Help! I don’t remember how to treat…

Update on treatment of Hypercholesterolemia, Diabetes and Hypertension

Drs. Marin Franchetto and Sarah Leonard

Objectives

At the completion of this learning activity, participants will comprehend how the management of hypercholesterolemia, diabetes and hypertension is affected by oncology medications. Participants will be able to identify when dietary intervention isn't adequate, and will be able to instruct their patients on appropriate medical management.

Faculty/Presenter Disclosure

- **Faculty:** Dr. Marin Franchetto

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Faculty/Presenter Disclosure

- **Faculty:** Dr. Sarah Leonard

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

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- **<u>Potential for conflict(s) of interest</u>:**
  - None

Mitigating Potential Bias

- N/A

Wait, I thought we were treating cancers, not heart disease…

- Increasing recognition of cardiovascular toxicity of cancer therapies
- Systemic treatments under-recognized risk factor
- Combination of risk factors can predispose patient to premature cardiovascular disease

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology* 35, no. 8 (March 2017) 893-911

Out of scope for today:

- Congestive Heart Failure
- Cardiomyopathies
- Arrhythmias
- QT prolongation
- Valvular disease
- Pericardial disease
- Peripheral arterial disease (other than as a consequence of atherosclerosis)

I know all about anthracyclines…

- Subtler changes than HF, not found with routine monitoring echos
- Fluoropyrimidines (e.g. 5-FU) and coronary vasospasm, endothelial injury
- Platinum-based therapy and endothelial injury, procoagulant effects
- Anti-VEGF and endothelial injury, hypertension induction/destabilization
- Mediastinal or neck irradiation, endothelial injury

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *European Heart Journal*, Volume 37, Issue 36, 21 September 2016, Pages 2768–2801,https://doi.org/10.1093/eurheartj/ehw211

Recommendations for EVERYONE

- Smoking cessation
- Regular exercise
- Mediterranean diet
- NO NEED for fasting lipid tests

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology* 32 (2016) 1263-1282

Dyslipidemia

Dyslipidemia

- Androgen-deprivation therapy
- mTOR inhibitor (e.g. everolimus)
- Fluoropyrimidines (e.g. 5-FU, capecitabine)
- Platinum-based therapies

But the dyslipidemia guidelines are ALREADY so confusing…

- Groups automatically at high-risk and benefit from statins
  - Secondary prevention
  - AAA
  - CKD
  - Diabetes
  - LDL >5
  - Framingham risk score at least 20% - benefit from HIGH-intensity statin therapy

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology* 32 (2016) 1263-1282

But the dyslipidemia guidelines are ALREADY so confusing…

- Patients who might benefit from statins
  - Framingham Risk Score 10-19%
  - Elevated ASCVD risk level (ACC)
  - Patients at “Advanced Cardiovascular Age” or with high 30-year risk
  - Patients at lower risk but with dyslipidemia associated with malignancy ??? UNCLEAR

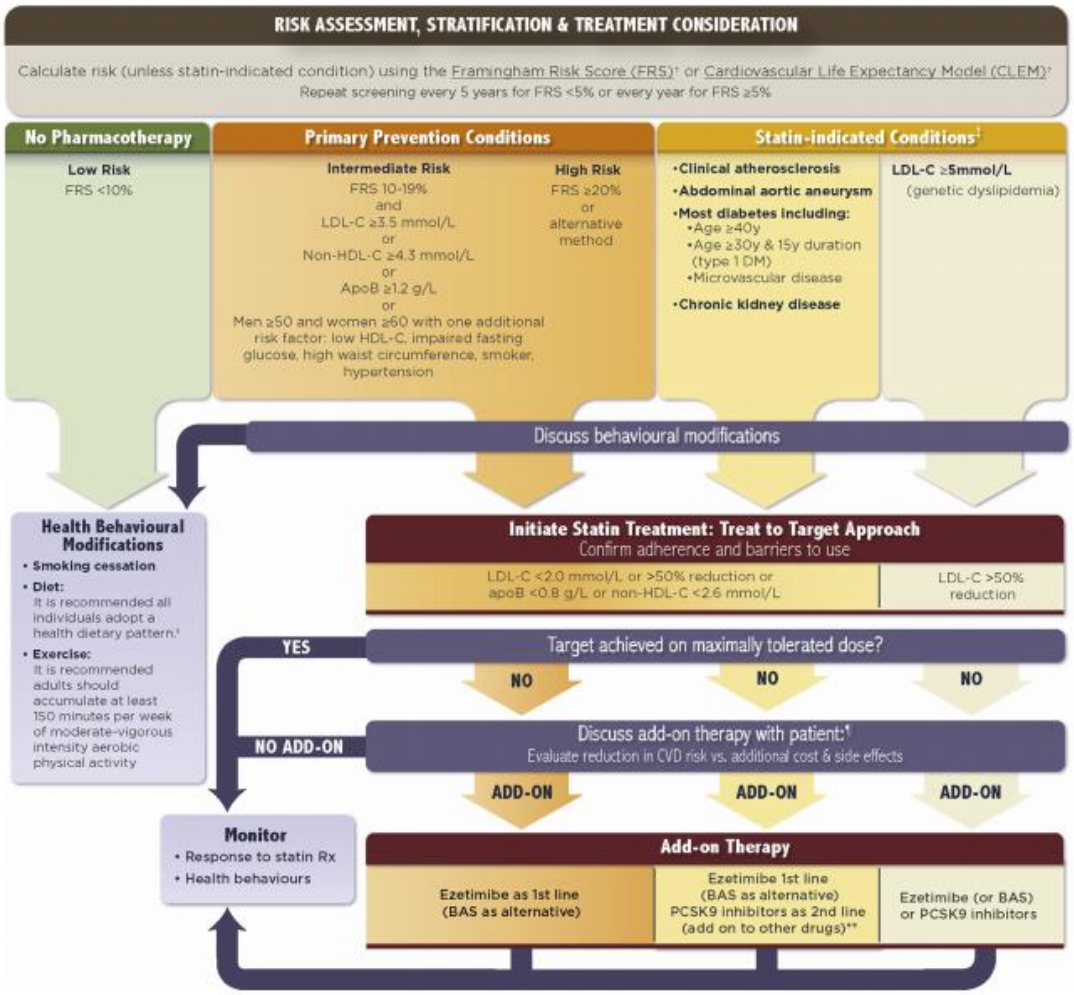
2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology* 32 (2016) 1263-1282

