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Palais des Congrès de Montréal

Deprescribing for the Elderly and in Advanced Illness

**Presented by: Mary Lynn McPherson, PharmD,
MA, MDE, FAAHPM**

CONFLICTS OF INTEREST DECLARATION

- None



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LEARNING OBJECTIVES

At the conclusion of this presentation, participants will be able to:

- Describe a systematic approach to deprescribing in the elderly and those with advanced illness
- Describe best practices in deprescribing in metabolic syndrome
- Describe best practices in deprescribing in Alzheimer's disease
- Weigh benefits and burdens of anticoagulation in the elderly and those with advanced illness

CanMEDS COMPETENCY FRAMEWORK

- Professional CanMEDS competency



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What is polypharmacy and why should we care about it?

- A. Taking two or more medications concurrently
- B. Taking five or more medications concurrently
- C. Taking nine or more medications concurrently
- D. A patient who uses two or more different pharmacies

Prevalence of polypharmacy in the US:

Approximately 8.2% in 1999-2000
Approximately 15% in 2011-2012

Polypharmacy in long-term care:

91% of residents \geq 5 medications
74% of residents \geq 9 medications
65% of residents \geq 10 medications

Consequences of polypharmacy:

Frailty
Dementia
Cognitive decline
Disability
Hospitalization
Mortality

Consequences of polypharmacy at EOL:

As above, plus:
Anticholinergic burden
Sedation burden
Disease-associated and age-associated
pharmacokinetic and pharmacodynamic
changes

Polypharmacy at the end of life

- How does the number of medications patients take as they near the end of life, compare with patients in a similar age bracket?
 - A. The same
 - B. More
 - C. Less

Morin et al reconstructed the medication regimens for the previous 12 months of over 500,000 older adults who died in Sweden between 2007 and 2013.

- Average results showed during the year before death, the percentage of patients taking \geq 10 medications increased from 30.3 to 47.2%

Retrospective study of > 500 older nursing home residents in Sydney, Australia evaluated changes in the prescribing of symptomatic and preventative medications in last year of life.

Overall medication use changed little:

- Symptom management medications increased slightly
- Disease-prevention medication use decreased slightly
- At the time of death, \sim 1/3 of patients had actively prescribed antithrombotic agents, antihypertensive medications and osteoporosis medications

179 patients in last week of life in hospital, hospice, or home in Netherlands

- Mean number of medications used per patient was nine on day 7 before death.
 - 30% of patients received a preventative medication on the day of death.

Am J Med 2017;130(8):927-36;
Front Pharmacol 2018;8:990;
J Palliat Med 2018;21(2):149-55.

If polypharmacy is the problem, what's the solution?

The geriatrician's salute!

De-intensification!

Deprescribing!

- “Deprescribing” – defined as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.”

Goal-concordant care!

Who's with me??

Survey says...

Survey of community-dwelling older adults living in Canada

- “I am comfortable with the number of medications that I am taking” - > 80% strong agreed/agreed
- Half thought they were taking a large number of medications
- Half stated they would like to reduce the number of medications they were taking
- ~ 75% said they would be willing to stop ≥ 1 medications if their doctor said it was possible
- ~80% said they would also they would take more medications if necessary

Survey in Australia in aged care facilities

- 40% said they wished to stop taking ≥ 1 of their medications
- This number increased to 80% if their doctor said this was appropriate

Survey of older adults admitted to a teaching hospital in Sydney, Australia

- 90% said they would be willing to stop ≥ 1 medications if their doctor was this was possible
- 95% were willing to discontinue their statin, and a similar number were concerned about statin side effects

Medicare beneficiaries in the USA surveyed about deprescribing (~ 2,000 respondents)

- “If my doctor said it was possible, I would be willing to stop one or more of my regular medicines” – 92% SA/agreed
- “I would like to reduce the number of medicines I am taking” – 2/3 SA/agreed

So what do the prescribers think about this?

Survey says...

160 physicians in Parma surveyed

- 75% reported general confidence in their ability to deprescribe, including preventative medications
- 53% were comfortable stopping guideline-recommended medications
- 40% were reluctant to discontinue a medication prescribed by another physician
- 45% felt uncomfortable stopping a medication in cases where patient/caregiver thought it was important to continue

General practitioners in Australia

- Comfortable with deprescribing and felt they had the skills to communicate this information to their patients

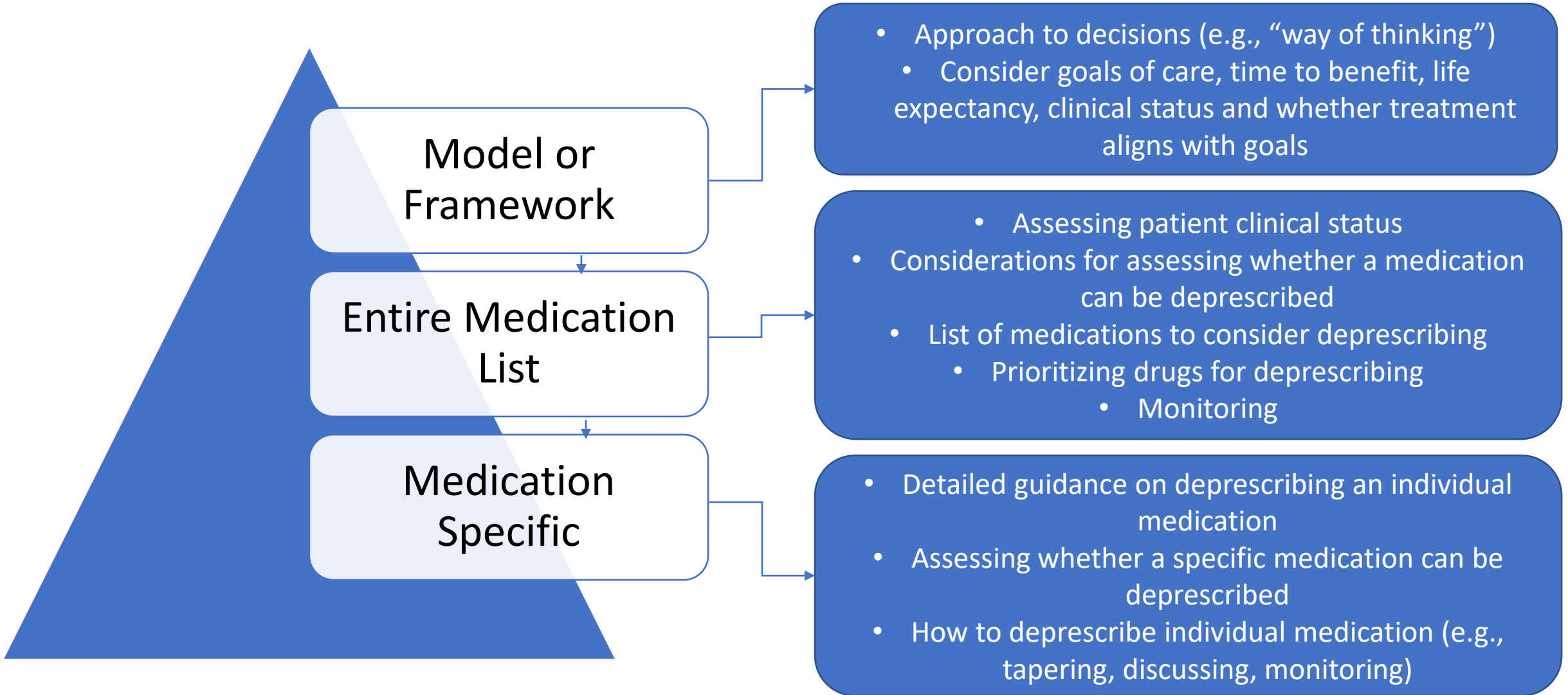
Primary care physicians

- Deprescribing feels like “swimming against the tide” due to:
 - The medical culture of prescribing (deprescribing not taught to physicians)
 - Patient expectations (prescriptions fix things, not stopping prescriptions)
 - Organizational constraints (lack of time, fragmentation of care, lack of access to expert guidance, etc.)

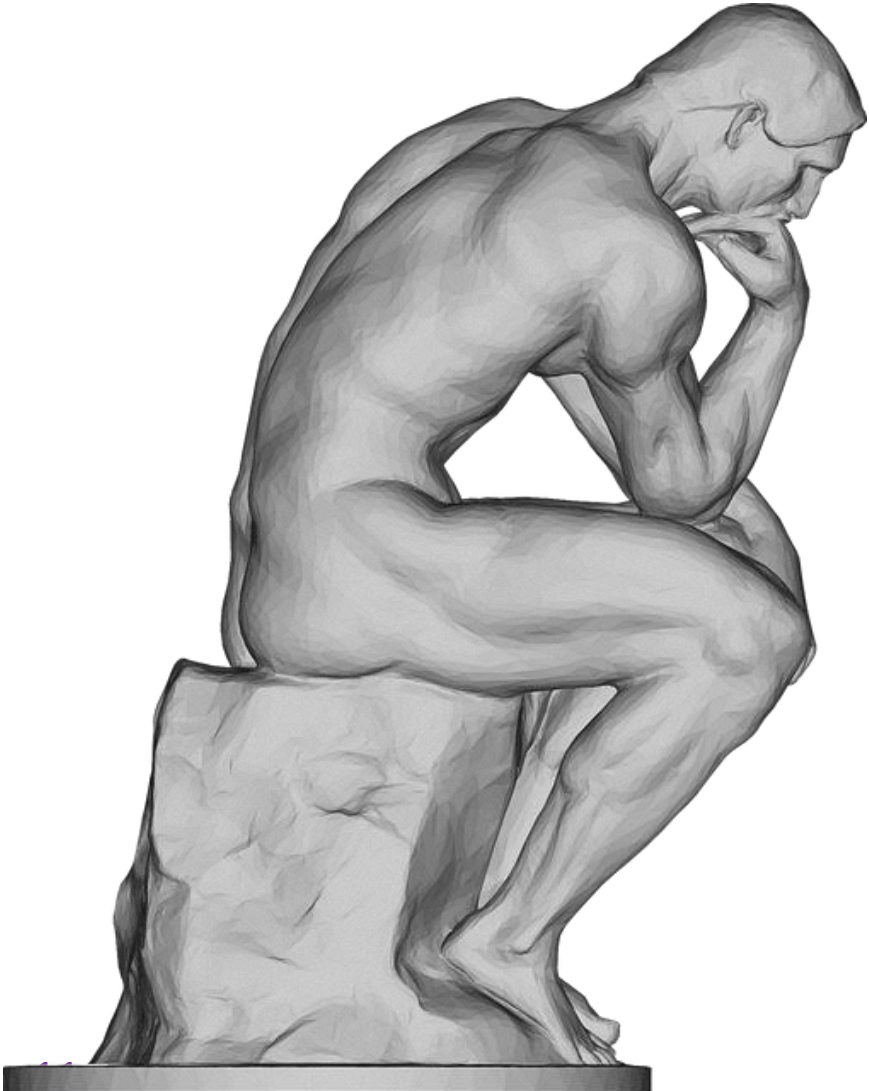
16 general practitioners in Denmark

- Themes of barriers to deprescribing include lack of interprofessional communication, patients not on board, culture encouraged continuing medications and not deprescribing

Let's DO this! Ok....how exactly do I DO this??



