending), 43% modified ACC-AHA lesion B2 or C

RESULTS

follow-up: 30 and 33 months

TABLE 1: EFFICACY & SAFETY

PRIMARY ANALYSIS PERIOD: ITT & superiority

MONTHS 12 TO 30

CLINICAL ENDPOINTS	DAPT n=5020	PLACEBO + ASA n=4941	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH	COMMENTS
Co-PRIMARY EFFICACY ENDPOINTS						
Stent thrombosis	0.4%	1.4%	0.29 (0.17-0.48)	<0.001	100/30 MONTHS	- **MACCE** rates primarily driven by MI - **MI not related to stent thrombosis:** DAPT 1.8% vs placebo + ASA 2.9%, HR 0.59, p<0.001 - **All-cause mortality** was primarily driven by non-cardiovascular death - **Cancer-related deaths** DAPT n=31 vs placebo + ASA n= 14, p=0.02 - **Discontinuation Rate:** DAPT 21.4% vs placebo + ASA 20.3%, NS
MACCE (death, MI, stroke)	4.3%	5.9%	0.71 (0.59-0.85)		63/30 MONTHS	
SECONARY EFFICACY ENDPOINTS						
Myocardial Infarction	2.1%	4.1%	0.47 (0.37-0.61)	<0.001	50/30 MONTHS	
Stroke	0.8%	0.9%	NS	0.32	-	
All-Cause Mortality	2%	1.5%	1.36 (1.00-1.85)	0.052	-	

SECONDARY ANALYSIS PERIOD: ITT & superiority

MONTHS 12 TO 33

CLINICAL ENDPOINTS	DAPT x 30 MONTHS THEN ASA x 3 MONTHS n=5020	PLACEBO + ASA n=4941	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH
Stent thrombosis	0.7%	1.4%	0.45 (0.29-0.69)	<0.001	143/33 MONTHS
MACCE (death, MI, stroke)	5.6%	6.5%	0.82 (0.7-0.97)	0.02	112/33 MONTHS
Myocardial Infarction	3%	4.5%	0.61 (0.49-0.76)	<0.001	67/33 MONTHS
Stroke	1%	1.1%	NS	0.48	-
All-Cause Mortality	2.3%	1.8%	1.36 (1.02-1.82)	0.04	200/33 MONTHS

PRIMARY SAFETY ENDPOINT: patients who could be evaluated; superiority & non-inferiority

MONTHS 12 TO 30

CLINICAL ENDPOINTS	DAPT n=4710	PLACEBO + ASA n=4649	HAZARD RATIO (95% CI)	P-VALUE	NNT/NNH
GUSTO moderate or severe bleeding	2.5%	1.6%	1.61 (1.21-2.16)	0.001 NS for non-inferiority	112/30 MONTHS

SECONDARY SAFETY ENDPOINTS: patients who could be evaluated

CLINICAL ENDPOINTS	DAPT n=4710	PLACEBO + ASA n=4649	RISK DIFFERENCE % (95% CI)	P-VALUE	NNT/NNH 30 MONTHS
GUSTO severe bleeding Intracranial bleed or hemodynamic compromise requiring intervention	0.8%	0.6%	0.2 (-0.1-.06)	0.15	-
GUSTO moderate bleeding transfusion, but hemodynamically stable	1.7%	1%	0.7 (0.2-1.2)	0.004	143
BARC Type 2, 3 or 5	5.6%	2.9%	2.6 (1.8-3.5)	<0.001	37
BARC Type 2 overt, actionable bleed	3.1%	1.5%	1.5 (0.9-2.1)		63
BARC Type 3 overt bleed, ↓Hgb & transfusion	2.6%	1.5%	1.1 (0.6-1.7)		91
BARC Type 5 fatal bleed	0.15%	0.09%	0.1 (-0.1-0.2)	0.38	-

Events 3 Months After Discontinuing DAPT:*

DAPT Arm (last 3 months of tx vs 3 months after)
- Stent thrombosis: HR 0.12 (0.01-0.22) → 0.31 (0.13-0.50)
- MACCE: HR 0.8 (0.53-1.07) → 1.59 (1.2-2)
- MI: HR 0.43 (0.23-0.63) → 1.12 (0.8-1.5)

DAPT vs Placebo + ASA (months 12-15, p<0.001)
- Stent thrombosis: HR 0.05 (0.01-0.39)
- MACCE: HR 0.38 (0.25-0.59)
- MI: HR 0.24 (0.13-0.42)

*HR/day

In a separate analysis, the DAPT investigators evaluated extended DAPT in patients who had a **BMS** inserted.[10] The authors concluded there was no benefit or harm, but the study was underpowered.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Largest randomized controlled trial assessing DAPT therapy beyond 1 year of stent placement.
- Clinically meaningful endpoints (stent thrombosis, MACCE [including death], bleeding) with ITT analysis for efficacy outcomes.
- Blinded adjucation of clinical outcomes (and unblinded, independent safety committee).
- Extended follow-up. Patients were followed for 3 months after discontinuation of their thienopyridine to assess for rebound ischemia. There was an increased risk of stent thrombosis & MACCE in both groups after discontinuation.
- Only ~5% of patients lost to follow-up.

