SPECIAL FEATURE

Major publications in the critical care pharmacotherapy literature: January–December 2014

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Purpose. Nine recently published articles and one guideline with important implications for critical care pharmacy practice are summarized.

Summary. The Critical Care Pharmacotherapy Literature Update (CCPLU) group includes more than 40 experienced critical care pharmacists across the United States. Group members monitor 29 peer-reviewed journals on an ongoing basis to identify literature relevant to pharmacy practice in the critical care setting. After evaluation by CCPLU group members, selected articles are chosen for summarization and distribution to group members nationwide based on applicability to practice, relevance, and study design and strength. Hundreds of relevant articles were evaluated by the group in 2014, of which 114 were summarized and disseminated to CCPLU group members. From among those 114 publications, 10 deemed to be of particularly high utility to the critical care practitioner were selected for inclusion in this review for their potential to change practice or reinforce current evidence-based practice. One of the selected articles presents updated recommendations on the management of patients with atrial fibrillation (AF); the other 9 address topics such as albumin replacement in patients with severe sepsis, use of enteral statins for acute respiratory distress syndrome, fibrinolysis for patients with intermediate-risk pulmonary embolism, the use of unfractionated heparin versus bivalirudin for primary percutaneous coronary intervention, and early protocol-based care for septic shock.

Conclusion. There were many important additions to the critical care pharmacotherapy literature in 2014, including a joint guideline for the management of AF and reports of clinical trials.

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Healthcare practitioners have an obligation to remain current with the most recently published data, as new findings can potentially have a significant impact on patient care and may ultimately lead to improved patient outcomes. In vulnerable populations such as the critically ill, it is especially important to keep abreast of the growing body of literature. This becomes progressively challenging with the increasing volume and frequency of relevant articles published. To aid in this endeavor, the Critical Care Pharmacotherapy Literature Update (CCPLU) group has published annual summaries of key guidelines and articles pertaining to high-quality critical care pharmacotherapy since 2012.[1,2]

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The CCPLU group was established to provide monthly reviews of critical care literature recently published in peer-reviewed journals. It is composed of over 40 critical care pharmacists across the United States who volunteer time and expertise to prospectively review 29 peer-reviewed journals for methodologically sound, strong, and applicable clinical trials pertaining to pharmacotherapy in critical care patients. Over the course of 2014, hundreds of articles were reviewed and 114 were summarized in a concise format: study question, methodology, results, and perspective/relevance to clinical practice (6 of these articles were published in December 2013 but were not included in a monthly CCPLU publication until January or February 2014). Monthly summaries are nationally disseminated to CCPLU members in a publication and via social media outlets.

Articles for this review were selected on the basis of objective criteria. All articles summarized in the monthly CCPLU publication were assigned a rating according to the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) methodology.[3,4] In addition to GRADE assessments, the articles' applicability to critically ill patients in medical, surgical, neurology, cardiac, and trauma populations and their potential to change practice or reinforce current evidence-based practice were considered. Based on these criteria, one guideline and nine other articles were selected for inclusion in this review.

January et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation[5]

The 2014 atrial fibrillation (AF) guideline is a joint production from the American College of Cardiology (ACC) and the American Heart Association (AHA). Evidence-based methodology developed by the ACC–AHA task force was used for data analysis and recommendation development.[6] The guideline recommendations were ranked using a classification of recommendation (COR) scheme: class I (procedure/treatment should be performed/administered), class IIa (additional studies with focused objectives needed; reasonable to perform procedure/administer treatment), class IIb (additional studies with broad objectives needed; may consider procedure/treatment), and class III (procedure/treatment has no proven benefit or procedure/treatment is harmful). Recommendations were also ranked by level of evidence (LOE), as follows: level A (multiple clinical trials or meta-analyses), level B (a single randomized trial or nonrandomized studies), and level C (consensus expert opinion, case studies, or standard of care). The goal of this guideline was to provide recommendations for optimal AF management based on an extensive literature review covering the period 2006–October 2012 and selected reference review through March 2014. All recommendations are for patients with nonvalvular AF unless otherwise stated.

Significant changes to the guidelines are found in the thromboembolic risk and treatment recommendations due to the availability of new oral anticoagulants (NOACs) since the last published update in 2011.[7] Use of the CHA_2DS_2-VASc score, which takes into account multiple factors (congestive heart failure or left ventricular dysfunction, hypertension, diabetes mellitus, stroke or transient ischemic attack [TIA], or thromboembolism, vascular disease, age of 65–74 years, age of ≥75 years, and patient sex) for stroke risk assessment, was a new recommendation (COR, I; LOE, B) based on the score's improved predictive value for thromboembolism in patients with AF relative to the classic $CHADS_2$ score.[8] In patients with AF and mechanical heart valves, warfarin continues to be recommended, with an International Normalized Ratio (INR) target based on prosthesis type and location (COR, I; LOE, B). In patients with nonvalvular AF, there are new recommendations for the use of oral anticoagulants. Dabigatran, a direct thrombin inhibitor, and the factor Xa inhibitors rivaroxaban and apixaban are NOACs with unique mechanisms of action that are included in these guidelines for the first time. Patients with a history of stroke or TIA or a CHA_2DS_2-VASc score of ≥2 should receive oral anticoagulant therapy using warfarin (COR, I; LOE, A), dabigatran, rivaroxaban, or apixaban (COR, I; LOE, B). Warfarin should be

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used with therapeutic drug monitoring (COR, I; LOE, A), and dabigatran, rivaroxaban, or apixaban may be used if renal function permits (COR, I; LOE, B). If a target INR cannot be maintained with warfarin, the use of dabigatran, rivaroxaban, or apixaban is recommended (COR, I; LOE, C). Dabigatran should not be used in patients with AF and mechanical heart valves (COR, III [harmful]; LOE, B).

