

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.

Improved Outcomes in your CV Patients: Current Guidelines, Risk of Recurrent Events and Adherence



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BRILINTA, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

STREAMLINED AUTHORITY CODE 5746

PBS Information: Authority Required (STREAMLINED). Treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin.

BEFORE PRESCRIBING PLEASE REVIEW FULL PRODUCT INFORMATION
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1. Ticagrelor Approved Product Information

BRILINTA is a registered trademark of AstraZeneca Pty Ltd. AstraZeneca Pty Ltd ABN 54 009 682 311. 66 Talavera Road, North Ryde NSW 2113. AstraZeneca Medical Information: 1800 805 342. www.astrazeneca.com.au 441288.022 August 2016.

STREAMLINED AUTHORITY CODE

PBS Information: Authority Required ⁵⁷⁴⁶(STREAMLINED). Treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin.

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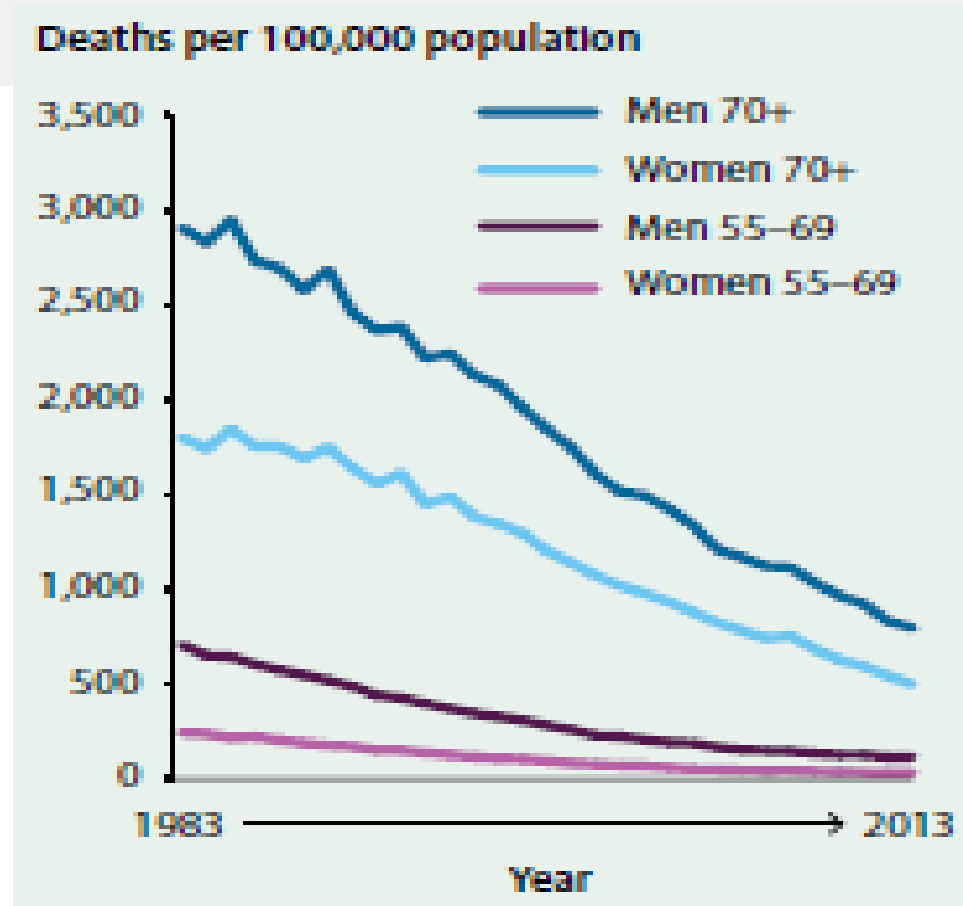
BRILINTA®(ticagrelor) **Indications:** BRILINTA, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). **Dosage:** Initiate with a single 180 mg loading dose (two tablets of 90 mg) and then continue at 90 mg twice daily; with or without food. Patients taking BRILINTA should take aspirin (ASA) daily unless specifically contraindicated. Following an initial dose of ASA, BRILINTA should be used with a recommended maintenance dose of ASA 100 mg daily. If required, the ASA maintenance dose may vary from 75-150 mg according to clinical need. Treatment is recommended for at least 12 months unless discontinuation is clinically indicated. Overdosage may result in prolonged bleeding. No dose adjustment is needed for elderly patients, or patients with renal / mild hepatic impairment. **Contraindications:** Hypersensitivity to ticagrelor or any of the excipients (refer to adverse effects), active pathological bleeding, history of intracranial haemorrhage, moderate to severe hepatic impairment, co-administration with strong CYP3A4 inhibitors. **Precautions:** Increased risk of PLATO-defined non-CABG major bleeding and combined major + minor bleeds (refer to adverse effects); bleeding risk; co-administration with