University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Yudi, MB;Farouque, O;Andrianopoulos, N;Ajani, AE;Brennan, A;Murphy, AC;Lefkovits, J;Reid, CM;Oqueli, E;Sebastian, M;Duffy, SJ;Clark, DJ

Title:
Prognostic significance of suboptimal secondary prevention pharmacotherapy after acute coronary syndromes

Date:
2021-03-01

Citation:
Yudi, M. B., Farouque, O., Andrianopoulos, N., Ajani, A. E., Brennan, A., Murphy, A. C., Lefkovits, J., Reid, C. M., Oqueli, E., Sebastian, M., Duffy, S. J. & Clark, D. J. (2021). Prognostic significance of suboptimal secondary prevention pharmacotherapy after acute coronary syndromes. Internal Medicine Journal, 51 (3), pp.366-374. https://doi.org/10.1111/imj.14750.

Persistent Link:
https://hdl.handle.net/11343/298284

Murphy Alexandra (Orcid ID: 0000-0002-4248-7537)
Duffy Stephen (Orcid ID: 0000-0002-4518-5948)

Prognostic Significance of Suboptimal Secondary Prevention Pharmacotherapy After Acute Coronary Syndromes

Matias B Yudi, MBBS,[1,2*] Omar Farouque MBBS, PhD,[1,2] Nick Andrianopoulos, MBBS, MBiostat,[3] Andrew E Ajani, MBBS, MD,[2,3,4] Angela Brennan, RN,[3] Alexandra C Murphy, MBBS,[1,2] Jeffrey Lefkovits, MBBS,[3,4] Christopher M Reid, BA, MSc, PhD,[3,5] Ernesto Oqueli, MBBS,[6] Martin Sebastian, MBBS,[7] Stephen J Duffy, MBBS, PhD,[3,8] David J Clark, MBBS, DMedSci,[1,2*] on behalf of the Melbourne Interventional Group.

[1]Department of Cardiology, Austin Health, Melbourne, Australia, [2]Department of Medicine, University of Melbourne, Melbourne, Australia, [3]Centre of Cardiovascular Research and Education in Therapeutics (CCRE), Monash University, Melbourne, Australia, [4]Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia, [5]School of Public Health, Curtin University, Perth, Western Australia, [6]Department of Cardiology, Ballarat Base Hospital, Ballarat, Australia [7]Department of Cardiology, Barwon Health, Geelong, Australia [8]Department of Cardiology, Alfred Health, Melbourne, Australia.

[*]Corresponding author:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.14750

This article is protected by copyright. All rights reserved.

Author Manuscript

Dr Matias Yudi

Structural and Interventional Cardiologist

Austin Health

145 Studley Road

Heidelberg, Victoria 3084

Phone: 03 9496 5527

Fax: 03 9459 0971

Email: matias.yudi@austin.org.au

Word Count: Manuscript: 2,851, Abstract: 250

Melbourne Interventional Group Investigators

MIG Data Management Centre, CCRE, Monash University:

Professor Chris Reid, Dr Nick Andrianopoulos, Ms Angela Brennan, Ms Vibhasha Chand, Dr Diem Dinh.

MIG Steering Committee:

Professor Chris Reid, A/Professor Andrew Ajani, Dr Stephen Duffy, Dr David Clark, Professor Gishel New, Dr Melanie Freeman, Dr Chin Hiew, Dr Nick Andrianopoulos, Dr Ernesto Oqueli, Ms Angela Brennan.

The following Investigators, Data Managers and Institutions participated in the MIG Database:

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

Alfred Hospital: SJ Duffy, JA Shaw, A Walton, A Dart, A Broughton, J Federman, C Keighley, C Hengel, KH Peter, D Stub, W Chan, J O'Brien, L Selkrig, K Rankin, R Vandernet, R Huntington, S Pally;

Austin Hospital: DJ Clark, O Farouque, M Horrigan, J Johns, L Oliver, J Brennan, R Chan, G Proimos, T Dortimer, B Chan, V Nadurata, R Huq, D Fernando, A Al-Fiadh, M Yudi, H Sugumar, J Ramchand, H Han. S Picardo, L Brown;

Ballarat Base Hospital: E Oqueli, C Hengel, A Sharma, B Zhu, N Ryan, T Harrison;

Box Hill Hospital: G New, L Roberts, M Freeman, M Rowe, G Proimos, Y Cheong, C Goods, D Fernando, A Teh, S Parfrey, J Ramzy, A Koshy, P Venkataraman, D Flannery;

Geelong Hospital: C Hiew, M Sebastian, T Yip, Michael Mok, C Jaworski, A Hutchinson, C Cimenkaya, P Ngu, B Khialani, H Salehi, M Turner, J Dyson, B McDonald, D Van Den Nouwelant, K Halliburton;

Monash University: H Krum, C Reid, N Andrianopoulos, AL Brennan, V Chand, D Dinh, BP Yan;

Royal Melbourne Hospital: AE Ajani, R Warren, D Eccleston, J Lefkovits, R Iyer, R Gurvitch, W Wilson, M Brooks, S Biswas, J Yeoh.