Although its safety and efficacy have not been established, reduced-dose therapy with a direct thrombin inhibitor or a factor Xa inhibitor may be considered in moderate-to-severe chronic kidney disease (CKD) and patients with a CHA_2DS_2-VASc score of ≥2 (COR, IIb; LOE, C). Dabigatran and rivaroxaban are not recommended in end-stage CKD or in patients receiving dialysis (COR, III [no benefit]; LOE, C). There are limited data on apixaban use in patients with end-stage renal disease receiving dialysis based on pharmacokinetic data[9]; however, clinical data are not yet available in this setting, and the revised guideline provides no recommendation. The most recently approved factor Xa inhibitor, edoxaban,[10] is not yet recommended by the guidelines and will likely appear in a future update. Similar to apixaban and rivaroxaban, edoxaban has been shown to have efficacy for stroke prevention in AF comparable to that of warfarin in terms of stroke, ischemic stroke, and hemorrhagic stroke endpoints, with a lower associated risk of intracranial bleeding.[11,12] A meta-analysis found that all four NOACs have a favorable risk–benefit profile but pose a higher risk of gastrointestinal bleeding than warfarin.[13] No published trials directly comparing NOACs are available.

Similar to previous recommendations, the revised guideline recommends that patients with a CHA_2DS_2-VASc score of 1 may receive no antithrombotic therapy or can be considered for an anticoagulant or aspirin (COR, IIb; LOE, C). The decision to implement bridge therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) during interruptions of oral anticoagulant therapy should balance stroke and bleeding risks in patients with and without mechanical heart valves (COR, I; LOE, C). In patients with AF undergoing percutaneous coronary intervention, bare metal stents should be considered in order to minimize the duration of dual antiplatelet therapy. In patients with a CHA_2DS_2-VASc score of 2, it may be reasonable to use clopidogrel concomitantly with anticoagulants and no aspirin after revascularization (COR, IIb; LOE, B).

The recommendations for AF rate control are largely unchanged. The use of a β-blocker or a nondihydropyridine calcium channel blocker for all types of AF, including paroxysmal AF (LOE, B), and the use of an i.v. β-blocker or a nondihydropyridine calcium channel blocker in the acute setting for ventricular rate slowing without preexcitation (LOE, B) remain class I recommendations. Also unchanged are the recommendations on assessment of heart rate control during exercise, with therapy adjustment to keep the heart rate within physiological range in patients with symptomatic AF on exertion (COR, I; LOE, C) and electrical cardioversion advised in patients with hemodynamic instability (COR, I; LOE, B).

Unchanged since the 2011 guideline revision,[7] the recommended heart rate goals are less than 80 beats per minute in symptomatic AF (COR, IIa; LOE, B) and less than 110 beats per minute in asymptomatic patients with preserved ventricular systolic function (COR, IIb; LOE, B). The use of i.v. amiodarone for rate control in critically ill patients without preexcitation (COR, IIa; LOE, B) and the use of atrioventricular node ablation with permanent ventricular pacing for patients in whom pharmacologic treatment fails (COR, IIa; LOE, B) continue to be recommended; without prior attempts to achieve rate control with medications, nodal ablation is not recommended (COR, III [harm]; LOE, C). A nondihydropyridine calcium channel blocker should not be used in patients with decompensated heart failure due to the risk of further hemodynamic compromise (COR, III [harm]; LOE, C). Patients with preexcitation and AF should not be given digoxin, a nondihydropyridine calcium channel blocker, or i.v. amiodarone due to the risk of increased ventricular response leading to ventricular fibrillation (COR, III [harm]; LOE, B). Dronedarone increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, and cardiovascular death and should not be used for ventricular rate control in patients with permanent AF (COR, III [harm]; LOE, B).

For patients with AF of ≥48 hours' or unknown duration, anticoagulation with warfarin (COR, I; LOE, B), dabigatran, rivaroxaban, or apixaban (COE, IIa; LOE, C) is recommended for at least three weeks before and four weeks after cardioversion unless immediate cardioversion is required for hemodynamic instability, in which case anticoagulation should be started as soon as possible and continued for at least four weeks (COR, I; LOE, C). In the absence of contraindications, flecainide, dofetilide, propafenone, and i.v. ibutilide are useful for pharmacologic cardioversion (COR, I; LOE, A); this recommendation has not changed since the release of the previous guideline edition. Oral amiodarone may be a reasonable option (COR, IIa; LOE, A), and dofetilide should not be initiated outside of a hospital due to Q-T prolongation risk (COR, III [harm]; LOE, B). Maintenance of sinus rhythm may be achieved with amiodarone, dofetilide, dronedarone, flecainide, propafenone, or sotalol, with agent selection depend-

ing on comorbidities (COR, I; LOE, A). The appropriate agent should be initiated only after treatment of any reversible causes and consideration of medication risks (COR, I; LOE, C). Antiarrhythmic medications should not be continued if AF becomes permanent (COR, III [harm]; LOE, C [LOE, B for dronedarone]), with the exception of dronedarone (LOE, B). Overall, recommendations for rhythm-control strategies are relatively unchanged from the most recent previous version and update of the AHA–ACC guideline.[7,14]