But the dyslipidemia guidelines are ALREADY so confusing…

- Disagreement between Canadian Cardiovascular Society and American College of Cardiology
  - ASCVD vs. Framingham Risk vs. CLEM (McGill)
    - Only Framingham and CLEM validated for Canada *but* still not validated for all populations in Canada
  - Treating to target
  - Non-statin lipid-lowering drugs
  - Age to start screening

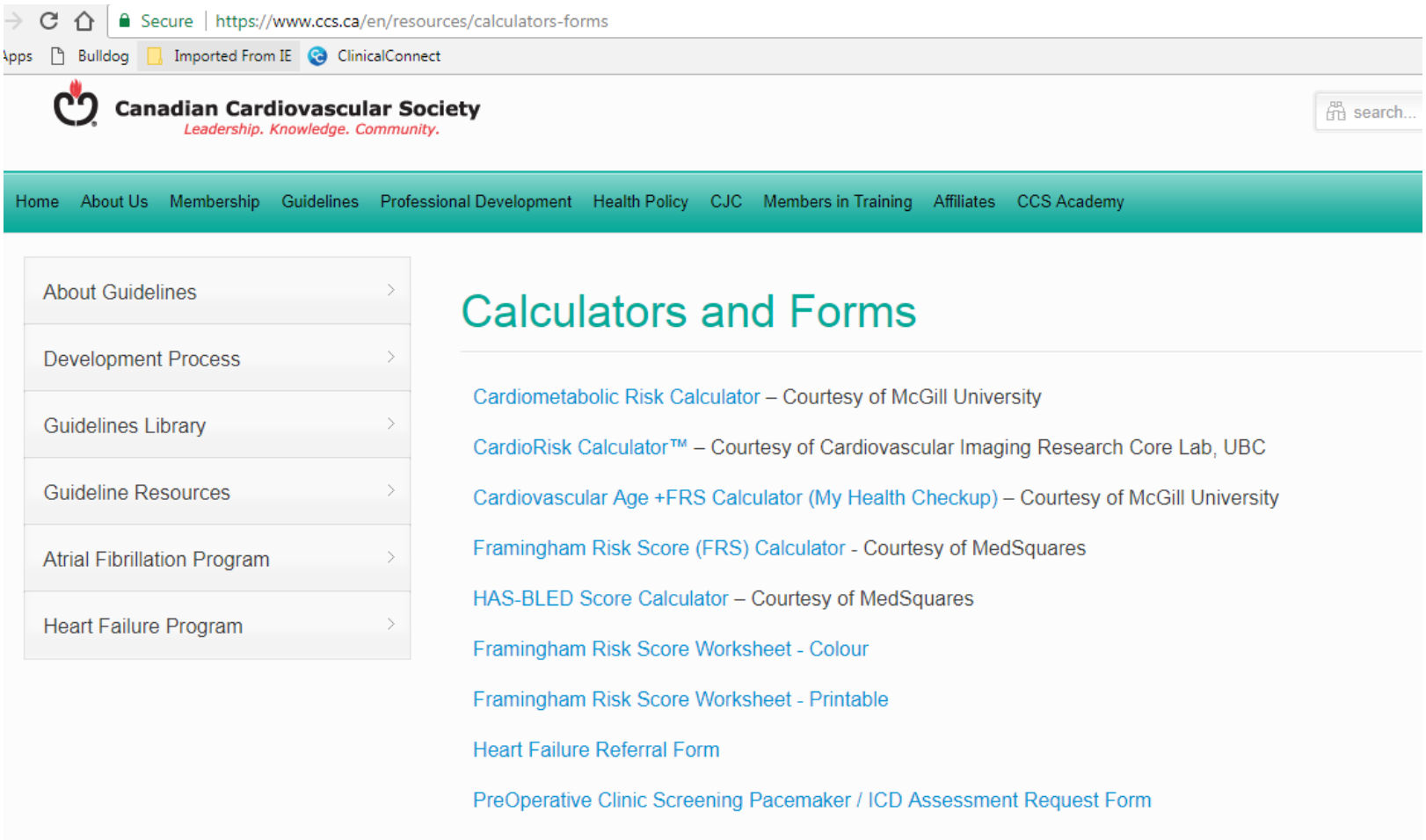
2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology* 32 (2016) 1263-1282