Acknowledgements:

The Melbourne Interventional Group acknowledges unrestricted educational grant funding from: Abbott Vascular, Astra-Zeneca, Medtronic, MSD, Pfizer,

This article is protected by copyright. All rights reserved.

Servier, and The Medicines Company. These companies do not have access to the data, and do not have the right to review manuscripts before publication.
Dr. Yudi is supported by a combined National Health and Medical Research Council Postgraduate Scholarship (APP 1115163) and a National Heart Foundation Health Professional Scholarship (Award ID 101130).
Dr. Duffy's & Professor Reid's work is funded by National Health and Medical Research Council of Australia Grants.

The Melbourne Interventional Group acknowledges and thanks all patients who have been involved in the registry.

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

ABSTRACT

BACKGROUND: Optimal secondary prevention pharmacotherapy is the cornerstone of post-acute coronary syndrome (ACS) management. The prognostic impact of not receiving five guideline-recommended therapies is poorly described.

AIM: We aim to ascertain the prognostic significance of suboptimal pharmacotherapy in ACS survivors.

METHODS: Consecutive patients with ACS from the Melbourne Interventional Group registry who were alive at 30-days following their index percutaneous coronary intervention were included. Patients were divided into three categories based on the number of secondary prevention medications prescribed. The optimal medical therapy (OMT), near-optimal medical therapy (NMT), suboptimal medical therapy (SMT) groups were prescribed 5, 4 and ≤3 medications, respectively. Primary endpoint was long-term mortality. Cox-proportional hazard modelling was undertaken to assess independent predictors of survival.

RESULTS: Of the 9,375 patients included, 5,678 (60.6%) received OMT, 2,903 (31.0%) received NMT and 794 (8.5%) received SMT. Patients receiving SMT were older, more likely to be female and had higher burden of co-morbidities (renal impairment, congestive heart failure, diabetes, peripheral vascular disease; $p<0.01$ for all). SMT was associated with higher long-term mortality at 3.9±2.2 years when compared to NMT and OMT (16.8% vs. 10.5% vs. 8.2%,

This article is protected by copyright. All rights reserved.

p<0.001). Compared to OMT, SMT was an independent predictor of long-term mortality (HR 1.62, 95% CI 1.30-2.02, p<0.01) while NMT was associated with a clinically significant 14% mortality hazard (HR 1.14, 95% CI 0.97-1.34, p=0.11).

CONCLUSIONS: There is a graded long-term hazard associated with not receiving OMT after an ACS. Improvements in secondary prevention pharmacotherapy models of care are warranted to further decrease long-term mortality.

Keywords: secondary prevention; survival; acute coronary syndromes; percutaneous coronary intervention.

INTRODUCTION

Mortality from coronary heart disease has decreased substantially in the past three decades with a significant portion of the decline attributed to evidence-based therapies in the management of acute coronary syndrome (ACS).[1-3] Thus optimal secondary prevention pharmacotherapy has become an integral component of the management of patients who survive from ACS.

National and international guidelines recommend the prescription of five cardio-protective medications post ACS, namely aspirin, P2Y12 inhibitor, statins, beta-blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers. [4-7] However, short- and long-term adherence to secondary

This article is protected by copyright. All rights reserved.

Author Manuscript

prevention pharmacotherapy is suboptimal and underutilization is associated with higher risk of mortality.[8-17] Furthermore, studies assessing the synergistic effect of medical therapy post ACS have primarily focused on four medications or less,[9, 12-15, 17, 18] often omitting the effect of dual antiplatelet therapy, despite proven efficacy.[19, 20] Thus, the long-term hazard associated with early suboptimal medical therapy in patients who survived an ACS has not been fully explored.

Consequently, utilizing an established and well-recognized interventional cardiology registry, we aimed to assess the prognostic significance of receiving near optimal medical therapy (4 medications) and suboptimal medical therapy (≤3 medications) post ACS in comparison to optimal medical therapy (5 medications).

METHODS

The study cohort included consecutive patients enrolled in the Melbourne Interventional Group (MIG) registry who underwent percutaneous coronary intervention for management of their index acute coronary syndrome between Jan 2005 and November 2013.

The MIG registry is a multicentre PCI registry and has been previously described in detail.[21] Briefly, demographic, clinical, procedural and in-hospital

This article is protected by copyright. All rights reserved.

