

# **Is it time to repair a Fairly Fast SAAB Convertible?**

## **Testing an evidence-based mnemonic for the secondary prevention of cardiovascular disease.**

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## Abstract

**Objectives:** Optimising secondary prevention of cardiovascular disease has the greatest potential to reduce recurrent events, yet despite major guidelines there are ongoing treatment gaps. **FFSAABC (Fish oils, Fibrates, Statins, Aspirin, Angiotensin converting enzyme inhibitors or angiotensin 2 receptor antagonists, Beta blockers and Clopidogrel)** is one mnemonic previously adopted to assist clinicians in remembering medications for use in secondary prevention. The aim of this narrative review is to examine the current evidence base for medications recommended for patients with established cardiovascular disease and the current applicability of this, or a revised mnemonic for their use.

**Study design:** Randomised controlled trials and systematic reviews were sought examining **Fish oils, Fibrates, Statins, Aspirin, Angiotensin converting enzyme inhibitors or angiotensin 2 receptor antagonists, Beta blockers or Clopidogrel vs placebo** in secondary prevention. The emerging evidence base for other contemporary therapies including the P2Y12 inhibitors (Ticagrelor and Prasugrel) and aldosterone antagonists was also reviewed.

**Results:** Definitive evidence supports the use of statins, aspirin, angiotensin converting enzyme inhibitors or angiotensin 2 receptor antagonists, and clopidogrel or newer P2Y12 antagonists (ticagrelor or prasugrel) for the secondary prevention of cardiovascular disease. Aldosterone antagonists have strong evidence in the presence of systolic heart failure. There is a weaker evidence base for the routine use of omega-3 fatty acid supplementation although this therapy carries minimal harms. Fenofibrate reduces cardiovascular events in dyslipidaemic patients, with additional benefits in patients with diabetes.

**Conclusions:** Mnemonic upgrading from a Fairly Fast SAAB Convertible to a Fairly Fast SA<sup>2</sup>A<sup>2</sup>B (Fish oils, Fibrate, Statin, Antiplatelets (Aspirin + Other), ACE/ARB, Aldosterone

Antagonist, **B**eta-blocker) may help to ensure patients receive best practice evidence-based pharmacotherapies for the secondary prevention of cardiovascular disease.

## Introduction

Acute coronary syndrome (ACS) is a substantial cause of morbidity and mortality, accounting for 75000 hospitalisations in Australia in 2010. Just over 1/3 of these hospitalisations were for recurrent events, accounting for nearly one half the overall economic cost of ACS and a 20% absolute mortality rate – double that of those suffering their first event.<sup>1</sup> Individuals who survive an ACS therefore stand to derive substantial absolute benefits from pharmacological interventions that reduce recurrent cardiovascular events, highlighting the importance and cost-effectiveness of secondary prevention. Despite national guidelines,<sup>2</sup> currently only a half to two thirds of eligible patients in Australia receive at least four out of five guideline based pharmacotherapies on hospital discharge following a diagnosis of ACS.<sup>3</sup>

Mnemonics have been used as learning aids dating back to Ancient Greek and Roman times, classically representing a means of connecting a series of dissociated items into a unified whole. Medical education, characterised traditionally by endless lists of causes, differentials and treatments, has frequently adopted mnemonics for learning. To aid clinicians in remembering potentially useful therapies, our senior author adopted the mnemonic *SAAB* in the 1990s, which was extended to *SAAB Convertible* in 2001 and later *Fairly Fast SAAB Convertible* (FFSAABC) in approximately 2009. This mnemonic represents Fish oils, Fibrates, Statins, Aspirin, Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), Beta-blockers and Clopidogrel. However, many new studies have been conducted in the last five years, in particular investigating fish oils, newer P2Y12 inhibitor medications and aldosterone antagonists. The purpose of this review is to evaluate whether the existing evidence supports the continued use of FFSAABC as a mnemonic for pharmacotherapy in the secondary prevention of CVD, or if a revision is appropriate.

## Fibrates

Fibric acid derivatives typically reduce triglyceride concentrations by 30-50% and increase HDL cholesterol concentrations by up to 10%. A meta-analysis by Lee *et al.* of randomised controlled trials investigating fibrate therapy found that compared to placebo, fibrates given to secondary prevention patients with both hypertriglyceridaemia (defined as triglycerides > 2.3mmol/L or nearest equivalent) and low HDL-C (defined as HDL-C < 1.03mmol/L or nearest equivalent) reduced the risk of cardiovascular events by 28%, noting there were no significant mortality reductions observed.<sup>4</sup> In patients with neither lipid abnormality in the overall population (patients with CHD or diabetes) there was no effect of fibrates on cardiovascular events.