A picture is worth a thousand words



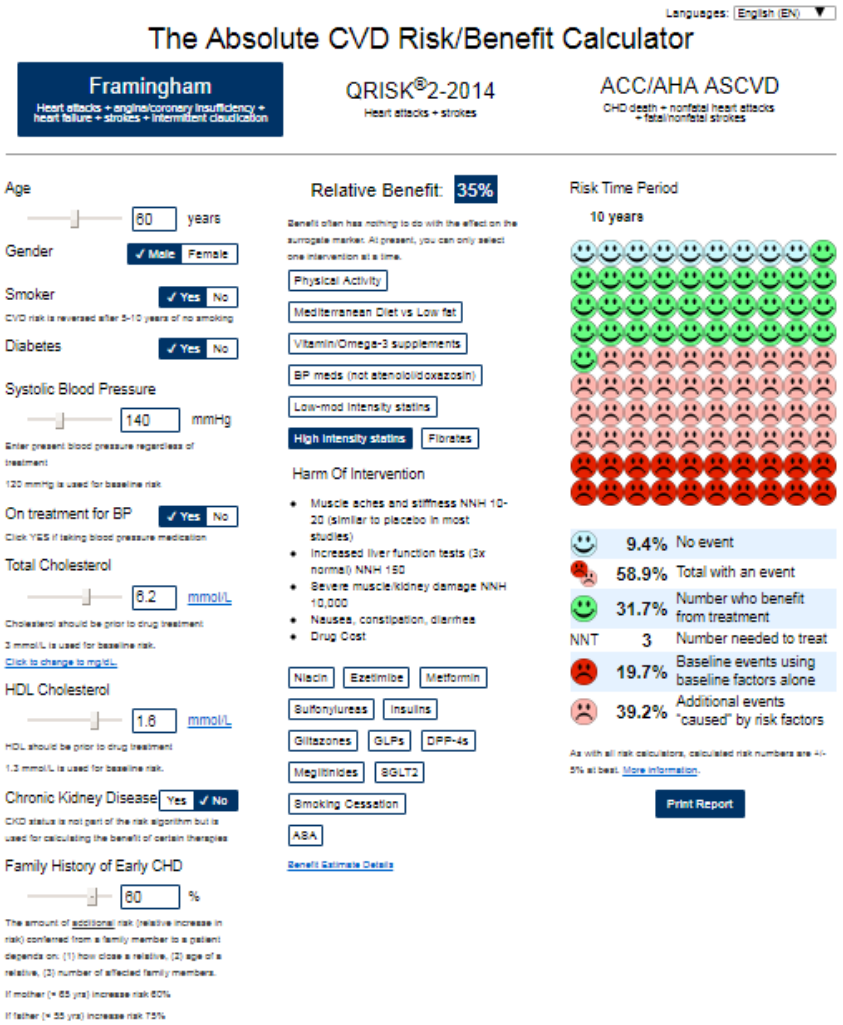
2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology* 32 (2016) 1263-1282

How do I reliably estimate risk?



Canadian Cardiovascular Society: https://www.ccs.ca/en/resources/calculators-forms

But how to explain this to my patients?



Therapeutics Education Collaboration, University of British Columbia. http://chd.bestsciencemedicine.com/calc2.html

But what if I don't expect my patient's life expectancy to be long?

- Statins shown to have benefit with 6 months of therapy
- If patient on CYP450 inhibitors may need to use pravastatin or simvastatin
- For mTOR inhibitors goal also preventing pancreatitis

Busaidy et al., Management of Metabolic Effects Associated With Anticancer Agents Targeting the PI3K-Akt-mTOR Pathway. *Journal of Clinical Oncology* 30, no. 23 (August 2012) 2919-2928.

Hyperglycemia

Hyperglycemia

- Why
  - Improved microvascular and macrovascular morbidity
  - Symptomatic – unwell, polydipsia, polyuria
  - Complications – infection, dehydration, AKI, DKA/HNK (rare), catabolic state (can be confused with cachexia), poor surgical wound healing, hypercoagulability
  - Clinical Trials – maintain eligibility for and to remain in clinical trials
  - Increased mortality – NEJM study 2011 found increased risk of premature death from several cancers independent of other major risk factors

Seshasai, R. et al (2011). Diabetes mellitus, fasting glucose and risk of cause-specific death. *NEJM, 364*(9):829-841

Hyperglycemia

- Who
  - Pre-existing diagnosis of diabetes or insulin resistance at higher risk
  - Can develop without any previous history
  - Common side effect of many cancer therapy or symptom control drugs

Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E., Leigh. R., Brown, J., Cohen, A., & Kim, H. (2013). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol, 9*(1):30.