Author Manuscript

outcome data are prospectively recorded on case-report forms using standardized definitions for all fields with follow up performed at 30 days and 12 months via telephone and record review. Medication history is provided by patient self-reporting.[22]

The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics; an independent research body within the School of Public Health and Preventive Medicine at Monash University (Melbourne, Australia). An audit of a number of verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically.[23] In the most recent audit, 27 fields were assessed with data accuracy of 98%. This compares favorably to audits from other large registries.[24] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. To "opt-out" means consent is presumed unless the patient "opts out". All participating sites give each patient a "Patient Information Sheet". If a patient informs a staff member that they do not wish to participate, the patient's data is not collected.

Patients who underwent PCI for acute coronary syndrome (ACS) and survived to 30-days were included. ACS encompasses the spectrum of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. STEMI was defined as ECG changes (new ST-segment elevation at the J-point or development of Q-waves in two or more contiguous leads) with confirmed myocardial necrosis (elevation in troponin T

Author Manuscript

This article is protected by copyright. All rights reserved.

or I or creatine-kinase MB (CK-MB) on at least one occasion within 24 hours from index event). NSTEMI was defined as biomarker elevation consistent with myocardial necrosis and one of: either ST-segment depression or T-wave abnormality on ECG; or ischaemic symptoms. Unstable angina is defined by clinical history suggestive of progressive, unstable ischaemic symptoms without cardiac biomarker elevation.

Acute management of all patients including interventional strategy, stent selection and antithrombotic therapy were left at the discretion of the operator in all procedures. Optimal secondary prevention pharmacotherapy was encouraged according to guidelines [25, 26]. No records were made of contraindications to medications or decisions regarding use/omission of particular guideline-directed therapies.

Patients were divided into three groups based on their prescribed secondary prevention pharmacotherapy at 30-days post PCI for ACS. Those prescribed the five guideline-directed secondary prevention medications (aspirin, P2Y12 inhibitor, statin, beta-blocker, angiotensin converting enzyme inhibitor [ACE-I]/angiotensin receptor blocker [ARB]) were included in the optimal medical therapy (OMT) group. Those who had 4 medications prescribed were included in the near-optimal medical therapy (NMT) group while those prescribed ≤ 3 medications were in the suboptimal medical therapy (SMT) group.

The primary outcome was long-term all-cause mortality. Long-term

Author Manuscript

This article is protected by copyright. All rights reserved.

mortality data were obtained by linkage to the Australian National Death Index (NDI), as previously reported. The Australian NDI is a database housed at the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. Data are obtained from the registries of births, deaths, and marriages in each state and territory. The following variables for each deceased patient were identified: name, date of birth (or estimated year of birth), age at death, gender, date of death, state/territory of registration, and registration number. Successful matching of patients through this linkage process was achieved in 99.4% of patients in the MIG registry.

Secondary outcomes were 12-month mortality, myocardial infarction, stroke and major adverse cardiovascular events (MACE). MI was defined as: an increase in creatine kinase or creatine kinase-MB ≥3 times the upper limit of normal; and/or a significant ST-segment change, development of new Q waves in ≥2 contiguous electrocardiographic leads, or new left branch bundle block pattern in the context of new clinical symptoms.

Continuous variables are expressed as mean ± SD, and categorical data are expressed as numbers/percentages. Continuous variables were compared using Kruskal-Wallis equality-of-populations rank test. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. Variables were tested for linear trends across the years 2005-2013 using Stata's *nptrend* command. This is a nonparametric test for trend across ordered groups which is an extension of the Wilcoxon rank-sum test. Cumulative incidence of

Author Manuscript

This article is protected by copyright. All rights reserved.

survival was estimated by the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups. A cox-proportional hazard model was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for survival. Univariate variables with $p<0.10$ were included for stepwise removal for the final multivariate model. The variables considered were: medication status, age, sex, eGFR, hypertension, diabetes, hypercholesterolemia, family history of coronary disease, previous MI, previous PCI, previous CABG, heart failure, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction, multi-vessel CAD, angina type, chronic lung disease, cardiogenic shock, glycoprotein IIb/IIIa use, drug-eluting stent use and treated left main lesion.

All statistical analyses were performed using Stata 13.1, StataCorp LP, College Station, TX, USA. P-values < 0.05 were considered to be statistically significant.

Author Manuscript

This article is protected by copyright. All rights reserved.

RESULTS

Of the 9,375 patients who were alive 30-days after their index ACS, 5,678 (60.6%) received OMT, 2,903 (30.9%) received NMT and 794 (8.5%) received SMT. There has been a significant change in the percentage of patients receiving OMT over the 9-year period from 2005-2013; there was a gradual increase from 2005 to 2011 followed by a decline in 2012 and 2013 (p for trend <0.001, Figure 1).

