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Expert Review

2021 Update for the Diagnosis and Management of Acute Coronary Syndromes for the Perioperative Clinician

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In this review, recent key publications related to acute coronary syndrome (ACS) are summarized and placed into context of contemporary practice. Landmark trials examining vascular access in ST-elevation myocardial infarction, the management of multivessel disease, acute myocardial infarction and cardiac arrest are discussed. An update in pharmacology for ACS provides updates in major trials relating to P2Y12 inhibitor initiation, deescalation, and use in special populations. Additional updates in the use of lipid-lowering agents and adjunctive medications in ACS are reviewed. Finally, cardiac pathology related to coronavirus disease 2019 (COVID-19), as well as the impact of the COVID-19 global pandemic on the care of patients with ACS, is summarized.

Key Words: acute coronary syndrome; perioperative; myocardial infarction; anesthesia

DESPITE ADVANCES in the management of heart disease, cardiovascular disease remains a leading cause of death. Patients with acute coronary syndrome (ACS) represent one of the highest risk groups in this cohort. Advances in the diagnosis and management of ACS have shaped the way that these patients are identified,and treatment strategies have evolved. In this review,the authors discuss the most impactful publications related to ACS in 2020 and place them in the context of this evolving field. The year 2020 was also historic as the global spread of coronavirus disease 2019 (COVID-19) predominated clinical medicine and biomedical research. In this review,the authors also discuss the impact that the COVID-19 pandemic has had on the management of patients with ACS as well as the cardiac manifestations of COVID-19

Epidemiology

The long-term epidemiology of coronary heart disease has been studied in multiple longitudinal cohort studies. The 50-year follow-up of the European Seven Countries Study was published in 2020.[1] This study followed 6,500 men who were 40-to-59 years old at the time of enrollment and illustrated changes in the prevalence of risk factors over time, notably demonstrating reductions in smoking and serum cholesterol levels, as well as increases in average blood pressure. As the frequency of risk factors decreased over the study period, the hazard rate for mortality decreased.

Similarly, temporal trends in hospitalizations for acute myocardial infarction (MI) have shown marked reductions over time, with a large cohort from Kaiser Permanente demonstrating a

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48% reduction in hospitalizations for ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) between 2000 and 2014.[2] Analysis of acute MI (AMI) hospitalization trends by race revealed that Caucasian patients had a disproportionate reduction in hospitalizations for AMI compared with Hispanic and Black patients during this period. These findings shed light on persistent racial disparities in cardiovascular disease awareness, treatment, and risk factor optimization. Analysis of the same cohort demonstrated similar disparities when patients were stratified by gender, with the rate of reduction in hospitalization lower among women than men.[3] Despite higher rates of primary prevention, women with AMI are less likely to undergo revascularization and receive treatment for secondary prevention than men.[4] Identification of groups with lagging improvements in outcomes is a key step in achieving equitable healthcare outcomes.

Risk Factors

Further risk factor elucidation in 2020 was notable for new insights into the role of malnutrition and smoking in ACS. In a retrospective study in northern Spain, researchers evaluated the nutritional status of patients discharged with a diagnosis of ACS.[5] Using validated tools to determine nutritional status, 8% of patients were found to have moderate-to-severe malnutrition. While the worst nutrition scores were associated with a low body mass index, 8% to 36% of malnourished patients had a body mass index $\geq$25 kg/m^2 depending on the nutritional index used. Poor nutritional status was associated with a two-fold increase in the risk for all-cause death. These findings highlighted the importance of identifying and intervening on this modifiable risk factor.

Smoking tobacco, an important risk factor for ACS, was examined in a large pooled analysis of primary percutaneous coronary intervention (PCI) patients. Increased rates of STEMI among smokers have been well-established. Previous studies have observed a favorable prognosis after STEMI among smokers, with the "smoker's paradox" phenomenon posited to be related to ischemic preconditioning and perhaps reduced infarct size among smokers. Redfors et al. analyzed data from ten randomized controlled trials in which patients underwent primary PCI for STEMI, and infarct size subsequently was characterized by cardiac magnetic resonance imaging or Single Photon Emission Computed Tomography (SPECT).[6] Smokers were, on average, ten years younger than nonsmokers at the time of STEMI and, after adjustment for age and other risk factors, had a higher risk of death or heart failure hospitalization, as well as reinfarction compared with nonsmokers. These findings suggested that the "smoker's paradox" is more likely to be related to the younger age and lower comorbidity burden at the time of STEMI in smokers rather than any protective effect of tobacco use.

Diagnostics

After the publication of the Fourth Universal Definition of Myocardial Infarction in 2018, the classification of acute and chronic myocardial injury has increased among patients with elevated troponin biomarkers.[7] The myocardial injury group previously has been shown to have increased mortality. Validation studies of the newly published Fourth Universal Definition have shown reclassification rates up to 30% compared with the classification based on the Third Universal Definition of MI.[8] The majority of reclassified patients were reclassified to acute or chronic myocardial injury. This group had significantly higher rates of cardiovascular events compared with nonreclassified patients. Another study of patients aged 50 and younger compared patients with type-1 MI, type-2 MI, or myocardial injury based on the Fourth Universal Definition.[9] Increased mortality in the type-2 MI and myocardial injury groups was striking, with nearly half of patients withtype-2 MI and one-third of patients with myocardial injury dying within ten years.

While the Fourth Universal Definition has improved the identification of patients at high risk for subsequent cardiovascular events, particularly among those classified as myocardial injury, significant controversy continues in the application of these definitions to clinical trials. Multiple large clinical trials comparing revascularization strategies have used varying definitions of periprocedural MI, including the Third and Fourth Universal definitions, as well as the Society for Cardiovascular Angioplasty definition. As periprocedural MI is a commonly included component of the composite primary endpoint, nuances between the different definitions have large repercussions on the outcomes of pivotal clinical trials. As investigators learn more about the clinical significance of periprocedural MI, the definition and role of this endpoint in clinical trials remain controversial.[10-12]

The Fourth Universal Definition also codified the adoption of hs-troponin assays in the diagnostic algorithms for MI and myocardial injury. Adoption of hs-troponin resulted in the increased diagnosis of type-1 MI, type-2 MI, and myocardial injury by 11%, 22%, and 36%, respectively.[13] Despite an increased number of patients diagnosed with MI and myocardial injury, similar increases were not observed in treatment or improved outcomes.