Other recommendations for specific patient groups and AF management are also largely unchanged from previous guideline versions, although there are slight changes in COR ratings.[7,14] This update of the AF guideline provides new recommendations on the use of NOACs (direct thrombin and factor Xa inhibitors), which have all been approved by the Food and Drug Administration since the last guideline version. The AHA–ACC guideline continues to provide the most comprehensive and detailed recommendations for AF management currently available in the medical literature.[7]

Caironi et al. Albumin replacement in patients with severe sepsis or septic shock[15]

The Albumin Italian Outcome Sepsis (ALBIOS) study was a multicenter, open-label randomized controlled trial evaluating albumin replacement therapy in patients with severe sepsis or septic shock. Eligible patients were randomly assigned within 24 hours of diagnosis to receive crystalloid therapy alone (n = 908) or in combination with 20% albumin dosed to maintain a serum albumin concentration of ≥30 g/L (n = 910) from randomization to intensive care unit (ICU) discharge or day 28. Fluids were administered according to tenets of early goal-directed therapy (EGDT)[16] in early resuscitation phases, and synthetic colloids were prohibited. The primary outcome was 28-day all-cause mortality, with a principal secondary outcome of 90-day all-cause mortality.

Baseline characteristics were similar between groups, including the initial mean serum albumin concentration (24.1 g/L in the albumin group versus 24.2 g/L in the crystalloid group). Although only the satisfaction of criteria for severe sepsis was required for study inclusion, approximately 63% of patients in each group met the criteria for septic shock. No significant difference between the albumin and crystalloid-only groups was observed in terms of either 28-day all-cause mortality (31.8% versus 32%, p = 0.94) or 90-day all-cause mortality (41.1% versus 43.6%, p = 0.29). Relative to the crystalloid-only group, the albumin group had a significantly lower mean heart rate and a higher mean arterial pressure during the first 7 days and a higher mean albumin concentration for the study duration (29.4 g/L versus 23.1 g/L on day 7, $p < 0.001$). The median total daily amount of fluids administered did not differ significantly between the albumin and crystalloid-only groups during the first 7 days (3738 mL versus 3825 mL, p = 0.10); however, the albumin group had a significantly lower median net fluid balance (347 mL versus 1220 mL, p = 0.004). Patients in the albumin group also had a shorter median duration of vasopressor therapy than the crystalloid group (3 days versus 4 days, p = 0.007).

The ALBIOS study explored albumin therapy for hypoalbuminemia as an adjunct to standard fluid administration and best described albumin use after EGDT completion and initial crystalloid administration, as the majority of the patients underwent randomization within six hours of diagnosis. Albumin therapy was previously evaluated as the sole fluid administered for initial resuscitation. The Saline versus Albumin Fluid Evaluation (SAFE) Study evaluated 4% albumin versus 0.9% sodium chloride for fluid replacement and, unlike the ALBIOS study, prohibited the combined use of albumin and crystalloid therapy.[17] No difference was found in the primary outcome of 28-day mortality (p = 0.87) for the entire cohort or in a subgroup analysis of patients with severe sepsis (30.7% with albumin versus 35.3% with 0.9% sodium chloride, p = 0.09). In another trial conducted by the SAFE investigators, a decreased odds ratio (OR) for death at 28 days was reported with the use of albumin versus 0.9% sodium chloride after adjustment for baseline patient characteristics (OR, 0.71; 95% confidence interval [CI], 0.52–0.97; p = 0.03).[18] In contrast, a recent meta-analysis of 16 clinical trials (including the ALBIOS study) found no net benefit with albumin therapy in terms of reducing all-cause mortality.[19]

This well-designed randomized controlled trial was the first to judiciously use albumin resuscitation in patients with severe sepsis or septic shock with hypoalbuminemia. Although low serum albumin has been associated with mortality, replacing albumin appears to have little impact on clinical outcomes.[20] Despite the findings of significant between-group differences in heart rate and mean arterial pressure in this study, the clinical significance of those differences is debatable, as they did not translate to improved clinical outcomes apart from a slightly shorter vasopressor therapy duration. The 2012 Surviving Sepsis Campaign guidelines recommend albumin for fluid resuscitation when patients require substantial amounts of crystalloids or as a component of initial fluid resuscitation.[21] The practice of reserving albumin therapy for septic patients solely on the basis of hypoalbuminemia to target a prespecified albumin level is refuted by the literature and should not be adopted.

Amrein et al. Effect of high-dose vitamin D_3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial[22]

The Correction of Vitamin D Deficiency in Critically Ill Patients (VITdAL-ICU) study was a single-center, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of high-dose oral vitamin D_3 (cholecalciferol) to improve outcomes of critical illness. The primary endpoint was hospital length of stay (LOS) from study drug receipt until death or hospital discharge. Eligible patients with an expected ICU stay of ≥48 hours who were found to have a serum 25-hydroxyvitamin D (25[OH]D) concentration of ≤20 ng/mL (to convert to nmol/L, multiply by 2.496) were randomly assigned to receive a placebo (n = 243) or cholecalciferol (n = 249). A subgroup of patients with severe 25(OH)D deficiency (i.e., a serum concentration of <12 ng/mL) was prespecified. Lower supplementation doses of vitamin D were not expected to adequately restore 25(OH)D levels within a reasonable time period; therefore, a higher one-time oral loading dose (540,000 IU of cholecalciferol dissolved in 45 mL of oleum arachidis) was used. Patients received five monthly maintenance doses of 90,000 IU of oral cholecalciferol or a placebo starting 28 days after the loading dose. Standard vitamin D supplementation was permitted at the treating physician's discretion.