Secondary prevention pharmacotherapy at 12-month stratified by their medical therapy status at 30-days is shown (Figure 2). Only 59% of patients originally on OMT remained in that category by 12-months. Of the patients with NMT, 14% achieved OMT but 27% regressed to SMT. Three-quarter of patients on SMT at 30-days remained in that category at 12-months.

Baseline clinical characteristics stratified by medical therapy at 30-days are shown (Table 1). Those patients receiving SMT were older, more likely to be female and had higher rates of diabetes mellitus, congestive heart failure, peripheral vascular disease, stroke and chronic lung disease (p-value for all <0.01). Patients receiving SMT were also more likely to have renal dysfunction and impaired left ventricular ejection fractions (p-value <0.01).

Clinical presentation, angiographic characteristics and in-hospital outcomes are evident in Table 2. OMT was most likely to be prescribed after STEMI. There was a step-wise increase in length of stay between groups (OMT 4.7±4.2, NMT 5.2±5.6, SMT 6.1±7.0 days, p<0.001).

Author Manuscript

This article is protected by copyright. All rights reserved.

Full description of medical therapy at 30-days is shown in Table 3. There is a significant decrease in prescription of all classes of medication from NMT to SMT. Interestingly, SMT had higher rates of warfarin and ezetimibe use.

At mean follow-up 3.9±2.2 years, there was an unadjusted incrementally higher mortality rate based on medical therapy (OMT 8.2% vs. NMT 10.5% vs. SMT 16.8%, p<0.001; Table 4). The same significant trend was evident at 12-months in mortality, target-vessel revascularisation and MACE, but not in myocardial infarction or stroke.

Univariate analysis revealed that patients receiving NMT (HR 1.46, 95% CI 1.27-1.68, p<0.001) and SMT (HR 2.58, 95% CI 2.12-3.13, p<0.001) had a greater risk of mortality when compared to those on OMT. However, Cox proportional hazard modelling found that SMT was an independent predictor of long-term mortality (HR 1.62, 95% CI 1.30-2.02, p<0.001) while NMT was associated with a clinically significant 14% higher risk of death, although not statistically significant (HR 1.14, CI 0.97-1.34, p=0.11). All independent predictors of long-term mortality are shown in Figure 3. Figure 4 shows Kaplan-Meier survival curves between the three groups.

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

DISCUSSION

In a contemporary cohort of patients with ACS who were treated with PCI and survived to 30-days, optimal secondary prevention pharmacotherapy was prescribed in only 60% of patients. Patients with higher risk features including older age, renal impairment, congestive heart failure, diabetes mellitus, chronic lung disease and peripheral vascular disease were more likely to receive suboptimal medical therapy. It is notable that an incremental relationship between medication use and long-term mortality exists with an alarming decline in OMT prescription over recent years which warrants further research. When compared to optimal medical therapy, suboptimal therapy was an independent predictor of long-term mortality and near optimal therapy was associated with a 14% higher risk of death, although not statistically significant. These data suggest improvements in models of care are warranted to further decrease long-term cardiovascular mortality.

Secondary prevention pharmacotherapy is the cornerstone of management of ACS after hospital discharge.[4-7] Consistent with trends worldwide, we have shown a significant increase in the proportion of patients receiving five guideline recommended therapies over a 9 year period.[3, 16, 27, 28] However, there is still significant room for improvement with overall only 60% of patients optimally managed early post ACS hospitalization. An important observation is the trend reversal evident in 2012-2013 with a decrease in the proportion of patients receiving optimal medical therapy. The reasons for this

This article is protected by copyright. All rights reserved.

are not immediately apparent from our data though it could be attributed to both patient and physician factors.[29, 30] These may include poor understanding of the benefits of the medication, prescription of overly complex regimen, cognitive impairment or the presence of psychological problems.

The in-hospital and early post-ACS period is crucial for optimization of medical therapy. Patients who are not on appropriate medications at 30-days are unlikely to be started on them later.[11, 13] For example, one study showed that only 10% of patients start taking beta-blockers or ACE inhibitors after this period. [13] This is consistent with our study as only 6% of patients on suboptimal medical therapy at 30-days were optimally treated by 12 months. The importance of early optimization of therapy is highlighted by its association with improved long-term term adherence[13] and lower 12-month mortality.[11] The suboptimal medical therapy cohort had longer hospital length of stay and the extra time may provide an opportunity to introduce missing evidence-based medications. As demonstrated in the CONCORDANCE registry, failure to discharge patients on indicated therapies is the most important modifiable predictor of adherence failure 6-months after an ACS. As such, ongoing education of primary care physicians and cardiologists is imperative to ensure patients are not disadvantaged.[31]

Patients with adverse prognostic features theoretically have the most to gain from optimal medical therapy. However, a paradox is evident where patients with higher risk features are more likely to receive suboptimal medical

This article is protected by copyright. All rights reserved.

