Acute Coronary Syndrome Registries

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Abstract: Objective: Coronary heart disease is the most common cause of death in the US and Europe.[1,2] ACS, a common complication of coronary heart disease, is associated with more than 2.5 million hospitalizations worldwide each year [3]. This review provides a contemporary overview of key new findings on the pathophysiology, diagnosis, treatment, prognosis of ACS, ACS registries, its importance and discussing most famous and well established registries. **Data Sources:** medical text books, medical journals, and medical websites that have updated researches with key words (Acute Coronary Syndrome) in the title of the paper. **Study Selection:** systematic reviews that addressed Acute Coronary Syndrome and studies that addressed Acute Coronary Syndrome Registries. **Data Extraction:** a special search was conducted at midline with the key words Acute Coronary Syndrome in the title of the paper; extraction was performed, including the assessment of the quality and the validity of the papers that met with the prior criteria that describe the review. **Data Synthesis:** the main result of the review. Each study was reviewed independently; the data obtained were rebuilt in a new language according to the need of the researcher and arranged into topics through the article.

Recent Findings:

- The diagnosis, management and treatment of the various forms of acute coronary syndromes (ACS) which include ST- segment elevation myocardial infarction (STEMI), non-ST- segment elevation (non-STEMI), and unstable angina (UA) have been rapidly evolving in recent years.
- Surveys and registries are an effective meaning of assessing the implementation of guidelines. Although the adherence to guidelines has been shown to be associated with improved outcomes, their implementation remains sub-optimal.
- Smoking, Hypertension, and diabetes are most common risk factors, which didn‘t change over years. This finding necessitates the formulation of programs for primary and secondary prevention of coronary artery disease.
- Evidence based therapies were widely used unless contra- indicated.
- The intervention strategies have seen some flourishment. The percentage of PCI increased significantly, but still thrombolysis is the primary reperfusion modality. That shows the need for developing our insurance system to cover a broader spectrum with more services.
- In hospital complication has decreased significantly.
- Mortality has decreased significantly due to the increase in the use of Primary PCI.

Conclusions: ACS is a potentially life-threatening condition that affects millions of individuals each year. Despite declining rates of hospitalization for MI, the identification and prevention of ACS continues to be an important public health concern. Over the past several years, studies have led to an improved understanding of the pathophysiology of ACS and advancements have been made in the medical management of this condition. Initial ACS management should include risk stratification, appropriate pharmacologic management including DAPT, anticoagulation and appropriate adjuvant therapies, and a decision to pursue an early invasive or conventional treatment strategy. Long-term management following an ACS event should follow evidence-based recommendations and should be individualized to each patient. Observational studies have revealed large differences in the clinical management of patients with cardiovascular diseases when comparing different regions within a country, different countries in specific regions, or different regions across the globe. Because these studies were conducted predominantly in developed countries, there is a need to establish registries in developing countries to increase awareness of cardiovascular disease burden and establish appropriate preventive and management strategies.

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Introduction

Acute coronary syndromes (ACS) represent the acute life threatening phase of coronary artery disease [(4)]. Current knowledge regarding the characteristics, treatments and outcomes of patients diagnosed with the complete spectrum of acute coronary syndromes is limited to data derived from clinical trials and/or from national registries. ACS patients enrolled in randomized, clinical trials are a highly selected, lower-risk subgroup. Hence, unless the trial is very large and heterogeneous, it tends to reflect an ideal study set rather than the diversity of clinical practice. [(5)].

In contrast, registries and surveys have the potential to define the gaps between evidence and practice as well as implementation of guidelines. [(6)]

Randomized trials provide robust evidence for the impact of pharmacological and interventional treatments in patients with ST- segment elevation and non–ST segment elevation acute coronary syndromes (NSTE ACS), leading to changes in practice guidelines. [(7)]

However, the extent and time course of changes in clinical practice are uncertain, and it is unknown whether such changes are associated with improved outcome. Previous studies have documented substantial gaps between guideline recommendations and clinical practice. Thus, there is a clinical priority to determine the extent to which evidence is [(8)]

In recent years, progress has been made in the management of ACS, particularly related to optimizing pharmacotherapy. [(9,10)] Family physicians care for patients presenting with ACS in office as well as emergency settings and play an important role in both acute and long-term management of such patients. In this article, we review the topic of ACS with particular emphasis on initial management and use of the newer medications.

Materials and methods:

The guidance published by the Centre for Reviews and Dissemination was used to assess the methodology and outcomes of the studies. This review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. The institutional review board and ethics committee of Menofiya University approved this study.