NSAIDs; oral anticoagulants and fibrinolytics/ thrombolytics; surgery; renal dialysis; bradycardia and drugs inducing bradycardia; dyspnoea; elderly; patients <60kg; patients of Asian descent; creatinine elevations, monitor renal function in appropriate patient populations; hyperuricaemia; Pregnancy (Category B1); breastfeeding is not recommended; not for use in children (<18 years), high dose ASA (>300mg) is not recommended; discontinuation of therapy. **Interactions:** Strong CYP3A4 inhibitors (ketoconazole, clarithromycin, nefazadone, ritonavir, atazanavir), other CYP3A4 inhibitors such as diltiazem, amprenavir, aprepitant, erythromycin, fluconazole, verapamil and CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital; cyclosporin (CYP3A inhibitor), simvastatin at doses >40mg, statins metabolised by CYP3A4; CYP3A4 substrates with narrow therapeutic indices (i.e. ergot alkaloids); monitor when giving narrow therapeutic index P-gp dependent drugs like digoxin, cyclosporin; Concomitant administration with drugs known to alter haemostasis; should not be administered with clopidogrel or prasugrel; drugs known to induce bradycardia; SSRIs may increase the risk of bleeding. **Adverse Effects:** PLATO-defined non-CABG major bleeding and combined major + minor bleeding; PLATO-defined non-procedural major bleeding and combined non-procedural major + minor bleeding, intracranial bleeds, gastrointestinal bleeding, epistaxis, dyspnoea; Lab abnormalities; uric acid and creatinine elevations; Treatment emergent adverse events (>2.5%): atrial fibrillation; bradycardia; cardiac failure; nausea; diarrhoea; vomiting; constipation; non-cardiac chest pain; fatigue; chest pain; pyrexia; oedema peripheral; back pain; headache; dizziness; cough; contusion; hypertension; hypotension. PLATO study adverse events (>1%): vertigo, abdominal pain, dyspepsia, post-procedural haemorrhage, blood creatinine increased, urinary tract bleeding, rash, pruritus, subcutaneous or dermal bleeding or bruising. For less common adverse events, see full PI. **Post marketing experience:** Immune system disorders: hypersensitivity reactions including angioedema, *rash. Date of first inclusion in the ARTG: 21 June 2011. Date of most recent amendment: 18 December 2015