In recent years fibrates used in patients with diabetes have also been shown to reduce the progression of retinopathy (37%), need for amputations (36%), and progression of nephropathy (with possible improvements), effects which are independent of baseline lipid profiles.<sup>5</sup>

Fenofibrate is the only drug of this class safely recommended for concomitant administration with statins, due to increased risks of myotoxicity and rhabdomyolysis with other fibrates. The most frequently reported adverse effects are gastrointestinal, while there are with rare risks of pancreatitis (0.3%) and pulmonary embolism (0.4%).<sup>6</sup>

Current evidence indicates fibrates are effective in the prevention of cardiovascular events without a clear mortality reduction, but benefits appear limited to patients with residual dyslipidaemia. There are additional pronounced microvascular benefits for people with diabetes.

## Fish oils

Research arising from long term population studies linking high seafood intake with lower rates of cardiovascular events and mortality led to the isolation of omega-3 polyunsaturated fatty acids as the most likely active constituent. However randomised trials examining cardiovascular outcomes with fish oils have produced conflicting evidence. A systematic review in 2012, including twenty trials and data from around 63000 trial participants, found fish oils had no effect on the primary composite cardiovascular outcome.<sup>7</sup> Amongst the thirteen trials reporting on cardiovascular mortality, there was a significant 14% reduction in risk overall, noting significant trial heterogeneity ( $I^2=60.7\%$ ,  $P=0.001$ ). No effect was seen on all-cause mortality, sudden cardiac death or individual cardiovascular outcomes. The two individual trials with results most supportive of a positive effect of fish oil supplementation have been the primary prevention Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) and secondary prevention Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI) Prevenzione study, both of which were open-label. Some factors suggested as potentially contributing to trial heterogeneity have also included baseline triglyceride levels (greater benefits with higher baseline triglyceride levels); age of trial participants (greater benefits in younger patients); and the presence of hypertension or diabetes (greater benefits in patients without these comorbidities).<sup>7</sup> Several trials in this meta-analysis had control groups which were on a Mediterranean diet, used olive oil as a control or had a fish rich diet, all of which could have masked the benefits of omega-3 supplementation with their own cardio-protective effects. A linear response to fish oil intake and CVD protection has never been established, suggesting supplementation beyond a certain level of intake may not confer additional benefits.<sup>8</sup>

The commonest side effect of oral fish oil use is gastrointestinal upset (fishy aftertaste, reflux and diarrhoea), although this can often be lessened with enteric coating. Limited evidence exists regarding serious adverse effects of omega-3 fatty acids. No effect on cancer incidence has been reported in meta-analyses of eight randomised studies from a systematic review.<sup>7</sup>

Currently the evidence base for the use of fish oils to reduce cardiovascular or mortality endpoints is limited, and general conclusions are that the available evidence is not adequate to strongly support the *use or cessation* of omega-3 fatty acids in the secondary prevention of CVD.<sup>7</sup> Australian secondary prevention guidelines (Reducing Risk in Heart Disease, 2012) recommended an average daily intake of 1g of fish oils through either dietary or supplemental means, and only specifically recommended capsules/liquid for those with elevated triglycerides.<sup>2</sup> The AHA/ACCF Secondary Prevention Guidelines (2011) state it “*may be reasonable*” to recommend omega-3 fatty acids from fish or fish oil supplements.<sup>9</sup>

## Statins

A large-scale individual patient meta-analysis of 27 randomised controlled trials of statin therapy by the Cholesterol Treatment Trialists’ Collaboration has shown that amongst ~100000 randomised trial patients with prior cardiovascular disease, statins reduced the risk of major cardiovascular events by 23% per 1.0mmol/L reduction in LDL-cholesterol (LDL-C), irrespective of baseline LDL-C level.<sup>10</sup> Amongst five randomised trials of patients with known ischaemic heart disease comparing more intensive statin regimens to less intensive regimens, more intensive dose statin therapy reduced LDL cholesterol concentrations by an additional 0.51mmol/L and was associated with a further 15% reduction in the risk of major vascular events.<sup>11</sup> Amongst all trials, allocation to statin/more intensive statin therapy significantly reduced the risk of non-fatal MI and coronary revascularisation by about a



quarter and ischaemic stroke by about a fifth (with a 15% reduction in any stroke) per mmol/L LDL-cholesterol reduction. The risk of cardiovascular mortality was reduced by 14% and all-cause mortality by 10% per mmol/L LDL cholesterol reduction. Amongst these endpoints the relative benefits of statin therapy were maintained across all levels of absolute cardiovascular risk.<sup>10</sup> Since patients with previous vascular disease have the highest absolute risks of recurrent cardiovascular events, they therefore stand to benefit the most from statin/more intensive treatment.

