Oral Digoxin Shortage

Table 1: Canadian Suppliers of Oral Digoxin[1]

Product	Strength	DIN	Manufacturer
Toloxin Tablets	0.0625 mg	02335700	PendoPharm Inc.
	0.125 mg	02335719	
Toloxin Elixir	0.05 mg/mL	02316870	

Health Canada Approved Indications of Oral Digoxin[2]:

- treatment of chronic atrial fibrillation (AF)
- treatment of mild to moderate heart failure (HF)

Background Information

- PendoPharm Inc. is the only Canadian supplier of oral digoxin in Canada and it is experiencing a disruption in the manufacturing of Toloxin; anticipated end date of this shortage is 21 Feb 2020.[3]
- While end dates are never guaranteed, supply disruption does appear to be short-term.
- Digoxin bulk powder may be available to some compounding pharmacies but at considerable price; confirm with compounding pharmacies before referring patients.

General Considerations

- Determine the indication of digoxin: atrial fibrillation (AF), heart failure (HF) or atrial fibrillation with heart failure (AF+HF).
- This is a good opportunity to evaluate digoxin as it lends itself to deprescribing.
- When possible, taper digoxin dose using existing supply
    - under ideal conditions, the dose is reduced by 50% every 1-2 weeks; once at 25% of the original dose for 1-2 weeks, stop if no symptoms.[4]
        - 0.125 mg tablets can be split in half
        - 0.0625 mg tablets are not amenable to splitting; the half-life is 36-48[5] hours so consider increasing the dosing intervals to every 2 days.
    - in many cases supply may not allow for such tapers so taper as best as possible
- All patients need to be monitored but especially those with HF for signs/symptoms of exacerbation, which could lead to hospitalization (see information below).
- Depending on the situation, the patient's condition may not change (and thus validates deprescribing).
- See figures below regarding next steps should signs and symptoms worsen.

Atrial Fibrillation

- Symptoms of AF include palpitations ('heart flutters'), fatigue, dizziness, exercise intolerance, chest pain, and weakness.[6-8]
- Pharmacological strategies to treat AF include rate control and rhythm control; there is no difference in terms of reduction of mortality and stroke risk between the two strategies.[8]
- Rate control is used to slow heart rate (HR); a fast HR is one of the main features of AF and pharmacotherapy is used to ensure the HR stays below 100 beats per minute (BPM).[6]
- For a patient with AF, failing to control a fast HR can have two main consequences:

    1) a fast HR can cause symptoms if the heart does not have enough time to fill with blood in between beats.

    2) a fast HR that is left uncontrolled for long periods of time can cause changes to the heart and cause it to become weaker.