An additional application of hs-troponin is the potential role of this biomarker to rule out MI in patients presenting to the emergency department with chest pain. An analysis from the APACE study, an international multicenter study aimed at early diagnosis of MI, a single hs-troponin C measurement with a cut-off value of $<$3 ng/L had a negative predictive value of 100%, and a cut-off of $>$60 ng/L had a 77% positive predictive value.[14] Application of hs-troponin in the diagnostic algorithm of suspected MI was able to rule out 55% of patients, with ruled-out patients having an event rate of 0% at 30 days and 1.6% at two years.

Among patients ruled in for non-ST elevation ACS (NSTEACS), coronary computed tomography angiogram (CTA) has become another diagnostic modality under investigation to identify those who would benefit most from invasive coronary angiography. In the VERDICT trial, patients with NSTEACS were randomized to very early or standard invasive coronary angiography.[15] Clinically-blinded coronary CTA was performed in both groups to determine the accuracy of

coronary CTA in ruling out stenoses <50% compared with invasive coronary angiography. In this study, the negative predictive value of CTA was 91%, suggesting that among patients with NSTEACS, coronary CTA may be appropriate to identify the group of patients who are less likely to derive benefit from invasive imaging.

Vascular Access and Bleeding

The relationship of bleeding with recurrent thrombotic events and mortality in patients with ACS has been well-established. The implications of postdischarge bleeding were further elucidated by Marquis-Gravel et al in a large posthoc analysis of data from four randomized trials comprising more than 45,000 patients.[16] Among patients with noncoronary artery bypass grafting-related Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries moderate, severe, or life-threatening bleeding landmarked to seven days after presentation, mortality was higher, particularly in the 30 days following discharge. Increased mortality in association with bleeding was similar among groups managed medically versus those who underwent PCI. While the application of these findings to individualized patient care decisions remains nuanced, these findings provide important insight into post-ACS bleeding among patients managed medically for ACS.[17]

The importance of vascular access selection in ACS has been studied extensively over the last decade. Multiple trials have examined the role of femoral versus radial arterial access in primary PCI. Previous randomized control trials largely have shown reduced bleeding and lower mortality in patients with radial access compared with femoral access in the setting of STEMI.[18-20] The SAFARI-STEMI trial, published in 2020, brings these findings into question.[21] In this open-label randomized trial, nearly 2,300 patients at five Canadian centers were randomized to radial versus femoral access in primary PCI, with a primary endpoint of 30-day all-cause mortality. The trial was stopped prematurely due to futility, with no difference in mortality or bleeding observed between the radial versus femoral groups. The low overall bleeding and mortality rates reflected a less sick cohort of patients than studied in previous trials, as well as the adoption of multiple bleeding mitigation strategies, including high rates of bivalirudin use, low rates of GP IIB/IIIA inhibitors, and high rates of femoral closure device use. These differences between the SAFARI-STEMI trial and historic studies make it difficult to rule out small differences between access site groups in contemporary practice. Overall, controversy remains regarding default femoral or radial access in STEMI. While this study is unlikely to lead to any significant changes in guidelines, it is encouraging to see that that with contemporary pharmacology and bleeding mitigation strategies, mortality and bleeding can be comparable regardless of access sites among highly experienced operators.[22]

Reperfusion Strategies

The superiority of primary PCI over fibrinolysis in the acute management of STEMI was established by a series of key trials in the late 1990s and early 2000s. This year, the 16-year follow-up data were published from the DANAMI-2 trial, which randomized nearly 1,600 patients in Denmark to fibrinolysis versus primary PCI. Consistent with previously published 30-day and three-year outcomes, the 16-year follow-up demonstrated a persistent benefit among patients treated with primary PCI compared with fibrinolytics, with a lower composite primary outcome of death or rehospitalization for MI, as well as lower cardiac mortality compared with patients treated with fibrinolysis.[23] These findings also were seen in the subgroup of patients who required transfer to a different facility for primary PCI.

Ten-year data examining patient outcomes in STEMI with primary PCI with bare-metal stents versus everolimus-eluting stents from the EXAMINATION trial were presented.[24] Patients in the everolimus-eluting stent arm had lower rates of the primary composite endpoint of all-cause mortality, recurrent MI, or revascularization, which was driven by the lower rates of all-cause mortality (4.4% absolute risk reduction). Additionally, target lesion revascularization was higher among patients randomized to bare-metal stents. These long-term findings are reassuring as they supported the current practice of near-universal adoption of drug-eluting stents in ACS.

Adjunctive therapies in primary PCI in STEMI have evolved similarly over time. The role of intracoronary fibrinolytics in STEMI was studied by McCartney et al in an effort to determine if low-dose alteplase after percutaneous transluminal coronary angioplasty could reduce microvascular obstruction as measured by cardiac magnetic resonance imaging.[25] The authors postulated that degrading fibrin-bound thrombotic debris in the microcirculation could result in reduced microvascular obstruction. Unfortunately, the authors found the opposite, with increased microvascular obstruction among patients treated with alteplase in a dose-dependent fashion. These findings were postulated to be due to hemorrhagic transformation and vascular injury in the setting of ischemia and were particularly striking among patients with four-to-six hours of ischemia compared with those with less ischemic time. These findings continue to reduce the role of intracoronary lytics as the potential for harm is further appreciated.

For the review authors here, a further contribution to the understanding of the role of PCI in NSTEACS came from Kaura et al, who examined outcomes in patients aged 80 and older.[26] This group largely has been excluded from prospective trials examining the role of PCI versus medical therapy in ACS. In the propensity-matched observational data from the United Kingdom, researchers found that patients treated with PCI had markedly lower five-year mortality (hazard ratio [HR] 0.66) and heart failure admissions compared with matched patients who were medically treated. Despite advanced age, these patients showed clinically significant improvement in both quality of life and mortality outcomes. These findings support the invasive management of NSTEACS in elderly patients when clinically appropriate.

Management of Multivessel Disease

Over the last decade, a growing body of evidence has supported the revascularization of nonculprit lesions in the setting

of STEMI (Fig 1).[27-30] The COMPLETE trial, published in late 2019, randomized more than 4,000 nonshock patients with multivessel coronary disease presenting with STEMI to complete revascularization versus culprit lesion-only intervention.[31] The COMPLETE trial demonstrated that in patients with STEMI and multivessel disease, complete revascularization was superior to culprit-only PCI, with reduced rates of death or MI, as well as reduced cardiovascular death, MI, or ischemia- driven revascularization in the complete revascularization group.

