INTRODUCTION
Atrial Fibrillation (AF) is the most common sustained dysrhythmia. It is more prevalent in the elderly and is a common complication of cardiac surgery. Treatment of AF is often based on previous experience and the most appropriate therapeutic regimen for each patient may not be selected. Therefore, this Therapeutic Alternative Chart for AF was developed to help both medical and pharmacy clinicians choose and utilize the most appropriate therapy for the treatment of AF in a specific patient. Currently the chart is used by practicing pharmacists at St. Michael’s Hospital as a tool in providing pharmaceutical care. Additionally, it is used as an educational tool for pharmacists, residents, students, and other health professionals.

METHODS
A thorough review of the current biomedical literature was undertaken using a Medline search of the primary literature back to 1984. All effective agents captured in this literature search were then reviewed specifically for:

a) efficacy in: controlling ventricular response rate (VRR); converting to normal sinus rhythm (NSR); and, maintaining NSR after initial conversion;
b) onset of effect;
c) usual dosing regimens;
d) pharmacokinetics;
e) toxicity;
f) drug interactions; and
g) availability/cost.

These agents were also classified into groups by their pharmacologic effects which:
i) only control VRR (i.e., beta-blockers, calcium channel blockers, digoxin);
ii) only convert to NSR (i.e., procainamide, quinidine, disopyramide);
iii) control both VRR and convert to NSR (i.e., sotalol, amiodarone, flecainide, propafenone).

Disopyramide was not included in the chart as the authors felt that its use is quite infrequent secondary to its negative inotropic and anticholinergic effects.

DISCUSSION
While the therapeutic chart only includes esmolol under the beta-blocker row, other beta-blockers would be equally effective when used in equipotent doses to control the VRR. Esmolol was considered the prototype because of its short half-life, and ease of titration. Use of esmolol can demonstrate how a patient will respond to a beta-blocker in terms of causing hypotension or brady-cardia. The short half-life of esmolol should ensure a short duration of the adverse effect. Other less expensive beta-blockers such as metoprolol, propranolol, atenolol, and others may be substituted for longer-term control of VRR once response to a beta-blocker has been demonstrated. For the post-operative patient, the intravenous forms of these drugs are used initially because of their more rapid onset; the parenteral forms can be substituted with oral agents once the patient is stabilized and is absorbing enterally. Similar oral conversions for other anti-arrhythmic drugs can also be made.

Although no column in the chart was set aside specifically for the duration of action, the overall duration of action of a drug is a function of the pharmacokinetic half-life (listed on the chart under kinetics), pharmacodynamic half-life, and receptor response (i.e., up or down regulated). The duration of effect may, therefore, differ depending on the patient, the