Search strategy:

A systematic search of several bibliographical databases was performed to identify relevant reports in any language. These included MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, TRIP database, Clinical Trials Registry, ISI Web of Knowledge, and Web of Science. Articles electronically published ahead of print were included. The search was performed in the electronic databases from the start of the database up to 2016.

Study selection:

All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria.

Participants: patients presented by ACS.

Interventions: primary PCI as a primary reperfusion therapy to STEMI patients Rescue PCI was performed in cases of failed thrombolysis.

Outcomes: Surveys and registries are an effective meaning of assessing the implementation of guidelines. Although the adherence to guidelines has been shown to be associated with improved outcomes, their implementation remains sub-optimal.

If the studies did not fulfill the above criteria, they were excluded. Articles in non-English languages were translated. The article title and abstracts were screened initially, and then, the selected articles were read in full and further assessed for eligibility. All references from eligible articles were reviewed to identify additional studies.

Data extraction:

Study quality assessment included whether ethical approval was gained, the prospective design, the specified eligibility criteria, whether appropriate controls were used, whether adequate follow-up was achieved, and defined outcome measures such as changes in LV mechanics.

Quality assessment:

The quality of all the studies was assessed. Important factors included the prospective study design, attainment of ethical approval, evidence of a power calculation, the specified eligibility criteria, appropriate controls, specified outcome measures, and adequate follow-up. It was expected that confounding factors would be reported and controlled for and appropriate data analysis would be made in addition to an explanation of the missing data.

Data synthesis:

Because of the heterogeneity in postoperative follow-up periods and outcome measures reported, it was not possible to pool the data and perform a meta-analysis. Comparisons were made by a structured review.

Discussion:

Cardiovascular disease remains the primary cause of mortality, and a major cause of disability in the developed world. This significant burden necessitates ongoing improvements in patient management, to minimize the impact of cardiovascular conditions on both patients and healthcare systems. These improvements in cardiovascular care are promoted by an evidence-based approach, shaped by comprehensive clinical guidelines. [(11)]

ACSs include a variety of clinical scenarios ranging from unstable angina and ST elevation myocardial infarction to non ST elevation myocardial infarction. Many new pharmacological and technical approaches to ACSs have been introduced into clinical practice in recent years. This has resulted in a significant heterogeneity in the management and treatment of patients presenting with ACS [12]

ACS patients enrolled in randomized, clinical trials are a highly selected, lower-risk subgroup. Hence, unless the trial is very large and heterogeneous, it tends to reflect a ideal study set rather than the diversity of clinical practice.

ACS Diagnosis:

Patients with ACS typically present with acute chest pain. The main methods used to confirm a diagnosis of ACS and to distinguish between the three types of ACS are as follows: [13]

ECG: UA and NSTEMI are associated with ST depression/transient elevation and/or T-wave changes; persistent ST elevation is characteristic of STEMI.

Cardiac troponins: Troponin levels are sensitive markers of myocardial injury; elevated troponin levels as a result of myocardial damage can be used to distinguish UA from NSTEMI.

As shown (Figure 1, 2)