Two meta-analyses of more than 7,000 patients in ten randomized trials of nonculprit PCI in STEMI were published in 2020.[32,33] Both analyses demonstrated reduced cardiovascular mortality and subsequent MI without increased risk of vascular complications, bleeding, or acute kidney injury in the complete revascularization groups compared with the culprit-only groups.

In a subgroup analysis of the COMPLETE trial, severe stenoses, defined as quantitative coronary angiography lesions of ≥60%, were found to be associated with the coprimary endpoints of the trial.[34] The findings that cardiovascular death and MI were reduced to a greater extent in the group of lesions meeting criteria for severe stenosis by quantitative coronary angiography provided insights on the mechanism of recurrent spontaneous MI after STEMI. While procedural MI predominates the etiology of coronary events in the first 30 days after PCI for ACS, more than 80% of recurrent ACS beyond 30 days are spontaneous, rather than stent thrombosis or procedure-related MI.[35] Controversy has remained regarding which types of lesions are most likely to be future culprits, with conflicting data as to the importance of mild-to-moderate lesions versus more severe stenoses. Based on this subgroup analysis, recurrent spontaneous MI was associated with severe stenosis, providing some biologic insight as to the mechanism for reduced cardiovascular mortality and MI observed in the COMPLETE trial. While caution must be exercised in interpreting subgroup analyses, these conclusions provided insights as to the direction for future studies.[36]

Further analyses examining the types of noninfarct-related lesions most likely to result in spontaneous MI following STEMI were conducted on data from the COMPARE-ACUTE trial.[37] In this substudy, noninfarction-related arteries were interrogated by fractional flow reserve (FFR) following successful primary PCI. The investigators were blinded to the FFR results, and all noninfarction-related lesions were medically treated. In this 24-month natural history study, lesions with a lower FFR (eg, more physiologically significant lesions) were more likely to have major adverse cardiac events, MI, and target vessel revascularization.

Overall, the preponderance of data support the revascularization of noninfarction-related angiographically severe lesions following STEMI in patients who do not present with cardiogenic shock. Less robust evidence is available for patients with multivessel coronary disease presenting with NSTEMI. A retrospective analysis by Kim et al compared three-year outcomes among patients with multivessel coronary disease presenting with NSTEMI who underwent culprit-only, single-staged, or multistaged complete revascularization.[38] The authors found higher rates of all-cause death, non-fatal MI, or repeat revascularization among the group of patients who underwent culprit-only revascularization compared with those who underwent complete revascularization. No significant

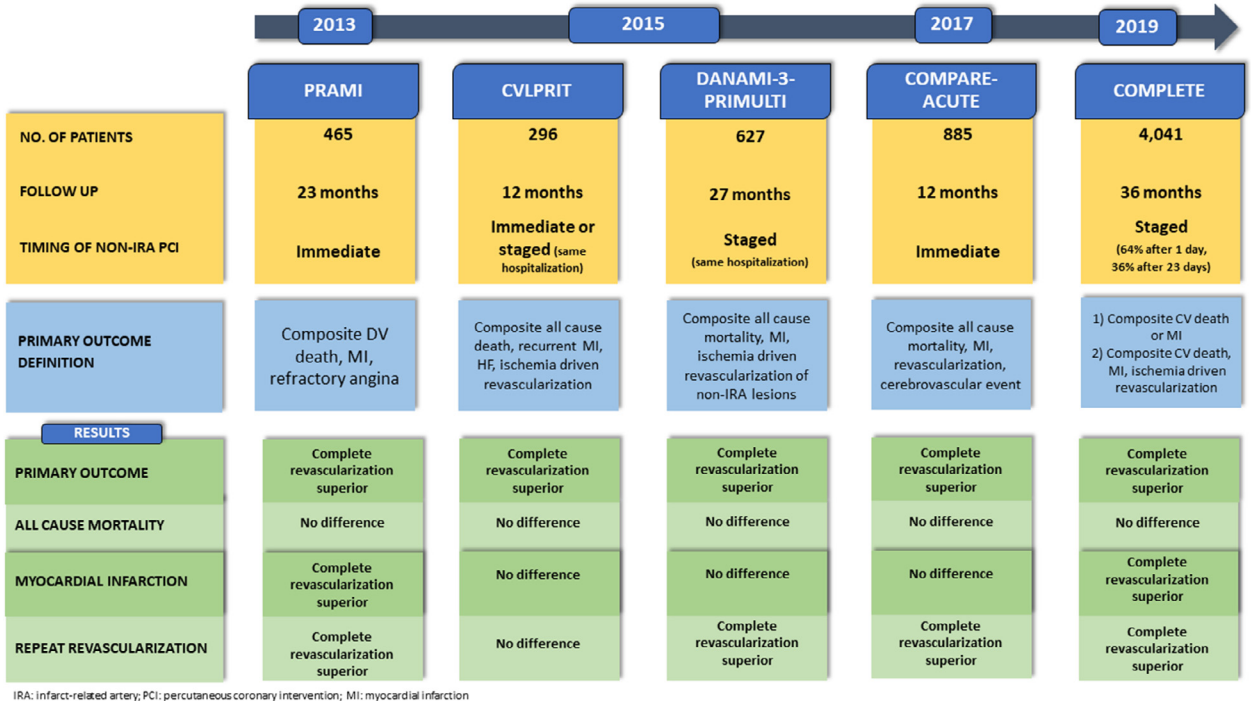

Fig. 1. A summary of contemporary randomized trials of complete revascularization following STEMI, all of which show a benefit with respect to the primary endpoint in patients undergoing complete revascularization.

difference was seen between the complete revascularization groups whether the noninfarction-related lesions were treated in the index procedure or staged. While retrospective analyses have significant limitations, these findings are certainly hypothesis-generating as the role of complete revascularization following ACS is further elucidated.

Acute MI and Cardiac Arrest

Despite advances in the management of acute MI, patients presenting with MI and out-of-hospital cardiac arrest continue to have high rates of mortality. Several key publications in 2020 have further defined the role of immediate angiography in out-of-hospital ventricular fibrillation/ventricular tachycardia (VT/VF) arrest survivors, characterized as patients with MI most likely to present with cardiac arrest, and identified optimal treatment strategies for this group (Fig 2).

