Review

Almanac 2013: acute coronary syndromes

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Summary

Unstable coronary artery plaque is the most common underlying cause of acute coronary syndromes (ACS) and can manifest as unstable angina, non-ST segment elevation infarction (NSTE-ACS), and ST elevation myocardial infarction (STEMI), but can also manifest as sudden cardiac arrest due to ischaemia induced tachyarrhythmias. ACS mortality has decreased significantly over the last few years, especially from the more extreme manifestations of ACS, STEMI, and cardiac arrest. This trend is likely to continue based on recent therapeutic progress which includes novel antiplatelet agents such as prasugrel, ticagrelor and cangrelor.

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Introduction

In the USA every year nearly 1.2 million patients are hospitalised for acute coronary syndrome (ACS) [1]. However, the proportion of ACS with ST elevation myocardial infarction (STEMI) appears to be declining [2,3]. We can only speculate upon the reasons: potential explanations include the reduction in smoking, the age structure of the population (STEMI is more common in middle age while non-ST segment elevation (NSTE-ACS) occurs more in the elderly), and broader use of statin therapy. Over the last few years there has been a significant improvement in outcomes after STEMI in regard to mortality, cardiogenic shock, and heart failure [1]. Similar trends have been seen for other manifestations of ACS, such as sudden cardiac arrest (SCA) [4,5]. Astonishingly, the clinical outcomes for NSTE-ACS now appear to be worse than for STEMI. However, such figures are misleading, and short term (in-hospital) outcome is still better for NSTE-ACS than for STEMI, while the longer term mortality rate is higher for NSTE-ACS, but this is probably influenced by the different age and risk structure of the STEMI and NSTE-ACS populations: NSTE-ACS patients are generally older and often have multivessel (MV) coronary artery disease (CAD).

ST Elevation myocardial infarction

A major reason for the improved outcomes for STEMI over the last decades has been the increasing availability of primary percutaneous coronary intervention (PCI) services, which all try to continuously improve their performance ('door-to-balloon time'). Initiatives include telemetric transmission of ECGs from the ambulance services, and training of ambulance staff in ECG interpretation. More important than door-to-balloon time is of course the overall 'symptom onset to balloon time'. Patients have become much better informed about symptoms of 'heart attacks', and many ambulance services transfer patients with a suspected STEMI directly to a primary PCI service rather than going to the nearest hospital.

Primary percutaneous coronary intervention

Not only has the rate of primary PCI increased over the years, but progress in device technolo-

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gies and adjunctive pharmacology has also improved the procedural success rate – for example, the availability of stents and second generation drug eluting stents, thrombus aspiration devices, and safer and more effective periprocedural anticoagulation/antiplatelet treatments. Thrombus aspiration has been shown to improve outcomes in smaller randomised trials and is currently recommended by European and American PCI guidelines. However, its effect should probably not be overrated. A recent large scale randomised trial in 452 patients, INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction) did not demonstrate an effect of manual thrombus aspiration on infarct size when used in conjunction with bivalirudin (and intracoronary abciximab) [6,7]. Intravenous glycoprotein (Gp) IIb/IIIa inhibitors have an immediate and potent platelet inhibitory effect and certainly improve thrombus resolution; they may reduce infarct size [6] while their effect on clinical outcomes is somewhat more debatable. Bivalirudin, a direct thrombin inhibitor, which has anticoagulant and probably also antiplatelet effects (via suppression of thrombin dependent platelet activation [8]), can be used as an alternative to heparin and Gp IIb/IIIa inhibitors, and has shown reduced bleeding and even reduced mortality in the HORIZON-AMI trial (Heparin plus a glycoprotein IIb/IIIa Inhibitor versus Bivalirudin Monotherapy and Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction) [6]. Bleeding reduction has become a key aim in primary PCI because of the well documented (but less well understood) association with increased mortality (Table 1).

