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## Acute coronary syndromes and acute heart failure

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*Published in:*  
European Journal of Heart Failure

*DOI:*  
[10.1002/ejhf.1831](https://doi.org/10.1002/ejhf.1831)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Harjola, V-P., Parissis, J., Bauersachs, J., Brunner-La Rocca, H-P., Bueno, H., Celutkiene, J., Chioncel, O., Coats, A. J. S., Collins, S. P., de Boer, R. A., Filippatos, G., Gayat, E., Hill, L., Laine, M., Lassus, J., Lommi, J., Masip, J., Mebazaa, A., Metra, M., ... Yilmaz, M. B. (2020). Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*, (8), 1298-1314. <https://doi.org/10.1002/ejhf.1831>

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# Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology

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Received 8 August 2019; revised 4 April 2020; accepted 6 April 2020; online publish-ahead-of-print 29 April 2020

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Acute coronary syndrome is a precipitant of acute heart failure in a substantial proportion of cases, and the presence of both conditions is associated with a higher risk of short-term mortality compared to acute coronary syndrome alone. The diagnosis of acute coronary syndrome in the setting of acute heart failure can be challenging. Patients may present with atypical or absent chest pain, electrocardiograms can be confounded by pre-existing abnormalities, and cardiac biomarkers are frequently elevated in patients with chronic or acute heart failure, independently of acute coronary syndrome. It is important to distinguish transient or limited myocardial injury from primary myocardial infarction due to vascular events in patients presenting with acute heart failure. This paper outlines various clinical scenarios to help differentiate between these conditions and aims to provide clinicians with tools to aid in the recognition of acute coronary syndrome as a cause of acute heart failure. Interpretation of electrocardiogram and biomarker findings, and imaging techniques that may be helpful in the diagnostic work-up are described. Guidelines recommend an immediate invasive strategy for patients with acute heart failure and acute coronary syndrome, regardless of electrocardiographic or biomarker findings. Pharmacological management of patients with acute coronary syndrome and acute heart failure should follow guidelines for each of these syndromes, with priority given to time-sensitive therapies for both. Studies conducted specifically in patients with the combination of acute coronary syndrome and acute heart failure are needed to better define the management of these patients.

### Keywords

Acute coronary syndrome • Acute heart failure • Diagnosis • Management • Myocardial injury • Myocardial infarction • Troponins • Clinical scenario

## Introduction

Acute heart failure (AHF) can be precipitated by numerous events, one of which is myocardial ischaemia. Acute coronary syndrome (ACS) in the setting of AHF is a complex clinical scenario that requires careful evaluation. ACS can manifest either as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). The diagnosis of ACS in the setting of AHF is particularly challenging as the pillars of an ACS diagnosis may be confounded by AHF. Cardiac biomarkers are frequently elevated due to myocardial injury in patients with chronic or AHF even in the absence of ACS, and the electrocardiogram (ECG) is often insensitive. Unfortunately, most ACS studies have excluded patients with AHF and vice versa; thus, the evidence supporting the efficacy and safety of treatment approaches in patients simultaneously with both conditions is less clear. The aim of this paper is to provide clinicians with tools to aid in the recognition of ACS as a cause of AHF and to review the evidence for managing both conditions with invasive and non-invasive strategies. We acknowledge that cardiogenic shock as an extreme of AHF may also complicate ACS; however, it represents a small proportion of the overall population with AHF and ACS. Thus, this manuscript focuses primarily on patients with AHF and ACS without cardiogenic shock.

## Epidemiology and prognosis

Acute heart failure is a frequent complication of ACS, and the combination is associated with a particularly poor prognosis.<sup>1,2</sup> Contemporary estimates of the incidence of AHF complicating ACS vary from 6% to >45% in observational registries.<sup>1,3,4</sup> This variation may be related to the type of ACS (e.g. unstable angina, NSTEMI vs. STEMI), the methods used to define AHF, or even the

location where patients were studied [e.g. emergency department (ED), cardiology ward, or intensive care unit]. The Global Registry of Acute Coronary Events (GRACE) is a prospective, observational study of patients hospitalized with ACS including data from 14 countries in North America, South America, Europe, Australia, and New Zealand.<sup>2</sup> It showed that, among >14 000 patients with ACS, the incidence of AHF was similar in STEMI (15.6%) and NSTEMI (15.7%), but it was lower among patients with unstable angina (8.2%).<sup>2</sup>

Acute coronary syndrome has been considered as a precipitant, rather than a specific entity, by some AHF registries.<sup>3,5-9</sup> Some data report a 32% to 52% prevalence of ACS as a precipitating factor for AHF.<sup>10,11</sup> However, contemporary AHF registries<sup>12,13</sup> have included ACS-heart failure as a distinct clinical profile and have usually reported a lower prevalence of this profile (13–14%).<sup>12,13</sup> Of note, in those registries, only patients with myocardial infarction (MI) were included in the ACS-AHF group excluding thus patients with unstable angina.<sup>12,13</sup> The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry reported data from 6629 patients with AHF, of whom 954 (14%) presented with an associated ACS.<sup>12</sup> Compared to other clinical profiles, a higher proportion of patients with AHF and ACS were male, had undergone previous percutaneous coronary intervention (PCI), presented with new onset AHF, and most had a prior MI. Coronary angiography was performed in 45.9% of the patients with AHF and ACS, and 33.9% underwent revascularization with PCI or coronary artery bypass grafting during the index hospitalization. In-hospital mortality for patients in the ESC-HF-LT registry presenting with ACS and AHF was 4.2% and 1-year all-cause mortality was 20.6%, whereas in the overall population of patients with AHF, in-hospital and 1-year mortality was 5.5% and 26.7%, respectively.<sup>12</sup> In the Finnish Acute Heart Failure Study, 30-day mortality was 13% in patients presenting with AHF precipitated by ACS compared to 8%

in patients with AHF without concomitant ACS. Five-year mortality was similar in the two cohorts.<sup>11</sup>

In the GRACE registry, AHF (Killip class II or III) was shown to be associated with reduced in-hospital and 6-month survival across all ACS subsets, including patients with unstable angina.<sup>2</sup> In an analysis of pooled patient-level data from seven clinical trials representing 46 519 patients with non-ST-segment elevation ACS, patients with AHF at presentation [odds ratio (OR) 1.74, 95% confidence interval (CI) 1.35–2.26] or who developed AHF during hospitalization (OR 2.34, 95% CI 1.58–3.49) had a higher risk of 30-day mortality than patients without AHF.<sup>14</sup> Recent data from the GREAT Network showed that the risk of death among patients with AHF precipitated by ACS was highest within the first weeks after admission.<sup>10</sup>

Advances in evidence-based pharmacologic treatment and PCI over time have been accompanied by decreases in the rates of in-hospital AHF and cardiogenic shock.<sup>1,15</sup> However, some data suggest that fewer patients with ACS and AHF receive evidence-based ACS therapies or interventions compared to ACS patients without AHF.<sup>2,16</sup> This observation may be related to the paucity of data supporting the efficacy and safety of ACS therapy in patients with AHF, since many randomized clinical trials of patients with ACS have excluded patients with AHF. Additionally, the application of some ACS therapies may be precluded by haemodynamic instability, impaired renal and liver function, or other clinical factors that may be present in patients with AHF.<sup>16</sup>

## Definitions and classification

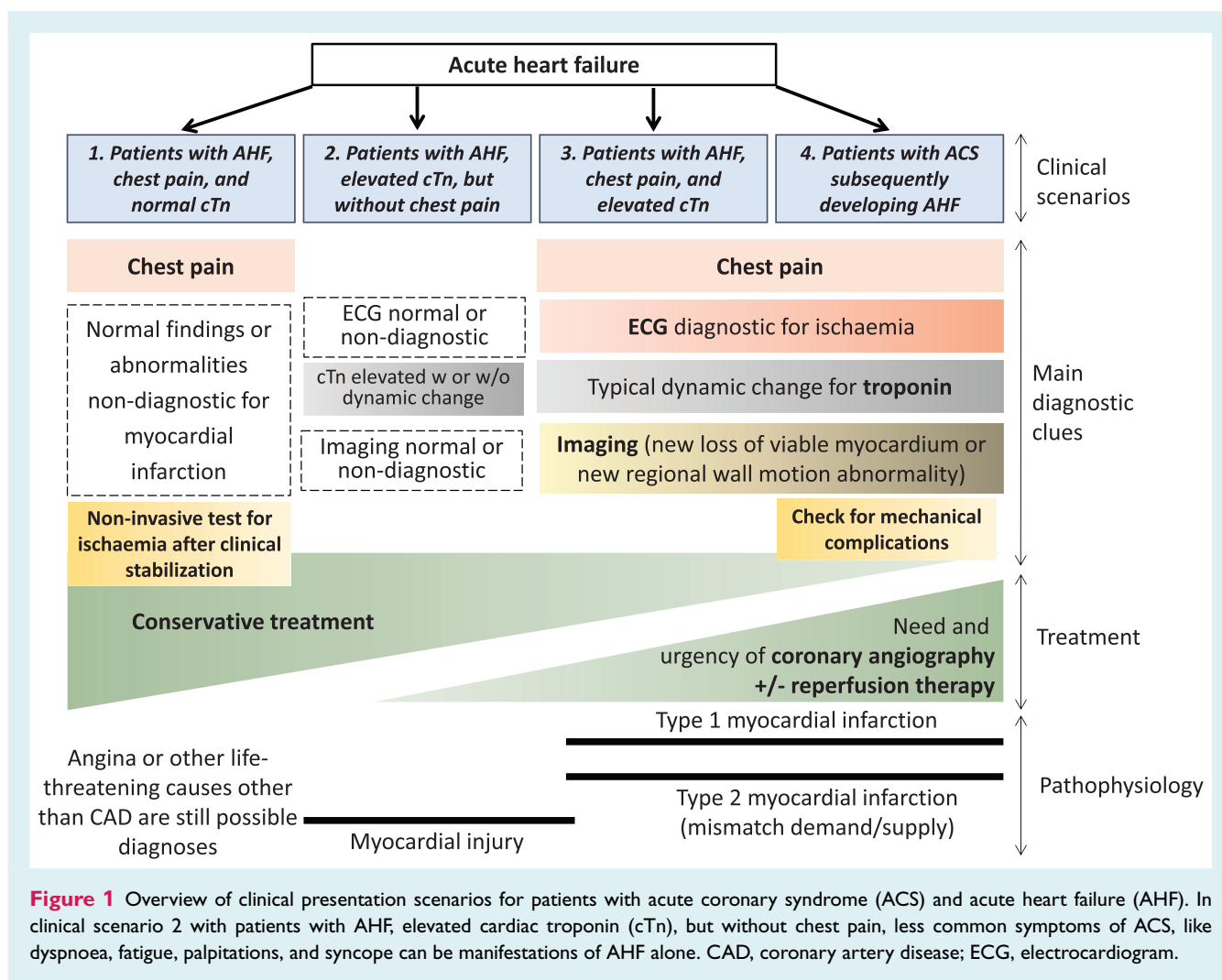
Unstable angina refers to the small proportion of ACS patients without ST-segment elevation who present with myocardial ischaemia without cell loss. According to the fourth universal definition, MI refers to evidence of myocardial necrosis in the setting of acute myocardial ischaemia (online supplementary Table S1).<sup>17</sup> MI was classified into five different subtypes to reflect pathologic and clinical differences (online supplementary Table S1). Of these classifications, type 1 and type 2 MI are most relevant to the topic of ACS and AHF. As part of the fourth universal definition, there is a greater attempt to distinguish MI from myocardial injury. Myocardial injury is defined as the detection of an elevated cardiac troponin (cTn) value above the 99th percentile of upper reference limit. The injury is considered acute if there is a rise and/or fall of cTn values. Under this new definition, patients with AHF may be considered to have myocardial injury, rather than MI, unless acute ischaemia is present and one of the type 1 or 2 MI criteria are present. Type 1 MI, i.e. spontaneous MI due to intraluminal thrombus of a coronary artery, is a common precipitant of AHF,<sup>7</sup> and it may either lead to new-onset AHF or exacerbate existing chronic heart failure.<sup>12,18</sup> It also requires additional features including (i) symptoms of acute myocardial ischaemia; (ii) new ischaemic ECG changes; (iii) development of pathological Q waves; (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities in a pattern consistent with an ischaemic aetiology; or (v) identification

