Longer-term Oral Antiplatelet Use in Stable Post-Myocardial Infarction: Insights from the long Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease (TIGRIS) observational study

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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ABSTRACT

Objective: To describe contemporary patient characteristics and treatment patterns, including antithrombotic management, of post-myocardial infarction (MI) stable coronary artery disease (CAD) patients at high atherothrombotic risk from different geographical regions.

Methods: Patients ≥50 years with prior MI 1-3 years ago and ≥1 risk factor (age ≥65 years, diabetes, 2nd prior MI>1 yr ago, multivessel CAD, creatinine clearance 15-<60 mL/min) were enrolled by 369 physicians (96% cardiologists) in 25 countries (2013-14) in the prospective TIGRIS study (NCT01866904).

Results: 9,225 patients were enrolled (median 1.8 years) post-MI: 52% with prior ST-elevation MI, median age 67 years, 24% women, 67% caucasian, 55% had ≥2 additional qualifying risk factors, 14% current smokers, 67% overweight/obese, 34% with blood pressure ≥140/90 mm Hg. 81% underwent percutaneous coronary intervention (PCI; 66% with drug-eluting stents) for the index MI. 75% of patients had been discharged on dual antiplatelet therapy (DAPT; acetylsalicylic acid [ASA]+ADP receptor inhibitor [ADPri]), mainly clopidogrel (75%). 63% had discontinued antiplatelet treatment (60% ADPri) around 1 year, most commonly by physician recommendation (90%). At enrolment, 97% were taking an antithrombotic drug, most commonly ASA (88%), with 27% on DAPT (median duration 1.6 years); continued DAPT>1 year was highest (39%) in Asia-Pacific and lowest (12%) in Europe.

Conclusions: Despite guideline recommendations, 1 in 4 post-MI patients did not receive DAPT for ~1 year. In contrast to guideline recommendations supporting newer ADPris, clopidogrel was mainly prescribed. Prior to recent RCT data supporting

DAPT>1 year post-MI/PCI, >1 in 4 patients have continued on DAPT, though with substantial international variability.

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Coronary artery disease (CAD) is the leading cause of death worldwide and is increasing as a result of population growth, the aging population, and epidemiological changes in disease.[1] The early treatment and risks of death, myocardial infarction (MI), and stroke have been well characterized following presentation with an acute coronary syndrome (ACS),[2-7] particularly among those participating in randomized clinical trials (RCTs).[8-13] However, the later management of atherothrombotic risk factors, quality of life, and outcomes of a contemporary stable CAD (including post-MI) patient population from different geographic regions and non-RCT cohorts remain less clearly defined.[14-20] Thus, the long Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease (TIGRIS) study was designed to better understand the course of stable CAD patients 1-3 years post-MI in routine clinical practice. Specifically, TIGRIS aims to provide contemporary data on patient characteristics, treatment patterns, the burden of disease events such as cardiovascular (CV) death, recurrent MI, stroke, and associated CV-related healthcare resource utilization, and patient-reported quality of life from different geographical regions in an observational ('real world') patient population at high atherothrombotic risk. The objective of the current analyses was to describe contemporary patient characteristics and treatment patterns, including guideline-recommended dual antiplatelet therapy, of high atherothrombotic risk patients from different geographical regions.

METHODS

Stable CAD patients aged 50 years or older with a documented history of presumed spontaneous MI, with their most recent MI occurring 1 to 3 years prior to

enrolment, providing informed written consent, and with at least 1 of the following risk factors, were included: (a) age ≥ 65 years; (b) diabetes mellitus requiring medication; (c) documented history of a second prior presumed spontaneous MI (>1 year prior to enrolment); (d) documented history of angiographic evidence of multivessel CAD; and/or (e) chronic, non-end stage renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation 15 mL/min to <60 mL/min).

Patients were not eligible to participate if any of the following exclusion criteria were present: (a) presence of any condition/circumstance which, in the opinion of the investigator, could significantly limit the complete follow up of the patient; (b) presence of serious/severe co-morbidities which could limit life expectancy (<1 year); (c) ongoing participation in a blinded randomized clinical trial such that specific treatment(s) were not identifiable; and/or (d) patients receiving treatment of ticagrelor beyond 12 months post-MI (or off-label use of ticagrelor).