The baseline mean 25(OH)D concentration was 13 ng/mL, and 42% of patients had severe vitamin D deficiency. There was no significant difference in the primary endpoint between the cholecalciferol and placebo groups (median hospital LOS, 20.1 days versus 19.3 days; p = 0.98). The median ICU LOS was also similar between groups (9.6 days versus 10.7 days, p = 0.38), and between-group differences in both hospital and ICU LOS were nonsignificant in the subgroup with severe vitamin D deficiency. Hospital, ICU, 28-day, and six-month mortality were not significantly different between groups in the overall cohort; however, in the subgroup analysis of patients with severe vitamin D deficiency, the cholecalciferol group had lower hospital, 28-day, and six-month mortality than the placebo group. After testing for interaction between subgroups, only hospital mortality remained significantly different (28.6% with active treatment versus 46.1% with placebo use, p = 0.04). Causes of death were not different between groups.

Studies have linked low vitamin D levels to increased mortality and infection risk in critically ill patients; however, no studies prospectively assessed the effects of vitamin D replacement prior to the VITdAL-ICU study, making it the first randomized controlled trial to evaluate this connection.[23-26] Despite the achievement of adequate statistical power, attainment of the primary study endpoint in this study did not differ between groups. It is interesting to note that the primary endpoint was hospital LOS instead of mortality. In reporting their findings, the investigators commented that when the study was initiated, only mortality data from one small observational study were available and it was presumed that LOS could be influenced by general health improvement from vitamin D supplementation. Although lower hospital mortality was observed in the subgroup with severe vitamin D deficiency, this should be considered a hypothesis-generating finding, and future studies should be designed to evaluate clinical outcomes such as mortality. Based on the available literature, routine high-dose vitamin D supplementation in critically ill patients cannot be recommended due to a lack of data demonstrating a mortality benefit.

Shahzad et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial[27]

Investigators at the Liverpool Heart and Chest Hospital in the United Kingdom conducted How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI), a single-center, open-label randomized controlled trial that enrolled adult patients with acute ST-elevation myocardial infarction (STEMI) requiring emergent angiography with delayed consent. Upon arrival to the catheterization laboratory for primary percutaneous coronary intervention (PPCI), patients were randomly assigned to receive heparin as a bolus followed by an infusion (n = 907; goal activated clotting time [ACT], >200 seconds) or bivalirudin as a bolus followed by an infusion (n = 905; goal ACT, >225 seconds). Abciximab use was allowed in selected cases (those involving angiographic evidence of massive thrombus, slow or no reflow, or a thrombotic complication); no other treatment restrictions were defined. The primary efficacy outcome was the proportion of patients who had at least one major adverse cardiac event (MACE) (all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization) by 28 days. The primary safety outcome was the proportion of patients who had major bleeding by 28 days; bleeding was classified as type 3, 4, or 5 according to the Bleeding Academic Research Consortium (BARC) definition (a hemoglobin drop of ≥3 g/dL with varying interventions). Secondary outcomes included the stent thrombosis rate, cardiac enzyme release (the MB isozyme of creatine kinase [CK]), and minor bleeding (BARC type 2).

Of the 1917 patients undergoing emergency angiography who were

initially screened, 1829 were eligible for study inclusion and underwent randomization, with similar baseline characteristics in the two groups. Aspirin and P2Y12 inhibitor loading (89% of patients received prasugrel or ticagrelor) was achieved in more than 99% of patients, and rates of abciximab use were similar (13% in the bivalirudin group versus 15% in the heparin group). The occurrence of the primary efficacy outcome of MACE by 28 days was significantly higher in the bivalirudin group than in the heparin group (8.7% versus 5.7%, $p = 0.01$) and was driven primarily by a significant increase in reinfarction. Most reinfarction events were related to stent thrombosis events. There was no significant difference in the rates of the primary safety outcome of major bleeding in the bivalirudin and heparin groups (3.5% versus 3.1%, $p = 0.59$). There were no significant between-group differences in the other secondary outcomes.

This trial was the first in which patients were randomly assigned to heparin versus bivalirudin therapy, with optional use of a glycoprotein IIb/IIIa inhibitor (a contemporary practice for STEMI treatment) in each group. The HORIZONS-AMI and EUROMAX trials reported favorable results in the bivalirudin groups (with similar, albeit lower, 28-day cardiac mortality), primarily in terms of bleeding complications.[28,29] In contrast, the HEAT-PPCI trial entailed higher use of glycoprotein IIb/IIIa inhibitors, which are known to increase bleeding risk (as seen in the ACUITY trial).[30] Limitations of this trial included a single-center design and the fact that only 83% of patients received a percutaneous procedure, compared with 92% of those in the HORIZONS-AMI trial. Additionally, this study used ACT to guide therapy adjustments; that practice is not commonly used or recommended by established guidelines.[31,32] The use of more potent P2Y12 inhibitors (prasugrel and ticagrelor) in the HEAT-PPCI study may have influenced the MACE outcome, as prior studies primarily utilized clopidogrel. The recently published randomized, multicenter BRIGHT study looked at contemporary practice in patients with STEMI receiving PPCI and found decreased minor bleeding with the use of bivalirudin versus heparin but no change in the MACE rate at 30 days or one year.[33] Clopidogrel was the only P2Y12 inhibitor used in the BRIGHT study. Outside of the HEAT-PPCI trial, prasugrel and ticagrelor have been primarily studied in the setting of heparin antithrombotic therapy; however, there is little published evidence on combination therapy with bivalirudin and the subsequent impact on MACE risk.