of a coronary thrombus by angiography, including intracoronary imaging, or by autopsy. Type 2 MI describes myocardial ischaemia and necrosis due to an imbalance between myocardial oxygen supply and demand that is caused by conditions other than coronary plaque instability.<sup>19</sup> Patients must also have objective evidence of this imbalance, requiring at least one of the following: (i) symptoms of acute myocardial ischaemia; (ii) new ischaemic ECG changes; (iii) development of pathological Q waves; and (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. Potential mechanisms underlying type 2 MI may be cardiac or non-cardiac and include coronary artery spasm, coronary endothelial dysfunction, tachyarrhythmias, bradyarrhythmias, anaemia, respiratory failure, hypotension and severe hypertension. Additional type 2 MI mechanisms that might specifically relate to AHF include elevated transmural pressure, myocardial dilatation, elevated cardiac pressures, diastolic stiffening, or small-vessel coronary obstruction.<sup>18,20</sup> Type 2 MI might also result from iatrogenic effects of pharmacological agents (e.g. inotropes or vasopressors) in critically ill patients, toxins in sepsis, or operative stress in those undergoing major non-cardiac surgery.

It is important to note that, although many patients with AHF present with evidence of myocardial injury (i.e. elevated cTn), not all patients with cTn above the 99th percentile of upper reference limit will otherwise meet the criteria for MI. A dynamic change pattern on serial cTn testing along with evidence of ischaemia based on symptoms, ECG changes, or imaging findings is usually necessary for the diagnosis of MI,<sup>18,21,22</sup> although the interpretation of ECG and echocardiograms can be challenging in patients with AHF.

In an analysis of 2122 consecutive patients presenting to a tertiary care centre with cTn  $\geq 0.05$   $\mu\text{g/L}$  (cTnI ARCHITECT<sub>STAT</sub> assay, Abbott Laboratories, Abbott Park, IL, USA), 55.2% were adjudicated as suffering type 1 MI, 20.2% type 2 MI, and 24.6% myocardial injury.<sup>23</sup> Heart failure was the primary diagnosis in 12.4% of the 429 patients with type 2 MI and 12.8% of the 522 patients with myocardial injury.<sup>23</sup>

Patients with type 2 MI generally have a higher-risk profile, are older, more often female and carry a more substantial comorbidity burden. Coronary atherosclerosis is frequently demonstrated in patients with type 2 MI undergoing coronary angiography, and this finding generally portends a worse prognosis than for patients without atherosclerotic coronary arteries.<sup>23,24</sup> Observational data suggest patients with type 2 MI have an increased risk of all-cause death, both in-hospital and at 30 days, 1, 2, and 5 years compared to patients with type 1 MI,<sup>23,25–27</sup> although attenuation of this risk after multivariate adjustment has also been reported.<sup>28</sup> The occurrence of major adverse cardiovascular events within 30 days may also be higher for patients with type 2 vs. type 1 MI.<sup>26</sup> The data on heart failure are variable: it may be higher following discharge in type 2 vs. type 1 MI<sup>29</sup> or similar.<sup>23</sup> It should be observed that almost all studies presenting differing outcomes of type 2 vs. type 1 MI do not specifically look at patients admitted with a combination of ACS and heart failure, rather at ACS itself.



**Figure 1** Overview of clinical presentation scenarios for patients with acute coronary syndrome (ACS) and acute heart failure (AHF). In clinical scenario 2 with patients with AHF, elevated cardiac troponin (cTn), but without chest pain, less common symptoms of ACS, like dyspnoea, fatigue, palpitations, and syncope can be manifestations of AHF alone. CAD, coronary artery disease; ECG, electrocardiogram.

## Diagnosis and monitoring: differentiating between myocardial infarction and injury

### Clinical presentation

The patient's clinical presentation can provide important information necessary to support the diagnostic workup of ACS in the setting of AHF and to begin the determination of MI subtype. Early determination of underlying aetiology and MI subtype is important because the approach for diagnostic assessment and treatment may be altered according to the type of MI. Identifying the dominant symptom in the context of the patient's medical history may help distinguish type 1 MI, type 2 MI, and myocardial injury in AHF. For example, a patient with known chronic symptomatic heart failure who develops chest pain and worsening dyspnoea or peripheral or pulmonary oedema may differ from a patient with no prior cardiomyopathy who develops acute chest pain followed by dyspnoea.

Most patients with ACS and AHF present with symptoms and initial findings that are reflected within one of the following

scenarios (Figure 1). Physicians may find it useful to consider these clinical categories to guide decision-making towards the most appropriate assessment and treatment strategies during the early phases of care (e.g. in the ED).

#### Scenario 1: patients with acute heart failure, chest pain, and normal cardiac troponin

Few data are available describing the frequency of chest pain as a symptom in patients with AHF. Characteristics of chest discomfort can be similar in patients with AHF presenting to the ED with or without ACS.<sup>30</sup> Patients with AHF may perceive discomfort or tightness in the thorax due to the ventilatory effort and dyspnoea associated with AHF. If MI is ruled out via ECG and serial cTn testing, then the differential diagnosis of chest pain in patients with AHF is very broad and may include AHF itself, unstable angina, myocarditis, tachyarrhythmia, hypertensive emergencies, aortic valve stenosis, Takotsubo cardiomyopathy, coronary spasm, cardiac trauma, and non-cardiac causes such as pulmonary embolism (PE), tension pneumothorax, bronchitis, pneumonia, aortic dissection, or aortic aneurysm.<sup>22</sup>

### Scenario 2: patients with acute heart failure, elevated cardiac troponin, but without chest pain

In the absence of typical chest pain, elevations in cTn should be interpreted carefully to differentiate between myocardial injury and infarction. Some patients present with less typical ACS symptoms such as shortness of breath, nausea/vomiting, fatigue, palpitations, or syncope.<sup>31</sup> Since dyspnoea is one of the most frequent AHF, but less typical ACS symptoms, it often does not help in differentiating myocardial injury from MI. Indeed, fatigue, palpitations, and syncope can be manifestations of AHF alone. ECG changes and imaging should also be assessed and may help make the diagnosis. In most cases where classic ischaemic symptoms and ECG changes are absent, elevated cTn will be related to myocardial injury.<sup>27</sup> One analysis showed that dyspnoea, syncope, and confusion predominate in patients with myocardial injury, whereas more patients with type 1 or 2 MI report ischaemic chest pain.<sup>27</sup> Peak cTn values are typically higher in patients with type 1 MI compared to type 2 MI,<sup>21,32–34</sup> but they are often similar in patients with either type 2 MI or myocardial injury. Thus, peak cTn cannot be used to distinguish reliably between type 1 or 2 MI and myocardial injury.

To qualify as an MI, guidelines recommend that a dynamic change pattern in cTn levels should be observed.<sup>21,22</sup> In order to rapidly identify patients with AHF following ACS and initiate early coronary angiography and early revascularization, application of the ESC 0/1 h-algorithm is recommended. High initial high-sensitivity cardiac troponin T or I (hs-cTnT/I) concentrations (at least four times the upper limit of normal or more) or a relevant assay-specific increase from 0 to 1 h (time from first blood test) provides a high positive predictive value for the identification of these patients for early coronary angiography. NSTEMI can be ruled out already at presentation, if the hs-cTn concentration is very low and onset of chest pain occurred >3 h before. NSTEMI can also be ruled out by the combination of low baseline levels and the lack of a relevant increase within 1 h.

Most other patients with AHF will remain in the observe zone. In these, an additional hs-cTnT/I measurement at 3 h, and early echocardiography will identify additional patients with high likelihood of ACS who may benefit from early coronary angiography.<sup>35–38</sup>

In the absence of a dynamic change in cTn, the possibility of a late presentation (i.e. missing the time window for detection of a change) should also be considered, especially for patients with atypical or absent symptoms who may have delayed seeking medical attention. More extensive diagnostic workup (e.g. imaging, angiography) should be considered for late presenters in whom the suspicion for ACS is high.<sup>39</sup> AHF patients without chest pain or a dynamic cTn change and with low ACS risk scores [e.g. GRACE<sup>40,41</sup> <https://www.outcomes-umassmed.org/grace/>, or HEART (History, Electrocardiogram, Age, Risk Factors, Troponin)<sup>42,43</sup>; online supplementary Table S2] can generally be managed conservatively in terms of invasive testing for ACS, and AHF should be the primary treatment focus.

### Scenario 3: patients with acute heart failure, chest pain, and elevated cardiac troponin

This scenario represents the most straightforward presentation, since the classic elements of the MI diagnostic criteria are evident. These patients may either have type 1 or type 2 MI. The clinical context including ECG and biomarker changes should guide differential diagnosis between type 1 and type 2 MI in the majority of the patients. However, in uncertain cases, coronary angiography is needed in order to define the cause of MI. Therefore, an immediate or early invasive strategy will be indicated in many patients with this clinical presentation,<sup>22</sup> requiring transfer to a facility with cardiac catheterization and PCI capabilities. Early risk stratification is a cornerstone of patient management because it will dictate how quickly the patient should be transferred. Type 2 MI constitutes a clinical challenge in this scenario because no definitive data are available to guide treatment. Thus, antithrombotic drugs or invasive therapy cannot currently be recommended.

### Scenario 4: patients with acute coronary syndrome subsequently developing acute heart failure

This clinical presentation is dominated by symptoms and findings consistent with ACS (e.g. sudden onset of chest pain). Dyspnoea is initially absent, but subsequently develops within hours or days. Many of these patients will have a STEMI, although NSTEMI is also possible. A STEMI is usually a type 1 MI.<sup>31,44</sup> Thus, an immediate invasive management strategy is recommended unless a clear contraindication exists.<sup>31</sup> Risk assessment of patients with AHF in the setting of STEMI should be based on the Killip classification,<sup>31</sup> as it strongly correlates with the prognosis. The AHF presentation may range from mild to moderate pulmonary congestion to cardiogenic shock (6–10% of all STEMI cases with in-hospital mortality rates of  $\geq 50\%$ ).<sup>31</sup>

## Electrocardiography

In patients with suspected ACS, the 12-lead ECG is a first-line assessment.<sup>22,31</sup> It permits evaluation of acute ischaemia, left ventricular (LV) hypertrophy, arrhythmia, and previous MI. However, ECG in the setting of AHF and ACS may be difficult to interpret because of numerous ECG abnormalities associated with heart failure.<sup>12,45</sup> In the 954 patients with ACS and AHF in the ESC-HF-LT registry, a possible prior MI (Q-wave) was present in 91.0%, left bundle branch block in 10.1%, atrial fibrillation in 21.4%, and bradyarrhythmia or ventricular arrhythmia in 15.3%.<sup>12</sup> Thus, the initial ECG in patients with AHF and suspected MI, particularly in case of NSTEMI, may be non-diagnostic or obscured by the underlying cardiomyopathy. Continuous ECG monitoring of the ST-segment during the 'rule-out' phase can identify high-risk patients with transient myocardial ischaemia, even when symptoms are poorly represented. In patients with known previous ECG alterations, dynamic ECG changes together with serial biomarker findings may be helpful.

