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Acute coronary syndrome in the Asia-Pacific region

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ABSTRACT

More than 4.2 billion inhabitants populate the Asia-Pacific region. Acute coronary syndrome (ACS) is now a major cause of death and disability in this region with in-hospital mortality typically exceeding 5%. Yet, the region still lacks consensus on the best approach to overcoming its specific challenges in reducing mortality from ACS. The Asia-Pacific Real world evIdenCe on Outcome and Treatment of ACS (APRICOT) project reviewed current published and unpublished registry data, unmet needs in ACS management and possible approaches towards improving ACS-related mortality in the region. There was striking heterogeneity in the use of invasive procedures, pharmacologic practice (hospitalization/post-discharge), and in short- and long-term clinical outcomes across healthcare systems; this heterogeneity was perceived to be far greater than in Western Europe or the United States. 'Benchmark' short-term clinical outcomes are preferred over long-term outcomes due to difficulties in follow-up, recording and maintenance of medication adherence in a geographically large and culturally diverse region. Key 'barriers' towards improving outcomes include patient education (pain awareness, consequences of missing medication and secondary prevention), geographical landscape (urban vs. metropolitan), limited long-term adherence to guideline-based management and widespread adoption of cost-based rather than value-based healthcare systems. Initiatives to overcome these barriers should include implementation of pre-hospital management strategies, toolkits to aid in-hospital treatment, greater community outreach with online patient/physician education and telemedicine, sustainable economic models to improve accessibility to effective pharmacotherapies and the acquisition of high-quality 'real-world' regional data to tailor secondary prevention initiatives that meet the unique needs of countries in this region.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for 17.3 million deaths in 2008 (or ~30% of all deaths worldwide). Coronary artery disease and acute coronary syndrome (ACS) together account for approximately 7 million deaths each year [1,2]. The Asia-Pacific region comprises ~50 countries, including seven from 10 of the most densely populated countries worldwide. The region is populated by more than 4.2 billion inhabitants, equivalent to ~60% of the world's population, with a combined gross domestic product of ~US $18 trillion growing at ~6% per annum [3,4]. ACS is now a leading cause of mortality in the Asia-Pacific region, accounting for around half of the global burden [2]. In fact, due to rapid industrialization, fewer than 50% of patients across the Asia-Pacific region attain the National Cholesterol Education Program Adult Treatment Panel lII low-density lipoprotein cholesterol target [5,6].

Guidelines for the management of ACS in Australia and New Zealand are generally comparable with those from Europe and the USA [7–13] while guidelines across other parts of Asia show variability according

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to the clinical situation [14–16]. In the industrialized Western world, improved adoption of evidence-based recommendations over the last decade strongly correlates with reduction in both in-hospital and post-discharge ACS-related mortality (up to 25%) [17,18]. These improvements have largely been attributed to timely and effective reperfusion, as well as standardized pharmacological approaches [17]. In contrast, registry-based data from the Asia-Pacific region suggest that ACS-related mortality rates have remained relatively high at ~5% during hospitalization and up to double this at 1-year post-discharge (Table 1, and Supplementary Table 1), with the exception of Australia and New Zealand.

In evaluating trends in management practice, 'real-world' registry-based outcomes data are intuitively representative of the spectrum of patients encountered in actual clinical practice and a focus on such data will help in driving future healthcare policy and establishing region-specific guideline recommendations. Available registry-based data show strong regional heterogeneity in the use of invasive and pharmacologic practice patterns, and in short- and long-term clinical outcomes across the Asia-Pacific region [19,20]; a situation compounded by the ethnic diversity both within and between Asia-Pacific countries [19,21].

Existing data strongly suggest that there is much potential for improvement in the management of ACS in the Asia-Pacific region. We assembled leading academic teams from seven countries across this region in the Asia-Pacific Real world evIdenCe on Outcome and Treatment of ACS (APRICOT) project, to consider possible approaches towards improving clinical outcomes in this region based on their experience and available data towards developing a broad and comprehensive insight into the issues contributing to ACS-related mortality across

Table 1
Mortality data across Asian-Pacific countries according to (A) disease status and (B) invasive versus non-invasive intervention [21–37,40,43,45,47–50,52,54,61–64,68–70].