***Please note changes in Product Information.**

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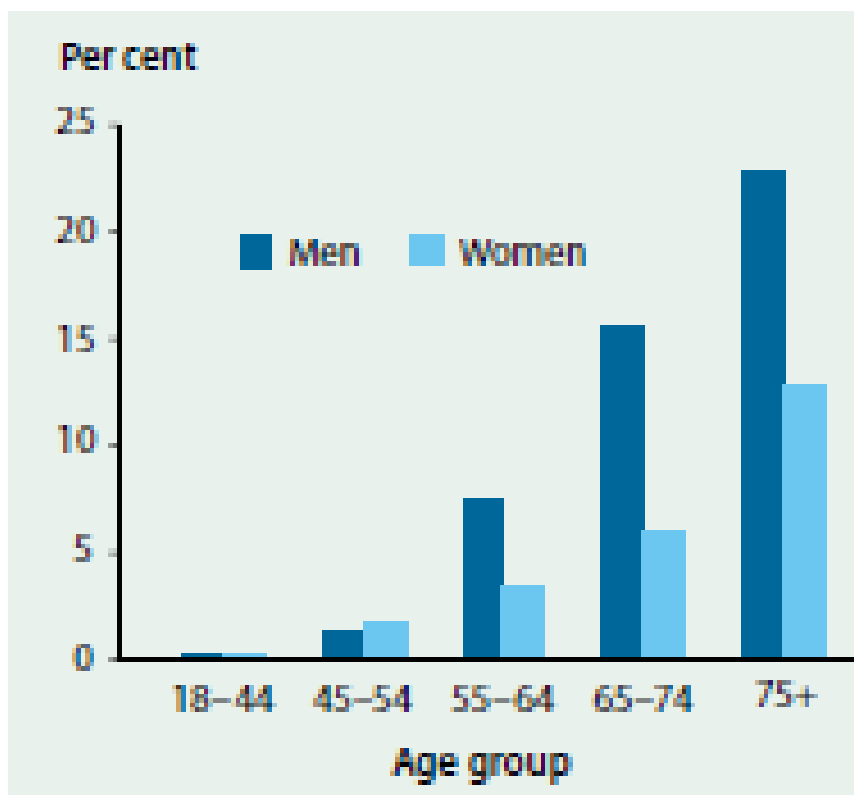
Is ACS really still a problem?

Coronary heart disease death rates, people aged 55 and over, by selected age groups and sex, 1983-2013



In whom is CHD a problem?

Self-reported coronary heart disease,
people aged 18 and over, by age and by sex, 2014-15



Is ACS really still a problem?

Table 3.2.1: Top 10 leading causes of premature death by sex, 2011-2013

Males			Females			People		
Cause of death	Number	%	Cause of death	Number	%	Cause of death	Number	%
1 Coronary heart disease	11,887	12.7	Lung cancer	5,336	9.3	Coronary heart disease	15,223	10.1
2 Lung cancer	8,141	8.7	Breast cancer	5,259	9.2	Lung cancer	13,477	8.9
3 Suicide	5,161	5.5	Coronary heart disease	3,336	5.8	Suicide	6,881	4.6
4 Colorectal cancer	3,572	3.8	COPD	2,303	4.0	Colorectal cancer	5,867	3.9
5 COPD	3,003	3.2	Colorectal cancer	2,295	4.0	COPD	5,306	3.5
6 Cerebrovascular disease	2,995	3.2	Cerebrovascular disease	2,268	4.0	Breast cancer	5,296	3.5
7 Land transport accidents	2,672	2.9	Cancer, unknown, ill-defined	1,770	3.1	Cerebrovascular disease	5,263	3.5
8 Liver disease	2,665	2.8	Suicide	1,720	3.0	Cancer, unknown, ill-defined	4,346	2.9
9 Cancer, unknown, ill-defined	2,576	2.8	Ovarian cancer	1,600	2.8	Liver disease	3,836	2.5
10 Diabetes	2,425	2.6	Pancreatic cancer	1,589	2.8	Pancreatic cancer	3,826	2.5

But hang on a second!!! You have to die of something! This is just old folks, right? And what about the sharks?! You haven't even mentioned all those fatal attacks yet...



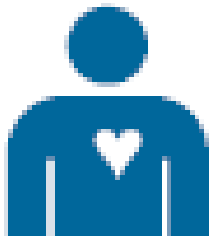
Top five leading causes of premature death, by age, 2011-13

		Age group					
		Under 1	1–14	15–24	25–44	45–64	65–74
1	Perinatal & congenital	Land transport accidents	Suicide	Suicide	Coronary heart disease	Coronary heart disease	
2	SIDS	Perinatal & congenital	Land transport accidents	Accidental poisoning	Lung cancer	Lung cancer	
3	Ill-defined causes	Brain cancer	Accidental poisoning	Land transport accidents	Breast cancer	COPD	
4	Accidental threats to breathing	Accidental poisoning	Assault	Coronary heart disease	Colorectal cancer	Cerebrovascular disease	
5	Selected metabolic disorders	Cerebral palsy & related	Event of undetermined intent	Breast cancer	Suicide	Colorectal cancer	