Transradial versus transfemoral access

Another rather elegant option used increasingly, which may reduce bleeding, involves the transradial approach instead of the traditional transfemoral access [9]. An increasing wealth of data indicate that this reduces bleeding in general; some data even suggest that it reduces mortality when used for primary PCI, but the latter effect is debatable [10,11]. A recent meta-analysis of nine studies involving 2977 patients with STEMI demonstrated an impressive nearly 50% reduction in mortality for the transradial approach (OR 0.53, 95% CI 0.33 to 0.84; $p = 0.008$) [10]. While the authors concluded that the transradial approach should be preferred in STEMI patients, an accompanying editorial high-lighted some limitations of these data [11]. Some data indicate a negative impact of transradial PCI. Baklanov et al. [12] showed a longer median door-to-balloon time with transradial PCI. Another retrospective comparison by Cafri et al. [13], however, showed similar door-to-balloon time irrespective of the access route. Even in elderly people, where there is more advanced atherosclerosis, the radial access does not seem to delay reperfusion as it does not lead to any increase in the door-to-balloon time [14]. There have also been concerns that transradial access may increase the risk of neurological complications compared to transfemoral access. However, in a retrospective analysis of the British Cardiovascular Intervention Society database conducted between January 2006 and December 2010, Ratib et al. [15] have shown that there is no significant association between the use of radial access and the occurrence of neurological complications.

Overall, transradial PCI is certainly a promising technique when used by experienced operators.

Table 1.
Bleeding avoidance strategies [9]

Strategy	Comments
Radial instead of femoral access	Reduces access site bleeding risk (and potentially also mortality in high risk groups)
Bivalirudin	Bivalirudin superior to heparin and glycoprotein IIb/IIIa inhibitors, reduces bleeding (and reduces mortality in STEMI patients)
Fluoroscopy guided puncture for femoral access	High (or low) puncture to be avoided. The femoral head has a consistent relationship with the common femoral artery, and localisation using fluoroscopy is a useful landmark. However, randomised studies failed to show a clinical benefit but were underpowered
Ultrasound guided puncture for femoral access	Fewer vascular complications with this approach in randomised trials
Vascular closure devices	Controversial study results. Increasing evidence pointing towards a positive effect of vascular closure devices, especially if used with bivalirudin
Individualised bleeding risk assessment	Individualised risk assessment and adjustment of clinical practice using risk models, for example, NCDR CathPCI bleeding risk model (bivalirudin, radial access, etc.)

Notes: NCDR – National Cardiovascular Database Registry; PCI – percutaneous coronary interventions; STEMI – ST elevation myocardial infarction.

However, despite its benefits, its use is highly variable across countries. In France and Japan it is the predominant access route [11]. In the UK, its use increased nearly fourfold from 17.2% in 2006 to 57% in 2011 [16]. The USA has the lowest rate of radial access adoption for PCI worldwide (only one in six PCIs) [17]. Even here, there has been an increase in use of radial access. In the first quarter of 2007, 1.2% of PCIs were by the transradial approach; this increased to 16.1% in the third quarter of 2012. There is little doubt that the increasing use of transradial PCI has led to a reduction in access site complications [12,16–18].

While some data indicate that the transradial route may reduce mortality in STEMI patients, this has not been demonstrated in NSTE-ACS. In the RIVAL (Radial vs Femoral Access for Coronary Intervention) trial, currently the largest randomised trial on this topic, there was no difference in major clinical outcomes in NSTE-ACS patients [19]. In a cohort of high risk NSTE-ACS patients enrolled in the EARLY-ACS trial (Early Glycoprotein IIb/IIIa Inhibition in non-ST-Segment Elevation Acute Coronary Syndrome), there were no significant differences in either bleeding or ischaemic outcomes whether radial or femoral access was used [20].

A recent consensus statement by the European Society of Cardiology (ESC) states that a default radial approach is feasible in routine practice in both stable and unstable patients [21]. The ESC recommends performing transradial PCI in STEMI patients only after the operator has become familiar with this approach in stable patients and in diagnostic procedures.

Culprit lesion PCI

Culprit lesion only treatment versus a 'complete revascularisation' approach remains the subject of some debate. One could argue either way: a complete revascularisation strategy may improve overall myocardial perfusion in the critical initial phase; but on the other hand, we know that major adverse complications are increased during acute PCI, and this also may have an impact on the outcome following treatment of non-acute, non-culprit lesions. A randomised study of 214 patients showed that angioplasty of the culprit vessel only was associated with higher rates of adverse events (50.0%) during a mean follow up of 2.5 years than MV PCI, regardless of simultaneous complete revascularisation (23.1%) or a staged complete revascularisation (20.0%) [22]. A recent report of the Ibaraki Cardiovascular Assessment Study registry of Japan showed significantly higher mortality with PCI of a non-culprit lesion in the same setting as the culprit lesion than with PCI of only the culprit lesion [23]. In contrast, results based of the American College of Cardiology National Cardiovascular Database Registry (NCDR-CathPCI) showed similar morbidity and mortality rates with either single vessel or MV PCI [24]. While these data were conflicting, most studies were non-randomised and need to be interpreted with caution. A large meta-analysis of 18 randomised controlled trials (RCTs), including the above mentioned RCT, involved 40 280 patients and showed that staged PCI was associated with lower short and long term mortality compared to culprit vessel PCI and MV PCI [25]. Therefore, current guidelines discourage the performance of multivessel PCI for STEMI and suggest that non-culprit lesions should be staged [26,27]. However, if STEMI patients present in cardiogenic shock or after an SCA, they should be considered for complete revascularisation in one sitting.