A. Disease status

		Overall				
		Mortality (%)			MACE (%)	
Country/ registry	STEMI (%)	IH	12-month	PCI (%)	IH	12-month
Australia/ New Zealand	~35	2–4	5–10	100	–	14–16
	42	–	10	14–71	–	–
	~10*	4.5	–	43	5-29	–
China	~44	1–7	–	49	–	–
	43	5	–	38†	–	–
	63	≥19	–	<25	–	–
	0	–	8[d]	23	–	–
	99	–	–	12	10	–
	100	–	12–25	20–31	–	–
	16	1	3	65	2	9
	0	1	–	44	3	–
India	61	–	7[a]	8	–	–
	37	4	–	12	6	–
Japan	79	9	–	74	40	–
	100	3	–	97	–	–
	–	6	9	100	7–11	14–21[e]
	59	2	4	94	–	6[d]
Korea	60	4–6	11–14	–	–	20–23
	100	–	7–13	96–97	–	10–17
Malaysia	47	4–10	–	13–17	–	–
	52	1	–	100	–	–
Singapore	–	–	25[b]	–	–	–
	30	43–55	–	–	–	–
	0	13 MM <1 PCI	21 MM <1 PCI	54–65	–	23–26 MM 11–13 PCI
	45	6–10	–	43–48	–	–
	0	–	–	100	–	9[c]
Taiwan	0	–	~8	98	–	–
	52	2	–	84	–	–
Thailand	41	13	–	39–49	–	–
	34	15	–	24–60	–	–
GRACE	30	8	–	18–40	–	–
	–	5	–	–	–	–
USA	38	2	–	71–87‡	–	–
	40	5	–	80	–	–
	21	2 (PCI)	–	100	–	–

Table 1 (*continued*)

B. Invasive versus non-invasive intervention

		Mortality (%) (invasive treatment)		Mortality (%) (non-invasive treatment)	
Country/ registry	STEMI (%)	IH	12-month	IH	12-month
Australia/ New Zealand	~35	2–4	5–6	–	–
	21	–	4	–	10
	42	–	<1[a]	–	2[a]
China	16	1	–	–	–
	0	1	–	–	–
Japan	ns	7	–	–	–
Korea	0	–	–	15	
Malaysia	52*	1	–	–	–
	100	–	12[a]	–	8–13[a]
Taiwan	ns (53–66 NSTE-ACS)	2–19	–	7–24	–
GRACE	30	2–8	–	2–8	–

1A: Abbreviations: CPACS = Clinical Pathways for Acute Coronary Syndromes in China; GRACE = Global Registry of Acute Coronary Events; IH = in hospital; MACE = major adverse cardiovascular event; MM = medical management; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.
[a]1-month; [b]3-month; [c]6-month; [d]24-month; [e]36-month.
*4398 patients included 2033 (46%) with unlikely ischaemic chest pain, or other diagnosis; STEMI patients included STEMI and left bundle branch block.
†Patients underwent invasive therapy. Reported in secondary CPACS publication [117].
‡Percent from STEMI cohort.
Rows highlighted green relate to Advisor/other registry data.
For full data set see Supplementary Table 1.
1B: Abbreviations: GRACE = Global Registry of Acute Coronary Events; IH = in hospital; ns, not specified; NSTE-ACS = non-ST-segment elevation ACS; STEMI = ST-segment elevation myocardial infarction[a]1-month.
*Figures based only on 44% of all cases who had a history of ACS.
Rows highlighted green relate to Advisor/other registry data; DESIRE (July 2001-June 2004); SUNDAY (Jan 2000-Jan 2002).
For full data set see Supplementary Table 1.

the Asia-Pacific region. This review provides a summary of the ensuing discussions.

2. Supporting data

2.1. Search strategy

A systematic PubMed search was conducted (29 May 2013) to identify 'real-world' ACS management data published in the last 20 years from the Asia-Pacific region. From 887 references identified, those considered by the discussants to provide a sufficiently broad overview of ACS management and mortality across the Asia-Pacific region (n = 54) were prioritized and used as a 'reference' dataset simply to support discussion (details in Supplementary materials). While potentially subjective, any additional studies/references or unpublished registry-based data available from the author's own center or region considered by the authors as appropriate to consider were included also.

3. Where are we now? Evidence-based insights to ACS outcomes and treatment status in the Asia-Pacific region

Based on personal experience and supportive data, the authors discussed the current status of ACS management in the Asia-Pacific region; identifying key factors and actions that will potentially impact on, or improve, outcomes in this region.