Electrocardiographic changes consistent with acute transmural or sub-epicardial myocardial ischaemia may be observed in patients with AHF and ACS.<sup>31</sup> New criteria have also been suggested for

patients with left bundle branch block (modified Sgarbossa criteria) and paced ventricular rhythm.<sup>46</sup>

Acute conditions other than AHF and ACS can be associated with ECG changes that resemble myocardial ischaemia and raise diagnostic challenges. Symptoms and clinical signs of acute PE may overlap with ACS, and the ECG may show the classic S1Q3T3 pattern (high specificity but low sensitivity for PE) as well as other non-specific ECG findings (including sinus tachycardia, rightward axis shift, P-pulmonale pattern, complete or incomplete right bundle branch block, T-wave inversion in leads V1–4, and ST-segment elevation or depression).<sup>47</sup> Patients with myocarditis may have depolarization and repolarization abnormalities, which are difficult to differentiate from ACS.<sup>48</sup>

## Cardiac troponin and other biomarkers

The diagnostic use and interpretation of hs-cTn have been discussed before. Elevated cTn in patients with AHF predicts an increased risk of subsequent adverse events.<sup>49–51</sup> While up to 50% of patients with AHF will have an elevated value with classical cTn assays,<sup>52–54</sup> up to 90% of patients with AHF may have a hs-cTn above the 99th upper reference limit at the time of initial evaluation.<sup>55</sup>

Other biomarkers to diagnose ACS have been evaluated. Copeptin can be helpful in the very early stage to rule out ACS, but it offers limited additive value to hs-cTn.<sup>22,35,56</sup> Novel biomarkers such as soluble ST2 (sST2) or galectin-3 may be useful for prognosis or to predict remodelling. In a sub-study of the CardShock registry, the combination of elevated sST2 and N-terminal pro B-type natriuretic peptide (NT-proBNP) at 12 h was associated with a higher 30-day mortality compared to elevation of only one of these biomarkers, or to no elevation of either biomarker. The addition of combined sST2 and NT-proBNP measured to the CardShock risk score correctly reclassified 11% of patients.<sup>57</sup> However, it is unclear how this generalizes to the large cohort of patients with AHF without cardiogenic shock. Galectin-3 may be useful to predict patients who will develop LV dysfunction post-MI.<sup>58</sup> In addition to protein-based biomarkers, there is evidence that circulating miRNAs and long non-coding RNAs such as LIPCAR may have some benefit in the diagnosis and prediction of heart failure post-MI.<sup>59,60</sup> Their value, however, needs to be validated in large, prospective trials. More research is needed to determine the role of these biomarkers for risk stratification and, more importantly, if they should be used in the acute setting or to target therapy and potentially improve outcomes for specific patient populations.

## Imaging

### Echocardiography

Emergency echocardiography at presentation is indicated in patients with cardiac arrest, cardiogenic shock, haemodynamic instability, or suspected mechanical complications, or if the diagnosis of STEMI is uncertain.<sup>31</sup> Echocardiography should be performed without delay in patients with suspected ACS and AHF. According

to the latest ESC heart failure and STEMI guidelines,<sup>31,61</sup> transthoracic echocardiography is mandatory for diagnosis, differential diagnosis, assessment of infarct extension, left and right ventricular function, detection of complications, and prognostic evaluation. Parameters predicting worse short-term outcome include markers of systolic and diastolic LV function [e.g. reduced LV ejection fraction (LVEF)], wall motion abnormalities, increased E/e' ratio, Doppler myocardial performance index, short E deceleration time, and elevated pulmonary artery pressure.<sup>31,62–67</sup> Transient or persistent regional wall motion abnormalities are the imaging hallmark of acute myocardial ischaemia.<sup>68</sup> However, application of this sign for the diagnosis of new-onset ACS in the setting of worsening chronic heart failure can be challenging because pre-existing systolic dysfunction and myocardial dyssynchronous zones are common in these patients. It may not be feasible to detect regional abnormalities in patients with severe dilatation and global hypokinesis of the left ventricle, especially by visual evaluation. Contrast injection is helpful to delineate the endocardial border and visualize wall thickening in critical settings where image quality may be compromised. Alternative causes of segmental myocardial abnormalities include acute myocarditis, Takotsubo cardiomyopathy, hypertensive heart failure, and conduction disturbances.<sup>68</sup> Thus, the echocardiographic examination alone cannot guide reperfusion therapy.

Data are lacking to determine the accuracy of echocardiography for the diagnosis of ACS in patients with AHF or systolic LV dysfunction. In patients without previous coronary artery disease, the presence of wall motion abnormalities has a positive predictive value for acute ischaemia of approximately 50%. The absence of dyssynchronous zones has a negative predictive value of about 95%, but previous MI reduces the sensitivity and specificity.<sup>66,69</sup> A normal left ventricle has a wall motion score index of 1, an index of 1.1–1.9 indicates a small infarct size, and an index  $\geq 2.0$  is consistent with a severe infarction and is a predictor of complications.<sup>69</sup> Wall motion may be normal in patients with small subendocardial MIs involving <20% of wall thickness or <1–6% of LV mass.<sup>68</sup>

Deformation imaging is a technique that may increase the sensitivity for detection of myocardial damage corresponding to coronary territory. This method reveals new areas of impairment or extended areas of previous asynergy by reduced segmental longitudinal strain coupled with post-systolic shortening.

Due to incremental diagnostic and prognostic value, the European Association of Cardiovascular Imaging recommends reporting of global longitudinal strain in all patients with ACS.<sup>70</sup> The derivative parameter of LV mechanical dispersion calculated on the basis of time to peak segmental longitudinal strain has been shown to predict arrhythmic events after MI.<sup>71</sup> Residual myocardial ischaemia, viability, and contractile reserve may be assessed by pre-discharge pharmacological stress echocardiography.

Myocardial contrast echocardiography is a unique modality that provides real-time imaging of myocardial perfusion and enables rapid bedside detection of acute ischaemia. This technique is, however, limited by a lack of standardization and the need for appropriate training. It has a comparable accuracy to cardiac magnetic resonance (CMR) imaging for identifying myocardial viability and the no-reflow phenomenon.<sup>72</sup>

The echocardiographic parameters that may help to detect possible mechanical complications of MI and to discriminate new myocardial ischaemia from a previous MI are presented in *Table 1*.<sup>68</sup>

## Computed tomography angiography and magnetic resonance imaging

Early diagnostics to identify the aetiology of AHF is recommended followed by immediate initiation of specific treatment. Invasive coronary angiography remains the gold standard procedure for establishing the presence of coronary artery disease. Coronary angiography is not without risks (e.g. worsening renal dysfunction with contrast, bleeding, arterial dissection, stroke). Computed tomography angiography (CTA) and magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) are emerging as two reliable alternatives to invasive coronary angiography, although they may also be problematic in patients with impaired renal function. CTA should be reserved to patients with relatively low suspicion of coronary artery disease and therefore a low probability of further coronary angiogram. Patients with AHF may not be able to tolerate MRI, although open-field MRI or ultra-fast MRI may overcome this problem in the future. The role of these methods is not established in clinical practice.

### Computed tomography angiography

Regarding ACS, two different acquisition protocols are of clinical interest: computed tomographic coronary angiography protocols for the assessment of the coronary arteries; and triple rule-out protocols that include the simultaneous examination of the coronary arteries, aorta, pulmonary arteries, and adjacent intrathoracic structures. Multidetector computed tomography (MDCT) can identify plaque area and the degree of stenosis.<sup>73</sup> Computed tomographic coronary angiography demonstrates an excellent ability to rule out coronary stenosis with a high degree of confidence in low- and intermediate-risk populations. However, since coronary artery disease is highly prevalent in patients with AHF, MDCT may not be recommended in typical patients with AHF and suspected ACS.

Acute chest pain in patients with AHF can be caused by potentially life-threatening pathologies other than coronary artery disease. Triple rule-out protocols are designed to provide sufficient contrast to the coronary arteries, pulmonary arteries, and thoracic aorta to permit assessment of coronary artery disease, PE, aortic dissection, pneumothorax, and traumatic injuries by a single acquisition. Triple rule-out may be of value in selected patients, but its appropriate use needs to be further defined.<sup>74</sup>

### Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance imaging is the only cardiac imaging modality capable of precisely recognizing the presence and the extent of prior MI irrespective of its size.<sup>75</sup> A CMR-based approach uses LGE to determine ischaemic vs. non-ischaemic patterns and to assess viability. In the limited cases where echocardiography is suboptimal or inconclusive, CMR may be a good

alternative after primary PCI to assess resting LV function, as well as right ventricular and valve function, to exclude early post-infarction mechanical complications and LV thrombus.<sup>31</sup>

According to the 2016 ESC guidelines, CMR should be considered in patients with dilated cardiomyopathy to distinguish between ischaemic and non-ischaemic myocardial damage when clinical and other imaging data are inconclusive (class of recommendation IIa, level of evidence C). CMR imaging may also be used for the assessment of myocardial ischaemia and viability in patients with heart failure and coronary artery disease who are suitable candidates for coronary revascularization (class of recommendation IIb, level of evidence B).<sup>61</sup> In unclear cases, CMR imaging can reveal the cause of heart failure, including myocarditis, Takotsubo cardiomyopathy, and non-compaction cardiomyopathy. It can also be used to visualize atrial or ventricular thrombi. However, in patients with AHF complicated by ACS or vice versa, MRI usually will either not be tolerated or not be feasible to rapidly assess significant coronary artery stenoses.

## Coronary angiography and reperfusion or revascularization therapy

### Timelines and reperfusion strategies for invasive coronary angiography, percutaneous coronary intervention, or coronary artery bypass graft surgery

The ESC guidelines on STEMI, NSTEMI and heart failure are consistent in their recommendations that an immediate invasive strategy should be implemented in patients with ACS and AHF. For STEMI, primary PCI is indicated in all patients with symptoms of ischaemia of  $\leq 12$  h duration and persistent ST-segment elevation.<sup>31</sup> In patients treated with fibrinolysis, emergency angiography and PCI (if indicated) are recommended in patients with heart failure or shock. In patients with NSTEMI, an immediate ( $< 2$  h) invasive strategy is also recommended in very high-risk patients.<sup>22</sup> Patients with ACS and AHF are always considered a very high-risk group,<sup>22</sup> and an immediate invasive strategy is also recommended in these patients, regardless of ECG or biomarker findings.<sup>61</sup> Thus, ACS evaluation and treatments should be prioritized. AHF therapies should be administered as necessary to stabilize the patient in parallel with initiation of ACS therapies. However, most commonly complete normalization of volume overload cannot be waited for and is not necessary before angiography.