- In Australia, for the period since 2000, there were 26 fatal shark attacks compared to 225,000 premature deaths due to CHD, 45,000 fatal suicides and 7,508 road fatalities.
- For 15 to 44 year olds, suicide remains the leading cause of death
- CHD is the leading cause of premature death at all ages above 45 years old

CVD – co-morbidities

Cardiovascular disease



was reported as a
comorbidity among



63% of people
with diabetes



51% of people
with cancer



49% of people
with COPD

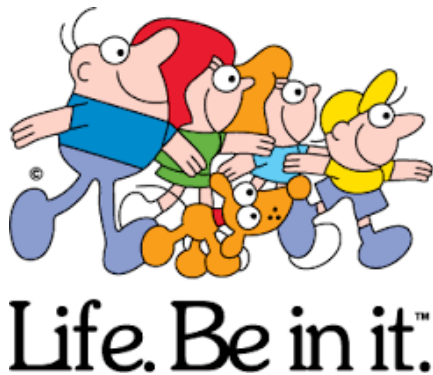


Who should we thank?

You

Improvements in reducing risk factors

- a range of effective, well-tolerated therapies
- Especially for hypertension and high cholesterol
- Effective campaigns to reduce smoking
 - Australia now lowest in OECD





Where have we struggled?

- Physical inactivity – world beating sports mad SPECTATORS
- Overweight and obesity – increased from 56% (1995) to 63% (2014)
- Among the best access to fresh fruit and vegetables in the world with among the lowest regular consumption
- Diabetes – increased from 2.3 (1995) to 4.4% (2014); childhood type I diabetes 7th highest in the world
- Indigenous Health – steady improvements but still a big gap

Compared with non-Indigenous Australians, Indigenous Australians were:



- 2 times as likely to have CHD
- 2.4 times as likely to be hospitalised for CHD
- 1.6 times as likely to die from CHD
- experiencing CHD at younger ages: in the 35–44 age group, 4.7 times as likely to report having CHD, and 7 times as likely to be hospitalised for CHD.

Compared with those living in Major cities, people in combined Remote and Very remote areas were:



- 1.6 times as likely to be hospitalised for CHD
- 1.3 times as likely to die from CHD.

Compared with those living in the highest socioeconomic areas, people living in the lowest socioeconomic areas were:



- 2.2 times as likely to have CHD
- 1.5 times as likely to be hospitalised for CHD
- 1.4 times as likely to die from CHD.





Contemporary ACS Management

- For suspected ACS - Early presentation to hospital care by ambulance
- Early ECG with review by appropriately trained health professional
- Prompt recognition of STEMI and the need for early-reperfusion (PCI or lysis)

Chest pain? Get to care...





Contemporary ACS Management

- For all ACS (STEMI and NSTEMI) -
 - Aspirin 300 mg orally dissolved or chewed
- For all intermediate or high risk NSTEMI -
 - P2Y₁₂ inhibitor - ticagrelor or prasugrel preferred to clopidogrel
 - Ticagrelor indicated across broad spectrum of ACS patients (in the absence of AV conduction disorder or asthma)
 - Prasugrel may be considered in whom PCI is planned but avoided in those >75 yo, low bodyweight or a history of TIA/stroke
- Antithrombotic therapy (GP IIb/IIIa inhibitor, heparin, LMWH or bivalirudin)



NB: All listed therapies should be given in the absence of a specific contraindication and/or prior documented intolerance or hypersensitivity

Chew D, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. MJA 2016; 205(3): 128-133