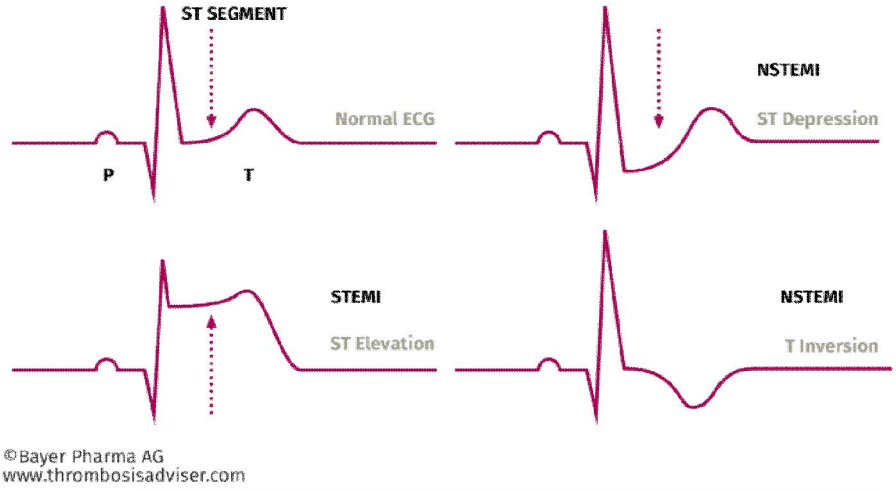

Figure 1. Illustration of normal ECG and ECGs showing STEMI and NSTEMI

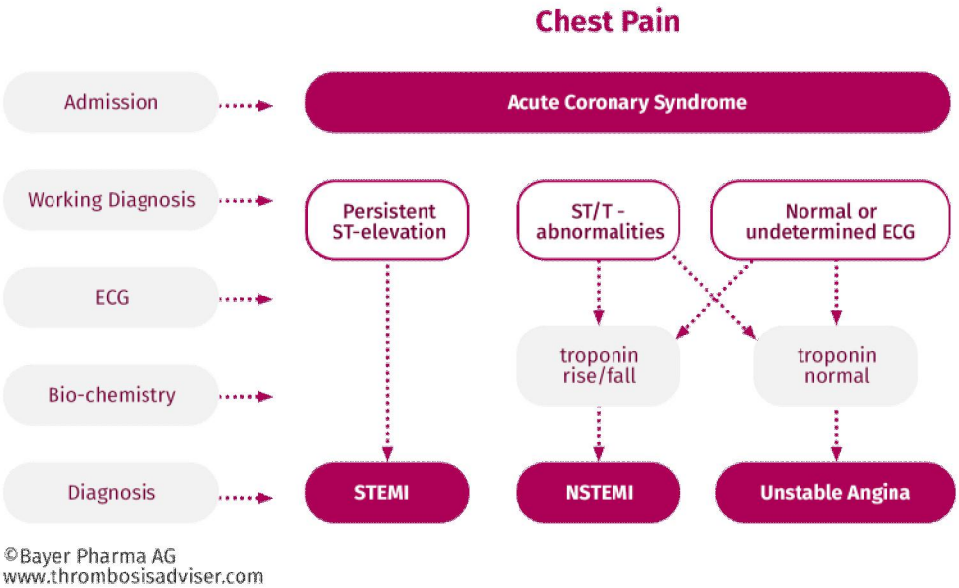

Figure 2. Diagnosing the spectrum of ACS [13]

Echocardiography:

- Identified Echocardiograms may play an important role in the setting of ACS. Regional wall-motion abnormalities can be with this modality, and echocardiograms are especially helpful if the diagnosis is questionable [(14)]
- An echocardiogram can also help in defining the extent of an infarction and in assessing overall function of the left and right ventricles. In addition, an echocardiogram can help to identify complications, such as acute mitral regurgitation, LV rupture, and pericardial effusion [(14)].

Cardiac Angiography:

- Cardiac catheterization helps in defining coronary anatomy and the extent of a patient's disease.
- Patients with cardiogenic shock, intractable angina (despite medication), severe pulmonary congestion, or right ventricular (RV) infarction should immediately undergo cardiac catheterization. (Cardiogenic shock is defined as a systolic BP of less than 90 mm Hg in the presence of organ hypo perfusion) [(15)].
- The earlier that coronary angiography is performed, the lower the risk of recurrent ischemia. This also shortens the hospital stay for those patients.

Computed Tomography Coronary Angiography and CT Coronary Artery Calcium Scoring:

- CT coronary artery scoring is emerging as an attractive risk stratification tool in patients who are low risk for ACS. This imaging modality exposes the patient to very little radiation (1-2 msV). No contrast is needed, and the study does not have a requirement for heart rate [(16)].

Pathophysiology

Most cases of ACS are caused by the erosion or rupture of an atherosclerotic plaque, a thickening of the vessel wall in a coronary artery. [(17)]

Plaque rupture results in exposure of the contents of the atherosclerotic plaque and subendothelial fibres to the blood, leading to: [(17, 18, 19)].

- Thrombus formation
- Platelet activation and adherence to subendothelial structures; aggregation of additional platelets causes the thrombus to grow.
- Activation of the coagulation cascade, resulting in the production of thrombin, which stimulates further platelet recruitment and aggregation. Thrombin also catalyses the generation of fibrin, which forms the main protein component of the thrombus.

The thrombus restricts the flow of blood to the heart. A prolonged lack of blood supply resulting in necrosis (death) of heart muscle tissue is defined as an MI.4 The degree of arterial blockage caused by the thrombus determines the amount of myocardial damage that occurs and the type (and severity) of ACS that results: [(3,18)] (Figure 3).