Angiography is also the only definitive method to differentiate between type 1 MI with evidence of plaque rupture/coronary thrombosis and type 2 MI. However, before invasive assessment, it is logical to re-evaluate ischaemia in type 2 MI after the cause of oxygen supply/mismatch has been corrected. In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and AHF.<sup>22,31</sup> Management strategies for patients with



**Table 1** Echocardiographic features of acute coronary syndrome, old myocardial infarction, and complications of myocardial infarction

	New ACS	Old MI	MI complications
Regional myocardial function	Wall motion abnormalities with preserved wall thickness in diastole	Hypo-/akinesis with thin highly reflective wall	Aneurysm, pseudoaneurysm, hyperdynamic LV in ventricular wall or septal rupture
Type of myocardial injury	Dyssynergic regions may have the potential of recovery	Viability in the form of stunning or hibernation may be present	Infarct expansion, progressive remodelling
Ischaemic mitral regurgitation	Acute ischaemia of posterior papillary muscle	Scarring, rupture of posterior papillary muscle	Increasing distance between papillary muscles

ACS, acute coronary syndrome; LV, left ventricle; MI, myocardial infarction.

myocardial injury should focus on treating the underlying problem associated with AHF (e.g. reducing elevated filling pressures, optimizing guideline-recommended chronic heart failure therapies) rather than invasive interventions targeting coronary artery disease.<sup>61,76</sup>

## Pharmacologic management of patients with acute heart failure and acute coronary syndrome

The initial pharmacologic management of ACS in patients with AHF should not differ from standard pharmacologic treatment of ACS,<sup>22,31</sup> with adjustments specific to AHF where indicated. For example, AHF is associated with physiologic changes that may influence the pharmacokinetic<sup>77,78</sup> or adverse effect profiles of some drugs (Table 2).<sup>77,78</sup> In addition, patients with AHF may have organ impairment due to congestion or hypoperfusion.<sup>79</sup> Physicians should evaluate the extent of renal or hepatic impairment in patients with ACS and AHF and adjust medication doses appropriately, or avoid drugs contraindicated in such settings. Hepatic impairment related to AHF may also lead to coagulopathy, which could influence bleeding risk and should be considered when making treatment decisions (Table 2). Many heart failure patients are anticoagulated due to concomitant atrial fibrillation, which affects the use of antiplatelet therapies. Similarly, the extent to which treatments for AHF may aggravate ACS should also be considered. For example, hypotension should be avoided if vasodilators are administered, to minimize the potential for pro-ischaemic effects. Inotropes are only recommended (class of recommendation IIb, level of evidence C) in the setting of hypotension and hypoperfusion,<sup>31</sup> but if required, the potential for these drugs to worsen ischaemia and induce arrhythmias in the setting of ACS should be considered.

The treatment of type 1 MI in patients with concomitant AHF should generally follow the ESC guidelines for STEMI or NSTEMI.<sup>22,31</sup> The mainstay of management of type 2 MI is correction of the underlying cause of supply/demand mismatch (if identified), and stabilization of the patient's haemodynamic status. Most patients with type 2 MI have known coronary artery disease

(reported prevalence of 36% to 78%<sup>23</sup>) or cardiovascular risk factors. Thus, indications for most standard post-MI therapy may be extrapolated to patients with type 2 MI, recognizing that evidence specifically in this subset of patients is lacking. One exception is antiplatelet therapies, which specifically target the pathophysiologic mechanism underlying type 1 MI. The relevance of these agents for type 2 MI is uncertain and they cannot be recommended. A systematic review of 57 randomized trials evaluating dual antiplatelet therapy in 188 347 patients with ACS revealed that patients with type 2 MI were excluded from all trials.<sup>80</sup> An overview of recommendations for management of AHF in patients with STEMI is shown in Table 3.<sup>31</sup>

## Initial pharmacologic management of acute coronary syndrome with concomitant acute heart failure

### Initial relief of pain and anxiety

Immediate and effective pain relief is important in ACS complicated by AHF. Pain can lead to sympathetic activation and its sequelae of vasoconstriction, increased cardiac workload, aggravated ischaemia, and depressed myocardial function. Oxygen is indicated in patients with pulmonary congestion and arterial oxygen saturation <90% to maintain a saturation >95%.<sup>31</sup> Opiates (e.g. morphine sulphate) might be used to reduce pain, dyspnoea or anxiety, but their use has been shown to impair the absorption of oral antiplatelet agents.<sup>81–83</sup> Even more importantly, concerns have been raised about the safety of opiates and their potential to cause hypopnoea or increase mortality in patients with severe symptoms of AHF and pulmonary congestion.<sup>31,61,84,85</sup> Thus, opiates are not routinely recommended in the management of patients with AHF and STEMI (Table 3). Benzodiazepines are also described in the ESC STEMI guidelines as an option to treat anxiety (class of recommendation IIa, level of evidence C) and cautious use of a benzodiazepine for anxiety, agitation, or delirium is described in the ESC heart failure guidelines.<sup>61</sup> Yet, in the elderly benzodiazepines may also trigger confusion.

Nitrates are commonly used for ischaemia-related pain, hypertension and pulmonary oedema in patients with ACS. Intravenous nitrates are more effective than sublingual nitrates for symptom

**Table 2** Potential impact of acute heart failure on standard therapies for acute coronary syndrome<sup>77,78</sup>

Procedure or intervention for acute coronary syndrome	Specific considerations for acute heart failure
Diagnostic/laboratory/imaging	
Coronary angiography	Contrast may worsen renal dysfunction in the setting of AHF
Cardiac troponin	Elevations may be due to myocardial injury rather than MI
Treatments	
General pharmacokinetics	AHF can theoretically alter the pharmacokinetics of drugs, although it has not been well studied. <sup>77,78</sup> <ul style="list-style-type: none"> <li>• Absorption: gut oedema or decreased GI motility due to hypoperfusion may reduce absorption of some drugs</li> <li>• Distribution: alterations in plasma proteins due to hepatic impairment or increased volume of distribution due to peripheral congestion; can lead to higher or lower plasma levels depending on drug and extent of alterations</li> <li>• Metabolism: hepatic congestion may lead to decreased metabolism and higher plasma levels of hepatically metabolized drugs</li> <li>• Excretion: renal or hepatic impairment may lead to higher plasma levels of some drugs; greater potential for toxicity or side effects</li> </ul>
Dual antiplatelet therapy	Organ dysfunction (e.g. renal, hepatic) due to AHF may warrant dose adjustments or avoidance if contraindication; hepatic impairment may increase bleeding risk
Opiates	Concerns about increased mortality in patients with AHF
Beta-blockers	Intravenous administration could worsen AHF; avoid until haemodynamically stable and patient is no longer congested
ACE-inhibitors, ARBs	Renal impairment in the setting of AHF may worsen with initiation; monitor for hypotension in the setting of AHF
MRA	Renal impairment in the setting of AHF may worsen with initiation; monitor for hyperkalaemia
Glucose-lowering therapy	Avoid drugs with cautions/contraindications for heart failure (e.g. thiazolidinediones, DPP-4 inhibitors)
Verapamil/diltiazem	Verapamil/diltiazem should not be used in patients with AHF with reduced ejection fraction

ACE, angiotensin-converting enzyme; AHF, acute heart failure; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist.

relief and regression of ST-segment depression.<sup>22</sup> Careful blood pressure monitoring is mandatory to avoid hypotension. Beyond symptom control, there is no evidence for an effect of nitrates on clinical outcome.<sup>86–92</sup> Specifically in patients with AHF and STEMI ACS, nitrates are recommended in patients with symptomatic heart failure with systolic blood pressure >90 mmHg to improve symptoms and reduce congestion (class of recommendation I, level of evidence C). Furthermore, intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated systolic blood pressure to control blood pressure and improve symptoms (class of recommendation IIa, level of evidence C).<sup>31</sup>

### Beta-blocker therapy

Beta-blockers competitively inhibit the effects of circulating catecholamines on the myocardium and reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and myocardial contractility. Since beta-blocker therapy administered at the time of presentation reduces infarct size and early mortality in patients with acute MI, they should be initiated in the first 24 h following ACS in patients who do not have signs of heart failure, low output state, or increased risk for cardiogenic shock (class of recommendation IIa, level of evidence A for

beta-blockers at presentation in patients undergoing primary PCI; class of recommendation III, level of evidence B for the use of intravenous beta-blockers in patients with AHF).<sup>22,31</sup> Continued long-term therapy with up-titration to guideline-recommended doses also reduces mortality. Importantly, patients who do not receive a beta-blocker during the first 24 h because of early contraindications should be re-evaluated for beta-blocker candidacy once stabilized.

### Angiotensin-converting enzyme inhibitors

Early initiation (within 24 h) of angiotensin-converting enzyme (ACE) inhibitors is associated with reduced mortality, and chronic use with up-titrated doses further lowers rates of mortality and hospital admission for heart failure in patients with LV dysfunction post-MI.<sup>93,94</sup> Therefore, guidelines strongly recommend that an ACE-inhibitor should be administered within the first 24 h to all patients with ACS and evidence of heart failure, LV systolic dysfunction, diabetes mellitus, or an anterior infarct (class of recommendation I, level of evidence A).<sup>31</sup> Valsartan is an alternative to ACE-inhibitors in patients who have clinical signs of heart failure and/or a LVEF <40%, particularly in patients who do not tolerate an ACE-inhibitor (class of recommendation I, level of evidence B).<sup>31,95,96</sup> Coronary angiography should not delay the initiation of these drugs.

**Table 3 Recommendations for the management of patients with left ventricular dysfunction, acute heart failure and acute coronary syndrome**

Recommendation	Class of recommendation	Level of evidence
ACE-inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF $\leq$ 40% and/or heart failure to reduce the risk of hospitalization and death.	I	A
Beta-blocker therapy is recommended in patients with LVEF $\leq$ 40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.	I	A
An MRA is recommended in patients with heart failure and LVEF $\leq$ 40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.	I	B
Loop diuretics are recommended in patients with acute heart failure with symptoms/signs of fluid overload to improve symptoms.	I	C
Nitrates are recommended in patients with symptomatic heart failure with SBP $>$ 90 mmHg to improve symptoms and reduce congestion.	I	C
Oxygen is indicated in patients with pulmonary oedema with SaO <sub>2</sub> $<$ 90% to maintain a saturation $>$ 95%.	I	C
Patient intubation is indicated in patients with respiratory failure or exhaustion, leading to hypoxaemia, hypercapnia, or acidosis, and if non-invasive ventilation is not tolerated.	I	C
Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) should be considered in patients with respiratory distress (respiratory rate $>$ 25 breaths/min, SaO <sub>2</sub> $<$ 90%) without hypotension.	IIa	B
Intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated SBP to control blood pressure and improve symptoms.	IIa	C
Opiates may be considered to relieve dyspnoea and anxiety in patients with pulmonary oedema and severe dyspnoea. Respiration should be monitored.	IIb	B
Inotropic agents may be considered in patients with severe heart failure with hypotension refractory to standard medical treatment.	IIb	C

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist, SaO<sub>2</sub>, arterial oxygen saturation; SBP, systolic blood pressure.