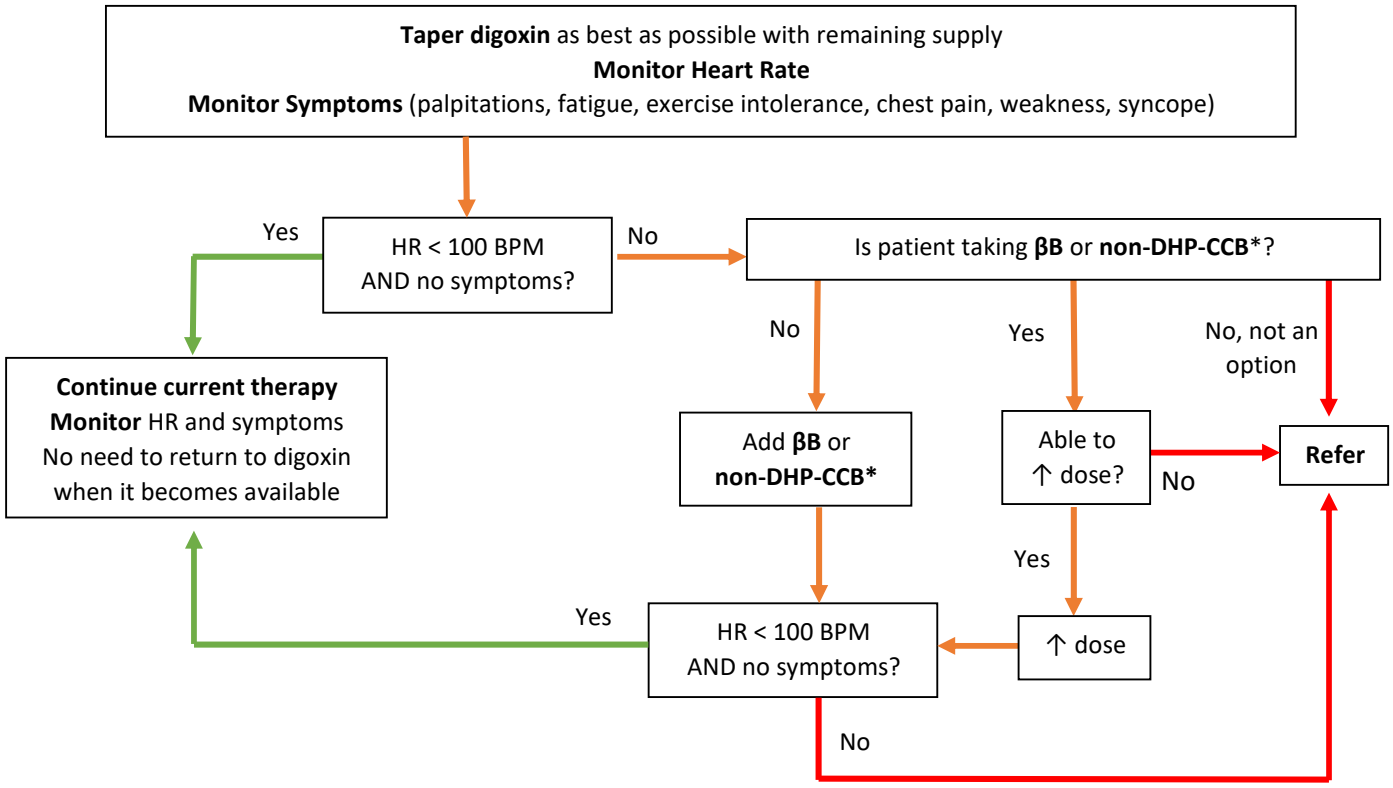
- The mainstay of rate control is a beta blocker (βB) or a non-dihydropyridine calcium channel blocker (non-DHP-CCB) (verapamil and diltiazem). [6,8]
- Digoxin is typically only used as add-on therapy to βBs and non-DHP-CCBs.[8]
- See Table 1 for dosing and Figure 1 for management strategies.

Table 1: Rate Control Agents for Atrial Fibrillation[8,9]

Agent	Dose		
Beta Blockers		Non-Dihydropyridine Calcium Channel Blockers	
Atenolol	50 to 150 mg PO daily	Diltiazem	120 to 480 mg MR PO daily
Bisoprolol	2.5 to 10 mg PO daily	Verapamil	120 to 240 mg SR PO BID
Metoprolol	25 to 200 mg PO BID 100 to 200 mg SR PO daily		
Nadolol	20 to 160 mg PO once to twice daily		

BID = twice daily; MR = modified release and includes CD and XC; PO= by mouth; SR = sustained/slow release

Figure 1: Atrial Fibrillation Treatment Algorithm



*Avoid calcium channel blockers in patients with heart failure with reduced ejection fraction.[10]
βB = beta blocker; BPM = beats per minute; HR = heart rate; non-DHP-CCB = non-dihydropyridine calcium channel blocker

Heart Failure (including Heart Failure with Atrial Fibrillation)

