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ORIGINAL ARTICLE

Sex- and Age-Specific Differences in Risk Profiles and Early Outcomes in Adults With Acute Coronary Syndromes

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Background Adults <55 years of age comprise a quarter of all acute coronary syndromes (ACS) hospitalisations. There is a paucity of data characterising this group, particularly sex differences. This study aimed to compare the clinical and risk profile of patients with ACS aged <55 years with older counterparts, and measure short-term outcomes by age and sex.

Method The study population comprised patients with ACS enrolled in the AUS-Global Registry of Acute Coronary Events (GRACE), Cooperative National Registry of Acute Coronary Syndrome Care (CONCORDANCE) and SNAPSHOT ACS registries. We compared clinical features and combinations of major modifiable risk factors (hypertension, smoking, dyslipidaemia, and diabetes) by sex and age group (20–54, 55–74, 75–94 years). All-cause mortality and major adverse events were identified in-hospital and at 6-months.

Results There were 16,658 patients included (22.3% aged 20–54 years). Among them, 20–54 year olds had the highest proportion of ST-elevation myocardial infarction compared with sex-matched older age groups. Half of 20–54 year olds were current smokers, compared with a quarter of 55–74 year olds, and had the highest prevalence of no major modifiable risk factors (14.2% women, 12.7% men) and of single risk factors (27.6% women, 29.0% men), driven by smoking. Conversely, this age group had the highest proportion of all four modifiable risk factors (6.6% women, 4.7% men). Mortality at 6 months in 20–54 year olds was similar between men (2.3%) and women (1.7%), although lower than in older age groups.

Conclusions Younger adults with ACS are more likely to have either no risk factor, a single risk factor, or all four modifiable risk factors, than older patients. Targeted risk factor prevention and management is warranted in this age group.

Keywords Acute coronary syndrome • Risk factors • Registry • Age-specific

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Introduction

Increasing age is a strong predictor of the onset of cardiovascular disease (CVD) [1]. However, population-level studies in Australia and elsewhere have reported unfavourable trends in acute coronary syndrome (ACS) in younger adults, underpinned by rising rates of myocardial infarction (MI) [2–4]. Additionally, previous declines in mortality rates for coronary heart disease have plateaued in this age group [5,6]. These data portend a rising burden of ACS in young adults, and thus characterising these patients is paramount to enable targeted prevention measures.

While there is evidence for the association of nontraditional risk factors including novel biomarkers such as C-reactive protein and interleukin-6 with CVD [7], traditional risk factors including smoking, hypertension, dyslipidaemia and diabetes contribute significantly to vascular risk in younger adults [8]. The INTERHEART study reported that smoking, adverse lipid profile, hypertension and diabetes explained a greater proportion of incident risk in younger than older adults, with the combination of these risk factors exponentially increasing the risk of MI [9]. Data from the national ACS registry in New Zealand confirm that it is more common for patients with ACS aged <55 years to have two or more risk factors than older patients, with half of this age group being smokers and nearly one-fifth having diabetes [10]. Additionally, there may be an age and sex interaction in this age group, although evidence is inconsistent, with some studies reporting a higher comorbidity burden, lower receipt of evidence-based medicines, and higher readmission rates in women than similarly aged men [11], while others report higher incidence and worse in-hospital mortality in men than women [12].

Whether these sex differences persist in younger adults with ACS is unclear, and thus identification of risk factor profiles by age and sex is required to understand the occurrence of ACS at a younger age. The lower absolute ACS rates in people aged <55, particularly in women, increase the difficulty of sourcing robust data. Therefore, we used a large combined Australian registry of ACS patients to investigate burden and risk profiles focussing on younger adults. The aims of this study were to compare the clinical and risk factor profile of hospitalised patients with ACS aged <55 years with older patients, to evaluate sex differences in these characteristics in younger adults, and to measure in-hospital and 6-month outcomes following ACS by age and sex.

Methods

Data Source and Setting

Data were obtained from three Australian ACS registries containing information on demographics, clinical characteristics, management and risk factors for patients hospitalised with ACS. Data was available from the Australian centres collaborating in the Global Registry of Acute Coronary Events (GRACE), the Cooperative National Registry of Acute Coronary Syndrome Care (CONCORDANCE) and the SNAPSHOT ACS registry. The methods for these registries have been described elsewhere. Briefly, GRACE was an international observational ACS registry which enrolled the first 10–20 patients per month with suspected ACS at five Australian hospitals between 1999 and 2007 [13]. CONCORDANCE was a prospective ACS registry that enrolled patients at 43 hospitals across Australia from 2009 to 2018, enrolling the first 10 consecutive suspected patients with ACS per month per site [14]. SNAPSHOT ACS was a binational 2-week audit of all suspected ACS presentations to hospitals in Australia and New Zealand in May 2012 [15]. The ethics of the GRACE and CONCORDANCE registries were approved by the Sydney Local Health District Concord Human Research Ethics Committee (CH62/6/98-037; HREC/08/CRGH/180). SNAPSHOT ACS was approved by the New South Wales (NSW) Population and Health Services Research Ethics Committee (HREC/11/CIPHS/39).