Common Culprits

Table 1. Presentations of Diabetes Related to Cancer or Cancer Treatment

Causes of Iatrogenic Hyperglycemia in Cancer Treatment	Mechanism	Notable Features	Unique Aspect of Therapy
Corticosteroid-induced	Increased insulin resistance	Very common; reversible when drug is stopped; postprandial elevations greater than fasting elevations	All antidiabetes drugs are potentially useful but insulin is often needed
PI3K/AKT/mTOR inhibitor–induced	Increased insulin resistance and impaired secretion	Reversible when drug is stopped	
Immune checkpoint inhibitor–induced	Autoimmune destruction of beta cells	At least six cases reported to date.[10,11] Important to recognize due to potentially fulminant presentation with ketoacidosis	Insulin required
Unresectable pancreatic cancer	Destruction or impairment of islet cells due to tumor growth and inflammation	Poor patient oral intake often limits its severity and makes less aggressive treatment advisable	Low-dose once-daily basal insulin is often a suitable option, but extreme care should be taken to avoid hypoglycemia
Pancreatic cancer resection	Removal of part or all of the pancreas	Should be treated as type 1 phenotype initially, although patients with pancreatic remnant often recover function with time There is significant evidence that good glycemic control improves surgical outcomes in this population[12]	Endocrine should be consulted preoperatively and patient should be prepared for discharge from hospital taking basal-bolus insulin

AKT = protein kinase B; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide 3-kinase.

Flory, J., & Farooki, A. (2016). Diabetes management in cancer patients. *Oncology, 30*(6):565-570

When to Screen

- mTOR inhibitor
  - Check fasting BG at baseline
  - Early side effect (hyperglycemia seen in days to weeks)
  - CCO recommendation “baseline BG and periodic (more frequently with concomitant use of drugs that can cause hyperglycemia”
    - Check FBG q 2 weeks during first month of treatment
    - Then q monthly
    - HbA1c q 3months
- Steroids
  - Immediate effect
    - Often seen as early as 8 hours post first dose
    - Inpatient – monitor daily for 48 hours
    - Outpatient – within 24-48 hours
    - With dose changes
  - Dose dependent

Busaidy, N., Farooki, A., Dowlati, A., Perentesis, J., Dancey, J., Doyle, L., Brell, J., & Siu, L. (2012). Management of metabolic effects associated with anticancer agents targeting the P13K-Akt-mTOR pathway. *J. Clin Oncol, 30*(23):2919-2928.

Starting therapy and Targets

- Variation
  - Some suggest following CDA (If fasting >7 mmol/L, or random >11.1 mmol/L or HbA1c >6.5% start therapy
  - CTCAE and the PAM Taskforce of the National Cancer Institute Investigational Drug Steering Committee different suggest different thresholds

- Targets
  - Avoid acute symptoms and subacute complications, avoid hypoglycemia, maintain trial status
    - Fasting plasma glucose < 8.9 mmol/L
    - Random plasma glucose <11.1 mmol/L
    - HbA1c < 8 %
    - Avoid hypoglycemia!

Busaidy, N., Farooki, A., Dowlati, A., Perentesis, J., Dancey, J., Doyle, L., Brell, J., & Siu, L. (2012). Management of metabolic effects associated with anticancer agents targeting the P13K-Akt-mTOR pathway. *J. Clin Oncol, 30*(23):2919-2928.

Grade	Fasting Glucose (mmol/L)	Recommendations	Dose change required? (mTOR inhibitor)
1	7 – 8.9	Start once daily BG monitoring Lifestyle interventions (dietitian consult, increased aerobic exercise, +/- referral to diabetes educator	Continue same dose
2	9 – 13.9	BID glucose monitoring (ac Breakfast and dinner) Lifestyle	Continue same dose
3	14 - 27.8	Lifestyle TID-QID BGs Insulin basal or basal/bolus	Interrupt therapy until grade 1 or less achieved then restart therapy at one dose level down
4	>27.8	Lifestyle QID BG's Insulin Expert Consultation Beware complications	Discontinue

Busaidy, N., Farooki, A., Dowlati, A., Perentesis, J., Dancey, J., Doyle, L., Brell, J., & Siu, L. (2012). Management of metabolic effects associated with anticancer agents targeting the P13K-Akt-mTOR pathway. *J. Clin Oncol, 30*(23):2919-2928.