3.1. Mortality

Registry-based mortality data across APAC countries was considered in terms of disease status and invasive versus non-invasive intervention (Table 1 and Supplementary Table 1) [21–55].

According to the multinational Global Registry of Acute Coronary Events (GRACE), which studied 43,810 patients from 1999–2005 in 14 countries excluding Africa and Asia [22] large differences exist in management practice both by hospital type and geographic location despite comparable use of antiplatelets and anticoagulants [22]. While mortality rates at 6 months post-discharge, for example, were comparable with in-hospital rates (~5%), optimal revascularization and statin use could prevent up to 32% and 10% of deaths by 6 months, respectively [23]. Greatest survival at 6 months was associated with timely CABG (odds ratio [OR] for death 0.60; 95% confidence interval [CI] 0.39–0.90) and PCI (OR 0.57; CI 0.48–0.72), and use of clopidogrel (OR 0.84; CI 0.72–0.99) and statins (OR 0.85; CI 0.73–0.99) [56,57].

In terms of national economic status, the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-1 (low- and middle-income countries, 1995–1996) and OASIS-2 (middle- and high-income countries, 1999–2000) registries – both 2-year prospective studies of outcomes in NSTE-ACS patients [19] – show little difference in 2-year mortality, despite wide variability in management practices. With the exception of China, where 2-year mortality was only 7% (attributed to an inherent low risk of patients in OASIS-2), overall event rates in OASIS-2 remained high (up to 15%), demonstrating continued risk for long-term mortality, subsequent MI, refractory angina, and stroke, and the need for new approaches to reduce risk [19].

Large registries in the Asia-Pacific region such as the Melbourne Interventional Group Registry (MIG-R) and the Acute Coronary Syndrome Prospective Audit (ACACIA) in Australia comprise populations similar to registries in Europe and Canada [24,25,51,58–60]. Perhaps as expected, ACACIA, which included propensity adjusted scoring for early invasive management, showed little difference both in in-hospital and 12-month ACS-related mortality (2–5%) [26] compared with other large international registries [61–63].

In China, registry-based studies reporting guideline-recommendations show treatments are implemented in only one-third of STEMI patients, with many patients not reperfused within recommended times [28] and generally high mortality [29,31,32]. Here, the authors expressed caution given clear heterogeneity in the thoroughness of patient follow-up, highly variable methods of data collection and treatment preferences across China (e.g. preferred thrombolysis use in small hospitals versus PCI in grade 3 hospitals providing specialist health services), and broad geographical variation in patient risk profiles i.e., East versus West. Nevertheless, trends towards decreased mortality rates do relate to improved practice in the emergency room/coronary care unit, including increased use of coronary angiography (CS Ma, personal communication).

Data from the treatment and outcomes of acute coronary syndromes in India (CREATE) registry [33] and the more recent Kerala [34] registry show that primary PCI rate is much lower in India compared with more developed countries and while mortality rates are generally comparable they are significantly higher in 'poor' (8.2%) versus 'wealthy' patients (5.5%) [33,34].

In PCI-oriented countries e.g., Japan and Korea, in-hospital and longer-term (6–12 months) mortality rates of 7% and 11%, respectively, were generally higher than for the non-Asian GRACE population (5–6%) [22,23,52,64–67]. Recent reports of low mortality rates in-hospital (2%), and at 12 (4%) and 24 (6%) months from the Prevention of AtherothrombotiC Incidents Following Ischemic Coronary Attack (PACIFIC) registry, [38], can be attributed to proactive performance of PCI. ACS-related outcomes in Korea, are generally comparable with Japan [39], although the Korea Acute Myocardial Infarction Registry (KAMIR) data did show relatively high rates for invasive intervention versus other registry reports and greater mortality for NSTEMI patients long-term (11 month) compared with in-hospital and 1-month mortality [39,68]. These observations suggest a need for more patient-centric intensive surveillance and treatment while the KAMIR cohort data per se may present unique characteristics in Korean PCI practice as well as contemporary trends in PCI.

Based on the Malaysian National Cardiovascular Disease (NCVD)-ACS registry (Malay 49%, Chinese 23%, Indian 23%), fibrinolysis use was relatively high (>70%) and use of invasive procedures low (13–17%) versus other registries. Reported in-hospital and 1 month mortality was reported as higher in Malay patients (7%) compared with other ethnic groups (4–6%) and rates from other Asian registries [41,42,54,69,70] and attributed to a high prevalence of risk factors and complex and high-risk coronary lesions in the Malay cohort along with relatively low use of invasive management and timely reperfusion.