The time effect

The current ESC guidelines recommend that STEMI patients should be immediately transported within 2 h of onset of symptoms to a PCI-capable centre without delay [28]. In clinical practice, it is extremely difficult to achieve this goal of symptom onset-to-balloon time [29]. System delays have been shown to be associated with mortality at a median follow-up of 3.4 years in STEMI patients treated with primary PCI [30]. In a more recent study, shorter symptom onset-to-balloon time predicted lower mortality in the long term [31]. A longer treatment delay was seen in females, patients living in a rural area > 22 km from hospital, and when patients were admitted to the emergency department of the hospital instead of direct emergency medical services (EMS) transportation. Researchers suggest that a more generalised use of ambulance/EMS would reduce treatment delays and associated mortality.

Optimal duration of monitoring/hospital stay

The duration of hospital stay has decreased dramatically over the years, which has a major impact on health care expenditure and on patient quality of life. Current practice is widely variable across countries and centres, but it is unclear whether early hospital discharges are safe [32]. It is very reassuring that, despite the continuous reduction in hospital stay, outcomes have significantly improved (Figure 1).

Two new studies have demonstrated that discharging low risk STEMI patients within 2 days following primary PCI is safe and feasible [34,35]. Over 40% of the STEMI patients in one of the studies met early discharge criteria [34]. An early

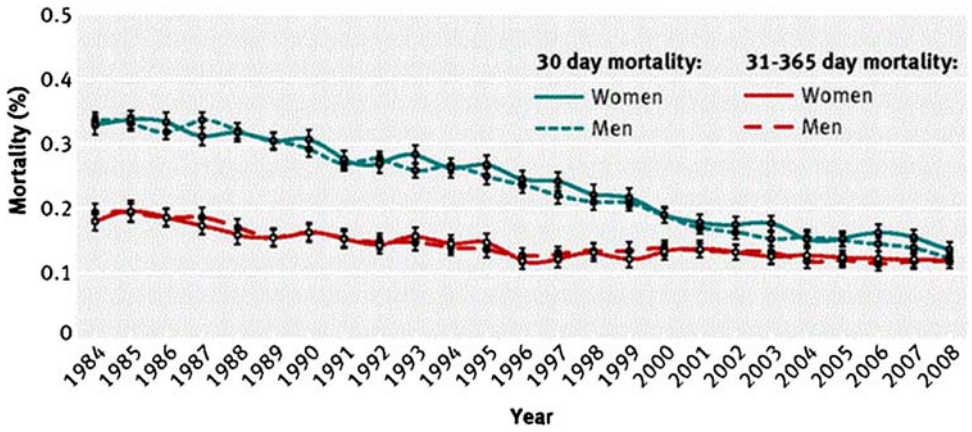

Figure 1. Change in short and intermediate term mortality after ST elevation myocardial infarction. Standardised 30 day and 31–365 day mortality after first hospitalisation for myocardial infarction among men and women between 1984 and 2008 in Denmark [33]. Reprinted with permission from BMJ Publishing Group.

discharge could lower healthcare costs considerably.

Based on the literature, we propose the following criteria to define low risk patients for early discharge:

1. Age < 70 years
2. Short pain to reperfusion interval (<4 h)
3. Uncomplicated primary PCI with good result (TIMI (Thrombolysis in Myocardial Infarction) 3 flow and prompt complete ST elevation resolution)
4. Left ventricular ejection fraction > 45% without symptoms of heart failure
5. No significant arrhythmias during the first 24 h
6. Socially supported, collaborative/compliant patient.

Non-ST elevation ACS

Risk prediction

There is a great need for proper risk prediction in ACS patients for clinical decision making, especially with regard to coronary angiography. There are several risk prediction models in use. The Global Registry of Acute Coronary Events (GRACE) is among the most commonly used scores. Recently, a mini-GRACE (MG) risk score has been developed which excludes creatinine and Killip class from the original eight-factor GRACE risk model. The adjusted mini-GRACE (AMG) risk score includes 'prescription of a loop diuretic during admission' in place of Killip class and creatinine concentration. Both risk scores showed good accuracy in the Myocardial Ischaemia National Audit Project (MINAP), with the AMG risk score performing somewhat better than the MG risk score [36].