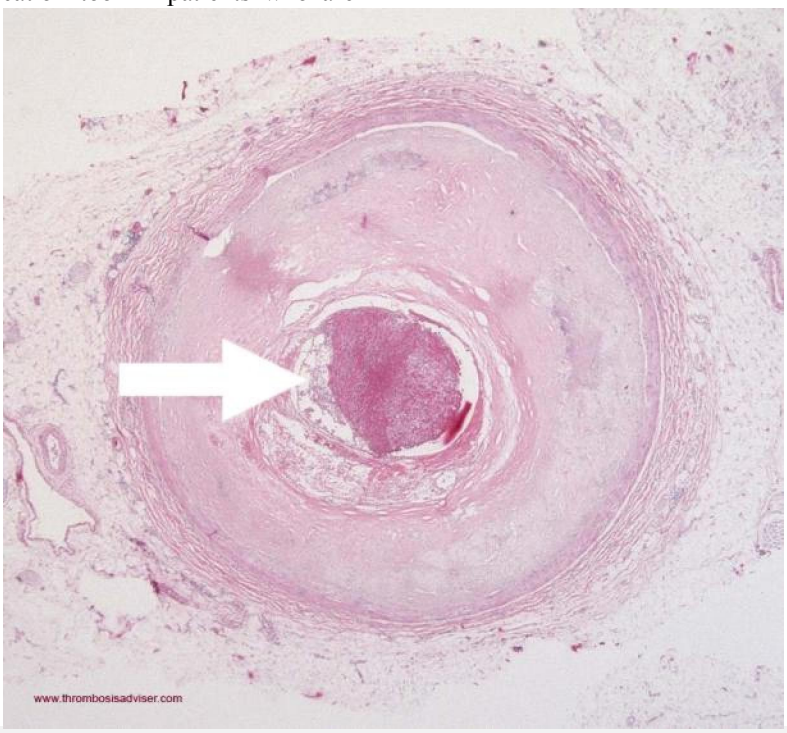

Figure 3. Coronary artery with thin muscular media and prominent intimal hyperplasia with calcification. Lumen obstructed by thrombus (arrow)

- UA – partial/intermittent occlusion, no myocardial damage.
- NSTEMI – partial/intermittent occlusion, myocardial damage.
- STEMI – complete occlusion, myocardial damage.

Management:

In 2015, the American College of Cardiology/American Heart Association (ACC/AHA) released the guidelines recommendations on the management of acute coronary syndromes (ACSs) to assist in maximizing patient outcomes, including the following: [20]

- Standard initial medical therapies include supplemental oxygen for arterial oxygen saturation < 90% or respiratory distress; sublingual nitroglycerin; oral beta-blocker therapy within the first 24 hr. in the absence of heart failure, low output state, increased risk for cardiogenic shock, or other contraindications to beta-blockade; non dihydropyridine calcium channel blocker for continuing or recurrent ischemia and contraindication to beta-blockade (in the absence of clinically significant left ventricular dysfunction). [20]
- Non steroidal anti-inflammatory drugs (except aspirin) should not be initiated and should be discontinued during the hospitalization for NSTE-ACS because of the increased risk of major adverse cardiac events associated with their use.
- Initial antiplatelet/anticoagulant therapy includes 325 -mg chewable aspirin at presentation, followed by a daily maintenance dose of aspirin at 81-126 mg daily. A P2Y12 inhibitor (clopidogrel or ticagrelor) should be used in addition to aspirin for up to 12mo in patients treated with either an early-invasive or ischemia-guided strategy. In addition to antiplatelet therapy, parenteral anticoagulation is indicated with enoxaparin, bivalirudin, fondaparinux, or unfractionated heparin. [20]
- A high-intensity statin should be initiated or continued in all patients without contraindications. Angiotensin-converting enzyme inhibitors should be started and continued indefinitely with a left ventricular ejection fraction <40% or hypertension, diabetes, or stable chronic kidney disease unless contraindicated.
- An early invasive strategy is indicated for patients with refractory angina or hemodynamic or electrical instability and those at elevated risk for clinical events. An early invasive strategy is not recommended for patients with extensive comorbidities (eg, hepatic, renal, or pulmonary failure; cancer) in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. An ischemia-guided strategy is appropriate for low-risk score patients (Thrombolysis In Myocardial Infarction or Global Registry of Acute Coronary Events), for low-risk troponin-negative women, and by patient or clinician preference in the absence of high-risk features. When an ischemia-guided strategy is chosen, noninvasive stress testing is recommended prior to hospital discharge to detect severe ischemia occurring at a low-stress threshold. [20]
- Patients undergoing percutaneous coronary intervention (PCI) should be treated with a P2Y12 inhibitor: clopidogrel, prasugrel, or ticagrelor. Discharge planning should include detailed patient education about symptoms, lifestyle interventions, standard medication with dual antiplatelet therapy, cholesterol management, referral to cardiac rehabilitation, timely follow-up with the healthcare team, and influenza and pneumococcal vaccines. [20]
- NSTE-ACS patients with prior revascularization PCI or coronary artery bypass grafting should receive antiplatelet and anticoagulant therapy and be strongly considered for an early invasive strategy because of their increased risk. Medical treatment in the acute phase of NSTE-ACS and decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus. [20]
- Patients who develop NSTE-ACS following noncardiac surgery should receive guideline-directed medical therapy, with additional management directed at the underlying cause of the pathophysiologic process.
- Older patients with NSTE-ACS, because of their high-risk status, should be treated with guideline-directed medical therapy and an early invasive strategy with revascularization as appropriate; pharmaco-therapy should be individualized and dose adjusted by weight and creatinine clearance to reduce adverse events. Management 'decisions should be patient centered, incorporating patient preferences, comorbidities, functional and cognitive status, and life expectancy. [20]
- Women with NSTE-ACS should be managed with the same pharmacologic therapy as men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk. Women with NSTE-ACS and high-risk features (eg, troponin positive) should undergo an early invasive strategy. [20]