Singapore is one of few countries in the Asia-Pacific region with a state-funded national MI registry i.e., the Singapore Myocardial Infarct Registry (SMIR) Patients hospitalized for AMI from 2000–2005 showed in-hospital mortality (6–10%) to be generally comparable with the non-Asian GRACE cohort (7%) [46] but higher than the cohort from the study of ACS care across Australia and New Zealand (SNAPSHOT ACS: 4.5%) [26]. It was noted, however, that the Singapore population comprises primarily third and fourth generation migrants of Han Chinese, Indian (South Asian), and Malay (Austronesian) descent.

In Taiwan, a 12-month mortality rate of ~8% in patients with ACS admitted to the hospital within 24 h of symptom onset and where 97% received primary PCI, was perhaps higher than expected [47,48,71]. Notably, there is, a significant lag/deviation from evidence-based guidelines in ACS management in Taiwan, notably, use of DAPT, which fell from 75% at discharge to 25% at 1-year follow-up, and other secondary preventive therapies [47,71] suggest more stringent policy adherence may improve long-term outcomes in ACS patients.

Similarly high ACS-related mortality is evident in Thailand (~10–15% in-hospital, and up to 25% at 12 months follow up) although generally confined to elderly patients and those who received only conservative (non-invasive) treatment without coronary angiogram [49,50,72,73]. A more recent evaluation of registry data did show a significant decrease in in-hospital mortality (~6%), with 12-month mortality for NSTEMI [25%] remaining virtually double that for STEMI [74]; however, differences in characteristics and severity of the enrolled patients confound

interpretation and the invasive strategy for these groups of patients should be considered further.

3.2. Practice patterns and access to resources

Data from the MIG-R indicate significant changes in interventional management between 2004–2005 and 2007–2008, with fewer elective but more urgent PCIs, and increased long-term use of clopidogrel for DES [75]. Consequently, the generally lower ACS-related mortality seen in Australia compared with the US [61–63], for example, was attributed in part, to greater uniformity of treatment in teaching hospitals and more timely access to reperfusion including triage from ambulance to catheterization department (D Eccleston, personal communication). Additionally, transition of care is considered increasingly critical to improve outcomes and many major cities in Australia now have centers with 24/7 primary PCI facilities with paramedics 'upskilled' to perform ambulance-based triage (i.e., in-ambulance ECG and direct transfer to catheterization laboratory for PCI).

Benefits from optimal acute and pre-/post-discharge treatment are supported by other registry-based studies, such as the SNAPSHOT ACS study, and the Genesis Heart Care Group Registry (GHCGR), which demonstrate variability in resources and in-hospital MACE rates across different healthcare jurisdictions [26,76].

Prospective observational studies confirm close compliance with guideline-based recommendations for medical management in China, although mortality in in-hospital and by 12 months post discharge remains high, particularly in STEMI patients (Table 1) and in women who are generally older than men, associated mainly with poor access to treatment and manifest delayed time to reperfusion [27–29,31,32,77,78]. Benefit of improved access to treatment is supported by two single-center registry studies in ACS patients (DESIRE and SUNDAY) – albeit mainly in relatively low-risk UA patients receiving PCI (61%) or CABG (94%), DAPT (60%) and antiplatelet monotherapy (30%) – where a median symptom-to-balloon time of only 8.1 h was associated with in-hospital mortality of 1%, which increased to only 4% at 2 years (DESIRE and SUNDAY; author unpublished data) (Table 1).

Benefits from optimal acute and pre-/post-discharge treatment are also supported by the Kerala registry, and the Detection and Management of Coronary Heart Disease (DEMAT) registry in India [20]. Although use of standard pharmacotherapies generally mirrors guidelines and Western registries [34], optimal in-hospital and post-discharge treatment rates are relatively low [20]. The observation that provision of optimal in-hospital medical care was associated with a 21% lower risk of in-hospital MACE and provision of optimal discharge medical care led to the suggestion that strategies to improve overall ACS care in India should initially focus on an improved in-hospital process-of-care. Indeed, in Japan where PCI is frequently used and ~94% of ACS patients are managed in centers with 24/7 primary PCI facilities, registry- and observational study-based data show that a shorter time from symptom onset to intervention is associated with better long-term clinical outcomes and, specifically, an onset-to-balloon time of ≤3 h provides better 3-year clinical outcomes [36,38,79].