Contemporary ACS Management

- For discharge:
- Dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor (ticagrelor or clopidogrel) should be considered in all patients with ACS regardless of PCI
- Up to 12 months therapy is recommended but some patients may be considered for longer-term or indefinite DAPT if ischaemic risks outweigh bleeding risk
 - e.g. prior ACS despite ongoing sole aspirin therapy, multi-vessel stenting, diabetes
- Prasugrel should be confined to patients who received PCI

NB: All listed therapies should be given in the absence of a specific contraindication and/or prior documented intolerance or hypersensitivity

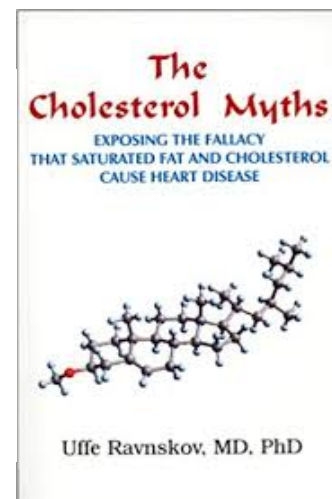
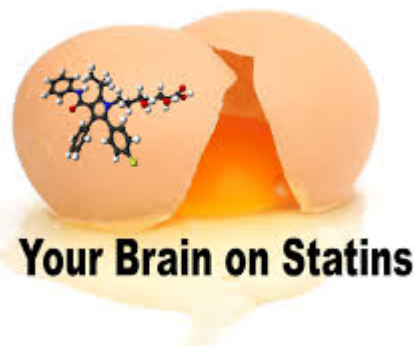
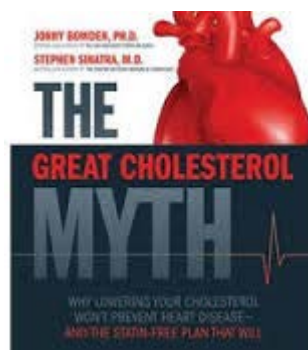
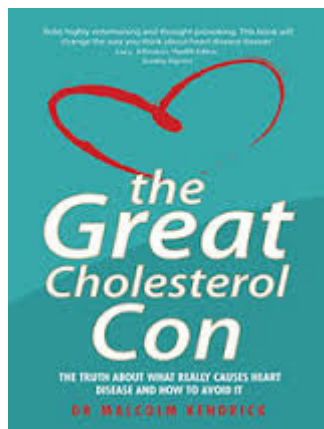
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Contemporary ACS Management

- Initiate and continue indefinitely, the highest tolerated dose of an HMG-CoA reductase inhibitor (statin)
 - Subsequent monitoring of LDL levels may help guide therapy with a target of <1.8 mmol/L initially (some evidence for <1.4 mmol/L)

THE
GREATEST
TRICK THE
DEVIL EVER
PULLED WAS
CONVINCING
THE WORLD
HE DIDN'T
EXIST



NB: All listed therapies should be given in the absence of a specific contraindication and/or prior documented intolerance or hypersensitivity

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Contemporary ACS Management

- Initiate and continue ACE inhibitor
- Angiotensin II type I receptor antagonists may be used for ACE Inhibitor intolerant patients
- ACEI or ARB therapy is particularly indicated among those with
 - heart failure,
 - reduced left ventricular systolic function (EF <40%),
 - diabetes,
 - anterior MI or
 - co-existent hypertension



NB: All listed therapies should be given in the absence of a specific contraindication and/or prior documented intolerance or hypersensitivity

Chew D, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. MJA 2016; 205(3): 128-133

Contemporary ACS Management

- Initiate treatment with vasodilatory β -blockers in patients with reduced left ventricular systolic function (EF <40%), or heart failure
- β -blockers may be useful in the post-ACS management of hypertension (but ACEI or ARB preferred) or angina



NB: All listed therapies should be given in the absence of a specific contraindication and/or prior documented intolerance or hypersensitivity

Chew D, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *MJA* 2016; 205(3): 128-133



Contemporary ACS Management

- Refer or recommend attendance and participation in cardiac rehabilitation with a structured secondary prevention service.
 - Individualised preventive interventions and involvement of partners/close family members may be beneficial