The results of the HEAT-PPCI study challenged contemporary use of bivalirudin over heparin for PPCI in STEMI due to the reported increase in MACE risk and similar bleeding rates. For patients with STEMI who are loaded with prasugrel or ticagrelor, anticoagulation therapy with heparin is recommended over bivalirudin until a randomized, multicenter study utilizing potent P2Y12 inhibitors is performed. For patients loaded with clopidogrel, appropriate stratification of bleeding risk is warranted, with bivalirudin preferred in the highest-risk patients.

Meyer et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism[34]

The Pulmonary Embolism Thrombolysis (PEITHO) study was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the role of fibrinolytic therapy in 1005 patients with intermediate-risk pulmonary embolism (PE). The study inclusion criteria were as follows: (1) objectively confirmed acute PE with symptom onset no more than 15 days prior to randomization, (2) evidence of right ventricular dysfunction on echocardiography or spiral computed tomography, and (3) myocardial dysfunction confirmed by a positive troponin test. Notable exclusion criteria were hemodynamic decompensation, uncontrolled hypertension at randomization, a known coagulation disorder (as indicated by the use of vitamin K antagonists or a platelet count of <100,000 cells/mm^3), and high bleeding risk. Hemodynamic decompensation was defined as the need for cardiopulmonary resuscitation, a systolic blood pressure (SBP) of <90 mm Hg for ≥15 minutes, and/or a decrease of SBP by at least 40 mm Hg for ≥15 minutes with end-organ hypoperfusion or vasopressor use.

Patients were randomly assigned within 2 hours of meeting the inclusion criteria to a weight-based bolus dose of tenecteplase (30–50 mg) plus UFH ($n = 506$) or a placebo plus UFH ($n = 499$). UFH was administered as a bolus followed by an infusion to a target activated partial thromboplastin time of 2–2.5 times the upper limit of normal for at least the first 48 hours after randomization. Baseline characteristics were similar between groups; more patients in the tenecteplase group received LMWH or fondaparinux prior to randomization (33.6% versus 26.6%, $p = 0.02$).

The primary efficacy outcome, a composite of all-cause mortality and hemodynamic decompensation within 7 days of randomization, was lower in the tenecteplase group (2.6% versus 5.6%, $p = 0.02$). With regard to the secondary outcomes, rates of recurrent symptomatic PE or death within 7 days and death within 30 days were not different between groups, but the rate of hemodynamic decompensation within 7 days was lower in the tenecteplase group (1.6% versus 5%, $p = 0.002$). Rates of both major and minor bleeding were significantly greater in the tenecteplase group. Stroke occurred more frequently in patients who

received tenecteplase (2.4% versus 0.2%, $p = 0.003$). Age and sex did not affect primary outcome occurrence; however, the authors reported a trend toward a higher rate of extracranial bleeding in the tenecteplase group among patients older than 75 years of age (OR, 20.38; 95% CI, 2.69–154.5; p for interaction = 0.09).

While fibrinolytic therapy for massive PE is endorsed by both AHA and American College of Chest Physicians guidelines, its utility in moderate (submassive) PE is controversial.[35,36] This study was the largest and most rigorously designed evaluation of the role of fibrinolytic therapy in submassive PE. Although single-dose tenecteplase reduced the composite outcome, this was primarily driven by the reduction in hemodynamic decompensation. Other study limitations included variability in interpretation of baseline right ventricular dysfunction, greater LMWH or fondaparinux utilization (an important confounder of bleeding events) in the tenecteplase group, and statistical reporting that may have underemphasized bleeding risk for patients older than 75 years (the authors evaluated interactions, or treatment effects, between subgroups on a relative scale rather than evaluating the absolute risk in this subgroup). Two previous smaller trials showed some benefit of fibrinolytic therapy on surrogate outcomes for patients with submassive PE.[37,38] The PEITHO, TOPCOAT, and MOPETT studies defined submassive PE similarly; however, comparing results was challenging due to the different fibrinolytics used as well as variable dosing strategies, efficacy and safety endpoints, and follow-up durations. To date, no trial has demonstrated a clear mortality benefit.

Fibrinolytics may be a therapeutic option for patients with evidence of submassive PE who are less than 75 years of age, normotensive, and at low bleeding risk. The PEITHO study revealed significant safety concerns over using a weight-based tenecteplase dosing strategy in hemodynamically stable patients with PE; for many of these patients, the risks of bleeding and stroke may outweigh the benefits. Future studies should focus on identifying an optimal fibrinolytic agent and a dosing strategy that mitigates bleeding risk in certain high-risk populations (e.g., research to determine if a half-dose strategy might enhance safety for patients older than 75 years),[39] developing the role of catheter-directed thrombolysis for submassive PE, and the impact of fibrinolytic therapy on the development of longer-term complications such as chronic thromboembolic pulmonary hypertension.