Therapeutic Options

- Transient Grade 1-2 does NOT need to be treated (follow with once daily home BG monitoring)
- Treat sustained grade 1,2 and asymptomatic grade 3→ start with oral agents
  - Metformin is first line – uptitrate to max dose over 1-2 weeks
  - Sulfonylureas second line (risk of hypoglycemia)
  - Could consider SGLT2 inhibitors but be very wary of infectious complications and diuresis
  - Beware weight loss with GLP-1 RAb
  - Difficult to titrate, mismatched pharmacokinetics

- **Often insulin is needed, either basal alone or basal/prandial dosing
  - BG < 15 mmol/L oral may be sufficient. If persistently >15 mmol/L will likely need insulin

Flory, J., & Farooki, A. (2016). Diabetes management in cancer patients. *Oncology, 30*(6):565-570

Table 2. Therapeutic Options for Diabetic Cancer Patients[a]

Class	Examples	Advantages	Disadvantages
Biguanide	Metformin	Safe in most settings, inexpensive	-Possible significant gastrointestinal side effects -Contraindicated in renal failure (in practice acceptable down to eGFR 30 mL/min),[13] hepatic failure, and severe heart failure
Sulfonylureas	Glimepiride, glyburide, glipizide	High potency and tolerability, inexpensive	-Hypoglycemia -Risk of accumulation in renal insufficiency
DPP-4 inhibitor[b]	Sitagliptin, linagliptin, vildagliptin	Very few side effects	-Low potency
GLP-1 RA[b]	Exenatide, liraglutide, dulaglutide	High potency	-Injected -Cases of pancreatitis; unclear if background incidence in DM
Thiazolidinedione	Pioglitazone	High potency	-Slow onset of action -May cause edema, volume overload (in susceptible patients), and increased fracture risk -Debatable small increase in risk of bladder cancer[15]
SGLT2 inhibitor	Canagliflozin, dapagliflozin, empagliflozin	High potency	-Increased risk of dehydration in susceptible patients -Increased risk of genital mycotic infections
Short-acting insulin	Aspart, lispro, glulisine (regular[c])	High potency, flexible dosing, flexible timing	-Requires home glucose monitoring multiple times daily, injections, and high health literacy to use safely -Hypoglycemia
Long-acting insulin	Insulin glargine, insulin detemir (NPH[c])	High potency, flexible dosing	-Home glucose monitoring advisable, requires daily injections -Hypoglycemia

DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; NPH = neutral protamine Hagedorn; SGLT2 = sodium-glucose co-transporter 2.

[a]Some less widely used classes (meglitinides, alpha-glucosidase inhibitors, bile acid sequestrants, and dopamine agonists) are omitted.

[b]Contraindicated in medullary thyroid cancer, in patients with family members who have medullary thyroid cancer, and in multiple endocrine neoplasia type 2. Patients may be alarmed by (unsupported) claims that these agents cause pancreatic cancer.[14]

[c]Lower cost alternative with more complex pharmacokinetics; primarily only useful when cost is a major issue.

Flory, J., & Farooki, A. (2016). Diabetes management in cancer patients. *Oncology, 30*(6):565-570

Insulin Pearls – Basal Insulin

- Steroid induced hyperglycemia
  - Pattern is worsening post-prandial hyperglycemia (opposed to impaired fasting glucose)
- Usually requires large doses
- Consider dosing basal insulin in the morning
  - Single daily dosing of prednisone or prednisolone → NPH preferred
    - Starting dose 0.15-0.3 U/Kg but if severe start at 0.4 U/kg
  - If multiple daily doses of steroids OR dexamethasone → Glargine preferred
    - Starting dose 0.15 – 0.3 U/kg
    - Many patients will require 0.4 -0.6 U/kg
  - Adjust basal by 20% q 2-3 days
  - If hypoglycemia reduce by 20%

Tamez-Perez, H.E., Quintanilla-Flores, D.L., Rodriguez-Guiterrez, R., Gonzalez-Gonzalez, J.G., Tamez-Pena, A.L. (2015). Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes, 6*(8):1073-1081,

Insulin Pearls – Prandial Insulin

- If insufficient control or multiple daily doses of insulin will likely need basal/prandial regimen
  - Start rapid acting mealtime insulin at 0.1 U/kg baseline
  - Prandial hyperglycemia adjustment:
    - If preprandial BG is 11 – 17 mmol/L add 0.04 U/kg to next prandial insulin
    - If >17 mmol/L add 0.08 U/Kg
    - (e.g 70 kg patient: if baseline rapid acting is 7U and ac lunch BG is 15 you would add 3 U to lunch time rapid acting insulin for total of 10 U)
    - If persistent prandial adjustments required increase baseline
  - If hypoglycemia reduce by 10-20%

Tamez-Perez, H.E., Quintanilla-Flores, D.L., Rodriguez-Guiterrez, R., Gonzalez-Gonzalez, J.G., Tamez-Pena, A.L. (2015). Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes, 6*(8):1073-1081,

Insulin Pearls – Dose adjustments

- Change in hyperglycemia can be sudden and unpredictable in patients on steroid tapers or escalating doses
  - In general: the percentage of insulin adjustment = half the percentage of steroid change
    - E.g. if the steroid dose is ↑or↓ by 50%, then the insulin dose should be ↑or↓ by 25% respectively
    - Frequent monitoring
    - Ask for help! Expert consultation

Tamez-Perez, H.E., Quintanilla-Flores, D.L., Rodriguez-Guiterrez, R., Gonzalez-Gonzalez, J.G., Tamez-Pena, A.L. (2015). Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes, 6*(8):1073-1081,