Continued Long-Term Risk of Death and Cardiovascular Events in Population Cohorts of MI From Two Australian States

- 19,617 MI patients from WA and SA (mean age 65, males 71%)
- Risk of CV death/MI/stroke was 12% at one year and 25% by five years.
- Increasing risk with age (HR 3.2 in oldest vs youngest group) but no difference between men and women at one year and five years.
- 5 year risk of CV death/MI/stroke in 12-month event-free patients was 17%

Prescription of statins post-ACS

Utilization of and Adherence to Guideline-Recommended Lipid-Lowering Therapy After Acute Coronary Syndrome

TABLE 1 Underutilization of Statin Therapy for Secondary Prevention

First Author (Ref. #)	Registry	Years	N	Statin Prescribed
Rosenson et al. (10)	CMS	2006-2010	8,762	27%*
Maddox et al. (8)	PINNACLE	2008-2012	1,029,633	72%†
Arnold et al. (11)	TRIUMPH	2005-2008	4,271	91%†/23%‡
Arnold et al. (12)	PREMIER + TRIUMPH	2003-2008	6,748	88%§/33%
Javed et al. (13)	GWTG	2005-2009	65,396	89%†/38%*
Ho et al. (32)	KPCO CAD Registry	2000-2005	15,767	86%†
Ho et al. (51)	PREMIER	2003-2004	2,498	80%†



Adherence to statins in clinical trials

Utilization of and Adherence to Guideline-Recommended Lipid-Lowering Therapy After Acute Coronary Syndrome

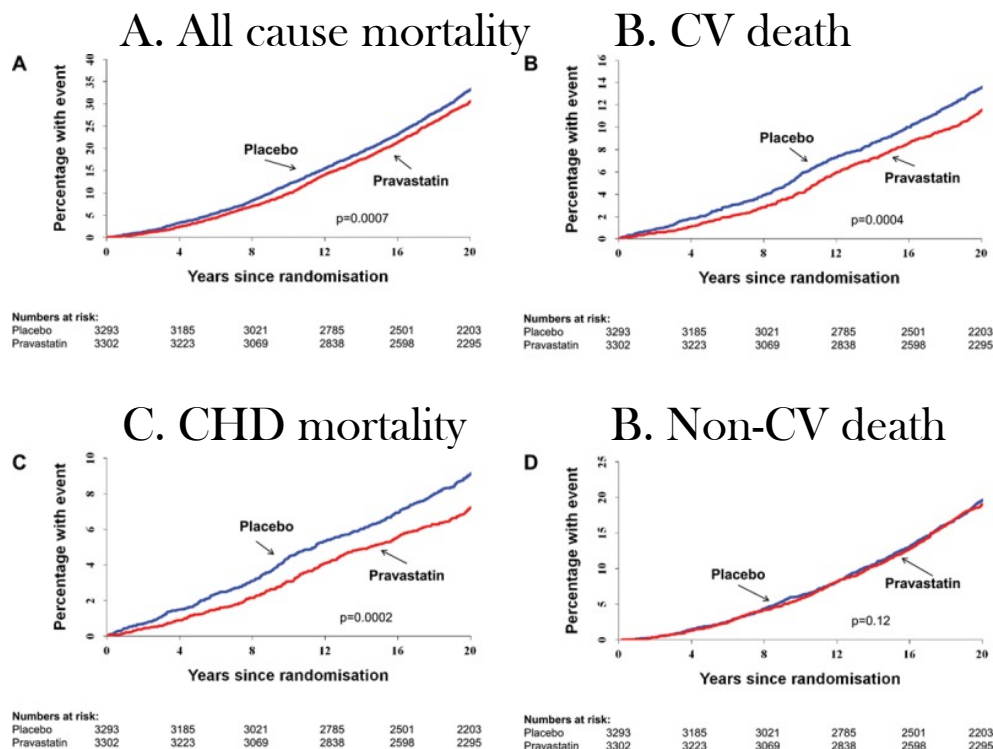
TABLE 2 Rates of Statin Discontinuation in RCTs With Statins Including Patients With Prior ACS