Potential adverse effects of statins include muscle conditions (ranging from myalgia to rhabdomyolysis), new onset type 2 diabetes mellitus, a very small increase in haemorrhagic stroke and transient reversible memory impairment.<sup>12</sup> Myalgia, by far the most common adverse effect, occurs in 1-5% of patients, whilst myopathy occurs in 0.1-0.5% and rhabdomyolysis in 0.01%.<sup>12</sup> Statin use has been associated with an increase in rate of diagnosis of incident diabetes by 9% in a meta-analysis of trials comparing statin to placebo,<sup>13</sup> and by 12% in a meta-analysis of trials comparing more vs. less intensive statin therapy.<sup>14</sup> This association is stronger in patients who are older and appears to be more common amongst patients with other risk factors for diabetes such as hypertension, higher BMI, higher baseline fasting glucose levels and higher triglycerides.<sup>12</sup> Despite the potential risk for new diabetes, which remains to be more definitively researched, the relative and absolute cardiovascular benefits from statin therapy vastly outweigh the risks associated with developing diabetes.<sup>10</sup>

There have been post marketing surveillance reports of a possible rare association of statin treatment with mild cognitive impairment that appears to be reversible over a median time of 3 weeks after treatment withdrawal. No adverse link between statin treatment and dementia has been found despite some false media reports to the contrary. Randomised

trials of statin therapy which specifically examined for cognitive changes did not identify any adverse effects.<sup>12</sup>

Previous concerns about increases in cancer with statins have been convincingly refuted, at least within the median five year timeframe of 27 randomised trials.<sup>10</sup> In addition, there is now long term follow-up data from previous statin trial participants indicating no worse outcomes out to over 10 years for cancer incidence or death amongst those originally randomised to statin therapy compared to those allocated to placebo.<sup>15</sup>

Current evidence strongly supports the use of statins in the secondary prevention of cardiovascular events, particularly as National Heart Foundation targets of LDL-C concentrations <1.8mmol/L for secondary prevention are difficult to achieve with lifestyle changes alone.<sup>2</sup> Adverse events are infrequent and serious events are extremely rare. Whilst there is debate regarding balancing absolute benefits against possible adverse events for low risk primary prevention, there should be no question about net benefit for secondary prevention, where the profound cardiovascular benefits of therapy firmly outweigh the risks.

## Aspirin

An individual patient data meta-analysis by the Anti-thrombotic Trialists of 16 secondary prevention trials showed that aspirin reduced annual rates of serious vascular events (myocardial infarction, any stroke or vascular death) by 19%, major coronary events by 20%, any stroke by 19%, cardiovascular mortality by 9% and all-cause mortality by 10%.<sup>16</sup>

Emerging data supports additional non-cardiovascular benefits of aspirin in reducing the 20-year risk of solid cancers (20%).<sup>17</sup>

Haemorrhage is the main hazard of aspirin. The Antithrombotic Trialists calculated an increased risk of any major bleed with aspirin of 169%. Small absolute increases in

haemorrhagic stroke are offset by much larger reductions in ischaemic stroke producing a net benefit with aspirin therapy, and no effect on fatal stroke.<sup>16</sup> Another meta-analysis of six secondary prevention trials using lower-dose ( $\leq 325$ mg) daily aspirin estimated an increased risk of gastrointestinal bleeds by 250%, representing an absolute increase from 0% to 2% (+/- 1.4%) over four years of follow up, with no deaths.<sup>18</sup> A comparison of the relative numbers needed to treat determined 1.5 deaths were prevented with aspirin for each GI bleed (of any severity) caused.

High-dose aspirin has not been shown to increase clinical benefits whilst definitely increasing the risk of bleeding complications.<sup>19</sup> Therefore in view of overwhelming evidence supporting the use of aspirin for secondary prevention of cardiovascular events, administering low-dose aspirin (75-150mg/day) will minimise the risk of adverse effects without compromising benefits.