Model or Framework



- High-level model or framework for making medication decisions in persons with limited life expectancy
- A “way” of thinking
 - Consider time to benefit of a medication, life expectancy, goals of care, and whether a medication is likely to achieve goals or targets
 - Multiple-step, person-centered approach that includes comprehensive assessment of the individual’s clinical status, diagnosis-specific status, and medications, with goals of care and shared decision-making incorporated at every step

Approaching the Entire Medication List

- Tools that outline approaches to identify and prioritize drugs for deprescribing
- Tools include general principles to use when evaluating the whole medication list
 - Weighing the benefits and harms of the medications
 - Considering whether a medication is likely to help an individual achieve goals of care
 - Considering burden of treatment
- Tools may have a stepwise approach or algorithm process

STOPPFrail (Screening Tool of Older Persons prescriptions in Frail Adults with Limited life expectancy)

Beer's List

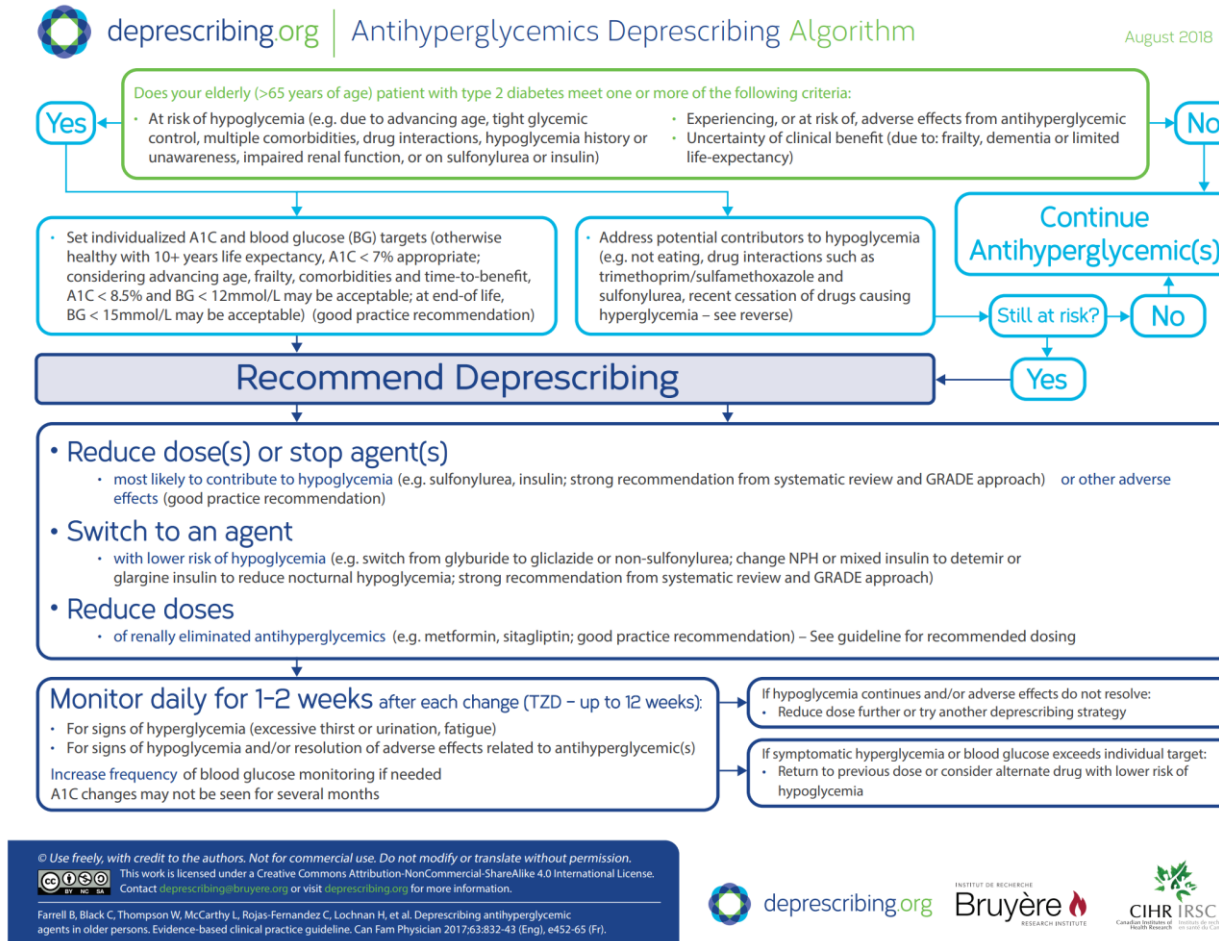
DE-PHARM

STOPPFrail v2

Section	
A: General	Any drug that the patient is not taking consistently; without a clear clinical indication; symptom now resolved
B: Cardiology	Lipid-lowering, antihypertensives, anti-anginal therapies
C: Coagulation	Anti-platelets, aspirin
D: Central nervous system	Neuroleptic antipsychotics, memantine
E: Gastrointestinal	PPIs, H2 receptor antagonists
F: Respiratory	Theophylline, leukotriene antagonists
G: Musculoskeletal	Calcium supplements, Vitamin D, anti-resorptive/bone anabolic drugs for OP, long-term oral NSAIDs, long-term oral corticosteroids
H: Urogenital	Drugs for BPH and overactive bladder
I: Endocrine	Anti-diabetic drugs
J: Miscellaneous	MVI, folic acid, nutritional supplements

Medication-Specific Tools

- Tools in this category provide more detail on how to approach deprescribing (monitoring, tapering, benefits, harms)



- Proton pump inhibitors
- Antihyperglycemics
- Antipsychotics
- Benzodiazepine receptor agonists
- Cholinesterase inhibitors and memantine

Metabolic Syndrome

Metabolic Syndrome?

- A cluster of risk factors that raise the risk of heart disease, diabetes, stroke, and other health problems
- According to the American Heart Association, about 1/3 of all adults have metabolic syndrome



Diagnosed with 3 of 5 Risk Factors

- National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III
- Metabolic syndrome is defined as:
 - Central obesity (defined by waist circumference)
 - Plus 2 of the following 4 factors:
 - Increased triglycerides, or treatment thereof
 - Reduced HDL cholesterol, or treatment thereof
 - Increased blood pressure or treatment thereof
 - Raised fasting plasma glucose or previously diagnosed diabetes

Mr. Herndon



- 76-year-old man admitted to hospice with stage 4 non-small cell lung cancer
- Prognosis is 4-6 weeks according to his oncologist
- He has comorbid conditions of:
 - Type 2 diabetes mellitus
 - Hypertension
 - Chronic kidney disease stage 4
 - Dyslipidemia
 - 80 pack-year history of smoking; stopped 1 year ago when diagnosed with lung CA

Medication History

Medication	Directions for Use/Indication	Date Started
Atorvastatin 40 mg (Lipitor)	Once a day for dyslipidemia	2010
Metformin ER 1,000 mg	2 tablets diabetes for T2DM	2009
Lantus insulin	20 units at bedtime daily for T2DM	2014
NovoLog insulin	Sliding scale 4 times daily for T2DM	2019
Lisinopril 10 mg	Once daily for hypertension	2015
Amlodipine 5 mg	Once daily for hypertension	2016
Multivitamin with iron	Once daily for general health	2000
Acetaminophen XR 650 mg	2 capsules every 8 hours for pain	2020
MS Contin 30 mg	Every 12 hours for pain	2021
Roxanol 10 mg	Every 2 hours as needed for pain	2021
Senna	2 tablets daily	2021

Mr. Herndon

- 5'10"
- Weighs 165 pounds at present (lost 100 pounds since diagnosis)
- Waist circumference 34
- Rarely, if ever, uses sliding scale NovoLog insulin
- Complaints of hypoglycemia symptoms occasionally
- Last A1c 6.9% six months ago
- BP about 120/70 seated, gets "woozy" when he stands





Mr. Herndon

- When you suggest slimming down his medication regimen, he gets VERY upset and cries:

“WHAT? My heart doctor and regular doctor said I had to stay on these medications ‘til the day I die! Are you saying I’m going to die tomorrow? You young whipper-snappers always want to upset the apple cart!”

- So, young whipper-snapper, how do you respond?

Multivitamin with Iron

- If Mr. Herndon feels strongly about keeping this medication, that's fine
- The iron and vitamins/minerals are probably increasing his risk of constipation and may cause a little nausea
- The iron may also turn his stools dark, making it hard for us to determine if he's bleeding internally, but that's unlikely
- Let's throw him a bone with the MVI!





Analgesics and Laxative

- Once someone is taking 60-70 mg a day of oral morphine, they can't tell the difference with or without acetaminophen
 - Patient's wishes? Liver disease? Alcoholism?
- Is morphine controlling the pain?
- Is Senna maintaining normal bowel function?

Words of the day...

TIME TO BENEFIT!

- “Time to benefit” is defined as the time to significant benefit observed in trials of people treated with a drug compared with controls

LEGACY EFFECT!

- “Legacy effects” are treatment effects that persist or emerge at some time after trial treatment ends.



Hypertension – the “silent killer”

- So what’s a goal BP? Well.....
 - ACC/AHA 2017 guidelines say < 130/80 mmHg
 - Including > 65 yo who are ambulatory and community-dwelling
 - European Soc of Cardiology and UK NICE guidelines say < 140/90 mmHg
 - UK/NICE guidelines recommend < 150/90 mmHg for fit patients \geq 80 yo
 - ACP/AAFP recommend SBP < 150 mmHg for adults > 60 yo (or < 140 mmHg with h/o CVA/CV risk)
- Time to benefit ranges from 2-5 years
- Legacy effect – 37% of patients remain normotensive 6 months after withdrawing therapy; effect persists in 26% of patients at 2 years
 - BP trajectories in the last 14 years of life continually decline regardless of treatment

Orthostasis

Hypotension

Syncope

Falls

Be careful of prescribing cascades

The story begins...

Dihydropyridine
(amlodipine or
felodipine) may
cause pedal edema

The story continues...

Prescriber orders
loop diuretic
(furosemide,
bumetanide,
torsemide)

You got what you get...

Electrolyte
derangements or
incontinence develop

And the guidelines say...