The study was conducted in compliance with the principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and applicable legislation on non-interventional studies in participating countries. The study protocol and informed consent was reviewed and approved by the corresponding health authorities and ethics boards for all participating study sites. The study was registered at Clinical Trials.gov (clinical trial identifier NCT01866904).

Data entry was completed through a standardized electronic case report form (eCRF). Baseline data included relevant medical history, demographics, details regarding the index MI that occurred 1-3 years before enrollment, variables from routine physical examination and existing routine laboratory testing where available if

performed within 3 months prior to, and up to 1 month following, the initial visit. In addition, medication use at baseline and healthcare resource utilization related to CV or bleeding events during the 6 months preceding enrolment were captured in the eCRF.

The EuroQol Research foundation survey instrument for measuring self-reported health status in 5 dimensions (EQ-5D™; mobility, self-care, usual activities, pain or discomfort, anxiety or depression) with 3 levels of severity (none, moderate, severe)[21;22] was completed by the subject during the baseline visit.

Recruitment of sites was based upon recommendations by national principal investigators; the vast majority of the 349 recruiting physicians were cardiologists (n=334; 95.7%), internists (n=10; 2.8%), or other specialists (n=2; 0.6%), with a minority from general practice (n=3; 0.9%).

TIGRIS is a descriptive observational study with no formal hypothesis testing of the primary and secondary objectives. The sample size was initially estimated at 10,170 patients, assuming a 3-year event rate of approximately 5-10%; this would allow the potential to describe an expected ischemic or bleeding event rate between 5% and 10% with a two- sided 95% confidence interval that would extend in ± 0.4% and ± 0.6% from the observed proportions, respectively. Patients will be followed prospectively for approximately 2 years.

The descriptive baseline analyses were conducted according to a pre-defined statistical analysis plan. Categorical data are expressed as frequencies and percentages. Continuous data are summarized by medians (25^{th} and 75^{th} percentiles). The proportions of patients in different geographic regions receiving antithrombotic treatments were compared using chi-squared tests; a p-value <0.05 was considered

significant but no adjustments were made for multiple comparisons. Statistical analysis was performed using SAS software version 9.4 and Enterprise Guide software version 6.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Population

From June 18, 2013 to November 29, 2014, 9,225 patients were enrolled by 369 principal investigators in 25 countries from Asia-Pacific/Australia (Australia, China, Japan, India and South Korea [n=2,850; 31%]), Europe (Germany, Spain, Netherlands, Italy, Romania, Denmark, United Kingdom, Turkey, Belgium, Portugal, Finland, Norway and France [n=4,240; 46%]), and North (United States and Canada [n=1,024; 11%]) and South America (Argentina, Colombia, Brazil, Venezuela and Mexico [n=1,111, 12%]). Eligible patients were 50 years of age or older, with a prior MI occurring 1-3 years before inclusion in the registry, and at least one additional risk factor (age ≥65 years [62.5%]; diabetes mellitus requiring medication [30.4%]; second prior MI >1 year ago [10.2%]; multivessel CAD [65.6%]; chronic, non-end stage renal dysfunction [7.7%]). More than half the patient population had 2 or more additional risk factors: 1 qualifying risk factor (44.8%), 2 (37.8%), 3 (14.0%), 4 (2.9%), and 5 (0.4%).

Selected patient demographics are also listed in Table 1, including by geographical region. The median age was 67 (25^{th}, 75^{th} percentiles: 60, 73) years, including 1,839 patients (19.9%) who were 75 years of age or older. Women represented 24.2% of the population. The majority of patients were caucasian (66.6%);

27.5% were asian/oriental, 1.0% were black, and 4.8% described another race. At baseline, 14.0% were current smokers.