Similarly, in Korea most ACS patients undergo PCI (~90% receiving DES) [39,40,53,68,80–82]. Here, triple anti-platelet therapy including adjunctive cilostazol is frequently used in high-risk PCI patients as it is more effective than standard DAPT in reducing cardiovascular and total mortality, both in-hospital and at 8 months. Although an increased pharmacotherapy index (up to nine concomitant therapies) provides a trend towards lower in-hospital mortality irrespective of disease status, the prescribing of evidence-based therapy in Korea is generally suboptimal with a need for new educational strategies to increase the use of secondary prevention measures [53,81].

According to the Malaysian NCVD-ACS registry, approximately half of patients with ACS undergo primary PCI generally with adoption of good practice for DAPT. Notably, such patients tend to be relatively young with a high prevalence of risk factors (e.g., diabetes), complex high-risk lesions and a median door-to-balloon time for primary PCI (98 min) higher than recommended (<90 min), nevertheless, high procedural success and good pharmacotherapy is associated with a low in-hospital mortality rate (1%) comparable with other registries [42].

In Thailand, which employs a non-PCI and a non-reimbursement policy, ACS-related mortality is generally high. Despite this, improvement in mortality was evident from the Thai Registry in Acute Coronary Syndrome (TRACS, 2007–2008) registry and attributed to a generally better disease status, more PCIs performed, and improved door-to-needle time [49,74]. Nevertheless, ACS-related mortality remains relatively high, and reduced times between first medical contact and treatment, and optimal use of pharmacotherapy post-discharge will perhaps be key to improving outcomes.

3.3. Ethnic differences

Ethnicity is an important factor in regard to outcomes. For example, 5-year follow-up of a contemporary cohort of Singapore Indian, Chinese and Malay patients showed clear ethnic disparities in long-term outcomes despite minimal disparities in in-hospital management with Singapore Indians having the lowest long-term mortality [83]. Although the reason is unclear, Singapore Indians generally belong to the highest socio-economic class, exercise most frequently, smoke the least and adhere most often to healthy food choices [84] suggesting that differential outcomes in different ethnic groups may be due to inter-ethnic socio-cultural and socioeconomic differences along with inherent (genetic) risk factors (e.g. diabetes in India). Further studies are needed to gain understanding of potential variability in compliance and racial differences in rates of disease progression or response to drug therapy.

3.4. Gender differences

US-based registry studies confirm that women with ACS are generally older and present more comorbidities than men [63], notably, between-gender differences in demographic, clinical, and treatment profiles are associated with greater risk of bleeding in female patients with MI undergoing PCI [85]. Similarly, in China, greater acute and post-discharge (1-year) mortality in women compared with men was associated with older age and less frequent receipt of reperfusion therapy [32]. In Korea, higher in-hospital and 1-year mortality in women was associated with a higher frequency of comorbidities, longer pain-to-door time, and more severe hemodynamic status [40,82,86]. In contrast, in India and Singapore, in-hospital management, discharge management, and outcomes generally did not differ between genders [20], although, in Singapore younger women with diabetes were considered to be at greater risk (adjusted hazard ratio [HR] vs >60 years, 1.35; 95% CI, 1.04–1.75) (F Gao, personal communication).

Collectively, these observations support an association between healthcare system quality, gender inequality, and ACS management and outcomes; women tend to be undertreated and, as both genders benefit from revascularization, a more aggressive approach is needed in women, including optimization of discharge medical regimens and improved compliance.

3.5. Education

Lack of patient education towards, chest pain awareness, the need for good treatment compliance, and the relative importance of medication types e.g., in multi-pill prescribing, alongside poor and/or delayed access to facilities, represents considerable barriers to improving outcomes. Specifically, poor patient education results in poor adherence/compliance with treatment associated with, for example, poor knowledge as to which dose/type of medication missed would present more significant consequences e.g., antiplatelet versus statin.

The implementation of post-hospital coaching programmes e.g., the Coaching patients On Achieving Cardiovascular Health (COACH)

programme in Australia has been shown to be effective in improving outcomes, both short-term (12 months) and longer-term (4-year follow-up) [87,88]; 'aware' patients are eight times more likely to be compliant than their counterparts as to the cardiac risks associated with non-compliance [89]. Along with the possibility the prevalence of non-compliance is likely underestimated due to recall bias and self under-reporting [89], improved patient education through sustained educational initiatives remains a key target for improving outcomes.