Study (Ref. #)	Year	N	Statin Studied	Discontinuation of Statin Therapy	Follow-Up Duration	Average Annual % Discontinuation
IMPROVE-IT (6)	2014	18,144	Simvastatin	42%	72 months*	7.0%
SEARCH (52)	2010	12,064	Simvastatin	27%	80 months†	4.1%
IDEAL (53)	2005	8,888	Atorvastatin	14%	58 months*	2.9%
TNT (54)	2005	10,001	Atorvastatin	7%‡	59 months*	1%‡
A to Z (19)	2004	4,497	Simvastatin	34%	24 months*	17.2%
PROVE IT-TIMI 22 (14)	2004	4,162	Atorvastatin	30%	24 months†	15.2%
HPS (55)	2002	20,536	Simvastatin	18%	60 months†	3.6%
LIPID (56)	1998	9,014	Pravastatin	19%	73 months†	3.1%
CARE (57)	1996	4,159	Pravastatin	6%	60 months*	1.2%
4S (58)	1994	4,444	Simvastatin	10%	65 months*	1.9%

*Median. †Mean. ‡Discontinuation due to treatment-related adverse events only. All-cause discontinuation was not reported.

4S = Scandinavian Simvastatin Survival Study; ACS = acute coronary syndrome(s); A to Z = Aggrastat to Zocor; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22; RCT = randomized controlled trial; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT = Treating to New Targets.

Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy 20-Year Follow-Up of West of Scotland Coronary Prevention Study



Design:
6595 men were randomized to receive pravastatin 40 mg once daily or placebo for an average of 5 years

All cause mortality reduced by 13%; CV mortality by 21%; CHD mortality by 27% and non-CV mortality was similar



ACS in 2007: Prescription of EBM

- 2007-08 Audit of CCU ACS Patients
- 477 patients with ACS (Mean age 63 y; Men 70%; STEMI 42%; NSTEMI 58%)
- 68% of patients received 5 EBM: aspirin 96%; clopidogrel 90%; beta-blocker 88%; statin 96%; ACE-inhibitor 88%.
- The proportion (%) where indicated treatments were not given for appropriate clinical reasons included: aspirin 3%; clopidogrel 5%; beta-blocker 9%; statin 1% and ACE-inhibitor 4%.
- Thus 'optimal' compliance was actually achieved in 89% of patients.



ACS in 2015: Prescription of EBM

- 2015 Audit of CCU ACS Patients:
- 200 consecutive patients with ACS (Mean age 64 y; Men 70%)
- 76% (n=151) were prescribed Aspirin following triage. The mean (\pm SD) triage to Aspirin time was 41 ± 65 minutes.
- Ticagrelor was the preferred P2Y₁₂ inhibitor (52% on admission and 55% at discharge).
- Aspirin, P2Y₁₂ inhibitors and Statin were prescribed for 92%, 84% and 91% of patients, respectively at discharge.



ACS in 2016: Rural Setting Prescription of EBM

- 2016 Audit of ED suspected ACS Patients in Albany –
- Southern Western Australia that services an area of 39,000 km²
- 82 consecutive patients with suspected ACS (Mean age 61 y; Men 72%)
- 77% (n=63) were prescribed Aspirin following triage.
- Ticagrelor was the preferred P2Y₁₂ inhibitor (58% post-triage).



Long-term adherence

- Adherence to secondary prevention medications following acute coronary syndrome (ACS) is disappointingly low, standing around 40-75% by various estimates.
- Puts patients at higher risk of poor outcomes post-ACS.
- Numerous factors contribute to low adherence including:
 - poor motivation,
 - forgetfulness,
 - lack of education about medications,
 - complicated polypharmacy of ACS regimens,
 - (fear of) adverse side effects and
 - limited practical support.