Case Selection

There were 16,996 ACS admissions to Australian hospitals captured in the three registries between 1999 and 2018, including ST-elevation MI (STEMI), non-STEMI (NSTEMI) and unstable angina (GRACE n=4077; CONCORDANCE n=11,142, SNAPSHOT ACS n=1777). Patients aged <20 (n=3) and ≥95 years (n=46), with missing age (n=26) or sex (n=4), or missing values for one or more of all major modifiable risk factors of interest (n=259), were excluded from the study (n=338, 2.0%).

Identification of Modifiable Risk Factors, Comorbidities and Treatment

Clinical characteristics, risk factors, comorbidities and treatment data were available across each of the registries. The GRACE risk score, which estimates the 6-month risk of death or MI, was calculated based on published methods [16]. Major modifiable risk factors included hypertension, diabetes, dyslipidaemia and smoking. A patient was considered to have a history of hypertension, diabetes and dyslipidaemia based on self-report or being on medication for these conditions at the time of hospital admission. Smoking status was based on self-report and classified as current, ex-smoker or never smoked. Height and weight were recorded in the dataset; however, as ~50% of patients had a missing value for either variable, body mass index was not calculated for the purposes of this study. Reported history of MI, percutaneous coronary intervention (PCI), coronary artery bypass grafting, coronary angiogram, atrial fibrillation, chronic renal failure, chronic heart failure, previous stroke, peripheral artery disease, and information on in-hospital coronary procedures and medications at discharge were also available.

Outcomes

In-hospital outcomes of interest were recurrent MI, stroke, major bleeding, congestive heart failure, cardiac shock, ischaemic symptoms and all-cause mortality. Outcomes

Table 1 **Baseline and presentation characteristics of men and women presenting with acute coronary syndrome in Australia from 1999 to 2018, by sex and age group (n=16,658).**

Variable	20–54 yr olds[a]		55–74 yr olds[a]		75–94 yr olds[a]		Age group comparison, Women[b] (p-value)	Age group comparison, Men[b] (p-value)
	Women (n=848)	Men (n=2,874)	Women (n=2,248)	Men (n=6,161)	Women (n=1,901)	Men (n=2,626)		
Mean age, years (±SD)	47.2 (5.9)	47.2 (5.8)	65.7 (5.6)	64.6 (5.6)[c]	82.1 (5.0)	80.9 (4.5)[c]	-	-
Diagnosis								
ST-elevation MI	242 (28.5)	1,168 (40.6)[c]	555 (24.7)	1,943 (31.5)[c]	448 (23.6)	533 (20.3)[d]	0.01	<0.0001
Non–ST-elevation MI	387 (45.6)	1,158 (40.3)[d]	1,065 (47.4)	2,701 (43.8)[d]	970 (51.0)	1,419 (54.0)[d]	0.004	<0.0001
Unstable angina	219 (25.8)	548 (19.1)[c]	628 (27.9)	1,517 (24.6)[d]	483 (25.4)	674 (25.7)	0.46	<0.0001
Indigenous status[e]	170 (25.0)	299 (14.2)[c]	126 (7.5)	163 (3.5)[c]	17 (1.2)	27 (1.3)	<0.0001	<0.0001
Prior MI	157 (18.5)	620 (21.6)	546 (24.3)[c]	1,941 (31.5)	675 (35.5)	1,138 (43.3)[c]	<0.0001	<0.0001
Prior PCI	111 (13.1)	474 (16.5)[d]	383 (17.0)	1,358 (22.0)[c]	309 (16.3)	600 (22.9)[c]	0.12	<0.0001
Prior CABG	27 (3.2)	121 (4.2)	167 (7.4)	868 (14.1)[c]	240 (12.6)	644 (24.5)[c]	<0.0001	<0.0001
Prior angiogram	171 (21.9)	665 (25.3)	610 (30.6)	2,092 (37.4)[c]	544 (33.7)	1,096 (48.0)[c]	<0.0001	<0.0001
Risk factors								
Diabetes	231 (27.2)	526 (18.3)[c]	739 (32.9)	1,837 (29.8)[d]	541 (28.5)	810 (30.9)	0.72	<0.0001
Hypertension	462 (54.5)	1,400 (48.7)[d]	1,654 (73.6)	4,252 (69.0)[c]	1,633 (79.5)	2,170 (82.6)[c]	<0.0001	<0.0001
Dyslipidaemia	409 (48.2)	1,502 (52.3)[d]	1,459 (64.9)	3,936 (63.9)	1,243 (65.4)	1,814 (69.1)[d]	<0.0001	<0.0001
Smoking history								
Never	257 (30.3)	675 (23.5)[c]	1,066 (47.4)	1,841 (29.9)[c]	1,324 (69.7)	1,049 (40.0)[c]	<0.0001	<0.0001
Ex-smoker	164 (19.3)	650 (22.6)[d]	633 (28.2)	2,713 (44.0)[c]	472 (24.8)	1,395 (53.1)[c]	0.06	<0.0001
Current smoker	427 (50.4)	1,549 (53.9)	549 (24.4)	1,607 (26.1)	105 (5.5)	182 (6.9)	<0.0001	<0.0001
Atrial fibrillation	15 (1.8)	47 (1.6)	178 (7.9)	481 (7.8)	415 (21.8)	559 (21.3)	<0.0001	<0.0001
Chronic renal failure	42 (5.0)	116 (4.0)	162 (7.2)	404 (6.6)	272 (14.3)[d]	472 (18.0)[d]	<0.0001	<0.0001
Prior heart failure	30 (3.5)	84 (2.9)	155 (6.9)	437 (7.1)	362 (19.0)	462 (17.6)	<0.0001	<0.0001
Prior stroke	24 (2.8)	50 (1.7)[d]	175 (7.8)	417 (6.8)	292 (15.4)	416 (15.8)	<0.0001	<0.0001
PAD	15 (1.8)	61 (2.1)	137 (6.1)	398 (6.5)	172 (9.1)	352 (13.4)[c]	<0.0001	<0.0001
GRACE score, mean (±SD)	70.9 (18.9)	73.5 (19.8)[d]	104.3 (22.9)	104.4 (22.3)	138.7 (24.7)	138.4 (23.5)	<0.0001	<0.0001
GRACE score, median (IQR)	69.5 (57.2–82.4)	72.0 (60.1–85.0)	102.5 (88.2–118.1)	102.4 (89.1–117.3)	136.8 (121.0–154.2)	135.8 (122.0–151.5)		
Killip Class								
I	803 (94.7)	2,695 (93.8)	1,922 (85.5)	5,446 (88.4)[d]	1,419 (74.6)	2,025 (77.1)[d]	<0.0001	<0.0001
II	33 (3.9)	128 (4.5)	240 (10.7)	514 (8.3)[d]	345 (18.2)	464 (17.7)	<0.0001	<0.0001
III	11 (1.3)	23 (0.8)	60 (2.7)	133 (2.2)	119 (6.3)[d]	101 (3.9)[d]	<0.0001	<0.0001
IV	-	12 (0.4)	16 (0.7)	43 (0.7)	11 (0.6)	25 (1.0)	0.15	0.02