3.6. Pharmacotherapy support

In Australia, clopidogrel administered in-hospital is reimbursed and largely subsidized post-discharge but a gap still exists in pharmacotherapy use for secondary prevention [90–92]. Moreover, while DAPT typifies standard of care in Australia, adherence up to 12 months is only 60–70% [92,93] suggesting improvement in controlling risk factors, while increasing access and adherence to new pharmacologic therapies e.g., single-tablet CoPlavix, might improve compliance and outcomes. In contrast, ACS-related prescription adherence at 12 months post discharge in Singapore remains relatively high i.e., ≥96% including for aspirin and $P2Y_{12}$ antagonists but improvement is needed, in monitoring of prescription adherence and patient adherence during transition from tertiary to primary care.

In China and India there is high reliance on thrombolysis reperfusion (53%) versus PCI (12%) and CABG (0.1%) and most patients receive DAPT for at least 1 year following such procedures (Supplementary Table 2) [31,33,34]; there have, however, been no recent approvals for newer antiplatelet agents. Recent evidence showing that short-term DAPT (3–12 months) provides favourable clinical outcomes versus long-term use (12–24 months) [94–97] and that prolonged DAPT may benefit high-risk patients (AMI, diabetic, ESRD), and those receiving intervention for management of complex lesions [98], suggests a need for patient management individualized according to patient risk factors, disease activity and severity.

Accumulating data support variable hypercoagulability and associated clinical risk, and pharmacokinetic, pharmacodynamic, and pharmacogenetic profiles of cardiovascular drugs across ethnic cohorts [99]. Compared with Western cohorts, East Asian populations (including Chinese, Japanese, and Korean) demonstrate unique clinical outcomes associated with antithrombotic therapy, including increased levels of platelet reactivity (clopidogrel) and risk of bleeding events [100–107], or increased exposure to active metabolite (prasugrel and ticagrelor) [108–110]. In fact, this so-called "East Asian Paradox" has resulted in a different target international normalized ratio (1.6 to 2.6) being implemented in clinical practice among East Asian patients [111,112].

Recent randomized clinical trials of prasugrel and ticagrelor in East Asian patients support earlier large-scale studies in demonstrating that potent $P2Y_{12}$ receptor inhibitors can provide clinical benefit over clopidogrel in reducing risk from serious bleeding [113–116]. The modest sample sizes of Asian-specific trials does, however, limit their ability to deliver reliable conclusions, although signals of ethnic differences in the efficacy-safety balance of conventional antithrombotic drugs in East Asian patients e.g., increased tendency for bleeding for ticagrelor, may pose concern and further support tailored management. Nevertheless, such trials may help identify effective combinations of new potent antiplatelet therapies with older agents e.g., aspirin and clopidogrel, and which potentially circumvent resistance and/or non-response to these agents. However, long-term real-world data from the Asia-Pacific region are needed to fully assess the benefit to risk profile for new antiplatelet therapies.

3.7. Cost and adherence to treatment

Treatment cost to the patient is also a major barrier to long-term medication use in most countries in the Asia-Pacific region, a situation shown recently to be associated with poor patient awareness of the consequences of non-compliance [89]. In China, fewer than 40% of patients remain adherent to medication at 12 months post-discharge, mostly due to patient refusal [117] Significantly, however, patient non-adherence to antiplatelet agents is frequently due to their doctor considering them not indicated for such treatment, a situation compounded by different reimbursement mechanisms in cities versus rural areas. Cost issues also apply in India where 75% of patients pay for their own treatment. Notably, poorer patients have significantly higher mortality versus richer patients, a trend associated with lower rates of appropriate treatments and delays to intervention and door-to-balloon or -needle times frequently outside of recommended limits [33]. While delays to treatment are often economic in origin, reliance on private or public transport often further delays access to secondary- or tertiary-care hospitals [33].

In Taiwan, most patients are covered by healthcare insurance but with evident lag/deviation from evidence-based guidelines in ACS management [47,71]. Although adherence to DAPT for ≥9 months is associated with significantly lower mortality at 12 months versus antiplatelet monotherapy, the prescription rate of post-PCI DAPT shows a decline following discharge to 12 months (62–13%) with physicians citing the Bureau of National Health Insurance guidelines as the reason for discontinuing [clopidogrel] in 25% of cases [47]. Additionally, reimbursement appears variable and dependent upon the treatment received and affordability, for example, clopidogrel is covered for only 3 months following BMS implantation, compared with 9 months for other treatment modalities. Thus, overall, patient/physician education, adherence both to treatment and guidelines, and appropriate cost to the patient are crucial factors towards improving outcomes across the Asia-Pacific region.