## **ACE Inhibitors and Angiotensin Receptor Blockers**

A large scale individual patient data meta-analysis of ~100000 pooled trial participants showed ACE inhibitors given in the acute phase (0-36h from symptom onset) of an MI significantly reduced 30 day mortality rates by 7%.<sup>20</sup> Another individual patient data meta-analysis pooling data from three long term trials amongst patients post MI with left ventricular dysfunction or clinical heart failure showed that ACE inhibitors reduced the risks of recurrent MI by 20%, readmission for heart failure by 27% and all-cause mortality by 26% over four years of follow-up.<sup>21</sup> Similar overall proportional benefits have been demonstrated in patients post MI with preserved ejection fractions.<sup>22</sup>

Trials comparing an angiotensin receptor blocker to an ACE inhibitor post MI with LV impairment have overall shown no difference in clinical benefits between the two classes in terms of reductions in MI, hospitalisation for heart failure, cardiovascular death and all-

cause mortality.<sup>23,24</sup> In contrast to some evidence in chronic heart failure patients, no additive benefits of combining the two classes for secondary prevention has been demonstrated, whilst the risk of side effects is increased.<sup>24</sup>

Potential adverse effects of either ACE inhibitors or ARBs include hypotension, hyperkalaemia, a reduced glomerular filtration rate and rare but potentially fatal anaphylactoid reactions, while cough has a well identified increased risk of about 10% with ACE inhibitors.<sup>21,25</sup> These effects are nearly always reversible with treatment withdrawal, if necessary. In most cases hyperkalaemia develops in the presence of other comorbidities or medications and can be managed without ceasing the ACE inhibitor or ARB. Similarly, glomerular filtration rates can fall in some patients (usually with comorbidities such as chronic kidney disease or bilateral renal artery stenoses) but both medication types are nevertheless reno-protective and recommended for use in most patients, even with chronic renal failure.

Overall, treatment with either an ACE inhibitor or ARB has clear evidence for cardiovascular event and mortality reductions after an acute coronary syndrome, irrespective of the presence of systolic ventricular impairment. There is no compelling evidence for combining them in this setting, which risks hyperkalaemia without added benefit.

## **Beta Blockers**

Beta-blockers have longstanding evidence of efficacy in secondary prevention. A systematic review of nearly 25000 patients included in 31 long term randomised trials found beta-blockers reduce the risk of all-cause mortality by 23%. The number needed to treat over one year to prevent one death was 84 patients and to prevent one non-fatal cardiac reinfarction was 107.<sup>26</sup> Mortality benefits have also been established in populations in which underuse may be more common including patients aged  $\geq 80$ , patients with COPD or diabetes, patients

with resting heart rates <70 or systolic BP<100 and lower risk patients without any complications.<sup>27</sup>

A meta-regression analysis of 14 beta blockade trials found that reductions in cardiac death, sudden death and all-cause death as well as non-fatal MI were significantly related to the extent of heart rate reduction achieved.<sup>28</sup> However, a recent large randomised study investigating Ivabridine, a purely chronotropic agent, in patients with stable CAD found that despite significant heart rate reductions in the Ivabradine arm, the combined cardiovascular endpoint was not reduced, suggesting the cardiovascular benefits of beta blockers are not attributable solely to heart rate reductions.<sup>29</sup>

In patients with heart failure from systolic dysfunction (due to any cause but including myocardial infarction) a systematic review and network meta-analysis showed beta-blockers reduced all-cause mortality by 29% without any significant difference shown between the long acting beta-blockers indicated for use in this setting.<sup>30</sup>

The optimal long term duration of beta blockade therapy after MI is not currently known. Registry data and observational studies suggest reductions in cardiovascular events may extend out to four years, with stronger evidence extending to six years in higher risk patients such as those with heart failure.<sup>31,32</sup> In patients with normal left ventricular function, AHA/ACCF secondary prevention guidelines recommend beta-blocker therapy for at least three years and suggest ongoing treatment is reasonable (Class IIa, Level of evidence B).<sup>9</sup> Recently reported French registry data suggested there may be no additional mortality benefits from beta blockers beyond the first 12 months after an MI in patients with preserved systolic function (LVEF>40%), although likely confounding of this observational data has been raised as a major limitation in drawing strong conclusions.<sup>33</sup>

Effects of beta-blockade which can prompt discontinuation include bradycardia and hypotension. Rarely other adverse events can require cessation such as fatigue (1.5%), depression (0.4%), reduced libido (0.2%), dizziness, vivid dreams and cold extremities.<sup>26</sup>

Beta blockers have strong and longstanding evidence for cardiovascular event and mortality reductions in secondary prevention patients, particularly in patients with heart failure, noting there is some uncertainty about an ongoing benefit in patients with preserved systolic function beyond three years, and possibly sooner.