- Heart failure (HF) is associated with abnormal heart function that results in clinical signs and symptoms.
- The most common symptoms include fatigue, exercise intolerance, fluid retention and dyspnea.[10]
- The New York Heart Association (NYHA) Functional Classification is often used to classify symptoms[10,11]:
    - Class I: no symptoms
    - Class II: symptoms with ordinary activity; comfortable at rest
    - Class III: symptoms with less than ordinary physical activity; comfortable at rest
    - Class IV: symptoms at rest or with any minimal physical activity
- Ejection fraction (EF) is also used to classify HF;[10] It is estimated with echocardiography[10] and patients may not know their 'number'.
    - HF with reduced EF (HFrEF): EF ≤ 40% (systolic HF)
    - HF with mid-range EF (HFmEF): EF 41-49%
    - HF with preserved EF (HFpEF): EF ≥ 50% (diastolic HF)

  **Digoxin is only used in systolic HF (HFrEF)

Non-pharmacological options[12]

- See RxFiles Heart Failure: Treatment Overview for details
    - regular physical activity for those with stable HF
    - salt and fluid restriction

Pharmacological Options

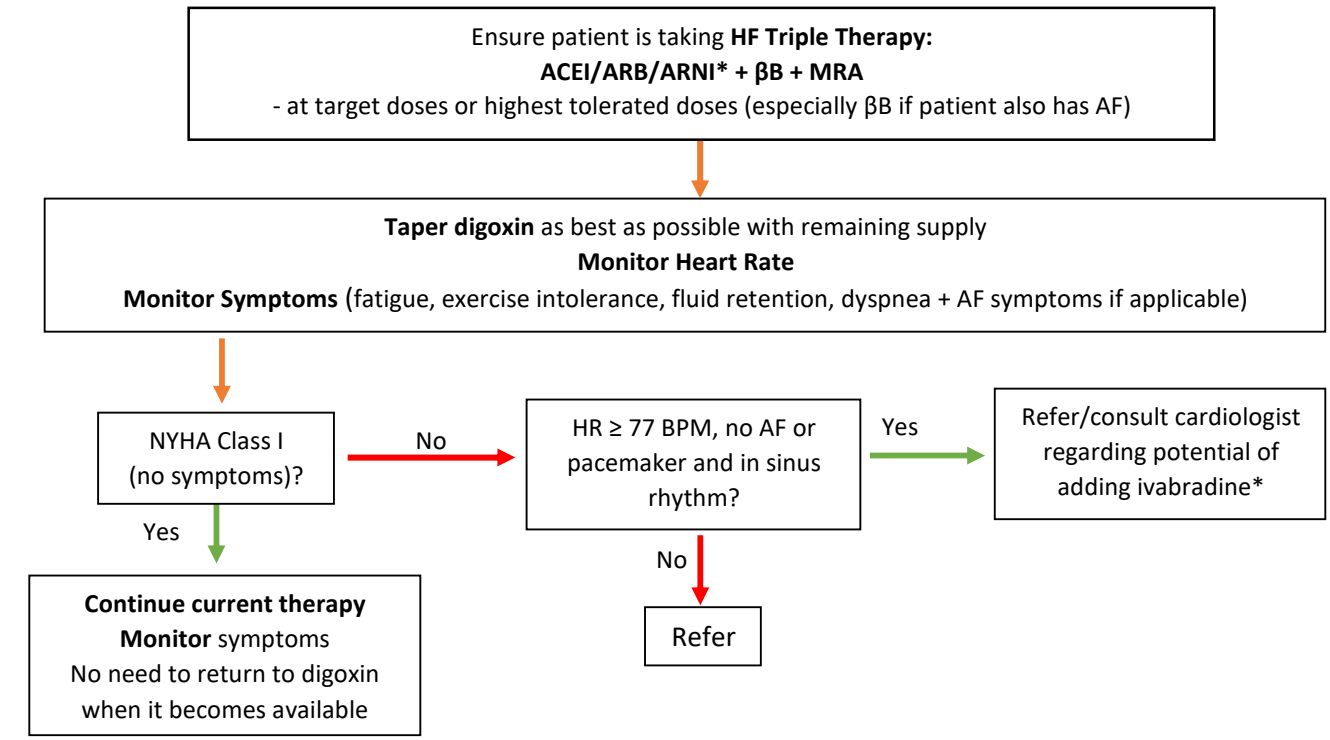
- All patients should be on target doses (or, if not tolerated, highest tolerated dose) of Triple Therapy which includes[10,12,13]:
    - angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), and
    - beta blocker, and
    - mineralocorticoid receptor antagonist (MRA)
- See Table 2 for target doses of Triple Therapy and Table 3 for information about newer HF therapies
- See Figure 2 for management strategies