Table 1 – Selected demographics and medical history by geographic region

	Total population	Asia-Pacific/Australia	Europe	North America	South America
Number of patients	9225 (100)	2850 (30.9)	4240 (46.0)	1024 (11.1)	1111 (12.0)
Inclusion Risk Factors					
Age ≥65 years	5766 (62.5)	1652 (58.0)	2814 (66.4)	666 (65.0)	634 (57.1)
Diabetes requiring medication	2805 (30.4)	999 (35.1)	1118 (26.4)	307 (30.0)	381 (34.3)
2nd Prior MI	943 (10.2)	210 (7.4)	491 (11.6)	131 (12.8)	111 (10.0)
Multivessel CAD	6052 (65.6)	1921 (67.4)	2714 (64.0)	715 (69.8)	702 (63.2)
Creatinine Clearance 15-60 ml/min	707 (7.7)	212 (7.4)	327 (7.7)	78 (7.6)	90 (8.1)
Age, years*	67 (60-73)	66 (59-73)	68 (62-73)	68 (61-74)	66 (59-73)
Women	2230 (24.2)	616 (21.6)	978 (23.1)	320 (31.3)	316 (28.4)
Hypertension	6663 (72.2)	1934 (67.9)	3014 (71.1)	847 (82.7)	868 (78.1)
Hyperlipidemia	6147 (66.6)	1386 (48.6)	3024 (71.3)	927 (90.5)	810 (72.9)
Smoking status					
Current smoker	1288 (14.0)	468 (16.4)	595 (14.0)	123 (12.0)	102 (9.2)
Former smoker	4482 (48.6)	1194 (41.9)	2201 (51.9)	505 (49.3)	582 (52.4)
Never smoker	3453 (37.4)	1187 (41.7)	1443 (34.0)	396 (38.7)	427 (38.4)
Diabetes Mellitus	3076 (33.3)	1079 (37.9)	1246 (29.4)	348 (34.0)	403 (36.3)
Type I	88 (2.9)	48 (4.5)	29 (2.3)	7 (2.0)	4 (1.0)
Type II	2928 (95.2)	989 (91.7)	1201 (96.4)	339 (97.4)	399 (99.0)
Unknown	60 (2.0)	42 (3.9)	16 (1.3)	2 (0.6)	0 (0)

If type II-Management[+]					
Diet only	253 (8.6)	73 (7.4)	119 (9.9)	39 (11.5)	22 (5.5)
Oral hypoglycemic	2293 (78.3)	812 (82.1)	921 (76.7)	226 (66.7)	334 (83.7)
Insulin	798 (27.3)	205 (20.7)	359 (29.9)	125 (36.9)	109 (27.3)
History of PCI	7913 (85.8)	2584 (90.7)	3598 (84.9)	836 (81.6)	895 (80.6)
History of CABG	1314 (14.2)	181 (6.4)	663 (15.6)	263 (25.7)	207 (18.6)
Chronic angina	90 (1.0)	12 (0.4)	54 (1.3)	20 (2.0)	4 (0.4)
Heart failure	937 (10.2)	273 (9.6)	472 (11.1)	82 (8.0)	110 (9.9)
Atrial fibrillation	1061 (11.5)	237 (8.3)	569 (13.4)	117 (11.4)	138 (12.4)
ICD	748 (8.1)	150 (5.3)	420 (9.9)	133 (13.0)	45 (4.1)
Pacemaker	198 (2.2)	28 (1.0)	104 (2.5)	59 (5.8)	7 (0.6)
TIA	211 (2.3)	32 (1.1)	131 (3.1)	34 (3.3)	14 (1.3)
Stroke	204 (2.2)	37 (1.3)	113 (2.7)	39 (3.8)	15 (1.4)
Peripheral vascular disease	413 (4.5)	123 (4.3)	189 (4.5)	58 (5.7)	43 (3.9)
Prior cerebrovascular revascularization	616 (6.7)	107 (3.8)	358 (8.4)	94 (9.2)	57 (5.1)
VTE	151 (1.6)	26 (0.9)	93 (2.2)	25 (2.4)	7 (0.6)
Valve repair/replacement	104 (1.1)	13 (0.5)	64 (1.5)	16 (1.6)	11 (1.0)
COPD	670 (7.3)	135 (4.7)	384 (9.1)	96 (9.4)	55 (5.0)
Chronic anemia	272 (3.0)	54 (1.9)	147 (3.5)	49 (4.8)	22 (2.0)
Cancer	626 (6.8)	124 (4.4)	330 (7.8)	131 (12.8)	41 (3.7)
Peptic ulcer	298 (3.2)	79 (2.8)	167 (3.9)	31 (3.0)	21 (1.9)
Severe liver disease	36 (0.4)	10 (0.4)	19 (0.5)	5 (0.5)	2 (0.2)
Esophageal varices	18 (0.2)	2 (0.1)	5 (0.1)	8 (0.8)	3 (0.3)
Major bleeding#	261 (2.8)	45 (1.6)	138 (3.3)	43 (4.2)	35 (3.2)