Laboratory markers may further help with this risk stratification. The maximal troponin value in patients presenting with NSTE-ACS has been shown to be an independent predictor of in-hospital morbidity and mortality [37]. Other predictive markers include interleukin 10, myeloperoxidase, and placental growth factor [38].

Role and timing of PCI in NSTE-ACS

For intermediate to high risk patients, there is strong evidence supporting routine angiography rather than conservative management. However, the optimal time for coronary angiography is not clear. Though an early invasive approach seems favourable, studies testing the timing effect used varying time points for 'early' and 'delayed' angiography. In very high risk patients such as those with refractory angina, severe heart failure, life threatening ventricular arrhythmias or haemodynamic instability or an evolving myocardial infarction (MI), an urgent invasive approach is indicated. For patients not belonging to this high risk category, the optimal timing is not clear. There is no clear benefit with regard to 'hard' clinical end points for an early invasive strategy within 24 h, but an increasing number of centres undertake an early invasive strategy within 24 h for intermediate to high risk patients. Such an approach is probably reasonable, as an earlier approach certainly helps to reduce hospital stay. Factors such as diabetes, renal function, left ventricular function, recurrent symptoms, and previous revascularisation should be considered along with the TIMI or GRACE score.

Intravascular imaging

Intravascular imaging guided PCI is a concept that evolved when devices such as intravascular ultrasound (IVUS) and more recently optical coherence tomography (OCT) became available. There are two different modes of use, either for

the pre-PCI assessment in order to better understand the coronary plaque (stable or unstable plaque, diameter and length, thrombus burden, etc.), or for post-PCI assessment of stent expansion and apposition. The advantages are obvious; in contrast to angiography as an eyeballing tool, which allows measurement of luminal diameters in a few orthogonal views, coronary IVUS provides a tomographic view. Furthermore, the resolution is much better than for angiography.

The first concept, pre-PCI assessment of lesions has been tested in the multicentre PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study [39]. This study showed that IVUS can be used to define characteristics of vulnerable plaques. The highest risk phenotypes associated with non-culprit major adverse cardiac events (MACE) included thin-cap fibroatheromas, plaque burden $> 70\%$, and minimal lumen area < 4.0 mm. However, these data are not sufficient to advocate using IVUS derived plaque characteristics to decide whether a lesion needs to be treated [40].

While IVUS is based on ultrasound, OCT is based on light, which has a much shorter wavelength, and therefore achieves 10-fold better spatial resolution compared to IVUS [41]. This allows better definition of the thin fibrous caps and the circumferential extent of the necrotic cores. It helps detect other microstructural features such as cholesterol crystals, thrombus, calcium deposits, fibrous plaques, and lipid-rich plaques [42]. OCT can visualise features not seen by IVUS such as intimal flaps and defects in the intima, disruptions in the media, and stent strut apposition.

A Japanese study that analysed the culprit lesion in AMI patients found that the incidence of plaque rupture observed by OCT was significantly higher than that observed by both angioscopy and IVUS [43]. OCT was also superior in detecting fibrous cap erosion and thin cap fibroatheroma, and OCT could also estimate the fibrous cap thickness.

However, the depth of imaging penetration is limited to only a few millimetres with this new technique [44]. So, it is unable to image the adventitia and assess the plaque burden. Therefore, Alfonso et al. [45] had the idea of a combined use of OCT and IVUS in patients with stent thrombosis. Since image length was shorter with OCT, they suggested overlapping OCT runs to circumvent the problem. The challenge of OCT is that it requires a field clear of blood for imaging.

Because OCT has superior resolution to IVUS, it clearly recognises stent struts on heavily calcified areas which are difficult to identify with IVUS. Post-intervention OCT also produces a sharper image of the neointimal–thrombus boundary and provides a reliable diagnosis of in-stent restenosis or neoatherosclerosis. In current practice, OCT and IVUS seem to complement each other with their respective advantages and disadvantages. However, we have to be aware that data on clinical outcomes are limited and that these techniques add to procedural costs.