Author Manuscript

therapy. This is consistent with previous studies.[16, 27, 32] In our study, ACE inhibitors/angiotensin receptor blockers were the class of drug most likely to be omitted. Although their indication is strongest in those with diabetes mellitus, congestive heart failure and renal impairment, patients with these co-morbidities were less likely to receive them. There are likely to be relative contraindications to their use, such as an eGFR <30ml/min/1.73m^2, however it doesn't not explain why nearly 70% of patients in the SMT cohort were not on an ACE inhibitor or ARB. Bagnall *et al* showed physicians do not prescribe evidence-based therapies due to subjective underestimation of patient's risk profiles as well as oversights in care delivery.[32] Thus, objective risk assessments and checklists with documented reasons for deviation from guidelines and innovative secondary prevention programs may improve care.[33]

Our study highlights specific treatment gaps that warrant special attention. Firstly, there is still a significant number of patients who are not on dual antiplatelet agents at 30-days despite the entire cohort having PCI. Dual-antiplatelet therapy for 12 months is recommended for ACS irrespective of interventional treatment strategy.[19, 20, 25] Only in the small subset of ACS patients who also require anticoagulation is dual antiplatelet therapy hazardous.[34] Secondly, in spite of patients in the SMT cohort having the highest rates of non-coronary vascular disease, only 70% received statin therapy. In the recent IMPROVE-IT trial only 10% of patients discontinued their lipid lowering medications due to adverse events at median follow-up of six years.[35] As

Author Manuscript

This article is protected by copyright. All rights reserved.

adherence to statin therapy has been consistently associated with improved survival, it is of paramount importance that a greater proportion of ACS survivors receive statin therapy.[16, 17] Thirdly, beta-blocker use was suboptimal though our rate was consistent with other studies.[14, 36] Although contraindications to specific medications were not recorded in our study, we noted a significant number of patients with chronic lung disease did not receive beta-blocker therapy. A recent large-scale study has demonstrated the safety and potential mortality benefit of beta blocker use in patients with COPD. [37] These results advocate for change in prescribing behavior, and widespread provider education is required to enact this change.

Optimal medical therapy should be a lifelong pursuit in patients with known CAD and given their proven benefit in reducing cardiovascular mortality. [1-3] However, long-term medication adherence remains poor for a variety of complex reasons and is associated with worse outcomes.[12, 16, 17, 29, 30] Even when there is no out of pocket expense for medications, less than 50% of patients are fully adherent.[36] The "healthy adherer" phenomenon has been debunked in cardiology as survival benefit is actually associated with class-specific medication adherence rather than overall healthy behavior of compliant patients.[17] In the future, the concept of a secondary prevention polypill may play a role given all secondary prevention therapies, apart from ticagrelor, are now generic and relatively inexpensive.[39]

Author Manuscript

This article is protected by copyright. All rights reserved.

The main advantages of our study are the inclusion of the 5 guideline recommended medications and our long-term follow-up. We have clearly shown an incremental higher risk of long-term mortality when patients receive 4 or ≤3 medications at 30 days. Thus optimization of early post ACS care can translate to improved long-term outcomes. Previous studies have focused solely on the prognostic benefit of 4 or less secondary prevention therapies, usually omitting the importance of dual antiplatelet therapy.[9, 12-15, 17, 18] Dual antiplatelet therapy for 12 months is standard of ACS care and extending treatment even beyond a year has been associated with improved cardiovascular outcomes.[40, 41]

Limitations to our study warrant attention. Firstly, we analyzed medication adherence by simply asking patients what medications they are taking as registry follow up is performed via phone calls at 30 days and 12-months. This approach is open to bias and possible overestimation. Secondly, we do not record indications nor contraindications to medications thus it is feasible patients with NMT or SMT had a legitimate reason for not receiving guideline-directed therapy. For example, the efficacy of beta-blocker use has been questioned in ACS patients without heart failure or LV dysfunction.[42] In regards to ACEi/ARB prescription, modern guidelines have broadened the indication for use to include patients with diabetes, anterior myocardial infarction or co-existent hypertension in addition to the traditional recommendation for patients with heart failure. Notably, of the patients studied 62% had hypertension, 22% had diabetes and 36% presented with a LVEF <45% and as such a large

This article is protected by copyright. All rights reserved.

Author Manuscript

proportion of the population would have an indication for ACEi/ARB prescription. Thirdly, we did not report or assess the impact of medication doses on outcomes. Fourthly, we were unable to differentiate between non-adherence and nonprescription; this is essential in order to implement strategies to rectify the treatment gaps identified. Lastly, inherent to observational studies there are likely to be factors, either unmeasured or unaccounted for, that influence the outcome.