Group	Recommendation
AGS/Beers Criteria	<ul style="list-style-type: none">• Recommend against use of alpha-1 blockers (doxazosin, prazosin, terazosin)• Centrally acting alpha-agonists (guanfacine, methyldopa) should be avoided• Clonidine should be avoided• Avoid immediate-release nifedipine
European Consensus	<ul style="list-style-type: none">• Adults ≥ 75 yo with anticipated life expectancy ≤ 3 mo<ul style="list-style-type: none">• Diuretics of questionable value (excluding torsemide and furosemide)• Inappropriate to initiate ACEi, ARB, peripheral vasodilator, verapamil• Questionable value to continuing alpha-agonist, ACEi, ARB, CCB, non-selective BB, diuretic (except loop diuretics and spironolactone)• Inappropriate to continue peripheral vasodilator• No consensus re: continuing loop diuretics, spironolactone, selective BB, carvedilol, labetalol
STOPP/FRail	<ul style="list-style-type: none">• Recommended to carefully reduce or discontinue antihypertensive therapies with SBP persistently < 130 mmHg
Choosing Wisely/AMDA	<ul style="list-style-type: none">• Do not initiate antihypertensive therapy in patients ≥ 60 for SBP < 150 mmHg or DBP < 90 mmHg

Pulling the trigger...

- Evaluate co-morbid conditions
 - Atrial fibrillation – beta blocker or nondihydropyridine may be beneficial for both
 - Heart failure – ACEi or loop diuretic may be beneficial for both
- Gradually withdraw beta-blockers and centrally-acting alpha-agonists
- Monitor for withdrawal effects
 - Beta-blockers – angina, anxiety, MI, palpitations
 - Centrally acting alpha-agonists – agitation, headache, palpitations
 - BP – target , 150/90 mmHg, but symptoms unlikely with BP < 180/110 mmHg (risk for target organ damage)

Antihypertensives

- “HELLO” – Mr. Herndon is experiencing side effects from his antihypertensive regimen right NOW!
- His BP is low-normal and he is complaining of orthostasis
- Minimally we should stop one (lisinopril or amlodipine) now
- He’s lost 100 pounds, so his BP has naturally declined
- Let’s stop the amlodipine and re-evaluate
- Chances are good we can reduce the lisinopril to 5 mg for a few days, then stop that as well
- Reassure the patient.....





I don't care about no stinkin' cholesterol!

Dyslipidemia

- Increases risk for ASCVD → cardiovascular events, cerebrovascular events, peripheral vascular disease
- Statin therapy/other medications can slow or prevent atherosclerotic disease by reducing progression or formation of atherosclerotic lesions in artery walls
- Goal of therapy is to prevent morbidity/mortality associated with ASCVD
 - MI, ischemic stroke, angina, need for revascularization procedures, peripheral artery disease, arrhythmias, heart failure, sudden death
- Time to benefit – one year or longer (much shorter following an acute coronary event)
 - Usually 2-5 years for MI protection; 2 years to impact all-cause mortality; 4-5 years for CVA/TIA protection
- A recent meta-analysis showed a legacy effect on all-cause mortality and CVD mortality in those taking a statin for **primary prevention**.

Atorvastatin

- Kutner, et al. evaluated 381 patients within 1 year of death, taking a statin
 - Randomized to continue or stop statin therapy
 - Primary outcome – rate of death at 60 days
 - No statistically significant difference

Discontinued Statin	20.3% died by 60 days	Median time to death 229 days
Continued Statin	23.8% died by 60 days	Median time to death 190 days

8 years AFTER study completed evaluating atorvastatin impact, patients who HAD been taking atorvastatin had fewer deaths from CV and non-CV disease!

Guidelines say what...

Organization	Recommendation
STOPP/START Criteria	<ul style="list-style-type: none">• No recommendation for primary prevention• START statin for patients with h/o coronary, cerebral or PVD, unless patient's status is EOL and age is > 85 yo
STOPPFrail	<ul style="list-style-type: none">• Risks > benefits for patients with life-expectancy < 1 year• No differentiation between primary and secondary prevention
ACC/AHA 2018 Cholesterol Guidelines	<ul style="list-style-type: none">• Primary prevention in patients > 75 yo WITH diabetes – may be reasonable to continue statin• Primary prevention in patients > 75 yo WITHOUT diabetes and LDL-C \geq 70 mg/dl, may be reasonable to start statin therapy• In patients > 75 yo may be reasonable to stop statin with functional decline, multimorbidity, frailty, reduced life expectancy
Nat'l Lipid Association	<ul style="list-style-type: none">• Patients 65-79 yo who are statin eligible should be managed similarly to younger patients• Older patients – have discussion with provider re: primary prevention• For patients 65-80 yo with clinical ASCVD or diabetes, consider statin (evaluate risk/benefit)• For patients \geq 80 yo statins for secondary prevention should be considered after discussion with provider

Bring it on home...

- Primary prevention
 - Conflicting information for patients ≥ 75 yo
 - Generally speaking, ok to discontinue lipid-lowering therapy in patients with life expectancy $< 1-2$ years
- Secondary prevention
 - Evidence supports time to benefit is earlier in lipid-lowering therapy
 - Continue statin therapy if recent acute coronary syndrome, recent stroke or TIA, or if patient has unstable, symptomatic disease (e.g., recurrent angina)
- Statins/lipid-lowering therapies may be stopped abruptly!

Statin Chat...

- “Mr. Herndon, kudos to you for taking atorvastatin all these years.
- Clearly, it’s been providing you benefit because you’ve not had a heart attack or stroke.
- But the good news is that research has shown that the benefit you accrued from taking atorvastatin all those years was like putting money in the bank, and even if we discontinue the atorvastatin now, you will continue to reap the benefits.
- Research has further shown there is not an increased risk of a heart attack or stroke for people clinically similar to you.
- While statins do not cause major side effects, it would be one less tablet you have to take, and you’d have less risk of side effects such as muscle weakness.”



Go get the donuts and sweet tea!

- Prevalence of diabetes mellitus
 - 2019 – 37.3 million Americans (11.3% of population)
 - Of these, 28.7 million were diagnosed, 8.5 million were undiagnosed
- Prevalence in seniors
 - The percentage of Americans aged 65 and older remains high, at 29.2%, or 15.9 million seniors (diagnosed and undiagnosed)



Image from pixabay.com

DCCT Trial – Early 1990s

- Patients with T1DM divided into 2 groups – tight BG control and usual BG control
 - Half had no complications of DM; half had early complications
- Those who achieved tight BG control had a 40%-60% reduction in development of complications; and those with complications had much slower progression.
- Fast forward to 17 years after STARTING the DCCT trial
 - Those who had been in the tight glycemic arm had:
 - 42% risk reduction in any cardiovascular event
 - 57% risk reduction in risk of nonfatal MI, stroke, or death from CV disease

American Diabetes Association

- Healthy (few coexisting chronic illnesses, intact cognitive and functional status)
 - A1c <7.0-7.5%; FBG 80-130 mg/dl
- Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)
 - A1c < 8.0%; FBG 90-150 mg/dl
- Very complex/poor health (LTC or end-stage chronic illnesses, or moderate-to-severe cognitive impairment or 2+ ADL impairments)
 - Avoid reliance on A1c; base decisions on avoiding hypoglycemia and symptomatic hyperglycemia
 - FBG 100-180 mg/dl

Approach to Individualization of Glycemic Targets

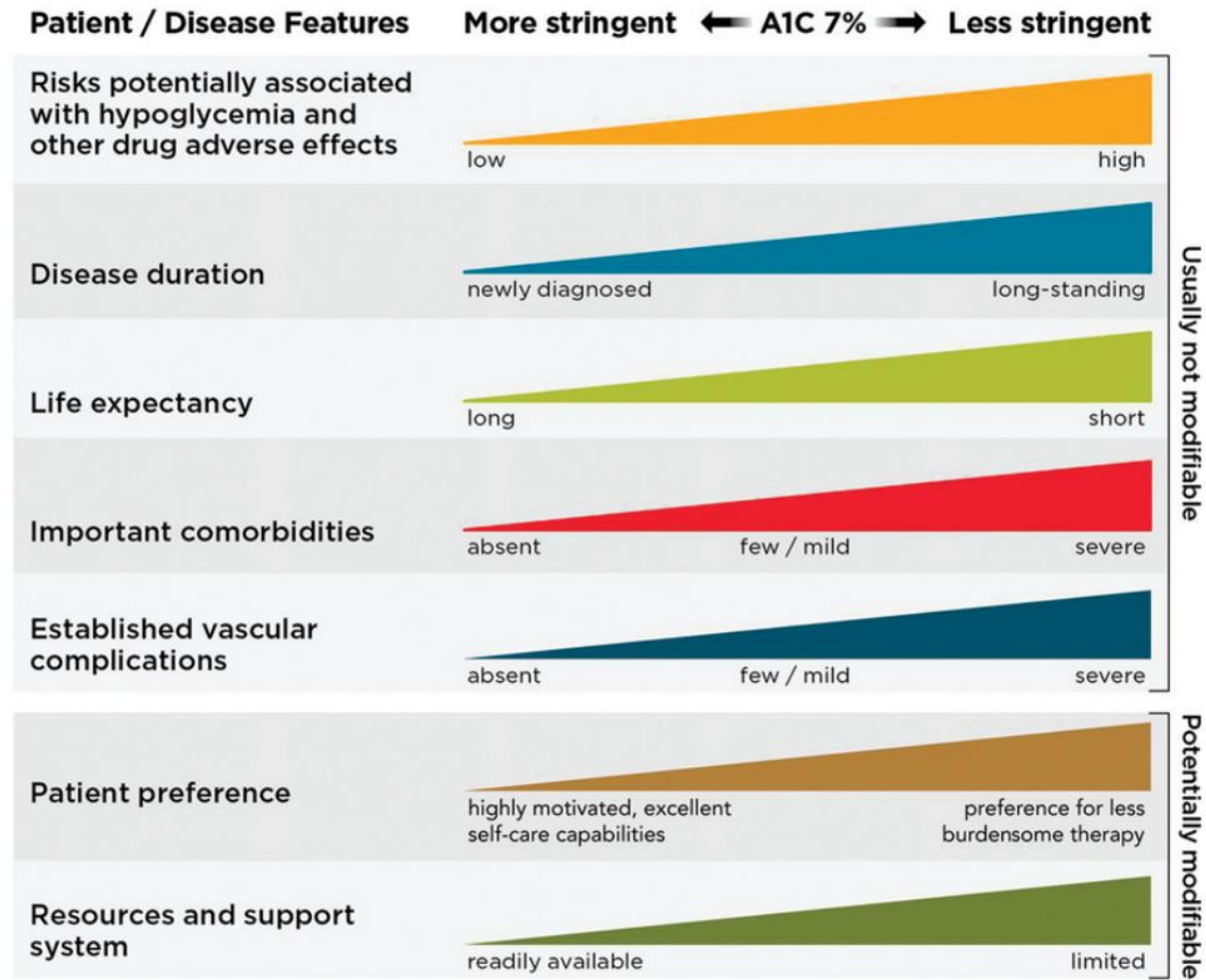
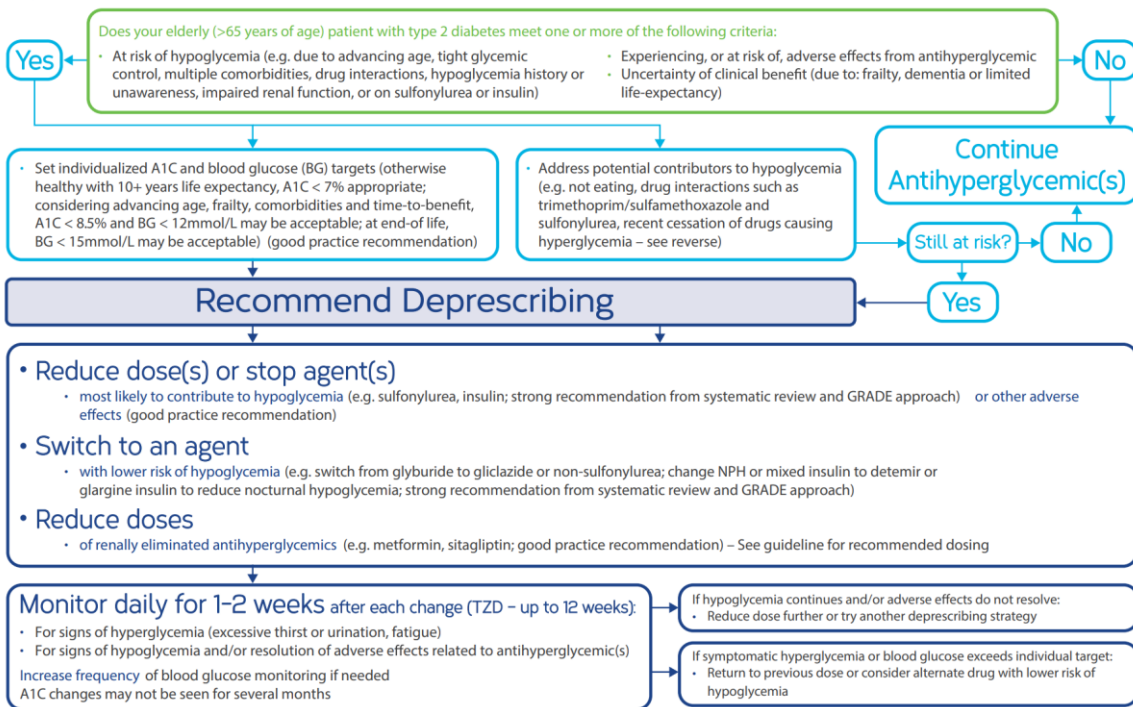


Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (68).

Deprescribing.org



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Farrell B, Black C, Thompson W, McCarthy L, Rojas-Fernandez C, Lochnan H, et al. Deprescribing antihyperglycemic agents in older persons. Evidence-based clinical practice guideline. Can Fam Physician 2017;63:832-43 (Eng), e452-65 (Fr).



Antihyperglycemics and Hypoglycemia Risk

Drug	Causes hypoglycemia?
Alpha-glucosidase inhibitor	No
Dipeptidyl peptidase-4 (DPP-4) inhibitors	No
Glucagon-like peptide-1 (GLP-1) agonists	No
Insulin	Yes (highest risk with regular insulin and NPH insulin)
Meglitinides	Yes (low risk)
Metformin	No
Sodium-glucose linked transporter 2 (SGLT2) inhibitors	No
Sulfonylureas	Yes (highest risk with glyburide and lower risk with gliclazide)
Thiazolidinediones (TZDs)	No

Drugs affecting glycemic control

- Drugs reported to cause hyperglycemia (when these drugs stopped, can result in hypoglycemia from antihyperglycemic drugs) e.g. quinolones (especially gatifloxacin), beta-blockers (except carvedilol), thiazides, atypical antipsychotics (especially olanzapine and clozapine), corticosteroids, calcineurin inhibitors (such as cyclosporine, sirolimus, tacrolimus), protease inhibitors
- Drugs that interact with antihyperglycemics (e.g. trimethoprim/sulfamethoxazole with sulfonylureas)
- Drugs reported to cause hypoglycemia (e.g. alcohol, MAOIs, salicylates, quinolones, quinine, beta-blockers, ACEIs, pentamidine)

Engaging patients and caregivers

- Some older adults prefer less intensive therapy, especially if burdensome or increases risk of hypoglycemia
- Patients and/or caregivers may be more likely to engage in discussion about changing targets or considering deprescribing if they understand the rationale:
 - Risks of hypoglycemia and other side effects
 - Risks of tight glucose control (no benefit and possible harm with A1C < 6%)
 - Time to benefit of tight glucose control
 - Reduced certainty about benefit of treatment with frailty, dementia or at end-of-life
- Goals of care: avoid hyperglycemic symptoms (thirst, dehydration, frequency, falls, fatigue, renal insufficiency) and prevent complications (5-10 years of treatment needed)
- Many countries agree on less aggressive treatment of diabetes in older persons
- Reviewing options for deprescribing, as well as the planned process for monitoring and thresholds for returning to previous doses will help engage patients and caregivers

Hypoglycemia information for patients and caregivers

- Older frail adults are at higher risk of hypoglycemia
- There is a greater risk of hypoglycemia with tight control
- Symptoms of hypoglycemia include: sweating, tachycardia, tremor BUT older patients may not typically have these
- Cognitive or physical impairments may limit older patient's ability to respond to hypoglycemia symptoms
- Some drugs can mask the symptoms of hypoglycemia (e.g. beta blockers)
- Harms of hypoglycemia may be severe and include: impaired cognitive and physical function, falls and fractures, seizures, emergency room visits and hospitalizations

Tapering advice

- Set blood glucose & A1C targets, plus thresholds for returning to previous dose, restarting a drug or maintaining a dose
- Develop tapering plan with patient/caregiver (no evidence for one best tapering approach; can stop oral antihyperglycemics, switch drugs, or lower doses gradually e.g. changes every 1-4 weeks, to the minimum dose available prior to discontinuation, or simply deplete patient's supply)
- Doses may be increased or medication restarted any time if blood glucose persists above individual target (12-15 mmol/L) or symptomatic hyperglycemia returns

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Antihyperglycemics

Mr. Herndon has had diabetes for many years and is on:

- Metformin XR 1000 mg, 2 tablets per day
- Lantus insulin 20 units at bedtime
- NovoLog insulin sliding scale 4 times daily

Metformin

- Patient has chronic kidney disease, stage 4, CLcr 15-30 ml/min; contraindicated

NovoLog sliding scale insulin

- Not requiring; increases risk of hypoglycemia

Lantus? First...

- Let's consider what we know about diabetes and glucose control first before we address the Lantus



What does this mean for Mr. Herndon?

- All those years he watched his diet, took his medications, monitored his BG – it was like putting money in the bank!
- Now we can loosen the reins a bit and he can “draw his dividends,” secure in the knowledge that his risk of diabetes-related complications is extremely low
- We will monitor him for symptoms suggestive of hyperglycemia



So, what
about the
Lantus?

- Let's stop the metformin and NovoLog insulin now
- Let's check the fasting BG 3 times in the next week
- Even if his BG is up to 200 mg/dl, it's probably ok
- We may be able to reduce the Lantus, or even stop it at some point
- STOP checking his BG 4 times a day – that's NOT very palliative!

Diabetes Convo...

- “Mr. Herndon, you deserve an ENORMOUS amount of credit for following your diet and your diabetes medication regimen for all these years.
- And like the statins, research has shown that tighter blood glucose control starting at the time of diabetes diagnosis leads to an accrued benefit in reduction of complications later in life.
- You’re not even using the NovoLog insulin because your blood glucose isn’t getting high enough to warrant it.
- You’ve lost a lot of weight and you’re not eating like you used to.



Diabetes Convo...

- “Given your kidney disease, we really should stop the metformin so you won’t have any side effects.
- Let’s stop the metformin and the NovoLog insulin.
- Let’s follow your blood glucose over the next week or so and make a decision about whether or not to continue the Lantus at your current dose, or to reduce it.
- In the meantime, we can liberalize your meal plan, and stop checking your blood glucose so frequently, **You’ve earned it!**”



Mr. Herndon

- A. Sir, you are a few weeks away from death; does it really matter what your cholesterol, blood pressure, and blood glucose are?
- B. You aren't dying TODAY but within a month or so, and it's really unlikely you'll have a heart attack or stroke, so I feel lucky!
- C. Clearly you aren't dying today, but all medications have risks and benefits, and no medication is meant to be continued FOREVER (and you start humming "Let It Go" under your breath)
- D. We'll take a look at each of your medications, and you and I and your family will discuss this with your doctor and make decisions that give you the most benefit from your medications and cause the least harm. Sound good?





Alzheimer's Disease



Alzheimer's Disease

- Most common cause of dementia (60-70% of 50 million affected worldwide)
- Relentlessly progressive neurodegenerative disease; average age > 75 years old
- Worsening memory; declines in language, visuospatial, and executive functioning
- Behavioral and psychological symptoms (depression, anxiety, agitation, psychosis, wandering)
- Survival after diagnosis is approximately 4-8 years on average
- Goals of care – slow functional and cognitive decline; maximize symptom control and QOL



Treatment of Alzheimer's Disease

- **Non-pharmacologic**

- Physical activity
- Cognitive training/rehabilitation

- **Management of co-morbid conditions**

5	3			7				
6			1	9	5			
	9	8					6	
8				6				3
4			8		3			1
7				2				6
	6					2	8	
			4	1	9			5
				8			7	9

- **Cholinesterase Inhibitors**

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

- **NMDA Antagonist**

- Memantine (Namenda)

- **Combination**

- Donepezil/memantine (Namzaric)

- **Aducanumab (Aduhelm)**

The Case of Miss Judy

Judy is a 78-year-old female

- **CC:** Repeated falls in the past 3 months
- **PMH:** Breast cancer, hypertension, dyslipidemia, nonvalvular atrial fibrillation (no h/o CVA), Alzheimer's disease (FAST 7C - > 10% weight loss, recent UTI)
- Lives with daughter, Laura, in Maryland
- Son, Frederick, is a lawyer who lives in California

The Case of Miss Judy

Judy is a 78-year-old female

Current Medication Regimen

- Donepezil (Aricept®)
- Memantine (Namenda®)
- Lisinopril
- Atorvastatin (Lipitor®)
- Warfarin
- MVI
- Ferrex
- Calcium and vitamin D3

- When you suggest slimming down on the medications, Laura is agreeable.
- Frederick, on the other hand, goes ballistic and angrily says, **“What’s WRONG with you people – are you TRYING to kill her off?”**
- So.....any issues here?