Pizzaro et al. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction[40]

The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial was a multicenter, randomized, parallel-group, single-blind clinical trial that evaluated outcomes associated with initiating metoprolol before versus after PPCI in patients with anterior wall STEMI. Eligible patients with electrocardiogram changes showing ST elevation who presented no more than 4.5 hours after symptom onset were included in the study. Notable exclusion criteria were Killip class III or IV STEMI, SBP of <120 mm Hg, persistent bradycardia (heart rate of <60), chronic β-blocker therapy, atrioventricular block, and previous myocardial infarction. The primary objective was to evaluate the impact of i.v. metoprolol versus no metoprolol (control group) administered before PPCI on myocardial infarct size, as evaluated by magnetic resonance imaging (MRI) five to seven days after STEMI.[41] Patients in the i.v. metoprolol group received metoprolol tartrate 5 mg i.v. every two minutes up to three times prior to PPCI. If no contraindications were present after PPCI, patients in both groups were initiated on oral metoprolol tartrate within 24 hours of STEMI according to clinical guidelines.[32,42] All other recommended therapies for STEMI management, including metoprolol therapy at discharge, were at the physician's discretion. Results from the METOCARD-CNIC study for the primary objective showed that i.v. metoprolol decreased infarct size on MRI at one week after STEMI (these data were previously published[43]). This article discussed secondary outcomes that were assessed in the METOCARD-CNIC trial, including therapy impact on the left ventricular ejection fraction (LVEF) and clinical endpoints, defined as a composite of death, readmission due to decompensated heart failure, reinfarction, and malignant ventricular arrhythmias in the six months after STEMI.

A total of 270 patients underwent randomization. Of 220 patients who received MRI five to seven days after STEMI, 202 patients (101 in each group) received MRI six months after PPCI. The use of medications that would affect left ventricular remodeling was similar between groups. Patients in the i.v. metoprolol group had a higher mean LVEF at six months relative to the control group (48.7% versus 45.0%; adjusted treatment effect, 3.49% [95% CI, 0.44–6.55%]; $p = 0.025$). In addition, the mean left ventricular end-systolic volume was lower in the i.v. metoprolol group (98.2 mL versus 112 mL; adjusted treatment effect, –13.25 mL [95% CI, –24.47 to –2.03 mL]; $p = 0.021$). Fewer patients in the i.v. metoprolol group had an LVEF of ≤35%, as compared with the control group (11% versus 27%, $p = 0.006$). There was no significant difference in the composite clinical endpoint at one year between the i.v. metoprolol and control groups (10.8% versus 18.3%; hazard ratio, 0.55 [95% CI, 0.26–1.04]; $p = 0.065$); a lower rate of

hospital readmission for heart failure was observed in the i.v. metoprolol group (2.2% versus 6.9%, $p = 0.046$).

LVEF, left ventricular end-systolic volume, and myocardial infarct size have been shown to predict outcomes after STEMI.[44] The METOCARD-CNIC study investigators concluded that i.v. metoprolol administration prior to PPCI resulted in a higher LVEF and decreased left ventricular dysfunction at six months after Killip class I or II anterior wall STEMI. Favorable MRI findings were also observed by study investigators five to seven days after STEMI, as previously published.[43] Although several benefits of i.v. metoprolol administered before PPCI were seen on MRI six months after STEMI, no difference was found in the composite clinical endpoint. Similarly, the COMMIT trial found no difference in either death or the composite clinical outcome of death, reinfarction, ventricular fibrillation, and cardiac arrest in patients who were initiated on metoprolol within 24 hours of myocardial infarction relative to placebo users.[45] Patients in the metoprolol group had lower rates of reinfarction and ventricular fibrillation but higher rates of cardiogenic shock. A subset of patients similar to those included in the METOCARD-CNIC trial, however, were found to benefit from metoprolol therapy, suggesting that patients at low risk for cardiogenic shock (i.e., those who are nonhypotensive and without Killip class III or IV myocardial infarction) may benefit from early β-blocker therapy. The METOCARD-CNIC trial was not powered to detect a difference in the specified secondary endpoints, which leaves the impact of i.v. metoprolol on long-term (e.g., more than six months) clinical outcomes in this population an area of further research. Despite these unknowns, the METOCARD-CNIC study highlighted that early β-blocker use in STEMI may reduce infarct size; however, the impact on clinically significant outcomes such as long-term left ventricular function and mortality, as well as the appropriate approach to patients at high risk for cardiogenic shock, needs to be evaluated in future studies.

McAuley et al. Simvastatin in the acute respiratory distress syndrome[46]

Truwit et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome[47]

The HARP-2 study[46] and the SAILS study[47] were multicenter, prospective, randomized, double-blind, placebo-controlled trials designed to evaluate if enteral statin therapy would improve clinical outcomes in critically ill patients with acute lung injury (ALI). The HARP-2 study was conducted by the Irish Critical Care Trials Group and evaluated simvastatin versus placebo use in patients with ALI (irrespective of etiology),[48] whereas the SAILS trial was conducted by the National Heart, Lung, and Blood Institute's Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network and evaluated rosuvastatin versus placebo use in sepsis-associated ARDS. Both trials included mechanically ventilated patients enrolled within 48 hours of meeting American-European Consensus Conference criteria for ALI.[49] Additional enrollment criteria for the SAILS trial included known or suspected infection and one of two selected criteria for systemic inflammatory response syndrome (SIRS). Patients who previously received statin therapy for other indications were excluded from the HARP-2 study if any statin was ingested within the two weeks prior to enrollment and from the SAILS trial if statins were ingested within the 48 hours prior to randomization. Patients with contraindications to statin therapy were excluded from both trials.