Table 2: Target Doses in Heart Failure of Triple Therapy[10,12]

Agent	Target Dose
Angiotensin Converting Enzyme Inhibitors	
Enalapril	10 mg PO BID
	20 mg PO BID in NYHA Class IV
Lisinopril	20-40 mg PO daily
Perindopril	4 to 8 mg PO daily
Ramipril	5 mg PO BID
Trandolapril	4 mg PO daily
Angiotensin II Receptor Blockers	
Candesartan	32 mg PO daily
Valsartan	160 mg PO BID
Losartan	150 mg PO daily
Angiotensin Receptor-Neprilysin Inhibitor	
Sacubitril/Valsartan†	97/103 mg PO BID
Beta Blockers	
Carvedilol	25 mg PO BID 50 mg PO BID if >85 kg
Bisoprolol	10 mg PO daily
Metoprolol SR*	200 mg PO daily
Mineralocorticoid Receptor Antagonists	
Spironolactone	50 mg PO daily
Eplerenone†	50 mg PO daily

*This is the tartrate salt; however, evidence is based on the succinate salt, which is not available in Canada.
†Exceptional Drug Status for the Saskatchewan Drug Plan and Limited Use Benefit for Non-Insured Health Benefits
BID = twice daily; NYHA = New York Heart Association; PO = by mouth

Figure 2: Heart Failure Treatment Algorithm
(including patients who have both Heart Failure and Atrial Fibrillation)



* For beneficiaries of the **Saskatchewan Drug Plan**, exceptional drug status criteria for both ivabradine and ARNI (sacubitril/valsartan) include "under the care of a specialist experienced in the treatment of heart failure."[14] For beneficiaries of the **Non-Insured Health Benefits**, criteria for limited use benefit status of sacubitril/valsartan (but not ivabradine) includes that it must be: "initiated by a physician experienced in the treatment of heart failure."[15]
ACEI= angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; βB= beta blocker; BPM = beats per minute; HR = heart rate; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association

Table 3: Additional Information Regarding Newer Heart Failure Therapies[12,13]

Class **Drug**	**Angiotensin Receptor-Neprilysin Inhibitors** Sacubitril/Valsartan	**I_f Current Inhibitor** Ivabradine
Dose in Heart Failure	Initial: 49/51 mg PO BID Target: 97/103 mg PO BID	2.5 to 7.5 mg PO BID

Comments	• Consider starting with 24/26 mg if:
	  ◦ risk of hypotension
	  ◦ not currently taking target ACEI/ARB dose
	• Replaces existing ACEI/ARB (36 hour washout after stopping ACEI – risk of angioedema)
	• Monitor for hypotension; be mindful of diuretic and other antihypertensive use
	• Monitor potassium (hyperkalemia) and renal function
		• Considered for NYHA Class II or higher patients who have HR ≥77 BPM, no AF or pacemaker and are in sinus rhythm
		• Prolongs QTc
		• Avoid in patients at risk of bradycardia
		• Contraindicated drugs: concomitant strong CYP3A4 inhibitors, diltiazem, verapamil
		• If taking moderate CYP3A4 inhibitors, consider starting ivabradine at a lower dose

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BID = twice daily; BPM = beats per minute; PO = by mouth

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