All numbers are given as numbers (%), except *median (25^{th}, 75^{th} percentiles)

[+] Oral hypoglycemic agent(s) and insulin use are not mutually exclusive
CABG=Coronary Artery Bypass Graft surgery; CAD=Coronary Artery Disease;
COPD=Chronic Obstructive Pulmonary Disease; ICD=Implantable Cardioverter Defibrillator;

PCI=Percutaneous Coronary Intervention; TIA=Transient Ischaemic Attack; VTE=Venous Thromboembolism;
# that required hospitalization or urgent medical care, and/or blood transfusion and/or caused haematocrit drop

A minority reported no formal education (4.0%), with 30.6% having 1-9 years, 31.5% having 10-12 years, 17.6% having 13-15 years, and 16.2% having 16 or more years of education. The majority lived in a metropolitan area (64.8%), 99% reported home as type of residence, with only 13.6% living alone.

The majority of patients were retired (57.8%), with 25.6% working, 5.5% working as a homemaker, 4.9% were unemployed, and 4.4% were on sick/disability leave. Household income (U.S. dollars/month) was reported by half of the study population (n=4766, 51.7%) and was less than or equal to $1,250 for 49.2% of patients, $1,251-5,000 for 37.1%, and >$5,000 for 13.7%. Health care insurance status (among the 98.7% of patients who responded) included: government (62.9%), private (19.4%), employer-provided (3.5%), other (4.8%), and none (5.5%).

Index Myocardial Infarction

The median time from the index MI to enrolment in the study was 1.8 (1.3, 2.4) years. ST-segment elevation MI (STEMI) had occurred in 52.1%, non-ST-segment elevation MI (NSTEMI) in 41.8%, and in 6.1% the index MI type was unknown. Management at the time of the index MI included percutaneous coronary intervention (PCI; 80.0%), coronary artery bypass surgery (CABG; 7.4%), or medical treatment only (12.6%)(Table 2). Compared to NSTEMI patients, a significantly greater proportion of STEMI patients underwent PCI (71.9% vs. 88.0%); however, fewer STEMI patients underwent CABG (11.6% vs. 3.6%) or received medical management only (16.5% vs. 8.4%).

Table 2 – Coronary revascularization during the index myocardial infarction by geographical region

	Total population	Asia-Pacific/ Australia	Europe	North America	South America
Number of patients	9225 (100)	2850 (30.9)	4240 (46.0)	1024 (11.1)	1111 (12.0)
Percutaneous Coronary Intervention	7376 (80.0)	2472 (86.7)	3358 (79.2)	747 (72.9)	799 (71.9)
Drug-Eluting Stent	4146 (56.2)	1750 (70.8)	1753 (52.2)	414 (55.4)	229 (28.7)
Bare Metal Stent	1476 (20.0)	267 (10.8)	730 (21.7)	159 (21.3)	320 (40.1)
Both stent types	59 (0.8)	13 (0.5)	34 (1.0)	9 (1.2)	3 (0.4)
No stent	207 (2.8)	42 (1.7)	118 (3.5)	19 (2.5)	28 (3.5)
Unknown/incomplete type	1488 (20.2)	400 (16.2)	723 (21.5)	146 (19.5)	219 (27.4)
Coronary artery bypass surgery	678 (7.4)	98 (3.4)	332 (7.8)	143 (14)	105 (9.5)