### **Clopidogrel / Other P2Y12 Antagonists (Ticagrelor, Prasugrel)**

A systematic review and meta-analysis of randomised trials of dual antiplatelet therapy in patients with acute coronary syndrome or undergoing percutaneous coronary intervention showed the addition of clopidogrel to aspirin reduced the risk of cardiovascular mortality by 7%, recurrent MI by 20% and stroke by 16% without any effect on the risk of intracranial haemorrhage.<sup>34</sup> Conflicting findings regarding bleeding risks have been reported. A recent meta-analysis amongst mostly secondary prevention trials reported a 40% increased relative risk of major bleeding using both clopidogrel and aspirin compared to aspirin alone,<sup>35</sup> while in other instances no increased risk was seen.<sup>36</sup> Loading doses likely contribute to bleeding risk - a higher loading dose of clopidogrel of 600mg (compared to 300mg) is recommended before percutaneous intervention in clopidogrel naïve patients due to improved cardiovascular outcomes, but this is at the expense of a higher major bleeding risk.<sup>37</sup>

In recent years two additional P2Y12 inhibitors have emerged as potential alternatives to clopidogrel as a second antiplatelet agent: prasugrel and ticagrelor. Like clopidogrel, prasugrel is an irreversible thienopyridine P2Y12 inhibitor which is ingested as a pro-drug and metabolised by cytochrome P450 enzymes to its active form. It has a faster onset and greater degree of platelet inhibition than clopidogrel due to more efficient metabolism into its active form, and reduced function CYP polymorphisms do not appear to impact on prasugrel metabolism like they do up to 40% of patients who take clopidogrel.<sup>38</sup> In TRITON-TIMI 38, a randomised trial of 13600 people presenting with moderate-high risk ACS and

scheduled for PCI, allocation to prasugrel compared to clopidogrel resulted in 19% fewer combined cardiovascular events, 24% fewer MIs and 52% fewer stent thromboses, with no effect on cardiovascular or all-cause mortality at 15 months follow-up.<sup>39</sup> This was at the expense of a 32% increase in non-CABG related TIMI major bleeding and a 473% increase in CABG related TIMI bleeding. Post-hoc subgroup analyses suggested that patients with a previous stroke or TIA were at a net risk of harm taking prasugrel, whilst those aged  $\geq 75$  or with body weight  $< 60$ kg appeared to have a neutral outcome. As a consequence prasugrel is contraindicated in patients with a previous stroke or TIA and a lower dose is recommended for those aged  $\geq 75$  or with body weight  $< 60$ kg.<sup>40</sup>

The TRILOGY-ACS trial compared prasugrel to clopidogrel in 7200 patients with either unstable angina or NSTEMI for medical management excluding patients with previous stroke/TIA.<sup>41</sup> Over 30 months of follow up there was no difference between prasugrel and clopidogrel in all cardiovascular, mortality and bleeding outcomes.

In terms of non-bleeding adverse events, hypersensitivity reactions are identified with all thienopyridines (clopidogrel and prasugrel). Clopidogrel reactions occur in about 1-2% of patients and mostly manifest within the first week of treatment as a diffuse erythematous progressively confluent rash.<sup>42</sup> Desensitisation can be attempted in mild cases. More severe outcomes including anaphylaxis are very rare. Substitution with another thienopyridine in the event of hypersensitivity is not recommended.