[a]n (%) unless otherwise specified.

[b]Age group comparisons estimated from unadjusted logistic or linear regression models for categorical variable and continuous variables respectively, separately by sex.

[c]Statistical comparison of women vs men using unadjusted logistic or linear regression models. p<0.0001.

[d]Statistical comparison of women vs men using unadjusted logistic or linear regression models. p<0.05.

[e]Indigenous status was unavailable for the first period (1999–2008); missing values for Indigenous status in 2009–2018 were n=68 (20–54 years); n=156 (55–74 years); n=65 (75–94 years).

Abbreviations: SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range.

identified at 6 months post-ACS were MI, stroke, recurrent angina, major bleeding, and coronary revascularisation. All-cause mortality at 6 months was identified in patients who survived to discharge. Analyses were restricted to GRACE and CONCORDANCE registries, with all patients from these registries available for in-hospital analysis (n=14,889), and 12,665 (83.2%) of these patients with follow-up for the 6-month analyses. The age- and sex-specific distributions of patients without follow-up data at 6 months are shown in Supplementary Table 1.

Statistical Analysis

All analyses were stratified by sex and age group (20–54, 55–74, 75–94 years). Clinical characteristics and risk factors are presented as frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables. Unadjusted logistic (categorical variables) and linear (continuous variables) regression models were used to test for differences in clinical characteristics and risk factors by age group and sex. We also undertook age and sex comparisons separately for the early (1999–2008) and later (2009–2018) periods. For each of the four major modifiable risk factors, patients were grouped into mutually exclusive groups (no risk factors, and one, two, three or four risk factors), presented as frequencies and percentages. To reflect contemporary management, in-hospital coronary procedures and medications at discharge are reported in the main results for 2009–2018, with data for the early period in Supplementary Material. Differences by age in receipt of treatment between the periods were tested separately for men and women using multivariable logistic regression models, adjusted for risk factors, medication use at discharge, prior and current coronary procedures, and an interaction term for age group and period. In-hospital and 6-month outcomes are presented as frequencies and percentages, with Kaplan–Meier survival analyses used to estimate unadjusted risks for 6-month mortality. Time-to-event in the survival analyses was calculated from the admission date of the ACS hospitalisation to the date of death or the end of follow-up, whichever occurred first.

Results

The study cohort included 16,658 patients hospitalised with ACS between January 1, 1999, and June 30, 2018. The 20–54 year age group comprised nearly a quarter of the cohort (n=3,722, 22.3%) with around half of the cohort aged between 55 and 74 years (n=8,409, 50.5%). Nearly 23% of 20–54 year olds were women, lower than in the cohort overall (n=4,997, 30.0%).