All numbers are given as numbers (%)

Physical and Laboratory Findings

Physical examination findings at baseline, including by geographical region, are listed in SupplementaryTable 1. Body Mass Index was (BMI) was a median of 27 (24, 30) kg/m^2), with 43.4% in the overweight and 24.2% in the obese range, respectively. Waist circumference was a median 97 (89, 106) cm. The Asia-Pacific region had the lowest proportion of overweight/obese patients and the lowest waist circumference. Median resting heart rate was 68 (60, 75) beats/minute; the Asia-Pacific region had the highest heart rate. Median systolic and diastolic blood pressures (BP) were 130 (120, 140) and 77 (70, 82) mm Hg, respectively; the European region had the highest baseline systolic BP; 29% with a history of hypertension and 18.9% without a prior history of hypertension had a blood pressure ≥140/90 mm Hg.

Laboratory Values

Serum hemoglobin was available in 2,810 patients from existing routine laboratory testing (≤3 months prior to or ≤1 month following the initial visit) and was a median of 13.9 (12.8, 15.0) g/dL. Serum creatinine was available in 3,285 patients and was a median of 0.97 (0.83, 1.17) mg/dL; 2.5% had an estimated creatinine clearance (CrCl) of <30 ml/min/1.73 m^2, with 19.2% having a CrCl of 30-60 ml/min/1.73 m^2, and 78.4% having a CrCl of >60 ml/min/1.73 m^2, respectively. Median fasting glucose was 106 (94, 127) mg/dL (n=2,034) and hemoglobin A1c was 6.3 (5.8, 7.0)% (n=1,565), including in patients with diabetes: 132 (111, 164) mg/dL (n=731) and 6.9 (6.4, 7.7)% (n=821), respectively. Total cholesterol (n=2,954), fasting low-density lipoprotein (LDL; n=2,027), high-density lipoprotein (n=2,871), and fasting triglycerides (n=2,123), were 151 (131, 176), 78 (63, 99), 45 (38, 54), and 115 (86, 157) mg/dL, respectively. The proportion of patients with a fasting LDL <70 mg/dL was 37%.

Antithrombotic Therapy

Antithrombotic therapy prescribed at hospital discharge following the index MI included: single antiplatelet therapy in 21.3% (ASA 14.5%, adenosine-diphosphate [ADP] receptor inhibitor 6.8%), dual antiplatelet therapy (DAPT) in 74.9% (clopidogrel 55.8%, prasugrel 10.7%, ticagrelor 7.9%, or ticlopidine 0.1%), and oral anticoagulant therapy in 5.5%.

Post-MI Discontinuation

Antithrombotic therapy prescribed following the index MI and discontinued prior to enrolment (n=5,868; 63.6%) included antiplatelet (62.8%) and anticoagulant (2.5%) treatment. Antiplatelet therapy discontinued was primarily an ADP receptor inhibitor:

clopidogrel (40.3%), prasugrel (10.1%), ticagrelor (9.0%), or ticlopidine (0.2%). ADP receptor inhibitor therapy was discontinued around 1 year for clopidogrel (median of 370 [353, 424] days), prasugrel (367 [363, 397]), and ticagrelor (365 [356, 372]) and around 6 months for ticlopidine (201 [103, 280]). The most commonly reported reason for ADP receptor inhibitor cessation was the patient's physician's recommendation (89.6%)(Supplementary Table 2).

Post-MI Continuation

At study enrolment, 97% of patients were taking an antithrombotic (antiplatelet or anticoagulant) agent (Table 3 and Figure 1), with modest differences between regions (Asia-Pacific lowest at 95.8% and South America highest at 98.7%). Antiplatelet therapy was being used in 94.2%, most commonly ASA (88.0%). Single antiplatelet therapy included ASA in 61.6%, and ADP receptor inhibitor in 5.7%, and other in 0.1%. Dual antiplatelet therapy (DAPT) use was 26.8%, including 24.0% on ASA and clopidogrel and 2.4% on ASA and prasugrel (ticagrelor use was an exclusion criterion). The median duration of DAPT amongst those started at the time of the index MI and continued until the time of enrolment was 592 (444-807) days. There was substantial variation across geographic region with the lowest use of ASA alone (43.1%) and the highest rate of DAPT (39.4%) in Asia-Pacific and the highest use of ASA alone (74.8%) together with the lowest rate of DAPT (12.2%) in Europe. Anticoagulant therapy was used in 594 (6.4%) at study entry.