Ticagrelor is a directly acting reversible P2Y<sub>12</sub> inhibitor which has both a more rapid onset of effect and achieves a greater level of platelet inhibition than clopidogrel.<sup>43</sup> In the PLATO trial which compared ticagrelor to clopidogrel in ACS patients, ticagrelor reduced the rates of the primary composite cardiovascular endpoint by 16%, myocardial infarction by 16%, stent thrombosis by 33%, cardiovascular death by 21% and all-cause mortality by 22%.<sup>43</sup> There was no difference in overall major bleeding events or fatal bleeding between the two treatments. Subgroup analyses have demonstrated similar net benefits irrespective of

revascularization status, age (including those  $\geq 75$ ), diabetes, renal failure or previous TIA/stroke.<sup>44</sup>

Ticagrelor can cause a non-pathological dyspnoea which is mostly a single self-limiting event early after treatment is commenced. It occurred in 5% more patients than clopidogrel in PLATO and 0.9% of patients discontinued treatment because of dyspnoea.<sup>43</sup> Patients reporting dyspnoea with ticagrelor had the same cardiovascular and mortality benefits as those without dyspnoea without evidence of altered pulmonary function. It is thought the mechanism for these symptoms may relate to increased extracellular adenosine levels from inhibition of adenosine reuptake. In PLATO ticagrelor also caused more ventricular pauses ( $\geq 3s$ ) than clopidogrel (5.8% vs 3.6%) in the first week of treatment whilst a month later there were no differences between treatment groups.<sup>43</sup> Despite this there was no difference in the incidence of bradycardic adverse events, including syncope, pacemaker insertion or cardiac arrest.

Overall the evidence base clearly supports international guideline recommendations that any patient with acute coronary syndrome be treated with dual antiplatelet therapy for twelve months, irrespective of revascularisation status. European guidelines (STEMI 2011, NSTEMI 2012) management recommend the use of Ticagrelor or, if coronary anatomy is known and PCI planned, Prasugrel over the use of Clopidogrel.<sup>45</sup> American society guidelines (STEMI 2013, UAP/NSTEMI 2012) recommend the use of any of these three agents without preference, noting that prasugrel is not recommended for UA/NSTEMI patients in whom conservative management is planned.<sup>9</sup> Australian secondary prevention guidelines make similar recommendations.<sup>2</sup>



## Aldosterone Antagonists

Randomised controlled trials investigating aldosterone antagonists in patients with systolic heart failure have demonstrated significant reductions in all-cause mortality, driven by reductions in cardiovascular mortality, including sudden cardiac death.<sup>46,47</sup> Hospitalisations for heart failure are also significantly reduced. Apart from reduced hospitalisations for heart failure, other cardiovascular benefits were not seen in a recently published study amongst patients with heart failure and a preserved ejection fraction.<sup>48</sup> As a consequence major international guidelines (ACC/AHA Secondary prevention 2011<sup>9</sup>, ESC STEMI 2012<sup>45</sup>) recommend the use of either spironolactone or eplerenone in patients suffering from severe systolic heart failure of any aetiology (LVEF $\leq$ 35% and NYHA class II-IV with some additional provisions for class II patients) **or** STEMI patients with LVEF $\leq$ 40% on an ACE inhibitor and beta blocker and with heart failure signs or diabetes.

Of note all these trials excluded patients with hyperkalaemia (K $\geq$ 5.0mmol/L) or moderate or worse renal impairment (eGFR $<$ 30mL/min/1.73m<sup>2</sup> or serum Cr $>$ 221 $\mu$ mol/L) due to the increased risk of hyperkalaemia with aldosterone antagonists, particularly in the presence of renal failure. Other endocrine side effects are possible including gynaecomastia, menstrual irregularities and increased libido. Eplerenone carries a much lower risk than spironolactone of these hormonal effects due to greater receptor specificity, but is more expensive.

Overall evidence supports prescription of aldosterone antagonists in secondary prevention patients with systolic heart failure, with significant mortality reductions. Renal function must be considered prior to prescription of either agent, whilst the endocrine side effect profile is more favourable for eplerenone than spironolactone.

## Other Non-Pharmacological Interventions

Lifestyle interventions including smoking cessation, participation in exercise based cardiac rehabilitation, increased physical activity and avoiding excess alcohol consumption significantly reduce the risk of all-cause mortality. Annual influenza vaccination and dietary modification, particularly adopting a Mediterranean type diet, have both been showed to reduce major vascular events. Screening for depression is also important due to a strong association between depression and increased cardiovascular mortality after a myocardial infarction.<sup>2</sup>

## Discussion

Whilst treatment prescription in medicine will always require an individualised approach there are notable ongoing deficiencies in the prescription of evidence based treatments for cardiovascular disease, in terms of overall rates and regional discrepancies. Mnemonics are frequently used in medicine to assist learning and rapid recall, and have the potential to aid clinicians in this regard. FFSAABC, a letter based mnemonic adopted over the last decade for treatments used in the secondary prevention of cardiovascular disease, has been re-examined in this review in light of updated evidence.