“Cognitive Enhancers”

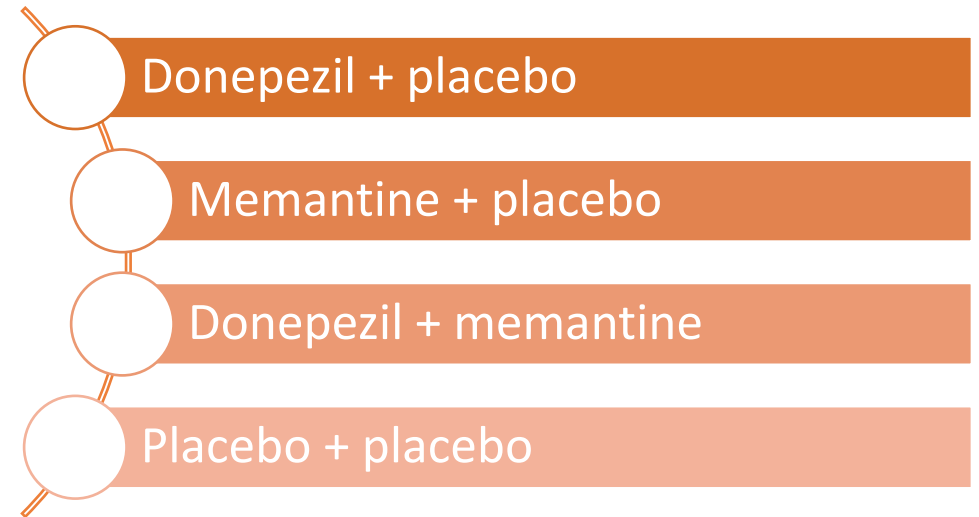
Drug Category	Drug Name(s)	Indication(s)
Cholinesterase Inhibitors (\$10-100/month)	Donepezil	Treatment of dementia of the Alzheimer’s type. Efficacy has been demonstrated in patients with mild, moderate and severe Alzheimer’s dementia.
	Galantamine	Treatment of mild and moderate dementia of the Alzheimer’s type.
	Rivastigmine	Treatment of mild, moderate and severe dementia of the Alzheimer’s type. Treatment of mild to moderate dementia associated with Parkinson’s disease.
NMDA Antagonist (\$15/month)	Memantine	Treatment of moderate to severe dementia of the Alzheimer’s type.

FAST Criteria

1. Normal adult
 2. Normal older adult
 3. Early dementia
 4. Mild dementia
 5. Moderate dementia
 6. Moderately severe dementia
 7. Severe dementia
- 7a. Ability to speak limited to approximately a half dozen different words or fewer, in the course of an average day or in the course of an intensive interview.
 - 7b. Speech ability limited to the use of a single intelligent word in an average day or in the course of an interview (the person may repeat the word over and over).
 - 7c. Ambulatory ability lost (cannot walk without personal assistance)
 - 7d. Ability to sit up without assistance lost (e.g., the individual will fall over if there are no lateral rests [arms] on the chair)
 - 7e. Loss of the ability to smile

Donepezil and Memantine for Moderate-to-Severe AD

- 295 community-dwelling moderate-to-severe AD patients treated with donepezil for at least 3 months (MMSE 5-13); 52 weeks
- Stratified by
 - Study center
 - Duration of donepezil treatment before entry (3-6 mo vs ≥ 6 mo)
 - Baseline MMSE (5-9 vs 10-13)
 - Age (< 60; 60-74; ≥ 75)



Donepezil and Memantine for Moderate-to-Severe AD

- **Outcomes:**

- Score on MMSE - Clinically important difference:
 - **Scoring 1.4 points or greater higher than comparator**
- Caregiver-rated Bristol activities of Daily Living Scale (BADLS): Clinically important difference:
 - **Scoring 3.5 points or greater lower than comparator**
- **Baseline MMSE 9.1-9.2 in all groups**
- **Baseline BADLS 26.9-28.6**

Donepezil and Memantine for Moderate-to-Severe AD

- Clinically important difference:
 - MMSE \geq 1.4 point increase or greater
 - BADLS \geq 3.5 point decrease or greater

Treatment group	MMSE	BADLS
All donepezil vs no donepezil	+1.9	-3.0
All memantine vs no memantine	+1.2	-1.5

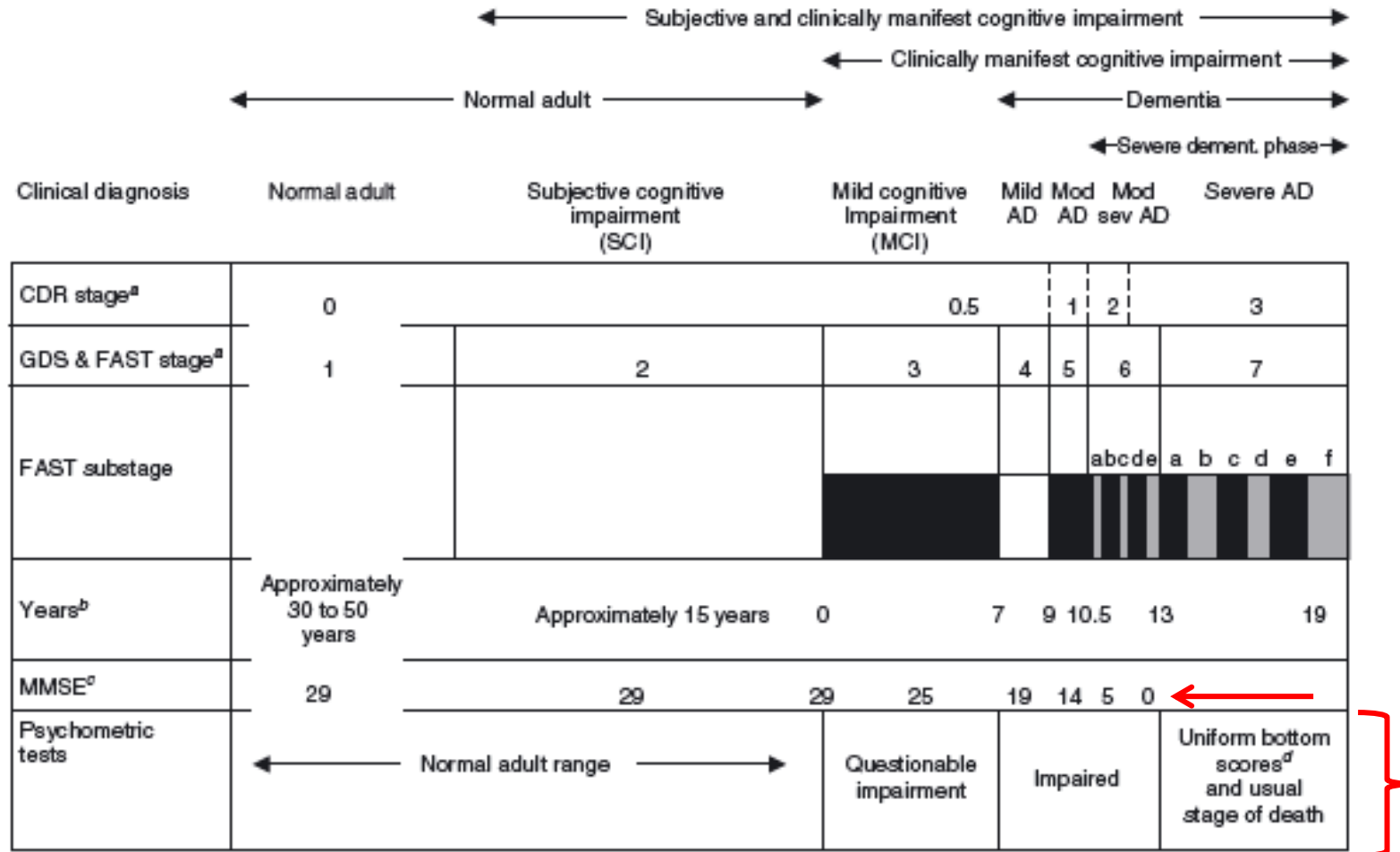
- Effect of donepezil and memantine did not differ significantly in the presence or absence of either
- Donepezil plus memantine showed no difference vs donepezil alone

Donepezil and Memantine for Moderate-to-Severe AD

Baseline MMSE	Impact of donepezil therapy on MMSE
MMSE 10-13	+2.6
MMSE 5-9	+1.3

Donepezil only showed clinical significance in patients with baseline MMSE ≥ 10

FAST and MMSE



Adverse Effects

- Memantine
 - Dizziness, headache, confusion, constipation
- ChEIs
 - Nausea, vomiting, diarrhea, anorexia, insomnia, fatigue, muscle cramps
 - Warning: “Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block”

Outcome Measure	ChEI recipients	Controls
Hospital visits for syncope	31.5/1000 person-years (HR 1.76)	18.6/1000 person-years
Hospital visits for bradycardia	6.9/1000 person years (HR 1.69)	4.4/1000 person-years
Permanent pacemaker insertion	4.7/1000 person-years (HR 1.49)	3.3/1000 person-years
Hip fracture	22/4.1000 person-years (HR 1.18)	19.8/1000 person-years

Bottom Line: Dementia Drugs

- Dementia medications are LESS HELPFUL and MORE HARMFUL in advanced disease (see adverse effects)
- NOT indicated or provided with FAST 7 without clear and ongoing benefit in managing identifiable and distressing behaviors
- MAY be covered with FAST 6; discuss goals/outcomes with hospice team leadership
- 2 week tapering supply should be provided if medication discontinued

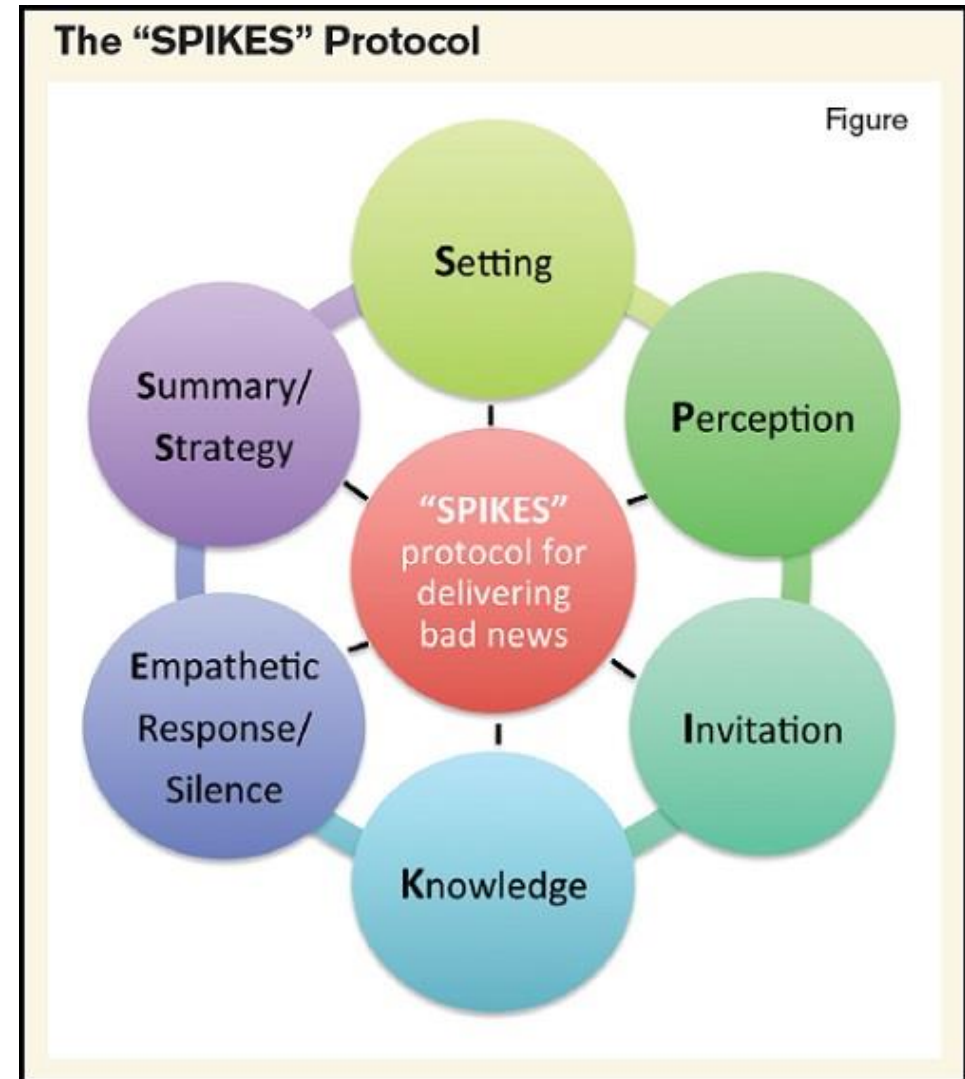


But is Frederick
buying what you're
selling?