Immediate coronary angiography and PCI were recommended by both American and European guideline documents in patients presenting with out-of-hospital cardiac arrest found to have STEMI following the return of spontaneous circulation.[39,40] In resuscitated cardiac arrest patients with an initial shockable rhythm who do not have a STEMI on an electrocardiogram following resuscitation, coronary angiography historically has been recommended without high-quality evidence supporting this practice. The COACT trial randomized cardiac arrest survivors presenting with an initial rhythm of VT/VF and no STEMI on an electrocardiogram to immediate coronary angiography versus delayed coronary angiography following neurologic recovery.[41] In 2019, the 90-day results were published, which showed no difference in survival or any secondary endpoints between the immediate angiography and the delayed angiography groups. One-year follow-up of the COACT trial was published in 2020.[42] The findings at one year were consistent with the 90-day outcomes, with no differences in several key endpoints, including survival, MI, revascularization, implantable cardioverter-defibrillator shocks, quality of life, and heart failure hospitalization between the immediate versus delayed angiography groups. This data suggested that it is safe to defer angiography in this group of patients until neurologic recovery without any adverse short- or long-term consequences.

Among patients undergoing urgent PCI for AMI, Kosugi et al identified the characteristics of patients most likely to present with out-of-hospital cardiac arrest.[43] In this study, the authors retrospectively analyzed 480 patients at a single center

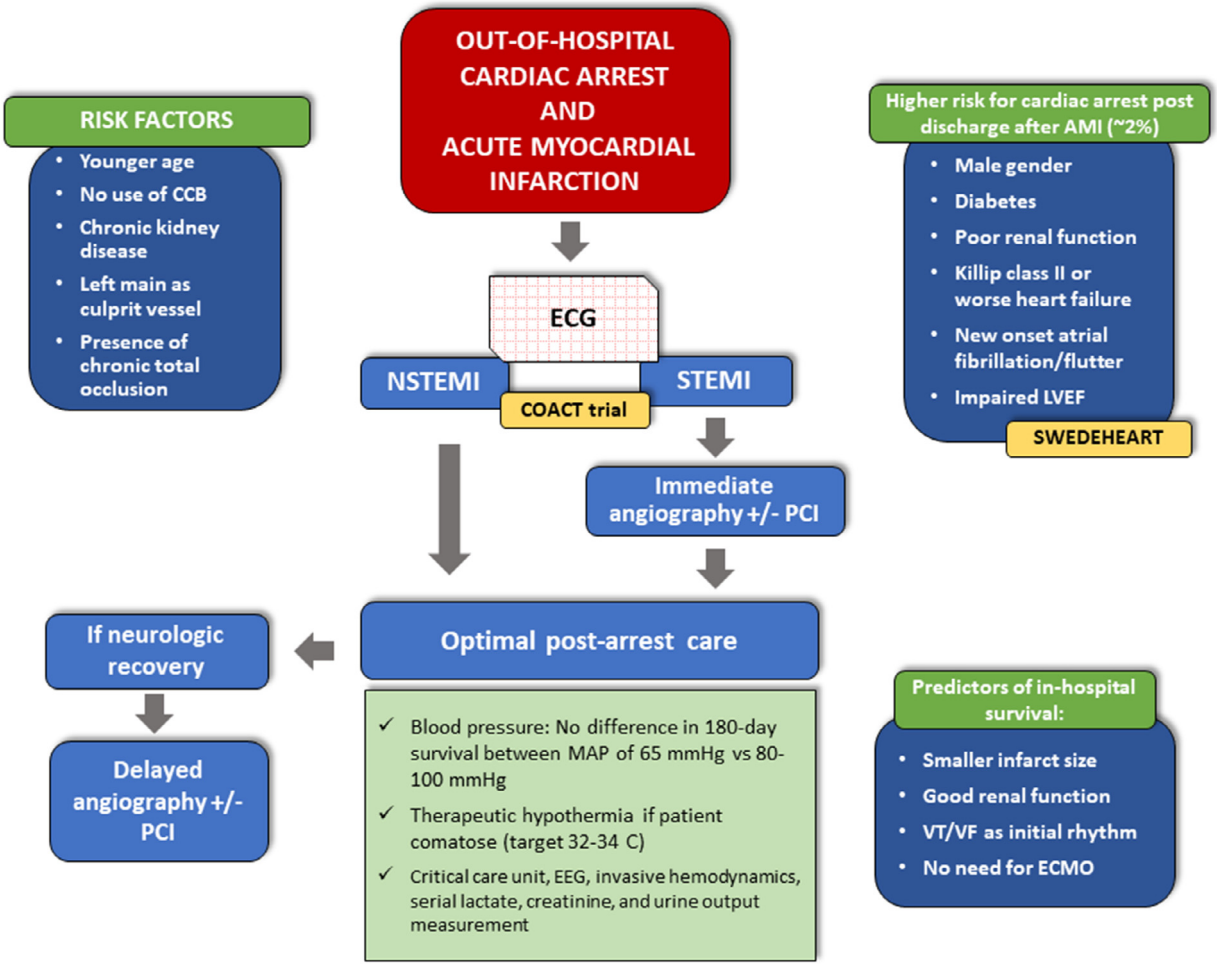

Fig. 2. Multiple trials in 2020 have further elucidated the optimal care of patients with AMI and cardiac arrest, enhancing the appropriate use of diagnostics, post-arrest care, and subsequent risk stratification in this cohort.

in Japan who underwent PCI for AMI. Patients who underwent angiography for AMI and presented with out-of-hospital cardiac arrest were compared with patients with AMI not complicated by cardiac arrest. In this selected group of patients, cardiac arrest survivors had a considerably lower in-hospital survival compared with those who presented without cardiac arrest (62% *v* 96%). The authors found that younger age, no use of calcium-channel blockers, worse renal function, higher peak CK-MB, culprit lesion as the left main coronary artery, and presence of a chronic total occlusion were associated with AMI presenting with out-of-hospital cardiac arrest. Smaller infarction size, good renal function, VT/VF as the presenting rhythm, and no need for extracorporeal membrane oxygenation were predictors of in-hospital survival among those presenting with out-of-hospital cardiac arrest.

Optimal postarrest care continued to evolve in 2020. The ideal blood pressure goal in postarrest patients with AMI has been controversial; low blood pressure may result in end-organ hypoperfusion leading to worse neurologic outcomes and larger infarction sizes, while higher blood pressure targets may require higher doses of pressors and lead to more dangerous atrial and ventricular arrhythmias. A patient-level pooled analysis of two randomized controlled trials in postarrest patients with AMI evaluated optimal blood pressure targets.[44] Patients were randomized to a lower or higher target blood pressure (mean arterial pressure [MAP] of 65 mmHg *v* 80-100 mmHg). Despite higher doses of inotropes and pressors, the higher MAP group did not have higher rates of arrhythmias, and the infarction size was smaller. There was no difference in 180-day survival between the two groups. While this analysis failed to demonstrate differences in patient-centered outcomes, the lack of increased arrhythmias at higher doses of pressors provides reassurance that the strategy of higher MAP targets is safe.