There is currently strong evidence to support the use of statins, aspirin, ACEI/ARBs,  $\beta$ -blockers and clopidogrel in the secondary prevention of cardiovascular disease. The newer P2Y<sub>12</sub> inhibitors Ticagrelor and Prasugrel have indications for use as a substitute at least, if not in preference to clopidogrel in various settings. Aldosterone antagonists have strong evidence for reducing cardiovascular events and mortality amongst patients with moderate-severe systolic heart failure. Fenofibrate is effective at reducing events in dyslipidaemic

patients, irrespective of the presence of cardiovascular disease, noting that secondary prevention patients have a much higher absolute risk of future events and therefore stand to benefit more. It also prevents several microvascular diabetic complications. The evidence for fish oil supplementation is somewhat less definitive, but a small cardiovascular mortality benefit is suggested and potential harms are minimal. It has been estimated the combined prescription of evidence based pharmacotherapy together with lifestyle modification measures would reduce the post-ACS risk of recurrence by more than 50%.<sup>49</sup>

## Conclusion

Effective secondary prevention of CVD can substantially reduce mortality and morbidity in Australia. It is important to ensure that clinicians in both hospital and community settings are prescribing evidence-based therapies, and are facilitating a high rate of patient adherence. Considering the current pharmacologic evidence base for secondary prevention, upgrading from a **Fairly Fast SAAB Convertible** to a **Fairly Fast SA<sup>2</sup>A<sup>2</sup>B** (Fish Oils, Fibrate, Statin, Antiplatelets (Aspirin + Adjuvant Other Antiplatelet), ACE inhibitor/Angiotensin Receptor Blocker, Aldosterone Antagonist and Beta-blocker) appears to be timely.

## Table and Figure Legend.

Figure 1. A Fairly Fast SAAB Convertible. Time to upgrade?

## References

1. Deloitte Access Economics. ACS in Perspective: the importance of secondary prevention, 2011.
2. The Cardiac Society of Australia and New Zealand. Clinical Practice Guidelines. 2014. <http://www.csanz.edu.au/resources/clinical-practice/> (accessed 30/10/2014 2014).
3. Chew DP, French J, Briffa TG, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. *Med J Aust* 2013; **199**(3): 185-91.
4. Lee M, Saver J, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis* 2011; **217**(2): 492-8.
5. Noonan JE, Jenkins AJ, Ma JX, Keech AC, Wang JJ, Lamoureux EL. An update on the molecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. *Diabetes* 2013; **62**(12): 3968-75.
6. Keech A, Simes R, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial.[Erratum appears in Lancet. 2006 Oct 21;368(9545):1415; PMID: 17055933], [Erratum appears in Lancet. 2006 Oct 21;368(9545):1420]. *Lancet* 2005; **366**(9500): 1849-61.
7. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012; **5**(6): 808-18.
8. Marik P, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol* 2009; **32**(7): 365-72.
9. American College of Cardiology / American Heart Association. ACC/AHA Statements and Guidelines. 2014. [http://my.americanheart.org/professional/StatementsGuidelines/ByTopic/TopicsA-C/ACCAHA-Joint-Guidelines\\_UCM\\_321694\\_Article.jsp](http://my.americanheart.org/professional/StatementsGuidelines/ByTopic/TopicsA-C/ACCAHA-Joint-Guidelines_UCM_321694_Article.jsp) (accessed 30/10/2014 2014).
10. Cholesterol Treatment Trialists (CTT) Collaboration. Lack of Effect of Lowering LDL Cholesterol on Cancer: Meta-Analysis of Individual Data from 175,000 People in 27 Randomised Trials of Statin Therapy. *PLoS ONE* 2012; **7**(1): e29849.
11. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376**(9753): 1670-81.
12. Fulcher J, Keech A. The case for more intensive use of statins. *Therapeutic Advances in Chronic Disease* 2012; **3**(5): 201-10.
13. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; **375**(9716): 735-42.
14. Preiss D, Seshasai SRK, Welsh P, et al. Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy. *JAMA: The Journal of the American Medical Association* 2011; **305**(24): 2556-64.
15. Strandberg TE, Pyorala K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004; **364**(9436): 771-7.
16. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**(9678): 1849-60.
17. Rothwell P, Fowkes G, Belch J, Ogawa H, Warlow C, Meade T. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; **377**(9759): 31-41.
18. Weisman S, Graham D. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med* 2002; **162**(19): 2197-202.
19. Antiplatelet Trialists' C. Collaborative overview of randomised trials of antiplatelet therapy Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**(6921): 81-106.
20. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of