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### Mineralocorticoid receptor antagonists

Initiation of eplerenone within 7 days after an MI significantly reduced the rates of all-cause mortality, sudden cardiac death, and cardiovascular mortality or hospitalization in the EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial.<sup>97</sup> Therefore, it is recommended that a mineralocorticoid receptor antagonist (MRA) should be given to patients with STEMI and no contraindications who are already receiving an ACE-inhibitor and beta-blocker, and who have a LVEF  $\leq$ 40% and either symptomatic heart failure or diabetes mellitus (class of recommendation I, level of evidence B).<sup>31</sup>

### Antithrombotic treatment

The use of antithrombotic drugs is a cornerstone in the treatment of ACS. The use of aspirin and additional antiplatelet drugs is a central part of initial treatment and stabilization for any ACS, with or without PCI.<sup>22</sup> The use of dual antiplatelet therapy is under constant investigation, but usually is advocated for 1–2 years,

depending on bleeding risk.<sup>22</sup> During the acute phases of ACS, patients are co-treated with (low molecular weight) heparin. A recent study reported a benefit of low dose non-vitamin K antagonist oral anticoagulants (NOAC) in combination with antiplatelet therapy in patients with vascular disease.<sup>98</sup>

In heart failure on the other hand, the use of anticoagulant and antiplatelet drugs is not supported by solid data from randomized controlled trials.<sup>99</sup> Therefore, there is controversy and most physicians do not advocate its standard use in heart failure, although safety does not appear to be a major issue.<sup>99,100</sup> The recent COMMANDER-HF trial (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) with low-dose NOAC also yielded a neutral effect in heart failure,<sup>101</sup> lending further support to the ESC guidelines,<sup>61</sup> where there is no recommendation for the use of antithrombotic drugs in patients with heart failure in sinus rhythm. When atrial fibrillation or another reason for initiation of antithrombotic drugs develops, they can be administered for that indication. We propose

that the same holds true for ACS or venous thromboembolism prophylaxis in the setting of AHF.

### Management of hyperglycaemia

Glycaemia should be evaluated on admission in all patients with AHF and ACS, and it should be monitored frequently in patients with diabetes or hyperglycaemia. Critically ill patients have a high risk of hypoglycaemia-related events with intensive insulin therapy.<sup>102,103</sup> In patients with AHF and ACS, it is reasonable to maintain a blood glucose concentration  $\leq 11.0$  mmol/L (200 mg/dL) being careful to avoid hypoglycaemia. It seems reasonable to avoid glucose-lowering agents that can worsen heart failure symptoms in patients with ACS and AHF, such as thiazolidinediones<sup>104</sup> and dipeptidyl peptidase-4 inhibitors.<sup>105</sup> Decisions about whether to continue metformin should be made on an individual patient basis, depending on the degree of hypoperfusion, renal, or hepatic impairment since these conditions increase the risk for lactic acidosis.<sup>106</sup> It may be reasonable to continue sodium–glucose co-transporter-2 (SGLT2) inhibitors empagliflozin<sup>107</sup> and canagliflozin<sup>108</sup> and the glucagon-like peptide-1 receptor agonist liraglutide.<sup>109</sup> Renal function should be carefully monitored in patients receiving SGLT2 inhibitors to prevent acute kidney injury.<sup>61,110–114</sup>

### Ventilatory support

Some patients with ACS may develop acute cardiogenic pulmonary oedema. Non-invasive ventilation (NIV) has demonstrated to improve oxygenation and respiratory parameters in NSTEMI patients<sup>115–117</sup> with no differences between the two main modalities: continuous positive airway pressure and pressure support ventilation. Therefore, both techniques may be considered in patients with NSTEMI or a type 2 MI complicated with acute cardiogenic pulmonary oedema, but its use in STEMI patients cannot be widely extended because these patients were not included in the trials.<sup>118</sup> Patients with ACS with altered mental status and those showing progressive respiratory failure, not responding to NIV, would need intubation and invasive mechanical ventilation.

### Management of mechanical complications of acute coronary syndrome

Mechanical complications of ACS include acute mitral regurgitation, ventricular septal rupture, and ventricular free-wall rupture, and any of these may lead to cardiogenic shock.<sup>119</sup> Their incidence has declined since the advent of thrombolytic therapy and PCI. Physicians should carefully evaluate for the presence of mechanical complications in any patient with ACS, signs of cardiogenic shock, or a systolic murmur. Rapid diagnosis is pivotal to delivering aggressive and timely medical and surgical treatment, although prognosis may be dismal for a substantial proportion of these patients. Echocardiography must be immediately performed to confirm the diagnosis. Medical treatment and mechanical circulatory support may be used as a bridge to surgical repair.

Acute mitral regurgitation was the cause of 8.3% of cardiogenic shock presentations in the SHOCK (Should We Use Emergently Revascularize Occluded Coronaries in Cardiogenic Shock) registry.<sup>120</sup> Risk factors include female gender, older age, diabetes mellitus, and pre-existing coronary artery disease.

Ventricular septal rupture was the aetiology for 4.6% of patients in the SHOCK registry.<sup>121</sup> It usually has a delayed presentation, with an average onset of 2–4 days post-MI. Patients at risk are those with *de novo* coronary artery disease, transmural MI, anterior or anterolateral MI, and a left anterior descending coronary artery culprit lesion.

Free-wall rupture or tamponade accounted for 1.7% of presentations in the SHOCK registry with a 30-day mortality rate of 55%. Risk factors include female gender, older age, hypertension, large infarct size, delayed or incomplete revascularization, and limited collateral coronary blood supply.

The intra-aortic balloon pump (IABP) is not routinely recommended in cardiogenic shock associated with acute MI (class of recommendation III, level of evidence B) by current guidelines,<sup>61</sup> mainly due to the results of the IABP-SHOCK II trial, in which IABP did not reduce 30-day mortality in patients with acute MI and cardiogenic shock.<sup>113</sup> However, it may serve as a bridge to surgery in selected patients with ongoing ischaemia or mechanical complications.

### Management after clinical stabilization and follow-up strategies

Left or right ventricular dysfunction can be transient, resolving within days to weeks after discharge, or it can progress to clinically overt chronic heart failure in the months to years post-MI as a result of impaired cardiac function leading to reverse remodelling. The degree of LV dysfunction depends on the infarct size and the extent of remodelling. During the post-acute phase, minimizing progression of left or right ventricular dysfunction and remodelling is an important goal of early treatment. Thus, therapies known to slow progression of LV dysfunction and promote reverse remodelling should be started in low doses ideally prior to discharge in all patients with cardiac impairment and without contraindications, including beta-blockers, ACE-inhibitor or angiotensin receptor blocker and MRA.<sup>31</sup> Finally, the PARADISE-MI (Prospective ARNI vs. ACE inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI, NCT02924727) trial is evaluating whether sacubitril/valsartan will improve outcomes in patients with left ventricular dysfunction post-MI.

For patients with LV dysfunction, echocardiography should be repeated 6–12 weeks post-ACS, in concomitance with a complete clinic visit. Patients with heart failure benefit from regular follow-up and monitoring of biomedical parameters to ensure the safety and optimal dosing of medicines and to detect the development of complications or disease progression that may require a change in management (e.g. the onset of atrial fibrillation or development of anaemia).<sup>61</sup> At discharge, care should be taken to instruct the primary caregiver how to up-titrate the disease-modifying therapies in order to reach guideline-recommended doses as soon as possible. Also, at every visit, guideline-directed medical therapy

should be reviewed and up-titrated if the patient has not reached optimal doses.

International guidelines recognize the essential provision of patient education to enable a seamless transition from hospital to primary care.<sup>61,122</sup> In patients with AHF and ACS, discharge education and post-discharge follow-up should cover principles related to both ischaemic heart disease and heart failure. The provision of information from the multidisciplinary team (i.e. nurses, physicians, pharmacists) prior to discharge, alongside a planned and prompt follow-up can facilitate an earlier discharge, improve patients' quality of life, enable self-care,<sup>123</sup> promote medication adherence,<sup>124,125</sup> and reduce readmissions.<sup>126,127</sup> Importantly, adherence to medical treatment and physician directions strongly influence outcomes in outpatients with a recent (within 15 months) heart failure hospitalization.<sup>128</sup>

In an analysis of 3261 patients in the EuroHeart Failure Survey recently discharged from an AHF admission, patients recalled 46% of the lifestyle and additional advice provided during the hospital stay.<sup>129</sup> Within a variety of clinical settings, patients are often not provided with adequate information appropriate to their needs.<sup>130,131</sup> The information provided must be accurate, concise, as well as appropriate to stage of illness, psychological needs, and cognitive ability. It should be delivered to both patients and caregivers/family members.<sup>132</sup> Verbal information, reinforced with written, video, or patient-orientated educational websites encourage a multimodal style of learning and enhances comprehension.<sup>133,134</sup> Randomized trials have shown one-on-one nurse-led teaching sessions improved quality of life and reduced heart failure symptoms.<sup>126,135</sup> More research is needed to determine the most effective format for pre-discharge education to ensure comprehension, information retention, and to prevent recurrent rehospitalizations.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on heart failure recommend (class IIa, level of evidence B) scheduling an early follow up visit (within 7–14 days of discharge) and early telephone follow-up within 3 days after a hospital discharge for AHF.<sup>122</sup> Although not specific to ACS, this recommendation is reasonable for patients with both AHF and ACS.

Cardiac rehabilitation is an evidence-based intervention post-acute MI and is recommended for all patients.<sup>22,31</sup> Although not specifically evaluated in patients with ACS and AHF, exercise training has also been studied in chronic heart failure with reduced ejection fraction.<sup>136</sup> The ESC heart failure guidelines recommend regular aerobic exercise in stable patients to improve symptoms, functional capacity and to reduce heart failure hospitalizations.<sup>61</sup> Thus, considering the STEMI, NSTEMI, and heart failure guidelines, cardiac rehabilitation is also appropriate for patients with ACS and AHF.<sup>22,31,61</sup>

## Knowledge gaps and future research

Although an extensive body of evidence guides the treatment of ACS, few studies dedicated to the sub-population of patients

**Table 4** Topics for future research

- Prognostic differences between patients with AHF on admission for ACS and those who develop AHF during the ACS hospitalization
- Better characterization of type 2 MI in patients with AHF and implications for prognosis and treatment
- Improved detection of ischaemia as a causative or precipitating factor for AHF
- Develop and validate diagnostic algorithms (rule-in/rule-out) specifically in patients with AHF and ACS; evaluate role of novel biomarkers to assist with diagnosis
- Methods to improve interpretation of ECG findings, and echocardiography in patients with AHF and ACS (i.e. most patients with AHF have abnormal initial ECG and echocardiographic findings)
- Strategies to improve the implementation of angiography and revascularization (if indicated) in patients with AHF and ACS; methods to manage patient stability to facilitate these procedures
- Strategies to improve the adoption of evidence-based medication for both ACS and heart failure
- Studies on treatment efficacy in specific patient groups based on risk assessment (e.g. by using biomarkers)
- Studies in patients with ACS and AHF with mid-range and preserved ejection fraction
- Studies to understand the influence of AHF on therapies for ACS (e.g. dosing, adverse effects, bleeding risk) and to understand the influence of AHF therapies on ACS (e.g. vasodilators/hypotension and risk of pro-ischaemia; inotropes and risk of pro-ischaemia or pro-arrhythmia in the setting of ACS)

ACS, acute coronary syndrome; AHF, acute heart failure; ECG, electrocardiogram; MI, myocardial infarction.

presenting with both AHF and ACS have been conducted. Thus, current approaches to diagnosis and treatment should follow guidelines for each disease, with disease-specific modifications as clinically indicated. An important step to fill the knowledge gap is to design future studies specifically targeting patients with both AHF and ACS. Observational registries may be useful to explore some questions. The differentiation of myocardial injury and infarction in patients with unspecific symptoms like dyspnoea remains a clinical challenge. Therefore, new diagnostic tools, like biomarkers and imaging, should be examined. Examples include: (i) prognostic differences between patients with AHF on admission for ACS and those who develop AHF during the ACS hospitalization; (ii) better characterization of type 2 MI in patients with AHF and implications for prognosis and treatment; (iii) improved detection of ischaemia as a causative or precipitating factor for AHF; and (iv) studies in patients with heart failure with mid-range and preserved ejection fraction. Other key areas for future research are presented in *Table 4*.