Finally, analyses of the SWEDEHEART registry attempted to improve identification of patients at the highest risk of cardiac arrest in the 90 days following hospital discharge for AMI.[44] The authors found that out-of-hospital cardiac arrest was relatively rare in the 120,000 patients included in the analysis, with a <0.3% incidence of subsequent cardiac arrest. In an effort to better identify post-MI patients at the highest risk of out-of-hospital cardiac arrest in the 90 days after discharge, the authors analyzed clinical variables to stratify risk, creating a risk score incorporating six parameters (male sex, diabetes, poor renal function, Killip class II or worse heart failure, new-onset atrial fibrillation and/or flutter, and impaired left ventricular ejection fraction). While this risk score performed better than depressed left ventricular ejection fraction alone, patients in the highest risk group only had a 2% risk of out-of-hospital cardiac arrest. Further research is required to identify the post-MI group at the highest risk of out-of-hospital cardiac arrest which, while rare, is devastating.

Pharmacology

Antiplatelet Agents

Antiplatelet therapy is a pharmacologic cornerstone of the management of ACS. In particular, P2Y12 inhibitors have been the subject of scrutiny as the optimal agent, timing of initiation, and duration of therapy continue to be defined. Several key studies published in 2020 have helped to further elucidate the optimal strategies for the initiation and cessation of P2Y12 inhibitors as well as their roles in special populations.

P2Y12 Inhibitor Initiation

Timely P2Y12 inhibitor initiation in STEMI has been recommended by the United States and European guideline documents. Despite emphasis on early P2Y12 inhibitor administration, data demonstrating improved clinical outcomes with prehospital P2Y12 inhibitor administration is lacking.[45] A hypothesized reason for this lack of benefit is the prolonged time required for gastric transit and absorption. One method that has been explored to address this barrier is crushing P2Y12 inhibitors prior to administration. Vlachojannis et al conducted a randomized trial of more than 700 STEMI patients in the Netherlands investigating the clinical effect of crushed prasugrel.[46] Eligible patients who presented within six hours of symptom onset and were scheduled for primary PCI were randomized to a 60-mg loading dose of prasugrel, administered as crushed or integral tablets. The authors were unable to demonstrate any differences between the two groups with respect to the coprimary endpoints of TIMI 3 flow in the infarct-related artery on initial angiography or the resolution of ST elevation one hour after primary PCI. As the rates of stent thrombosis and mortality in STEMI have decreased dramatically due to improvements in stent engineering, PCI techniques, and STEMI systems of care, it has become increasingly difficult to demonstrate significant outcome differences with new agents or strategies in the setting of STEMI. In this study, the average time from randomization to angiography was just slightly more than 20 minutes. Oral agents, regardless of the administration method, are unlikely to be able to demonstrate a significant difference in such a compressed timeframe.

In order to address the delay in onset of action with current oral agents, the novel P2Y12 inhibitor selatogrel has been developed. This agent is administered subcutaneously and has been shown in pharmacodynamic studies to have a rapid onset of action. In a phase II clinical trial, 47 patients presenting with AMI were randomized to a single dose of selatogrel, 8 or 16 mg, followed by ticagrelor.[47] At 30 minutes, 91% of low-dose and 96% of high-dose patients had effective platelet inhibition that was sustained at 60 minutes. No major side effects or bleeding complications were noted. These initial findings are promising as the agent of choice in the preprocedural management of STEMI continues to be emphasized, and the phase III trial of selatogrel is planned.[48]

The timing of P2Y12 inhibitor initiation in NSTEMI similarly has been a historic area of controversy. The largest study questioning routine pretreatment with P2Y12-inhibitor administration in NSTEACS was the ACCOAST trial, which found that patients pretreated with prasugrel had no benefit in ischemic endpoints and had higher rates of serious bleeding.[49] The DUBIUS study, published in 2020, was an open-label randomized controlled trial

of more than 1,400 patients with NSTEMI. Patients were randomized to ticagrelor administration upstream (pretreatment) versus downstream (at the time of angiography).[50] The study was terminated prematurely due to futility at the interim analysis, with no differences in the primary composite efficacy and safety endpoints. These findings, in concert with previously published work, showed that routine P2Y12 pretreatment in NSTEMI is at best not helpful and at worst harmful, with increased bleeding events.[51]

Following the publication of PLATO and TRITON-TIMI 38, the P2Y12 inhibitor of choice in patients with NSTEACS has been prasugrel or ticagrelor.[52,53] Limited data have supported the choice of one of these agents over the other. Posthoc analysis of the unstable angina and NSTEMI groups of the ISAR-REACT 5 trial compared patients randomized to ticagrelor versus prasugrel.[54] The authors found prasugrel to be superior in reducing the one-year composite endpoint of death, MI, and stroke without increasing the risk of serious bleeding. This posthoc analysis is hypothesis-generating and was limited by the initial open-label trial design; however, the findings are reassuring in that no differences in bleeding were observed when directly comparing prasugrel and ticagrelor in patients with NSTEACS.[55]

Antiplatelet Therapy De-escalation

As the significance of bleeding events has become widely appreciated, P2Y12 inhibitor deescalation and cessation have been an area of considerable interest in ongoing clinical trials. The TWILIGHT trial randomized 9,000 patients who were identified as highrisk for bleeding or ischemic complications to dual-antiplatelet therapy (DAPT) with ticagrelor and aspirin versus ticagrelor monotherapy after successfully completing three months of DAPT.[56] The investigators found a lower risk of serious bleeding in the ticagrelor monotherapy group, with no increase in ischemic outcomes. Several subgroup analyses of the TWILIGHT trial subsequently have been published. In a prespecified subgroup analysis of patients undergoing complex PCI as defined by coronary anatomy and extensive and/or complex stenting techniques, patients in the ticagrelor monotherapy group continued to show benefit compared with those treated with DAPT despite a theoretically higher risk of stent thrombosis in more complex stenting.[57]

In patients presenting with ACS, a subgroup analysis of patients in the TWILIGHT trial also showed a benefit with ticagrelor monotherapy over DAPT, with the benefit of reduced bleeding events more pronounced among patients with ACS than those with stable ischemic heart disease.[58] Similar results were observed in the TICO study that was designed similarly to TWILIGHT with the exception of limiting enrollment to patients who underwent stenting for ACS.[59] After tolerating DAPT with aspirin and ticagrelor for three months, patients were randomized to ticagrelor monotherapy versus DAPT for the next nine months. Similar to TWILIGHT, the authors found reduced composite bleeding, cardiovascular, and cerebrovascular events in the ticagrelor monotherapy group driven by a reduction in major bleeding (HR 0.56 for major bleeding).