Coronary Revascularization in STEMI:

In patients presenting with a STEMI, reperfusion therapy should be administered to all eligible patients with symptom onset within the prior 12 hours. [21] Percutaneous coronary intervention (PCI) is the recommended method of reperfusion when it can be

performed in a timely fashion, with the goal of time from first medical contact to device time of less than or equal to 90 minutes (strength of recommendation A).[3] If patients are unable to get to a PCI-capable hospital within 120 minutes of a STEMI, then fibrinolytic therapy should be administered within 30 minutes of hospital arrival, provided there are no contraindications to its use (strength of recommendation A). [21] (Figure 4)

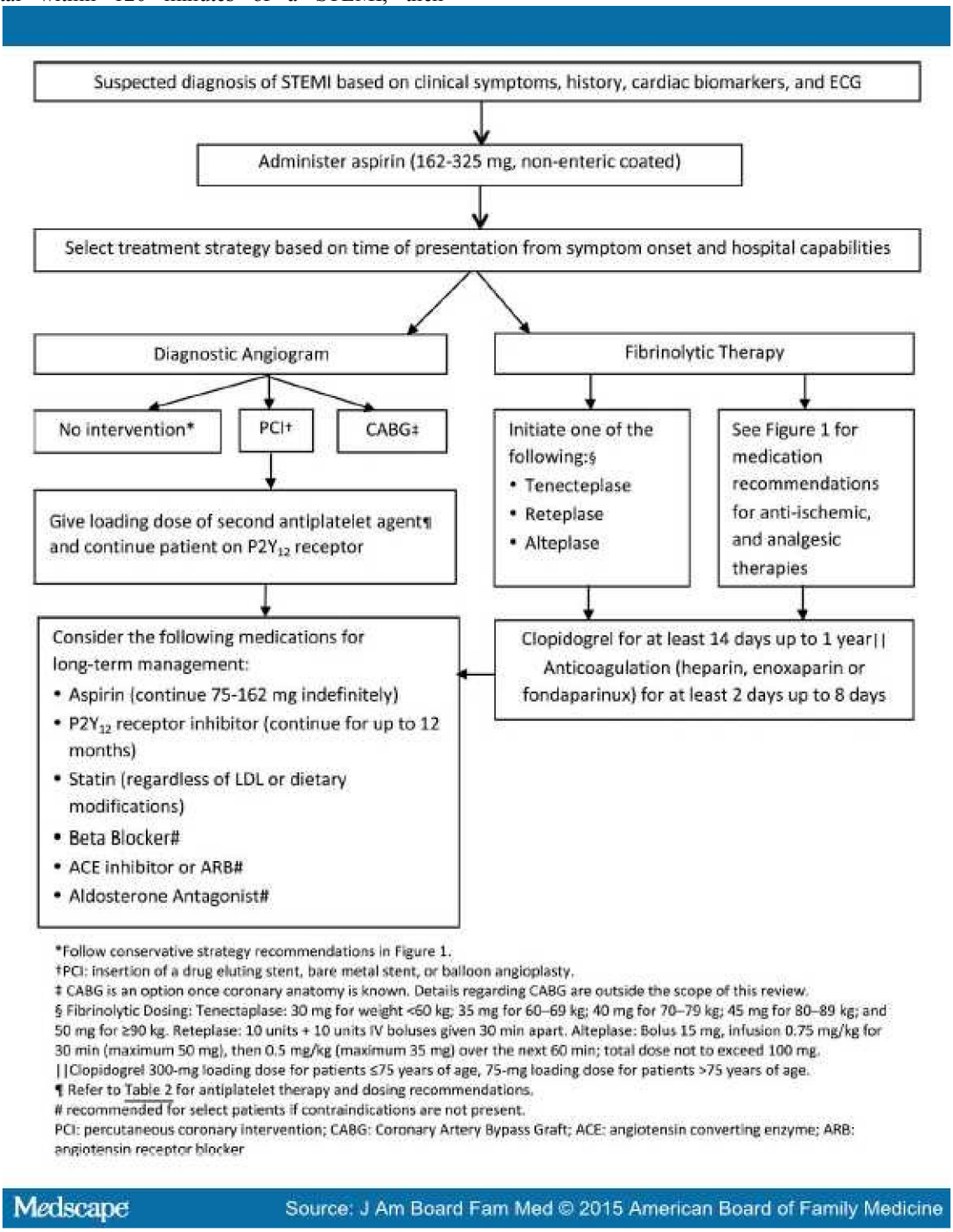

Figure 4. Pharmacologic management of patients with ST-elevated myocardial infarction (STEMI). ECG, electrocardiogram. [21]