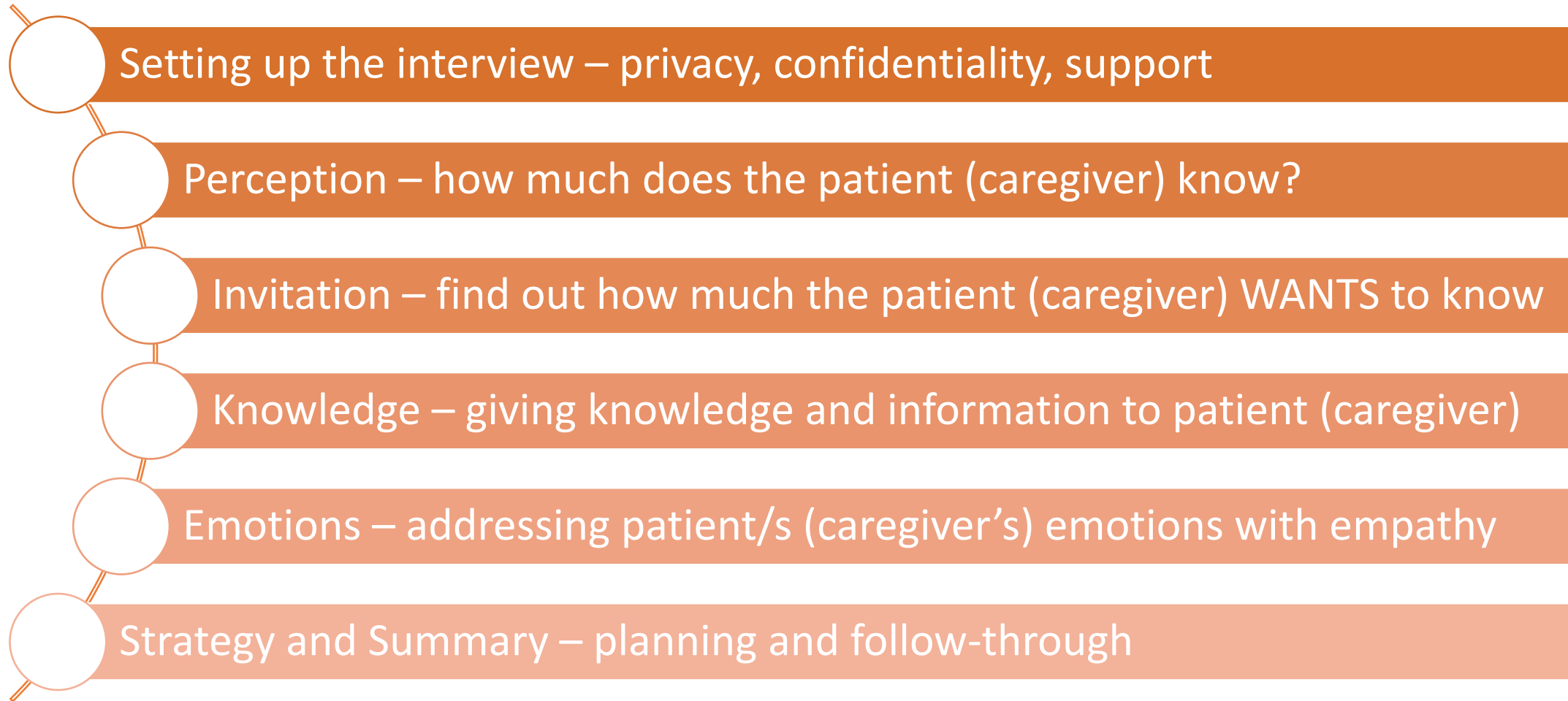
SPIKES – Having those Conversations

- S – setting
- P – perception
- I – invitation
- K – knowledge
- E – emotion
- S – summarize recommendation

Slide from McPherson, Walker, Pruskowski, Talebreza. “Right Sizing Medication Regimens in Serious Illness: Doing the Prescribing and Deprescribing Dance”



Having the Conversation: Breaking “Bad” News: SPIKES



Guideline Consensus

Guideline	Opinion
Beers List	ChEIs cause bradycardia; avoid in older adults with syncope due to bradycardia
STOPPFrail*	ChEIs – no consensus Memantine – recommended to discontinue with moderate to severe dementia, unless clearly shows improvement of BPSD
European Consensus 2018	Prognosis \leq 3 months – use of drugs for AD “inadequate”; “special circumstances” may warrant consideration
Australian Guidelines	Recommend a trial of discontinuation of ChEIs and memantine if receiving \geq 12 months and have worsening of disease, or no benefit noted, or have end-stage disease. Can resume if behavior worsens with discontinuation
Deprescribing.org	Trial discontinuation if taking $>$ 12 months and significant cognitive/functional decline over past 6 months, or no benefit seen, or severe disease
Choosing Wisely/AGS	ChEIs – long term use $>$ 1 year not studied sufficiently; if improvement not seen within 12 weeks, consider discontinuing

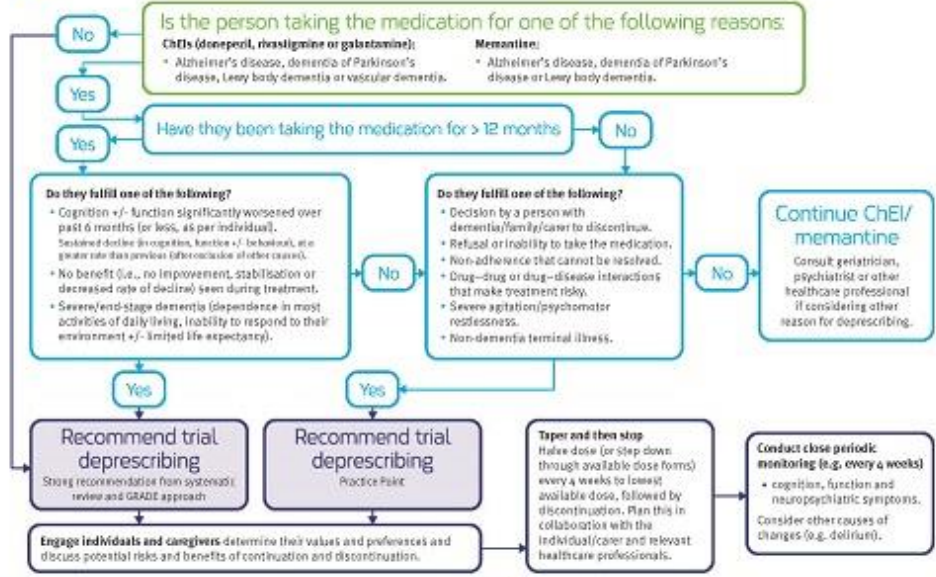
* - STOPPFrail criteria include end-stage irreversible pathology, poor 1 year survival prognosis, severe functional or cognitive impairment, symptom control is priority)

JAGS 2019;67(4):674-694; Age Ageing 2017;46(4):600-607; Eur J Clin Pharmacol 2018;74:1333-1342

Deprescribing.org; AAFG online

Deprescribing Cholinesterase Inhibitors/Memantine

- Developing organizations:
 - The University of Sydney
 - NHMPRC Partnership Centre: Dealing with Cognitive and Related Functional Decline in Older People (Cognitive Decline Partnership Centre)
 - Bruyere Research Institute, Deprescribing Guidelines in the Elderly Project
- sydney.edu.au/medicine/cdpc/resources/deprescribing-guidelines.php
- EBR – evidence-based recommendations
- CBR – consensus-based recommendations
- PP – practice points



Monitoring during tapering and after discontinuation

Timing of symptoms after dose reduction/discontinuation	Types of symptoms	Action to be taken by family/nurses/care staff	Possible cause*
Less than 1 week	Severe symptoms, including agitation, aggression, hallucinations or reduced consciousness	Restart previous dose immediately and contact responsible healthcare professional as soon as possible	Adverse drug withdrawal reaction
2 to 6 weeks	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional and consider restarting previous dose and/or make an appointment to see responsible healthcare professional at the next available time	Re-emergence of symptoms that were being treated by ChEI/memantine
6 weeks to 3 months	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional at the next available time to make an appointment	Likely progression of condition or possible re-emergence of symptoms that were being treated by ChEI/memantine
> 3 months	Any	As per usual care	Progression of condition

- *Exclude other causes of change in condition (e.g. infection or dehydration) first.
- Discuss monitoring plan with the individual/family/carer and write it down for them (e.g. frequency and type of follow-up). Ensure they have a way to contact a clinician if needed.

Engaging individuals and family/carers

Determining suitability for deprescribing

- Discuss treatment goals – what do they value the most (cognition, quality of life, remaining independent)?
- Ask about experience with dementia symptoms when treatment started and over last 6 months.
- Ask about side effects.

Helping the individual and family/carers to make an informed decision

- Deprescribing is a trial – medication can be restarted if appropriate.
- There are uncertain benefits and harms to both continuing and discontinuing the medication.
- Tailor discussion about benefits and harms to the individual.
- Explore fears and concerns about deprescribing.
- Consider medication costs and local reimbursement/subsidisation criteria.
- If the recommendation to deprescribe is being made due to progression of dementia, remind family/carers that the person with dementia may continue to decline after deprescribing, and explain why.

Non-pharmacological management and ongoing care after deprescribing

See (<http://sydney.edu.au/medicine/cdpc/resources/dementia-guidelines.php>) for Australian guidelines in care of people with dementia, including behavioural and psychological symptoms.