ACKNOWLEDGEMENTS

The Melbourne Interventional Group acknowledges unrestricted educational grant funding from: Abbott Vascular, Astra-Zeneca, Medtronic, MSD, Pfizer, Servier, and The Medicines Company. These companies do not have access to the data, and do not have the right to review manuscripts before publication.

Dr. Yudi is supported by a combined National Health and Medical Research Council Postgraduate Scholarship (APP 1115163) and a National Heart Foundation Health Professional Scholarship (Award ID 101130).

Dr. Duffy's & Professor Reid's work is funded by National Health and Medical Research Council of Australia Grants.

The Melbourne Interventional Group acknowledges and thanks all patients who have been involved in the registry.

CONCLUSION

This article is protected by copyright. All rights reserved.

Author Manuscript

There is a graded long-term hazard associated with not receiving optimal medical therapy after an ACS, particularly evident in patients prescribed ≤3 medications. Improvements in secondary prevention pharmacotherapy models of care are warranted to further decrease long-term mortality.

Author Manuscript

This article is protected by copyright. All rights reserved.

REFERENCES

1 Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE*, et al.* Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *The New England journal of medicine*. 2007; **356**: 2388-98.
2 Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G*, et al.* Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. *Jama*. 2010; **303**: 1841-7.
3 Setoguchi S, Glynn RJ, Avorn J, Mittleman MA, Levin R, Winkelmayer WC. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *Journal of the American College of Cardiology*. 2008; **51**: 1247-54.
4 Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F*, et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016; **37**: 267-315.
5 Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr.*, et al.* 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; **130**: 2354-94.
6 Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA*, et al.* AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *Journal of the American College of Cardiology*. 2011; **58**: 2432-46.
7 O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA*, et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013; **127**: 529-55.
8 Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *The American journal of medicine*. 2012; **125**: 882-7 e1.
9 Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation*. 2008; **117**: 1028-36.

Author Manuscript

This article is protected by copyright. All rights reserved.

10 Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009; **119**: 3028-35.
11 Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ*, et al.* Impact of medication therapy discontinuation on mortality after myocardial infarction. *Archives of internal medicine*. 2006; **166**: 1842-7.
12 Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L*, et al.* Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *American heart journal*. 2014; **167**: 51-58 e5.
13 Gislason GH, Rasmussen JN, Abildstrom SZ, Gadsboll N, Buch P, Friberg J*, et al.* Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *European heart journal*. 2006; **27**: 1153-8.
14 Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN*, et al.* Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *American heart journal*. 2008; **155**: 772-9.
15 Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation*. 2004; **109**: 745-9.
16 Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER*, et al.* Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 2006; **113**: 203-12.
17 Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *Jama*. 2007; **297**: 177-86.
18 Rogers AM, Ramanath VS, Grzybowski M, Riba AL, Jani SM, Mehta R*, et al.* The association between guideline-based treatment instructions at the point of discharge and lower 1-year mortality in Medicare patients after acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) initiative in Michigan. *American heart journal*. 2007; **154**: 461-9.
19 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C*, et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2009; **361**: 1045-57.
20 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S*, et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2007; **357**: 2001-15.
21 Ajani AE, Szto G, Duffy SJ, Eccleston D, Clark DJ, Lefkovits J*, et al.* The foundation and launch of the Melbourne Interventional Group: a collaborative interventional cardiology project. *Heart, lung & circulation*. 2006; **15**: 44-7.
22 Chan W, Clark DJ, Ajani AE, Yap CH, Andrianopoulos N, Brennan AL*, et al.* Progress towards a National Cardiac Procedure Database--development of the

Author Manuscript

This article is protected by copyright. All rights reserved.

Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and Melbourne Interventional Group (MIG) registries. *Heart, lung & circulation*. 2011; **20**: 10-8.
23 Andrianopoulos N, Dinh D, Duffy SJ, Clark DJ, Brennan AL, Chan W*, et al.* Quality control activities associated with registries in interventional cardiology and surgery. *Heart, lung & circulation*. 2011; **20**: 180-6.
24 Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L*, et al.* Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *The New England journal of medicine*. 2007; **356**: 1009-19.
25 Chew DP, Scott IA, Cullen L, French JK, Briffa TG, Tideman PA*, et al.* National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ*. 2016; **25**: 895-951.
26 Davidson P, Stocks N, Aggarwal A, Waddell J, Lee R. Reducing Risk in Heart Disease—An Updated Heart Foundation Guide to Secondary Prevention of Coronary Heart Disease. *Heart, Lung and Circulation*. 2012; **21**: S49.
27 Somma KA, Bhatt DL, Fonarow GC, Cannon CP, Cox M, Laskey W*, et al.* Guideline adherence after ST-segment elevation versus non-ST segment elevation myocardial infarction. *Circulation Cardiovascular quality and outcomes*. 2012; **5**: 654-61.
28 Peterson ED, Shah BR, Parsons L, Pollack CV, Jr., French WJ, Canto JG*, et al.* Trends in quality of care for patients with acute myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *American heart journal*. 2008; **156**: 1045-55.
29 Desai NR, Choudhry NK. Impediments to adherence to post myocardial infarction medications. *Curr Cardiol Rep*. 2013; **15**: 322.
30 Osterberg L, Blaschke T. Adherence to medication. *The New England journal of medicine*. 2005; **353**: 487-97.
31 Brieger D, Chow C, Gullick J, Hyun K, D'Souza M, Briffa T*, et al.* Improving patient adherence to secondary prevention medications 6 months after an acute coronary syndrome: observational cohort study. *Intern Med J*. 2018; **48**: 541-49.
32 Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C*, et al.* Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circulation Cardiovascular quality and outcomes*. 2010; **3**: 530-7.
33 Yudi MB, Clark DJ, Tsang D, Jelinek M, Kalten K, Joshi S*, et al.* SMARTphone-based, early cardiac REHABilitation in patients with acute coronary syndromes [SMART-REHAB Trial]: a randomized controlled trial protocol. *BMC cardiovascular disorders*. 2016; **16**: 170.
34 Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP*, et al.* Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013; **381**: 1107-15.