William John Perks, B.Sc.Phm. is a Staff Pharmacist, Department of Pharmacy, St. Michael’s Hospital, Toronto, Ontario.
Carmine Stumpo, B.Sc.Phm, at time of writing, Mr. Stumpo was a Pharmacy Resident, St. Michael’s Hospital, Toronto, Ontario. Currently Mr. Stumpo is a Pharm.D. candidate at the College of Pharmacy, Wayne State University, Detroit, Michigan.
Brian Jurewitsch, B.Sc.Phm., is a Staff Pharmacist, Department of Pharmacy, St. Michael’s Hospital.
Christian Klem, Pharm.D. at time of writing, Dr. Klem was Clinical Coordinator, Critical Care at St. Michael’s Hospital. Currently Dr. Klem is a Pharmacotherapy Specialist, Tampa General HealthCare and Assistant Professor, University of South Florida, Tampa, Florida.
Address Correspondence to: Mr. Wm. Perks, B.Sc.Phm., Department of Pharmacy, St. Michael’s Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8.
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Onset</th>
<th>Dose</th>
<th>Kinetics</th>
<th>Toxicity</th>
<th>Drug Interactions</th>
<th>Comments</th>
<th>Availability/Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
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</tr>
<tr>
<td>Esmolol</td>
<td>VRR = excellent (similar to metoprolol)</td>
<td>IV = 2-5 min (may take longer to tolerate)</td>
<td>300-500 mcg/kg in 1 min then 300 mcg/kg/min</td>
<td>Extracellular blockade</td>
<td>Bradycardia, symptom</td>
<td>calcium channel blockers, digoxin, dipyridamole</td>
<td>little risk of proarrhythmic effects / tardos pontes</td>
<td>IV: 100mg/10ml = $9.48 2.5% (10ml) = $134.10</td>
</tr>
<tr>
<td>(Brevibloc)</td>
<td>CONV = similar to propranolol may be higher than placebo if hyperadrenergic state</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Metoprolol</td>
<td>VRR = excellent (similar to metoprolol)</td>
<td>IV = 2-5 min (2-3 hours)</td>
<td>0.25 mg/kg over 2 min, no response in 15 min then 0.25 mg/kg/min</td>
<td>Hepatic elimination</td>
<td>Bradycardia, less QT, neotopic effects vs. verapamil</td>
<td>50%28 (120) 10%</td>
<td>- HR is dose-related</td>
<td>IV: 25mg/5ml = $13.00 160mg/10ml = $24.00</td>
</tr>
<tr>
<td>(Lopresin)</td>
<td>CONV = similar to propranolol may be higher than placebo if hyperadrenergic state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcium infarction may decrease hypotension</td>
<td>60%46 = $0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Use dependent effects</td>
<td>120mg SR = $0.38</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>VRR = excellent (similar to diuretics)</td>
<td>IV = 2-5 min (30 min duration post bolus)</td>
<td>2.5-10 mg IV (0.375-0.5mg/kg) over 2 min then 2.5-10 mg/hr</td>
<td>Hepatic elimination</td>
<td>Bradycardia, less QT, neotopic effects vs. verapamil</td>
<td>50%21 (may require dose adjustment)</td>
<td>- Cardiac infarction may decrease hypotension</td>
<td>IV: 5mg/2ml = $7.80 80mg/10ml = $20.00</td>
</tr>
<tr>
<td>(Isoptin)</td>
<td>CONV = similar to placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Use dependent effects</td>
<td>140mg SR = $0.33</td>
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<td></td>
<td></td>
<td></td>
<td>150mg SR = $0.41</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>VRR = moderate (loss of effect with 7 ateftic states)</td>
<td>IV = 3-4 hrs PO = 4-6 hrs</td>
<td>Loading = 10-15 mcg/kg (7-11 mcg/kg if renal dysfunction) in divided doses over 24 hours then 0.025-0.25 mg/kg/hr</td>
<td>Renal elimination</td>
<td>Bradycardia, nausea, GI effects, anthymid, TPR interval, AV block, CNS effects</td>
<td>80-120 mg PO Q6-8h</td>
<td>- Diltiazem -warfarin digoxin</td>
<td>IV: 0.5mg/3ml = $2.27 2.0mg/1ml = $0.25 10mg/1ml = $0.09</td>
</tr>
<tr>
<td>(Cardizem)</td>
<td>CONV = similar to placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Beneficial effects in LV dysfunction - requires prior VRR control</td>