Antiplatelet therapy

Aspirin is still the basis of every antiplatelet therapy. However, dual antiplatelet therapy of aspirin and a $P2Y_{12}$ receptor blocker is clearly more effective and clopidogrel is the most commonly used agent for this purpose at the moment. However, the problems with this treatment are the rather long delay until maximal platelet inhibition is reached and the high rate of poor responders [46]. One approach that has been tested repeatedly is triple antiplatelet therapy using cilostazol. Even though results of this approach have indicated some benefit, it is rarely used [47,48]. One reason for this is probably the development of newer generation $P2Y_{12}$ receptor blockers such as prasugrel, ticagrelor, and cangrelor. They block the binding of ADP to the platelet receptor $P2Y_{12}$, thereby inhibiting platelet aggregation. Naturally, we would expect that stronger antiplatelet inhibition comes with an increased bleeding risk. Many patients therefore receive proton pump inhibitors (PPI). However, the data do not completely following this logic.

Prasugrel: The TRITON-TIMI 38 trial was a head-to-head comparison between aspirin and prasugrel versus aspirin plus clopidogrel in 13,608 moderate to high risk ACS patients under- going PCI. In most cases, the study drug was given after coronary angiography. At 15 months follow-up, MACE (cardiovascular death, non-fatal MI, or non-fatal stroke) was reduced with prasugrel (9.9% vs 12.1%; HR 0.81, 95% CI 0.73 to 0.90). This composite end point was mainly driven by a reduction in non-fatal MI. Major bleeding was somewhat increased with prasugrel (2.4% vs 1.8%; HR 1.32, 95% CI 1.3 to 1.68). Bleeding was mainly increased in those with a history of stroke or transient ischaemic attack, age ≥ 75 years or a bodyweight ≤ 60 kg. The TRILOGY ACS trial tested prasugrel versus clopidogrel with NSTE-ACS not undergoing PCI. There was no statistically significant difference in MACE rate (13.9% vs 16.0%; HR 0.91, 95% CI 0.79 to 1.05).

Ticagrelor: In contrast to clopidogrel and prasugrel, ticagrelor binds reversibly to the $P2Y_{12}$ platelet receptor. This agent was tested in the PLATO trial (18,624 patients) in patients with ACS, and also those who did not undergo PCI

but had medical therapy. Treatment was started early, at a median of 5 h after hospital admission. This study showed a reduced risk for MACE (defined as cardiovascular death, MI, or stroke) in the ticagrelor arm (9.8% vs 11.7%, HR 0.84, 95% CI 0.77 to 0.92), and there was also a reduced risk for cardiovascular mortality as a single end point. Overall, there was no significant difference in the rates of major bleeding between the ticagrelor and clopidogrel groups (11.6% vs 11.2%, respectively). However, there was a higher risk of non-coronary artery bypass surgery related major bleeding (4.5% vs 3.8%).

Cangrelor: In contrast to these drugs, cangrelor is administered intravenously. It has been tested against placebo and against clopidogrel. The CHAMPION-PLATFORM trial (placebo control) was stopped early because an interim analysis showed disappointing results. The CHAMPION-PCI trial (clopidogrel as a comparator) failed to show a significant benefit as well. The most recent and largest study, the CHAMPION-PHOENIX trial, compared cangrelor against pre- loading with 300–600 mg of clopidogrel. This study not only included ACS but also patients with stable CAD. It found a reduced risk for ischaemic events (death, MI, ischaemia-driven revascularisation or stent thrombosis) over the first 48 h without any increase in major bleeding risk [49]. Its role in clinical practice in the context of having ticagrelor and prasugrel available is not clear yet, and it has never been compared against these agents.

With additional and more potent antiplatelet therapies now available, the challenge is to decide which agent to use and when. Currently, the decision is usually based on clinical and risk factors; pharmacogenetics may also play a role in guiding therapies in the future [50].

Gastrointestinal (GI) bleeding is one of the more common risks of strong antiplatelet therapy. Therefore, PPI are often pre-scribed as well. A recent study found, interestingly, that lower GI bleeding is more common than upper GI bleeding in patients on PPI [51]. Furthermore, the impact of PPI on the clopidogrel effect has been a matter of controversy for some time. Laboratory studies have suggested a reduced antiplatelet effect if PPI are used. However, studies looking at clinical end points have shown conflicting results. A recent systematic review provides a very good overview, including 33 studies, and concludes that clinical data are highly conflicting but that even newer, better designed studies do not show evidence of a relevant adverse effect of PPI in patients on clopidogrel regarding clinical outcomes [52].