Clinical Trials

- Do not use HbA1C as screening eligibility criterion
- Eligibility – Grade 1 hyperglycemia or less (<8.9 mmol/L)
- If greater, a period of 1-2 weeks of reasonable BG control should be demonstrated before a patient can be eligible for study participation

Flory, J., & Farooki, A. (2016). Diabetes management in cancer patients. *Oncology, 30*(6):565-570

Hypertension

Hypertension as a consequence of cancer therapy

- Common culprits
  - *VEGF inhibitors/Angiogenesis inhibitors (Ang-Is)
    - Antioangiogenic agents →Interrupt the VEGF signalling pathway which is essential for angiogenesis
    - Tumors cannot grow beyond 1-2 mm without a vascular supply
  - Corticosteroids
  - mTOR inhibitors
  - Erythropoietin
  - NSAIDS
  - Damage to baroreceptors following cervical radiotherapy

Mouhayar, E., Salahudeen, A., & Yeh, E. (2011). Hypertension in cancer patients. *Tex Heart Inst J, 38*(3):263-265.

Angiogenesis Inhibitor induced HTN

- Examples → bevacizumab, sunitinib, sorafenib, regorafabinib, axitinib etc
- Exact mechanism of Ang-I induced hypertension not known
  - VEGF is a known vasodilator via its effects on NO production
    - Consequences of VEGF inhibition
      - Decreased NO generation
      - Impaired vasodilation
      - Increased vasoconstriction
      - Result → increased peripheral vascular resistance
- HTN is not a side effect but rather a mechanism-dependent on-target toxicity

Small, H.V., Montezano A.C., Rios, F.J., Savoia, C., Touyz, R.M. (2014). Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: Understanding and managing a new syndrome. *Canadian Journal of Cardiology, 30*(5):534-543.

Incidence and Risk Factors

- Incidence
  - Almost 100% of patients treated with Ang-Is will have an absolute increase in blood pressure
  - Incidence of overt HTN 19-67%
    - Incidence of ~90% seen with the use of newer high potency VEGFIs (axitinib)
  - First cycle of treatment is the phase during which the greatest magnitude of increase in BP occurs
- Risk factors
  - Previous history of HTN, combination therapy for more than 1 anti-VEGF, age >65, smoking, ?hypercholesterolemia
  - *BMI, eGFR, race, fhx of htn or CVD not considered risk factors.

Small, H.V., Montezano A.C., Rios, F.J., Savoia, C., Touyz, R.M. (2014). Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: Understanding and managing a new syndrome. *Canadian Journal of Cardiology, 30*(5):534-543.

When to Screen

- Ang-I induced HTN has a characteristic profile
  - Occurs rapidly (within hours to days of treatment initiation)
  - SBP affected more than DBP
  - Often severe and resistant to antihypertensive therapy
  - Withdrawal of the VEGFI is associated with rapid decrease in BP
- Screen prior to initiation - Management of preexisting HTN prior to the initiation of Ang-Is is critical
- Monitor frequently – at least weekly for the first 6 weeks of treatment
  - High risk patients (preexisting htn, other cardiac risk factors) should monitor BP daily with home BP cuff for first 6 weeks)

Small, H.V., Montezano A.C., Rios, F.J., Savoia, C., Touyz, R.M. (2014). Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: Understanding and managing a new syndrome. *Canadian Journal of Cardiology, 30*(5):534-543.

Targets

- Cardiovascular Toxicities Panel of the National Cancer Institute
  - Goal <140/90 (130/80 with comorbid CKD or DM)
- Manage short term morbidity
  - Heart failure, renal failure, encephalopathy
  - Cases of posterior reversible leukoencephalopathy have been seen with severe uncontrolled AI induced hypertension (<1% patients)
- Allow continuation of therapy
    - Maximal benefit of Ang-I's is obtained in patients who can stay on therapy continuously over prolonged period of time

Nazer, B., Humphreys, B.D., Moslehi, J. (2011). Effects of novel angiogenesis inhibitors for the treatment of cancer on the cardiovascular system: Focus on hypertension. *Circulation, 124*(15):1687-1691

Defining HTN

- No consensus, can follow CHEP guidelines
- Consider therapy in patients with a single manual office BP >140/90 and signs of end-organ damage or >160/100 in the absence of end-organ damage OR persistent BP >140/90
- If the diagnosis of HTN is uncertain:
  - CHEP guidelines
  - Ambulatory blood pressure of >130/80 in 24 hours or a daytime recording (0600 – 2200 hrs) of 135/85

Leung, A.A., Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. 2016. *Canadian Journal of Cardiology.* Volume 32, Issue 5, Pages 569–588

Small, H.V., Montezano A.C., Rios, F.J., Savoia, C., Touyz, R.M. (2014). Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: Understanding and managing a new syndrome. *Canadian Journal of Cardiology, 30*(5):534-543.