<td>20mg/2ml = $0.79 240mg SR = $0.33</td>
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<tr>
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<td></td>
<td>Monitoring of levels with digitalis</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>Procainamide</td>
<td>VRR = poor (similar to diltiazem)</td>
<td>IV = 10-30 min PO = 2-4 hrs</td>
<td>10-15 mg/kg IV (max 30 mg/min then 2-4 mg/min)</td>
<td>Hepatic &amp; renal (5%) elimination</td>
<td>Bradycardia, nausea, GI effects, anthymid, TPR interval, AV block, CNS effects</td>
<td>PO = 250mg = $0.18 120mg = $0.33 240mg SR = $0.33</td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>10mg/0.5ml = $1.05</td>
</tr>
<tr>
<td>(Proradyn)</td>
<td>CONV = moderate (poor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>120mg = $0.33</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>Quinidine</td>
<td>VRR = poor (similar to diltiazem)</td>
<td>IV = 1-2 hrs PO = 4-24 hrs</td>
<td>Loading = 10-15 mcg/kg (7-11 mcg/kg if renal dysfunction) in divided doses</td>
<td>Hepatic elimination</td>
<td>Bradycardia, nausea, GI effects, anthymid, TPR interval, AV block, CNS effects</td>
<td>PO = 250mg = $0.18 120mg = $0.33 240mg SR = $0.33</td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>(Quinidex)</td>
<td>CONV = moderate (poor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>180mg SR = $0.58</td>
</tr>
<tr>
<td>Propafenone</td>
<td>VRR = moderate to good</td>
<td>CONV = 5-50mg/5ml (po)</td>
<td>2mg/kg IV (slow) then 10-30 min PO = 1-3 hrs</td>
<td>Hepatic elimination</td>
<td>Bradycardia, nausea, GI effects, anthymid, TPR interval, AV block, CNS effects</td>
<td>PO = 25mg SR = $0.18 120mg = $0.33 240mg SR = $0.33</td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>10mg/0.5ml = $1.05</td>
</tr>
<tr>
<td>(Rhythm)</td>
<td>CONV = moderate to good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>VRR = moderate</td>
<td>CONV = 50-200mg; 12-14 mg/12 h</td>
<td>2 mg/kg IV over 10 min (max 100-200 mg PO Q12h)</td>
<td>Cardiac (sustained)</td>
<td>Bradycardia, nausea, vomi, diastolic, cyanosis, insuff, nausea (22%) blood dyscrasia</td>
<td>PO = 25mg SR = $0.18 120mg = $0.33 240mg SR = $0.33</td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>10mg/0.5ml = $1.05</td>
</tr>
<tr>
<td>(Tambocor)</td>
<td>CONV = moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>VRR = poor (similar to diltiazem)</td>
<td>IV = 20-30 min PO = 2-1 hrs</td>
<td>5 mg/kg IV bolus over 0.5-1 hr (2 min for emergency) then 5-20 mg/kg over 24 hrs for 5-7 days then 200-400 mg PO daily</td>
<td>Hepatic elimination</td>
<td>Bradycardia, nausea, vomi, diastolic, cyanosis, insuff, nausea (22%) blood dyscrasia</td>
<td>PO = 25mg SR = $0.18 120mg = $0.33 240mg SR = $0.33</td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>10mg/0.5ml = $1.05</td>
</tr>
<tr>
<td>(Cordene)</td>
<td>CONV = moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Requires prior VRR control - levels: 4.8 mcg/ml (17.34 µmol/L) may require dose adjustment and/or closer monitoring with β blockers</td>
<td>150mg SR = $0.48</td>
</tr>
<tr>
<td>Sotalol</td>
<td>VRR = excellent (similar to metoprolol)</td>
<td>IV = 0.5-2 mcg/kg IV over 5 min</td>
<td>300-500 mg PO Q12h</td>
<td>Extracellular blockade</td>
<td>Bradycardia, symptom</td>
<td>Calcium channel blockers, digoxin, dipyridamole</td>
<td>Calcium channel blockers, digoxin, dipyridamole</td>
<td>- Reverse use-dependent effects</td>
</tr>
<tr>
<td>(Sotalol)</td>
<td>CONV = similar to propranolol may be higher than placebo if hyperadrenergic state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcium channel blockers, digoxin, dipyridamole</td>
<td>150mg SR = $0.33 240mg SR = $0.33</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcium channel blockers, digoxin, dipyridamole</td>
<td>150mg SR = $0.33 240mg SR = $0.33</td>
</tr>
</tbody>
</table>