Author Manuscript

This article is protected by copyright. All rights reserved.

35 Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P*, et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *The New England journal of medicine*. 2015; **372**: 2387-97.
36 Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M*, et al.* Full coverage for preventive medications after myocardial infarction. *The New England journal of medicine*. 2011; **365**: 2088-97.
37 Nielsen AO, Pedersen L, Sode BF, Dahl M. beta-Blocker Therapy and Risk of Chronic Obstructive Pulmonary Disease - A Danish Nationwide Study of 1.3 Million Individuals. *EClinicalMedicine*. 2019; **7**: 21-26.
38 Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *Bmj*. 2011; **342**: d2549.
39 Hedner T, Kjeldsen SE, Narkiewicz K, Oparil S. The polypill: an emerging treatment alternative for secondary prevention of cardiovascular disease. *Blood Press*. 2016; **25**: 276-9.
40 Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC*, et al.* Long-term use of ticagrelor in patients with prior myocardial infarction. *The New England journal of medicine*. 2015; **372**: 1791-800.
41 Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG*, et al.* Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *The New England journal of medicine*. 2014; **371**: 2155-66.
42 Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H*, et al.* beta-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. *Journal of the American College of Cardiology*. 2017; **69**: 2710-20.

Author Manuscript

This article is protected by copyright. All rights reserved.

Figure 1. Trends in Secondary Prevention Pharmacotherapy (p-value for trend <0.001)

Figure 2. Secondary Prevention Pharmacotherapy at 12-months Stratified by Medication Status at 30-days (Includes only patients alive at 12 months with full medication history)

Figure 3. Cox Proportional Hazard Model

Figure 4. Kaplan Meier Survival Curve

Author Manuscript

This article is protected by copyright. All rights reserved.

Table 1. Baseline Clinical Characteristics Stratified by Medication Status at 30-days

	Optimal Medical Therapy N = 5,678	Near-Optimal Medical Therapy N = 2,903	Suboptimal Medical Therapy N = 794	p-value
Age (years)	63.1±12.3	64.2±12.5	65.6±13.0	<0.001
Age >75	1,166(20.5)	712 (24.5)	228 (28.7)	<0.001
Male	4,365 (76.9)	2,201 (75.8)	563 (70.9)	0.001
Body Mass Index	28.5±5.3	28.0±5.1	27.7±5.5	<0.001
Hypertension	3,539 (62.3)	1,791 (61.7)	489 (61.6)	0.82
Hypercholesterolaemia	3,619 (63.8)	1,874 (64.6)	500 (63.1)	0.65
Diabetes Mellitus	1,243 (21.9)	652 (22.5)	209 (26.3)	0.02
Current Smoker	1,784 (31.4)	843 (29.0)	206 (25.9)	0.001
Family History of Coronary Artery Disease	2,221 (39.3)	1,125 (39.1)	228 (36.7)	0.37
Previous Myocardial Infarction	1,219 (19.9)	616 (21.2)	174 (21.9)	0.20
Previous Stenting	1032 (18.2)	540 (18.6)	147 (18.5)	0.26
Previous Bypass Surgery	343 (6.0)	220 (7.6)	46 (5.8)	0.02
Heart Failure	147 (2.6)	111 (3.8)	34 (4.3)	0.001
Peripheral vascular Disease	280 (4.9)	186 (6.4)	77 (9.7)	0.001
Stroke	298 (5.3)	198 (6.8)	61 (7.7)	0.001
Chronic Lung Disease	469 (8.3)	369 (12.8)	132 (16.7)	0.001
eGFR ≥ 60	4,449 (80.9)	2,205 (77.6)	561 (72.3)	0.001
eGFR 30-59	945 (17.2)	543 (19.1)	171 (22.0)	0.001
eGFR < 30	106 (1.9)	93 (3.3)	44 (5.7)	0.001

Author Manuscript

This article is protected by copyright. All rights reserved.