Acute Coronary Syndrome Registries:

Patient registries (PRs) are organized systems using observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease with predetermined scientific, clinical, or policy purposes. Because well-designed and well-performed PRs can provide a real-world view of clinical practice, they are increasingly popular. Furthermore, the information they provide is sometimes used in clinical guidelines to establish the range of benefit or harm of interventions. [22]

The World Health Organization (WHO) predicts that cardiovascular diseases would be the leading cause of morbidity and mortality in the developing countries by the year 2020. Cardiovascular disease is the leading cause of death in Egypt and worldwide, placing great strain on the world's health systems. High-quality treatment of CVD requires a valid, reliable measurement for ensuring evidence-based care. [23-24]

Importance of registries in clinical practice:-

The scientific basis of recommendations is an important feature of clinical guidelines, and influences the degree to which they are followed in clinical practice. [25]

Recent studies have assigned the highest evidence grading to randomized controlled trials (RCTs) that are clinically important, and representative of the clinical population covered by the guideline recommendation. [26]

Non-randomized prospective registries document the treatment and outcomes for consecutive patients in clinical practice. Therefore, data are gained from a real-world selection of patients, many of whom would be excluded from RCTs, in a variety of clinical settings. RCTs are costly, which limits the size of the populations under study. In contrast, registries can survey large populations, providing a powerful scientific tool. [27]

Registries can survey large populations, providing a powerful scientific tool. For example, The Global Registry of Acute Coronary Events (GRACE), launched in 1999, currently includes over 100 000 patients with (ACS) in 30 countries worldwide. [27]

Another example is The Reduction of Atherothrombosis for Continued Health (REACH) Registry set out to recruit 68 000 outpatients at risk for, or suffering from, atherothrombotic diseases from 44 countries worldwide. [28]

Key attributes of an effective clinical registry [27]:

- Standardized data collection with definitions and reporting.
- Integrated tools for rapid feedback to participating institutions.
- Appointment of a single principal investigator or a small steering committee.
- Proper ethical review procedures.
- Electronic data capture with clear, simple explanations of definitions and instructions for participants, and plausibility controls to highlight incorrectly entered data.
- Randomized selectionof centers (ideally, 100% participation).
- Consecutive enrolment of patients for representativity.
- Audit of at least a small group of randomly selected centers.
- Centralized data compilation and statistical analysis, performed by professional statisticians.
- Reporting of all collected data, with conclusions appropriate to study the design.
- Transparent reporting of investigators and funding sources in all publication.

A crucial problem of many RCTs is that the treatment groups are similar to each other but not to the patient population that appears in clinical practice. However, in observational studies, characteristics and risk profiles of the treatment groups are usually different, so estimates and statistical tests of treatment effects may be biased. This bias pertains only to situations where the registry is regarded as an observational study to estimate treatment effects, not as a survey, for instance. [27]

If higher-risk patients are not adequately represented in RCTs, registries have an important role in validating trial findings in groups that are excluded or under-represented. [29]

Registry data have also been used to determine areas in which treatment practices are suboptimal or conflicting with guideline recommendations, or vary substantially between geographical areas23, 46 or between patient sub-groups. [30]

An encouraging increase in adherence to guidelines was identified by the second Euro Heart Survey on Acute Coronary Syndromes (EHS– ACS-II) when compared with EHS–ACS-I, which was completed 4 years earlier. Use of primary reperfusion therapy increased from 56 to 64%, and mortality rates fell by 20%, both in hospital and at 30 days follow-up. [31]

Examples of Important registries and findings:-

Three of the Most Famous and well established registries are: - The **G**lobal **R**egistry of **A**cute **C**oronary **E**vents **(GRACE),** the **N**ational **R**egistry of **M**yocardial **I**nfarction **(NRMI),** and the **Euro Heart Survey ACS Registry**

As those registries are relevant to our work, we

will be discussing some of their results in this chapter.

1- Euro Heart Survey ACS Registry

• **Objectives:** to document the current presentation of ACS in Europe and to determine the adherence to current ESC guidelines for the management of the different kinds of ACS:

• Acute reperfusion treatment (ST-elevation myocardial infarction (STEMI).