4. Discussion

Based on current practice patterns, the authors considered where we are now and what the barriers are to further improve outcomes in the Asia-Pacific region.

4.1. Barriers to improving ACS outcomes in the Asia-Pacific region

Several key areas were discussed, a consistent observation across the Asia-Pacific region being the strong emphasis on 'benchmark' short-term clinical outcomes (e.g. in-hospital events and those occurring within 6 months of the index event) and relatively weak emphasis on long-term outcomes associated with inherent challenges posed by long-term follow-up per se and maintaining compliance.

Geography is the key barrier to timely in-hospital and post-discharge management in Australia and New Zealand. To support transition of care e.g., from remote areas, Australian health authorities are trialling pre-hospital/in-transit antithrombotic intervention supported by communication with the main cardiology treatment center. Evidence suggests that this approach, along with a clear in-hospital rapid triage pathway, markedly reduces door-to-balloon times. However, the potential real world utility of such intervention remains to be confirmed. In China, Hong Kong, India, and Taiwan, the provision of patient/public education towards chest pain awareness, need for compliance, and effective primary (e.g., lifestyle changes) and secondary prevention requires further considerable resource e.g., trained nurses and improved medical/health system procedures. These are not sufficiently robust at present, which contributes markedly to protracted total ischemic time i.e., prolonged symptom-to-treatment times in Taiwan and India. Effective assessment of patient understanding may help optimize compliance. From a study of adherence to antiplatelets post-coronary stenting, greatest awareness and compliance was seen among patients provided with information through the media and health talks, rather than a cardiologist [89]. Similarly, physician education may help through improved information transfer to patients. In China, many

patients do not receive evidence-based therapies as the treating physician considers them 'not indicated'. Adoption of guideline-recommended pharmacotherapy is poor over both the short- and medium-term and appears to be determined by factors other than risk of a recurrent event [117]. In India, there is a need to implement robust protocols for in-hospital treatment, reperfusion procedures, allocation of discharge medications, and the appropriate use of thrombolysis.

Continuity of care, i.e., transition from tertiary to primary care, is a major barrier to improved outcomes in Japan and Singapore, as is secondary prevention in Hong Kong. Improved patient and doctor awareness and improved outcomes might accrue through national medical education programmes (not yet implemented in Japan) and focus on educating those patients likely to understand the importance of compliance. In Singapore, improving continuity of care represents a policy-based resource allocation problem, currently better for the tertiary versus primary care sector.

4.2. Strategies to improve ACS outcomes in the Asia-Pacific region

The APRICOT working group made several key strategic recommendations to improve ACS outcomes in the Asia-Pacific region: longer-term patient surveillance, greater patient education (pain awareness, compliance, primary/secondary prevention), overcoming geographical challenges to pre-hospital and post-discharge care, and the adoption of value-based over cost-based healthcare systems. The group recommended a greater emphasis on improving longer-term outcomes in ACS. Also, an opportunity exists to improve follow-up and monitor compliance, particularly where patient history is already on record; programmes such as the ongoing NCDR-GWTG programme in the USA [118] have confirmed that recording of treatment received and outcomes achieved improved quality of care [119]. Poor patient compliance and adherence may be improved through community outreach to record adherence at 12 months, possibly via mail, telephone questionnaire, or during a hospital visit. Selected high-risk/low-compliance patients may then be entered into a compliance pathway to allow focus of resources towards patients most at risk. Technology-based solutions such as telemedicine may also aid community outreach programmes by circumventing the need to commute long distances between remote regions and healthcare facilities.

Greater patient education is needed to improve awareness of ACS-related chest pain to reduce time-to-treatment, and understanding of the need for adherence. Likewise, the US NCDR initiative has shown that performance measurement and feedback to hospitals and healthcare providers is effective in improving adherence to guidelines and could form a basis for medical reform and development of quality-of-care indicators. Against this scenario, patient engagement might be improved through implementation of broad community outcomes, including online consultation programs in large community hospitals.