Ejection Fraction >45%	3,576 (69.2)	1,931 (74.3)	518 (74.9)	0.001

Data are expressed as mean ± standard deviation or count (percentage). eGFR = estimate glomerular filtration rate.

Author Manuscript

This article is protected by copyright. All rights reserved.

Table 2. ACS Presentation, Angiographic Characteristics and Acute Outcomes

	Optimal Medical Therapy N = 5,678	Near-Optimal Medical Therapy N = 2,903	Suboptimal Medical Therapy N = 794	p-value
ST-elevation Myocardial Infarction	2,833 (49.9)	1,144 (39.4)	282 (35.5)	< 0.001
Non-ST-elevation Myocardial Infarction	2,181 (38.4)	1,259 (43.4)	357 (45.0)	< 0.001
Unstable Angina	664 (11.7)	500 (17.2)	155 (19.5)	< 0.001
Multivessel Coronary Artery Disease	3,176 (56.1)	1,628 (56.2)	455 (57.4)	0.78
Left main disease	49 (0.9)	25 (0.9)	9 (1.1)	0.74
No stent deployed	226 (3.4)	185 (6.4)	103 (13.0)	<0.001
Bare Metal Stent	3,160 (55.7)	1,453 (50.1)	391 (49.2)	<0.001
Drug Eluting Stent	2,292 (40.4)	1,265 (43.6)	300 (37.8)	<0.001
Number of stents inserted	1.2±0.6	1.2±0.6	1.1±0.6	<0.001
Successful Procedure	5,678 (100)	2,902 (100)	793 (100)	0.06
Unplanned Bypass Surgery	9 (0.2)	31 (1.1)	41 (5.2)	0.001
Cardiogenic shock	104 (1.8)	64 (2.2)	23 (2.9)	0.10
Arrhythmia	503 (8.9)	268 (9.2)	88 (11.1)	0.13
New Renal impairment	31 (0.6)	42 (1.5)	10 (1.3)	<0.001
New Heart Failure	209 (3.7)	122 (4.2)	29 (3.7)	0.47

Author Manuscript

This article is protected by copyright. All rights reserved.

Length of Hospital Stay (days)	4.7±4.2	5.1±5.6	6.1±7.0	0.01

Data are expressed as mean ± standard deviation or count (percentage).

Author Manuscript

This article is protected by copyright. All rights reserved.

Table 3. Cardiovascular Pharmacotherapy at 30-days

	Optimal Medical Therapy N = 5,678	Near-Optimal Medical Therapy N = 2,903	Suboptimal Medical Therapy N = 794	p-value
Aspirin	5,678 (100)	2,817 (97.0)	682 (85.9)	<0.001
P2Y12 inhibitor	5,678 (100)	2,201 (75.8)	458 (57.7)	<0.001
Statin	5,678 (100)	2,759 (95.0)	558 (70.3)	<0.001
Beta-blocker	5,678 (100)	1,897 (65.4)	272 (34.3)	<0.001
ACE-I/ARB	5,678 (100)	1,938 (66.8)	253 (31.9)	<0.001
Warfarin	439 (7.7)	217 (7.5)	93 (11.7)	<0.001
Spironolactone	113 (2.0)	65 (2.3)	24 (3.0)	0.16
Eplerenone	142 (2.5)	44 (1.5)	9 (1.1)	0.002
Ezetimibe	173 (3.1)	138 (4.8)	56 (7.1)	<0.001
Fibrate	55 (1.0)	56 (1.9)	14 (1.8)	0.001

Data are expressed as count (percentage). ACEI = Angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker.

Author Manuscript

This article is protected by copyright. All rights reserved.

Table 4. Clinical Outcomes

	Optimal Medical Therapy N = 5,678	Near-Optimal Medical Therapy N = 2,903	Suboptimal Medical Therapy N = 794	p-value
Long-term Mortality	467 (8.2)	306 (10.5)	133 (16.8)	0.001
12-month Mortality	77 (1.4)	67 (2.4)	37 (4.8)	0.001
12-month Myocardial Infarction	261 (4.8)	141 (5.1)	49 (6.4)	0.18
12-month Stroke	46 (0.9)	25 (0.9)	12 (1.6)	0.15
12-month Target Vessel Revascularization	348 (6.4)	207 (7.4)	82 (10.7)	0.001
12-month MACE	581 (10.7)	346 (12.4)	144 (18.8)	0.001

Data are expressed as count (percentage). MACE = major adverse cardiovascular event.

Author Manuscript

This article is protected by copyright. All rights reserved.