Sex and Age Group Comparisons

The proportion of STEMI cases declined with increasing age in men and women (Table 1). In 75–94 year old men, NSTEMI (54.0%) and unstable angina (25.7%) were more frequent compared with 20–54 year olds (40.3% and 19.1% respectively). This pattern was seen for NSTEMI in older vs younger women (51.0% vs 45.6%) but not for unstable angina (age group p=0.46). Generally, levels of risk factors were higher in 75–94 year olds relative to 55–74 and 20–54 year olds for men and women ($p<0.0001$ for all age group comparisons). The exception was current smoking, which was significantly higher in younger vs older age groups in men (53.9%, vs 26.1% in 55–74 years, and 6.9% in 75–94 years) and younger vs older women (50.4%, vs 24.4%, and 5.5%, respectively). There was no statistically significant difference in the prevalence of diabetes in women by age (age group p=0.72). Hypertension and diabetes were more frequent in younger women than men, while younger men more often had dyslipidaemia than similarly aged women (52.3% vs 48.2%, $p<0.05$). The prevalence of chronic renal failure, heart failure and peripheral artery disease were similar between young men and women and were the lowest across the age groups. While there were some differences in the prevalence of risk factors between periods, age and sex comparisons were generally comparable, with the exception of an increase in the later period in the proportion of NSTEMI cases across all age and sex groupings (Supplementary Tables 2 and 3). When restricted to STEMI cases, the proportion of 20–54 year olds with diabetes, hypertension and dyslipidaemia was lower than in the cohort overall (Supplementary Table 4), whereas the prevalence of smoking in younger patients with STEMI was 12% higher in women and 7% higher in men compared with in the cohort overall. These patterns were also seen in 55–74 year old patients with STEMI.

Combinations of Risk Factors

Overall, 9% of women and 11% of men had no major modifiable risk factors, however this figure was highest in 20–54 year olds (women 14.2%, men 12.7%) (Table 2). The 20–54 year group also had the highest prevalence of single risk factors, underpinned by current smoking (16.9% women, 20.3% men). Over two-thirds of 55–74 and 75–94 year olds had two or more risk factors; in 20–54 year olds, this figure was 57.4% and 54.6% in women and men respectively. Hypertension and dyslipidaemia, with or without diabetes, were the most common combination of multiple risk factors across all age and sex groupings. The highest proportion of patients with all four risk factors was in the 20–54 year age group (women 7.2%, men 5.6%).

Treatment

Between 2009 and 2018, the majority of patients in all age groups underwent a coronary angiogram during hospital admission (Table 3). Just over one-third of women in the 20–54 and 55–74 year age groups received a PCI, compared to over half of their male counterparts. The proportion of patients receiving angiography and revascularisation was higher in 2009-2018 compared to 1999-2008 across all sex and age groupings (Supplementary Table 5). However, the receipt of PCI increased by 10% in 20–54 year old women, compared with a 20% increase in older women (interaction $p<0.0001$). In contrast, the increase in PCI use over time in

Table 2 Combinations of major modifiable risk factors by sex and age group for acute coronary syndrome patients (n=16,658).