Although large-scale randomized clinical trials such as TRITON-TIMI 38 [115] and PLATO [116] show an overall benefit of potent $P2Y_{12}$ inhibitors versus clopidogrel in ACS, these studies enrolled only less than 6% of patients from the Asia-Pacific region. Significantly, many cardiovascular drugs show differing pharmacokinetic, pharmacodynamic, and pharmacogenetic profiles across ethnic cohorts. For example, East Asian patients (including China, Japan, and Korea) show a lower antiplatelet effect to clopidogrel compared with Western patients, due to genetic polymorphisms that confer resistance to this drug [120–123]; recent clinical studies have shown East Asians may have an inherently different therapeutic zone of platelet reactivity during $P2Y_{12}$ inhibitor treatment and require different dosing regimens compared with Western populations [99]. The recent PRASFIT-ACS study supported this concept, showing that low-dose prasugrel therapy (20 mg loading and 3.75 mg daily) reduced the risk of composite ischemic events by 23% compared with standard-dose clopidogrel therapy (300 mg loading and 75 mg daily) [113]. Dedicated pharmacodynamic studies and clinical trials are urgently required to elucidate specific guidelines for antiplatelet agents among East Asians, in particular, antiplatelet effects with prasugrel and ticagrelor. We also need to strongly consider the paradigm shift from 'one-guideline-fits-all races' to 'tailored antiplatelet therapy' for different ethnic cohorts.

Asian subjects derive similar benefits as Western subjects at lower statin doses [124]. Unfortunately, the pharmaceutical industry often considers it financially non-viable to fund a large Asian-specific late-phase trial after a successful pivotal trial. A possible alternative would be to design and perform registry-based randomized controlled trials, such as the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial [125], that leverage existing ACS registries in Asia-Pacific countries.

Background medications other than DAPT are equally important in lowering residual risk and improving outcomes after an ACS. While generic formulations are now widely available for many proven background medications for ACS, including ACE-I/ARB, β-blockers, and statins, their long-term use for several decades after an ACS event will entail significant costs to healthcare systems. The APRICOT group recommends seeking more sustainable models of prescription financing, including private-public partnerships of cost sharing and a 'right patient, right drug' approach. Such a model is presently practised in selected public hospitals in Singapore, in which universal access to high-cost but high-efficacy medication like ticagrelor is restricted to patients with troponin-positive ACS. As the efficacy-safety balance is maximised in troponin-positive ACS [126], healthcare management systems may be more willing to pay for a high-efficacy but high-cost drug for a limited 12-month period. Such a 'right patient, right drug' approach is already widely applied to high-efficacy high-cost drugs such as herceptin for oestrogen receptor-positive breast cancer. Further incentives for both public and private partners could be a reduced drug cost if patients adhere to the full 12-month prescription and the exclusive use of generic formulations manufactured by the original company after patents end.

It was generally acknowledged that multi-pill prescribing can adversely impact upon compliance in many countries disadvantaged by geographic distance, while randomized controlled trials of the poly-pill formulation have shown significantly improved medication adherence in patients at high CVD risk [127] and potential utility in the acute ACS setting [34]. Strategies to improve in-hospital and discharge medical therapies, perhaps including the poly-pill formulation in the acute phase along with timely reperfusion, are important towards improving local process-of-care measures and ACS outcomes in remote geographic regions [20].

5. Conclusions

ACS remains a leading cause of mortality and morbidity in the Asia-Pacific region. While much effort has been made over the last decade to improve disease management, high variability in management practices and outcomes between countries and regions is still prevalent. This manuscript provides comprehensive insight for seven countries across the Asia-Pacific region into the problems currently being experienced in managing ACS across this region.

ACS-related mortality rates in this region remain high – around 5% in in hospital and up to double this post-discharge – and there is much potential for improvement. Inherent risk factors are key determinants of outcomes in different ethnic groups, for example, a situation compounded by regional differences in AMI incidence in metropolitan versus rural districts. Improving outcomes will be multifactorial. Key 'barriers' towards improving outcomes in this region include patient education, the impact of geographical landscape, limited long-term adherence to guideline-based management, and the widespread adoption of cost-based rather than value-based healthcare systems.

Initiatives to overcome these barriers should include the implementation of pre-hospital management strategies, toolkits to aid in-hospital

treatment, greater community outreach with online patient/physician education and telemedicine, sustainable economic models to improve accessibility to effective pharmacotherapies, and secondary prevention initiatives distilled from high-quality 'real-world' data.

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Appendix A. Supplementary data

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