ChEI and memantine availability (Australia)

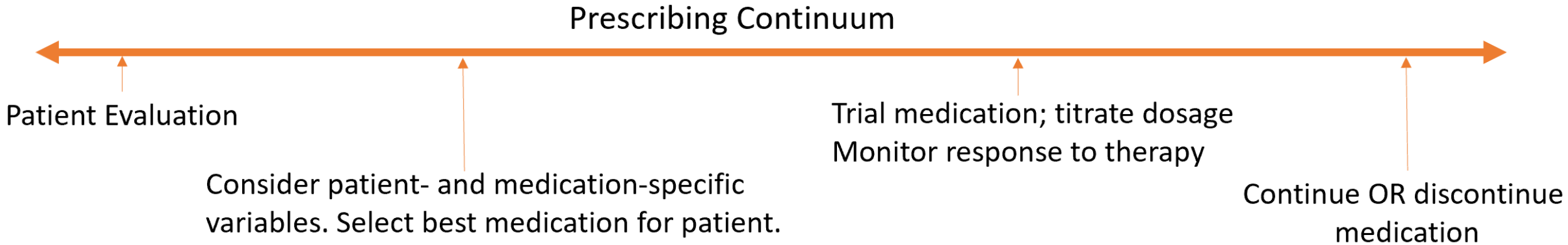
Drug	Strength
Donepezil (Aricept®, Aridon®, Arazil®)	Tablet – 5mg, 10mg
Galantamine (Galantyl®, Gamine XR®, Reminyl®)	Controlled release capsule – 8mg, 16mg, 24mg
Rivastigmine (Exelon®)	Capsule – 1.5mg, 3mg, 4.5mg, 6mg Patch – 4.6mg/24 hours, 9.5mg/24 hours, 13.3mg/24 hours
Memantine (Ebixa®, Memanza®)	Tablet – 10mg, 20mg

- ChEI and memantine side effects**
- Common: include gastrointestinal effects, dizziness, confusion, headache, insomnia, agitation, weight loss and falls.
 - Rare (ChEI): may include urinary, cardiovascular (e.g. bradycardia), pulmonary and dermatological (e.g. Stevens-Johnson syndrome) complications, Pisa syndrome, seizures, gastrointestinal haemorrhage and rhabdomyolysis.
 - Lack of evidence of potential harms in complex older adults.

Proton pump inhibitors; antihyperglycemics; antipsychotics; benzodiazepine receptor antagonists

Conclusion

- Deprescribing is part of the prescribing continuum



- Practitioners must weigh the benefits and burdens of drug therapy in all patients, but especially in advanced or serious illness
- Conversations with patients, families and other healthcare providers are VERY important



Anticoagulation



Why do we anticoagulate hospice patients?

- *Venous thromboembolism*
- *Atrial fibrillation*
- Acute coronary syndrome / percutaneous coronary intervention
- Atherosclerotic cardiovascular disease
- Valvular heart disease

What are these anticoagulants/antiplatelets of which you speak?

Pharmacologic Category	Examples
Vitamin K antagonists	Warfarin (Coumadin, Jantoven)
Direct acting oral anticoagulants (DOACs) Direct thrombin inhibitor Factor Xa inhibitors	Dabigatran (Pradaxa) Apixaban (Eliquis) Edoxaban (Savaysa) Rivaroxaban (Xarelto)
Other anticoagulants	Heparin (IV and SQ) Low molecular weight heparins (e.g., dalteparin, enoxaparin, etc.) Fondaparinux (Arixtra)
Antiplatelets Aspirin P2Y12 inhibitors Other	Aspirin; aspirin + dipyridamole Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta) Cilostazol, dipyridamole, vorapaxar (cangrelor, eptifibatide, tirofiban)

How common is antithrombotic use at the end of life?

- Antithrombotics are frequently prescribed for patients with limited life expectancy
- Chart review of 180 patients who died of malignant or non-malignant disease in the Netherlands
 - At home, in hospice, or hospital; reviewed last three months of life
- 108/180 (60%) of patients had used antithrombotics in the last three months of life
 - 33% died at home; 21.3% died in a hospice; 45.4% died in a hospital
- 157 antithrombotic prescriptions among the 108 patients
 - 30/157 warfarin; 60/157 heparin; 66/157 platelet aggregation inhibitors
 - Of 51 patients using heparins, 32 only received a prophylactic dose
 - 75.9% of antithrombotics were continued until the last week before death

Venous Thromboembolism

- VTE – deep vein thrombosis (DVT) and pulmonary embolus (PE) – occurs in 1 in 1,000 adults
- Increases with age, reduced mobility and concurrent chronic illness including cancer
- Treatment approach has changed from a nihilistic point of view, to more individualized care
- *“a large PE might be a nice way to go”* - **NOT!**
 - Asymptomatic in about 10% of patients. Majority suffer a prolonged symptomatic death averaging 2 hours (dyspnea, tachycardia, distress)
- Likely underdiagnosed in hospice and palliative care
 - PE - Dyspnea, anemia, pulmonary edema, infection, pleural effusion – seen in advanced illness
 - DVT – Swollen legs (r/t hypoalbuminemia), left ventricular failure or pelvic lymphadenopathy - seen in advanced illness

Venous Thromboembolism

- Treatment for CAT (cancer-associated thrombosis) is low-molecular weight heparin
 - Superior to warfarin in preventing recurrent VTE, without an increase in bleeding complications
 - LMWH has fewer drug-drug interactions and rarely requires monitoring
 - Trials excluded patients with < 3 mo prognosis, poor performance status, increased bleeding risk, renal impairment, weight < 40 kg, thrombocytopenia, other comorbidities associated with palliative patients
 - Daily SQ injection(s) may reduce QOL and be less acceptable than an oral equivalent
- Guidelines recommend indefinite anticoagulation for patients with ongoing active cancer
 - None address management of anticoagulation at the end of life

Venous Thromboembolism

- Recent study of 1,199 patients admitted to 22 hospices/palliative care units (90% cancer patients) (Tardy)
 - Low incidence VTE, but a high incidence of clinically relevant bleeding (9.8%)
 - Analysis showed bleeding was associated with thromboprophylaxis
 - Concluded risks of bleeding may outweigh benefits in this population
- Hospice inpatient Deep Vein Thrombosis Detection study (White)
 - Prospective, longitudinal observational study
 - 343 cancer patients underwent bilateral femoral vein ultrasonography on admission and weekly until death or discharge (prognosis > 5 days)
 - Patients had an AKPS of 49 and survival of 44 days
 - Femoral DVT observed in 28% of participants with minimal symptoms; no difference in survival with/without DVT

Tardy B, et al. J Thromb Haemost 2017;15:420-428.

White C, et al. Lancet Haematol 2019;6:e79-88.

This is a tough one...

- No clear clinical guidance...limited outcomes data
- Risks vs. benefits
 - Shared decision-making
 - Symptoms, morbidity, mortality
 - Monitoring
- Location of VTE
 - Proximal vs. distal
 - Upper vs. lower
- Any risk factors or reversible causes?
- Patient's prognosis?
- Adherence? History of INR values?



What about...



CHA₂-DS₂-VASc Risk Stratification Score for Stroke Risk for Nonvalvular Atrial Fibrillation

Criteria		Poss. Point
Congestive heart failure Signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction	Yes No	+1
Hypertension Resting BP > 140/90 mmHg on at least 2 occasions <u>or</u> current antihypertensive pharmacologic treatment	Yes No	+1
Age 75 years or older	Yes No	+2
Diabetes mellitus Fasting glucose > 125 mg/dL or treatment with oral hypoglycemic agent and/or insulin	Yes No	+1
Stroke, TIA, or TE Includes any history of cerebral ischemia	Yes No	+2
Vascular disease Prior MI, peripheral arterial disease, or aortic plaque	Yes No	+1
Age 65 to 74 years	Yes No	+1
Sex Category (female) Female gender confers higher risk	Yes No	+1

Points	Absolute Risk per Year
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

Ref: <https://clincalc.com/Cardiology/Stroke/CHADSVASC.aspx>

CHA₂-DS₂-VASc Risk Stratification

Points	Absolute Risk per Year	Risk While Anticoagulated per year	Absolute Risk for Mean Hospice LOS (92.6 days)	Risk While Anticoagulated for Mean Hospice LOS (92.6 days)	Absolute Risk for Median Hospice LOS (18 days)	Risk While Anticoagulated for Median Hospice LOS (18 days)
0	0.2%	0.07%	0.05%	0.02%	0.01%	0.0035%
1	0.6%	0.20%	0.15%	0.05%	0.03%	0.01%
2	2.2%	0.73%	0.55%	0.18%	0.11%	0.04%
3	3.2%	1.06%	0.8%	0.27%	0.16%	0.05%
4	4.8%	1.58%	1.20%	0.40%	0.24%	0.08%
5	7.2%	2.38%	1.80%	0.60%	0.36%	0.12%
6	9.7%	3.20%	2.43%	0.8%	0.485%	0.16%
7	11.2%	3.70%	2.80%	0.93%	0.56%	0.19%
8	10.8%	3.56%	2.70%	0.89%	0.54%	0.18%
9	12.2%	4.03%	3.05%	1.01%	0.61%	0.20%

Risk of Bleeding – HAS-BLED

- HAS-BLED stands for hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol

Criteria	Points
Hypertension (uncontrolled hypertension (SBP > 160 mmHg))	+1
Abnormal renal function (chronic dialysis, renal transplant, serum creatinine \geq 2.3 mg/dl)	+1
Abnormal liver function (cirrhosis, bilirubin > 2 x UNL with AST/ALT/AP > 3 x UNL)	+1
Stroke	+1
Bleeding (bleeding history or predisposition (anemia))	+1
Labile INR (therapeutic time in range < 60%)	+1
Elderly (greater than 65 years old)	+1
Drugs (receiving other antiplatelet agents or NSAIDs)	+1
Alcohol (more than 8 drinks per week)	+1
TOTAL	

HAS-BLED Score and Recommended Action

HAS-BLED Score	Risk Group	Risk of Major Bleeding	Bleeds/100 patient-years	Recommendation
0	Relatively low	0.9%	1.13	Anticoagulation should be considered
1		3.4%	1.02	
2	Moderate	4.1%	1.88	Anticoagulation can be considered
3	High	5.8%	3.72	Alternatives to anticoagulation should be considered
4		8.9%	8.70	
5		9.1%	12.50	
> 5	Very high	-	-	considered

<https://www.mdcalc.com/has-bleed-score-major-bleeding-risk#evidence>

Scores greater than 5 were too rare to determine risk, but are likely over 10%

Let's consider a case...