• Invasive versus conservative treatment (NSTEMI/unstable angina).

• Adjunctive medical treatment (all ACS).

The first Euro Heart Survey ACS Registry collected data on 10,484 patients with ACS between September 2000 and May 2001. The survey assessed a number of in-hospital and 30-day outcomes for these patients, including:

• Correlation between initial and final diagnoses.

• Diagnostic and therapeutic modalities.

• In-hospital complications.

• Post-discharge event rates and mortality rates [32]

The second registry collected data on 6385 patients with ACS between March and October 2004. The survey enabled the assessment of temporal trends in the diagnosis, management, and outcomes of ACS (in-hospital and 30-day follow-up), while comparing the results with those from the initial survey. [33]

The third registry collected data on 21,582 consecutive patients between October 2006 and October 2008. After 1 year follow-up, the immediate, in-hospital and 1-year outcome of patients with ACS were assessed, which included the following factors:

• Gender disparities in the management and outcomes in patients presenting with acute myocardial infarction (MI). [34]

• Performance measures (such as appropriate and timely therapy use) in STEMI and their result on patient outcomes [35]

• Validation of the Killip classification in patients presenting with ACS [36]

• The determinants of stroke and its impact on the outcomes of

Patients with presenting with an ACS event [37]

• Patient demographics, subsequent intervention/ therapy use and clinical outcome ([38]

2- GRACE:-

• **Objectiv**e: to track the outcomes of patients presenting with ACS.

• Large, ongoing, observational registry, launched in 1999.

• Involves over 100,000 patients who have presented to 247 hospitals in 30 countries, including those in North America, South America, Europe, Asia and Australia.

• Incorporates the data from the first 10-20 consecutive cases that present with qualifying symptoms plus evidence of coronary artery disease each month at each center, and follows these patients for 6 Months.

GRACE provides data on:

• Demographics.

• Symptoms at presentation.

• Management.

• Outcomes.

• Guideline compliance rates [39]

• Risk factors for adverse or fatal outcome [40-41]

The GRACE ACS risk model score; [42] which has been validated extensively, was incorporated into the 2007 European Society of Cardiology (ESC) guidelines for the treatment of patients with non-ST-elevation myocardial infarction (NSTEMI) [43]

3- NRMI

The National Registry of Myocardial Infarction (NRMI) was a large, prospective US registry, running from 1990 to 2006, which collected data on reperfusion therapy, including door-to-needle (D2N) and door-to-balloon (D2B) times, and outcomes of more than 2.5 million patients with acute myocardial infarction, of which 1,374,232 patients had STEMI. [44]

A key finding of the NRMI has been the documentation of changes in the use and type of reperfusion therapy for patients with (STEMI) and changes in door-to-needle (D2N) times for fibrinolysis and door-to-balloon (D2B) times for primary percutaneous coronary intervention (PPCI).

Over the duration of the study, the proportion of STEMI patients eligible for but nor receiving reperfusion therapy decreased significantly, from 44.9% in 1990 to 28.1% in 2006 ($p<0.001$). [45]

In 1990, the predominant reperfusion therapy was fibrinolysis (52.5%), with primary PCI used in only a very small proportion of patients (2.6%). However, by 2006, primary PCI had overtaken fibrinolysis as the predominant form of reperfusion therapy (43.2% versus 27.6%). These findings mirror results from the international GRACE registry. [45] (Figure 5)

Among eligible STEMI patients that were treated with fibrinolysis, the D2N time decreased from 59 min in 1990 to 29 min in 2006 ($p <0.001$ for trend). This corresponded to a decrease in in- hospital mortality for patients treated with fibrinolysis from 7.0% in 1994 to 6.0% in 2006 ($p <0.001$ for trend). The relative improvement in mortality attributable to reductions in D2N was estimated to be between 14.3 and 16.3%. [45]

Among eligible STEMI patients that were treated with primary PCI, the D2B time decreased from 120 min in 1994 to 87 min in 2006 ($p <0.001$ for trend). For non-transfer patients, D2B time decreased from 111 to 79 min, whereas for patients transferred from other hospitals or emergency departments, D2B time

decreased from 226 to 139 min. This corresponded to a decrease in in-hospital mortality for patients treated with PCI from 8.6% in 1994 to 3.3% in 2006. The relative improvement in mortality attributable to reductions in D2B was estimated to be between 5.8% and 7.5%. [45] (Figure 6)

The rate of overall reperfusion for patients diagnosed with ST- elevation myocardial infarction increased from 1990 to 2006, with proportionally more patients receiving PPCI than thrombolysis in 2006.