LIMITATIONS:
- Only 43.6% (9961/22,866) of the enrolled participants who received a DES were randomized at 12 months. 11.5% (2638/22,866) had an event(s) during the first 12 months of therapy and approximately 2/3 (61%, 1620/2638) of these individuals required revascularization. 25.4% (5808/22,866) withdrew consent.
- Low risk compliant patient population, i.e. those who had an event (thrombosis, bleed, death) or were non-compliant were excluded from the randomization phase. Only 22% of the study population was on a proton-pump inhibitor at randomization.

UNCERTAINITIES:
- Benefits & risks in a higher-risk population
- Potential increase in non-cardiac deaths, e.g. cancer-related, fatal trauma
- Outcomes with other stent types or non-thienopyridine P2Y12 inhibitors (e.g. ticagrelor)
- **Difference in outcomes for 1st vs 2nd generation DES**
  - The risk of stent thrombosis is thought to be higher with 1st generation DES (e.g. paclitaxel, 27% of patient population). When these individuals were excluded for a post-hoc analysis, the difference in stent thrombosis between groups lessened (months 12-30: DAPT 0.23% vs placebo + ASA 0.72%, HR 0.33 [95% CI 0.15-0.72], p=0.004, ARR=0.49%, NNT=205).[3]

RxFiles COPD Training Day
Home Assignment #2: Clinical Controversies in COPD
Led by: Alex Crawley

For this homework assignment, your job will be to do a little pre-reading into some "clinical controversies" surrounding COPD. These are situations where the path forward isn't always crystal clear. Don't worry! We've listed some articles that should help inform your viewpoints.

Please be familiar with all 5 of the following issues - but you will be asked to discuss in depth only one or two issues (depending on time).

1. Does using tiotropium respimat increase mortality (vs using the Handihaler)?
Articles:
1a. Singh, Sonal, et al. "Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials." *bmj* 342 (2011).
1b. Wise, Robert A., et al. "Tiotropium Respimat inhaler and the risk of death in COPD." *New England Journal of Medicine* 369.16 (2013): 1491-1501.

2. Patients, especially with severe COPD, are often put on the "triple therapy" of LAMA + LABA + ICS. Is this sufficiently beneficial compared to using a LAMA alone to justify the extra adverse effects and dollars?
Articles:
2a. Rodrigo, Gustavo J., Vicente Plaza, and José A. Castro-Rodríguez. "Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review."*Pulmonary pharmacology & therapeutics* 25.1 (2012): 40-47.
2b. Karner, Charlotta, and Christopher J. Cates. "Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease." The Cochrane Library (2011).
2c. Dalhousie Meta and Systematic Review Summary. See pages 19-22 (starting at Table 9)

3. Since LABAs can cause arrthymias and increase heart rate, they are cautioned in patients with cardiovascular disease. At the doses used in COPD, is this an issue?
Articles:
3a. Cazzola M, Matera MG, Donner CF. Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs* 2005;65:1595–1610.
3b. Gershon, Andrea, et al. "Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease."*JAMA internal medicine* 173.13 (2013): 1175-1185.
3c. Woodruff, Prescott G. "Double-edged Sword?: Long-Acting Bronchodilators in Chronic Obstructive Pulmonary Disease." *JAMA internal medicine* 173.13 (2013): 1184-1185.

4. Theophylline has fallen out of favour in recent years. Is this justified?
Articles:
4a. Gold 2015 guidelines (see page 24)
4b. Ram, Felix SF, et al. "Oral theophylline for chronic obstructive pulmonary disease." *The Cochrane Library* (2002).

5. Should patients on a LABA+ICS be switched to a LAMA?
Articles:
5a. INSPIRE. Wedzicha, Jadwiga A., et al. "The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide." *American journal of respiratory and critical care medicine* 177.1 (2008): 19-26.
5b. Dalhousie Meta and Systematic Review Summary. Refer to pages 12 to 14 (starting at Table 6)