Prasugrel was studied in a similar fashion in the HOST-REDUCE-POLYTECH-ACS trial, which randomized 2,300 patients who underwent stenting for ACS to DAPT with full-dose prasugrel and aspirin versus low-dose prasugrel and aspirin after completing three months of DAPT.[60] Consistent with TWILIGHT and TICO, patients who were treated with low-dose prasugrel and aspirin had lower net adverse clinical events at one year, driven by a reduction in the risk of bleeding. Overall, the available data support early deescalation of P2Y12 inhibitor intensity, particularly among patients at a high risk for bleeding complications.

Special Populations

Special consideration for the P2Y12 inhibitor use in the elderly must take into account unique risk factors in this age group, including increased risk of bleeding, risk of ischemic events, and cotreatment with anticoagulation. Analysis from the SWEDEHEART registry compared patients aged 80 or older who were prescribed DAPT with clopidogrel versus ticagrelor at hospital discharge for a diagnosis of MI.[61] After inverse probability weighting of Cox regression models to adjust for differences in patient and therapy characteristics, the authors found no difference in ischemic outcomes with clopidogrel versus ticagrelor. Ticagrelor use was associated with a significantly higher risk of death and bleeding.

This hypothesis put forth by the registry data was tested in the POPular AGE trial, which randomized 1,000 patients older than 70 presenting with NSTEACS to loading and maintenance doses of clopidogrel versus ticagrelor for one year of treatment.[62] Several key findings are notable from this trial. Premature cessation of ticagrelor was very common, with 47% patients in the ticagrelor group stopping treatment due to bleeding or shortness of breath. Bleeding also was frequent in all subjects but was significantly more common in the ticagrelor group, with 24% of patients experiencing PLATO major or minor bleeding compared with 18% in the clopidogrel group. The composite clinical benefit outcome was noninferior for clopidogrel versus ticagrelor. Overall, this study highlighted the high frequency of bleeding in elderly patients treated with P2Y12 inhibitors and demonstrated reduced bleeding with similar ischemic endpoints with clopidogrel versus more potent P2Y12 inhibitors.

An additional group that merits special consideration are those with known cytochrome p-450 polymorphisms that confer reduced clopidogrel metabolism. Patients with loss of function mutations of the CYP2C19 gene have reduced concentrations of the active metabolites of clopidogrel, increased platelet reactivity, and an increased risk of subsequent ischemic events.[63] Despite these findings, evidence of improved clinical outcomes when antiplatelet therapy is tailored to individual genetics is lacking.[64] The findings of the TAILOR-PCI randomized trial were consistent with the lack of benefit in gene-tailored antiplatelet therapy seen in previous studies. In this trial, 5,300 patients who underwent PCI were

randomized to standard therapy with clopidogrel versus genotype-guided therapy with ticagrelor substituted for clopidogrel in patients with CYP2C19 loss of function mutations.[65] There were no differences in composite efficacy or bleeding endpoints in the standard versus genotype-guided therapy groups. These findings underlined previous work that has shown that while genotyping can identify higher risk individuals, no effective interventions have been identified to ameliorate this risk.

Lipid-Lowering Agents

The role of lipids in atherogenesis is foundational in the pathogenesis of coronary artery disease. Identifying and targeting lipid metabolites have further elucidated the mechanistic role of lipid-lowering therapies. The importance of very-low-density lipoproteins (VLDL) was demonstrated in analysis from the Copenhagen General Population Study.[66] This observational study found that elevated VLDL cholesterol explained half of the MI risk from elevated apoB-containing lipoproteins, whereas VLDL triglycerides did not account for risk. This was theorized to be due to an increased direct uptake of VLDL into macrophages, which then morphologically become foam cells, a key component of atherosclerotic lesions. These findings guided future directions for study to reduce MI risk by identifying novel lipid targets.

The most recent major advance in anti-lipid therapy has been the development and approval of evolocumab and alirocumab, monoclonal PCSK-9 inhibitors. In the landmark FOURIER and ODYSSEY trials, these agents were shown to significantly reduce low density lipoprotein (LDL) levels and adverse cardiovascular outcomes.[67,68] A prespecified analysis from the ODYSSEY trial evaluated the effect of alirocumab-induced changes in lipoprotein A (Lp(a)) and LDL-C on major adverse cardiovascular events.[69] The authors found that both baseline levels and relative reductions of Lp(a) and LDL-C were associated independently with a reduction in major adverse cardiovascular events. While providing mechanistic insight into the effect of alirocumab, these findings suggested that Lp(a) may have additional value as an independent treatment target after ACS.

The role of plaque burden and composition in ACS has continued to guide future directions for research. In a large CTA dataset, investigators found that after stratifying patients by calcified plaque burden, the degree of stenosis did not predict future cardiovascular events.[70] That is to say, patients with a similar amount of plaque had a similar risk for subsequent MI whether the plaque was diffuse; eg, non-obstructive versus focal; eg, obstructive. These findings suggested that plaque burden rather than the degree of stenosis may predict future risk.

Intracoronary imaging has furthered the study of plaque burden and characteristics in vivo. Using near-infrared spectroscopy intravascular imaging, investigators in an international prospective cohort study imaged nonculprit segments in 1,500 patients undergoing cardiac catheterization for suspected coronary artery disease.[71] Investigators were able to demonstrate the association of large lipid-rich plaques with major cardiac events over the next two years at both a patient and plaque level.