- Mr. Jones is a 76-year-old man admitted to hospice with a diagnosis of advanced Alzheimer's disease.
- He lives in an assisted living facility, although his medical needs are becoming more complicated and he may need to be transferred to a long-term care facility.
- He has comorbidities of hypertension (BP usually 140/90 – 150/95 mmHg), type 2 diabetes, nonvalvular atrial fibrillation, and a stroke 3 years ago.
- Medications include:
 - Metoprolol 50 mg po twice daily
 - Metformin 1000 mg po twice daily
 - Glipizide 10 mg po once daily
 - Warfarin 5 mg po once daily
 - Clopidogrel 75 mg once daily
 - Aspirin 81 mg once daily



CHA₂-DS₂-VASc
Risk Stratification
Score for Stroke
Risk for
Nonvalvular Atrial
Fibrillation



Criteria		Poss. Point
Congestive heart failure Signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1
Hypertension Resting BP > 140/90 mmHg on at least 2 occasions <u>or</u> current antihypertensive pharmacologic treatment	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1
Age 75 years or older	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+2
Diabetes mellitus Fasting glucose > 125 mg/dL or treatment with oral hypoglycemic agent and/or insulin	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1
Stroke, TIA, or TE Includes any history of cerebral ischemia	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+2
Vascular disease Prior MI, peripheral arterial disease, or aortic plaque	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1
Age 65 to 74 years	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1
Sex Category (female) Female gender confers higher risk	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	+1

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HAS-BLED

Criteria	Points
Hypertension (uncontrolled hypertension (SBP > 160 mmHg))	+1
Abnormal renal function (chronic dialysis, renal transplant, serum creatinine \geq 2.3 mg/dl)	+1
Abnormal liver function (cirrhosis, bilirubin > 2 x UNL with AST/ALT/AP > 3 x UNL)	+1
Stroke	★ +1
Bleeding (bleeding history or predisposition (anemia))	+1
Labile INR (therapeutic time in range < 60%)	★ +1
Elderly (greater than 65 years old)	★ +1
Drugs (receiving other antiplatelet agents or NSAIDs)	★ +1
Alcohol (more than 8 drinks per week)	+1
TOTAL	

HAS-BLED Score and Recommended Action

HAS-BLED Score	Risk Group	Risk of Major Bleeding	Bleeds/100 patient-years	Recommendation
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4		8.9%	8.70	
5		9.1%	12.50	
> 5	Very high	-	-	

Ref: <https://www.mdcalc.com/has-bleed-score-major-bleeding-risk#evidence>

Mr. Jones...

- Annual risk of having a stroke is a little less than 10% (9.7%)
 - Assume length of stay of 18 days, risk is about 0.485%
- Annual risk of major bleeding is 8.9%
- Alternatives to anticoagulation recommended
- Attending physician agrees to discontinue warfarin therapy

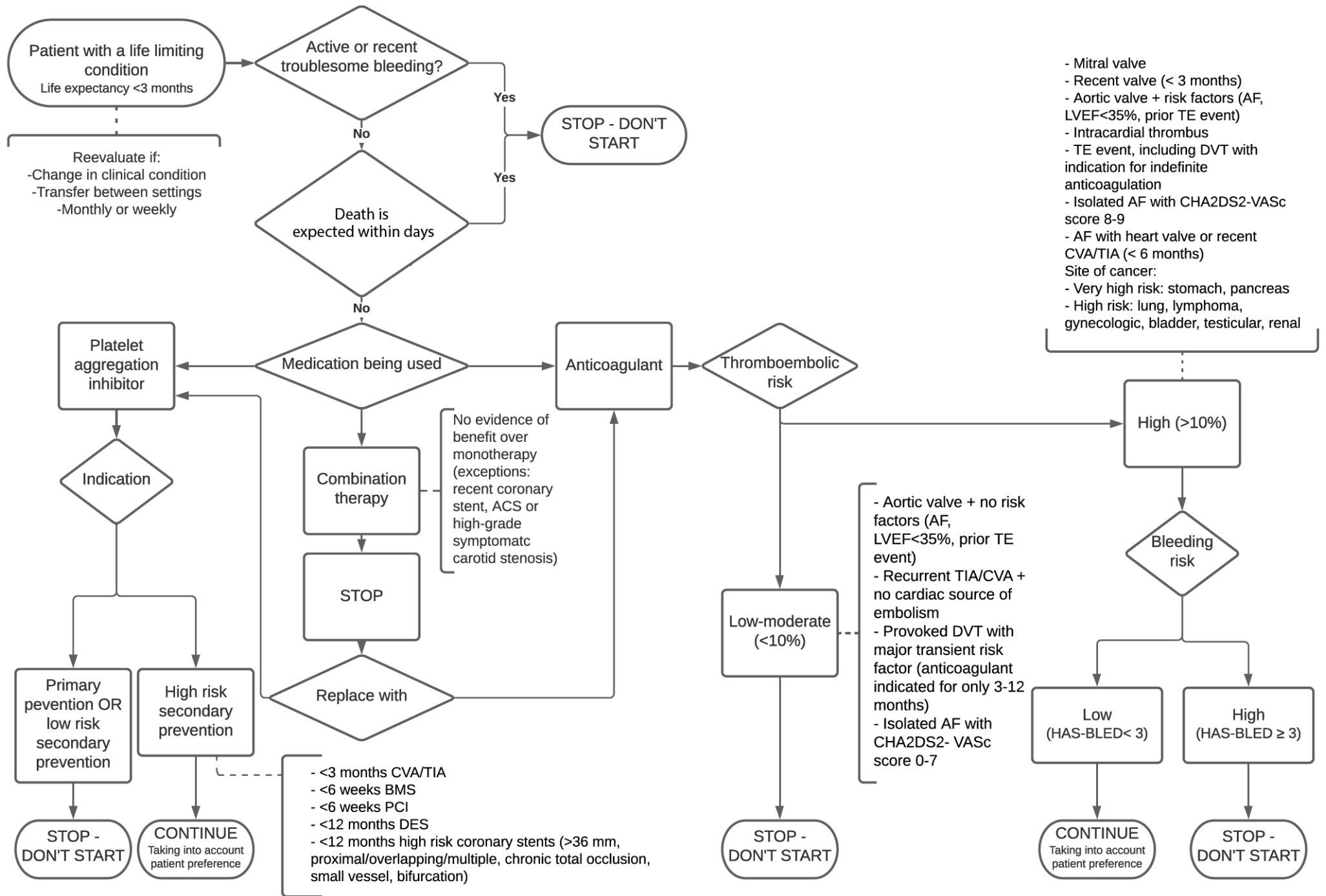


Shared Decision Making



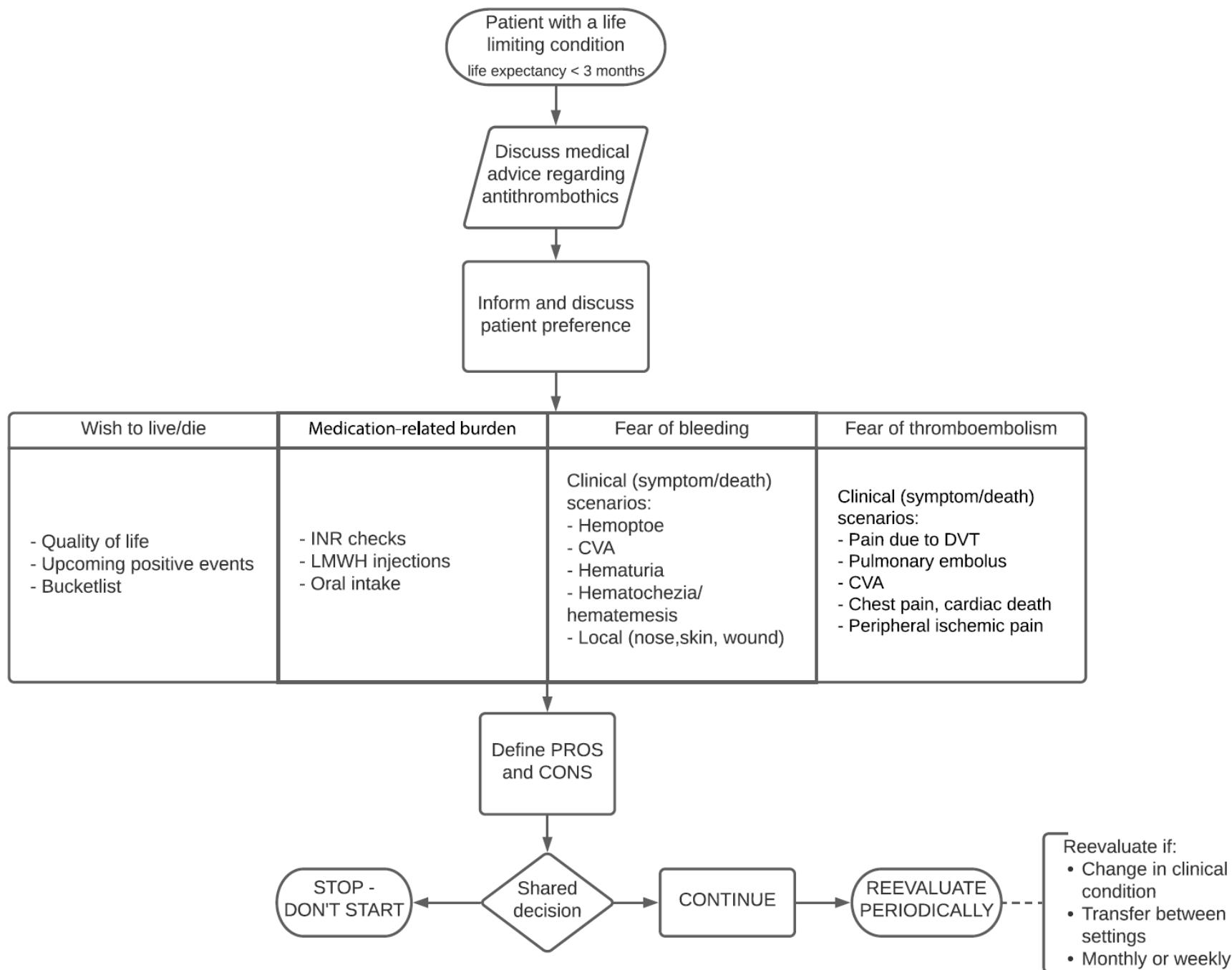
Huisman BAA, et al.
 Use of antithrombotics at the end of life: an in-depth chart review study. BMC Palliative Care 2021;20:110. Open Access, no permission required; Creative Commons Attribution 4.0 International License.
<https://bmcpalliativecare.biomedcentral.com/articles/10.1186/s12904-021-00786-3>

ACS – acute coronary syndrome
 AF – atrial fibrillation
 BMS – bare metal stent
 CVA – cerebrovascular accident
 DES – drug-eluting stent
 DVT – deep venous thrombosis
 LVEF – left-ventricular ejection fraction
 PCI – percutaneous coronary intervention
 TE – thromboembolic
 TIA – transient ischemic attack



Huisman BAA, et al. Use of antithrombotics at the end of life: an in-depth chart review study. BMC Palliative Care

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October 18–21 octobre 2022

Palais des Congrès de Montréal

Deprescribing for the Elderly and in Advanced Illness

**Presented by: Mary Lynn McPherson, PharmD,
MA, MDE, FAAHPM**