Relative risk of all-grade and high-grade (grade≥3) hypertension of several VSP inhibitor agents, described in meta-analyses

	All grade hypertension			High grade hypertension		
	RR[a]	95 % CI	*p* Value	RR[a]	95 % CI	*p* Value
Bevacizumab [33]	3.02	2.24–4.07	<0.001	5.28	4.15–6.71	0.001
Sunitinib [52]	3.44	0.62–19.15	0.16	22.72	4.48–115.29	<0.001
Axitinib [38]	3.00	1.29–6.97	0.01	1.71	1.21–2.43	0.003
Sorafenib [62]	3.07	2.05–4.60	<0.01	3.31	2.21–4.95	<0.01
Pazopanib [65]	4.97	3.38–7.30	<0.001	2.87	1.16–7.11	0.023
Lenvatinib [69]	7.44	4.31–12.85	<0.001	18.2	5.90–56.32	<0.001
Vandetanib [36]	5.10	3.76–6.92	<0.001	8.06	3.41–19.04	0.001
Regorafenib [74]	3.76	2.35–5.99	<0.001	8.39	3.10–22.71	0.001

Abbreviations: RR relative risk, *CI* confidence interval

[a] Relative risk of new onset hypertension during trial period in interventional group compared to control

Management

- Lifestyle
  - Exercise, weight reduction, dietary change etc
  - Generally very difficult to apply in oncology patients but may be considered in selected patients
- Pharmacotherapy
  - No specific guidelines. Most studies recommend following CHEP guidelines for treatment of HTN
    - Ace-I/ARB, dihydropyridine calcium channel blocker, beta blockers, (diuretics and non-dihydropyridine calcium channel blockers more interactions and risks)
- Caution in drug protocols with “off” periods
  - Development of hypotension

Pharmacotherapy

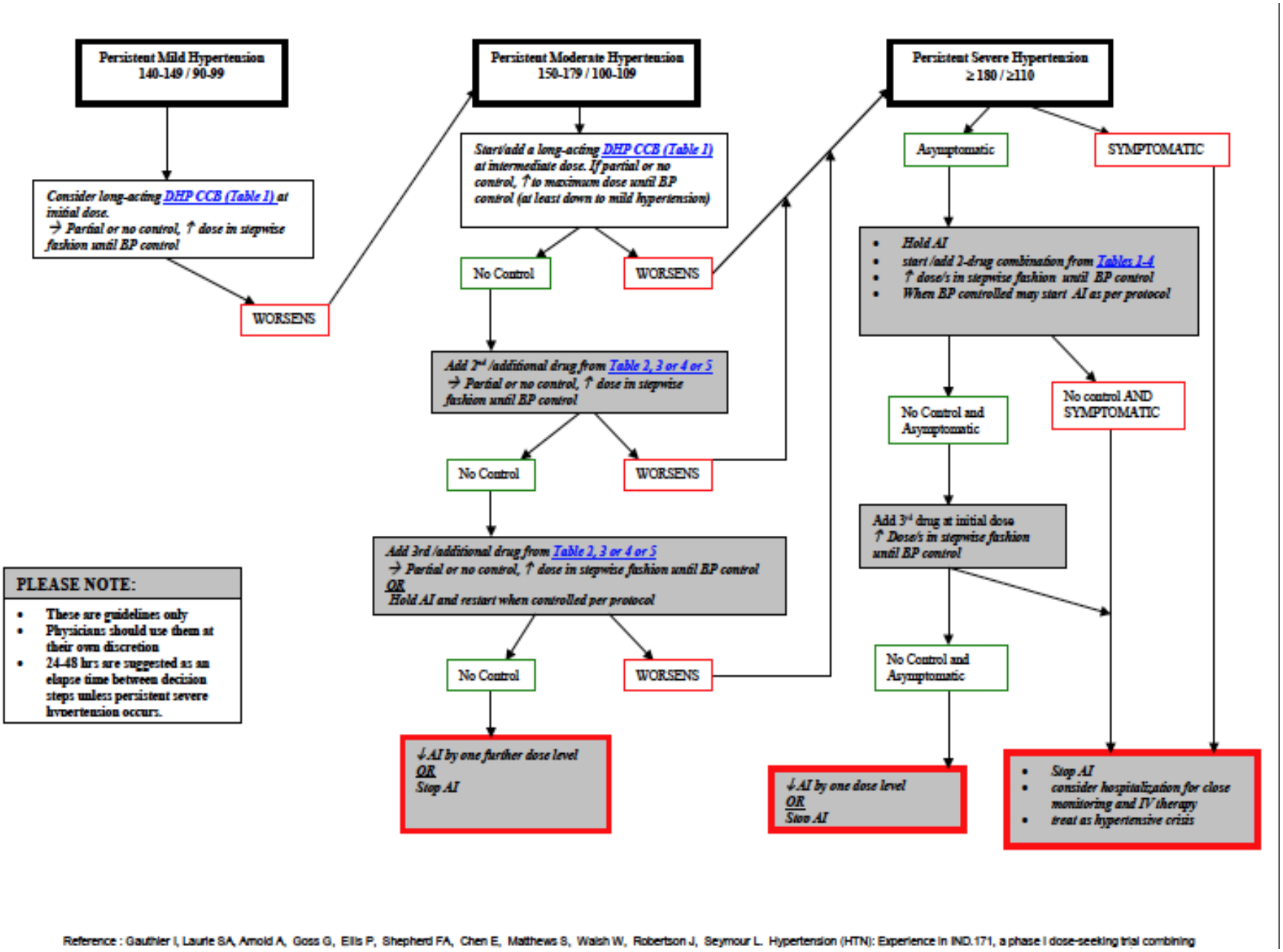
- Level V evidence recommends ACE inhibitors (protect against Ang-I induced proteinuria) or calcium channel blockers (dihydropyridine – counteract the impaired NO signaling) as first line
  - Rapid titration within the first week after initiation
  - Do not use nondihydropyridine CCB (diltiazem, verapamil) → inhibit CYP450 3A4 which may lead to high plasma levels of Ang-I.
  - Diuretics increase electrolyte loss and, in combination with risk of diarrhea on these drugs can lead to prolonged QTc
- Beta blockers useful in underlying arrhythmia or LV dysfunction