Risk factors	20–54 yrs, n (%)		55–74 yrs, n (%)		75–94 yrs, n (%)		Total, n (%)	
	Women (n=848)	Men (n=2,874)	Women (n=2,248)	Men (n=6,161)	Women (n=1,901)	Men (n=2,626)	Women (n=4,997)	Men (n=11,661)
No modifiable risk factors	**120 (14.2)**	**364 (12.7)**	**211 (9.4)**	**702 (11.4)**	**132 (6.9)**	**220 (8.4)**	**463 (9.3)**	**1,286 (11.0)**
1 modifiable risk factor	**241 (28.4)**	**940 (32.7)**	**516 (23.0)**	**1,399 (22.7)**	**450 (23.7)**	**575 (21.9)**	**1,171 (23.4)**	**2,911 (25.0)**
Hypertension	58 (6.8)	141 (4.9)	239 (10.6)	532 (8.6)	371 (19.5)	376 (14.3)	668 (13.4)	1,049 (9.0)
Diabetes	9 (1.1)	31 (1.1)	31 (1.4)	69 (1.1)	8 (0.4)	42 (1.6)	48 (1.0)	142 (1.2)
Dyslipidaemia	31 (3.7)	184 (6.4)	125 (5.6)	365 (5.9)	62 (3.3)	123 (4.7)	218 (4.4)	672 (5.8)
Smoker	143 (16.9)	584 (20.3)	121 (5.4)	433 (7.0)	9 (0.5)	34 (1.3)	273 (5.5)	1,051 (9.0)
2 modifiable risk factors	**234 (27.6)**	**835 (29.0)**	**777 (34.6)**	**2,194 (35.6)**	**874 (46.0)**	**1,129 (43.0)**	**1,885 (37.7)**	**4,158 (35.7)**
Hypertension + diabetes	18 (2.1)	29 (1.0)	72 (3.2)	183 (3.0)	116 (6.1)	104 (4.0)	206 (4.1)	316 (2.7)
Hypertension + dyslipidaemia	96 (11.3)	379 (13.2)	538 (23.9)	1,504 (24.4)	718 (37.8)	969 (36.9)	1,352 (27.1)	2,852 (24.5)
Hypertension + smoker	52 (6.1)	147 (5.1)	76 (3.4)	203 (3.3)	17 (0.9)	22 (0.8)	145 (2.9)	372 (3.2)
Diabetes + dyslipidaemia	8 (0.9)	25 (0.9)	26 (1.2)	88 (1.4)	11 (0.6)	26 (1.0)	45 (0.9)	139 (1.2)
Diabetes + smoker	20 (2.4)	45 (1.6)	16 (0.7)	39 (0.6)	1 (0.1)	5 (0.2)	37 (0.7)	89 (0.8)
Dyslipidaemia + smoker	40 (4.7)	210 (7.3)	49 (2.2)	177 (2.9)	11 (0.6)	3 (0.1)	100 (2.0)	390 (3.3)
3 modifiable risk factors	**192 (22.6)**	**573 (19.9)**	**645 (28.7)**	**1,619 (26.3)**	**426 (22.4)**	**665 (25.3)**	**1,263 (25.3)**	**2,857 (24.5)**
Hypertension + diabetes + dyslipidaemia	81 (9.6)	172 (6.0)	457 (20.3)	1,111 (18.0)	378 (19.9)	584 (22.2)	916 (18.3)	1,867 (16.0)
Hypertension + diabetes + smoker	19 (2.2)	31 (1.1)	23 (1.0)	64 (1.0)	4 (0.2)	9 (0.3)	46 (0.9)	104 (0.9)
Hypertension + dyslipidaemia + smoker	77 (9.1)	339 (11.8)	150 (6.7)	408 (6.6)	40 (2.1)	69 (2.6)	267 (5.3)	816 (7.0)
Diabetes + dyslipidaemia + smoker	15 (1.8)	31 (1.1)	15 (0.7)	36 (0.6)	4 (0.2)	3 (0.1)	34 (0.7)	70 (0.6)
4 modifiable risk factors								
Hypertension + diabetes + dyslipidaemia + smoker	**61 (7.2)**	**162 (5.6)**	**99 (4.4)**	**247 (4.0)**	**19 (1.0)**	**37 (1.4)**	**179 (3.6)**	**446 (3.8)**

men was similar irrespective of age group (interaction p=0.23).

During 2009–2018, a lower proportion of 20–54 year old women received evidence-based medications at discharge compared to similarly aged men, except for warfarin and clopidogrel (Table 3). This pattern was seen in the two older age groups except for ACEi/ARBs and beta-blockers in 75–94 year olds. Receipt of evidence-indicated medications was higher in 2009–2018 compared to the earlier period across all age and sex groups (Supplementary Table 5).

Outcomes

Rates of in-hospital outcomes were generally similar between men and women in each age group (Table 4). There were 495 in-hospital deaths, with similar rates by sex within each age group. Post-discharge outcomes at 6 months were also similar by sex within each age group, except for a higher rate of stroke in 55–74 year old men (5.4%) vs women (0.7%), and higher rates of PCI and coronary artery bypass grafting in men across all age groups, with the greatest differential in the 20–54 year age group. There were 841 deaths by 6 months, with a higher mortality rate in women aged 75–94 years (16.2%) compared with similarly aged men (14.7%) (Figure 1).

Discussion

In an Australian cohort of over 16,000 patients with ACS, our study demonstrates distinct patterns of cardiovascular profiles and risk factors in people aged <55 years. Men and women in this age group were more likely to present with a STEMI and be current smokers compared with older patients. While diabetes prevalence increased with age in younger adult men, over a quarter of women had diabetes, irrespective of age. Patients aged <55 years more often had no standard modifiable risk factors, and conversely, the highest prevalence of four standard modifiable risk factors. While combinations of hypertension, dyslipidaemia and smoking were the most common risk factors across all age groups, the youngest age group had double the prevalence of

Table 3 In-hospital coronary procedures and medications at discharge for acute coronary syndromes patients (n=16,658) stratified by sex and broad age group, 2009–2018.