The concept that high-risk plaques can be identified and prophylactically treated before progressing to ACS was explored in the PROSPECT ABSORB study.[72] In this pilot trial, patients who underwent successful PCI for STEMI or NSTEACS underwent three-vessel intravascular imaging with intravascular ultrasound and near-infrared spectroscopy. Of the 902 patients enrolled, 182 had lesions eligible for randomization. Lesions that were $<70\%$ stenosed with $\geq 65\%$ plaque burden were randomized to treatment with Absorb bioresorbable vascular scaffold and guideline-directed medical therapy versus medical therapy alone. The investigators found that PCI of angiographically mild lesions with large plaque burdens was safe and associated with a larger minimal lumen area on follow-up angiography. There were similar rates of target lesion failure at 24 months. While underpowered to detect any differences in long-term clinical outcomes, this trial provided reassuring safety data in preparation for a larger pivotal trial. Further study and refinement of identification of the highest risk plaques, as well as robust outcome and safety data, are required before the adoption of PCI with bioresorbable vascular scaffold is adopted.[73]

Miscellaneous Medications

Intravenous (IV) morphine historically has been recommended to control pain in patients with ACS despite the absence of safety data. Given the negative effects of opioids on gastrointestinal motility, IV morphine prior to PCI in the setting of ACS has been theorized to delay the absorption of P2Y12 inhibitors that rely on gastric motility for transit to the intestine where absorption occurs. Delayed absorption with lower circulating concentrations of P2Y12 inhibitors and their metabolites in the time period immediately surrounding PCI has been theorized to increase thrombotic events and lead to higher mortality in patients receiving IV morphine prior to PCI. Previous data in this area have been conflicting, with some studies showing an impact on all-cause mortality and composite endpoints and other studies failing to show any difference in outcomes in those receiving IV morphine versus those who do not.[74,75]

A posthoc analysis from the EARLY ACS trial examined a group of patients pretreated with clopidogrel prior to coronary angiography for NSTEACS and compared the group who received IV morphine to those who did not.[76] After propensity matching, the group treated with morphine had a higher rate of the composite endpoints of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours (odds ratio 1.40). Periprocedural MI also was increased significantly in the morphine group, suggesting that stent thrombosis and thrombotic complications may be driving these findings. These findings demonstrated the evolving role of opioids in patients with ACS, particularly among patients pretreated with clopidogrel, as pharmacologic studies have shown both delay in absorption, as well as reduced levels of clopidogrel and its metabolites when coadministered with IV

morphine. In patients receiving clopidogrel and IV opioids prior to PCI, intensive antiplatelet therapy with IV cangrelor, an IV GP IIB/IIIA inhibitor, or a reloading dose in six hours can be considered to reduce the risk of acute thrombotic events.[77]

Following MI, the use of nonsteroidal antiinflammatory drug (NSAID) medications has been shown to be associated with increased rates of cardiovascular events and bleeding. Despite recommendations to avoid NSAIDs in patients with a history of ischemic heart disease, rates of exposures to NSAIDs remain high due to the presence of other comorbidities.[78] In a nationwide cohort study from Korea with data from more than 100,000 patients who were diagnosed with their first MI, NSAID use was associated significantly with cardiovascular events (HR 9.96) and bleeding events (HR 4.08).[79] Among the NSAIDs prescribed, celecoxib and meloxicam had the lowest adjusted rates of cardiovascular events and bleeding, suggesting that these agents may be the NSAIDs of choice in patients with a history of MI in whom NSAIDs cannot be avoided.

Inflammation has been known to play an important role in the pathophysiology of ACS. After the pivotal CANTOS trial, which demonstrated improved cardiovascular outcomes after treatment with an anti-inflammatory agent, interest has grown in the use of other immunomodulating agents in patients with coronary artery disease.[80] Multiple key publications in 2020 investigated colchicine for secondary prevention in this group. The LoDoCo2 trial randomized patients with angiographic or computed tomography evidence of coronary disease to colchicine versus placebo.[81] In this group of stable patients who had no clinical events in the six months leading to enrollment, colchicine was associated with a reduction in the composite endpoints of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven revascularization (HR 0.69).

These results were concordant with the previously published COLCOT trial, which randomized nearly 5,000 patients with recent MI to colchicine versus placebo.[82] In COLCOT, treatment with low-dose colchicine was associated similarly with lower composite risks of cardiovascular death, cardiac arrest, MI, stroke, or urgent coronary revascularization at two years. A subsequent analysis of time to treatment with colchicine in the COLCOT trial demonstrated that the benefit of colchicine was greatest in those who started treatment with colchicine within three days of MI (HR of 0.52) compared with those who started treatment more than eight days after revascularization (HR 0.82).[83]

These positive findings were tempered with contradictory data from a smaller multicenter randomized controlled trial from Australia (the Australian COPS trial).[84] In a design similar to COLCOT, investigators randomized patients who presented with ACS with angiography showing coronary artery disease to one year of colchicine versus placebo prior to hospital discharge. No difference was found with respect to the primary composite endpoint and, concerningly, a higher rate of noncardiovascular mortality was observed in the colchicine group. Several important limitations are notable, including the premature cessation of the trial prior to enrolling the target number of subjects due to slow enrollment, as well as a significant number of patients lost to follow-up. Despite concerns regarding statistical power and generalizability of this study, the findings limited enthusiasm for the wide uptake of colchicine in the post-MI population as further safety data are awaited.

Some exploratory studies have examined the role of colchicine at the time of PCI. The COLCHICINE-PCI randomized trial was a single-site trial, which randomized patients undergoing PCI to a one-time oral dose of colchicine versus placebo at the time of PCI.[85] Patients were followed for 30-day composite endpoints of death, MI, and target-vessel revascularization, periprocedural MI, and inflammatory biomarkers. Despite attenuation in IL-6 and hs-CRP concentrations at 24 hours after PCI, no differences were seen in clinical endpoints. Pre- and periprocedural use of colchicine remains an ongoing question which is a subject of ongoing research.

COVID-19

Medicine in 2020 was shaped largely by the COVID-19 global pandemic. Much of what is known about COVID-19 was first described and reported in the medical literature in 2020 (Fig 3). COVID-19 infection is the result of the severe acute respiratory syndrome-related coronavirus 2 virus infecting cells by binding to the human angiotensin-converting enzyme-2 receptor with the viral surface spike protein.[86] While respiratory pathology dominates the clinical presentation of COVID-19, a range of cardiovascular manifestations have been described, particularly in patients with preexisting cardiovascular conditions.[86,87] Cardiac manifestations of COVID-19 are varied and are theorized to be related to the adrenergic drive, systemic inflammatory sequelae, and the direct infection of myocardial and endothelial cells.[88]

The association of COVID-19 with myocardial injury and structural abnormalities was studied in a large multinational study.[89] In this study, investigators compared the in-hospital morality of COVID-19 patients with myocardial injury who were found to have structural abnormalities on echocardiography, such as regional wall motion abnormalities, LV systolic or diastolic dysfunction, Right Ventricle (RV) dysfunction, or pericardial effusions, to those with structurally normal hearts. In this cohort of 305 patients, 62% of COVID-19 patients were found to have myocardial injury demonstrated by elevated cardiac biomarkers. Of those with myocardial injury, two in three had evidence of structural abnormalities on imaging, the most common of which was right ventricular dysfunction. A worse prognosis was observed in those with structural abnormalities on echocardiography, who had a 32% in hospital mortality compared with a 19% mortality in patients with biochemical evidence of myocardial injury with no significant structural abnormalities.