Table 3 – Antithrombotic treatment at enrolment by geographic region

	Total population	Asia-Pacific	Europe	North America	South America	P-value

Number of patients	9225	2850	4240	1024	1111	
Any antithrombotic therapy	8949 (97.0)	2729 (95.8)	4134 (97.5)	990 (96.7)	1096 (98.7)	*<0.001*
Any antiplatelet therapy	8693 (94.2)	2701 (94.8)	3932 (92.7)	971 (94.8)	1089 (98.0)	*<0.001*
Use of antiplatelet therapy						*<0.001*
Single						
ASA	5681 (61.6)	1229 (43.1)	3170 (74.8)	578 (56.5)	704 (63.4)	
Clopidogrel	499 (5.4)	246 (8.6)	154 (3.6)	63 (6.2)	36 (3.2)	
Prasugrel	29 (0.3)	12 (0.4)	12 (0.3)	4 (0.4)	1 (0.1)	
Ticagrelor	Exclusion criterion					
Other*	7 (0.1)	4 (0.1)	3 (0.1)	0 (0)	0 (0)	
Dual (DAPT)						
ASA + Clopidogrel	2222 (24.1)	1122 (39.4)	517 (12.2)	252 (24.6)	331 (29.8)	
ASA + Prasugrel	221 (2.4)	64 (2.3)	72 (1.7)	71 (6.9)	14 (1.3)	
ASA + Other	26 (0.3)	17 (0.6)	3 (0.1)	3 (0.3)	3 (0.3)	
Oral anticoagulant**	589 (6.4)	135 (4.7)	351 (8.3)	78 (7.6)	25 (2.3)	*<0.001*
Parenteral anticoagulant***	8 (0.1)	2 (0.1)	6 (0.1)	0 (0)	0 (0)	

All numbers are given as numbers (%)

*Other: cilostazol, sarpogrelate, dipyridamole ± ASA, trifusal, and carbasalate calcium
**Oral anticoagulant: warfarin, acenocumarol, phenprocoumon; dabigatran, rivaroxaban, apixaban
***Parenteral anticoagulant: heparin, certoparin, enoxaparin, dalteparin, or tinzaparin

Other Medical Therapy

Other selected medical treatments at enrolment are listed in Table 4 and included: beta-blocker (79.9%), angiotensin converting enzyme (ACE) inhibitor (47.9%), angiotensin receptor blocker (ARB; 29.2%), statin (92.8%), other lipid-lowering (9.4%), diuretic (25.4%), and antidepressant (7.0%) therapy. Beta-blocker use was highest in

South America (86.7%) and lowest in Asia-Pacific (70.9%). ACE or ARB use was highest in Europe (80.9%) and lowest in North America (71.5%). While statin use was uniformly high (≥92%) across all geographic regions, other lipid-lowering therapy was highest in North America (15.6%). Among patients with diabetes (n=2,805), 81.8% of those with Type II diabetes were on at least one oral hypoglycemic drug and 28.5% were on insulin.