## Conclusion

The concomitant presentation of ACS and AHF is a common clinical scenario. It is associated with a worse prognosis than for patients who present with ACS alone. Its diagnosis is made challenging because symptoms are often atypical, ECG changes may be obscured by pre-existing abnormalities, and biomarkers can be difficult to interpret. These features can make differentiation between myocardial injury and infarction difficult. Consideration of the four described clinical scenarios may help guide physicians towards the most appropriate assessment and treatment strategies for specific patients. Patients with confirmed ACS and AHF are always considered a high-risk group, and an immediate invasive strategy (i.e. for type 1 MI) is recommended by guidelines, regardless of ECG or biomarker findings. In general, the evaluation and treatment of the ACS component should be prioritized, with AHF therapies administered in parallel as needed for stabilization and symptomatic management. Designing future studies specifically targeting patients with both AHF and ACS is needed to better inform the assessment and management of these patients.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Universal classification of myocardial infarction.

**Table S2.** The HEART score for chest pain patients at the emergency department.

## Acknowledgements

The authors acknowledge the Heart Failure Association of the European Society of Cardiology for organizing the meeting during which this topic was discussed. The authors acknowledge T.J. for her expert review of the manuscript, and W.G. S., PharmD (Campbell University College of Pharmacy and Health Sciences), supported by the Heart Failure Association of the European Society of Cardiology for contributions to content development, writing, and editing the manuscript. J.M., C.M. and F.P. performed their expert review of the paper on behalf of Acute Cardiovascular Care Association of the European Society of Cardiology. J.B. and T.T. were supported by the Deutsche Forschungsgemeinschaft, Clinical Research Group 311 (KFO 311) '(Pre-)terminal heart and lung failure: unloading and repair' (DFG; TP1 and TP11).

**Conflict of interest:** V.P.H. reports personal fees from Bayer, Boehringer Ingelheim, BMS, Orion Pharma, Novartis, and Roche Diagnostics, research grant from Abbott Laboratories. J.P. reports personal fees for lectures and advisory boards from Orion Pharma, Novartis, Servier, and Roche Diagnostics. J.B. reports personal fees from Novartis, Vifor, Bayer, Servier, Orion, CVRx, Abiomed, Abbott, Medtronic, Boehringer Ingelheim; research support from Zoll, CVRx, Bayer, Vifor, Abiomed, Medtronic. H.P.B.L.R. reports research grants from Roche Diagnostics, Novartis Pharma, Vifor Pharma; personal fees from Roche Diagnostics, Novartis Pharma, Vifor Pharma. J.C. reports personal fees from Amgen, Novartis, Orivas, Servier, Berlin-Chemie. O.C. reports research grants from

Servier, Novartis, Vifor Pharma. A.J.S.C. reports personal fees from Actimed, AstraZeneca, Faraday, Gore, Impulse Dynamics, Menarini, Novartis, Nutricia, Resmed, Respicardia, Servier, Stealth Peptides, Verona, Vifor. S.P.C. reports research grants from NIH, PCORI, AHRQ, AHA, Ortho Clinical; personal fees from Novartis, Medtronic, Vixiar. G.F. reports to be clinical trial/registry committee member for Bayer, Novartis, Servier, Medtronic, Vifor. J.L. reports personal fees from Bayer, Boehringer Ingelheim, Novartis, Pfizer, Roche Diagnostics, Orion Pharma, Servier, and Vifor Pharma. A.M. reports personal fees from Cardioentis, Novartis, Orion, Roche, Servier, Adrenomed, Abbott, Neuro Tronik, Sphingotec; research grants from Adrenomed, Abbott, Sphingotec. M.M. reports personal fees (advisory boards) from Novartis and Bayer. W.F.P. reports research grants from Abbott, Boehringer Ingelheim, Braincheck, CSL Behring, Daiichi-Sankyo, Immunarray, Janssen, Ortho Clinical Diagnostics, Portola, Relypsa, Roche; consultant for Abbott, AstraZeneca, Bayer, Beckman, Boehringer-Ingelheim, Ischemia Care, Dx, Immunarray, Instrument Labs, Janssen, Nabriva, Ortho Clinical Diagnostics, Relypsa, Roche, Quidel, Siemens; expert testimony for Johnson and Johnson; stock/ownership interests: AseptiScope Inc, Brainbox Inc, Comprehensive Research Associates LLC, Emergencies in Medicine LLC, Ischemia DX LLC. M.P. reports personal fees from Novartis, Vifor Pharma, Roche Diagnostics (lectures); stock ownership in Orion. F.R. reports research grants from St. Jude Medical/Abbott, Servier, Novartis, Bayer, Mars; personal fees (for lectures, advisory board meetings, steering committee) from St. Jude Medical/Abbott, Servier, Zoll, AstraZeneca, Sanofi, Novartis, Amgen, BMS, Pfizer, Fresenius, Vifor, Roche, Bayer, Cardioentis, Boehringer Ingelheim, Heartware. A.S. reports research grants and personal fees from Singulex Inc. J.R.T. reports research support/personal (consulting) fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cytokinetics, Janssen, Medtronic, Novartis, Relypsa. T.T. reports personal fees from Novartis, Sanofi/Genzyme, Beiersdorf, Shire, Amicus; grant/research support from Novartis, Sanofi/Genzyme, Beiersdorf.; he is founder and holds shares of Cardior Pharmaceuticals GmbH. J.M.W. reports personal fees from Novartis (lectures). M.B.Y. reports research grants from Amgen, Novartis, Bayer, Dalcour Pharmaceuticals; institutional consultancy fees from Servier. The other authors have nothing to disclose.

## References

- McManus DD, Chinali M, Saczynski JS, Gore JM, Yarzebski J, Spencer FA, Lessard D, Goldberg RJ. 30-year trends in heart failure in patients hospitalized with acute myocardial infarction. *Am J Cardiol* 2011;**107**:353–359.
- Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J, Budaj A, Goldberg RJ, Klein W, Anderson FA Jr. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). *Circulation* 2004;**109**:494–499.
- Follath F, Yilmaz MB, Delgado JF, Parisiss JT, Porcher R, Gayat E, Burrows N, McLean A, Vilas-Boas F, Mebazaa A. Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF). *Intensive Care Med* 2011;**37**:619–626.
- Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail* 2010;**12**:239–248.

5. Chioncel O, Vinereanu D, Datu M, Ionescu D, Capalneau R, Brukner I, Dorobantu M, Ambrosy A, Macarie C, Gheorghide M. The Romanian Acute Heart Failure Syndromes (RO-AHFS) registry. *Am Heart J* 2011;**162**:142–153.
6. Logeart D, Isnard R, Resche-Rigon M, Seronde M, de Groot P, Jondeau G, Galinier M, Mulak G, Donal E, Delahaye F, Juilliere Y, Damy T, Jourdain P, Bauer F, Eicher J, Neuder Y, Trochu J. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail* 2013;**15**:465–476.
7. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
8. Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, Nieminen MS, Harjola VP; FINN-AKVA Study Group. Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure. *Eur Heart J* 2006;**27**:3011–3017.
9. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M; Italian Survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006;**27**:1207–1215.
10. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, Alhabib KF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A; GREAT Network. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017;**19**:201–208.
11. Tarvasmaki T, Harjola VP, Nieminen MS, Siirila-Waris K, Tolonen J, Tolppanen H, Lassus J; FINN-AKVA Study Group. Acute heart failure with and without concomitant acute coronary syndromes: patient characteristics, management, and survival. *J Card Fail* 2014;**20**:723–730.
12. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254.
13. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Di Lenarda A, Mortara A, Oliva F, Maggioni AP; IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: the one-year follow-up results of IN-HF Outcome Registry. *Circ Heart Fail* 2013;**6**:473–481.
14. Bahit MC, Lopes RD, Clare RM, Newby LK, Pieper KS, Van de Werf F, Armstrong PW, Mahaffey KW, Harrington RA, Diaz R, Ohman EM, White HD, James S, Granger CB. Heart failure complicating non-ST-segment elevation acute coronary syndrome: timing, predictors, and clinical outcomes. *JACC Heart Fail* 2013;**1**:223–229.
15. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 2007;**297**:1892–1900.
16. Jeger RV, Pfister O, Radovanovic D, Eberli FR, Rickli H, Urban P, Pedrazzini G, Stauffer JC, Nossen J, Erne P; AMI-Plus Investigators. Heart failure in patients admitted for acute coronary syndromes: a report from a large national registry. *Clin Cardiol* 2017;**40**:907–913.
17. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2018;**40**:237–269.
18. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghide M. Troponin elevation in patients with heart failure: on behalf of the Third Universal Definition of Myocardial Infarction Global Task Force: heart failure section. *Eur Heart J* 2012;**33**:2265–2271.
19. McCarthy CP, Vaduganathan M, Januzzi JL Jr. Type 2 myocardial infarction – diagnosis, prognosis, and treatment. *JAMA* 2018;**320**:237–269.
20. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Gabriel SP, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghide M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
21. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS; Study Group on Biomarkers in Cardiology of ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;**33**:2252–2257.
22. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen S, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
23. Chapman AR, Shah AS, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan FE, Newby DE, Mills NL. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation* 2018;**137**:1236–1245.
24. Lambrecht S, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Diederichsen AC, Thygesen K, Mickleth H. Different causes of death in patients with myocardial infarction type 1, type 2, and myocardial injury. *Am J Med* 2018;**131**:548–554.
25. Saaby L, Poulsen TS, Diederichsen AC, Hosbond S, Larsen TB, Schmidt H, Gerke O, Hallas J, Thygesen K, Mickleth H. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. *Am J Med* 2014;**127**:295–302.
26. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovasc Diagn Ther* 2017;**7**:348–358.
27. Shah AS, McAllister DA, Mills R, Lee KK, Churchhouse AM, Fleming KM, Layden E, Anand A, Fersia O, Joshi NV, Walker S, Jaffe AS, Fox KA, Newby DE, Mills NL. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med* 2015;**128**:493–501. e3.
28. Baron T, Hambraeus K, Sundstrom J, Erlinge D, Jernberg T, Lindahl B. Type 2 myocardial infarction in clinical practice. *Heart* 2015;**101**:101–106.
29. Arora S, Strassle PD, Qamar A, Wheeler EN, Levine AL, Misenheimer JA, Cavender MA, Stouffer GA, Kaul P. Impact of type 2 myocardial infarction (MI) on hospital-level MI outcomes: implications for quality and public reporting. *J Am Heart Assoc* 2018;**7**:e008661.
30. Lettman NA, Sites FD, Shofer FS, Hollander JE. Congestive heart failure patients with chest pain: incidence and predictors of acute coronary syndrome. *Acad Emerg Med* 2002;**9**:903–909.
31. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevanos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
32. Arora S, Strassle PD, Qamar A, Kaul P. Comparison of troponin peaks between type 1 and type 2 myocardial infarction [abstract]. *J Am Coll Cardiol* 2017;**69**(Suppl 11):1201.
33. Sandoval Y, Thygesen K. Myocardial infarction type 2 and myocardial injury. *Clin Chem* 2017;**63**:101–107.
34. Drexler B, Heinisch C, Balmelli C, Lassus J, Siirila-Waris K, Arenja N, Socrates T, Noveanu M, Potocki M, Meune C, Haaf P, Degen C, Breidhardt T, Reichlin T, Nieminen MS, Veli-Pekka H, Osswald S, Mueller C. Quantifying cardiac hemodynamic stress and cardiomyocyte damage in ischemic and nonischemic acute heart failure. *Circ Heart Fail* 2012;**5**:17–24.
35. Mockel M, Giannitsis E, Mueller C, Huber K, Jaffe AS, Mair J, Plebani M, Thygesen K, Lindahl B. Rule-in of acute myocardial infarction: focus on troponin. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:212–217.
36. Boeddinghaus J, Nestelberger T, Twerenbold R, Neumann JT, Lindahl B, Giannitsis E, Sorensen NA, Badertscher P, Jann JE, Wussler D, Puelacher C, Rubini Gimenez M, Wildi K, Strebel I, Du Fay de Lavallaz J, Selman F, Sabti Z, Kozhuharov N, Potlukova E, Rentsch K, Miro O, Martin-Sanchez FJ, Morawiec B, Parenica J, Lohrmann J, Kloos W, Buser A, Geigy N, Keller DI, Osswald S, Reichlin T, Westermann D, Blankenberg S, Mueller C; APACE, BACC, and TRAPID-AMI Investigators. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. *Eur Heart J* 2018;**39**:3780–3794.
37. Boeddinghaus J, Twerenbold R, Nestelberger T, Badertscher P, Wildi K, Puelacher C, du Fay de Lavallaz J, Keser E, Rubini Gimenez M, Wussler D, Kozhuharov N, Rentsch K, Miro O, Martin-Sanchez FJ, Morawiec B, Stefanelli S, Geigy N, Keller DI, Reichlin T, Mueller C; APACE Investigators. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. *Clin Chem* 2018;**64**:1347–1360.