There were significant reductions in D2N and D2B times for STEMI patients eligible for reperfusion therapy over the duration of the NRMI, which resulted in a significant improvement in in- hospital mortality for all reperfusion strategies. [46]

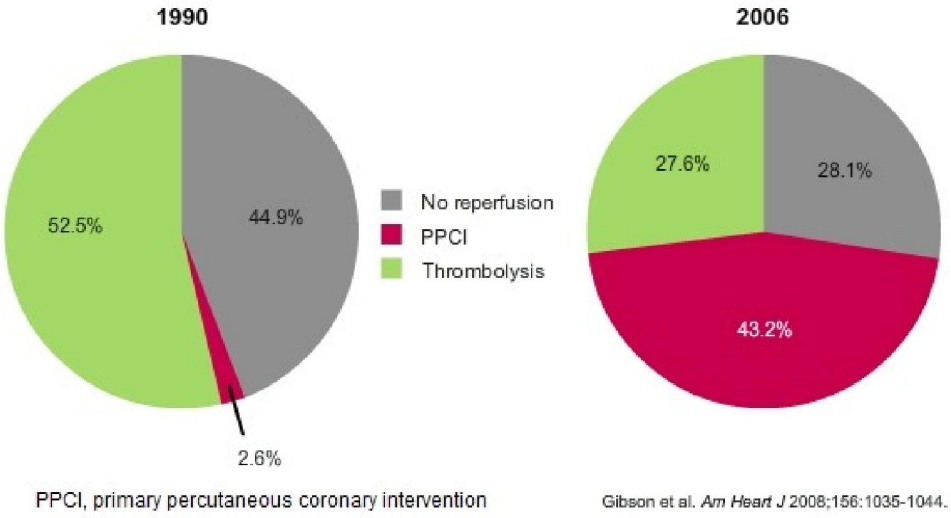

Figure 5. Trends in reperfusion for reperfusion-eligible STEMI patients, 1990 to 2006

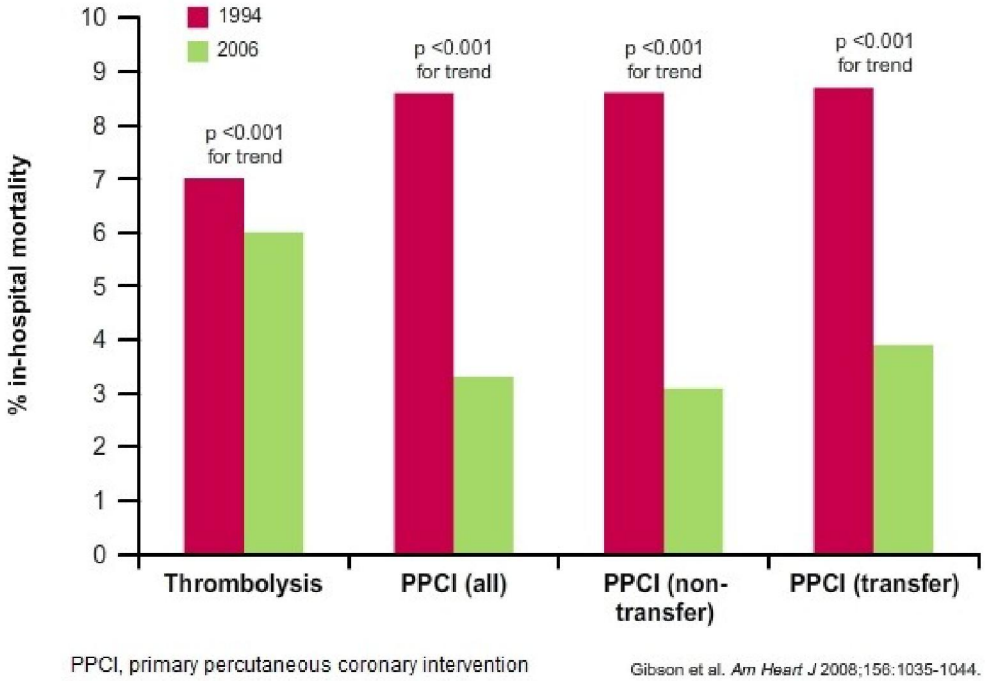

Figure 6. Door to Balloon times over the years

Conclusion

ACS is a potentially life-threatening condition that affects millions of individuals each year. Despite declining rates of hospitalization for MI, the identification and prevention of ACS continues to be an important public health concern. Over the past several years, studies have led to an improved understanding of the pathophysiology of ACS and advancements have been made in the medical management of this condition. Initial ACS management should include risk stratification, appropriate pharmacologic management including DAPT, anticoagulation and appropriate adjuvant therapies, and a decision to pursue an early invasive or conventional treatment strategy. Long-term management following an ACS event should follow evidence-based recommendations and should be individualized to each patient.

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