Management	20–54 yrs, n (%)		55–74 yrs, n (%)		75–94 yrs, n (%)		Total, n (%)	
	Women (n=695)	Men (n=2,160)	Women (n=1,729)	Men (n=4,767)	Women (n=1,391)	Men (n=2,055)	Women (n=3,815)	Men (n=8,982)
Coronary angiogram	562 (80.9)	1,898 (87.9)	1,374 (79.5)	4,024 (84.4)	833 (59.9)	1,342 (65.3)	2,769 (72.6)	7,264 (80.9)
Percutaneous coronary intervention	262 (37.7)	1,260 (58.3)	666 (38.5)	2,466 (51.7)	394 (28.3)	673 (32.7)	1,322 (34.7)	4,399 (49.0)
Coronary artery bypass grafting	26 (3.7)	176 (8.1)	105 (6.1)	548 (11.5)	56 (4.0)	186 (9.1)	187 (4.9)	910 (10.1)
Discharge medications								
Aspirin	599 (86.2)	1,930 (89.4)	1,459 (84.4)	4,251 (89.2)	1,062 (76.3)	1,626 (79.1)	3,120 (81.8)	7,807 (86.9)
Clopidogrel	286 (41.2)	838 (38.8)	633 (36.6)	1,917 (40.2)	539 (38.7)	864 (42.0)	1,458 (38.2)	3,619 (40.3)
$P2Y_{12}$ inhibitors	459 (66.0)	1,674 (77.5)	1,093 (63.2)	3,495 (73.3)	813 (58.4)	1,291 (62.8)	2,365 (62.0)	6,460 (71.9)
Warfarin	29 (4.2)	84 (3.9)	105 (6.1)	295 (6.2)	167 (12.0)	264 (12.8)	301 (7.9)	643 (7.2)
Beta-blockers	469 (67.5)	1,716 (79.4)	1,236 (71.5)	3,714 (77.9)	995 (71.5)	1,412 (68.7)	2,700 (70.8)	6,842 (76.2)
ACEi/ARBs	458 (65.9)	1,581 (73.2)	1,182 (68.4)	3,461 (72.6)	904 (65.0)	1,315 (64.0)	2,544 (66.7)	6,357 (70.8)
Statins	583 (83.9)	1,982 (91.8)	1,470 (85.0)	4,312 (90.5)	1,083 (77.9)	1,729 (84.1)	3,136 (82.2)	8,023 (89.3)
Any lipid lowering therapy	590 (84.9)	1,996 (92.4)	1,508 (87.2)	4,397 (92.2)	1,117 (80.3)	1,767 (86.0)	3,215 (84.3)	8,160 (90.8)

Abbreviation: ACEi/ARBs, Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

current smoking compared with the 55–74 year age group. Sex differences were apparent in the receipt of angiography and PCI and were more pronounced at a younger age.

Risk Factor Profiles

Our study showed that there are distinct patient groups in young adults with ACS. Firstly, an increasingly important group is those with no standard modifiable cardiovascular risk factors (SMuRFs). Zeitouni et al. [17] reported an ~10% prevalence of SMuRF-less patients in <55 year olds with premature coronary artery disease, slightly lower than seen in our study. While a previous Australian study reported the prevalence of those without SMuRFs in patients with STEMI [12], this is the first time this pattern has been shown in younger adults with ACS in Australia. Secondly, concomitant with this finding is that the <55 year age group also had the highest prevalence of all four standard modifiable risk factors. These data highlight the need for risk factor prevention in young adults, although the lower prevalence in older patients may reflect a survival bias. It is also likely that risk factor prevalence is underestimated in young adults, with reporting of high levels of unawareness of the presence of hypertension, dyslipidaemia and diabetes, particularly where borderline levels are present, and slower diagnosis compared to older patients [18,19]. Thirdly, smoking was the most common risk factor in the <55 year age group, similar to patterns seen in other similarly aged cohorts [10,17]. The high prevalence of smoking in this age group is a major contributor to the high levels of multiple risk factors in this age group. Over half of <55 year old patients were current smokers, with a further 20% ex-smokers. While secondary prevention measures following ACS may contribute to smoking cessation [20], around a third of young adults continue to smoke even after being diagnosed with coronary artery disease [17].

In our study, there was a higher proportion of younger adults presenting with NSTEMI than STEMI, yet patients with STEMI had a lower risk factor burden than the cohort overall, except for smoking, a pattern also seen in 55–74 year olds. Indigenous people comprise a higher proportion of younger patients with ACS than in the older age groups, which, given the high prevalence of cardiometabolic risk factors reported in this patient group [21], may contribute to the higher risk factor burden in this age group. The high risk factor prevalence at ACS onset indicates that prevention is paramount, particularly given that people with two or more major risk factors by the age of 50 have a lifetime risk of developing CVD of over 50% [22].

Sex and Age Differences in Treatment and Outcomes

Many studies show that women receive less reperfusion, invasive revascularisation and evidence-based drugs during an ACS admission compared with men [23]. While previous reports suggest this pattern in older patients, increasingly this is also seen in younger women. Our data suggest that while rates of revascularisation have increased over time, this increase has not been as high in younger women as in other age groups. A study of all STEMI admissions in Victoria showed a lower level of the use of reperfusion therapy in women irrespective of age [24]. The Variation in Recovery: Role of Gender on Outcomes of

Table 4 Unadjusted outcomes following acute coronary syndrome/s hospitalisation.