38. Twerenbold R, Neumann JT, Sorensen NA, Ojeda F, Karakas M, Boeddinghaus J, Nestelberger T, Badertscher P, Rubini Gimenez M, Puelacher C, Wildi K, Kozuharov N, Breitenbuecher D, Biskup E, du Fay de Lavallaz J, Flores D, Wussler D, Miro O, Martin Sanchez FJ, Morawiec B, Parenica J, Geigy N, Keller DI, Zeller T, Reichlin T, Blankenberg S, Westermann D, Mueller C. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. *J Am Coll Cardiol* 2018;**72**:620–632.
39. Katus H, Ziegler A, Kincin O, Giannitsis E, Stough WG, Achenbach S, Blankenberg S, Brueckmann M, Collinson P, Comaniciu D, Crea F, Dinh W, Ducrocq G, Flachskampf FA, Fox KA, Friedrich MG, Hebert KA, Himmelmann A, Hlatky M, Lautsch D, Lindahl B, Lindholm D, Mills NL, Minotti G, Mockel M, Omland T, Semjonow V. Early diagnosis of acute coronary syndrome. *Eur Heart J* 2017;**38**:3049–3055.
40. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
41. Fox KA, FitzGerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel SP, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;**4**:e004425.
42. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, Monnik SH, Van TR, Mast TP, van den Akker F, Cramer MJ, Poldervaart JM, Hoes AW, Doevendans PA. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013;**168**:2153–2158.
43. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, Monnik SH, van Tooren RM, Doevendans PA. Chest pain in the emergency room: a multicenter validation of the HEART score. *Crit Pathw Cardiol* 2010;**9**:164–169.
44. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; Working Group on Cardiovascular Pharmacotherapy. ESC Working Group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017;**38**:143–153.
45. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, Clark AL, de Silva R, Calvert MJ, Swedberg K, Komajda M, Mareev V, Follath F; EuroHeart Failure Survey Investigators. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. *Eur J Heart Fail* 2007;**9**:491–501.
46. Miranda DF, Lobo AS, Walsh B, Sandoval Y, Smith SW. New insights into the use of the 12-lead electrocardiogram for diagnosing acute myocardial infarction in the emergency department. *Can J Cardiol* 2018;**34**:132–145.
47. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svtil P, Vonk NA, Zamorano JL, Zompatori M; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;**35**:3033–3069.
48. Chen S, Hoss S, Zeniou V, Shauer A, Admon D, Zwas DR, Lotan C, Keren A, Gotsman I. Electrocardiographic predictors of morbidity and mortality in patients with acute myocarditis: the importance of QRS-T angle. *J Card Fail* 2018;**24**:3–8.
49. Collins SP, Jenkins CA, Harrell FE Jr, Liu D, Miller KF, Lindsell CJ, Naftilan AJ, McPherson JA, Maron DJ, Sawyer DB, Weintraub NL, Fermann GJ, Roll SK, Sperling M, Storrow AB. Identification of emergency department patients with acute heart failure at low risk for 30-day adverse events: the STRATIFY decision tool. *JACC Heart Fail* 2015;**3**:737–747.
50. Stiell IG, Perry JJ, Clement CM, Brison RJ, Rowe BH, Aaron SD, McRae AD, Borgundvaag B, Calder LA, Forster AJ, Wells GA. Prospective and explicit clinical validation of the Ottawa Heart Failure Risk Scale, with and without use of quantitative NT-proBNP. *Acad Emerg Med* 2017;**24**:316–327.
51. Stiell IG, Clement CM, Brison RJ, Rowe BH, Borgundvaag B, Aaron SD, Lang E, Calder LA, Perry JJ, Forster AJ, Wells GA. A risk scoring system to identify emergency department patients with heart failure at high risk for serious adverse events. *Acad Emerg Med* 2013;**20**:17–26.
52. Meigher S, Thode HC, Peacock WF, Bock JL, Gruberg L, Singer AJ. Causes of elevated cardiac troponins in the emergency department and their associated mortality. *Acad Emerg Med* 2016;**23**:1267–1273.
53. Felker GM, Hasselblad V, Tang WH, Hernandez AF, Armstrong PW, Fonarow GC, Voors AA, Metra M, McMurray JJ, Butler J, Heizer GM, Dickstein K, Massie BM, Atar D, Troughton RW, Anker SD, Califf RM, Starling RC, O'Connor CM, Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. *Eur J Heart Fail* 2012;**14**:1257–1264.
54. Metra M, Bettari L, Pagani F, Lazzarini V, Lombardi C, Carubelli V, Bonetti G, Bugatti S, Parrinello G, Caimi L, Felker GM, Dei Cas L. Troponin T levels in patients with acute heart failure: clinical and prognostic significance of their detection and release during hospitalisation. *Clin Res Cardiol* 2012;**101**:663–672.
55. Felker GM, Mentz RJ, Teerlink JR, Voors AA, Pang PS, Ponikowski P, Greenberg BH, Filippatos G, Davison BA, Cotter G, Prescott MF, Hua TA, Lopez-Pintado S, Severin T, Metra M. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail* 2015;**17**:1262–1270.
56. Scirica BM, Morrow DA. In search of the 1-hour rule-out for acute myocardial infarction. *Clin Chem* 2015;**61**:1427–1429.
57. Tolppanen H, Rivas-Lasarte M, Lassus J, Sadoune M, Gayat E, Pulkki K, Arrigo M, Krastinova E, Sionis A, Parissis J, Spinar J, Januzzi J, Harjola VP, Mebazaa A. Combined measurement of soluble ST2 and amino-terminal pro-B-type natriuretic peptide provides early assessment of severity in cardiogenic shock complicating acute coronary syndrome. *Crit Care Med* 2017;**45**:e666–673.
58. van der Velde AR, Lexis CP, Meijers WC, van der Horst IC, Lipsic E, Dokter MM, van Veldhuisen DJ, van der Harst P, de Boer RA. Galectin-3 and sST2 in prediction of left ventricular ejection fraction after myocardial infarction. *Clin Chim Acta* 2016;**452**:50–57.
59. Kumarswamy R, Bauters C, Volkmann I, Maury F, Fetisch J, Holzmann A, Lemesle G, de Groote P, Pinet F, Thum T. Circulating long noncoding RNA, LIPCAR, predicts survival in patients with heart failure. *Circ Res* 2014;**114**:1569–1575.
60. Viereck J, Thum T. Circulating noncoding RNAs as biomarkers of cardiovascular disease and injury. *Circ Res* 2017;**120**:381–399.
61. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
62. Biering-Sorensen T, Mogelvang R, Sogaard P, Pedersen SH, Galatius S, Jorgensen PG, Jensen JS. Prognostic value of cardiac time intervals by tissue Doppler imaging M-mode in patients with acute ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Circ Cardiovasc Imaging* 2013;**6**:457–465.
63. Fleischmann KE, Lee TH, Come PC, Goldman L, Cook EF, Caguioa E, Johnson PA, Albano MP, Lee RT. Echocardiographic prediction of complications in patients with chest pain. *Am J Cardiol* 1997;**79**:292–298.
64. Haecck ML, Hoogslag GE, Boden H, Velders MA, Katsanos S, Al Amri I, Debonnaire P, Schlij MJ, Vliegen HW, Bax JJ, Marsan NA, Delgado V. Prognostic implications of elevated pulmonary artery pressure after ST-segment elevation myocardial infarction. *Am J Cardiol* 2016;**118**:326–331.
65. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK. Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**:360–367.
66. Kontos MC, Arrowood JA, Paulsen WH, Nixon JV. Early echocardiography can predict cardiac events in emergency department patients with chest pain. *Ann Emerg Med* 1998;**31**:550–557.
67. Otasevic P, Neskovic AN, Popovic Z, Vlahovic A, Bojic D, Bojic M, Popovic AD. Short early filling deceleration time on day 1 after acute myocardial infarction is associated with short and long term left ventricular remodelling. *Heart* 2001;**85**:527–532.
68. Neskovic AN, Flachskampf FA, Picard MH. *Emergency Echocardiography*. Boca Raton, FL: CRC Press; 2016.
69. Autore C, Agati L, Piccininno M, Lino S, Musaro S. Role of echocardiography in acute chest pain syndrome. *Am J Cardiol* 2000;**86**(4A):41G–42G.
70. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2015;**4**:3–5.
71. Munk K, Andersen NH, Terkelsen CJ, Bibby BM, Johnsen SP, Botker HE, Nielsen TT, Poulsen SH. Global left ventricular longitudinal systolic strain for early risk assessment in patients with acute myocardial infarction treated with primary percutaneous intervention. *J Am Soc Echocardiogr* 2012;**25**:644–651.
72. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, Nihoyannopoulos P, Edvardsen T, Lancellotti P. Clinical practice of



- contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1205–1205af.
73. Zimmerman SK, Vacek JL. Imaging techniques in acute coronary syndromes: a review. *ISRN Cardiol* 2011;**2011**:359127.
  74. André F, Buss SJ, Friedrich MG. The role of MRI and CT for diagnosis and work-up in suspected ACS. *Diagnosis (Berl)* 2016;**3**:143–154.
  75. Aljazeera A, Sulaiman A, Alhulaimi N, Alsaileek A, Al-Mallah MH. Cardiac magnetic resonance imaging in heart failure: where the alphabet begins! *Heart Fail Rev* 2017;**22**:385–399.
  76. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2016;**68**:1476–1488.
  77. Ogawa R, Stachnik JM, Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 1, drugs administered intravenously). *Clin Pharmacokinet* 2013;**52**:169–185.
  78. Ogawa R, Stachnik JM, Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 2, drugs administered orally). *Clin Pharmacokinet* 2014;**53**:1083–1114.
  79. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V, Lainscak M, Lassus J, Legrand M, Masip J, Mueller C, Papp Z, Parissis J, Platz E, Rudiger A, Ruschitzka F, Schafer A, Seferovic PM, Skouri H, Yilmaz MB, Mebazaa A. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;**19**:821–836.
  80. Reid C, Alturki A, Danchin N, Yan A, Goodman S, Tanguay J, Mehta S, Huynh T. Dual antiplatelet therapy in type 1 and type 2 myocardial infarctions: a systematic review of randomized controlled trials and observational studies [abstract]. *Can J Cardiol* 2016;**32**:S70.
  81. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlavetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2014;**63**:630–635.
  82. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Nawarska EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D, Kozinski M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016;**37**:245–252.
  83. Parodi G, Bellandi B, Xanthopoulou I, Caprazano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antonucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2014;**8**:e001593.
  84. Iakobishvili Z, Cohen E, Garty M, Behar S, Shotan A, Sandach A, Gottlieb S, Mager A, Battler A, Hasdai D; Heart Failure Survey in Israel (HFSIS) Investigators. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. *Acute Card Care* 2011;**13**:76–80.
  85. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J* 2008;**25**:205–209.
  86. Cohn JN, Franciosa JA, Francis GS, Archibald D, Tristani F, Fletcher R, Montero A, Cintron G, Clarke J, Hager D, Saunders R, Cobb F, Smith R, Loeb H, Settle H. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1982;**306**:1129–1135.
  87. Cotter G, Metzker E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, Moshkovitz Y, Zaidenstein R, Golik A. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;**351**:389–393.
  88. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, Delgado JF, Follath F. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Med* 2011;**37**:290–301.
  89. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Mendez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32–43.
  90. Publication Committee for the VMAC Investigators (Vasodilation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002;**287**:1531–1540.
  91. Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, Blatt A, Simovitz A, Shaham O, Faigenberg Z, Metzger M, Stav D, Yogev R, Golik A, Krakover R, Vered Z, Cotter G. High-dose intravenous isosorbide-dinitrate is safer and better than bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol* 2000;**36**:832–837.
  92. Wakai A, McCabe A, Kidney R, Brooks SC, Seupaul RA, Diercks DB, Salter N, Fermann GJ, Pospisil C. Nitrates for acute heart failure syndromes. *Cochrane Database Syst Rev* 2013;**8**:CD005151.
  93. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moya L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–1581.
  94. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;**97**:2202–2212.
  95. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
  96. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;**360**:752–760.
  97. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-ACUTE Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
  98. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KR, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogossova N, Dans AL, Lanus F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusuf S, Steg PG, Metsarinen KP, Cook BRUNS N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–1330.
  99. Shantsila E, Lip GY. Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm. *Cochrane Database Syst Rev* 2016;**9**:CD003333.
  100. Siliste RN, Antohi EL, Pepoyan S, Nakou E, Vardas P. Anticoagulation in heart failure without atrial fibrillation: gaps and dilemmas in current clinical practice. *Eur J Heart Fail* 2018;**20**:978–988.
  101. Zannad F, Anker SD, Byra WM, Cleland JG, Fu M, Gheorghiane M, Lam CS, Mehra MR, Neaton JD, Nessel CC, Spiro TE, van Veldhuisen DJ, Greenberg B; COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018;**379**:1332–1342.
  102. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;**360**:1283–1297.
  103. Senthinathan A, Kelly V, Dzingina M, Jones D, Baker M, Longson D. Hyperglycaemia in acute coronary syndromes: summary of NICE guidance. *BMJ* 2011;**343**:d6646.
  104. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenovich CF, Smith S, Young LH, Kahn R. Thiazolidinedione use,

- fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003;**108**:2941–2948.
105. Scirica BM. The safety of dipeptidyl peptidase 4 inhibitors and the risk for heart failure. *JAMA Cardiol* 2016;**1**:123–125.
  106. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism* 2016;**65**:20–29.
  107. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Matthews M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUT-COME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
  108. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
  109. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322.
  110. U.S. Food and Drug Administration. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). <https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm> (14 April 2020).
  111. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, Hajjar LA, Lassus J, Lebreton G, Montalescot G, Park JJ, Price S, Sionis A, Yannopoulos D, Harjola VP, Levy B, Thiele H. Management of cardiogenic shock complicating myocardial infarction. *Intensive Care Med* 2018;**44**:760–773.
  112. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015;**17**:544–558.
  113. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebel T, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
  114. Ouweneel DM, Eriksen E, Seyfarth M, Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump for treating cardiogenic shock: meta-analysis. *J Am Coll Cardiol* 2017;**69**:358–360.
  115. Bellone A, Monari A, Cortellaro F, Vettorello M, Arlati S, Coen D. Myocardial infarction rate in acute pulmonary edema: noninvasive pressure support ventilation versus continuous positive airway pressure. *Crit Care Med* 2004;**32**:1860–1865.
  116. Ferrari G, Olliveri F, De Filippi G, Milan A, Apra F, Boccuzzi A, Converso M, Navalesi P. Noninvasive positive airway pressure and risk of myocardial infarction in acute cardiogenic pulmonary edema: continuous positive airway pressure vs noninvasive positive pressure ventilation. *Chest* 2007;**132**:1804–1809.
  117. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008;**359**:142–151.
  118. Masip J, Peacock WF, Price S, Cullen L, Martin-Sanchez FJ, Seferovic P, Maisel AS, Miro O, Filippatos G, Vrints C, Christ M, Cowie M, Platz E, McMurray J, DiSomma S, Zeymer U, Bueno H, Gale CP, Lettino M, Tavares M, Ruschitzka F, Mebazaa A, Harjola VP, Mueller C; Acute Heart Failure Study Group of the Acute Cardiovascular Care Association and the Committee on Acute Heart Failure of the Heart Failure Association of the European Society of Cardiology. Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur Heart J* 2018;**39**:17–25.
  119. Ng R, Yeghiazarians Y. Post myocardial infarction cardiogenic shock: a review of current therapies. *J Intensive Care Med* 2013;**28**:151–165.
  120. Thompson CR, Buller CE, Sleeper LA, Antonelli TA, Webb JG, Jaber WA, Abel JG, Hochman JS. Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry. Should we use emergently revascularize Occluded Coronaries in cardiogenic shock? *J Am Coll Cardiol* 2000;**36**:1104–1109.
  121. Menon V, Webb JG, Hillis LD, Sleeper LA, Abboud R, Dzavik V, Slater JN, Forman R, Monrad ES, Talley JD, Hochman JS. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry. Should we emergently revascularize Occluded Coronaries in cardiogenic shock? *J Am Coll Cardiol* 2000;**36**:1110–1116.
  122. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
  123. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, Gurvitz MZ, Havranek EP, Lee CS, Lindenfeld J, Peterson PN, Pressler SJ, Schocken DD, Whellan DJ. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation* 2009;**120**:1141–1163.
  124. Milfred-Laforest SK, Chow SL, Didomenico RJ, Dracup K, Ensor CR, Gattis-Stough W, Heywood JT, Lindenfeld J, Page RL 2nd, Patterson JH, Vardeny O, Massie BM. Clinical pharmacy services in heart failure: an opinion paper from the Heart Failure Society of America and American College of Clinical Pharmacy Cardiology Practice and Research Network. *J Card Fail* 2013;**19**:354–369.
  125. Milfred-Laforest SK, Gee JA, Pugacz AM, Pina IL, Hoover DM, Wenzell RC, Felton A, Guttenberg E, Ortiz J. Heart failure transitions of care: a pharmacist-led post-discharge pilot experience. *Prog Cardiovasc Dis* 2017;**60**:249–258.
  126. Guder G, Stork S, Gelbrich G, Brenner S, Deubner N, Morbach C, Wallenborn J, Berliner D, Ertl G, Angermann CE. Nurse-coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient-reported outcomes, and left ventricular remodelling. *Eur J Heart Fail* 2015;**17**:442–452.
  127. Lambrinou E, Kalogirou F, Lamnisos D, Sourtzi P. Effectiveness of heart failure management programmes with nurse-led discharge planning in reducing re-admissions: a systematic review and meta-analysis. *Int J Nurs Stud* 2012;**49**:610–624.
  128. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS; QUALIFY Investigators. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017;**19**:1414–1423.
  129. Lainscak M, Cleland JG, Lenzen MJ, Keber I, Goode K, Follath F, Komajda M, Swedberg K. Nonpharmacologic measures and drug compliance in patients with heart failure: data from the EuroHeart Failure Survey. *Am J Cardiol* 2007;**99**(6B):31D–37D.
  130. Fredericks S, Beanlands H, Spalding K, Da Silva M. Effects of the characteristics of teaching on the outcomes of heart failure patient education interventions: a systematic review. *Eur J Cardiovasc Nurs* 2010;**9**:30–37.
  131. Hill L, McIlfratrick S, Taylor BJ, Dixon L, Cole BR, Moser DK, Fitzsimons D. Implantable cardioverter defibrillator (ICD) deactivation discussions: reality versus recommendations. *Eur J Cardiovasc Nurs* 2016;**15**:20–29.
  132. Doherty LC, Fitzsimons D, McIlfratrick SJ. Carers' needs in advanced heart failure: a systematic narrative review. *Eur J Cardiovasc Nurs* 2016;**15**:203–212.
  133. Boyde M, Tuckett A, Peters R, Thompson D, Turner C, Stewart S. Learning for heart failure patients (the L-HF Patient Study). *J Clin Nurs* 2009;**18**:2030–2039.
  134. Boyde M, Tuckett A, Peters R, Thompson DR, Turner C, Stewart S. Learning style and learning needs of heart failure patients (the Need2Know-HF Patient Study). *Eur J Cardiovasc Nurs* 2009;**8**:316–322.
  135. Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation* 2005;**111**:179–185.
  136. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.