Zamorano, L. et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *European Heart Journal*, Volume 37, Issue 36, 21 September 2016, Pages 2768–2801.

Pharmacotherapy – treatment resistant

- VEGF-Is reduce NO generation → Nitric oxide donors may be reasonable targets
  - Isosorbide dinitrate
  - Nitroglycerin (patch)
  - Trials forthcoming…

Touyz, R.M., Lang, N.N., Herrmann, J., van den Meiracker, A.H., Danser, J. (2017). Recent advances in hypertension and cardiovascular toxicities with vascular endothelial growth factor inhibition. *Hypertension, 70*(2):220-226.



Reference : Gauthier I, Laurie SA, Arnold A, Goss G, Ellis P, Shepherd FA, Chen E, Matthews S, Walsh W, Robertson J, Seymour L. Hypertension (HTN): Experience in IND.171, a phase I dose-seeking trial combining

Table 1. Dihydropyridine calcium-channel blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Nifedipine XL	**30 mg po qd**	**60 mg po qd**	**90 mg po qd**	**CYP 3A4 substrate**
Amlodipine	**2.5 mg po qd**	**5 mg po qd**	**10 mg po qd**	**CYP 3A4 substrate**
Felodipine	2.5 mg po qd		10 mg po qd	CYP 3A4 substrate + inhibitor

▲ Top

Table 2: Selective β blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	**25 mg po qd**	**50 mg po qd**	**100 mg po qd**	**No**
Acebutolol	100 mg po bid	200mg-300 mg po bid	400 mg po bid	Yes (CYP 450???)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes (CYP 450???)

▲ Top

Table 3. Angiotensin Converting Enzyme Inhibitors (ACEIs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP 450???)
Lisinopril	**5 mg po qd**	**10-20 mg po qd**	**40 mg po qd**	**No**
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP 450???)
Rarely used:				
Perindopril	**4mg po qd**	**none**	**8mg po qd**	**Yes but not per CYP 450**
Quinapril	**10mg po qd**	**20 mg po qd**	**40 mg po /qd**	**No**

▲ Top

Table 4. Angiotensin II Receptors Blockers (ARBs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Losartan	25mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4mg po qd	8-16 mg po qd	32mg po qd	CYP 2C9 substrate
Irbesartan	75mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	**40 mg po qd**	**none**	**80 mg po qd**	**Yes but not per CYP 450**
Valsartan	**80 mg po qd**	**none**	**160mg po qd**	**Yes but not per CYP 450**

▲ Top

Table 5. α and β blocker

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate and inhibitor

▲ Top

NB. Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with angiogenesis inhibitors metabolised through CYP-450 (e.g. sunitinib and sorafenib)

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Cases

Now it’s your turn…

“Jim”

- 65yM metastatic colon cancer cycle #1 palliative FOLFIRI-bevacizumab
- PMHx: HTN, dyslipidemia, cholecystectomy
- Meds: chlorthalidone 12.5 mg po daily, atorvastatin 40 mg po daily

- Seen in clinic, random BP check 150/100mmHg
- What will you do?

“Angela”

- 55yF locally advanced ER+/PR+/Her2neu- breast cancer recently started exemestane + everolimus
- PMHx: well, participates in age-appropriate screening with FP and had HbA1c + lipids checked last year with no concerns

- First visit after starting new regimen, fasting BG 7.6, HbA1c 5.3%

“Angela” continued

- 2 weeks later random BG in clinic 12.4 mmol/L

“Angela” continued

- Of all the reasonable options you had, you started her on metformin and up-titrated her to 1000 mg po BID.
- Her next HbA1c at the 3 month mark is 6.4%, elevated from prior but well within target

- What would you change if her HbA1c were to increase to 7.5%?

“Angela” continued

- Angela continues to respond well to exemestane + everolimus for her breast cancer
- Her drug-induced diabetes is well-controlled

- You decide to recheck her lipid profile (which you have been checking q cycle)

“Angela” continued

- Total Cholesterol: 5.1 mmol/L
- HDL: 1.1 mmol/L
- Estimated LDL: 3.2 mmol/L
- Triglycerides: 3.5 mmol/L

- Let’s work out her risk together:
- http://chd.bestsciencemedicine.com/calc2.html

“Angela” continued

- What would you like to do next? What drug(s) will be your first choice?

Thank you for your attention and participation!