In the HARP-2 study, eligible patients were randomized 1:1 to either daily use of simvastatin 80 mg ($n = 258$) or placebo use ($n = 279$) for up to 28 days. Study sites were encouraged to use low-tidal-volume ventilation (6–8 mL per kilogram of predicted body weight) and maintain plateau pressures of <30 cm of water, but no specific ventilator management was required.[50] The primary outcome was ventilator-free days (VFDs), defined as days of unassisted breathing, from simvastatin initiation to day 28 after randomization. Secondary outcomes included changes in oxygenation index and Sequential Organ Failure Assessment (SOFA) scores[51] up to day 28, nonpulmonary organ failure–free days, all-cause mortality, and adverse events. In the SAILS trial, patients were randomly assigned in permuted blocks of 8 to receive rosuvastatin ($n = 379$) or a placebo ($n = 366$) within four hours of enrollment. The rosuvastatin regimen was 40 mg once and then 20 mg daily until the third day after ICU or hospital discharge, study day 28, or death. Lower daily doses of 10 mg were administered to patients with a serum creatinine concentration of ≥2.8 mg/dL who were not receiving renal replacement therapy. If not already being utilized, patients were transitioned to a modified ARDS Network lower-tidal-volume protocol (6 mL per kilogram of predicted body weight) within one hour after randomization.[50]

Of 5926 patients assessed in the HARP-2 study, 540 patients underwent randomization. Baseline characteristics were similar between groups except for a lower mean ± S.D. ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (PaO_2:FiO_2) in the simvastatin group (123 ± 54.8 mm Hg versus 132.4 ± 55.4 mm Hg, $p = 0.049$). Mean VFDs did not significantly differ between groups (12.6 versus 11.5, $p = 0.21$), and this finding persisted after adjustment for the baseline PaO_2:FiO_2 difference.

No difference in VFDs was detected in subgroup analyses by age group, vasopressor use, sepsis presence, and baseline C-reactive protein level. There was no difference between the simvastatin and placebo groups regarding secondary outcomes except that the simvastatin group had more adverse events related to the study drug (OR, 2.2; 95% CI, 1.1–4.2; p = 0.02), with the most common being elevated CK (OR, 2.5; 95% CI, 0.9–7.0; p = 0.05) and elevated transaminases (OR, 2.0; 95% CI, 0.9–4.3; p = 0.08). Types and rates of serious adverse events were similar between groups.

The SAILS trial was stopped early due to futility after 745 patients of a projected 1000 were enrolled. Baseline characteristics were similar except for small differences in tidal volume and central venous pressure. The study found no significant differences in the primary outcome of mortality before hospital discharge or up to study day 60 between the rosuvastatin and placebo groups (28.5% versus 24.9%, p = 0.21). There were no significant between-group differences in the secondary outcomes of mean VFDs (15.1 for both groups, p = 0.96) and mean ICU-free days (14.3 versus 14.4, p = 0.84). The data on organ failure–free days to day 14 demonstrated no difference in cardiovascular failure and coagulation abnormalities between groups; however, fewer patients in the rosuvastatin group were free of hepatic failure (mean, 10.8 days versus 11.8 days; p = 0.003) and renal failure (mean, 10.1 days versus 11.0 days; p = 0.01) to day 14.

The researchers who conducted the HARP-2 and SAILS trials concluded that statin initiation did not improve clinical outcomes or reduce mortality in the studied critically ill ARDS patient populations. Over the past 45 years, ARDS has been the focus of extensive basic science and clinical research. However, no single pharmacotherapy has been found to reduce ARDS mortality in a large, randomized, controlled, multicenter trial involving adult patients.[52] Previous small retrospective cohort studies showed no difference in mortality, with a trend toward improvement and no benefit in prevention of ARDS in postoperative patients.[53-55] The subsequent HARP-1 pilot study showed a mean 66% reduction in SOFA score at day 14 in simvastatin-treated patients (p = 0.01).[56] In the setting of sepsis or other infectious processes, several large observational studies, randomized controlled trials, and meta-analyses have suggested improved or intermediate outcomes with statin therapy, including a potential decrease in mortality.[53,54,57] However, other studies have failed to demonstrate a mortality benefit.[56,58,59]

Due to their multicenter, prospective, double-blind, randomized, placebo-controlled designs, the HARP-2 and SAILS trials produced some of the strongest evidence to date regarding statin therapy initiation in ARDS. Despite promising data from previous trials, the results of the HARP-2 and SAILS trials failed to demonstrate a benefit with routine initiation of statin therapy regardless of ARDS cause. Additionally, both trials identified potential harms from statin initiation, including elevated hepatic enzymes in the HARP-2 study and possible detrimental effects on renal or hepatic function in the SAILS trial. It is unlikely that the study results would have been different if another statin had been utilized, since the lack of benefit was demonstrated with both hydrophilic (rosuvastatin) and lipophilic (simvastatin) agents. These data validated current practice, suggesting that the initiation of statins should not be recommended solely to improve sepsis-associated or non-sepsis-associated ARDS outcomes.