Table 4 – Selected medical therapy at enrolment by geographic region

	Total population	Asia-Pacific/Australia	Europe	North America	South America
Number of patients	9113	2790	4203	1020	1100
Beta-blocker	7284 (79.9)	1977 (70.9)	3516 (83.7)	837 (82.1)	954 (86.7)
ACE inhibitor	4368 (47.9)	1026 (36.8)	2378 (56.6)	551 (54.0)	413 (37.6)
Angiotensin receptor blocker	2664 (29.2)	1028 (36.9)	1021 (24.3)	178 (17.5)	437 (39.7)
Statins	8453 (92.8)	2598 (93.1)	3894 (92.7)	938 (92.0)	1023 (93.0)
Other lipid lowering drug	855 (9.4)	272 (9.8)	304 (7.2)	159 (15.6)	120 (10.9)
Diuretics	2318 (25.4)	581 (20.8)	1190 (28.3)	271 (26.6)	276 (25.1)
Antidepressants	640 (7.0)	101 (3.6)	285 (6.8)	172 (16.9)	82 (7.5)

All numbers are given as numbers (%)

ACE=Angiotensin Converting Enzyme

Health Care Resource Utilization and Status

Health care resource utilization in the 6 months prior to enrolment included at least one visit to a cardiologist (31.7%), other specialist (7.7%), general practitioner or family physician (19.6%), or emergency room (5.8%). Hospitalization necessitating at least an overnight stay occurred in the previous 6 months in 5.4% for a cardiovascular

(4.8%) or bleeding (0.7%) event (including coronary angiography), with a median length of stay of 4 (2, 7) days.

Self-reported health status by EQ-5D assessment was available at baseline in 9,177 (99.5%) of patients, and limitations were identified with: mobility (24.7%), self-care (5.8%), usual activities (18.5%), pain/discomfort (36.0%), and anxiety/depression (22.8%). Overall health status measured by EQ-Index score was a median of 0.85 (scale from 0 to 1), and by EQ-VAS score was 80 (70, 90)(scale from 1-100).

DISCUSSION

This report provides unique contemporary enrolment data on the patient characteristics, treatment patterns, CV-related healthcare resource utilization, and quality of life in stable high-risk CAD patients 1-3 years post-MI from different geographical regions (25 countries) in routine clinical practice. At a median of 1.8 years after an MI, approximately 1 in 7 patients are current smokers, 2 in 3 are overweight or obese, and 1 in 4 had a blood pressure of ≥140/90 mm Hg. Regarding medication use, almost all patients were on at least one antithrombotic drug and a statin and/or other lipid-lowering therapy, and 8 in 10 were on beta-blocker and an ACE inhibitor or angiotensin receptor blocker. Specifically regarding antiplatelet therapy, we observed that 1 in 4 post-MI patients with ≥1 atherothrombotic risk factor did not receive DAPT for ~1 year. Further, in contrast to randomized clinical trial evidence and some international guideline recommendations supporting newer ADPris in the majority of these patients, clopidogrel was mainly prescribed as part of DAPT. Interestingly, prior to recent randomized trial data supporting DAPT >1 year post-MI/PCI, >1 in 4 patients

have continued on DAPT, though with substantial international variability. Health care resource utilization in the 6 months prior to enrolment included a visit to a physician or emergency room for approximately 1 in 5, and hospitalization for a CV or bleeding event for 1 in 20 patients. Despite some issues for the five dimensions (mobility [25%], self-care [5%], usual activities [19%], pain/discomfort [36%], anxiety/depression [23%]) of self-reported quality of life, overall health status is perceived as similar to that in a general age- and sex-matched U.K. population without cardiovascular disease.[23]

While the study specifically includes patients at least 50 years of age with additional high risk features, such as those ≥65 years (63%, with 20% ≥75 years), those with multivessel disease (66%), diabetes mellitus requiring medication (30%), a second prior MI >1 year ago (10%), or chronic, non-end stage renal dysfunction (8%), more than half (55%) have more than one of the qualifying, prognostically important factors. The older population (median 67 years) likely accounts for the majority (62%) being retired or on sick leave/disability. The higher proportion (52%) of STEMI patients and those who underwent coronary revascularization (88%) as part of the index MI management likely reflects the fact that the vast majority of recruiting physicians were cardiologists. Similarly, the majority of the TIGRIS population lives in a metropolitan area (65%) with an annual income (among those reported) of ≥$15,000 U.S. (51%).