Outcome	20–54 yr olds, n (%)		55–74 yr olds, n (%)		75–94 yr olds, n (%)		20v94 yr olds, n (%)	
In-hospital outcomes	Women (n=780)	Men (n=2,632)	Women (n=1,990)	Men (n=5,589)	Women (n=1,613)	Men (n=2,285)	Women (n=4,383)	Men (n=10,506)
Myocardial infarction	14 (1.8)	41 (1.6)	35 (1.8)	98 (1.8)	50 (3.1)	61 (2.7)	99 (2.3)	200 (1.9)
Stroke	2 (0.3)	4 (0.2)	11 (0.5)	24 (0.4)	19 (1.2)	19 (0.8)	32 (0.7)	47 (0.4)
Major bleeding	31 (4.0)	113 (4.3)	122 (6.1)	305 (5.5)	123 (7.6)	187 (8.2)	276 (6.3)	605 (5.8)
Congestive heart failure	37 (4.7)	109 (4.1)	182 (9.1)	449 (8.0)	252 (15.6)	365 (16.0)	471 (10.7)	923 (8.8)
Cardiac shock	11 (1.4)	39 (1.5)	44 (2.2)	148 (2.6)	71 (4.4)	108 (4.7)	126 (2.9)	295 (2.8)
Ischaemic symptoms	112 (14.4)	398 (15.1)	338 (17.0)	859 (15.4)	310 (19.2)	409 (17.9)	760 (17.3)	1,666 (15.9)
All-cause death	6 (0.8)	26 (1.0)	47 (2.4)	120 (2.1)	126 (7.8)	170 (7.4)	179 (4.1)	316 (3.0)
6-month outcomes[a]	Women (n=648)	Men (n=2,162)	Women (n=1,705)	Men (n=4,750)	Women (n=1,413)	Men (n=1,987)	Women (n=3,766)	Men (n=8,899)
Myocardial infarction	18 (2.8)	32 (1.5)	39 (2.3)	114 (2.4)	50 (3.5)	85 (4.3)	107 (2.8)	231 (2.6)
Stroke	4 (0.6)	7 (0.3)	12 (0.7)	34 (5.4)	22 (1.6)	17 (0.9)	38 (1.0)	58 (0.6)
Recurrent angina	59 (9.1)	119 (5.5)	105 (6.2)	256 (5.4)	81 (5.7)	130 (6.5)	245 (6.5)	505 (5.7)
Major bleeding	1 (0.2)	3 (0.1)	9 (0.5)	30 (0.6)	11 (0.8)	19 (1.0)	21 (0.6)	52 (0.6)
Percutaneous coronary intervention	36 (2.6)	185 (8.6)	105 (6.2)	413 (8.7)	49 (3.5)	101 (5.1)	190 (5.0)	699 (7.8)
Coronary artery bypass grafting	19 (2.9)	102 (4.7)	63 (3.7)	265 (5.6)	48 (3.4)	88 (4.4)	130 (3.4)	455 (5.1)
All-cause mortality	15 (2.3)	36 (1.7)	70 (4.1)	199 (4.2)	228 (16.2)	293 (14.7)	313 (8.3)	528 (5.9)

GRACE, Global Registry of Acute Coronary Events; CONCORDANCE, Cooperative National Registry of Acute Coronary Syndrome Care.
In-hospital and 6-month outcome data was available for the GRACE and CONCORDANCE studies only (n=14,889). For the 6-month outcomes, only those with 6-month follow-up data are included (n=12,665).
[a]6-month outcomes are those occurring following discharge after the acute coronary syndrome hospitalisation.

Young AMI Patients (VIRGO) study of patients aged ≤55 years also demonstrated a lower rate of reperfusion in women than men in reperfusion-eligible patients, with longer door-to-needle times [25]. Importantly, sex remained an independent predictor of poorer reperfusion strategy in multivariable analyses. Lower receipt of reperfusion therapy and evidence-based medications in younger women has been explained by the presence of atypical symptoms and non-severe angiographic data [26] while worse findings on angiography and lower treatment levels in younger