- individual data from 100,000 patients in randomized trials. . *Circulation* 1998; **97**(22): 2202-12.
21. Flather M, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000; **355**(9215): 1575-81.
  22. Saha S, Molnar J, Arora R. Tissue ACE inhibitors for secondary prevention of cardiovascular disease in patients with preserved left ventricular function: a pooled meta-analysis of randomized placebo-controlled trials. *J Cardiovasc Pharmacol Ther* 2007; **12**(3): 192-204.
  23. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**(20): 1893-906.
  24. The ONTARGET Investigators. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N Engl J Med* 2008; **358**(15): 1547-59.
  25. Ram C, S V. Angiotensin Receptor Blockers: Current Status and Future Prospects. *Am J Med* 2008; **121**(8): 656-63.
  26. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; **318**(7200): 1730-7.
  27. Gottlieb S, McCarter R, Vogel R. Effect of Beta-Blockade on Mortality among High-Risk and Low-Risk Patients after Myocardial Infarction. *N Engl J Med* 1998; **339**(8): 489-97.
  28. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J* 2007; **28**(24): 3012-9.
  29. Fox K, Ford I, Steg PG, Tardif J-C, Tendera M, Ferrari R. Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. *N Engl J Med* 2014; **0**(0): null.
  30. Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. *BMJ* 2013; **346**: f55.
  31. Nakatani D, Sakata Y, Suna S, et al. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. *Am J Cardiol* 2013; **111**(4): 457-64.
  32. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *The Lancet* 2003; **362**(9377): 7-13.
  33. Wood S. Can Beta-Blockers Be Stopped Post-AMI With Preserved LVEF? Insights from FAST-MI. 2014 <http://www.medscape.com/viewarticle/830730> (accessed 02/09/2014 2014).
  34. Aradi D, Komocsi A, Vorobcsuk A, Serebruany V. Impact of clopidogrel and potent P2Y<sub>12</sub> -inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention. A systematic review and meta-analysis. *Thromb Haemost* 2013; **109**(1): 9.
  35. Zhou Y-H, Wei X, Lu J, et al. Effects of Combined Aspirin and Clopidogrel Therapy on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *PLoS ONE* 2012; **7**(2): e31642.
  36. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial.[Erratum appears in JAMA. 2003 Feb 26;289(8):987.]. *JAMA* 2002; **288**(19): 2411-20.
  37. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010; **363**(10): 930-42.
  38. Wallentin L. P2Y<sub>12</sub> inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009; **30**(16): 1964-77.
  39. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**(20): 2001-15.
  40. Eli Lilly Australia Pty Ltd. MIMS Full Prescribing Information: Effient. 2013.
  41. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367**(14): 1297-309.

42. Cheema AN, Mohammad A, Hong T, et al. Characterization of clopidogrel hypersensitivity reactions and management with oral steroids without clopidogrel discontinuation. *J Am Coll Cardiol* 2011; **58**(14): 1445-54.
43. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009; **361**(11): 1045-57.
44. Wallentin L, Becker RC, Cannon CP, et al. Review of the accumulated PLATO documentation supports reliable and consistent superiority of ticagrelor over clopidogrel in patients with acute coronary syndrome: Commentary on: DiNicolantonio JJ, Tomek A, Inactivations, deletions, non-adjudications, and downgrades of clinical endpoints on ticagrelor: serious concerns over the reliability of the PLATO trial, *International Journal of Cardiology*, 2013. *Int J Cardiol* 2014; **170**(3): e59-62.
45. European Society of Cardiology. Clinical Practice Guidelines. 2014. <http://www.escardio.org/GUIDELINES-SURVEYS/ESC-GUIDELINES/Pages/GuidelinesList.aspx> (accessed 30/10/2014 2014).
46. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**(14): 1309-21.
47. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**(1): 11-21.
48. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**(15): 1383-92.
49. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet* 2004; **364**(9438): 937-52.

**Figure 1.** Fairly Fast SAAB Convertible. Time to upgrade?