There was evidence of regional differences, such as lower frequencies of obesity in Asia-Pacific compared to other regions, and lower rates of utilization of antithrombotic therapies and beta-blockers in Asia-Pacific, but higher rates of DAPT >1 year post-MI. ACE inhibitor or ARB use was highest in Europe and lowest in North America. One

possible explanation for higher continued use of DAPT in Asia-Pacific relates to the higher observed use of prior PCI in this region.

While the laboratory values available were limited arbitrarily by a 4 month window around the time of enrolment and were not study-wide given the capture of clinically obtained measures only, the proportion of patients with LDL-cholesterol above some (but not all) international guideline-recommended target(s) was approximately 60%, despite 93% of these patients receiving statin and/or other lipid-modifying therapy.

Consistent with several international guideline recommendations, and another earlier (2010-11) prospective observational international study of ACS hospital survivors,[24] approximately 75% of patients received dual antiplatelet therapy (DAPT) as an integral part of their index MI management, particularly in the setting of frequent PCI with stenting, for approximately 1 year post. However, in contrast to some guideline recommendations[25-27] and RCT evidence suggesting superiority of the newer ADP receptor inhibitors prasugrel[9] or ticagrelor,[10] clopidogrel was prescribed instead. Of interest, preceding more recent RCT data supporting DAPT beyond 1 year's time post-MI/PCI with stenting,[13;28-30] 27% of our cohort have been continued on DAPT for at least a median of 1.6 years until the time of enrolment into TIGRIS.

Limitations

A number of limitations are relevant to our study. First, principal investigator/site selection was not random or specifically population-based and predominantly consisted of cardiologists who were invited and chose to participate, were more likely to have resources to facilitate patient enrollment, data collection, and study follow-up, and are therefore not likely representative of routine non-specialist clinical practice. Second,

while consecutive patient selection was encouraged, TIGRIS is a prospective observational study with specific inclusion criteria (e.g., stable patients 1-3 years post-MI, age of at least 50 years, high risk features such as multivessel CAD, requirement for informed consent) that, while less selected than a typical RCT, resulted in a cohort that is not representative of all post-MI survivors. Third, information regarding the use of antecedent and current medications is based upon medical record information and does not address actual patient adherence. Fourth, we noted variations in patient characteristics, treatment/management, and non-adjudicated/systematically validated CV events in different geographic regions; however, the participating physicians reflect regional specialist practices and but do not necessarily reflect practice for specific countries. Fifth, despite enrolling patients from 25 countries in most continents, we did not have representation from Africa and only 1% were black. Sixth, it is challenging to compare our data with other contemporary large-scale observational studies (e.g., the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease [CLARIFY][31]) as each employs unique (with some overlapping) inclusion criteria to identify their coronary artery disease (stable vs. acute) cohort. Seventh, as ticagrelor did not have an indication for use >1 year post-MI when TIGRIS prospectively enrolled patients 1-3 after the index MI, patients receiving ticagrelor would have been excluded from the cohort.

CONCLUSIONS

Approximately 2 years after a MI, atherothrombotic risk factor (e.g., smoking, obesity, hypertension, dyslipidemia) modification in a large international cohort remains

suboptimal. However, the vast majority of patients were receiving evidence-based medical therapies, including antithrombotic, beta-blocker, ACE inhibitor or angiotensin receptor blocker, and statin drug(s). Further, despite some issues for the five dimensions of self-reported quality of life, overall health status was perceived as relatively high in this population. Consistent with guideline recommendations, patients received DAPT for approximately 1 year post-MI; however, in contrast to RCT evidence supporting newer ADPris, clopidogrel was mainly prescribed post-index MI. Preceding recent RCT data supporting DAPT >1 year's time post-MI/PCI, more than 1 in 4 patients have continued DAPT though with substantial international variability. These findings represent an opportunity to further improve upon routine antithrombotic management of post-MI patients.

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Dr Shaun Goodman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Figure 1. Antithrombotic Therapy at Enrolment

Antithrombotic therapy at enrolment (median 1.8 years post-myocardial infarction), including acetylsalicylic acid (ASA) only, adenosine diphosphate receptor inhibitor (ADPri) only, dual antiplatelet therapy (DAPT), and oral anticoagulant (OAC) therapy, for the overall population and by region.

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