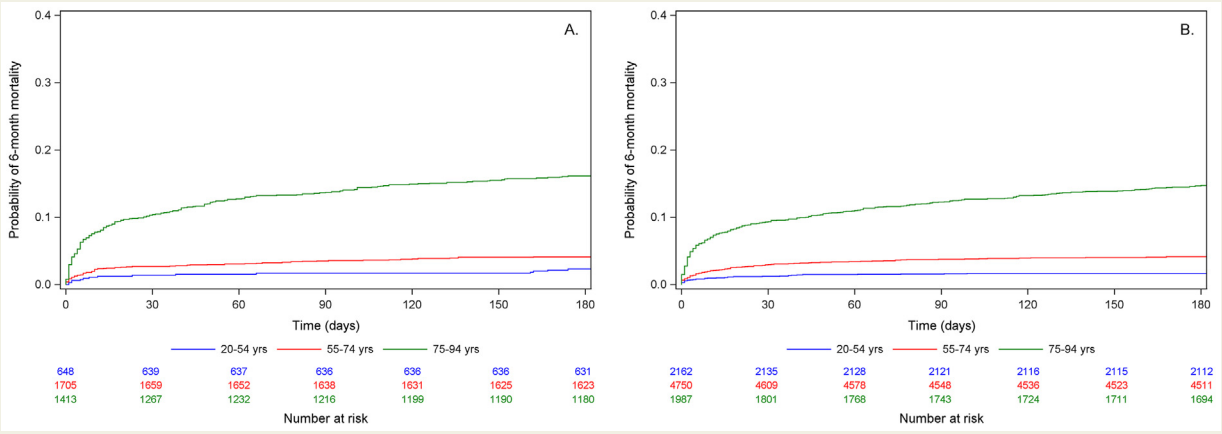

Figure 1 Kaplan–Meier survival curves for 6-month mortality following acute coronary syndrome presentation by age group in (A) women and (B) men.

women are associated with a higher risk of major adverse cardiovascular events at 30 days post-MI compared to men of a similar age [27]. Emerging evidence of alternative mechanisms of myocardial injury in younger women such as coronary artery dissection and microvascular dysfunction [28] are potential contributors to sex and age differences in receipt of treatment in this age/sex grouping.

ACS Burden in Younger Adults

There is increasing evidence that younger adults comprise a significant segment of the patient with ACS group, with nearly a quarter of our cohort aged <55 years, similar to whole-population studies [10]. Many studies are hampered by low event numbers in younger adults and the few studies focussing on younger adults often have no older patient comparator group [17,25,27] or use non-representative samples [17]. Rates of MI have increased in adults aged <55 years in multiple jurisdictions in Australia and elsewhere in recent years [2,3,29,30], contrasting with the impact of increasing detection of NSTEMI cases in older people [31]. The reasons for the increase in rates in younger adults are not clear, although increasing prevalence of diabetes and obesity are hypothesised as contributing factors. We have recently demonstrated with NSW whole-population data that although mortality rates from MI are falling in younger adults, this trend is underpinned by improvements in 30-day case fatality, with no contribution from improvements in MI event rates, suggesting that prevention efforts are suboptimal in this age group [30].

Implications

The increasing rates of MI in various populations including Australia are significant in light of our study findings. While some studies show increasing MI incidence [2,4], implying the need for improved primary prevention, others show increasing rates overall [3,30], suggesting enhanced secondary prevention is required. Given that half of the younger adults in our cohort were current smokers, prevention efforts targeted at smoking cessation programs in this age group are warranted. The high proportion of younger adults with ACS and no SMuRFs requires investigation for other possible mechanisms of myocardial injury but may also be an indicator of unrecognised cardiometabolic disease, representing a missed opportunity for prevention. Conversely, the high risk factor burden in some <55 year olds with ACS is of concern and suggests that optimised approaches to reducing the risk factor burden in this age group are essential. Improving the rate of utilisation of chronic disease management plans in general practice in Australia, where uptake is particularly low in younger people [32], may enable improved risk factor prevention and management.

Strengths and Limitations

The strength of our study is the inclusion of a broad representative cohort of patients with ACS across Australia. The size of the study database allows for in-depth exploration of risk factors, treatment and outcomes in younger adults with ACS, particularly in women, although the younger age group reflects those aged 40-54 years, with 89.0% of ACS events in younger adults occurring in this age range. Patient characteristics and risk factor data are collected prospectively at the time of admission, increasing the reliability of these measures. There are some limitations associated with our study. The cohort primarily represents type 1 MI patients, so findings may not be generalisable to the broader MI population. We were unable to present data on obesity because of the large proportion of missing values to derive this variable. We have focussed on four major risk factors because they are strong targets for prevention of ACS, however we acknowledge that other factors contribute to ACS onset. Categorisation of patients as having major risk factors was based on binary classification hence the nuances of a continuous measure were not assessed, and classification of smoking status was based on self-report. Additionally, the prevalence of risk factors at baseline may be underestimated due to the methods used to define risk factor presence (self-report or treatment); underestimation may be preferentially higher in younger adults, and therefore the proportion of younger adults with multiple modifiable risk factors could be higher than presented here. Our cohort also focuses on people who survive to hospital admission, and thus trends and patterns in out-of-hospital death could differ by age and sex.

Conclusions

Young adults presenting with ACS have a higher prevalence of no major modifiable risk factors than other age groups; conversely, they also have the highest prevalence of smoking, and of having all four major modifiable risk factors. These differing patterns of risk factor profile in young adults, combined with whole-population studies demonstrating a limited impact from prevention efforts in this age group, indicate that substantially intensified approaches are needed to optimise risk factor prevention and control. Given the major contribution of smoking in this age group to risk factor patterns and prevalence, significant effort is required to reduce smoking levels in younger adults and thus reduce the ACS burden in this younger adult population.

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Conflicts of Interest

The funding sources and registry sponsors had no involvement in: the conception or design; collection, analysis, and interpretation of data; in the writing, review, or approval of the manuscript; and, in the decision to submit the manuscript for publication.

Appendices

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