* Useful for controlling Ventricular Response Rate (VRR) only  
† Useful for converting to Normal Sinus Rhythm (NSR) or maintaining NSR only  
‡ Useful for converting VRR, converting to NSR and maintaining NSR  
§ Useful for controlling VRR, converting to NSR and maintaining NSR

VRR: Ventricular Response Rate Control  
CONV: Conversion to Normal Sinus Rhythm (variable period)  
MAINT: Maintenance of Normal Sinus Rhythm (once converted variable period)
dose used, the route of administration, and many other factors. Generally, the stated half-life will give an estimate of how long the drug will provide its given response.

Similarly, the onset of action of these drugs depends on a number of patient and drug specific factors. The listings for onset refer to the onset of activity, not necessarily the time to peak effect. In some cases, the peak effect may take days to occur as with amiodarone. Because of amiodarone's long half-life, and large volume of distribution due to a high degree of tissue binding, large loading doses of amiodarone are required for initiation of treatment. The intravenous route of administration of the drug will usually provide a faster onset of action compared to the oral route.

The drug interactions listed in the chart are not meant to be all inclusive. Those included were felt to be more commonly encountered and/or clinically significant. Interactions may result in either an increase in effect, with resultant toxicity, or a decrease in effect requiring additional monitoring or intervention. These may include adjustment of doses, withdrawal of a drug or more intense monitoring of clinical effects or toxicities, and serum concentration monitoring. More detail on any of the listed interactions may be found in standard drug interaction references.

The chart, when used in combination with patient-specific information and clinical judgement, will assist in the rational treatment of patients with AF. No one drug or drug combination listed in the chart is the drug of choice for every patient. The chart is useful because all the potential options are listed, and best regimen for a specific patient may be selected. Some of the specific patient information required before a rational choice for treatment of AF can be made includes assessment of:

- patient demographics (i.e., age, level of physical activity, etc.);
- cardiac conditions including:
  - left ventricular function;
  - left atrial size;
  - hemodynamic effect of the arrhythmia;
  - duration of dysrhythmia;
  - heart rate; and
  - cardiac conduction abnormalities.
- renal/hepatic function;
- pulmonary function (reversible airway disease);
- serum electrolytes and fluid status;
- thyroid function;
- past or present antiarrhythmic usage and present drug therapy;
- sympathetic state of patient (e.g., pain control, recent stress, etc.);
- other disease states (e.g., diabetes, etc.);
- patient preferences (i.e., adverse effects, drug plan coverage, etc.).

The approach to the patient with AF would first be to treat any underlying risk factors such as hypomagnesemia, hypokalemia, or hyperthyroidism. Consideration should be given towards withdrawal or dosage reduction of any arrhythmogenic medications the patient is receiving. These could include theophylline, catecholamines, thyroxine, etc. The patient should then be assessed to determine the hemodynamic effects of the arrhythmia. If the AF is causing hemodynamic compromise, electrical cardioversion may precede pharmacologic conversion. If the AF is new in onset, the goal of therapy would be to return the patient to normal sinus rhythm without any adverse drug effects. Initial control of AF may be achieved by controlling the rate with either beta-blockers, calcium channel blockers, or digoxin. Beta-blockers, which are normally useful only for rate control may be helpful in conversion of a patient with a hyperadrenergic state (e.g., postoperative patients). These and other rate controlling drugs can decrease the hemodynamic and symptomatic effects of the arrhythmia in preparation for electrical conversion, pharmacologic conversion with procainamide or quinidine, or chronic rate control along with adequate anticoagulation. Alternately, combined rate control and conversion to NSR may be achieved with amiodarone, flecainide, propafenone, or sotalol.

When using the chart, consider various factors about the patient and disease state of AF. Up to 40% or more of patients with recent onset AF (<48 hours) convert spontaneously to NSR. Unfortunately, approximately 75% of patients experience recurrence of the AF and, thus, some patients may require maintenance antiarrhythmic therapy to improve the chance of maintaining NSR. Patients with heart failure, enlarged left atrial size (> 45 mm), and longer duration of AF (> 2 months) have a smaller chance of remaining in NSR once converted. Patients whose AF was related to a definite risk factor which has been corrected e.g., electrolyte disorder, drugs, or hyperadrenergic state have a better chance of staying in NSR. In determining whether to employ maintenance antiarrhythmic therapy, the risks of drug treatment including the possibility for side effects, proarrhythmia and even increased mortality should be weighed against the risk of reverting back into AF, which although bothersome is not usually fatal.

In the acute setting of AF, a number of treatment choices are available including: controlling the VRR, controlling the VRR and converting pharmacologically or electrically or converting electrically. If the AF converts to NSR, the treatment options include: the use of VRR controlling agents to prevent rapid ventricular response if the patient reverts back to AF; using antiarrhythmic agents to increase the chance of remaining in NSR; or no therapy at all.

If the AF is felt to be resistant to conversion, chronic control of VRR may be employed with anticoagu-
information, the chart is helpful in assessing the many pharmacologic alternatives for the treatment of atrial fibrillation. We believe that the development of Therapeutic Alternative Charts for other disease states would be useful to help improve patient specific therapeutic decision making and to increase the visibility and responsibility of pharmacists in contributing to patient care.

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