Peake et al. Goal-directed resuscitation for patients with early septic shock[60]

Yealy et al. A randomized trial of protocol-based care for early septic shock[61]

The Australasian Resuscitation in Sepsis Evaluation (ARISE)[60] and Protocolized Care for Early Septic Shock (ProCESS)[61] studies were multicenter, prospective, randomized, open-label clinical trials aimed at further investigating the effect of EGDT[16] versus usual care (UC) on mortality in early septic shock. Both studies included adult patients who met at least two SIRS criteria, with suspected or confirmed infection accompanied by either refractory hypotension or hypoperfusion. The time to initiation of antibiotics was not specified in the ProCESS trial, and patients were randomly assigned to one of three groups: protocol-based EGDT for six hours, protocol-based standard therapy (no requirement of central venous catheter placement, inotrope administration, or blood transfusion) for six hours, and UC for six hours. The primary endpoint was 60-day hospital mortality. Patients in the ARISE trial had antibiotics administered within two hours of presentation before being randomly assigned to EGDT or UC for six hours, as directed by the clinical team, with a primary endpoint of 90-day all-cause mortality. EGDT in both trials was consistent with the original protocol from the 2001 landmark study in which EGDT was introduced[16] and was coordinated across sites by individuals trained in its delivery. Resuscitative efforts were aided by continuous central venous oxygen saturation ($ScvO_2$) monitoring in the EGDT groups. Specific secondary endpoints in both trials included organ dysfunction (need for mechanical ventilation, vasopressor or renal replacement therapy), hospital and ICU LOS, discharge disposition, and adverse events.

There were 1341 patients enrolled in the ProCESS trial (protocol-based EGDT, n = 439; protocol-based standard therapy, n = 446; UC, n = 456); in the ARISE trial, there were 1600 patients (EGDT, n = 796; UC, n = 804). In both trials, there were no differences at baseline between treatment groups, and adherence to medical therapy and protocols was high. Patients in both EGDT protocol–treated groups had significantly higher requirements for i.v. fluids ($p < 0.001$ in the ProCESS study) and vasopressor therapy ($p = 0.003$ in the ProCESS study; $p < 0.001$ in the ARISE study) during the first six hours than those in the UC group in either study. The EGDT group in the ARISE trial also had a significantly higher volume of i.v. fluids administered ($p < 0.001$) and a higher rate of vasopressor therapy usage than the UC group ($p < 0.001$). Both trials had similar findings with regard to significantly greater use of packed red-cell transfusions ($p = 0.001$ in the ProCESS trial, $p < 0.001$ in the ARISE trial) and dobutamine therapy ($p < 0.0001$ in the ProCESS trial, $p < 0.001$ in the ARISE trial) in the EGDT groups during the first six hours. In the ARISE trial, the EGDT group had a small but statistically significant improvement in mean arterial pressure relative to the UC group (76.5 mm Hg versus 75.3 mm Hg, $p = 0.04$); however, no other differences in recorded physiological or laboratory parameters were noted between the groups at six hours.

For their respective primary endpoints, both the ProCESS and the ARISE trials did not show a significant reduction in mortality with the use of EGDT in early septic shock (mortality was 21% with protocol-based EGDT versus 18.2% with protocol-based standard therapy versus 18.9% with UC [$p = 0.83$ for all comparisons] in the former trial and 18.6% with EGDT versus 18.8% with UC [$p = 0.9$] in the latter). Additionally, there were no statistically significant differences in 90-day mortality, ICU or hospital LOS, or duration of organ support. Based on the results from the ProCESS and ARISE trials, the authors concluded that protocol-based resuscitation did not reduce mortality and morbidity in early septic shock and may need to be reinvestigated as the standard of care.

The results of the ProCESS and ARISE trials contest earlier beneficial findings on EGDT therapy.[16] Both trials failed to demonstrate a mortality benefit with EGDT-driven resuscitative efforts after early septic shock. While these results may question the utility of EGDT, the enrolled patients generally presented with lower serum lactate levels in both trials and with lower mean Acute Physiology And Chronic Health Evaluation II scores in the ARISE trial relative to patients involved in the original landmark study.[16] Additionally, mortality from septic shock has decreased throughout the past decade,[62] likely due to earlier identification and improved overall management. The original EGDT study protocol has now been in practice for over a decade and has no doubt influenced patient care and outcomes and may have influenced what was considered UC in these trials. A primary management difference in the ARISE and ProCESS trials between the EGDT and UC groups was the utilization of invasive monitoring measures, such as $Scvo_2$ and central venous pressure values, to aid the direction of therapies. The results from these trials may provide further evidence to existing literature that utilizing these values alone may not lead to better outcomes in early septic shock management.[63-65] The ProMISe study, which was recently published in 2015 and not included in this review, also had results consistent with the ARISE and ProCESS trials.[66] Based on these recent findings, practitioners may forego routine implementation of invasive monitoring measures and rather focus on prompt antibiotic delivery and aggressive fluid resuscitation in the management of early septic shock.

Conclusion

There were many important additions to the critical care pharmacotherapy literature in 2014, including a joint guideline for the management of AF and reports of clinical trials.

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