Another characteristic of COVID-19 is the high prevalence of thrombotic complications. In a single-center study in the United Kingdom, patients with COVID-19 who presented with STEMI were found to have a higher thrombus burden than those with STEMI in the absence of COVID-19.[90] This

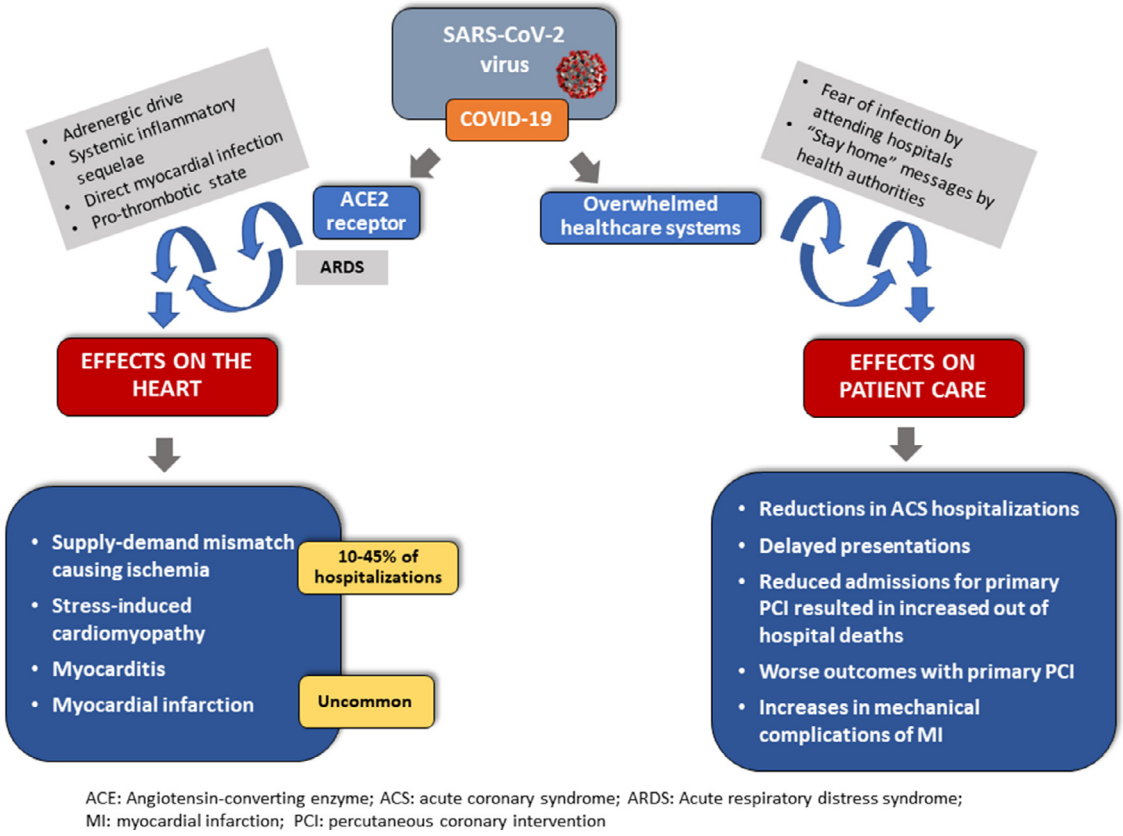

Fig. 3. The SARS-CoV-2 virus has had multiple effects on the cardiac health of patients, both directly through viral-mediated cardiac disease, as well as indirectly with disruption of systems of care. SARS-CoV-2, severe acute respiratory syndrome-related coronavirus.

observational study noted that patients with COVID-19 and STEMI showed higher risk of thrombotic complications, including stent thrombosis, high thrombus grade, and larger areas of myocardial damage, with a greater degree of left ventricular systolic dysfunction.[90] While the pathophysiology of the pro-thrombotic state of COVID-19 is not completely understood, COVID-19 has been associated with higher rates of prehospital cardiac arrest, intensive care admission, and in-hospital mortality in patients with STEMI.[90]

In addition to the direct effect of COVID-19 on cardiac pathology, important secondary effects due to stressors on healthcare systems adversely affected the care of patients with ACS. Data collected from studies around the world showed a significant decline in the number of patients admitted to hospitals due to ACS in the spring of 2020.[91] This phenomenon was attributed to messaging encouraging the public to remain at home in the early stages of the pandemic, as well as public fear of contracting the virus at medical facilities and hospitals. Global reductions in ACS hospitalizations was observed.[92-95] Delayed presentations and reduced admissions for PCI resulted in increased out-of-hospital deaths, worse outcomes with primary PCI, and increases in mechanical complications of MI.[86-88,91,96]

Italy was one of the first countries to have the healthcare system overwhelmed by COVID-19. Italian hospitals reported a 48% overall reduction in admissions for ACS during the spring of 2020, with a 65% reduction in NSTEMI and 27% reduction in STEMI admissions.[97] STEMI outcomes also suffered, with time from first medical contact to PCI increased 32% and case fatality rates of 17% compared with a historic control of 10%. Similar trends with a 40% reduction in admissions for ACS were seen in Australia, the UK, and the United States.[93,95,98]

Understanding the pathophysiology, management, and treatment of COVID-19 patients with ACS has been the result of global efforts. Primary PCI remains the standard of care in STEMI regardless of COVID-19 status. Similar management strategies are applied to early invasive management versus medical management of NSTEACS.[99] While much of the cardiac effects of COVID-19 remain to be learned, considerable progress has been made in identifying cardiac manifestations of COVID-19, as well as optimizing existing systems of care to provide effective care for cardiac patients during the global pandemic.

Conclusion

In the last year, there was considerable advancement in the care of patients with ACS. Particular emphasis on the management of multivessel disease, as well as advances in pharmacology, continue to shift the field to safer, more selective use of therapies to improve both short- and long-term outcomes. The COVID-19 pandemic resulted in major disruptions to clinical care in the spring of 2020. Despite these challenges, lessons learned and the application of clinical science continue to drive this evolving field forward.

Conflict of Interest

None.

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