Sudden cardiac arrest

SCA is a less common but often fatal presentation of ACS [53]. While there are other reasons for SCA, especially in younger patients, the most common cause for tachyarrhythmic cardiac arrests in patients over 40 is myocardial ischaemia [4,37]. Most of these cardiac arrests occur out of hospital (out-of-hospital cardiac arrest (OHCA)). Survival for OHCA patients has been poor for several decades, averaging <10% to hospital discharge, and may be even lower, particularly in remote areas. However, in recent years survival has increased, especially in metropolitan areas. The London Ambulance Service observed an increase in survival rates from 12% to 32% between 2007 and 2012 [5].

We can only speculate about the reasons for this improvement since few single interventions have really proven to be effective [54]. It is therefore more likely that it is the combination of multiple effective treatments that is responsible for the observed improvements in survival. Early chest compressions and early defibrillation are the undisputed game changers [55]. It is likely that the availability of public automatic defibrillators, defibrillators of the EMS and public awareness, and an increasing number of lay people trained in chest compression, played major roles [56].

However, other factors such as therapeutic hypothermia and immediate angiography to define and potentially treat the underlying cause are important as well [57,58]. An observational study of 9971 patients with OHCA of suspected cardiac cause were assessed regarding the hospital they were referred to. Those treated at hospitals with 24 h cardiac interventional services had a better survival (OR 1.40, 95% CI 1.12 to 1.74; $p = 0.003$).

Current guidelines recommend immediate angiography in patients after successful resuscitation for an OHCA (return of a spontaneous circulation) in case of ST elevations in the post-resuscitation ECG. However, the accuracy of post-resuscitation ECGs is unclear and there are grounds for recommending early angiography in all patients over 35–40 years, regardless of the ECG, if there is no obvious non-cardiac cause.

Cardiac rehabilitation after ACS

While it seems intuitive that cardiac rehabilitation programmes are beneficial by providing careful follow-up, supervised physical activity and guidance on lifestyle modification, clinical data on its effect are controversial. Very recently, cardiac rehabilitation for ACS has been challenged again by the multicentre RCT of comprehensive cardiac rehabilitation in patients following acute

MI (RAMIT: Rehabilitation After Myocardial Infarction Trial) [59]. In this study, cardiac rehabilitation in patients after an AMI had no effect on mortality or morbidity, cardiac medication, risk factors or lifestyle modification. However, we have to be aware that the RAMIT trial was small and if we look at the evidence more comprehensively, by pooling all available RCTs as done by a Cochrane review (combining 47 studies), there is a significant, albeit modest, effect on mortality [60]. This meta-analysis did not include the RAMIT findings which would have further reduced the estimated effect on all cause mortality from 13% to 11% [61]. It is important to note that the Cochrane review focused on physical exercise based rehabilitation, the probability being that non-exercise based rehabilitation (patient education) has little effect on mortality after MI [62].

The problem with combining results of multiple trials is, of course, that this does not account for the 'evolution' of such interventions [63]. The results of the recent OMEGA study, which was a non-randomised cohort study, have shown that a short term comprehensive cardiac rehabilitation programme after acute MI significantly improved the 1-year prognosis [64]. Those who attended rehabilitation programmes had lower all-cause mortality than those who did not, but without randomised treatment assignment, interpretation of such data is difficult. There was a significant dose–response relationship; the more sessions attended the lower the all-cause mortality. However, low attenders were more likely to be smokers, and when adjustments were made for baseline differences in smoking status the dose–response association disappeared.

Though cardiac rehabilitation as currently provided in many countries may not be effective in reducing hard clinical end points, it still helps provide information, advice, and reassurance and helps in long term secondary prevention [65].

Conclusions

The treatment options for ACS have improved significantly over the past few years, contributing to notable improvements in out- comes. This is especially the case for STEMI, while long term mortality after an NSTE-ACS is still considerable. The very recent introduction of third generation antiplatelet therapies (prasugrel, ticagrelor) and the most recent intravenous form, cangrelor, are likely to continue to improve clinical outcomes after ACS. These more potent agents can increase bleeding risks, and considering the association between bleeding and outcomes, periprocedural bleeding avoidance strategies are important. They may include radial access angiography, ultrasound guided femoral access, and the use of bivalirudin.

Contributors

PM drafted the manuscript. AJL and AB revised the manuscript critically for intellectual content. All three authors contributed significantly to this paper and have approved the final version.

Competing interests

None.

Provenance and peer review

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