Long-term adherence

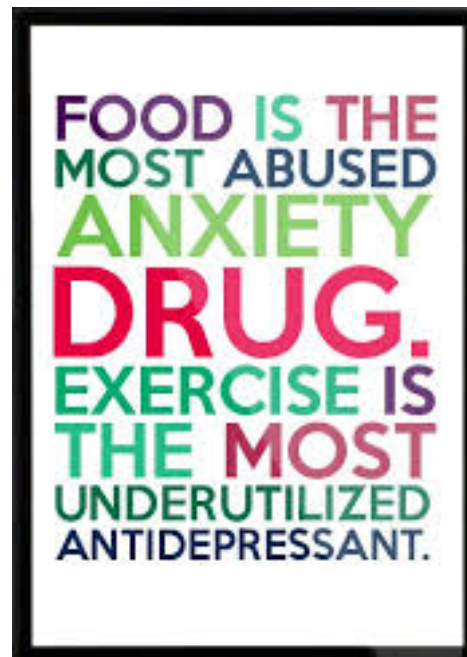
Secondary preventive medication use in a prevalent population-based cohort of acute coronary syndrome survivors.

- 20 years of people alive post-ACS in 2008 in Western Australia (1989-2008)
- 23 642 Participants (women 37%), alive and aged 65-89 years in mid-2008
- Guideline-recommended cardiovascular medications since last ACS hospitalization.

Most commonly prescribed medications:

- Statins - 80% of study cohort
- ACEi/ARBs 71%
- Aspirin or clopidogrel - 59%
- β -blockers - 55%
- Only 52% on 3 or more recommended medications
- Women with ACS were 18% less likely to be dispensed statins (95% CI 0.76-0.88).
- 8% lower rates of recommended medications per year (95% CI 0.92-0.93)

- ✓ Each patient should have a clear individualised plan with focus on the major modifiable risks.
- ✓ The message should be simple, consistent (across visits and health professionals) and acceptable to the patient.





Improving Adherence: SIMPLE?

SIMPLE

- Simplifying regimen characteristics
- Imparting knowledge
- Modifying patient beliefs
- Patient and family communication
- Leaving out the bias
- Evaluating adherence



Improving Adherence: SIMPLE

- Simplifying regimen characteristics
 - Adjusting timing, frequency, amount, and dosage
 - Matching to patients' activities of daily living
 - Using adherence aids, such as medication boxes and alarms



Improving Adherence: SIMPLE

- Imparting knowledge
 - Discussion with physician, nurse, or pharmacist
 - Distribution of written information or pamphlets
 - Accessing health-education information on the Web



Improving Adherence: SIMPLE

- Modifying patient beliefs
 - Assessing perceived susceptibility, severity, benefit, and barriers
 - Rewarding, tailoring, and contingency contracting



Improving Adherence: SIMPLE

- Patient and family communication
 - Active listening and providing clear, direct messages
 - Including patients in decisions
 - Sending reminders via mail, text, email, or telephone
 - Convenience of care, scheduled appointment
 - Home visits, family support, counselling



Improving Adherence: SIMPLE

- Leaving out the bias
 - ☐ Tailoring the education to patients' level of understanding
 - ☐ Acknowledge cultural values



Improving Adherence: SIMPLE

- Evaluating adherence.
 - ❖ Self-reports (most commonly used)
 - ❖ Pill counting, measuring serum or urine drug levels



What else do we need to do?

- Increase resources for targeted and general preventive strategies
 - Targeted: diabetes and metabolic syndrome
 - General: school physical activity & dietary guides
- More aggressively treat high risk subjects
 - Be prepared to down-titrate therapy in selected patients
- Avoid and discourage therapies that have no evidence or the current evidence suggests no benefit
 - Antioxidant vitamins and folate
 - Hormone replacement therapy
 - Chelation therapy
 - DHEA, testosterone



I ride, therefore I am

(but I won't judge you if you prefer to walk, jog, swim, play football...)



- Physical activity may be the carrier of change and of maintenance of healthy behaviours in the long-term
- It may have positive consequences on self-confidence and esteem, socialization, return to work, and normalization of daily life activities



Questions



Smith's Beach, WA